International Journal of Pharmaceutics, 47 (1988) 51–66
Elsevier

IJP 01581

Physicochemical aspects of drug release. VI. Drug dissolution rate from solid particulate dispersions and the importance of carrier and drug particle properties

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(Received 30 December 1987)
(Modified version received 18 March 1988)
(Accepted 24 March 1988)

Key words: Solid dispersion; Griseofulvin; Dissolution rate; Particle size distribution

Summary

Solid dispersions of a hydrophobic, sparingly soluble drug, griseofulvin, and a hydrophilic carrier, polyethylene glycol, were prepared by both a melting and a solvent method, with griseofulvin concentrations ranging from 1% to 20% w/w. All the dispersions prepared contained particulate griseofulvin in which, the size, surface and shape characteristics of the particles had been determined. The aqueous solubilities of griseofulvin incorporated in solid dispersions were analyzed. The dissolution rate measurements were determined with the paddle method (100 rpm), of the USP XXI. It was concluded that the use of solid dispersion particles in the sieve size range 300–500 μm was preferable in dissolution testing, since problems due to both floatation and sedimentation could be avoided. For both the melting and the solvent methods used the dissolution rate decreased with increasing drug concentration. This effect was more pronounced in the solvent method where the reduction was almost entirely due to an increase in drug particle size. All the griseofulvin concentrations prepared by the melting method gave relatively fine particulate dispersions, and the drug particle size could only to a limited extent explain the dissolution rate data. It was found that the dispersions prepared by the melting method containing higher drug concentrations, corresponded to a reduction in the dissolution rate of the carrier. The aqueous solubility of griseofulvin was higher after incorporation in solid dispersion compared to the untreated raw material. The highest solubility was obtained for the melting method containing higher concentrations of griseofulvin.

Introduction

For sparingly soluble drugs, a reduction of the particle size, i.e. an increase of the specific surface area, can enhance the rate of dissolution and subsequently improve the bioavailability. However, such an increase in surface area is normally accompanied by a proportional increase in the formation of agglomerates. This results in a decrease in the effective surface area, taking part in dissolution. When a sparingly soluble drug is to be formulated and a fast drug release is required, it is important to use a fine particulate material and to ensure rapid delivery to the dissolution medium as discrete primary particles of the drug. This could be achieved by adequately dispersing the drug in more soluble excipients. The use of solid dispersions in this context has been reviewed in the literature (Chiou and Riegelman, 1971; Ford, 1986).

Ordered mixtures have been evaluated as a means of obtaining deagglomerated systems of

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very fine particulate drugs (Nyström and Westerberg, 1986; Westerberg et al., 1986). This approach can only be applied for low dosage preparations, since only the external surface area of the excipient particles is utilized for carrying the smaller drug particles. The use of solid dispersions should represent a better approach when larger amounts of drugs are formulated in a solid, well deagglomerated form.

The concept of solid dispersions was introduced by Sekiguchi and Obi (1961). The term solid dispersion has been defined as 'the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method' (Chiou and Riegelman, 1971).

When dissolving these solid dispersions, it is believed that the drug substance is released as small discrete units owing to a fast dissolution of the easily soluble carrier. If the drug solubility in the carrier is high enough, a so-called solid solution can be obtained. Such a preparation will then give a system similar to a molecular solution after the carrier has been dissolved. For such systems it has been claimed that the dissolution of the carrier is the rate-limiting step (Dubois and Ford, 1985). The formation of solid solutions is therefore normally restricted to relatively low concentrations of drugs.

Many systems reported in the literature can be classified as solid dispersions with drug particles dispersed in the carrier. Griseofulvin in polyethylene glycol (PEG), the system investigated in this study, has often been shown to give particulate dispersions. It has frequently been observed that an increase in the amount of drug incorporated results in reduced dissolution rates. Normally, this effect has been attributed to a formation of coarser particulate dispersions of the drug (Chiou and Riegelman, 1971). However, very few attempts have been made to directly characterize the obtained drug particle properties, such as size distribution in solid dispersion preparations, and their corresponding impact on dissolution rate.

The aim of this study was to examine the influence of some formulation factors on drug particle properties in solid dispersions and subsequently on dissolution rate. Here the size distribution of drug particles in the solid dispersions was measured by a Coulter Counter and the drug surface area was measured by a light-blocking technique. The primary formulation factors studied were the concentration of drug and the method of solid dispersion preparation. To adequately evaluate the dissolution rate data, the obtained dissolution profiles of suspensions of well dispersed and size-characterized drug particles were used.

Experimental

Materials

Drug component

Griseofulvin microsized (Glaxo, U.K.) was used as a model of a fine particulate, sparingly soluble drug. Due to its cohesive nature, the material is strongly agglomerated. The primary characteristics of the griseofulvin used, have been characterized and described earlier (Nyström et al., 1985a). The primary characteristics are presented in Tables 1–3 and below. True density: 1.44 g/cm^3. Surface-to-volume shape factor according to Heywood (1954): 9.7 is calculated from the harmonic mean volume diameter by weight and a permeametric specific surface area. Aqueous solubility at ambient temperature: 7.6 mg/l. Melting point: 219 °C, measured with a DSC 20 (Mettler, Switzerland).

Sodium salicylate (Apoteksbolaget AB, Sweden) a substance, with high aqueous solubility (1 : 1) was used as the dispersed component in the evaluation of dissolution test procedure. Melting point: 283 °C, measured with a DSC 20.

Carrier component

Polyethylene glycol (PEG) with a mean molecular weight of 3000 (Apoteksbolaget AB, Sweden) has been used as the carrier material. The melting point is 48–54 °C and the aqueous solubility is 1 : 2 (Martindale, The Extra Pharmacopoeia, 28th edn.).

Methods

Preparation of solid dispersion

Melting method. Solid dispersions (50 g) of sodium salicylate in PEG 3000 were prepared by

TABLE 1

Particle size characteristics of griseofulvin in solid dispersions with PEG 3000 [a]

Type of solid dispersion		Geometric mean diameter [b] $\bar{d}_{v_g}$ (μm)	Harmonic mean diameter d_{v_h} (μm)	Amount recovered [c] (%)
Content of griseofulvin (%w/w)	Method of preparation			
1	Melting	2.14 (1.8)	1.82	82
2	Melting	1.92 (2.0)	1.60	82
4	Melting	1.83 (1.8)	1.58	67
10	Melting	2.69 (2.3)	2.07	70
20	Melting	3.73 (2.2)	2.78	79
2	Solvent	4.31 (1.8)	3.59	96
10	Solvent	7.13 (5.5) [d]	3.59	89
20	Solvent	12.6 (10) [d]	4.95	88
Pure untreated griseofulvin		2.97 (1.4)	2.75	95

[a] Weight frequency distributions obtained by Coulter Counter TA II.
[b] Log-normal distributions characterized by geometric mean and geometric standard deviations (dimensionless) given in brackets.
[c] Calculated weight amount of griseofulvin particles monitored during Coulter measurement, in relation to nominal amount.
[d] Arithmetic normal distributions characterized by arithmetic mean and standard deviations (in μm) given in brackets.

melting (90–100 °C) the carrier and adding amounts of sodium salicylate corresponding to 2%, 10% and 20% w/w with constant stirring. When no particles of sodium salicylate could be seen, the melt was cooled at ambient temperature and stored for at least 24 h before being pulverized in a mortar. The powder was sieved to obtain 3 fractions (90–180, 300–500 and 710–1000 μm).

