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Physicochemical aspects of drug release. VII. The effect of surfactant concentration and drug particle size on solubility and dissolution rate of felodipine, a sparingly soluble drug

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Summary

The surface-specific dissolution rates (*G*-values) of two size fractions of felodipine, a sparingly soluble drug, at different concentrations of polysorbate 80 were compared, using a Coulter Counter Model TAII. The solubilities of the drug at these surfactant concentrations were determined photometrically. The dependence of particle size on dissolution rate was also evaluated for a number of size fractions of felodipine at a low concentration of polysorbate 80, using the Coulter method. It was shown that the effect of particle fineness was stronger than could be predicted from the differences in initial surface area. The *G*-values for a number of felodipine qualities were calculated from dissolution data obtained by the USP XXI rotating paddle method at both low and high concentrations of the micellar solutions used. The data delivered by the two dissolution methods were in fairly good agreement. The higher polysorbate concentration gave the same discrimination of the size fractions tested, although higher *G*-values were obtained.

Introduction

Sparingly soluble drugs often offer problems when the dissolution rate is to be determined in vitro. Varying attempts to obtain near sink conditions and thus to imitate a rapid absorption in the gastrointestinal tract have been presented in the literature. The use of an organic solvent phase which can function as a reservoir for dissolved drug is one example (Gibaldi and Feldman, 1967). If an adsorbent is present in the solution, solute molecules could be adsorbed from solution onto its surface (Wurster and Polli, 1961). A well-known method to increase solubility and thereby obtain sink conditions, is to add a co-solvent, e.g. ethanol, to the dissolution medium. In one case an agent that oxidizes the dissolved drug to a more easily dissolvable compound is added to the solution (Felle et al., 1984).

Also the use of micellar solutions to increase solubility and thereby facilitate dissolution testing has been investigated (e.g. Nyström and Bisrat, 1986; Tsushima et al., 1986). The presence of surface active agents (e.g. bile salts and lysolecithin) in gastric and intestinal juice and its ability to increase the dissolution and absorption rate of sparingly soluble drugs (Finholt and Solvang, 1968; Bates et al., 1966a; Rhodes et al.,

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1969; Miyazaki, 1979; Shinkuma et al., 1985), supports the idea that this method could be relevant for in vitro testing.

Nyström and Bisrat, (1986) studied the effect of surfactant concentration on solubility (C_s) and surface specific dissolution rate (G) of felodipine in suspended form. Felodipine, with an aqueous solubility of 0.5 mg/l at ambient temperature, here represents a drug of extremely low solubility. The equilibrium solubility increased linearly with surfactant concentration and so did the G-value up to a certain concentration of surfactant (0.1 w/v%). At higher concentrations the effect of surfactant concentration on the G-value was less than predicted from the increased bulk solubility (Nicklasson and Brodin, 1984).

In order to further evaluate the usefulness of micellar solutions for in vitro dissolution testing under near sink conditions, several aspects ought to be clarified. It has been shown (Bisrat and Nyström, 1988; Nyström et al., 1985b) that particle size could influence the thickness of the diffusion boundary layer (Grijseels et al., 1981) and thereby the G-value obtained. Consequently the relation between particle size and dissolution rate, using micellar solutions has been evaluated in this study.

Another aim was to evaluate the effect of surfactant concentration on the G-value for a highly micronized quality of felodipine compared to an earlier established relation for a coarser felodipine quality (Nyström and Bisrat, 1986). It was in the present study considered of special importance to evaluate the possibility of using surfactant concentrations above the critical concentration where lower dissolution rates than predicted from solubility data were obtained; this, in order to obtain near sink conditions for a wide range of doses of sparingly soluble drugs.

Experimental

Materials

Felodipine (Hässle AB, Sweden), unmicronized, wet and dry micronized qualities, were used (Table 1). Felodipine is a derivative of dihydropyridine that has vasodilator properties (Felle et al., 1984). In two cases the fractions were obtained by wet sieving (< 35 μm, precision test sieve with circular openings, Veco, Holland) (Table 1, quality 11 and 12). The surfactant used was polysorbate 80 (Atlas, U.S.A.).

