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Coulter Counter measurements of solubility and dissolution rate of sparingly soluble compounds using micellar solutions*

C. NYSTRÖM AND M. BISRAT†

Department of Galenical Pharmacy, Biomedical Center, University of Uppsala, Box 580, S-751 23 Uppsala, Sweden

A Coulter Counter, Model TAII, was used to determine both solubility and surface specific dissolution rate of two sparingly soluble materials suspended in micellar solutions. The equilibrium solubility increased linearly with surfactant concentration, thereby making it possible by extrapolation to characterize materials with an aqueous solubility down to 1 ppm or less. At high concentrations (>0·1% w/v) the effect of surfactant concentration on the surface specific dissolution rate was less than that predicted from the increased bulk solubility.

In an earlier study (Nyström et al 1985), a Coulter Counter, Model TAII was used to determine both solubility and dissolution rates from suspensions of two drug compounds having solubilities about 8 ppm. By monitoring the size distribution with time it was possible to calculate both the weight and the external surface area of particles remaining undissolved, as a function of time. By subsequently calculating the amount dissolved and relating this to the external surface area of the undissolved particles for each time interval, it was possible to calculate the surface specific dissolution rate in $\mu g\ min^{-1}\ cm^{-2}$. Since the results also indicated that the dissolution of these suspended compounds was not significantly a diffusion controlled process, the determined surface specific dissolution rate was consequently regarded as a material constant.

To obtain results for dissolution rate that are practically independent of the concentration of dissolved material (e.g. Noyes & Whitney 1897) it is important to add only a fraction of the amount corresponding to the compound's solubility. The so-called sink condition is normally considered to exist up to approximately 10% of the amount needed for equilibrium saturation. In the previous study (Nyström et al 1985), the additions used to obtain sink condition, corresponded to 0·5 μg of suspended material per ml of dissolution media. Although very fine particulate powders were studied, giving a high specific number of particles (Martin et al 1969), the small weight additions resulted in a total number of particles of only a few thousands. To avoid statistical errors in the conductometric measurements, no substantial decrease in the number of particles added per ml is possible. The same problem exists in characterization of the equilibrium solubility with the technique described (Nyström et al 1985). Even though a large number of particles is added, i.e. a quantity in excess of the solubility amount, the changes obtained in particle size distribution must be fairly large. If the total amount dissolved is too small, the technique is not capable of detecting any significant change in the remaining weight of particles. Therefore, the technique decribed earlier for measuring solubility and surface specific dissolution rate is limited to compounds having an aqueous solubility above approximately 5 ppm. It is theoretically possible to increase the sensitivity of the method when compounds of extremely high fineness are characterized, because of the increase in the specific number of particles (Martin et al 1969). However, the lower limit of the Coulter Counter principle for the monitoring of particle size is approximately 0·5 μm, thereby limiting the effect of such changes in the physical character of the compound tested. To overcome these problems, different systems of obtaining an artificial or an apparent sink condition could be considered. In the literature, several approaches have been described. These are either based on the fact that a homogeneous dissolution medium with higher dissolving capacity than water is used, e.g. mixtures of water and organic solvents (e.g. Nicklasson & Brodin 1984), or based upon the addition of a new phase that could withdraw dissolved molecules from the water phase. Here, both the use of organic liquid phases (Levy 1966; Gibaldi & Feldman 1967) and the addition of suspended particles with high adsorption capacity (Wurster & Polli 1961) have been tested.

* Physicochemical aspects of drug release. Part 3.
† Correspondence.

However, to utilize the conductometric principle, and to gain the advantages of characterizing the undissolved fraction, neither of these approaches seem particularly useful. An alternative could be to add a surface active agent to the dissolution media to obtain a micellar phase (e.g. Elworthy & Lipscomb 1968; Rees & Collett 1974; Watari & Kaneniwa 1976). Such an addition would not significantly change the conductivity of the system tested, nor would the new disperse phase disturb the counting of the drug particles, owing to the relatively low size of micellar units (Elworthy et al 1968). Another potential advantage could be the physiological similarity to the in-vivo situation when a micellar solution is used (Bates et al 1966), compared with the other techniques mentioned.