Solid dispersions (50 g) of 1%, 2%, 4%, 10% and 20% w/w griseofulvin in PEG 3000 were made by melting the carrier and then adding griseofulvin. To prepare solid dispersions of higher concentra-

TABLE 2

Surface area and shape characteristics of griseofulvin in solid dispersions with PEG 3000

Type of solid dispersion		External surface area		Particle shape	
Content of griseofulvin (%w/w)	Method of preparation	Calculated [a] S_v ($cm^2 \cdot cm^{-3}$)	Measured [b] S_v ($cm^2 \cdot cm^{-3}$)	Calculated [c] α_{sv}	Corrected [d] $\alpha_{sv(corr)}$
1	Melting	33000	41000	7.5	12.0
2	Melting	38000	35000	5.6	9.0
4	Melting	38000	35000	5.5	8.9
10	Melting	29000	31000	6.4	10.3
20	Melting	22000	28000	7.8	12.5
2	Solvent	17000	30000	10.8	17.3
10	Solvent	17000	14000	5.0	8.1
20	Solvent	12000	11000	5.4	8.8
Pure untreated griseofulvin		22000	22000	6.0	9.7

[a] Calculated from harmonic mean diameter by weight (Table 1) and a surface-to-volume shape factor of 6.
[b] Characterized by light-blocking measurements.
[c] Surface-to-volume shape factors according to Heywood (1954).
[d] Calculated shape factors multiplied by the ratio of specific surface area of untreated griseofulvin as obtained by permeametry and light-blocking respectively.

TABLE 3

Aqueous solubility of griseofulvin in solid dispersions with PEG 3000

Type of solid dispersion		Aqueous solubility at 21.2 ± 1.2 °C [b] (mg/l)
Content of griseofulvin (%w/w)	Method of preparation	
1	Melting method	10.0 (±0.3)
2	Melting method	10.8 (±0.8)
4	Melting method	11.4 (±0.6)
10	Melting method	11.8 (±0.5)
20	Melting method	11.9 (±0.5)
2	Solvent method	9.8 (±0.4)
10	Solvent method	9.5 (±0.8)
20	Solvent method	9.6 (±0.4)
Pure, untreated griseofulvin		7.6 (±0.4)
Physical mixture of griseofulvin and PEG [a]		7.9 (±0.5)

[a] Griseofulvin and PEG 3000 added in a proportion of 1 : 100.
[b] The 95% confidence interval for the mean are given in brackets.

tions of griseofulvin higher temperatures were required (for 10% and 20% w/w griseofulvin 140–150 °C and 160 °C, respectively). These high temperatures make the solid dispersions brown and the colour becomes darker as the time of heating is prolonged, as described earlier by Chiou and Riegelman (1969). The change in colour is probably due to oxidation of PEG.

The melts were cooled on ice-blocks and placed in a freezer (−25 °C) overnight. The resulting solid was pulverized in a mortar and sieved to obtain the fraction 300–500 μm.

Solvent method. Amounts of griseofulvin corresponding to 2%, 10% and 20% w/w were mixed with PEG 3000 to produce a constant total weight of 50 g.

The mixture was dissolved in approximately 400 ml of absolute ethanol and concentrated in a water bath (75–80 °C) to about 100 ml. The resulting slurry was further concentrated in an oil bath (90 °C for 2 h (2% w/w), 100–115 °C for 1 h (10% w/w), and 120 °C for half-an-hour (20% w/w)) after which the formation of ethanol vapour bubbles was not longer observed. The dispersion was cooled on ice-blocks and placed in a freezer (−25 °C) overnight. To ensure that as little as possible of the solvent remained, the pulverized dispersion was kept on a tray at ambient temperature overnight. The solid dispersion was then sieved to obtain the fraction 300–500 μm.

Dissolution studies

Dissolution method. The dissolution test, USP XXI (Prolabo, France), was carried out with a rotational paddle speed constant at 100 rpm and the temperature of the water bath was equilibrated to room temperature (21.2 ± 1.2 °C).

The dissolution medium, 1000 ml for each experiment was 0.9% sodium chloride with 0.01% polysorbate 80 added to obtain optimal wetting and a condition approximately corresponding to the surface tension of gastric fluid (Finholt and Solvang, 1968).

To obtain near sink conditions during the dissolution test, the amounts of suspension or solid dispersion added to the medium did not exceed approximately 10% of the amount of drug needed to obtain saturation (0.6 and 20 mg of griseofulvin and sodium salicylate, respectively, was used in this study).

Samples were transferred to a UV spectrophotometer flow cell and the absorbance measured at 295 nm for both griseofulvin and sodium salicylate after prior filtration through 0.6 μm membrane filter. The results presented are mean values of at least 3 determinations.

Calculation of dissolution rate constants. To obtain a simple measure of the dissolution rate of each dispersion system tested, the dissolution process was expressed by the so-called cube-root law (Hixson and Crowell, 1931). Here the remaining weight of undissolved drug, raised to the power of 1/3, was plotted against dissolution time. For many systems, including nearly monodispersed and log-normally distributed suspensions, linear relationships are expected (Carstensen, 1980). This function then presents the dissolution process in a form where correction is made for the decrease in drug surface area as a function of time. The dissolution rate is then represented by the slope value (here in $mg^{1/3} \cdot min^{-1}$).

Characterization of drug properties in solid dispersion

Aqueous solubility. The aqueous solubility of pure griseofulvin and griseofulvin from solid dis-

persions was determined spectrophotometrically in an aqueous solution containing 0.9% sodium chloride and 0.01% polysorbate 80. Amounts of pure drug and solid dispersions corresponding to 100 mg griseofulvin were added to 1000 ml medium.

To study the influence of PEG 3000 on the solubility of griseofulvin, a physical admixture was prepared with pure, untreated griseofulvin and PEG 3000, using the same proportions as in the melting method. The suspensions were sonicated (Bransonic 220, 50 kHz, U.S.A.) for about 30 min and then agitated for 48 h at room temperature ($21.2 \pm 1.2°$ C). The samples were then allowed to stand for an additional period of 24 h without agitation to ensure that a sample temperature of $21.2 \pm 1.2°$ C was reached after which samples were withdrawn and centrifuged. The supernatant was passed through a 0.6 μm filter (Nuclepore, U.S.A.) before measurement. The results presented are mean values of at least three determinations.

Particle size. A Coulter Counter Model TAII fitted with 30 μm and 50 μm aperture tubes was used. A medium saturated with griseofulvin was prepared by suspending griseofulvin in distilled particle-free water containing 0.9% sodium chloride and 0.01% polysorbate 80. After 10 min treatment in the ultrasonic bath the suspension was agitated overnight and then passed through a 0.22 μm membrane filter. The griseofulvin concentration was then analyzed to confirm that the solution was saturated. This medium was used as the electrolyte for the TAII.

Stock suspensions, of pure griseofulvin and of griseofulvin from solid dispersions, were prepared by suspending amounts corresponding to 1 mg griseofulvin/ml of saturated medium. In each determination a known volume of these suspensions was added to the electrolyte saturated with griseofulvin, with the total volume always constant at 300 ml. To check that no substantial amounts of griseofulvin were dissolved during size characterization, the monitored weight was calculated (Nyström et al., 1985b) and compared to the known weight added. Tests were also made to ensure that PEG 3000 did not contribute with any particle counts that could affect the results. The results presented are mean values of at least 3 determinations.

External surface area. An amount of solid dispersion, corresponding to 2.5 mg griseofulvin, was suspended in 100 ml of a griseofulvin saturated medium with 0.01% polysorbate 80. The suspension was dispersed in the ultrasonic bath for 10 min. The specific surface area of griseofulvin in the solid dispersions was then measured by light-blocking using an EEL Photosedimentometer. The light transmission was in all experiments within 30–80%. The photosedimentometer has a narrow angle of acceptance and the surface areas were calculated by applying the correction for the extinction coefficient proposed by Rose and Sullivan (1959).

