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The use of ordered mixtures for improving the dissolution rate of low solubility compounds‡

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The dissolution rate of micronized griseofulvin has been investigated, both for the agglomerated raw material and the material formulated as an ordered mixture, by means of the USP XX paddle method. During the experiments, which were performed at sink condition and constant temperature, the effects of adding a surfactant and of agitation were tested. The ordered mixture with sodium chloride gave a fast dissolution rate, practically independent of the test parameters. Micronized griseofulvin alone gave dissolution profiles that were improved by adding polysorbate 80 and by increased agitation, but the dissolution rates obtained were much lower than those for the ordered mixture. It was concluded that the rate limiting step in the dissolution of griseofulvin as the raw material is the penetration of the dissolution medium into the agglomerates. With an ordered mixture, these agglomerates were deaggregated during the mixing process, producing a system in which the entire external surface area of the primary particles was exposed to the dissolution medium. This conclusion was supported by calculation of the contact surface areas taking part in the dissolution process for the systems tested. The procedure developed in this study could be applied to preformulation work where a cohesive, low solubility drug of hydrophobic nature is to be formulated.

The rate of absorption of slightly soluble drugs from the gastrointestinal tract and other sites is often limited by the rate of dissolution of the drug substance. Where this occurs the use of fine particulate drugs can improve bioavailability (e.g. Reinhold et al 1945; Atkinson et al 1962). The relation between dissolution rate (dC/dt) and surface area of a dissolving substance is demonstrated in, e.g. the equation of Noyes & Whitney (1897):

$$dC/dt = (D/h)\cdot S_c\cdot(C_s - C_t) \qquad (1)$$

where D is the diffusion coefficient, h is the thickness of the diffusion layer and S_c is the contact surface area between liquid and solid. C_s is the concentration in the diffusion layer (i.e. the solubility of the solid in the liquid). C_t is the concentration of dissolved solid in the bulk of the dissolution medium at time t.

In principle, therefore, for a given dose of drug, increasing the specific surface area by reducing the particle size will lead to a proportional increase in dissolution rate. However, formulations containing micronized drugs do not always exhibit an improved dissolution rate, even reduced rates have been reported (Aguiar et al 1967; Finholt & Solvang 1968; Lin et al 1968). This is due to differences in how *surface area* is defined. In equation 1, the term S_c defines the surface area taking part in the dissolution process, i.e. the contact area between solid and liquid. This parameter is not necessarily equivalent to the values of surface area determined experimentally by various techniques and expressed as a measure of powder fineness.

If the powder exists in an agglomerated or aggregated form, values for surface area will depend on whether primary particles or agglomerates are characterized. Even for primary particles the experimental value may either represent an external surface as measured e.g. by permeametry or photometry, or a larger total surface area including open intraparticulate pores (Orr & Dalla Valle 1959; Allen 1981).

For drug particles well dispersed in suspension, the external surface area of the primary particles has been shown to be adequate to allow interpretation of in-vitro dissolution data (Hoelgaard & Møller 1973). However, with micronized drugs that are strongly agglomerated, the contact surface area (S_c) is substantially lower than the external surface area of the primary particles (Finholt & Solvang 1968). In this case, the addition of surface active agents improves liquid penetration and thus increases the contact surface area.

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In an ordered powder mix (Hersey 1975), fine drug particles are distributed fairly evenly on coarse carrier particles. The drug powder is therefore deagglomerated in the dry state. This may be used to increase the dissolution rate of drug powders (Ampolsuk et al 1974; Crooks & Ho 1976) because a larger contact surface area is exposed to the dissolution medium. In a preliminary report, the use of ordered mixtures was shown to enhance strongly the dissolution rate of micronized griseofulvin (Nyström & Malmqvist 1984). To obtain a homogeneous ordered mix that is mechanically stable, parameters such as drug particle size, mixing time and batch size must be precautiously controlled (Malmqvist 1984).

In this study we have evaluated the extent to which ordered mixing can be used to improve the dissolution rate of a sparingly soluble drug.

MATERIALS AND METHODS

Materials

Griseofulvin (micronized, Glaxo, UK) was used as supplied. This was chosen as representing a fine particulate sparingly soluble drug which is cohesive and therefore, strongly agglomerated. Agglomerates in the sieve fraction 500–710 μm were used for all experiments. Sodium chloride (Puriss, Kebo Grave, Sweden) was used as a relatively coarse carrier material. This was fractionated by sieving and the fraction between 250 and 420 μm was used.

As surface active agent, in the dissolution media, polysorbate 80, (Tween 80, Kebo Grave, Sweden) was used.

Primary characterization—griseofulvin

Density. The density was measured with an air comparison pycnometer (model 930, Beckman, USA). The value in Table 1 is the mean of five determinations.