The object of the present study was to evaluate the use of micellar solutions during dissolution experiments with the Coulter Counter, Model TAII. It was then of special interest to characterize the solubility and the surface specific dissolution rate for some compounds of extremely low solubility.

MATERIALS AND METHODS

Materials

Micronized griseofulvin (Glaxo, UK) and felodipine (Hässle AB, Sweden) were used. By wet sieving, the fraction smaller than 35 μm (precision test sieve with circular openings, Veco, Holland) was prepared for felodipine. The particle size distributions for the two materials are presented in Table 1.

Table 1. Size, surface and shape characteristics of test materials.

Materials	Particle size distribution[a] Mean (μm)	s.d. (μm)	Specific surface area ($cm^2 cm^{-3}$)	Surface shape factor[f]
Griseofulvin	3·60[b]	1·6[b]	31 000[d]	5·06
Felodipine	15·8[c]	8·6[c]	8 100[e]	4·58

[a] Weight frequency distributions obtained by Coulter Counter TAII.
[b] Log-normal distribution characterized by geometric mean and geometric standard deviation.
[c] Arithmetic normal distribution characterized by arithmetic mean and standard deviation.
[d] Measured by permeametry as described earlier (Nyström et al 1985).
[e] Measured by narrow angle photometry as described earlier (Nyström et al 1980).
[f] Calculated according to Nyström et al (1985).

Coulter Counter procedure

A Coulter Counter, Model TAII, fitted with 50 or 100 μm aperture tubes was used for griseofulvin and felodipine, respectively. The tubes were chosen to cover the entire size distributions by weight (Table 1). In all experiments, 300·0 ml of suspension was analysed, and it was agitated at a rotational speed of 800 rev min^{-1}. The sample analysed after the addition of the requisite volume of stock suspension to the electrolyte was 0·05 ml for griseofulvin and 0·5 ml for felodipine. The numbers of particles in 14 size classes were recorded simultaneously and used for further calculations on a Hewlett Packard 9825T computer. The particle concentration in no case exceeded the level where correction for coincidence error was necessary. Before measurement, stock suspensions containing 0·3 and 0·2 mg ml^{-1} for griseofulvin and felodipine, respectively, were prepared by suspending the materials in particle-free water containing 0·9% sodium chloride and 0·01% polysorbate (Tween) 80. The stock suspensions were treated in an ultrasonic bath for 1 to 5 min, to break up any agglomerates present (Nyström et al 1980).

Solubility determination

To study the effect of increasing micellar concentration, dissolution media were prepared using distilled, particle-free water containing 0·9% sodium chloride and varying concentrations of polysorbate 80. For each solubility determination a known volume of the stock suspension was added to the dissolution medium, previously equilibrated to ambient temperature, with the total volume always constant at 300 ml. The final concentration of polysorbate 80 was in the range 0·025 to 0·2% w/v for the experiments with felodipine and between 0·08 and 1·0% w/v for griseofulvin. In all experiments, the amount of solid material added for the varying surfactant concentrations corresponded to 20–30% in excess of the corresponding equilibrium solubility. According to the earlier technique (Nyström et al 1985), the weights of materials remaining undissolved at specified time intervals were calculated. The dissolution process was followed until saturation was achieved and the remaining weight at equilibrium conditions was used to calculate the solubilities of both materials. Saturation was considered to be achieved after 30 min and 360 min for griseofulvin and felodipine, respectively.

