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Influence of the Carrier on the Intrinsic Rate of Dissolution of Diazepam in Interactive Mixtures

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Abstract

The use of interactive mixtures of drugs adhering to the surface of carriers can promote drug dissolution. The mechanism of dissolution of such mixtures has been studied using the rotating-disc method under conditions eliminating secondary influences such as carrier surface characteristics and drug particle aggregation. Levich plots were used to characterize the dissolution behaviour.

Diazepam-compactrol interactive mixtures had initial dissolution rates similar to that of pure diazepam owing to the deposition of a continuous layer of diazepam on the disc surface from the interactive mixture. Linear Levich plots were produced at all drug loadings and the presence of compactrol in the disc slightly enhanced dissolution rates. Dissolution rates for diazepam-emcompress interactive mixtures were lower than those of pure diazepam. The Levich plots for these systems were non-linear with increasing negative curvature as the diazepam loading decreased. The rate of dissolution of diazepam in the lactose interactive mixture was markedly higher than that of pure diazepam, but high diazepam loadings in the lactose mixtures inhibited diazepam dissolution. Rapid carrier dissolution caused surface retraction of the disc, enhancing the dissolution rate. The Levich plots showed an upward curvature due to turbulence.

Linear Levich plots for diazepam and other benzodiazepines and for diazepam-compactrol interactive mixtures showed that their dissolution in pH 5 phosphate buffer was diffusion-controlled. The Levich plots for diazepam-emcompress interactive mixtures were indicative of some interfacial control during dissolution, but the hypothesis of common ion precipitation of dissolved carrier, calcium phosphate, onto the disc surface did not fully explain this effect.

Interactive mixtures contain drugs that adhere to the surface of carriers (Hersey 1975). Mechanisms of adhesion include electrical interaction as a result of contact potential and coulombic forces, capillary interaction as a result of the development of liquid bridges between drug and carrier surface, molecular interaction, and solid bridging (Rumpf 1961; Krupp 1967; Zimon 1982). The dissolution of these systems has been studied in recent years because of their potential to increase the rate of dissolution of drugs. (McGinity et al 1985; Nystrom & Westerberg 1986; Westerberg et al 1986; de Villiers & van der Waat 1989; Ibrahim et al 1988). Several studies have examined the influence of carrier properties on the rate of dissolution of adhered drug. In general, soluble carriers were shown to increase the dissolution rate of grizeofulvin, oxazepam and frusemide because these drugs were presented as fine dispersed particles (Westerberg et al 1986; de Villiers & van der Watt 1989; Ibrahim et al 1988). More recently, concentration–dependent dissolution has been attributed to drug agglomeration at high drug loadings (Nystrom & Westerberg 1986). The dissolution of interactive systems containing less soluble carriers was generally slower than those containing soluble carriers, behaviour which has been interpreted by considering that the drug particles were attached to the carrier during dissolution (Westerberg et al 1986). The major objective of this study was to determine the intrinsic effect of the carrier on the dissolution behaviour of interactive mixtures by eliminating secondary influences such as carrier surface characteristics and drug particle aggregation. Intrinsic dissolution methodology utilizing the Levich equation was applied to the dissolution of model drugs and interactive mixtures to confirm whether dissolution was under diffusion or interfacial control (Abdou 1989). Specifically, the purpose of this research was to use the rotating-disc apparatus to study the influence of carrier type and drug loading on the dissolution of diazepam from compressed discs of the interactive mixtures.

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Materials and Methods

Materials

Micronized diazepam, oxazepam, nitrazepam and flunitrazepam (Alphapharm, Australia) with volume mean diameters of 4·8 μm, 3·0 μm, 3·9 μm and 4·6 μm, respectively, were used as adherent drugs in the interactive mixtures. Micronization was achieved by fluid-energy milling (Chrispro Jetmill, model 75P, UK, with compressed air at 5.8 atmospheres and 12.7 L s^{-1}).

Carriers were calcium sulphate dihydrate (compactrol; Mendell, USA), dibasic calcium phosphate (emcompress; Mendell, USA) and starch-lactose-povidone granules prepared from maize starch (Goodman Fielder Mill, Australia), lactose (Wyndale, New Zealand) and povidone (Kollidon 25; BASF, Germany). Emcompress was first compressed and comminuted to give suitable particle fractions. Starch-lactose-povidone (30 : 60 : 10) granules were prepared by wet granulation using aqueous povidone solution (10% w/w; 22 mL/100 g powder). Carrier fractions, 250–355 μm, were obtained by sieve classification (Analysette 3, Fritish, West Germany).

