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Modelling the dissolution of diazepam in lactose interactive mixtures

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Abstract

The dissolution of diazepam (1–10%) in lactose interactive mixtures was studied using the USP paddle method over rotational speeds of 50–200 rpm to elucidate the mechanism of dissolution and to model the process. Dissolution of diazepam was concentration dependent and occurred rapidly, i.e., greater than 95% dissolved within 10 and 20 min for the 1 and 10% mixtures, respectively. Conventional dissolution models like the Hixson-Crowell Cube Root Law, Wagner's log probability plot and monoexponential equations provided unsuccessful data fits. The hypothesis that dissolution occurred from both dispersed and aggregated particles was tested using a biexponential model. Data treatment using the Marquardt-Levenberg non-linear least squares algorithm (Peakfit®) provided good fits. The rate constants for diazepam dissolution from the dispersed and aggregated particles and their initial concentrations were estimated and was consistent with the observed concentration-dependent behaviour. Laser diffraction was used to demonstrate the existence of dispersed particles and aggregates during the dissolution process. Studies in surfactant solution provided further indirect evidence of aggregate formation.

Keywords: Interactive mixture; Dissolution; Soluble carriers; Dissolution model

1. Introduction

Interactive mixtures have improved dissolution rates of poorly soluble drugs. Soluble carriers (sodium chloride and lactose) were reported to promote rapid dissolution of griseofulvin, since the drug was available as fine primary particles (Westerberg et al., 1986). Lesser soluble carriers (tricalcium dicitrate) resulted in limited improvement in dissolution, whilst insoluble carriers (hydrophobic paraffin granules) decreased the rate compared with pure drug agglomerates. Carrier solubility was of major importance in determining the degree of improvement in dissolution efficiency using sucrose granules and Emcompress® (Ibrahim et al., 1988). The dissolution of mixtures containing a highly soluble carrier (sodium chloride) was comparable to the suspension depending on the particle size of the carrier (De Villiers and van der Watt, 1989). Dissolution

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of interactive mixtures was almost independent of agitation intensity for carriers of high solubility (Nystrom and Westerberg, 1986; Westerberg et al., 1986).

For interactive mixtures containing micronised griseofulvin with a soluble maltose/dextrose carrier, dissolution rates were inversely proportional to concentration, attributed to uneven coating of drug at higher loadings (McGinity et al., 1985). The degree of carrier saturation has been determined using external surface area calculations (Westerberg et al., 1986). Using these calculations, dissolution rates were shown to be extremely rapid for griseofulvin and oxazepam in granulated mannitol and anhydrous lactose interactive mixtures with low carrier surface coverage (Nilsson et al., 1988). Higher concentrations showed reduced dissolution rates particularly at loadings above monolayer coverage. The authors suggested that at oversaturation incomplete drug deagglomeration and the prevention of carrier solubilization due to the hydrophobic drug coating were responsible for the reduction in dissolution efficiencies.

Further studies demonstrated that carrier materials (sodium chloride and mannitol) dissolved quickly even with high degrees of surface coverage with hydrophobic drugs including micronised griseofulvin and oxazepam (Westerberg and Nystrom, 1993). Dissolved carrier material in the dissolution microenvironment did not affect the drug dissolution process. Fine drug particles were released almost immediately to the surrounding medium and the rapid dissolution rate was attributed to the increased surface area and the small apparent diffusional layer thickness. High concentrations of drug formed agglomerates rather than discrete particles with resulting decreased surface area and thicker diffusional layers causing reduction in dissolution rate.

The purpose of this research was to study further the influence of drug loading and rotational speed on a model drug diazepam in a water-soluble carrier system and to mathematically model the dissolution behaviour.

2. Materials and methods

2.1. Materials

Diazepam (Alphapharm, Australia) micronised, with number weighted mean diameter of 3.3 μm was the adherent model drug. Micronisation was achieved by fluid energy milling (Chrispro Jetmill model 75P compressed air 5.8 atm at 12.7 l/s) and stored at room temperature over silica gel in a dessicator. Lactose-povidone granules prepared from lactose (Wyndalle, New Zealand), 9 parts, and povidone (Kollidon® 25, BASF, Germany), 1 part, by wet granulation using 10% (w/w) povidone solution. The wet granules were tray dried in an incubator at 50°C for 24 h and a 250–355-μm sieve fraction were obtained by sieve classification using standard sieves (Labotechnics, Australia) and a sieve shaker (Fritsch, Australia). The dissolution medium was freshly distilled water (Fisons Still, England) degassed using a 0.45-μm Durapore membrane, HVLP 04700 Millipore Corporation, Ireland. Absolute ethanol (CSR, Australia) was used to extract diazepam for the homogeneity studies.

2.2. Methods

2.2.1. Particle size analysis

The particle size distribution of the micronized diazepam was determined using a single particle optical sensing instrument (AccuSizer 770, Particle Sizing Systems, USA). An aqueous sodium dodecyl sulphate suspension of diazepam was prepared and sonicated to break up aggregates. An autodilution facility was employed to provide optimum particle concentrations for analysis. Number weighted distributions were obtained by counting approximately 120 000 particles. The size distribution of the micronized diazepam in the interactive mixtures during dissolution in water was determined using a laser diffraction technique of particle sizing (Malvern Master Sizer X, Malvern Instruments, England). Weight of interactive mixture equivalent to approximately 1 ml was added into a cell/chamber filled with distilled water, and the mixture dispersed using a magnetic stirrer. The powder was added until the obscura-

tion value was between 1 and 3%. The focal lens of 100 mm was used to measure the particle size distribution between 1.0 and 600.0 μm. A beam length of 10.0 mm (without the use of ultrasound), was utilized for particle size determination. Particle size distributions were determined at several time intervals during the dissolution of the interactive mixtures.

