The influence of aggregate microenvironment on the dissolution of oxazepam in ternary surfactant interactive mixtures

Peter J. Stewart and Julie Liu

Abstract

The purpose of this research was to test the hypothesis that the dissolution rate of oxazepam in interactive mixtures was dependent on the influence of surfactant within the microenvironment of mixed oxazepam–surfactant aggregates produced during dissolution. The studies utilised both powder and intrinsic dissolution methodology; spectrophotometric assays were developed and validated and dissolution data were modelled using multi-exponential equations and dissolution rate constants estimated using non-linear least squares algorithms. For a series of water-soluble ternary additives to the oxazepam interactive mixture, sodium lauryl sulfate and cetrimide were shown not only to decrease aggregation through enhanced dispersion, but also to increase the dissolution rate constant. Such an increase in dissolution rate constant was observed in the intrinsic dissolution studies when surfactant concentrations exceeded the critical micelle concentration and the oxazepam solubility increased. Laser diffraction particle sizing during the dissolution process confirmed the presence of dispersed particles and aggregates and demonstrated that the presence of surfactant improved the state of dispersion. The results of studies using different rotational speeds produced unexpected increases in aggregation and decreases in dissolution rate constants at about 150 rev min^{-1}, consistent with the transient formation of loose aggregates containing dissolved surfactant.

Introduction

Studies into the dissolution of oxazepam in interactive mixtures have focused on improving dissolution rate and investigations have examined the influence of carrier type, surface loading of drug on the carrier and presence of surfactants (McGinity et al 1985; Westerberg et al 1986; Nilsson et al 1988; Westerberg & Nystrom 1993a, b; Alway & Stewart 1996; Alway et al 1996). In general, formulation with water-soluble carriers, decreased concentrations of drug on the surface and the addition of surfactants to the interactive mixtures increased the drug's dissolution rate. In the more recent studies, the degree of aggregation of drug particles during the dissolution of interactive mixtures of benzodiazepines was found to control the dissolution process (Alway & Stewart 1996; Alway et al 1996; Westerberg & Nystrom 1993b). Modelling of the dissolution data allowed the initial concentration of drug aggregates and the dissolution rate constants to be estimated (Alway & Stewart 1996; Alway et al 1996). In previous research from this laboratory, the presence of surfactants as ternary components in interactive mixtures of benzodiazepines decreased the extent of aggregation (Liu & Stewart 1998). Aggregates containing both the benzodiazepines and the micronised surfactant particles were observed in the interactive mixture in scanning electron microscope studies. This research suggested that the effect of the surfactant was related to its role within the benzodiazepine–surfactant aggregate formed after dissolution of the lactose-based carrier used to formulate the interactive mixture. The study hypothesised that, after rapid dissolution of the surfactant within the local environment of the benzodiazepine–surfactant aggregate, high local concentrations of surfactant were produced in the microenvironment of the aggregate causing dispersion of the

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aggregated particles. It was unclear whether the presence of surfactant in this microenvironment also accelerated dissolution by increasing the intrinsic dissolution rate constants or by modifying the dissolution mechanism. The purpose of the research reported in this manuscript was to test the hypothesis that the nature of the aggregate microenvironment was important in the dissolution of interactive drug mixtures and to more stringently define the mechanisms by which the increased dissolution rate was achieved in these systems.

Materials and Methods

Materials

Oxazepam supplied by Alphapharm (Brisbane, Australia), micronised, with volume mean diameter of 3.0 μm (d(10%) = 0.9 μm and d(90%) = 5.8 μm) was the adherent model drug. Sodium lauryl sulfate and cetrimide from Sigma (St Louis, MO) were micronised and possessed projected area diameters less than 10 μm when examined using scanning electron microscopy (SEM). Micronisation was achieved by fluid energy milling (Chrispro Jetmill model 75P compressed air 5.8 atm. at 12.7 L s^{-1}) and storage was at room temperature over silica gel in a desiccator. Excipients were lactose from Wyndale (New Zealand) and povidone from BASF (Kollidon 25, Germany). A lactose carrier of lactose–povidone, 9:1, was prepared by wet granulation using a 10% w/w povidone aqueous solution. The granules were tray-dried in an oven at 50°C for 24 h and carrier fractions of 250–355 μm were obtained by sieve classification (Analysette 3, Fritish, and West Germany). The dissolution medium was distilled water degassed using a 0.45-μm Durapore membrane, HVLP 04700 Millipore Corporation, Ireland.