Buffers at pH 1, 3, 5 and 7 were prepared as the dissolution media (USP XXII). Buffer components included hydrochloric

acid (BDH, Australia), citric acid monohydrate (Prolabo, France), potassium dihydrogen phosphate (May and Baker, Australia), anhydrous dibasic sodium phosphate (Mallinckrodt, France) and potassium chloride (Ajax, Australia). Benzoic acid (Mallinckrodt; France) was used to validate the rotating-disc method. All chemicals were analytical grade. Before use all dissolution media were degassed by vacuum filtration (0·45-μm membrane; Millipore Corporation, Ireland).

Preparation of interactive mixtures

Interactive mixtures were prepared by placing the micronized benzodiazepines between two layers of carrier in a glass vial and shaking vigorously by hand for 3 min. This method was chosen from a number of mixing procedures including mechanical tumbling and was found to produce good quality interactive mixtures. The procedure did not result in carrier comminution, i.e. the particle size distributions before and after mixing were almost identical. The interactive mixtures were examined by scanning electron microscopy using an environmental SEM (Electroscan Corporation, model E3, USA). Homogeneity was determined by spectrophotometric assay after removal of twenty 100-mg samples and extracting the benzodiazepine into absolute alcohol (CSR, Australia). Means of all mixtures were not more than 0.2% from the target values and CV values were less than 1.0%, indicating that mixing was satisfactory (Crooks & Ho 1976).

Adhesion profile

A specially designed aluminium centrifuge cell consisting of a sample and collection compartment separated by a replaceable screen (150 μm) was held in position within the centrifuge rotor so that the screen was normal to the axis of rotation (Kulvanich & Stewart 1987). The percentage of drug retained on the carrier was determined after centrifuging in a microprocessor-controlled, high-speed centrifuge (International Equipment Company, USA; B-20A with fixed rotor type 870). The temperature in the centrifuge chamber was 20°C and the interactive mix sample size was accurately known (40–70 mg). Adhesion profiles (i.e. percentage retained plotted against centrifuge speed) were determined by centrifuging eight replicates at 4000, 8000, 12 000, 16·000 and 20 000 rev min^{-1} for 30 s.

Spectrophotometric analysis

Spectrophotometric analysis was performed using a scanning ultraviolet-visible spectrophotometer (CE6700; Cecil Instrument Company, UK). Beers Law calibration plots were obtained in absolute alcohol for the homogeneity studies (diazepam, 315 nm, 2–10 mg%; oxazepam, 317 nm, 2–10 mg%; nitrazepam, 309 nm, 0·5–3·0 mg% and flunitrazepam, 309 nm, 0·5–2·5 mg%) and in the dissolution medium, phosphate buffer pH 5, for the dissolution studies (diazepam, 230·5 nm, 0·08–1·60 mg%; oxazepam, 230.5 nm, 0·1–1·0 mg%; nitrazepam, 217·5 nm, 0·15–1·50 mg% and flunitrazepam, 218·5 nm, 0·2–2·0 mg%). At least five 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. The presence of carriers did not influence the absorbance values. The calibration in the dissolution medium was determined at 37°C in the automated dissolution apparatus.

Determination of solubilities

The solubilities of individual benzodiazepines were determined in triplicate by addition of excess drug to phosphate buffer (pH 5; 10 mL) 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 buffer, pH 5 (1 : 10 for diazepam, oxazepam and nitrazepam and 1 : 5 for flunitrazepam) and spectrophotometric analysis.

Dissolution studies

The automated dissolution system consisted of the dissolution apparatus (Erweka, DT6, Germany), auto-controlled multichannel peristaltic pump (Watson Marlow 503V/RL; UK), an ultraviolet-visible spectrophotometer with 1- and 10-mm flow cells (CE6700; Cecil Instruments, UK) and 386 PC using Erweka software (Auspac, Australia). The Woods rotating-disc apparatus was used (Wood et al 1965). Half-inch discs were prepared in the compression die using a hydraulic press (Carver Laboratory Press, USA). Compression was at 17 800–44 500 N for 3 min. Disc thickness was approximately 2 mm. The rotating-disc assembly was removed from the press and connected to the stirring-controlled platform of the dissolution apparatus. Six replicates were run simultaneously in 300 mL dissolution medium. Four rotation speeds were used (25, 50, 100 and 200 rev min^{-1}). Dissolved drug was measured at 2-min intervals.

