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The rate of dissolution of powdered griseofulvin at different stirring rates

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The non-ionic surfactant, cetomacrogol, increased the rate of solution of powdered griseofulvin in water. At a stirring rate of 200 rev/min, the increase was similar to that found previously for solid discs of this drug. At 60 rev/min, the surfactant had a smaller effect on the rate of solution.

Previously, Elworthy & Lipscomb (1968c) have shown that non-ionic detergents and a polyoxyethylene glycol increased the rate of dissolution of griseofulvin. The results were analysed in terms of a zero order rate constant (k_1) for transfer of the drug from the crystal to the bulk of the solution, and a first order constant (k_2) for the reverse process. The presence of surfactants increased k_1 and decreased k_2, compared with the dissolution in pure water, measurements being made on a disc of griseofulvin. In the present paper the effect of stirring rate and cetomacrogol concentration are extended to a study of dissolution from the powdered drug.

EXPERIMENTAL

Materials

Griseofulvin, crystallized from ethanol, had the same analytical data as reported by Elworthy & Lipscomb (1968a). It was ground in a mortar, passed through a BS44 mesh sieve and had fines removed on a BS350 mesh sieve. Particle size analysis by microscopy gave a mean volume diameter of 104 μm. The same sample of cetomacrogol was used (Elworthy & Lipscomb, 1968b). A sample of fine particle griseofulvin was used as supplied by Glaxo Laboratories Ltd.

Method

Water or solution (1 litre) was placed in a 1 litre conical flask fitted with a 2 bladed stirrer (blade length 3·5 cm), placed 8 cm above the bottom of the flask. The stirrer was driven by a variable speed motor. A magnetic stirrer was not used in case attrition of drug particles took place. Griseofulvin (100 mg) was introduced into the solution, the stirrer started, and 3 ml samples removed through a pipette fitted with a No. 3 sintered glass filter. The samples were analysed spectrophotometrically as before (Elworthy & Lipscomb, 1968a). Incomplete wetting of the sample using pure water caused difficulties. The method adopted was to place 100 mg of the drug in a thin-walled glass bulb, which was then evacuated at 0·01 mm Hg for 10–15 min, sealed under vacuum, and broken beneath the water surface. Fine particle griseofulvin could not be readily wetted, even when washed with solvents, dried, and degassed as above.

Treatment of Results

Each experiment was duplicated, and the extinction-time curves treated as before (Elworthy & Lipscomb, 1968c) to evaluate k_1 and k_2.

Experiments were continued until approximately 2 mg of griseofulvin had dissolved. Calculations show that there is little change of surface area during this time, and it seemed reasonable, as the smallest particles exceeded 45 μm to assume that the number of particles present was constant during a run. Hence to a reasonable approximation the surface area is constant, so that the analysis previously described was applied.

A further difficulty was experienced with experiments in which the stirring rate was between 40–80 rev/min. The griseofulvin settled to the bottom of the flask in a heap. The type of extinction-time graph obtained in these experiments is shown in Fig. 1.

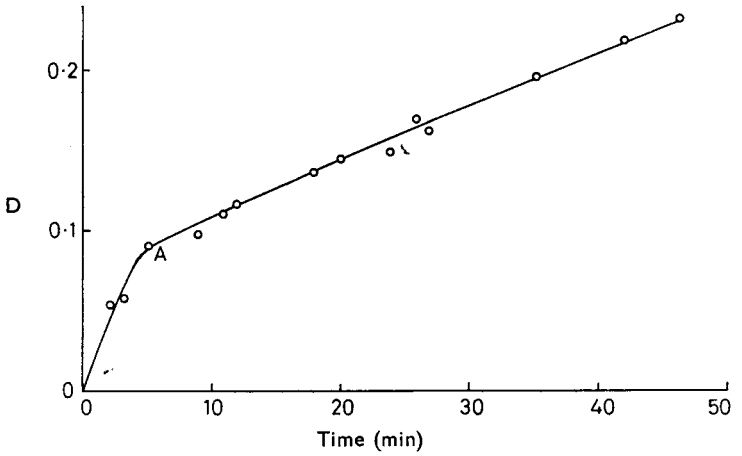

FIG. 1. Extinction in 1 cm cells (D) against time for griseofulvin dissolving in 9·13% w/w cetomacrogol solution at a stirring rate of 60 rev/min.