Particle size analysis

The particle size distribution of oxazepam was determined using laser diffraction (Mastersizer S, Malvern Instruments, UK) using water saturated with drug as the dispersion medium. Dispersion was achieved using an ultrasonic chamber. A reverse fourier lens with a 300 mm focal length was utilised with an active beam length of 2.4 mm to measure particles in the range 0.05–900 μm. The polydisperse standard presentation was chosen as the analysis model. For the interactive mixtures, distributions were determined with the Mastersizer S using the Small Volume Sample Dispersion Unit (MS1) filled with 100 mL of degassed media and dispersed using a constant speed stirrer. Interactive mixture (about 75 mg) was added to the dispersion unit until the obscuration was 10–15%.

Mixture preparation

Interactive mixtures were prepared by placing the micronised oxazepam (and surfactant) between two layers of carrier in a glass vial and shaking vigorously by hand for

5 min; this methodology has been validated previously (Alway & Stewart 1996; Alway et al 1996). Sieve analysis before and after mixing showed that the mixing methodology did not result in carrier comminution. SEM was used to determine the surface coverage of the carrier by the benzodiazepine particles (Hitoshi S570, Japan; 10 kV, platinum coated). Homogeneity of all mixtures was determined by removing 20 × 100 mg samples, extracting into absolute alcohol (CSR, Australia) and assaying spectrophotometrically.

Spectrophotometric analysis

Spectrophotometric analyses were performed using a scanning ultraviolet–visible spectrophotometer (Cecil 6000 series, model CE 6700, Cecil Instruments, UK). Beer's Law calibration plots were obtained in absolute alcohol for the homogeneity studies (oxazepam, 317 nm, 2–10 mg%) and in distilled water for the dissolution studies (oxazepam, 230.5 nm, 0.1–1.0 mg%). At least four concentrations and four replicates were used for the calibration. Linear regression analysis indicated no significant deviations from linearity and no significant deviations from a zero intercept. Absorbance of the lactose carrier was insignificant in the dissolution studies, and was small ($<$ 0.05) and accounted for in the homogeneity determinations. Correlation coefficients were greater than 0.999 and precision was generally below 1% (except the lowest concentration in ethanol where the CV was 2.4%). The calibration in the dissolution medium was determined at 37°C in the flow through cells in the automated dissolution apparatus.

Dissolution studies

An automated dissolution system consisting of the dissolution apparatus (model DT6, Erweka, Germany), auto-controlled multichannel peristaltic pump (Watson Marlow Ltd, UK; 503V/RL) an ultraviolet–visible spectrophotometer with 10-mm flow cells (Cecil Instrumentation Ltd, UK; CE6700) and 386 PC (Auspac, Australia) using Erweka software was employed in all of the dissolution studies. The powder dissolution studies were performed according to the USP/NF paddle method. 1000 mL of dissolution medium was introduced into the dissolution vessel, covered and incubated to 37 ± 0.5°C. Samples of interactive mix (100 mg) were sequentially added to the cells using the Erweka software count down. Sequential sampling using a filter probe occurred over 60 min at regular 2-min intervals using six replicates. The pH of the dissolution media was measured before and after the dissolution of the interactive mixtures and was not less than 6.0. The Woods' rotating disk apparatus was used for the intrinsic dissolution studies (Wood et al 1965). Disks (12.5 mm) of micronised oxazepam were prepared in the compression die using a hydraulic press (Carver Laboratory Press, USA). Compression was at 17 800–44 500 newtons for 3 min. Disk thickness was about 2 mm. The rotating disk assembly was removed from the press and connected to the stirring platform of the dissolution ap-

paratus. Six replicates were run simultaneously in 300 mL of dissolution medium. Four rotation speeds were used (25, 50, 100 and 200 rev min^{-1}). Dissolved oxazepam was measured at 2-min intervals using spectrophotometric analysis.