2.2.2. Interactive mixtures

Interactive mixtures containing 1.0, 2.5, 5.0 and 10.0% of diazepam were prepared by placing the miconised drug between two layers of carrier in a glass vial and shaking vigorously by hand for 5 min. This method was chosen after evaluating a number of mixing procedures including mechanical tumbling and was found to consistently produce good quality interactive mixtures. The procedure did not result in carrier comminution. Homogeneity was determined by removing 20 × 200-mg samples, extracting into absolute alcohol (CSR, Australia) and assaying spectrophotometrically. Coefficients of variation were less than ± 1.5% indicating satisfactory mixtures. Scanning electron microscopy was used to determine the surface coverage of the carrier by diazepam particles (Hitachi S570, Japan; 10 kV, platinum coated) and the behaviour of the interactive system during dissolution (Environmental Scanning Electron Microscope, Electroscan Corporation, model E3, USA).

2.2.3. Spectrophotometric analysis

Spectrophotometric analyses were preformed using a scanning ultraviolet-visible spectrophotometer (Cecil 6000 series, model CE 6700, Cecil Instruments, England). Beers Law calibration plots were obtained in absolute alcohol for the homogeneity studies (315 nm, 2.0–10.0 mg%) and in dissolution medium (231 nm, 0.04–1.0 mg%). At least four concentrations and three to six 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 0.9996. The calibration in the dissolution medium was determined at 37°C in the flow through cells in the automated dissolution apparatus.

2.2.4. Dissolution studies

An automated dissolution system consisting of the dissolution apparatus (model DT 6, Erweka, Germany), auto-controlled multichannel peristaltic pump (Watson Marlow Ltd., 503V/RL, England) an ultraviolet-visible spectrophotometer with 1- and 10-mm flow cells (Cecil Instrumentation Ltd., England, CE6700) and 386 PC using Erweka software (Auspac, Australia) was employed in all of the dissolution studies according to the USP/NF paddle method. One thousand 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. Four rotational speeds were used, i.e., 50, 100, 150 and 200 rpm. 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.

3. Results and discussion

3.1. Dissolution studies

The dissolution profiles of the 1.0, 2.5, 5.0 and 10.0% diazepam-lactose interactive mixtures were determined using the paddle method at rotational speeds of 50, 100, 150 and 200 rpm (Fig. 1). The profiles revealed that dissolution of diazepam in the interactive mixture occurred rapidly especially at low diazepam concentrations, i.e., greater than 95% dissolved within 10 and 20 min for the 1 and 10% mixtures, respectively. Previous studies demonstrated that the dissolution rate of diazepam in the lactose interactive mixtures was significantly greater than that of pure diazepam indicating the benefit of the carrier dispersion, e.g., at 50 rpm, about 100-times greater and, at 200 rpm, about 30-times greater (Sangchantra,