To calculate shape factors for griseofulvin particles in solid dispersions, the size data were in this study combined with surface area values as measured by the light-blocking technique. Since the shape factors obtained by this procedure probably are underestimated, the shape values were corrected by multiplying with the ratio of surface area of untreated griseofulvin as measured by permeametry and light-blocking, respectively. Further characterization of the particle shape, was carried out from photographs taken using a scanning electron microscope (Philips, SEM 525, The Netherlands).

Characterization of carrier dissolution

In order to obtain a fast and simple characterization of the dissolution rate of the carrier, compacted specimens of the solid dispersions were tested in a tablet disintegration test apparatus.

Compression of tablets. Flats-faced tablets (diameter 1.13 mm) were compressed by hand in an instrumented single punch press (Korch EK O, F.R.G.). The weighed amount of solid dispersion was chosen to keep the maximum upper punch pressure constant at 100 MPa. The tablet weight was kept within $\pm 4\%$ of 500 mg. The unlubricated solid dispersion particles were weighed on an analytical balance and filled into the die.

Dissolution testing. The disintegration apparatus was according to USP XXI, basket rack assembly (Erweka, F.R.G.), with a medium of 0.9% sodium chloride and 0.01% polysorbate 80 at room tem-

perature (21.2 ± 1.2° C). The dissolution time was measured for one tablet at a time and a dish was added to the tube. The results are mean values of 3 determinations.

Results and Discussion

Evaluation of dissolution test procedure

Results from the dissolution of preparations containing sodium salicylate of 3 different concentrations are presented in Fig. 1. Three different size fractions of solid dispersions were tested.

As a reference, a solution of sodium salicylate of known concentration was added to the dissolution medium, where the profile obtained of registered concentration of drug vs time corresponds to a system where the easily soluble carrier is dissolved immediately and is not a rate-determining step. An instantaneous peak was not obtained here because of the finite time needed to exchange the liquid content in the flow cell.

The effect of sodium salicylate concentration was small. The major differences in dissolution profiles were due to the different sieve size fractions tested. Fig. 1 shows that in most cases the smaller sieve fractions gave faster dissolution. The dissolution profiles were in many cases almost identical to the profile of the reference solution, independent of the sodium salicylate concentration.

These results, thus indicate that the incorporation of sodium salicylate in a carrier material like PEG, does not impair the dissolution of the carrier itself.

For the fraction 700–1000 μm, the deviation from the profile for the solution, was due to particulate sedimentation. The use of the smallest sieve fraction, 90–180 μm, would probably cause problems with floatation, for dispersions of especially hydrophobic drugs, such as griseofulvin, due to air entrapment around particles but also due to low particle weight, thereby leading to decreased dissolution rates. For the further experiments the fraction 300–500 μm was therefore used.

The influence of drug concentration on dissolution

The dissolution profiles for solid dispersions of 1%, 2%, 4%, 10% and 20% w/w griseofulvin in PEG 3000 prepared by the melting method are presented in Fig. 2. Two reference profiles have been obtained by adding both a solution of griseofulvin and a well-dispersed and size-characterized suspension of griseofulvin to the dissolution medium. The use of error bars clearly demonstrates that all systems tested represented different dissolution rates. Such significant differences were also obtained for the rapidly dissolving preparations of low griseofulvin contents.

The results show, as frequently reported in the literature (e.g. Chiou and Riegelman, 1969; Chiou and Niazi, 1976; Maulding, 1978), that lower con-

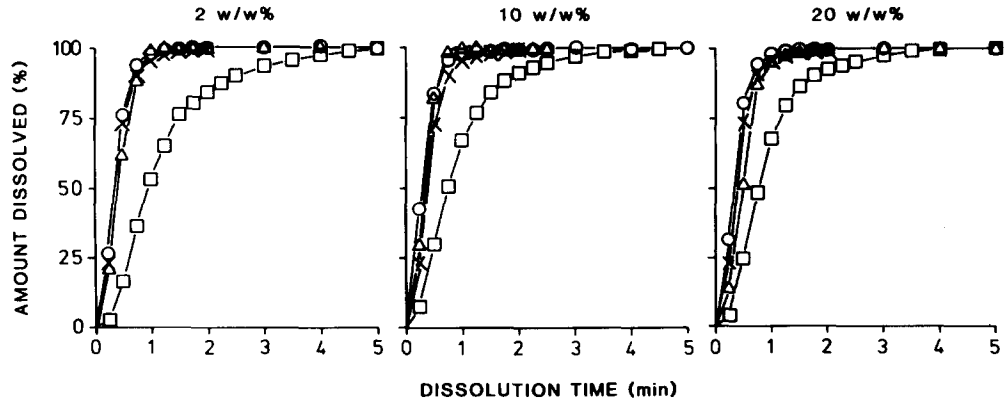

Fig. 1. Dissolution rate profiles for solid dispersions of different concentrations of sodium salicylate in PEG 3000, prepared by the melting method. Sieve size of solid dispersion: ○, 90–180 μm; △, 300–500 μm; □, 710–1000 μm; ×, solution of sodium salicylate (reference values corresponding to an instantaneous release of molecular units of the drug).

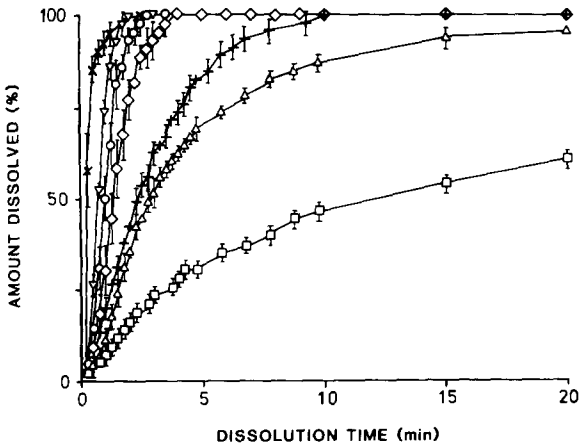

Fig. 2. Dissolution rate profiles for solid dispersions (300–500 μm) prepared by the melting method with PEG 3000 as a carrier and with different concentrations of griseofulvin: ▽, 1% w/w; ○, 2% w/w; ◇, 4% w/w; △, 10% w/w; □, 20% w/w; ×, solution of griseofulvin; +, suspension of griseofulvin. Error bars represent the 95% confidence interval for the mean.

centrations of drug in the solid dispersion give faster dissolution. The solid dispersions of the lower concentrations (1%, 2% and 4% w/w) gave a faster dissolution than the suspension, indicating that the fineness of the drug in these solid dispersions are higher than in the untreated raw material of griseofulvin. Comparisons with the profile obtained after adding the solution to the dissolution medium indicate, however, that a molecular dispersion is probably not obtained.

The solid dispersion with 10% w/w griseofulvin shows a dissolution rate profile which is slightly slower than the one obtained for the suspension. However, the dissolution rate for a 20% w/w solid dispersion is markedly decreased.

The influence of method of preparation

Solid dispersions of 2%, 10% and 20% w/w griseofulvin in PEG 3000 were prepared by the solvent method. The dissolution profiles of these are compared with the profiles obtained from solid dispersions of the same concentration of griseofulvin prepared by the melting method in Fig. 3.

Solid dispersions prepared by the melting method generally showed a faster dissolution. However, for some concentrations of griseofulvin a similar and even slightly faster dissolution can be seen initially for solid dispersions prepared by the solvent method.

Relation between drug particle properties and dissolution rate

The results presented in Figs. 2 and 3 were then treated according to the 'cube-root law' (Hixson and Crowell, 1931) and the corresponding results are presented in Fig. 4.