TABLE 1

Primary characteristics of test materials

Felodipine quality	Particle size distribution [a]		Calculated surface area [e] ($m^2 \cdot g^{-1}$)
	Mean (μm)	s.d. (μm)	
A [d,f]	15.8	8.6 [c]	0.56
B [h]	3.53	2.1 [b]	1.05
1 [h]	1.87	1.9 [b]	2.59
2 [h]	1.92	1.9 [b]	2.54
3 [g,h]	2.05	1.8 [b]	2.36
4 [h]	2.14	2.0 [b]	2.35
5 [g,h]	2.38	1.8 [b]	2.04
6 [h]	2.44	2.0 [b]	2.08
7 [g]	2.78	1.0 [c]	1.75
8 [g]	2.74	1.5 [b]	1.69
9 [g]	3.41	1.6 [b]	1.38
10 [g]	5.18	1.9 [b]	0.98
11 [f]	16.4	10 [c]	0.44
12 [f]	14.3	9.4 [c]	0.49

[a] Particle size distributions by weight obtained by the Coulter Counter TAII.
[b] Log-normal distribution characterized by geometric mean and geometric standard deviation (dimensionless).
[c] Arithmetic normal distribution characterized by arithmetic mean and standard deviation (in μm).
[d] Size, surface and shape characteristics according to Nyström and Bisrat (1986).
[e] Calculated from harmonic mean diameter by weight (Coulter Counter) and surface to volume shape factor of 6 (Heywood, 1954).
[f] Unmicronized.
[g] Dry micronized.
[h] Wet micronized.

Primary characterization of felodipine

Particle size distribution

The number of particles in 14 size classes were recorded by the Coulter Counter TAII and from these values the mean particle sizes and the particle size distributions for each quality were calculated (Table 1) (Nyström et al., 1985a). The sample concentrations chosen corresponded to amounts substantially exceeding the equilibrium

solubility at the same time as the concentrations were limited to amounts corresponding to a coincidence error, not higher than 5%.

The Coulter Counter was fitted with an aperture tube of 30 μm (felodipine qualities B and 1–9), 50 μm (felodipine quality 10) or 100 μm (felodipine qualities 11 and 12). The tubes were chosen to adequately cover the entire size distribution by weight. Results presented are mean values of 4 determinations; however, for quality 12, the experiment was performed in duplicate.

Calculated specific surface area

In order to obtain a simplified measure of the external surface area of the test materials, the harmonic mean diameter by weight (Allen, 1981) was used together with a surface-to-volume shape factor (Heywood, 1954) of 6, corresponding to a spherical shape. For test materials, having a irregular particle shape, such as the felodipine qualities tested, it must be emphasized that the calculated surface areas correspond to underestimated values. However, since direct measurements by permeametry or photometry of such very fine suspended particles could not be performed (Barnett et al., 1980), the calculated values must be regarded as adequate approximations regarding the initial surface area taking part in dissolution.

Determination of solubility

Coulter Counter method

Suspensions of the different felodipine qualities were equilibrated for 10 h or longer when needed at 23 ± 1° C in 0.05% polysorbate 80. The remaining weights of felodipine when solubility equilibrium was reached were determined utilizing the Coulter Counter (Nyström et al., 1985a; Nyström and Bisrat, 1986). The concentrations of felodipine were such that when equilibrium solubility was reached, the amount of particles left (1.2–6.8 mg/l) corresponded to a coincidence error lower than 5%. Results presented are mean values of 2–4 determinations.

Photometric method

As a reference method, the solubility was also determined using a conventional technique, where the dissolved fraction is analyzed. A suspension containing 200 mg/l of felodipine (10 times the solubility in 0.05 w/v% Tween 80) was equilibrated for not less than 10 h at 23 ± 1° C. A sample was then centrifuged at a rotational speed of 5500 rpm in 15 min and the concentration of the supernatant was determined at 362 nm (Zeiss Spectral-photometer PM 6, F.R.G.).

The increase in equilibrium solubility obtained at polysorbate 80 concentrations in the range 0.05 and 0.5 w/v% was also determined. Results presented are mean values of 3 determinations.

Determination of surface specific dissolution rate

Coulter Counter method

A Coulter Counter TAII was used as described above. According to earlier published equations (Nyström et al., 1985a), both weight amount 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 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 G ($\mu g \cdot min^{-1} \cdot cm^{-2}$) was calculated for specific time intervals during the dissolution process. The values quoted

TABLE 2

Solubility of felodipine in 0.05% polysorbate 80 at 23 ± 1 °C

Felodipine quality	Solubility	
	Photometric method (mg/l)	Coulter Counter method (mg/l)
1	24.7	–
2	19.1	19.7
3	24.0	21.9
4	22.4	22.6
5	21.4	23.9
6	18.0	22.5
7	17.8	20.8
8	22.7	22.1
10	23.5	–
12	20.6	18.8

represent mean rates calculated for the dissolution period where up to 85% of the initial weight amount was dissolved. The dissolution medium was saline with 0.05–0.5 w/v% polysorbate 80 and the temperature was $23 \pm 1°C$. Both the remaining weight and surface area of drug were calculated every minute from particle size data. All results presented are mean values of at least 3 determinations; however, for quality 1, in 0.05 w/v% polysorbate 80, the experiment was performed in duplicate.