Determination of solubility

The solubility of oxazepam was determined in triplicate by the addition of excess drug to 10 mL of the appropriate dissolution media in a capped vial, shaking at 37°C in a water bath for 24 h, filtration using a nylon filter membrane (Lida Manufacturing Corporation, USA), dilution with dissolution media (1–10 for oxazepam) and spectrophotometric analysis.

Powder dissolution modelling

The dissolution profile data were modelled by considering that the oxazepam dissolution occurred from distributions of dispersed and aggregated particles which existed following dissolution of the carrier after the interactive mixtures were placed in the dissolution medium (Alway et al 1996). Multiexponential equations were used to fit the dissolution data:

$$C = C_d \exp(-tk_d) + C_{a1} \exp(-tk_{a1}) + C_{a2} \exp(-tk_{a2}) + \dots \qquad (1)$$

where C was the percent of undissolved particles at time t, C_d, C_{a1} and C_{a2} were the initial percent of dispersed (d) and aggregated particles (a1, a2, …), respectively, and k_d, k_{a1} and k_{a2} were the dissolution rate constants for the dispersed (d) and aggregated particles (a1, a2, …) per minute, respectively. Combined data from replicate determinations were modelled using the non-linear least squares curve fitting software package Sigmaplot (Jandel Scientific) which utilised the Marquardt–Levenberg algorithm (Levenberg 1944; Marquardt 1963) to determine the absolute true minima for the sum of squared deviations. Data were unweighted and truncated when the mean of the dependent variable was not significantly different from the final data point. Residuals were shown to be randomly distributed using the runs test (Bennett & Franklin 1967). The modelling of dissolution data using this methodology has been previously described (Alway et al 1996).

Statistical analysis

In addition to the non-linear least squares parameter estimation described above, linear regression analyses were used to validate the linearity of the assay calibrations (5 concentrations and 4 replicates) and to estimate the rate constants from the slope of percent dissolved versus time plots during dissolution of oxazepam from the compressed disks. Six replicates were used in the rate constant estimations. Comparisons of oxazepam solubility in water and surfactant solutions were made using a *t*-test.

Results and Discussion

Interactive mixtures

The model interactive mixture used in this investigation consisted of micronised oxazepam, and sodium lauryl sulfate or cetrimide adhered to the surface of a lactose-based carrier. Oxazepam was used at 10% because of the relatively high degree of aggregation seen in binary interactive mixtures at this concentration (Liu & Stewart 1998). Concentrations of surfactant up to 5% were chosen to achieve complete deaggregation of the oxazepam particles during dissolution (Liu & Stewart 1998). The mixtures showed good homogeneity with all CVs less than $\pm 1.5\%$. SEM analysis of these systems has been reported previously (Liu & Stewart 1998) and demonstrated that the interactive mixture contained multilayer adhesion of the oxazepam and sodium lauryl sulfate/cetrimide on the carrier surface with particulate aggregation clearly seen on the lactose surface.