For the suspension and most of the melted dispersions straight line relationships were obtained. For some of the dispersion systems, a biphasic relation was obtained. The biphasic pattern was especially pronounced for some of the dispersions prepared by the solvent method. These dispersions showed, as commented above, a relatively fast initial dissolution rate followed by a slower release. In the discussion below, the dissolution rate is expressed as the initial slope from these cube-root law plots. The rationale for using the initial dissolution rate is obviously to correlate the data with initial drug particle properties in solid dispersions.

Particle size. The results support the idea that the probability that molecular units will precipi-

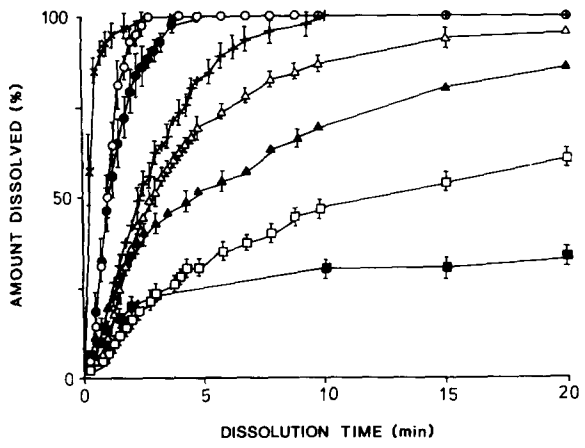

Fig. 3. Dissolution rate profiles for solid dispersions (300–500 μm) with griseofulvin in PEG 3000. Comparison between solid dispersions prepared by the melting method (open symbols) and the solvent method (closed symbols) with different concentrations of griseofulvin: ○, ●, 2% w/w; △, ▲, 10% w/w; □, ■, 20% w/w; ×, solution of griseofulvin; +, suspension of griseofulvin. Error bars represent the 95% confidence interval for the mean.

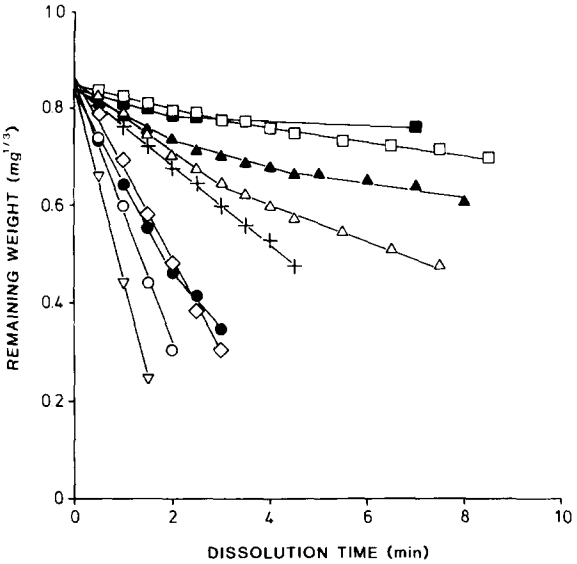

Fig. 4. Cube-root law profiles (remaining weight of undissolved drug raised to the power of 1/3 vs dissolution time) for solid dispersions prepared by the melting method (open symbols) and the solvent method (closed symbols), with different concentrations of griseofulvin: ▽, 1% w/w; ○, ●, 2% w/w; ◇, 4% w/w; △, ▲, 10% w/w; □, ■, 20% w/w; +, suspension.

tate to larger units is increased as the concentration of the drug is increased. This is shown in Table 1 where particle size data, obtained by the Coulter Counter TA II, for griseofulvin in suspension and in solid dispersions are presented. For low concentrations (1%, 2% and 4% w/w) the average mean particle size for the melting method is fairly constant, between 1.8 and 2.1 μm. As the concentration increases further, the mean particle size is increased.

For the solvent method the mean particle sizes are higher than for the corresponding dispersions prepared by the melting method. Furthermore the increase in mean particle size with increased griseofulvin concentration is more pronounced.

To verify the fact that no major fraction of the griseofulvin particles were dissolved during the measurements, the monitored particles were used to calculate the weight concentration (Nyström et al., 1985b). The amounts recovered were in most cases above 80% and no tendency in the variation in these amounts could be seen.

The difference in particle size expressed as mean volume diameter (Table 1) between solid dispersions prepared by the two methods can probably be explained by the differences in the technical procedure between the methods. When preparing solid dispersions by the solvent method, white cloudy systems were obtained when the solvent was evaporated, especially for higher concentrations of griseofulvin. This indicates that a relatively coarse particulate dispersion was obtained. In the melting method a higher temperature is used, especially for higher concentrations of griseofulvin, and this in combination with the rapid cooling explains why the particles in these solid dispersions are of smaller size.

The increase in dissolution rate with decreased griseofulvin concentration seems to correlate fairly well with mean particle sizes for each method of preparation separately and especially for the solvent method. However, when comparing the two methods, other parameters are also important. To further evaluate the influence of particle size, full size distributions are presented in Figs. 5 and 6. For the melting method (Fig. 5) it was observed as expected that the particle size distribution for lower concentrations (1%, 2% and 4% w/w) are quite similar. For solid dispersions with higher concentrations, 10% and 20% w/w, the distributions are wider, containing more larger particles.

The particle size distributions for griseofulvin from solid dispersions prepared by the solvent method (Fig. 6) are quite different from those prepared by the melting method. The size distributions are wider and higher concentrations of griseofulvin (10% and 20% w/w) show bimodal particle size distributions which might explain why these solid dispersions initially show a fast dissolution, followed by a relatively low dissolution rate. However, the different dissolution behaviour for the solid dispersions cannot simply be explained by the different particle size distributions, e.g. the solid dispersions of 2% w/w griseofulvin prepared by the two methods show initially similar dissolution rates, even though the particle size distributions are quite different.

This is clearly illustrated in Fig. 7, where the cube-root law constants are plotted against a measure of particle fineness. Here the fineness of griseofulvin is expressed in the form of a calcu-

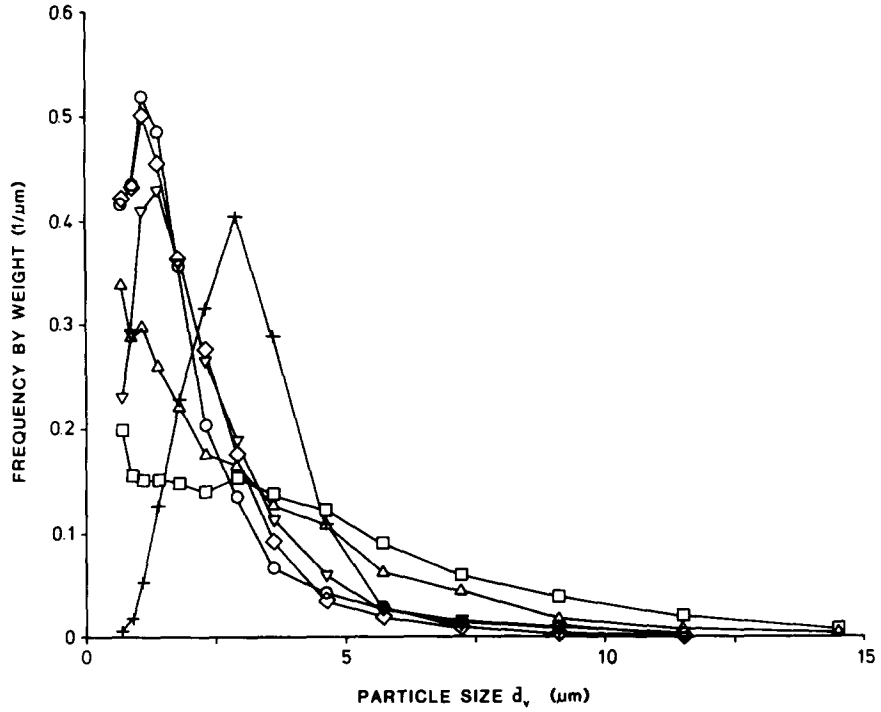

Fig. 5. Particle size distributions (Coulter Counter TAII) of griseofulvin in solid dispersions with PEG 3000 prepared by the melting method. Concentration of griseofulvin: ▽, 1% w/w; ○, 2% w/w; ◇, 4% w/w; △, 10% w/w; □, 20% w/w; +, suspension.