Results and Discussion

Validation of the rotating-disc method

Diazepam was compressed into discs using pure diazepam granules (< 710 μm) prepared by preliminary compression to minimize capping. Compression at 17 500 N produced discs with high surface roughness; some capping was observed at 35 600 and 44 500 N. Discs compressed at 26 700 N had a smooth surface without any capping. Discs prepared at all compression pressures could be used in intrinsic dissolution-rate determinations. The influence of pressure and media pH on the intrinsic dissolution rate constants (Table 1) showed that dissolution was rapid at pH 1 and 3 because the saturation solubility was increased by enhanced ionization of diazepam at pH values below its pKa of 3·3. Analysis of these dissolution media by high performance liquid chromatography revealed diazepam degradation by hydrolytic cleavage of the azomethine, producing an open-ring intermediate, 2-glycyl(methyl)amino-5-chlorobenzophenone, which degraded more slowly to 5-chloro-2-methylaminobenzophenone (Nakano et al 1979; Sangchantra 1995). At pH 5 and 7 the dissolution rate constants were not significantly different (non-

Table 1. Influence of compression and medium pH on the intrinsic dissolution rate constants (mg cm^{-2} s^{-1} × 10^5) for diazepam at 37°C.

Compression (N)	Intrinsic dissolution rate constant at pH:			
	1	3	5	7
17800	1940 ± 29	31·59 ± 0·30	8·99 ± 0·92	7·45 ± 0·08
26700	1934 ± 12	31·58 ± 0·29	8·04 ± 0·17	7·77 ± 0·26
35600	2046 ± 58	32·36 ± 0·31	8·82 ± 1·54	7·91 ± 0·31
44500	2048 ± 58	33·04 ± 0·11	8·48 ± 0·78	8·14 ± 0·10

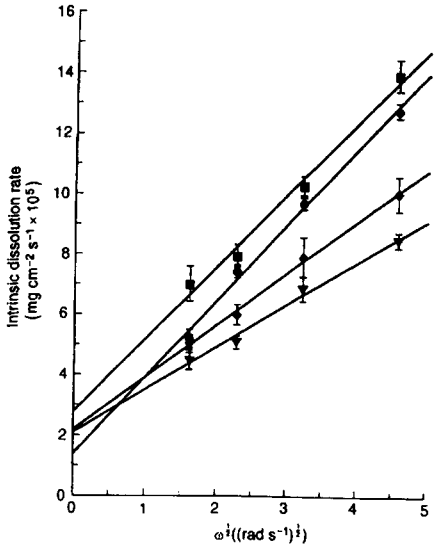

FIG. 1. Levich plot of the intrinsic dissolution rate constant against the square root of angular velocity for diazepam (●), oxazepam (▼), nitrazepam (■) and flunitrazepam (◆) in phosphate buffer (pH 5, μ = 0.5) at 37°C.

parametric Kruskal-Wallis test with one-way analysis of variance (Glantz 1992)) and were smaller than those at pH 1 and 3, being about 0·25 and 0·004 of these constants, respectively. There was, in addition, a significant difference ($P < 0.05$) between intrinsic dissolution rates at different pressures at pH 1 and 3, whereas no significant differences were found between the rates at different pressures at pH 5 and 7. For further experiments described in this study the dissolution medium was phosphate buffer at pH 5 and the discs were compressed using 26 700 N.

To validate the rotating-disc apparatus, dissolution of benzoic acid discs was undertaken in 0·1 M hydrochloric acid. Intrinsic dissolution profiles of amount of benzoic acid dissolved against time were linear and intrinsic dissolution rate constants were determined. The plot of intrinsic dissolution rate constant against the square root of the angular velocity was linear, with the intercept not significantly different from zero. The diffusion coefficient, determined from the slope ($0{\cdot}62\ D^{2/3}\gamma^{-1/6}C_S$, where D, g and C_S are the diffusion coefficient, kinematic viscosity and solubility, respectively) was $7{\cdot}3 \times 10^{-5}$ cm^2 s^{-1} at 37°C, which was similar to published experimental and theoretically calculated values for benzoic acid (Mooney et al 1981).