Effect of ternary components

To learn more about the microenvironmental effect within the aggregates, non-surfactant, water-soluble, ternary components such as potassium chloride and lactose were micronised and incorporated into the oxazepam (10%) interactive mixture. A comparison of added potassium chloride, lactose and sodium lauryl sulfate at the 5% level on oxazepam dissolution in a lactose interactive mixture showed that the two water-soluble, non-surfactant compounds improved the dissolution rate over the binary mixture but were not as effective as the surfactant in increasing the oxazepam dissolution rate. Dissolution data for a number of ternary configurations were modelled and the estimated parameters for initial concentration of aggregates and dissolution rate constants are shown in Figure 1. Binary interactive mixtures of oxazepam in a lactose carrier produced considerable initial aggregation (e.g. about 90%; Figure 1A). Increasing concentrations of sodium lauryl sulfate and cetrimide caused considerable deaggregation of oxazepam particles during its dissolution from interactive mixtures, reducing the initial concentration of aggregates to less than 10% when 5% surfactant was incorporated into the interactive mixture (Liu & Stewart 1998). Both potassium chloride and lactose at the 5% level had some effect in reducing the initial concentration of aggregates but were nowhere as effective as the surfactants. Surfactants incorporated into the dissolution medium at the levels used in these interactive mixtures have a negligible effect on the dissolution rate and dispersion process (Liu & Stewart 1998). The major deaggregation effect therefore probably was associated with the presence of dissolved surfactants and with their specific activity in
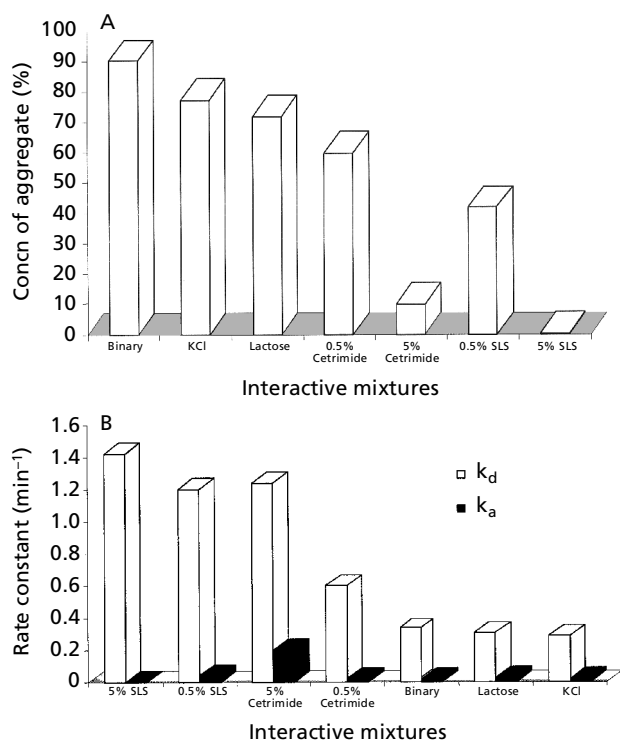
Figure 2 Particle size distributions of oxazepam (5%) binary and ternary interactive mixtures containing 5% surfactant, lactose or potassium chloride, determined using laser diffraction particle sizing in water, under non-sink conditions and after one minute when the lactose carrier was dissolved. SLS, sodium lauryl sulfate.

Figure 1 Estimated initial concentrations of aggregates (A) and dissolution rate constants (B) for dispersed (k_d) and aggregated (k_a) particles determined from a biexponential model for ternary interactive mixtures of oxazepam containing surfactant and non-surfactant third components. SLS, sodium lauryl sulfate.

the aggregate microenvironment during the early stages of dissolution.

The influence of other ternary components on the dispersed and aggregated particulate dissolution rate constants for the oxazepam–lactose interactive mixture is illustrated in Figure 1B. The dissolution rate constants of dispersed and aggregated particles for the binary and ternary potassium chloride and lactose mixtures were similar (i.e. 0.022, 0.020 and 0.026 min^{-1}, respectively, for k_a and 0.34, 0.31 and 0.29 min^{-1}, respectively, for k_d), indicating that the presence of the non-surfactant ternary components had little intrinsic effect on the dissolution process. The presence of surfactants in the interactive mixture produced increased dissolution rate constants for both dispersed and aggregated particles (e.g. the k_a and k_d for cetrimide at the 5% level were 0.20 and 1.22 min^{-1}, respectively, while the k_d for sodium lauryl sulfate at the 5% level was 1.52 min^{-1}). The increased dissolution rate constants could be caused by either a change in the size distribution of the dispersed particles or aggregates due to the presence of surfactant, or by changes in the intrinsic dissolution rate constants through increased solubility in the diffusion layer.