Surface specific dissolution rate determination

To obtain near sink condition for the range of micellar concentrations tested, and at the same time obtain an adequately large number of particles to be counted, sufficient amounts of the stock suspensions were added to the dissolution media to give the following final concentrations in the suspensions tested. For felodipine the concentration was 0·66 μg ml^{-1} for surfactant concentrations below

0·1% w/v and 1·3 μg ml^{-1} for surfactant concentrations equal to and above 0·1% w/v, whereas for griseofulvin the final concentration tested in all cases was 5 μg ml^{-1}. According to earlier equations (Nyström et al 1985), both weight dissolved (μg) and remaining external surface area (cm^2) were calculated as a function of time (min). These calculations are based upon the knowledge of material density, initial particle shape and specific surface area (Tables 1, 2). Furthermore, the calculations are based upon the assumption that the particles are dissolving in an isometric fashion, i.e. the particle shape is not substantially changed during dissolution. From a knowledge of the dissolved amount and the mean external surface area, the surface specific dissolution rate (μg min^{-1} cm^{-2}) was calculated for specific time intervals during the dissolution process. The values quoted represent mean rates calculated for the initial and intermediate stages of dissolution.

RESULTS AND DISCUSSION

Solubility

Solubility data for griseofulvin obtained at increasing concentrations of polysorbate 80 are plotted in Fig. 1. Here, a linear relation was established, the correlation coefficient obtained by linear regression being 0·994. Such linear relations between equilibrium solubility and concentration of surfactants have been observed for a number of drug compounds (e.g. Kakemi et al 1965; Barry & El Eini 1976) using much wider ranges of surfactant additions. The solubility of griseofulvin in pure water, as expressed by the intercept value obtained from linear regression (Fig. 1) is 8·9 μg ml^{-1}. This result is in good agreement with solubility data for griseofulvin, as measured by a conventional method (Table 2), using an HPLC technique to analyse the dissolved fraction (Nyström et al 1985). The value obtained is also in agreement with the result obtained from direct measurement with the Coulter Counter using a dissolution medium without any substantial amount of surfactant (0·01% polysorbate 80 was added before wetting). The linearity obtained in the narrow concentration range tested (Fig. 1), therefore supports earlier findings (Nyström et al 1985), that the Coulter Counter technique is capable of estimating the solubility of sparingly soluble materials.

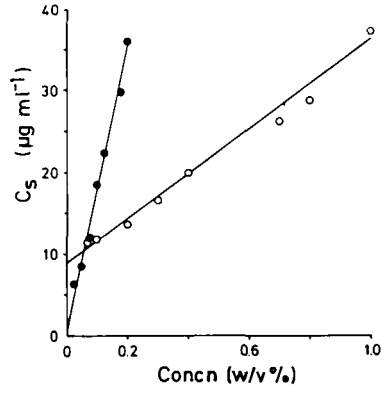

FIG. 1. Equilibrium solubility (C_s) data for griseofulvin (○) and felodipine (●) after 30 and 360 min dissolution time, respectively, obtained at different concentrations of polysorbate 80 using a Coulter Counter Model TAII.

Table 2. Density and solubility characteristics of test materials.

Material	Density (g cm^{-3})	Aqueous solubility at 20 °C (μg ml^{-1})
Griseofulvin	1·44[a]	8·7[a]
Felodipine	1·45[b]	0·5[c]

[a] According to an earlier described technique (Nyström et al 1985).
[b] Hässle AB, unpublished data.
[c] According to a technique described elsewhere (Felle et al 1984).

Solubility data for felodipine are presented in Fig. 1. It was not possible to detect any significant amount dissolved when testing the material in dissolution media containing minute concentrations of the surfactant. As discussed in the introduction, this is because no significant change in particle size distribution could be detected for compounds having such a low solubility. However, for surfactant concentrations exceeding 0·025%, solubility data were established. As obtained for griseofulvin, these data showed a good fit to a straight line (correlation coefficient being 0·995). The aqueous solubility was then obtained by calculating the extrapolated intercept value from the linear regression. The value obtained, 0·6 μg ml^{-1}, is in reasonable agreement with results (Table 2) obtained by techniques where the dissolved fraction is analysed (Felle et al 1984). It seems reasonable that the precision of the procedure is reduced when materials with decreasing aqueous solubility are to be characterized, i.e. when the extrapolated intercept value approaches zero. For such materials it could be necessary to increase the number of surfactant additions and thus the number of points used for linear regression. It seems,

however, that an extrapolation procedure from solubility data using varying surfactant additions could be used to estimate the approximate aqueous solubility of materials with extremely low solubility, which otherwise cannot be measured directly by the Coulter Counter technique.