Table 1. Primary characteristics of materials.

Material	Density ρ_s (g cm^{-3})	External surface area of primary particles (S_p) g^{-1} (cm^2 g^{-1})	External surface area of agglomerates (S_a) g^{-1} (cm^2 g^{-1})	Solubility C_s (μg ml^{-1})
Griseofulvin	1·44	21 500[a]	181	8·66[a]
Sodium chloride	2·17	100[b]	—	Very soluble

[a] Determined by Nyström et al (1985).
[b] Determined by Malmqvist & Nyström (1984a).

External surface area of griseofulvin agglomerates (S_a). The mean diameter of agglomerates in the sieve fraction 500–710 μm was taken to be 605 μM. All agglomerates were spherical and consequently the surface shape factor according to Heywood (1954) was estimated to π. The external surface area S_a of the agglomerates was then calculated in cm^2 as:

$$S_a = \pi \cdot (\bar{d})^2 \cdot n \qquad (2)$$

where d is the agglomerate mean diameter in cm and n is the number of agglomerates in the sample.

External surface area of griseofulvin primary particles (S_p). The external surface area was determined by permeametry, using a Blaine apparatus (Tonindustrie, West Germany). Due to the fine particulate materials used, the calculations of surface area also involved a correction for 'slip flow'. Using plugs of griseofulvin compressed at 5 MPa, the weight specific surface in cm^2 g^{-1} was calculated as described earlier (Alderborn et al 1985). Three measurements were determined.

Solubility. The solubility was determined by adding a large excess of the drug to 1 litre dissolution media. The suspensions were allowed to stand for 48 h at 23 °C in a mechanical shaking bath. After centrifugation the supernatant was assayed for amount of drug, as described earlier (Nyström et al 1985). The result in Table 1 is the mean of three determinations.

Intrinsic dissolution rate. In the present work we have taken 6·5 μg min^{-1} cm^{-2} for the surface specific dissolution rate of griseofulvin. This value was determined experimentally (Nyström et al 1985).

Primary characteristics of the test materials are summarized in Table 1.

Preparation of ordered mixture

Weight proportion of drug. To avoid 'oversaturation' of the carrier particles (Malmqvist 1984), the amount of drug substance should be limited to the maximum amount theoretically needed to obtain a monoparticulate layer covering the carrier particles (Malmqvist 1984; Nyström et al 1982), i.e. the so called surface area ratio (Nyström et al 1982) should not exceed unity. The surface area ratio was calculated to be 0·164, corresponding to 50·0 g sodium chloride and 0·153 g griseofulvin.

Mixing. The starting materials were stored at 45% r.h. for not less than 48 h before mixing in a Turbula mixer (W.A. Bachofen, Switzerland) at 65–90 rev min^{-1}. The size of the glass jar was chosen to give a fill volume of roughly 50%. To achieve total deagglomeration, sodium chloride and griseofulvin

were mixed for 3000 min (Malmqvist & Nyström 1984b).

Dissolution studies

Dissolution test. The dissolution test was performed according to the USP XX, using paddle agitation intensities of 10 and 100 rev min^{-1} at 23 °C. Test samples of griseofulvin agglomerates and of ordered mixtures were accurately weighed to 3 decimal places.

Dissolution media. In this study a 0·9% w/w solution of sodium chloride in distilled water was used. To evaluate the effect of surface tension, on both the water penetration into agglomerate drug and penetration around ordered drug particles adhering to the carrier particles, concentrations of 0·001 and 0·01% w/w polysorbate 80 were used.

The maximum concentration of polysorbate 80 was limited to 0·01 w/w%, since this corresponds approximately to the surface tension of gastric fluid (Finholt & Solvang 1968) and a further increase in concentration does not significantly decrease the surface tension (Wan & Lee 1974). Furthermore, it was desirable to avoid any significant interaction between drug molecule and a micellar structure.

Sampling. To obtain sink conditions during the dissolution test, the weight of drug added to the dissolution media was chosen to be approximately 10% of the drug solubility. In this study 0·7 mg of the agglomerated drug was added to 1 litre of dissolution media. The corresponding sample weight for the ordered mixture was 0·229 g. From the ordered mixtures, samples were obtained by scooping.

Analytical procedure. A semiautomatic sampling and analysis system was used. A pump transferred samples from the dissolution vessels to flow cells in a spectrophotometer (Zeiss PM 6, West Germany) where the UV absorbance was measured at 295 nm. Results are mean values of two determinations if not otherwise stated.