The initial steep rise in extinction occurs in the time when the particles are sedimenting, and is followed by a gentle curve. The effects would seem to arise from a decrease in surface area exposed to agitated solution as the heap is formed on the bottom of the flask. As we are interested in the dissolution rate when sedimentation is complete, the readings were corrected by subtracting the extinction and time at point A of Fig. 1 from these readings at later times, and evaluating k_1 as before. Alternatively, the curve after point A was extrapolated back to $t = 0$, and the extinction obtained subtracted from subsequent readings. Tests showed that both procedures gave the same value of k_1 ($\pm 1\%$), and the second method was used in evaluating most rate constants.

RESULTS AND DISCUSSION

The zero order rate constant k_1 was measured at different stirring rates (Fig. 2). At low stirring rates, up to 60 rev/min, the heap of griseofulvin is present at the bottom of the vessel, and hence a large proportion of the surface area of the powder is not in direct contact with stirred liquid. k_1 is thus quoted in units of mol litre^{-1} min^{-1} as the effective surface area cannot be measured. At 80 rev/min the heap can be seen to move, but is not in suspension. It is completely suspended above 130 rev/min. The initial increase in k_1 with stirring rate is likely to be due more to increased exposure

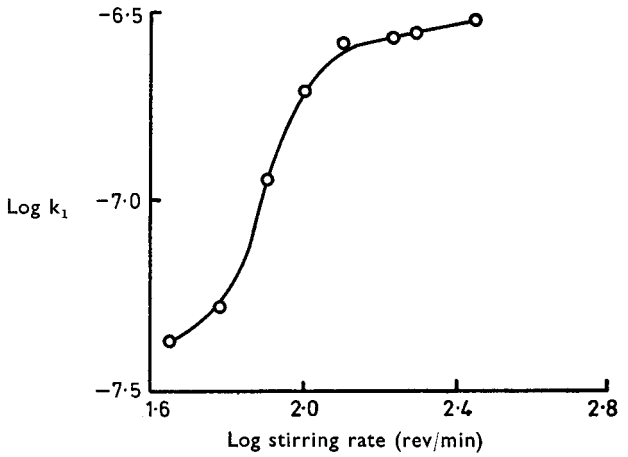

FIG. 2. Effect of stirring rate on zero order rate constant k_1 for 100 mg griseofulvin in 1 litre water.

of powder surface to stirred liquid, than to the effect of stirring itself. The final straight line portion of Fig. 2 has a slope of 0·21, compared with a slope of 0·54 found for dissolution rates from griseofulvin discs. This may be due to stirring being less effective in decreasing the thickness of a diffusion layer when the particles can move with the stirred liquid, instead of being fixed as with the disc.

Six repeat experiments at 200 rev/min gave a mean k_1 of $2{\cdot}8 \times 10^{-7}$ mol litre^{-1} min^{-1}. Using the mean particle diameter of 104 μm, and the density of griseofulvin of 1·31 (Matthews & Rhodes, 1968), 100 mg of the drug has a surface area of 22 cm^2, assuming that the particles are spherical. This gives an absolute value of $k_1 = 1{\cdot}3 \times 10^{-8}$ mol litre^{-1} min^{-1} cm^{-2} compared with $1{\cdot}14 \times 10^{-8}$ found from experiments with discs (Elworthy & Lipscomb, 1968c). The agreement is good considering the number of experimental quantities involved.