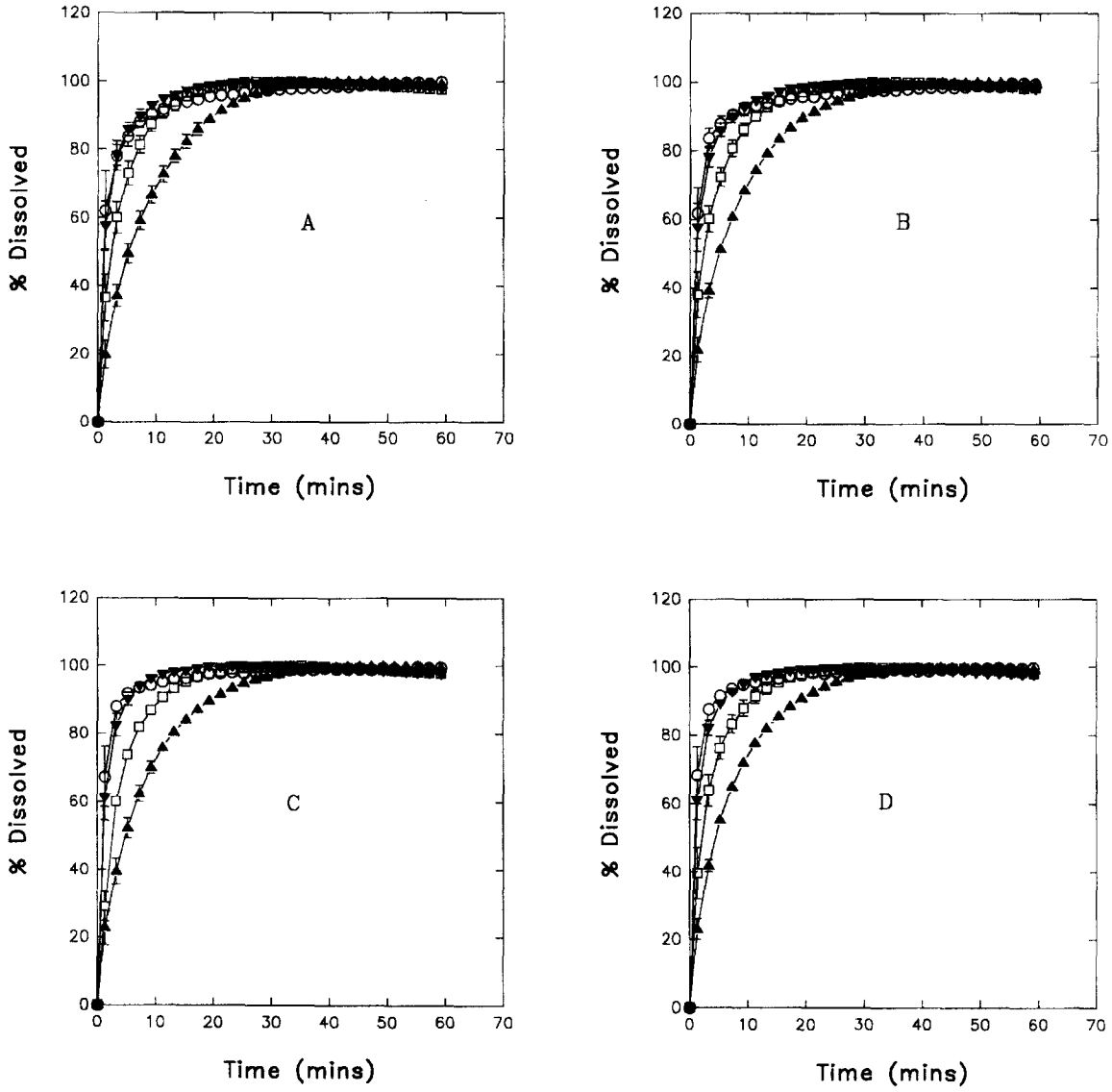

Fig. 1. Dissolution profiles of diazepam-lactose interactive mixtures at 37.0°C in distilled water using the USP paddle method: (A) 50 rpm; (B) 100 rpm; (C) 150 rpm; (D) 200 rpm; ○, 1%; ▽, 2.5%; □, 5.0%; △, 10.0% diazepam.

1995). The dissolution rate of the interactive mixes decreased with increasing diazepam load and the rotational speed appeared to have little effect on the rate of dissolution. These types of effects were observed in previous studies, i.e., concentration-dependent dissolution was seen for griseofulvin (McGinity et al., 1985) and griseofulvin and oxazepam (Nilsson et al., 1988; Westerberg and Nystrom, 1993), and dissolution independent of agitation intensity occurred for griseofulvin in carriers of high water solubility (Nystrom and Westerberg, 1986; Westerberg et al., 1986). Previous studies have demonstrated pH-independent dissolution of diazepam between pH 5 and 7 (Sangchantra, 1995). The pH of the dissolution media in these experiments did not