RESULTS AND DISCUSSION

Dissolution of agglomerates

The effect of different concentrations of polysorbate 80 on the dissolution of agglomerates or griseofulvin is shown in Fig. 1. As reported for other materials (e.g. Finholt & Solvang 1968), the addition of surface active agent markedly improves the dissolution rate. The addition of 0·001% w/w gives a large increase in dissolution rate but a further increase in concentration to 0·01% w/w gave a proportionally smaller increase. The mechanism of the surfactant is probably to enhance liquid penetration into the agglomerates, thereby increasing the amount of surface area in contact with the dissolution medium. Disintegration of the agglomerates may also have been facilitated.

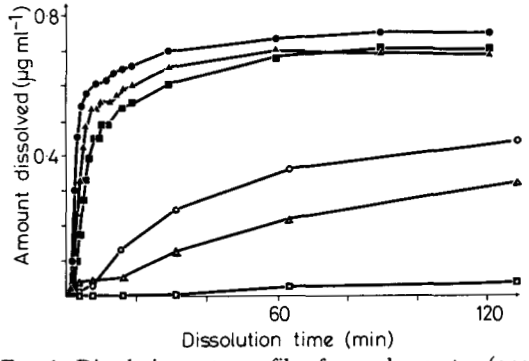

FIG. 1. Dissolution rate profiles for agglomerates (open symbols) and ordered mixtures (closed symbols) of griseofulvin as measured by the USP XX paddle method (100 rev min^{-1}). Concentration of polysorbate 80 in dissolution media: □, ■, 0% w/w; △, ▲, 0·001% w/w; ○, ●, 0·01% w/w. Results for the highest concentration are mean values of five determinations.*

According to Washburn (1921) liquid penetration is reduced by a decrease in surface tension. However, if there was a simultaneous decrease in the contact angle for a hydrophobic material like griseofulvin, the total effect would be an improved liquid penetration (Nogami et al 1963). The limited effect of increasing the concentration from 0·001 to 0·01% w/w is probably due to the limited effect that such an increase has on both the surface tension (Wan & Lee 1974) and the contact angle.

As shown in Fig. 2, a reduction in the agitation intensity from 100 to 10 rev min^{-1} markedly decreased the dissolution rate. Since it has been demonstrated earlier (Nyström et al 1985) that dissolution of suspended, fine particulate griseofulvin particles is not diffusion rate-limited, the results suggest that the mechanism of the higher agitation intensity is probably to enhance the disintegration of the agglomerates.

The results obtained for griseofulvin agglomerates imply that only a limited fraction of the surface area of the primary particles takes part in the dissolution process. Although the experiments were performed at sink condition, a substantial amount remained undissolved even after 2h.

* The choice of μg ml^{-1} as the unit for the amount dissolved was thought more advantageous than the use of percentage values which could mask possible errors in measurements.

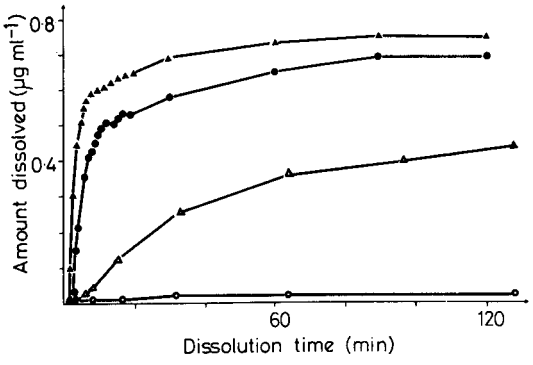

FIG. 2. The effect of agitation intensity on dissolution rate using 0·01% w/w polysorbate 80: ○, ●, 10 rev min^{-1}; △, ▲, 100 rev min^{-1}. Agglomerates (open symbols) and ordered mixtures (closed symbols). Results for the highest agitation intensity are mean values of five determinations.

Dissolution of ordered mixtures

The results for the ordered mixtures are in Figs 1 and 2. These clearly show that the ordered mixture with sodium chloride allows a fast dissolution of griseofulvin. After about 20 min, almost all the griseofulvin was dissolved. Furthermore, the dissolution rate was not substantially affected either by the addition of a surface active agent to the dissolution medium (Fig. 1) or the agitation intensity (Fig. 2). The results obtained, therefore, support the assumption that, in the mixtures tested, the griseofulvin is no longer present as agglomerates but is distributed as primary particles or minor clusters on the surfaces of the sodium chloride particles. Consequently, parameters such as surfactant concentration and agitation intensity were of little importance.

The improvement in the case of the ordered mixes could be due to the soluble nature of the carrier particles and other results might be obtained if carrier materials with other physicochemical properties are used. Nevertheless, the present results indicate the potential advantages in using ordered mixtures to reduce the effect of liquid penetration as a rate-limiting step during the dissolution of sparingly soluble compounds.