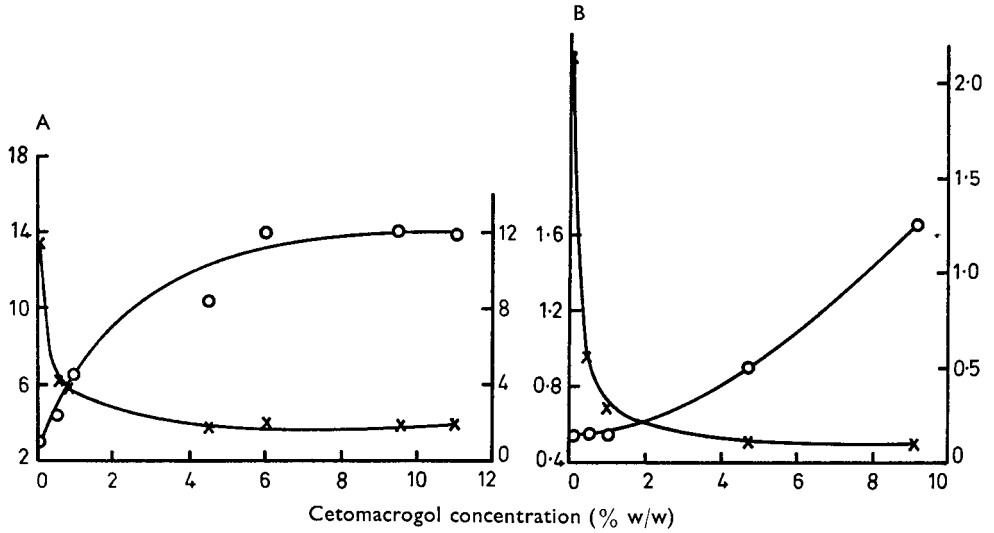

FIG. 3. Effect of cetomacrogol concentration on k_1 (○) and k_2 (×) at a stirring rate of A, 200 rev/min, B, 60 rev/min. Left hand ordinates $10^7 k_1$. Right hand ordinates $10^3 k_2$.

The experimental conditions at low stirring rates are similar in principle to those achieved in the "beaker" method (Levy & Hayes, 1960, Levy & Hollister, 1964). The effect of cetomacrogol was studied at 60 rev/min at which rate the heap of drug was present, and also at 200 rev/min, where suspension was complete.

The rate constants obtained at 200 rev/min are shown in Fig. 3A. The results are similar to those found for griseofulvin discs, in that k_1 increases and k_2 decreases with increase in cetomacrogol concentrations.

The overall effect is an increased dissolution of drug when the surfactant is present. Results of this type were fully discussed earlier (Elworthy & Lipscomb, 1968c), and all that need be said is that the same effects of the surfactant in facilitating the transfer of molecules of griseofulvin from the crystal into the solution apply, while the high viscosity of concentrated surfactant solutions causes the flattening of the plots in Fig. 3A. Linear relations between both $k_1\eta$ and $k_2\eta$ Ve, and surfactant concentration were found as before.

The effect of cetomacrogol on the rate constants determined at a stirring speed of 60 rev/min (Fig. 3B) is different from that on rate constants determined at 200 rev/min. At 200 rev/min the griseofulvin is suspended, at 60 rev/min it is in a pile on the bottom of the vessel and only the higher concentrations of cetomacrogol give an increase of dissolution rate over that in water. The lack of increase of k_1 with cetomacrogol concentration compared with the experiments at 200 rev/min may be due to the amount of surface relatively inaccessible to solvent movement when the drug is in a heap. The viscosity of cetomacrogol solutions only increased markedly when the concentration exceeded 3% w/w (Elworthy & Lipscomb, 1968c). The increased viscosity may allow an increased agitation to be transmitted to the heap, resulting in an increase of surface area exposed to the stirred liquid. This increase in area may be more important than the effects of the higher viscosity solutions on the transport properties of the solute. When the drug is in a heap there are a number of complex factors operating, which cannot be analysed completely.

Hamlin, Nelson & others, 1962, showed that *in vitro* dissolution tests on methylprednisolone correlated with *in vivo* ones only when the rate of stirring was low. Good correlation between *in vitro* dissolution of aspirin and *in vivo* absorption has been found by Levy (1961), using a low rate of agitation. The differences shown here between dissolution at high and low amounts of agitation, make it necessary to choose a stirring rate with care, especially if attempts to correlate *in vivo* and *in vitro* dissolution are to be made.

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