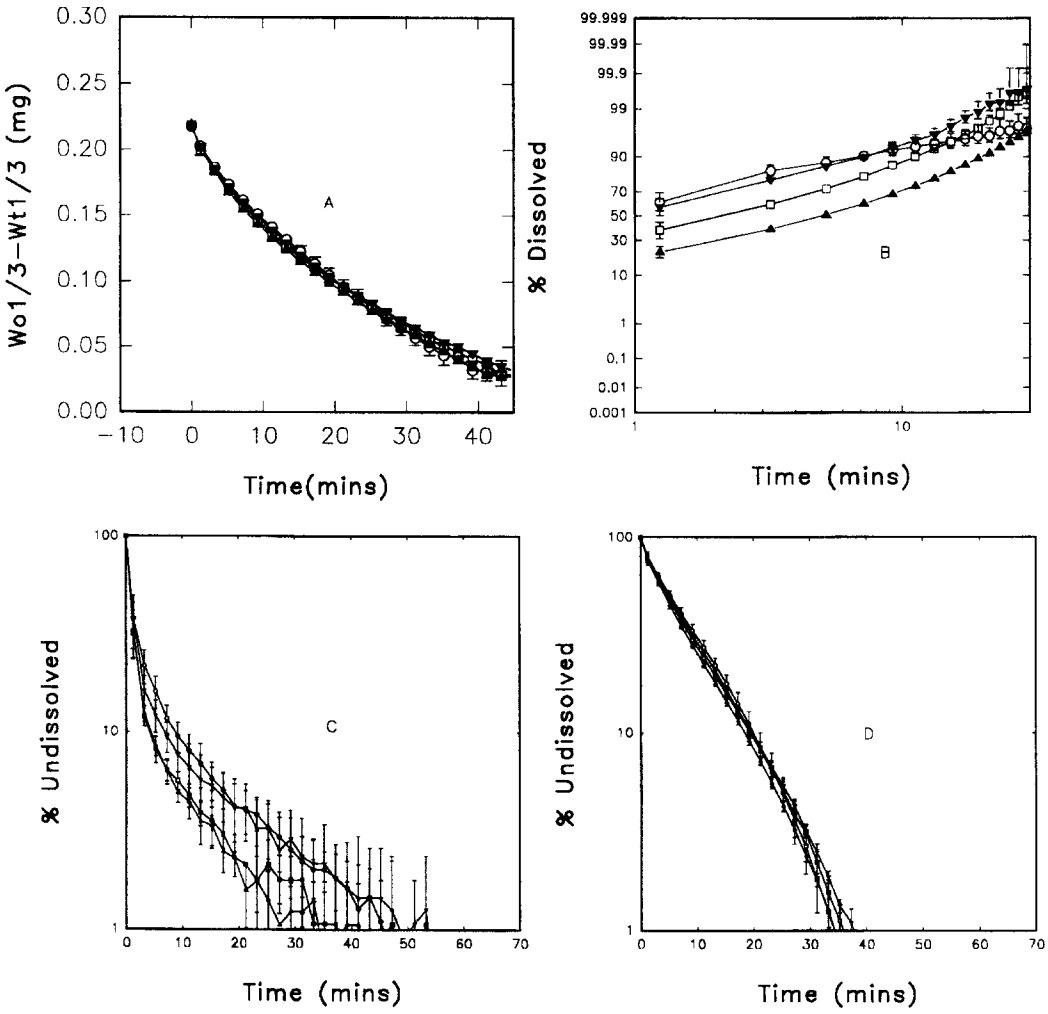

Fig. 2. Modelling of the dissolution profiles. (A) Hixson-Crowell Cubic Root Model for 10.0% diazepam-lactose interactive mixture at 50 (○), 100 (▽), 150 (□) and 200 rpm (△). (B) Wagner's log probability model for 1.0 (○), 2.5 (▽), 5.0 (□) and 10.0% (△) diazepam-lactose interactive mixtures at 100 rpm. (C) Mono-exponential model of percent undissolved versus time for 1.0% diazepam-lactose interactive mixtures at 50 (○), 100 (▽), 150 (□) and 200 rpm (△). (D) Mono-exponential model of percent undissolved versus time for 10.0% diazepam-lactose interactive mixtures at 50 (○), 100 (▽), 150 (□) and 200 rpm (△).

change significantly during the dissolution of the interactive mixtures and was not less than 6; pH variability therefore could not account for the concentration-dependent dissolution behaviour.

3.2. Modelling of dissolution data

In order to represent the dissolution profiles by a single parameter, e.g., a dissolution rate constant, attempts were made to fit the dissolution data to some conventional dissolution models including the Hixson-Crowell cube root law (Hixson and Crowell, 1931), Wagner's log probability model (Wagner, 1969) and the mono-exponential model of log of percent undissolved versus time (Wagner, 1969; Kitazawa et al., 1975; Kitazawa et al., 1977; El-Yazigi, 1981). The Hixson-Crowell cube root model did not linearize the dissolution data where sufficient data were available to enable the model to be tested and the non-linearity of the

fit is illustrated by the 10.0% diazepam interactive mixtures in Fig. 2A. It was not unexpected that this model did not fit the data since its derivation was based on the dissolution of spherical monodisperse particles. For the low concentration mixtures where dissolution occurred rapidly, the paucity of data did not allow adequate testing of the model. Wagner's log probability plots of percent dissolved versus time provided poor fits at high diazepam loadings but were generally satisfactory for the 1.0% interactive mixture (Fig. 2B). In general, the monoexponential treatment of the data provided reasonable linearity for the 5.0 and 10.0% interactive mixtures; however, for the lower diazepam concentrations, this model fitted the data for the initial rapid dissolution phase but did not provide an adequate fit for the entire dissolution and significant deviations from linearity were observed (Fig. 2C and D). The mono-exponential model has been shown to be theoretically valid only when the surface area available for dissolution decreased exponentially with dissolution time (Wagner, 1969). In practice, for multiparticulate systems which follow log normal distributions, mono-exponential models have been found to provide satisfactory linear fits once tablet disintegration has occurred (Wagner, 1969; Kitazawa et al., 1977; El-Yazigi, 1981) although, in the simulated dissolution of some theoretically calculated log normal particle distributions, deviations from linearity were observed (Wagner, 1969).

Since Wagner's log probability and the mono-exponential models were unsatisfactory in explaining the dissolution data of the diazepam interactive mixtures over the concentration range used in this study, a better understanding of the particulate behaviour during dissolution was required. An environmental SEM was utilized to observe the process of dissolution of diazepam interactive mixtures when small amounts of water were condensed onto the carrier surface. The carrier dissolved extremely rapidly releasing the adhered diazepam as both dispersed particles and aggregates into the surrounding medium. The SEMs of the interactive mixtures prior to dissolution (Fig. 3) showed that, for the low diazepam loadings, dispersion of the diazepam particles occurred on the carrier surface with only minor evidence of aggregation. For the higher concentration mixtures, aggregates of diazepam were clearly evident. The environmental SEM did not allow continued observation of the dispersion behaviour of the diazepam particles because the field of view was distorted during the dissolution of the lactose carrier. However, during the dissolution study of the interactive mixtures, aggregates were observed in the media especially for the 5.0 and 10.0% diazepam interactive mixtures. It was considered therefore that a two stage process involving dissolution from discrete particles and aggregates might occur. If this hypothesis were correct, the dissolution rate of the low concentration interactive mixtures could be predominantly determined by rapidly dissolving dispersed particles, whilst for the higher concentration mixtures the rate could be related to dissolution from aggregates formed during mixing or after removal from the carrier surface. In these extreme situations where dispersed or aggregated particles predominate, the use of a monoexponential model may allow reasonable fits over most of the data range; however, the estimated rate constant will represent dissolution from dispersed or aggregated particles and comparisons will be meaningless. In order to test the hypothesis that dissolution occurred from both dispersed and aggregated particles and to provide a better theoretical interpretion of the dissolution date, a bi-exponential model was proposed.