The characteristics of the particle size distributions of dispersed particles and aggregates during dissolution and the extent of deaggregation caused by the added third component were confirmed using laser diffraction particle
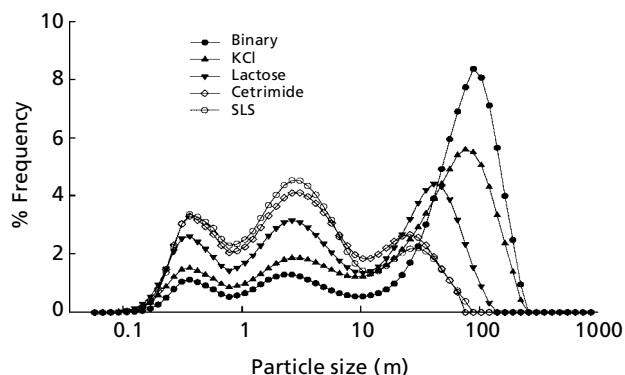
sizing of ternary interactive mixtures. The particle size distributions of oxazepam (10%)–interactive mixtures containing 5% of the third component determined after one minute in non-sink conditions are shown in Figure 2. Non-sink conditions were necessary to optimise the obscuration into the 10–30% range; the obscuration of oxazepam concentrations similar to those used in the dissolution studies was less than 1% and the particle size fitting showed large residuals. Figure 2 demonstrates that, when the lactose carrier dissolved after one minute, distributions characteristic of aggregated particles (about 15–225 μm) and micronised drug particles (less than 10 μm) were produced. The distribution for the dispersed micronised oxazepam demonstrated a decrease in particle frequency around 1 μm. This was due to the use of the standard presentation, which did not account for the true refractive index of the oxazepam. Attempts to experimentally determine the refractive index were unsuccessful and the standard presentation was used throughout the particle sizing. The identification of specific distributions representative of micronised drug particles and drug aggregates was consistent with the use of the biexponential model to estimate initial concentrations and rate constants for dispersed drug particles and aggregates. The areas under the particle size distribution of the aggregates and their relative position demonstrated that the binary mixtures produced the highest concentration of large aggregates. At the other extreme, the ternary mixtures containing surfactants caused the least aggregation and the aggregates were relatively small in size. The water-soluble, non-surfactants had some, but not a significant, effect on the deaggregation process and the results were consistent with the dissolution modelling. Observation of the distributions also showed that the means of the dispersed particle distributions did not change with added ternary component, giving support to the fact that increased dissolution rate constants are associated with increased intrinsic dissolution rates. However, the decrease in mean aggregate size in the presence of surfactant probably did contribute to the

changes in the dissolution rate constants of the aggregates seen in the modelling. The difference in conditions between the dissolution and particle sizing studies limited the strength of support for these effects on particle de-aggregation and intrinsic dissolution changes; however, the particle sizing study did provide good indirect confirmation of particulate behaviour during dissolution.

The potassium chloride and lactose, therefore, assisted in reducing initial aggregate concentration probably by dissolving rapidly in the mixed oxazepam–lactose (or potassium chloride) aggregate, destabilising the aggregates and resulting in some further dispersion of the oxazepam particles. Conversely, the surfactants not only reduced initial aggregate concentrations, but also resulted in significantly higher dissolution rate constants caused by some comminution of aggregated particulate distributions. It is also likely that the presence of dissolved surfactant modified the characteristics of the diffusion layer increasing the intrinsic dissolution of the oxazepam.