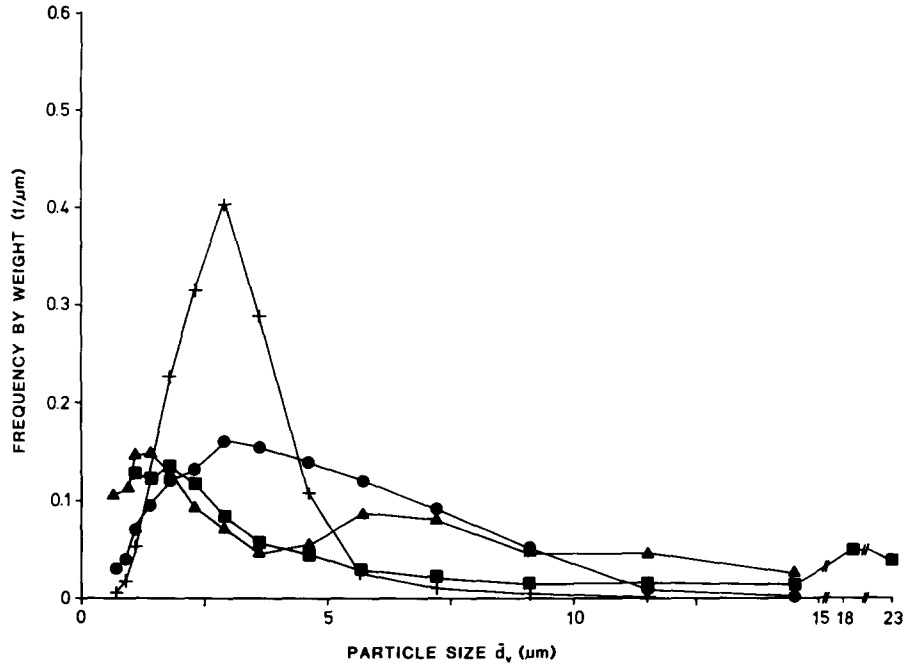

Fig. 6. Particle size distributions (Coulter counter TAII) of griseofulvin in solid dispersions with PEG 3000 prepared by the solvent method. Concentration of griseofulvin: ●, 2% w/w; ▲, 10% w/w; ■, 20% w/w; +, suspension.

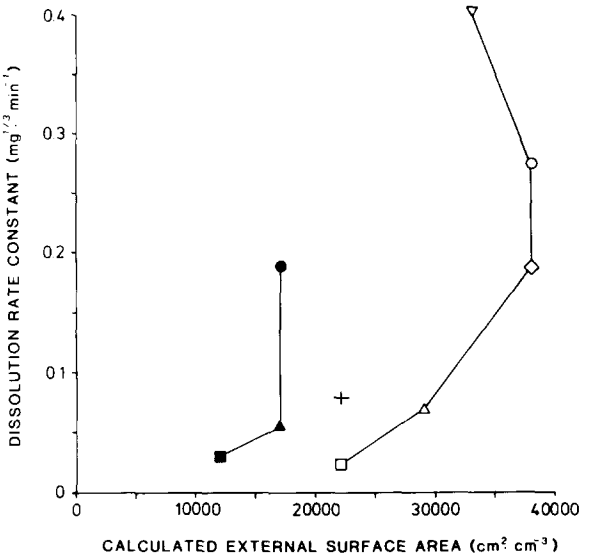

Fig. 7. Relation between dissolution rate constant (in mg$^{1/3}$·min^{-1}) and calculated external surface area of drug particles in solid dispersions prepared by the melting method (open symbols) and solvent method (closed symbols) with different concentrations of griseofulvin. Symbols as in Fig. 4.

lated external surface area. However, since this measure is based on the harmonic mean volume diameter by weight (Table 1) and a constant surface-to-volume shape factor of 6, this measure basically reflects an average particle size.

External surface area and particle shape. By combining measured surface area values with size data (harmonic means by weight, Table 1), surface-to-volume shape factors (Heywood, 1954) were calculated and presented in Table 2. The results demonstrate that the particle shape could not be regarded as a constant property for the systems tested. The highest value, corresponding to the most irregular shape, was obtained for the 2% w/w dispersion prepared by the solvent method.

Such differences in shape were also demonstrated with the aid of SEM photomicrographs (Fig. 9). Here, the most regular shape observed was for the solvent method and high griseofulvin concentrations (Fig. 9E), whereas extremely irregular particles (aggregates and re-entrant particles) were identified for low drug concentrations in dispersions prepared by the solvent method (Fig. 9C). Also for the melting method, aggregates were observed (Fig. 9B, D). The corrected shape values (Table 2) agreed fairly well with the qualitative information obtained by scanning electron microscopy. The measured values of specific external surface area of griseofulvin were related to dissolution data in Fig. 8.

The results indicate that the drug dissolution rate from the solid dispersions are in more direct proportion to the fineness of the drug, than indicated in Fig. 7. For the solvent method an almost linear relation was obtained; however, the dissolution rates are generally somewhat higher than expected from the data concerning the suspension of untreated griseofulvin. For the melting method the dissolution rate seems only to a limited extent be controlled by the surface area of the drug. For low concentrations, relatively high dissolution rates are obtained whereas for higher concentrations unexpectedly low values were monitored.

Aqueous solubility. The aqueous solubility of pure griseofulvin and griseofulvin in solid dispersions is shown in Table 3. The solubility of pure griseofulvin, obtained by the described method, is

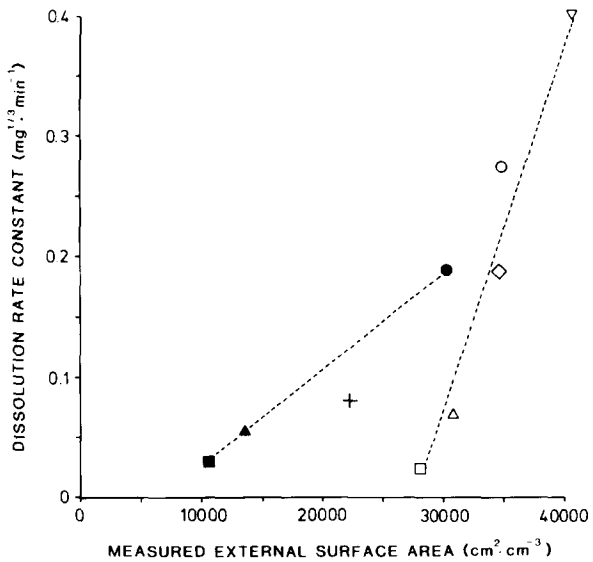

Fig. 8. Relation between dissolution rate constant (in mg$^{1/3}$·min^{-1}) and measured external surface area of drug particles in solid dispersions prepared by the melting method (open symbols) and solvent method (closed symbols) with different concentrations of griseofulvin. Symbols as in Fig. 4.