3.3. Bi-exponential modelling

The bi-exponential equation utilized to fit the dissolution data was:

$$C = C_d \exp(-t/k_d) + C_a \exp(-t/k_a)$$

where C is the concentration (%) of the undissolved diazepam particles at time t; C_d, C_a are the initial concentrations of particles in dispersed and aggregated forms at zero time, respectively; and k_d, k_a are the reciprocal dissolution rate constants (minutes) for the dispersed and aggregated particles, respectively. A computer software package Peakfit® (Jandel Scientific) for non-linear least squares curve fitting was used to model the dissolution data. Peakfit utilizes the Marquardt-Leven-

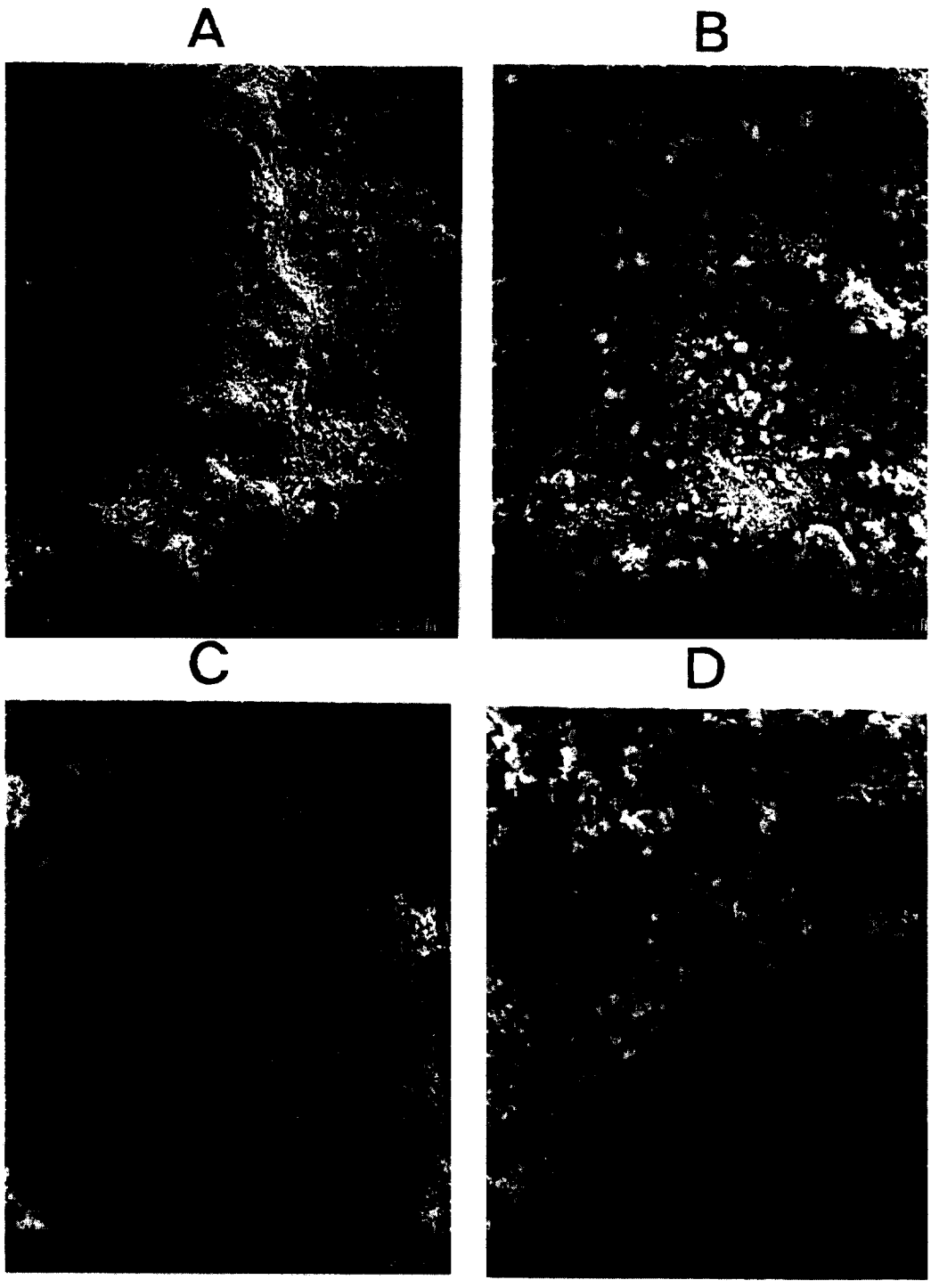

Fig. 3. Scanning electron micrographs of diazepam-lactose interactive mixtures: (A) 1.0% (× 350); (B) 1% (× 1.2k); (C) 10% (× 350); and (D) 10% (1.0k).