USP-paddle method

A rotating paddle apparatus (Prolabo, France) for dissolution testing according to USPXXI (100 rpm, 23° C) was used. The solutions were transferred via a peristaltic pump through a 0.6 μm standard Nucleopore polycarbonate membrane filter (Nucleopore, U.S.A.) to a spectrophotometer (Zeiss, Spectralphotometer PM6, F.R.G.) for assay of dissolved drug amount. The total volume in the sample beaker was 1000 ml.

The amount of dissolved drug was measured every 15 s for the first 5 min, every 30 s up to 10 min and then every 1 min up to 15 min. Thereafter measurements were made less frequently until all of the drug was dissolved.

To calculate the initial surface-specific dissolution rate (G), the amount dissolved after 30 s was divided by time (0.5 min) and the initial calculated surface area (Table 1) of the suspended particles to give a G-value in $\mu g \cdot min^{-1} \cdot cm^{-2}$. These calculations are based on the assumption that the decrease in surface area during the first 30 s of dissolution could be regarded as negligible. All results presented are mean values of 3 determinations.

Effect of surfactant concentration

The effect of surfactant concentration on the surface-specific dissolution rate for a highly micronized felodipine quality, $\bar{d}_v = 3.53$ μm, (Table 1, B) was characterized at polysorbate 80 concentrations between 0.05 and 0.5 w/v%. These measurements were performed with the Coulter Counter method and then compared with earlier established data for a coarser felodipin quality, $\bar{d}_v = 15.8$ μm (Table 1, A) (Nyström and Bisrat, 1986). In both experiments near sink conditions were applied. The final concentration in the suspension tested was 1.0 mg/l.

Effect of drug particle size

Low surfactant concentration. The surface-specific dissolution rates for a number of felodipine qualities were determined in a dissolution medium containing 0.05 w/v% polysorbate 80, giving a solubility of approximately 20 mg/l. At this surfactant concentration, the obtained G-values were directly related to the solubility in the medium and were close to calculated maximum values (Nicklasson and Brodin, 1984). Both dissolution methods described above were used.

With the Coulter method, felodipine qualities B and 1–11 (Table 1) were tested. Here the final concentration in the test suspensions in no case exceeded 2 mg/l.

With the USP-paddle method, qualities 2 and 6–10 (Table 1) were tested using suspensions giving final concentrations of approximately 10 mg/l. The rationale for using this high concentration, in relation to the equilibrium solubility, was that 10 mg is a probable therapeutic dose for oral administration. It was also considered of interest to compare the data with the results obtained at the higher surfactant concentration, corresponding to near sink conditions. However, since the surface-specific dissolution rate constants (G) were calculated for the initial dissolution phase (30 s), during which only a minor amount of drug was dissolved, all G-values calculated correspond to near sink conditions.

High surfactant concentration. The surfactant addition was chosen to 0.23 w/v%, giving a solubility of 102 mg/l. Thus, additions of felodipine corresponding to final concentrations of 10 mg/l could be tested under near sink conditions during the whole dissolution process. Here, only the USP-paddle method was utilized. The felodipine qualities tested were the same as for the lower surfactant concentration.

Results and Discussion

Solubility (C_s)

The equilibrium solubility (C_s) of the felodipine qualities are summarized in Table 2. The Coulter

method, where the amount of undissolved drug is characterized, delivered results which are in good agreement with the photometric method. The mean values of equilibrium solubility for the two methods were 21.4 and 21.5 mg/l, respectively. No significant effect on solubility of the mean particle size of the felodipine qualities was found. The effect of polysorbate concentration on equilibrium solubility is presented in Fig. 1. Within the whole range studied, the solubility increased linearly with surfactant concentration, as expected. Regarding the saturation ratio (Bates et al., 1966b), it could be noted that the slope value obtained was rather high.

Surface specific dissolution rate (G)

Effect of surfactant concentration

In Fig. 2 the *G*-values for quality A and B (Table 1) are presented.