Contact surface area

In an earlier study in which a Coulter Counter technique was used, the surface specific dissolution rate of well suspended, fine particulate griseofulvin particles was found to be 6·5 μg min^{-1} cm^{-2} (Nyström et al 1985). From the change in size distribution with time, it was possible to calculate both the amount dissolved and the external surface area of the undissolved particles for any time interval. Since the results also indicated that the dissolution of griseofulvin in the system tested was not diffusion controlled, it was possible to calculate the surface specific dissolution rate as a material constant.

Taking the above value of the surface specific dissolution rate (G), it is possible to calculate the mean contact surface area (S_c) in cm^2 taking part in the dissolution process during a specified time interval as:

$$S_c = (W/tG) \qquad (3)$$

where W is the amount of drug in μg dissolved during time t (min). We also compared the calculated contact surface areas (S_c) with the surface areas of griseofulvin determined for both agglomerates (S_a) and primary particles (S_p). The contact surface area should therefore ideally be calculated at an infinitely short time interval during the beginning of the dissolution experiment. However, the demand for sink conditions during dissolution required the use of small amounts of griseofulvin, that gave very low concentrations to be analysed spectrophotometrically; values for W and t corresponding to dissolution of approximately 30% of the 0·7 mg sample of griseofulvin, were therefore chosen.

Results for the contact surface areas obtained from dissolution experiments at 100 rev min^{-1} are compared with surface areas of 0·7 mg griseofulvin powder in Fig. 3. Using a dissolution medium without any surfactant, the use of ordered mixtures

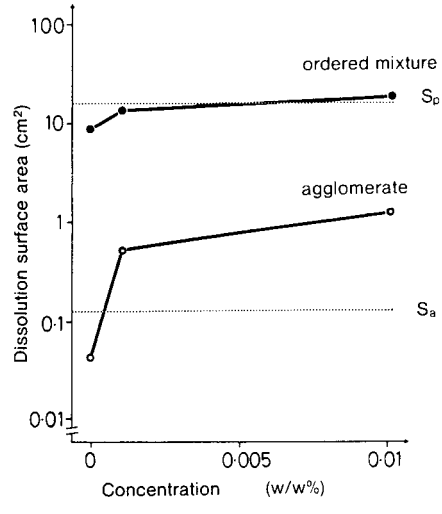

FIG. 3. Comparison of contact surface areas (S_c) calculated from dissolution at 100 rev min^{-1} with external surface areas of agglomerates (S_a) and of primary particles (S_p) of griseofulvin (0·7 mg). Results for the highest concentration of polysorbate 80 are mean values of five determinations.

provided a contact surface area a hundredfold greater than for griseofulvin agglomerates; the surface area of agglomerates taking part in dissolution was also in fairly good agreement with the external surface area of the agglomerates (S_a), calculated from equation 2. These results indicate that no penetration of the dissolution medium into the agglomerates was possible, resulting in an extremely low dissolution rate (Fig. 1). After the addition of polysorbate 80, the contact surface area of the agglomerates increased tenfold to approximately 1 cm^2. The initial addition of 0·001% w/w was most effective, while the higher concentration of polysorbate 80 did not give a proportional improvement, as discussed above.

Polysorbate 80 probably enhanced the penetration of dissolution medium into agglomerates but also facilitated a partial break up of the agglomerates as indicated by a higher value for contact surface area of the agglomerates compared with their geometrically calculated external surface.

The ordered mixture gave a high contact surface area for all polysorbate 80 concentrations tested. The value obtained was practically identical to the external surface area of the primary particles (S_p), as measured by permeametry. This indicates, therefore, that, in the mixture tested, all the external surface area of the griseofulvin was exposed to the dissolution medium, resulting in a high dissolution rate (Fig. 1). The mixture consequently delivers the drug at the maximum rate possible. If a further increase in dissolution rate is to be achieved, the starting griseofulvin material has to be further size reduced by milling or by formulating, e.g. a solid solution.

In conclusion, the use of a dry deagglomeration stage by producing an ordered mixture seems to be an effective means of utilizing all the surface area available for drug release of a sparingly soluble compound. For cohesive materials of hydrophobic nature especially, this principle could usefully be evaluated during preformulation work. It is important, however, to ensure that a total deagglomeration of the drug is obtained during the mixing of small batches in the laboratory. What may seem to be extremely long mixing times on a small scale basis, could correspond to much shorter times when larger batches are used (Malmqvist & Nyström 1984a). The results also suggest that the surface specific dissolution rate may be a useful parameter in evaluating the effect of pharmaceutical manipulation on drug dissolution rate.

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Note added in press: Subsequent to the preparation of this text a paper by McGinty, J. W., Ku Chi-Tze, Dodmeier, R., Harris, M. R. appeared in Drug Development and Industrial Pharmacy (1985, 11: 891–900), but it appears not to have an experimental section.

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