The use of the suggested technique, including the addition of a surfactant is obviously dependent upon some prerequisites. Of major importance is that the addition of micellar concentrations of the surface active agent will substantially enhance the solubility. The solubilizing capacity of the surfactant chosen is a complex function of several parameters, including drug properties such as polarity, drug molecular weight, size and shape (Attwood & Florence 1983). From Fig. 1, it can be seen that the dissolving, or interactive, capacity of the micellar phase is more than six times higher for felodipine than for griseofulvin, as calculated by dividing the respective slopes, which means that the suggested technique seems especially applicable for the combination of felodipine and polysorbate 80.

The lowest addition tested (0·025%) increased the solubility ten times for felodipine (Fig. 1) whereas almost no effect was obtained for griseofulvin. Since, CMC for polysorbate 80 is reported to be approximately 0·001% w/v (Wan & Lee 1974), the results demonstrate that even moderate concentrations in excess of CMC could be effective for solubilization. However, for other materials, it could be necessary to test a number of surfactants, to find a system that would enable an appropriate use of the Coulter Counter technique described.

To obtain accurate results, the method also requires that the dissolution time is long enough to ensure that saturation is achieved.

Surface specific dissolution rate

In the literature, equations have been presented that relate equilibrium solubility with surface specific dissolution rate (e.g. Hamlin et al 1965; Nicklasson et al 1982). These equations seem to be valid for a wide range of drug solubilities, provided the data are obtained at sink condition and that the hydrodynamic conditions, i.e. the thickness of the diffusion layer, is held constant. By an extrapolation procedure, Nicklasson et al (1982), obtained data that corresponded to a situation where the rate limitation of a diffusional process could be neglected, giving the following relation

$$\log C_s = \log G + 1{\cdot}94 \qquad (1)$$

where C_s is the equilibrium solubility in mg ml^{-1} and G is the surface specific dissolution rate in mg s^{-1} cm^{-2}. In an earlier report (Nyström et al 1985), data obtained for both C_s and G with the aid of the Coulter Counter technique used in this study, gave an acceptable fit with equation (1). It was thus concluded that the dissolution of sparingly soluble compounds in the suspended state, as measured by the Coulter Counter technique, was not significantly retarded by a diffusional process. Since the technique and the compound properties used in the present study were almost identical, it was of interest to compare experimentally obtained G values with values calculated according to equation (1) for the different surfactant concentrations. For the calculated values, the solubility data presented in Fig. 1 were used. Results of both experimental and calculated surface specific dissolution rates against surfactant concentrations are presented in Figs 2, 3. For griseofulvin (Fig. 2), low surfactant concentrations gave experimental G values that were in acceptable agreement with values calculated from equation (1).

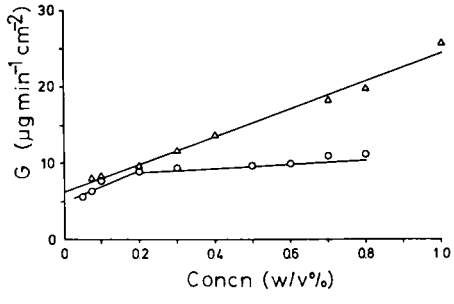

FIG. 2. Surface specific dissolution rate (G) for griseofulvin at different concentrations of polysorbate 80. Values obtained by calculations according to equation (1) (△) and from Coulter Counter data (○).