By an extrapolation procedure Nicklasson and Brodin (1984) obtained data that correspond to a situation where the rate limitation of a diffusional process could be neglected giving the following equation:

$$\log C_s = \log G + 1.94 \qquad (1)$$

where C_s is the equilibrium solubility at 37 °C in $mg \cdot ml^{-1}$ and G is the corresponding surface-specific dissolution rate in $mg \cdot s^{-1} \cdot cm^{-2}$. With the aid of this equation, theoretical *G*-values were calculated using the experimentally obtained solubility data (Fig. 1). These *G*-values subsequently represent the theoretical maximum dissolution rates at 37 °C and are noted in Fig. 2.

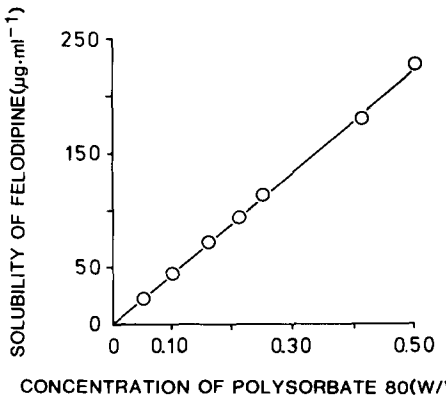

Fig. 1. Equilibrium solubility (C_s) at different concentrations of polysorbate 80 (23 ± 1 °C).

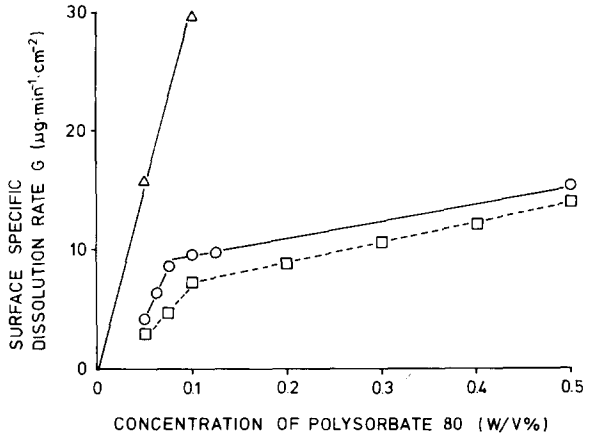

Fig. 2. Surface specific dissolution rate (G) for felodipine ○, 3.53 and □, 15.8 µm (Nyström and Bisrat 1986) at different concentrations of polysorbate 80 using a Coulter Counter TA II. △, values calculated from Eqn. 1.

At low surfactant concentration (less than 0.07–0.1 w/v%) the dissolution rate increased with surfactant concentration in fairly good agreement with the corresponding increase in solubility, especially for the fine felopdipine quality. The difference obtained for the two size qualities could probably be explained by the effect of particle size on the diffusion-controlled transport of dissolved molecules (Nyström et al., 1985b; Bisrat and Nyström, 1988).

It has been indicated for other sparingly soluble materials that the dissolution from fine particles (griseofulvin, $\bar{d}_v = 3.6$ µm, where the mean diameter was defined from log normal distributions by weight) seems not to be significantly diffusionally controlled (Nyström et al., 1985a). In another study (Nyström et al., 1985b) the *G*-values of two coarser materials (calcum carbonate, $\bar{d}_v =$ 15 µm and hydrocortisone acetate, $\bar{d}_v = 18$ µm) were compared with their maximum dissolution rates as calculated from Eqn. 1. The experimental values obtained were lower than the corresponding theoretical maximum rates. The results in this study for fine and coarse felodipine, using micellar solutions are in good agreement with these earlier established data.