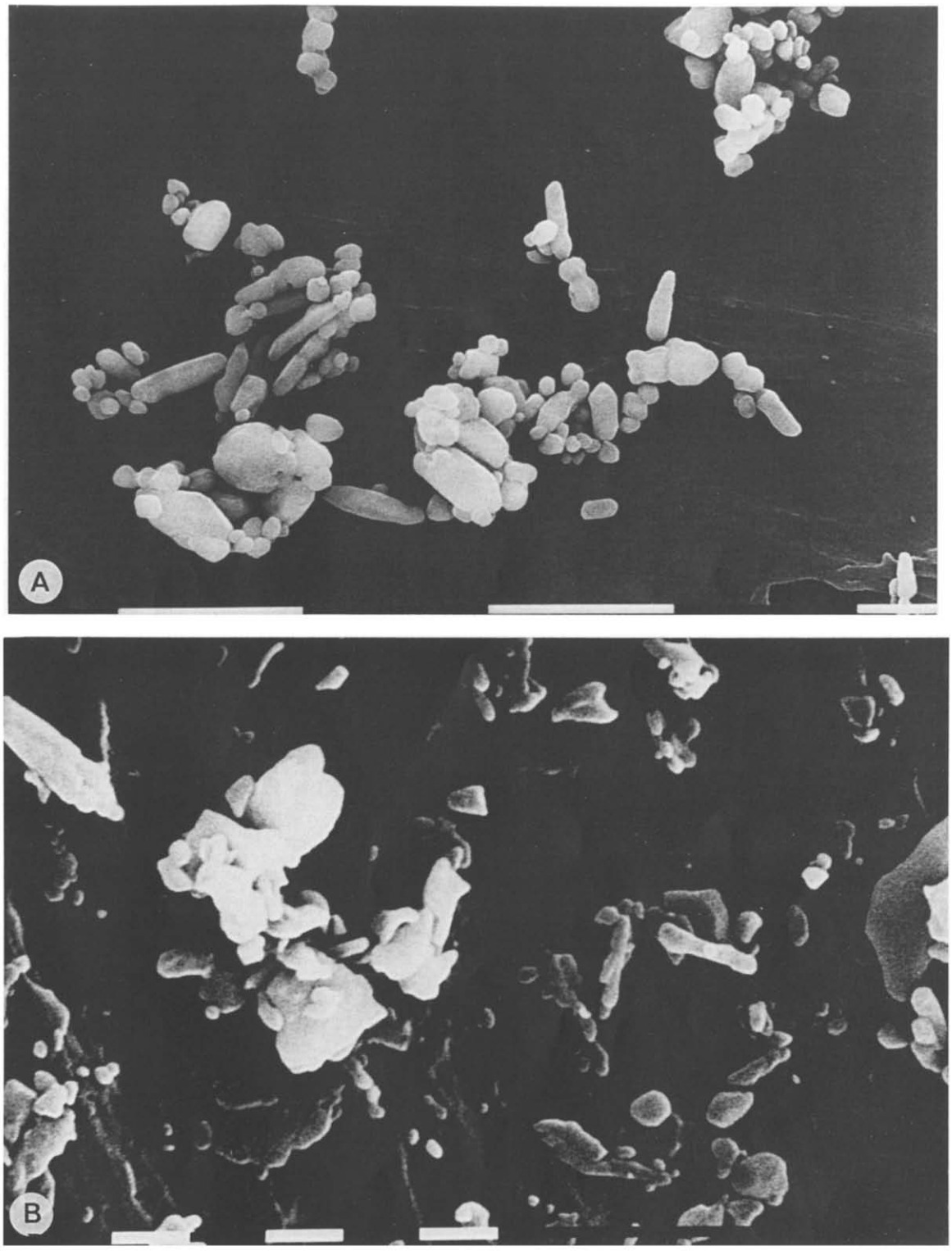

Fig. 9 *(legend on p. 63)*

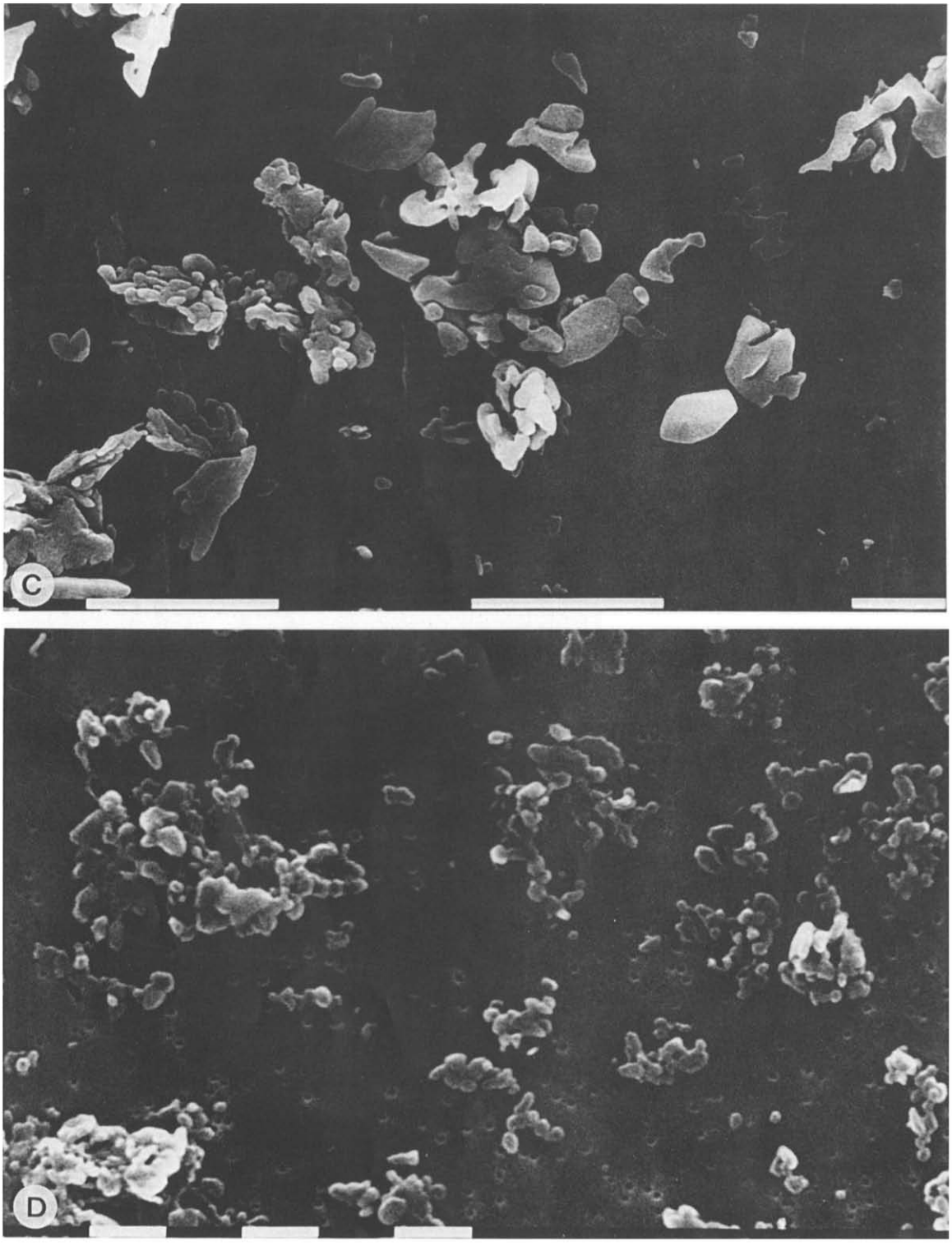

Fig. 9 *(legend on p. 63)*

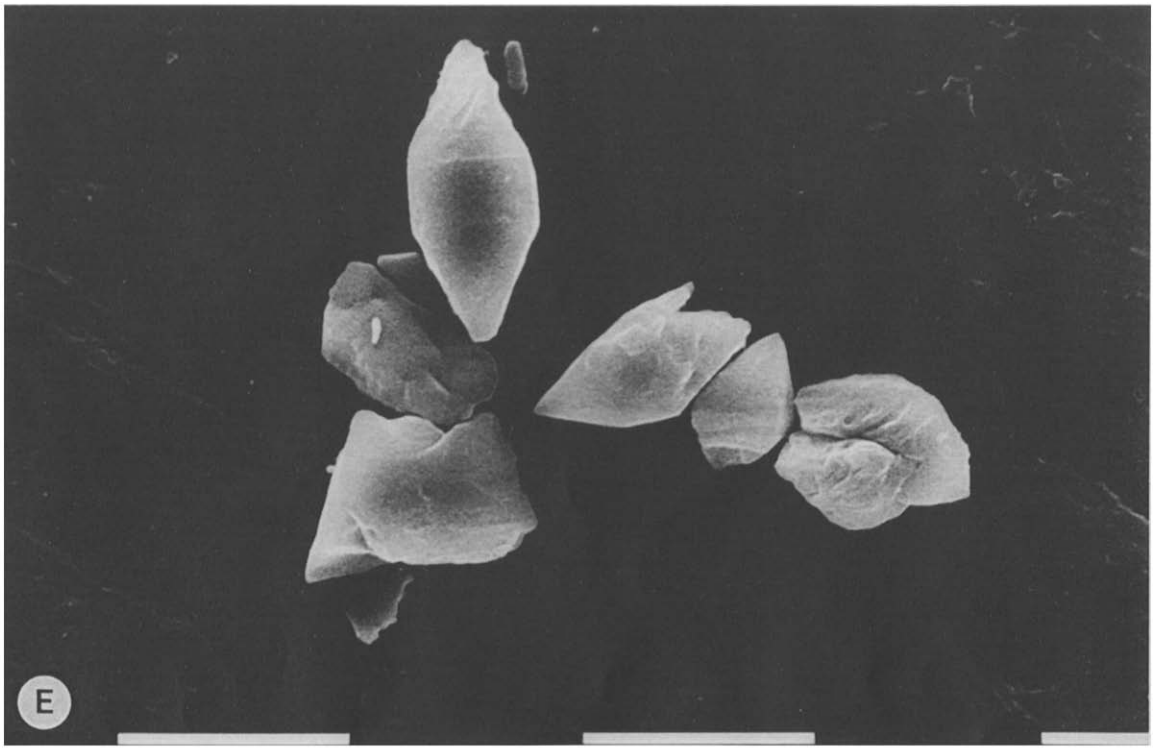

Fig. 9. Scanning electron photomicrographs of griseofulvin in solid dispersions. A: pure griseofulvin. B: 2% w/w griseofulvin, melting method. C: 2% w/w griseofulvin, solvent method. D: 10% w/w griseofulvin, melting method. E: 10% w/w griseofulvin, solvent method. The white bars denote 10 μm in Fig. 9A, C and E and 1 μm in Fig. 9B and D.

7.6 mg/l. For all solid dispersions tested, an increase in griseofulvin solubility, compared to the solubility of the pure, untreated drug, was found.

For the solvent method the solubility increases to an average of 9.6 mg/l, almost independent of the drug concentration. Solid dispersions prepared by the melting method with low concentrations of griseofulvin (1%, 2% and 4% w/w) gave an average solubility close to 11 mg/l. For solid dispersions with higher concentration (10% and 20% w/w), the solubility increases to approximately 12 mg/l. This could be explained by the fact that when preparing these solid dispersions with high concentrations by this method, it is necessary to use a higher temperature to visually dissolve all griseofulvin in PEG 3000. The melts are then quickly cooled in a freezer and it cannot be excluded that a more energy-rich solid structure of griseofulvin is obtained, corresponding to a higher aqueous solubility.

The established differences in solubility were then used to adjust the relation between measured drug surface area and dissolution rate, here expressed as the solubility specific dissolution rate (Fig. 10). As in Fig. 8, separate relationships were obtained for the two methods of preparation. However, in Fig. 10 the data for the solvent method were in better agreement with the data points for the suspension of untreated griseofulvin.

In Fig. 10 (and Fig. 8) straight lines have been drawn to indicate the relationship between the dissolution rate constants and the measured external surface areas of drug particles in solid dispersions prepared by the two methods. The straight lines have here solely been used to clearly differentiate between the two sets of results. It should, however, be emphasized that the correlations should be curvilinear, starting at the origin. If only the surface area of the drug would have influenced the dissolution rate, all data points would have

TABLE 4

Characterization of carrier dissolution from disintegration measurements of solid dispersion compacts [a]

Type of solid dispersion		Maximum upper punch pressure (MPa)	Tablet weight (mg)	Tablet thickness (mm)	Disintegration time [b] (min)
Content of griseofulvin (%w/w)	Method of preparation				