Table 1

Concentration[a] (%)	Rotational speed (rpm)	F-statistic	χ^2-statistic	r^2	$S_{\bar{x}}$[b]	η[c]	u[d]
1.0	50	581.9	6.30	0.993	0.724	1.855	5
	100	1186.5	2.75	0.996	0.428	1.703	9
	150	6400.3	0.24	1.000	0.173	2.704	8
	200	1799.0	0.77	0.999	0.331	2.364	7
2.5	50	6049.3	0.25	1.000	0.188	2.616	8
	100	2192.2	0.15	1.000	0.172	1.993	5
	150	6167.3	0.42	0.999	0.288	2.622	5
	200	46808.0	0.16	1.000	0.160	3.105	7
5.0	50	46808.0	0.16	1.000	0.010	2.039	7
	100	9821.0	0.07	1.000	0.222	1.871	5
	150	3365.5	0.39	0.999	0.321	#2.915	5
	200	2101.5	0.14	1.000	0.133	2.584	6
10.0	50	1142.4	11.40	0.997	0.975	#0.447	*4
	100	8683.0	1.44	1.000	0.334	#0.849	*5
	150	8857.2	1.33	1.000	0.320	#0.816	6
	200	7062.3	1.50	1.000	0.354	#0.957	6

[a]% of diazepam in interactive mixtures.
[b]Standard error of curve.
[c]Mean square successive difference analysis; $\alpha = 0.05$ for lower and upper percentage points: # is outside the critical limits.
[d]Runs test in which the u value is calculated for sample size $m = n_1 = n_2$, where n_1 and n_2 represent the number of values above and below the zero residual value, respectively; $\alpha = 0.05$ for lower and upper percentage points: * is at lower critical limit.

berg algorithm (Levenberg, 1944; Marquardt, 1963) to determine the absolute true minima for the sum of squared deviations, χ^2.

Initial fitting was via user manipulation to reduce the risk of landing in localised minima followed by optimization using the algorithm software. The main criteria which reflected the goodness of fit were the χ^2-value, which was always minimised; the r^2-value, the regression coefficient which was brought as close to one as possible; the standard deviation and confidence limits which were minimised for the parameters, and the magnitude of the f-value. These criteria for all mixtures are summarized in Table 1.

Data were truncated when the mean of the dependent variable was not significantly different from that of the final data point. A one-way repeated measures analysis of variance (15; Sigmastat®) was used to determine the appropriate data cut-off point and this co-incided with not more than 3% undissolved drug. The least squares non-linear regression assumes that all data points possess an equal variance. Since the residual variance was not homogenous, weightings of $1/Y$ were used (Boxenbaum et al., 1974). This procedure caused all terms to have a similar contribution to the weighted residual sum of squares.

Analysis using the runs test (Bennett and Franklin, 1967) showed that the residuals were randomly distributed for all fits (Table 1). However, a mean square successive differences analysis (Bennett and Franklin, 1967) agreed with the runs test except at the 10% loading where non-random residuals occurred (Table 1). This was not unexpected as the u-values calculated for the runs test were close to the critical limits for the 10% interactive mixtures. While the residuals at 10% were non-random, their magnitude was similar to all other fits. Given that the dissolution of the 10% interactive mixtures showed reasonable linearity for the mono-exponential equation in Fig. 2D, fitting of a single exponential was attempted; however residuals were non-random and greater than those for the bi-exponential model.

Estimates of the reciprocal rate constants (k_d and k_a) and the initial concentrations (C_d and C_a) were obtained during the non-linear least squares fitting. The plot of k_d and k_a against % concentration for all rotational speeds (Fig. 4) indicated that there were no major trends in k_d with the

diazepam concentration of the interactive mix and the rotational speed. However analysis of variance (Sigmastat®) did show a marginally significant concentration effect at the $P = 0.05$ level ($P = 0.04$). In general, the results were consistent with the dissolution of particles of similar size distributions over the concentration range and were likely to represent dissolution of primary particles. Rotational speed would have little effect on the primary particle size distributions and therefore not be expected to influence dissolution rate due to changing surface areas. However rotational speed might be expected theoretically to influence the hydrodynamics although previous studies have indicated that rotational speed did not influence the dissolution of interactive mixtures of griseofulvin with soluble lactose carriers (Nystrom and Westerberg, 1986; Westerberg et al., 1986). In contrast k_a showed marked concentration dependency (analysis of variance, $P < 0.001$). At 1% loadings the reciprocal rate constants were large and extremely variable, i.e., the mean and standard deviation of k_a across the four rotational speeds was 12.58 ± 3.07 min. The reciprocal rate constant k_a reached a minimum at 2.5% loading, indicating maximum rate of dissolution and slowly increased as the concentration increased to 10%. The variance of k_a between 2.5 and 10% was relatively low, i.e., 4.77 ± 0.60 and 8.59 ± 0.20 min respectively. This behaviour was characteristic of dissolution from different size distributions of aggregated particles. The wide variability in the 1% mixtures was unable to be explained but occurred consistently. Agitation speed did not significantly influence k_a except for the 1.0% mix where the rate constants were variable and not related to rotational speed.

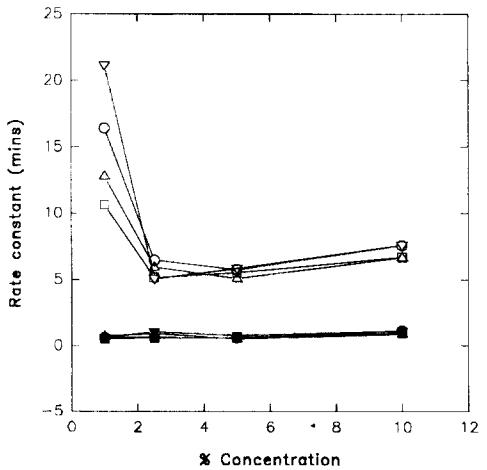

Fig. 4. Influence of diazepam concentration and rotational speed on the estimated rate constants, k_a (open) and k_d (closed): 50 (○,●); 100 (▽,▼), 150 (□,■) and 200 rpm (△,▲).