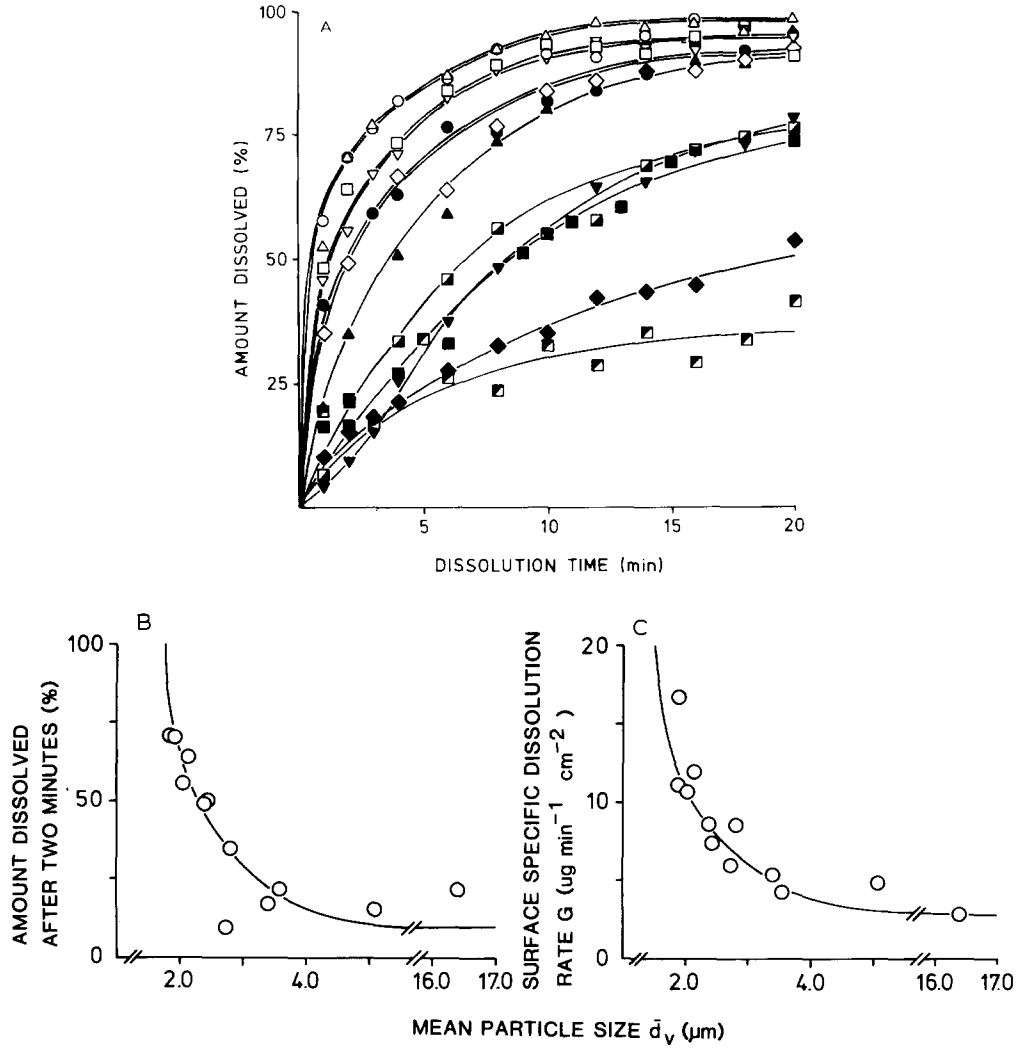

Fig. 3. Dissolution data characterized by the Coulter Counter at 0.05 w/v% polysorbate 80 of different particle sizes:
○, 1.87 μm △, 1.92 μm ▽,2.05 μm
□, 2.14 μm ◇, 2.38 μm ●, 2.44 μm
▼, 2.74 μm ▲, 2.78 μm ■, 3.41 μm
◪, 3.53 μm ◆, 5.18 μm ◩, 16,4 μm

The reason why the surface-specific dissolution rates are lower than expected at surfactant concentrations higher than 0.1 w/v% polysorbate 80 has been discussed by Nyström and Bisrat (1986). Especially the importance of the diffusion coefficients on the dissolution rate of the diffusing species in a micellar solution ought to be pointed out. The diffusion coefficient for a larger diffusion species, such as a mixed micelle will be smaller and thereby slow down the dissolution rate for the drug (Higuchi, 1967). In this context it cannot be excluded that the size and shape of the micelles

are functions of surfactant concentration. A shift to larger micelles would also correspond to a decrease in the volume-specific external surface area of the micellar phase, which thereby could decrease the formation rate of mixed micelles.

The lines connecting the results from the coarse felodipine quality in Fig. 2 are dashed to denote that these values were obtained with another batch of polysorbate than what had been used in the present study. According to the literature (e.g. Boon et al., 1961), the solubilizing power of polysorbate 80 can vary somewhat between batches. It cannot be excluded that such a difference, partly could explain the difference in surfactant concentrations at which the *G*-values level out for the two sets of results, respectively.

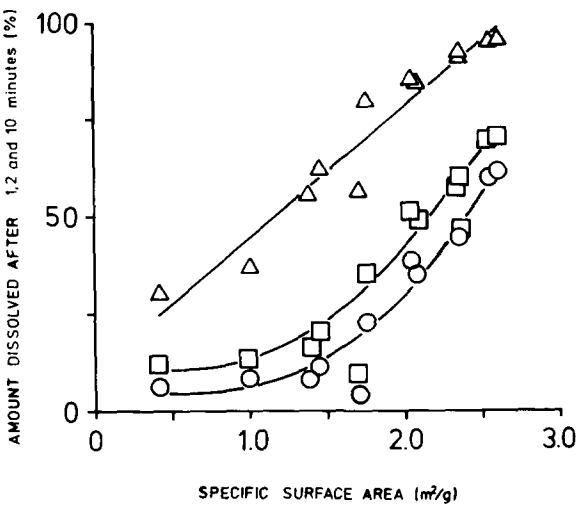

Fig. 4. Amount dissolved in percent after 1 (○), 2 (■), and 10 (△) min for the size fractions of felodipine used in Fig. 3.