Solid dispersion					
1	Melting	100	500	4.28	13.8
2	Melting	100	500	4.27	14.4
4	Melting	100	502	4.28	15.6
10	Melting	100	507	4.31	19.3
20	Melting	100	510	4.21	19.3
2	Solvent	100	500	4.27	13.7
10	Solvent	100	507	4.31	13.7
20	Solvent	100	520	4.26	13.9
Pure carrier					
Pure untreated carrier		75	500	4.23	12.5
Pure untreated carrier		100	495	4.18	12.3
Pure untreated carrier		125	500	4.28	13.2
Pure heated carrier [c]		100	500	4.26	13.3
Pure heated carrier [d]		100	496	4.29	13.8

[a] PEG 3000.
[b] According to USP XXI.
[c] Heated to 85 °C.
[d] Heated to 150 °C, to achieve oxidation.

been situated along a straight line from origin going through the value for the suspension. If it is also considered that the thickness of the diffusion boundary layer will decrease with a decrease in particle size (Niebergall et al., 1963, Nyström et al., 1985b), a curved correlation profile with positive deviation would be expected. From Fig. 10 it can be seen that such a correlation exists for the preparations obtained by the solvent method and the lower concentrations (1%, 2% and 4% w/w) obtained by the melting method. For the melted preparations containing 10% and 20% griseofulvin, some additional phenomena will influence and decrease the dissolution rate.

The relationship between dissolution rate of carrier and drug. The dissolution times and compact specifications are presented in Table 4. The effect of the compaction pressures tested was negligible as all the tablets tested dissolved, rather than disintegrated, during the test. For the dispersions obtained by the solvent method no substantial change was obtained due to the incorporation of griseofulvin particles. For the melting method, on the other hand, the increase in drug concentration resulted in a continuous prolongation in carrier dissolution time. This effect could probably explain the deviation in the results for the higher concentrations of dispersions prepared by the melting method (Fig. 10). These dispersions have in common the presence of a large number of fine, hydrophobic drug particles. This drug portion thus represents a large surface area of a hydrophobic nature. It cannot be excluded that, for these dispersions, problems with inadequate wetting could arise. It has in studies on wetting of compacted, heterogeneous surfaces been suggested that the hydrophobic portion of a surface ultimately determines the wettability of the speciemen (Buckton and Newton, 1986). Corrigan et al. (1979) have shown that the dissolution rate of polyethylene glycol from solid dispersions, with hydroflumethiazide and bendrofluazide as drugs, was lower than that of the pure polymer. However, for more hydrophilic drugs, such as sodium salicylate,