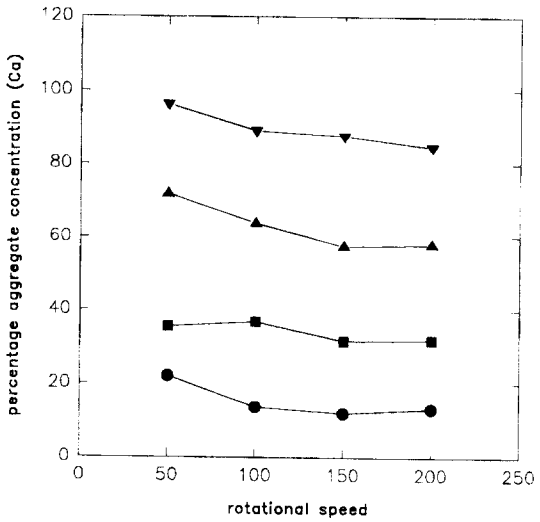

Fig. 5. Influence of diazepam concentration and rotational speed on the estimated initial concentration of the aggregated particles: 1.0 (○); 2.5 (▽); 5.0 (□); and 10.0% (△).

The plots of C_a versus rotational speed (Fig. 5) showed clearly that increasing diazepam concentration of the interactive mixtures increased the initial concentration of the aggregated particles (analysis of variance, $P < 0.001$). For example, the C_a values ranged from approximately 16 to 98% over the concentration range of 1–10%. There were also significant differences in magnitude of C_a across the four rotational speeds with the initial aggregate concentration decreasing with increasing rotational. This result is consistent with the expected effect of agitation on aggregate formation.

The overall rate of dissolution will be a function not only of the reciprocal rate constants k_d and k_a but also of the magnitude of the initial concentrations of the dispersed and aggregated particles C_d and C_a.

3.4. Particle size analysis of the interactive mixtures during dissolution

To verify the presence of dispersed and aggregated particles of diazepam during dissolution, repeated particle size distributions of the dissolving interactive mixture were determined using laser diffraction in distilled water over a 5-min time interval. The laser diffraction methodology chosen used the full solution of the Mie theory to estimate particle size in contrast to earlier apparatus which relied on the Fraunhofer theory and its inherent approximations. Laser diffraction also allowed repeated distributions to be determined at short time intervals. Reliable distributions were obtained for the 2.5, 5.0 and 10.0% mixtures; the obscuration of the 1.0% mixture was too low to produce meaningful distributions. A typical nest of log-probability distributions is shown in Fig. 6A for the 5.0% interactive mixture. The distributions obtained at early dissolution times depicted a wide particle size range from about 3 to 400 μm. Regions were observed corresponding to distributions which were consistent with the lactose carrier, probable aggregates in the range of 30–120 μm and dispersed primary diazepam particles. As dissolution proceeded a shift to a distinct bi-modal distribution occurred with the dissolution of the lactose carrier; this distribution was characteristic of aggregated and dispersed particles. In addition a marked shift to smaller primary particle size distributions was observed with increasing time indicating probable dissolution of the diazepam particles. This observation was consistent with dissolution profiles and modelling which indicated rapid dissolution from the dispersed particles in conjunction with a slower dissolution phase from the aggregated particles. The distributions of the aggregates stabilized after about 1–2 min. A distribution shift indicative of slightly increasing geometric mean diameters occurred with increasing diazepam concentration of the interactive mixture (Fig. 6B) and corresponded well with the rank order of the aggregate reciprocal dissolution rate constants shown in Fig. 4. The study of the particle size distribution of the interactive mixtures during dissolution reinforced the mechanism of dissolution observed in the modelling studies by providing verification of dispersed and aggregated particles. However, limitations to the methodology existed. The dissolution apparatus and conditions for the laser diffraction study were markedly different from the USP paddle method, e.g., apparatus design, mechanism and rate of stirring, and volume of dissolution medium. In addition, the amount of the interactive mixtures used in the particle size determinations was selected to optimize the obscuration and was greater than that used during the dissolution

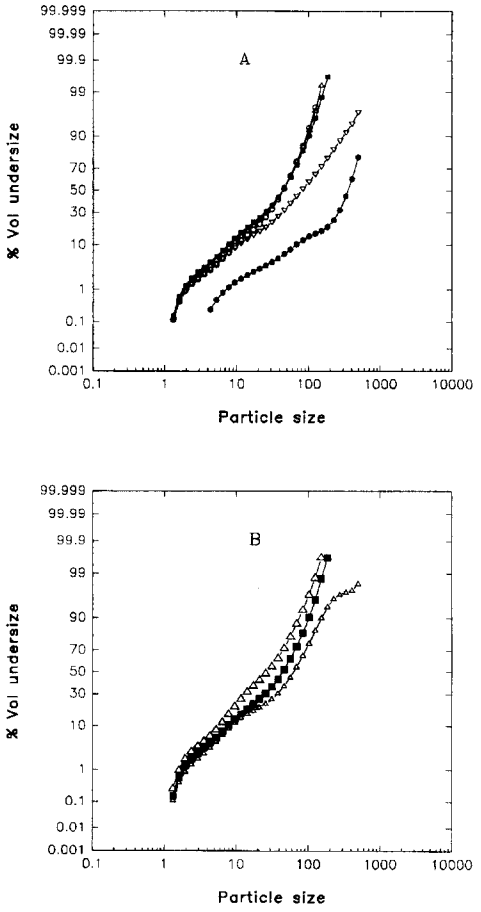

Fig. 6. Log probability particle size distributions of the diazepam interactive mixture during dissolution in the chamber of a Malvern Sizer x at room temperature. (A) 5% mixture at 10 (●), 39 (▽), 60 (■), 106 (△) and 194 s (○). (B) 2.5 (●), 5.0 (■) and 10.0% (△) mixes after dissolution of the lactose carrier.