Effect of drug particle size

The dissolution rates of a large number of felodipine qualities (Table 1, B and 1–11) were measured under sink conditions at a polysorbate concentration of 0.05 w/v% using the Coulter Counter technique. This low surfactant concentration was chosen because of the established, direct relation between solubility and the surface-specific dissolution rate (Fig. 2). The dissolution rate expressed as amount dissolved versus time are shown in Fig. 3A. As expected, the dissolution rate increased with the increased fineness of the felodipine quality tested. In order to evaluate this effect in more detail, the dissolution rate was expressed as amount dissolved after 2 min and plotted against mean particle size by weight (Fig. 3B). It could be observed that the effect of particle size was relatively marked, considering most qualities were within a limited size range.

It was verified in Fig. 3C that the effect of particle fineness was stronger than could be predicted solely from the differences in surface area, i.e. the *G*-values increased with a decrease in particle size. This effect was probably due to a corresponding decrease of the diffusion boundary layer thickness. This effect was especially pronounced below 3 μm. It should be emphasized that the solid curves denoted in Fig. 3, are estimated profiles, rather than obtained from curve-fitting techniques. The plot of amount dissolved after a specific time, versus mean drug particle size (Fig. 3B) was in this study used to illustrate in a rather common form the effect of *initial* drug surface area on dissolution rate. Because the surface area changes as a function of time, the best evaluation is obtained using an infinitesimally short dissolution time. However, in order to obtain significant quantities of dissolved material, 2 min was chosen as a compromise in this study. In this context it must be emphasized that a too long dissolution time does not correspond to the initial surface area of the powder tested. If such longer monitoring times are used, in combination with the starting drug particle size, misleading profiles could be obtained. This is illustrated in Fig. 4, where the data from Fig. 3A are used to plot the amounts dissolved after 1, 2 and 10 min. After both 1 and 2 min, the tendency of a non-linear relation is quite clear, but using the amounts dissolved after 10 min, an almost linear relation is obtained. In the latter case the use of initial mean drug particle size corresponds to a marked overestimation of the average dissolution surface area during the 10 min period, especially for the rapidly dissolving qualities. Another approach to overcome this problem is to either calculate the change in surface area as a function of time (e.g. cube-root law according to