Effect of rotational speed during dissolution

The effect of rotational speed on the dissolution of oxazepam in surfactant interactive mixtures containing oxazepam (10%)–lactose–surfactant (sodium lauryl sulfate or cetrimide; 1 and 5%) was studied over the range 50–200 rev min^{-1}. The dissolution data were modelled using the biexponential model and the estimated parameters are shown in Figure 3. In general, the study showed that, at a rotational speed of 100 rev min^{-1}, the degree of aggregation was minimised and the dissolution rate constants were maximised. These results were not consistent with the Nernst–Brunner's film theory, which would predict that increased stirring speed should decrease the diffusion layer thickness and increase the dissolution rate. In addition, increased rotational speed would be expected to comminute the aggregates, resulting in increased deaggregation as the speed increased. A previous study of the rotational speed effects on binary interactive mixtures demonstrated adherence to the above theory with increased stirring speed causing decreased aggregation (Alway et al 1996). The effect is clearly more complex in ternary surfactant mixtures. The microenvironment of the aggregate and consequently the diffusion layer surrounding the dissolving particles is likely to be surfactant rich initially due to the rapidly dissolving micronised surfactant particles present in the interactive mixture. Such an environment will be transient, but will initiate the deaggregation and increased dissolution effects. Increased stirring speeds are likely to rapidly decrease surfactant concentration in the microenvironment of the aggregate due to dispersion of the dissolving surfactant. The overall effect therefore will be a balance between diffusion layer effects and surfactant dilution effects in the microenvironment. In Figure 3, increase in dissolution rate constants and decrease in aggregation are consistent with diffusion layer effects. At higher stirring speeds, the decrease in dissolution rate constants and the increase in aggregation are consistent with increased surfactant dispersion in the aggregate microenvironment.
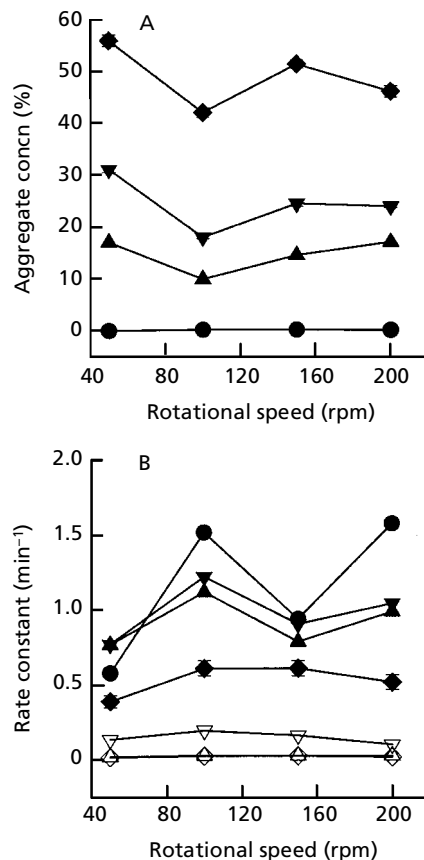

Figure 3 The estimated initial concentration of aggregates (A) and dissolution rate constants (B) for dispersed (closed) and aggregated (open) particles from the bi-exponential model fitting for oxazepam (10%)–lactose ternary interactive mixtures containing 1% cetrimide (◆), 5% cetrimide (▼), 1% sodium lauryl sulfate (▲) and 5% sodium lauryl sulfate (●).

These results provide further indirect evidence to support the proposed hypothesis.

Effect of surfactant on the intrinsic dissolution rate

To understand the effect of high surfactant concentration on the rate and mechanism of dissolution of oxazepam, the intrinsic dissolution rates were determined from compressed disks over the rotational speed range 25–200 rev min^{-1} for a range of sodium lauryl sulfate and cetrimide concentrations below and above the critical micelle concentration (CMC). Dissolution was monitored for at least 30 min; the profiles of milligrams dissolved versus time showed no significant deviation from linearity and the intercept was not significantly different from zero. Intrinsic dissolution rates were calculated from the slope of the linear profile determined by linear least-squares fitting. Levich plots of intrinsic dissolution rate of oxazepam versus the square root of angular velocity were compared in both sodium lauryl sulfate and cetrimide solutions. A typical
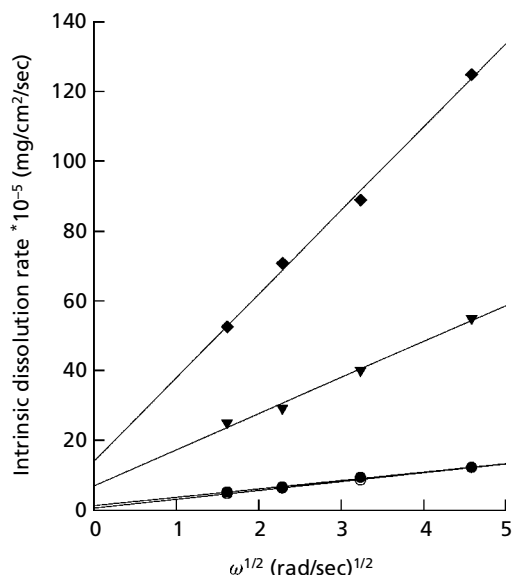
Figure 4 Levich plot of intrinsic dissolution rate versus square root of angular velocity of oxazepam in water (○) and different concentration of sodium lauryl sulfate solutions (●, 10 mg%; ▼, 350 mg%; ◆, 800 mg%) at 37°C.

Table 1 Solubility of oxazepam in aqueous solutions of sodium lauryl sulfate and cetrimide at 37°C.