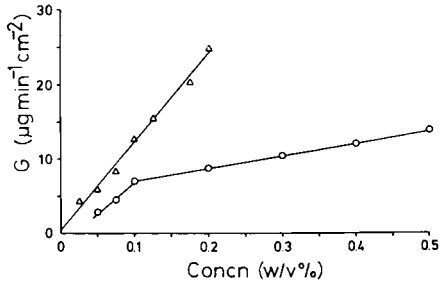

FIG. 3. Surface specific dissolution rate (G) for felodipine at different concentrations of polysorbate 80. Values obtained by calculations according to equation (1) (△) and from Coulter Counter data (○).

For felodipine (Fig. 3), the corresponding experimental values were significantly lower than the calculated data. Niebergall et al (1963) showed for more coarse crystalline materials that the thickness of the diffusion layer was proportional to the square root of the mean volume diameter of the dissolving particles. Although the two materials investigated in this study were more finely particulate, it seems possible that the difference in particle size between griseofulvin and felodipine corresponds to different diffusion layer thicknesses around the dissolving particles during the initial dissolution process. For griseofulvin, with a mean particle size of 3·6 μm (Table 1), it seems that the diffusion layer thickness is almost negligible, whereas for felodipine with a mean particle size of 15·8 μm (Table 1), the diffusion layer could be thicker, resulting in a measurable retardation of the diffusion process. At higher surfactant concentrations, the dissolution rates obtained by experiment for both materials were much lower than those predicted from equation (1). Similar observations, that the effect of micellar concentrations on dissolution rate could be less than predicted from increased bulk solubility, have been reported in the literature (e.g. Watari & Kaneniwa 1976). Although these authors used another surfactant-solubilizate system, there were some similarities between their results and data obtained in the present study. Watari & Kaneniwa (1976) obtained significant deviations from predicted dissolution rates at surfactant concentrations above 0·3 to 0·5% w/v, as compared with 0·1 (felodipine) and 0·2% w/v (griseofulvin) in the present study. Furthermore, the retarded increase in dissolution rates obtained at concentrations in excess of these values, seems to increase linearly with an increase in surfactant concentration. Watari & Kaneniwa (1976) explained their data on the basis of a relatively high CMC value reducing the effect of minor surfactant concentrations. For increasing concentrations, the retarded increase in dissolution was thought to be due to increased viscosity in the dissolution media. However, considering the low CMC value of polysorbate 80 (Wan & Lee 1974) and the lower surfactant concentrations studied in the present investigation, other explanations could be possible. Higuchi (1967) suggested that the effect of surfactant additions on dissolution rate would be related to the diffusion coefficients of the diffusing species rather than to their solubilities. The results could subsequently be interpreted as a diffusional phenomenon. When the surfactant concentration exceeds 0·1 and 0·2% w/v, respectively, the total diffusion process becomes significant and reduces the transfer rate of drug molecules from the solid surface. Comparing the data obtained in this study with that of Watari & Kaneniwa (1976), it seems that the level of surfactant concentration where this reduction becomes significant, is related to the solubilizing capacity of the system tested, and hence for felodipine the deviation from predicted data is seen at an addition of 0·1% w/v surfactant.

Chan et al (1976) have described the solubilization process by a model where the formation of mixed micelles takes place on the solid surface, followed by a desorption and diffusion into the bulk solution. The intrinsic rate of this formation could be reduced by higher concentrations of the surfactant. Elworthy & Lipscomb (1968) decribed the equilibrium between dissolution from, and deposition to the solid surface by reactions of different order. For minor additions of surfactants the deposition rate decreased strongly, possibly due to the interference of an adsorbed surfactant layer on the solid surface, whereas higher concentrations did not give a proportional reduction in the deposition process.

Irrespective of the correct interpretation of the data obtained, it can be concluded that the complex effect on surface specific dissolution rate, limits the use of micellar solutions for the estimation of dissolution rate in a pure water media. However, since the dissolution media in the gastrointestinal tract could be regarded as a micellar solution (e.g. Bates et al 1966), the kind of profiles obtained in this study (Figs 2, 3) could possibly be used in establishing correlation with in-vivo data.

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