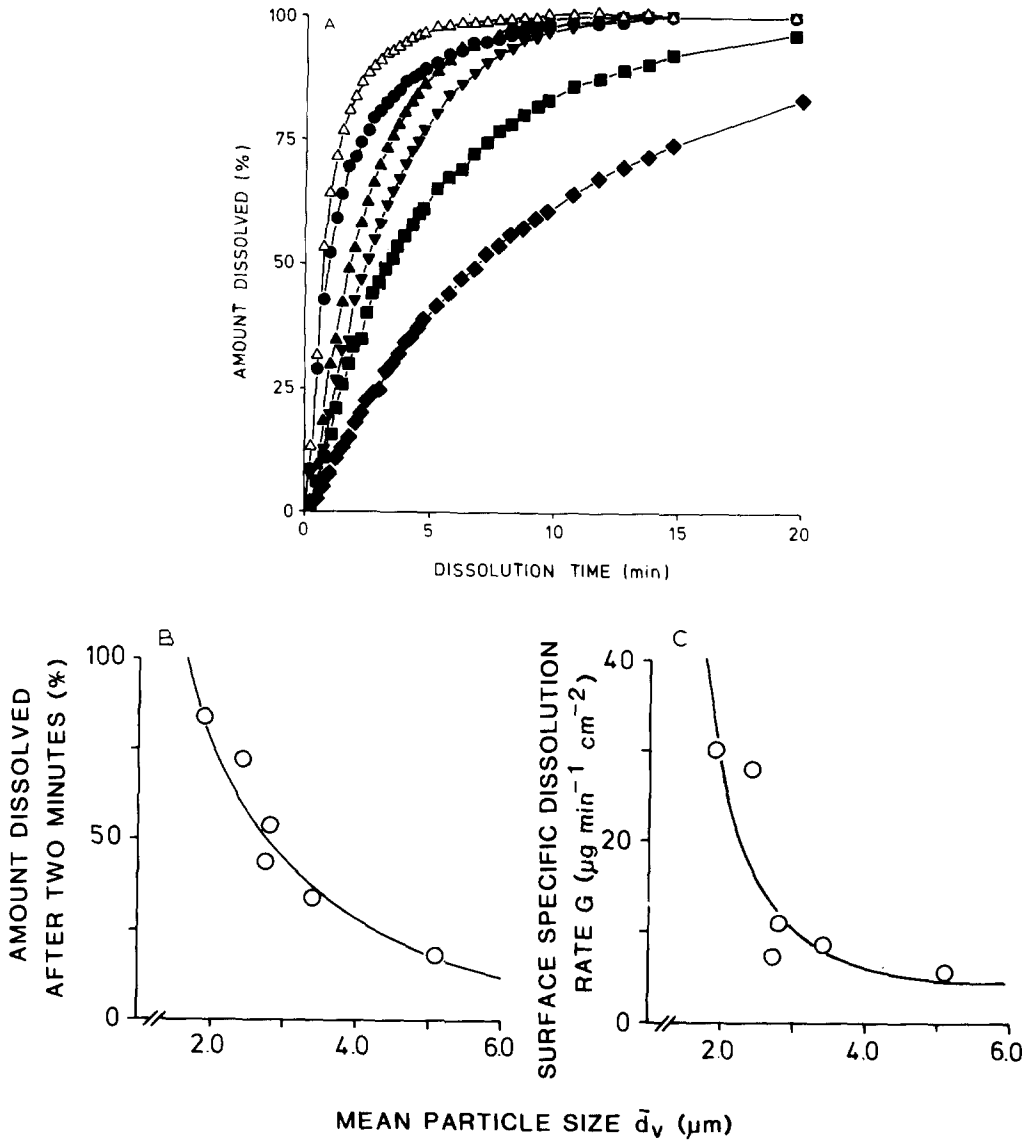

Fig. 5. Dissolution data characterized by photospectrometry at 0.05 w/v% polysorbate 80 of different particle sizes. Symbols as in Fig. 3.

Hixson and Crowell, 1931) or to directly measure the change in surface area with time (e.g. the Coulter Counter principle). The latter approach, utilized in this study has earlier been reported as favourable (Nyström et al., 1985b).

Surface-specific dissolution rates have also been obtained for 6 felodipine qualities using dissolution media containing both 0.05 and 0.23 w/v% polysorbate 80, with the aid of a USP rotating paddle method and a photometric analyzing technique. The results are shown in Figs. 5 and 6. For both concentrations of polysorbate 80, the results showed the same pattern as obtained by the Coulter Counter method (Fig. 3). The results