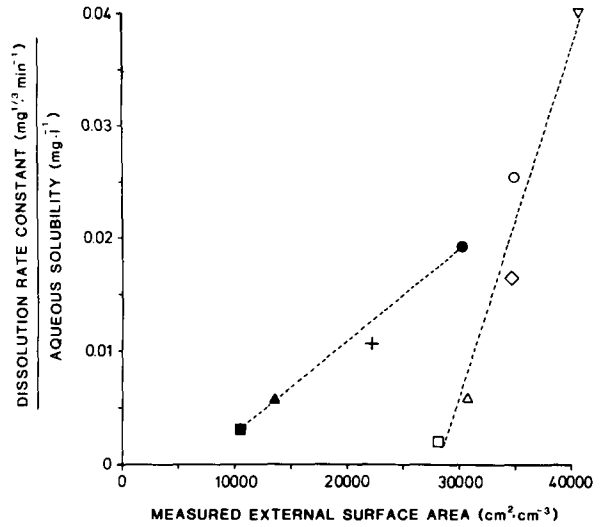

Fig. 10. Relation between dissolution rate (in $mg^{1/3} \cdot min^{-1}$)/ aqueous solubility ($mg \cdot l^{-1}$) and measured external surface area of drug particles in solid dispersions prepared by the melting method (open symbols) and solvent method (closed symbols) with different concentrations of griseofulvin. Symbols as in Fig. 4.

no such effects are expected. In Fig. 1 it was also demonstrated that dispersions containing 20% w/w, prepared by the melting method, gave an instantaneous release of the drug.

Conclusion

When a hydrophobic drug is incorporated in a hydrophilic carrier, in the form of a solid particulate dispersion, the dissolution rate seems to be strongly affected by the drug particle properties. When the drug is in relatively coarse particulate form, the dissolution rate is to a large extent related to the external drug particle surface area, taking part in dissolution, and only to a minor extent influenced by the dissolution of the carrier material. This type of dispersion was obtained by the solvent method in this study.

When the drug exists in fine particulate form, the dissolution of the carrier could be reduced and thereby become the major rate-limiting factor in the dissolution process, especially for high contents of drug. Such fine particulate dispersions were obtained by the melting method.

A solid dispersion intended for extremely fast drug dissolution ought therefore to be formulated in such a way that the incorporated drug represents a relatively small amount of hydrophobic drug surface area, since the dissolution of the carrier will then not be retarded. At the same time the drug must be in a fine particulate form, to represent a high specific surface area. This solid dispersion type was in this study only obtained for low dosage preparations. For higher drug contents, the solvent method gave coarse drug particulate dispersions, representing a low specific surface area of drug.

Dissolution rates have in the present study been tested on sieve fractions of dispersion particles. The rationales for utilizing this system, rather than using e.g. a rotating disc method, have been the following.

The in vitro dissolution rate from a compressed disc is considerably slower than from a particulate suspension, due to differences in interfacial surface area and hydrodynamic conditions. In the present study, a system was aimed for that could imitate the behaviour of a potential formulation intended for fast dissolution of a sparingly soluble drug. Such a formulation requires a rapid disintegration from e.g. compacted state to a particulate form. The use of rotating disc experiments would here probably mask the differences in dissolution rates obtained in the study, as indicated by the carrier dissolution results presented in Table 4.

These results support the findings in literature (e.g. Dubois and Ford, 1985) that the drug dissolution in many cases could be governed by the dissolution of the carrier. It seems therefore that in order to utilize the concept of solid dispersion or solid solution for fast dissolution of high dosage preparations, the dosage form must rapidly disintegrate and furthermore, a retarded carrier dissolution must be counteracted. Studies on carrier dissolution in this context are currently being undertaken.

Acknowledgements

The authors are very greatful to Glaxo U.K. for supplying the griseofulvin samples used. We also

wish to thank Mrs. Eva Nises Ahlgren for preparing the manuscript and Mrs. Elisabet Börjesson for making the drawings.

References

Barnett, M.I., Nyström, C. and Engvall, H., The importance of optical refraction in connection with the surface area measurement of powders by some photometric apparatus. *Int. J. Pharm.*, 6 (1980) 131–136.

Buckton, G. and Newton, J.M., Assessment of the wettability of powders by use of compressed powder discs. *Powder Technol.*, 46 (1986) 201–208.

Carstensen, J.T., *Solid Pharmaceutics: Mechanical Properties and Rate Phenomena*, Academic, New York, 1980, pp. 52–57.

Chiou, W.L. and Riegelman, S., Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci.*, 58 (1969) 1505–1509.

Chiou, W.L. and Riegelman, S., Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.*, 60 (1971) 1281–1302.

Chiou, W.L. and Niazi, S., Pharmaceutical applications of solid dispersion systems: Dissolution of griseofulvin–succinic acid eutectic mixture. *J. Pharm. Sci.*, 65 (1976) 1212–1214.

Corrigan, O.I., Murphy, C.A. and Timoney, R.F., Dissolution properties of polyethylene glycols and polyethylene glycol–drug systems. *Int. J. Pharm.*, 4 (1979) 67–74.

Dubois, J.-L. and Ford, J.L., Similarities in the release rates of different drugs from polyethylene glycol 6000 solid dispersions. *J. Pharm. Pharmacol.*, 37 (1985) 494–496.

Finholt, P. and Solvang, S., Dissolution kinetics of drugs in human gastric juice – the role of surface tension. *J. Pharm. Sci.*, 57 (1968) 1322–1326.

Ford, J.L., The current status of solid dispersions. *Pharm. Acta Helv.*, 61 (1986) 69–88.

Heywood, H., Particle shape coefficients. *J. Imp. Coll. Chem. Eng. Soc.*, 8 (1954) 25–33.

Hixson, A.W. and Crowell, J.H., Dependence of reaction velocity upon surface and agitation. I – Theoretical consideration. Ind. Eng. Chem. 23 (1931) 923–931.

Martindale, The Extra Pharmacopoeia, J.E.F. Reynolds (Ed.), 28th edn., The Pharmaceutical Press, London, 1982, pp. 710–711.

Maulding, H.V., Solid-state dispersions employing urethan. *J. Pharm. Sci.*, 67 (1978) 391–394.

Niebergall, P.J., Milosovich, G. and Goyan, J.E., Dissolution rate studies. II. Dissolution of particles under conditions of rapid agitation. *J. Pharm. Sci.*, 52 (1963) 236–241.

Nyström, C., Mazur, J., Barnett, M.I. and Glazer, M., Physicochemical aspects of drug release. I. Dissolution rate measurements of sparingly soluble compounds with the Coulter Counter model TAII. *J. Pharm. Pharmacol.*, 37 (1985a) 217–221.

Nyström, C., Barnett, M.I., Mazur, J. and Glazer, M., Determination of the solubility and dissolution rate of polydispersed materials from particle weight and surface area data using a TAII Coulter Counter. *Proceedings of the 5th Conference of Particle Size Analysis*, Bradford, September 1985b.

Nyström, C. and Westerberg, M., The use of ordered mixtures for improving the dissolution rate of low solubility compounds. *J. Pharm. Pharmacol.*, 38 (1986) 161–165.

Rose, H.E. and Sullivan, R.M., Rapid estimation of the specific surface of a powder. *Nature (Lond.)*, 184 (1959) 46–47.

Sekiguchi, K. and Obi, N., Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfatriazole in man. *Chem. Pharm. Bull.*, 9 (1961) 866–872.

Westerberg, W., Jonsson, B. and Nyström, C., Physicochemical aspects of drug release. IV. The effect of carrier particle properties on the dissolution rate from ordered mixtures. *Int. J. Pharm.*, 28 (1986) 23–31.