Sodium lauryl sulfate (mg%)	Solubility (μg mL^{-1})	Cetrimide (mg%)	Solubility (μg mL^{-1})
10	30.3±0.3	5	30.8±0.5
25	31.1±0.6	9	31.3±0.5
50	31.4±0.1	15	37.5±0.3
100	29.5±1.7	50	51.3±1.2
200	30.2±0.2	100	93.7±0.1
250	101.9±1.2	200	173.8±0.8
350	271.6±17.2		
500	599.4±14.7		
800	1107±8.4		
1000	1449±4.5		

Levich plot in sodium lauryl sulfate solutions is shown in Figure 4. For both surfactants, the Levich plots were linear at all surfactant concentrations. The plots can be represented mathematically by equation 2:

$$\text{Rate of dissolution} = 1.95\,D^{2/3}\nu^{-1/6}\omega^{1/2}(C_s - C_t)r^2 \qquad (2)$$

where D is the diffusion coefficient, ν is the kinematic viscosity, ω is the angular velocity, C_s is the saturation concentration of dissolved drug at the interface, C_t is the drug concentration in the bulk and r is the radius of the disk.

The magnitude of the slope was related to the solubility of the drug in the surfactant solution, provided the viscosity and diffusion coefficient remained constant. At concentrations below the critical micelle concentration, the solubility of the oxazepam in the sodium lauryl sulfate and cetrimide solutions was about 31 μg mL^{-1} and the slopes of the Levich plots were similar. There was no significant difference between the dissolution rate at 25–200 rev min^{-1} for oxazepam in water and 10 mg% sodium lauryl sulfate solution (one-sided t-test; $P = 0.431$) and for oxazepam in water and 5 mg% cetrimide solution (one-sided t-test; $P = 0.496$). At concentrations above the CMC (CMCs for sodium lauryl sulfate and cetrimide were 230 mg% and 10 mg%, respectively), the slope of the Levich plot increased with increasing surfactant concentration. The relationship between slope of the Levich plot and oxazepam solubility in the surfactant solution is summarised in Table 1.

The linearity of the Levich plots in all of the surfactant solutions indicated that the dissolution was probably diffusion controlled with the rate-determining step in the dissolution process being the diffusion of oxazepam across the stagnant layer. Non-zero intercepts were observed for all the Levich plots of oxazepam in water and surfactant solution. These observations do not agree with the expected theoretical behaviour predicted by equation 2, but are consistent with several previous studies (Mooney et al 1981; de Smith et al 1987; Supabphol & Stewart 1996). In these studies, this behaviour was attributed to an experimental error, additional dissolution mechanisms and changing properties of the disk surface during dissolution, but has not been definitively explained.

The results of these studies show that the intrinsic dissolution rate of oxazepam was increased in the presence of surfactant solutions at concentrations above the CMC. The mechanism of dissolution did not change and was diffusion controlled. It is likely, therefore, that the oxazepam dissolution rate increases observed in ternary surfactant interactive mixtures could be associated with the increased intrinsic dissolution rate of oxazepam in the transient high-concentration surfactant microenvironment of the aggregate.

Conclusions

This study provides a better understanding of the dissolution of micronised drugs, like oxazepam, formulated in mixtures containing surfactants. Deaggregation and increased intrinsic dissolution rate constants contribute to the increased dissolution rate. The results of the ternary-component and rotational-speed studies are consistent with the proposed hypothesis that mixed aggregates of oxazepam and micronised surfactant formed during the powder mixing phase are implicated in the dissolution process. These aggregates are likely to be transient and short-lived. Particle sizing experiments show the resulting distribution of dispersed and aggregated particles, but are not able to identify with any reliability the initial transient aggregates due to masking by the dissolution of the carrier particles. The aggregates provide a microenvironment where surfactant dissolution produces sufficiently high concentrations to partially disperse the aggregates and to increase the intrinsic dissolution rate of oxazepam by

increasing its solubility in the diffusion layer. The rotating-disk dissolution studies confirm that higher intrinsic dissolution rates occur at surfactant concentrations above the CMC. The evidence to support the dissolution mechanism is indirect, but is consistent with the proposed mechanism.

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