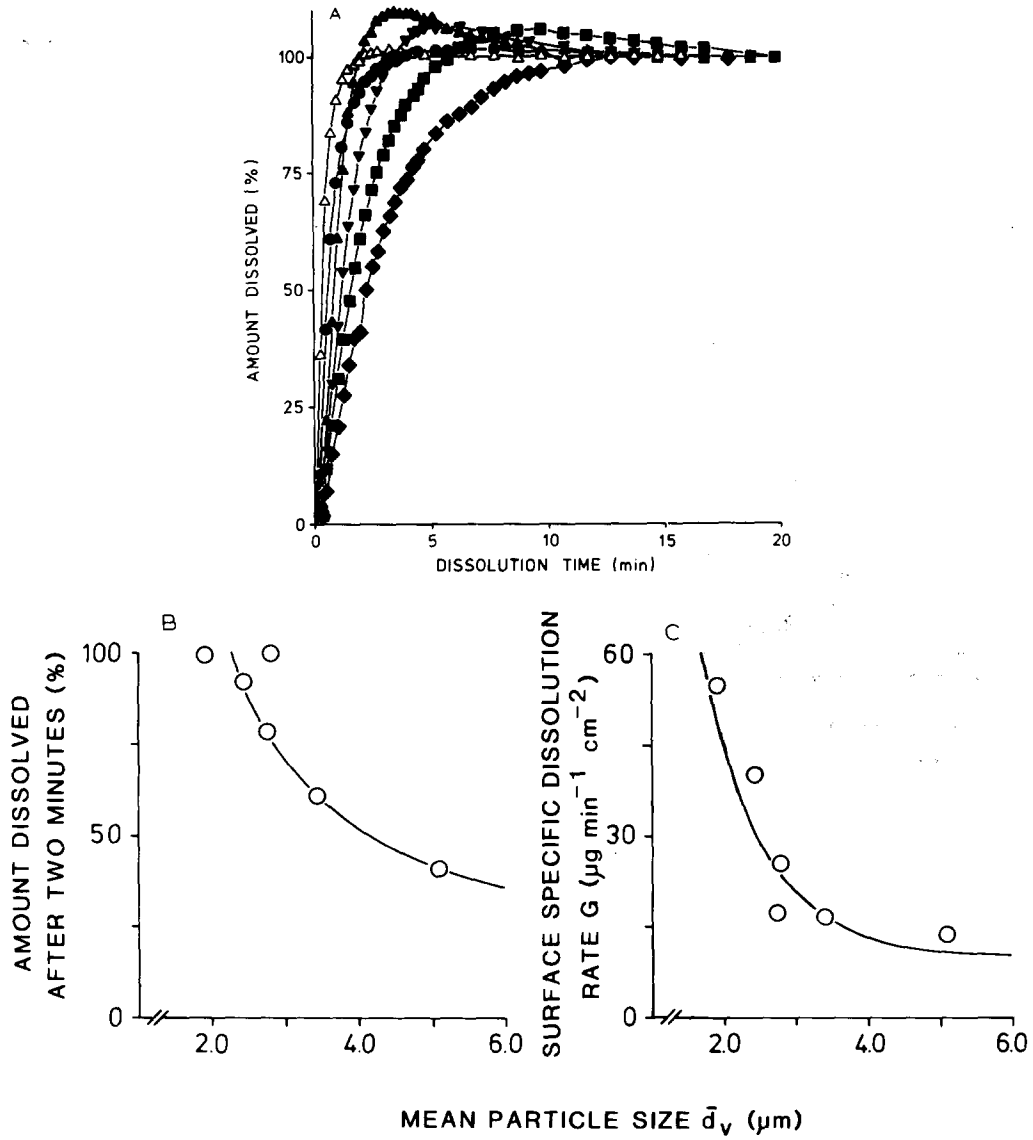

Fig. 6. Dissolution data characterized by photospectrometry at 0.23 w/v% polysorbate 80 of different particle sizes. Symbols as in Fig. 3.

obtained for both methods are summarized in Fig. 7. It can be seen that the Coulter Counter method and the rotating paddle method for the lower surfactant concentrations delivered data which were in fairly good agreement. The slightly higher *G*-values obtained by the paddle method was probably due to an accumulation of undissolved drug particles on the filter used, causing an overestimation of the dissolution rate. Another effect of this artifact can be seen in Fig. 6A where the initial recorded maximal value of amount dissolved for some size fractions was higher than

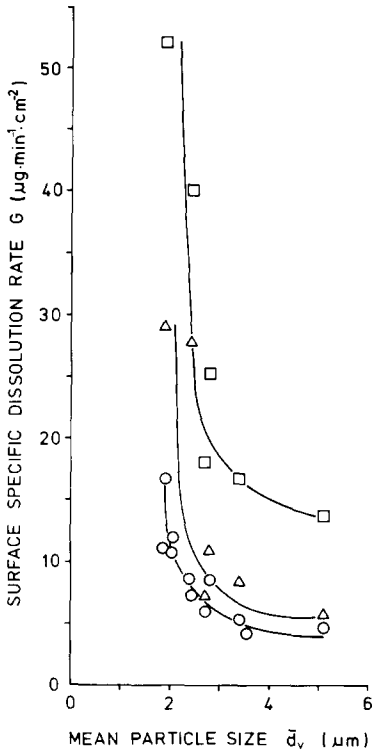

Fig. 7. Comparison between surface-specific dissolution rates (*G*-values) obtained using the Coulter Counter method at 0.05 w/v% polysorbate 80 (○) and the photometric method at polysorbate concentrations of 0.05 w/v% (△), and 0.23 w/v% (□).

100%. The higher polysorbate concentration gave higher *G*-values but the same discrimination of the size fractions tested.

Conclusions

The use of micellar solutions to increase drug solubility seems to be a possible way to reach near sink conditions when measuring the dissolution rate of sparingly soluble drugs. The results in this study also indicate that this is the case also when the surfactant concentration needed is such that the *G*-values obtained are lower than what could be predicted from solubility data.

The effect of particle size on dissolution rate, especially for particle sizes below 3 μm, utilizing micellar solutions seems to be in agreement with earlier findings, established for non-solubilizing medium and could be of both theoretical and practical interest.

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