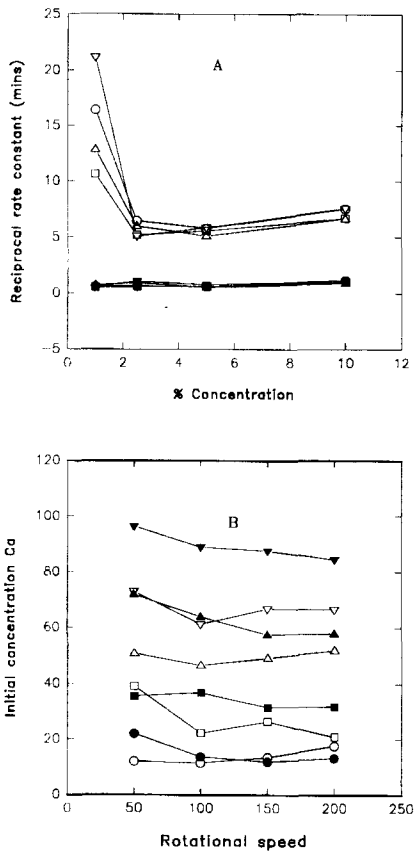

Fig. 7. Influence of diazepam concentration and rotational speed on the estimated values of the rate constants (k_a and k_d) and initial concentration of aggregates (C_a) in 0.02% polysorbate 80 at 37°C. (A) 50 (○,●); 100 (▽,▼); 150 (□,■) and 200 rpm (△,▲) (k_a open symbols; k_d closed symbols). (B) 1.0 (○,●); 2.5 (▽,▼); 5.0 (□,■) and 10.0% (△,▲) polysorbate 80 (open), water (closed).

resulting in non-sink conditions. Whether similar multi-modal distributions might have occurred in the dissolution apparatus used in this study was unknown; however, the evidence clearly identified that aggregation occurred and this was consistent with the modelling study.

3.5. Dissolution in the presence of surfactant

The dissolution of the diazepam interactive mixtures was undertaken in a 0.02% polysorbate 80 medium utilizing the same concentrations and rotational speeds used previously. The purpose of this experiment was to determine if the surfactant influenced the rate of dissolution by affecting the aggregation of the diazepam particles. In general, the presence of surfactant increased the dissolution rate of diazepam in the interactive mixtures; the effect was particularly evident at the higher diazepam loadings. For example, the percent dissolved at 10 min was increased from about 70% in water to 90% in polysorbate 80 solution for the 10% diazepam interactive mixture. The biexponential model fitted the dissolution profiles and yielded the reciprocal rate constants for dissolution from the dispersed and aggregated particles, k_d and k_a. As expected, no significant differences were seen for the reciprocal rate constants of the dispersed particles across all concentrations and between the media (analysis of variance; $P = 0.631$ and 0.270, respectively). However, the reciprocal rate constants of the aggregated particles appeared slightly lower than those in water especially for the 10% mixture (Fig. 7A). Analysis of variance showed no significant difference between the media ($P = 0.913$) but a significant media-concentration interaction ($P = 0.018$) supported the observed reduced reciprocal rate constants at the higher concentrations. The C_a values were reduced particularly at the higher concentrations (analysis of variance; $P < 0.001$) indicating that the presence of surfactant increased the dispersion of the diazepam particles (Fig. 7B). The increased rates of dissolution observed in the polysorbate 80 medium were related to the lower initial concentration and reciprocal rate constant of aggregated particles.

Laser diffraction particle size analyses of the 5.0 and 10.0% diazepam interactive mixtures in 0.02% polysorbate 80 showed similar trends and distributions to those in distilled water with initial broad distributions which reduced to bimodal distributions upon dissolution of the carrier. It was not possible to differentiate small aggregate size differences which led to the slightly lower reciprocal rate constants for the dissolution of aggregates observed previously in water and polysorbate 80 solution.

4. Conclusions

The modelling of a bi-exponential equation to the dissolution data, the verification of aggregates formed during dissolution using repeated laser diffraction particle size measurements and the dissolution behaviour of the interactive system in surfactant provided strong evidence to support the hypothesis that dissolution of diazepam in lactose interactive mixtures occurred from both dispersed and aggregated particles. The dissolution rate dependency on diazepam concentration in this interactive system was adequately explained by the hypothesis. Rotational speed did not influence the reciprocal rate constants for the dispersed and aggregated particles except at 1.0% where there was high variability; however, the initial concentration of aggregates displayed rotational speed dependency with higher speeds promoting the dispersion of the aggregates. The conclusions drawn in this paper were limited to diazepam in a lactose interactive mixture. Studies are being undertaken to test if the dissolution behaviour proposed in this study can be extended to other soluble and partially soluble carriers.

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