Intrinsic dissolution of benzodiazepines

The intrinsic dissolution rate constants for diazepam, oxazepam, nitrazepam and flunitrazepam over 25–200 rev min^{-1} were determined from the linear dissolution profiles of amount dissolved against time. The intrinsic dissolution behaviour of the benzodiazepines studied is summarized in the Levich plot (Fig. 1). The plots did not show any significant deviations from linearity over the range of speeds of rotation studied but all drugs displayed significant non-zero intercepts. The linear behaviour of the four benzodiazepines over the 25–200 rev min^{-1} range suggested that the dissolution process was diffusion-controlled with the rate-determining step being mass transfer through the layer of unstirred dissolution media located next to the disc surface. Non-zero intercepts have been reported for indomethacin (Mooney et al 1981). Those authors suggested that the non-zero intercept could be associated with experimental error or an additional mechanism at the surface of the disc as a result of the diffusivities of hydrogen and hydroxide ions being rotational-speed-dependent. One possible cause of the non-zero intercept in this study could be the changing surface properties of the disc with resultant variability in surface area, diffusion-layer thickness and possible turbulence. Although pitting was observed on the disc after the dissolution experiment, the cause of this was not investigated further in this study.

The solubilities of diazepam, oxazepam, nitrazepam and flunitrazepam in the dissolution medium (phosphate buffer, pH 5) were $45{\cdot}9 \pm 0{\cdot}4$, $29{\cdot}5 \pm 0{\cdot}7$, $47{\cdot}6 \pm 0{\cdot}3$ and $31{\cdot}5 \pm 0{\cdot}4$ μg mL^{-1}, respectively. The equation of the slope of the Levich plot depends on the drug's saturation concentration; the slopes in Fig. 1 correlated well with the calculated solubility of the four drugs. The diffusion coefficients of diazepam, oxazepam, nitrazepam and flunitrazepam were calculated as 4·54, 3·68, 3·96 and $4{\cdot}52 \times 10^{-6}$ cm^2 s^{-1}, respectively.

The dissolution of compressed discs of the interactive mixtures

Dissolution of interactive mixtures of micronized diazepam with compactrol, emcompress or starch-lactose-povidone granules was studied using the rotating-disc method for speeds of rotation between 25 and 200 rev min^{-1} and for diazepam concentrations between 1·0 and 15·0%. The degree of adhesion of the compactrol and starch-lactose-povidine interactive mixtures was determined by the centrifuge method (Kulvanich & Stewart 1987) and adhesion profiles revealed strong adhesion of the diazepam to the carriers; for example, in all mixtures the amount of diazepam retained on the carrier at 20 000 rev min^{-1} was greater than 95%. In general, as the concentration of drug in the interactive mixture increased, the adhesion decreased slightly. Examination of the mixtures by scanning electron microscopy revealed the formation of an interactive system with diazepam adhering to the carrier surface (Fig. 2). The SEMs at low and high drug loadings showed some aggregate formation on the surface especially for higher diazepam loading of the compactrol and emcompress mixtures. There was evidence of some detached drug in the SEMs of the emcompress mixtures.

The dissolution profiles of diazepam-compactrol interactive mixtures were determined over 60 min and showed a linear increase in dissolved diazepam followed by a sharp negative deviation from linearity (Fig. 3). The dissolution rate of diazepam in the interactive mixtures increased with speed of rotation, behaviour consistent with the diffusion-controlled mechanism of dissolution observed for the pure drug. The initial release rate of diazepam at each speed of rotation over the linear portion of the profile was similar to that of pure diazepam.

The compression of an interactive mixture with drug particles adhering uniformly to the carrier surface should, theoretically, result in a disc with a surface layer of pure diazepam, the thickness being dependent on drug loading. Dissolution from the compressed discs of the interactive mixtures should increase linearly until the surface diazepam layer is depleted, exposing patches of carrier and effectively reducing diazepam surface area. The results obtained (Fig. 3) support this theory

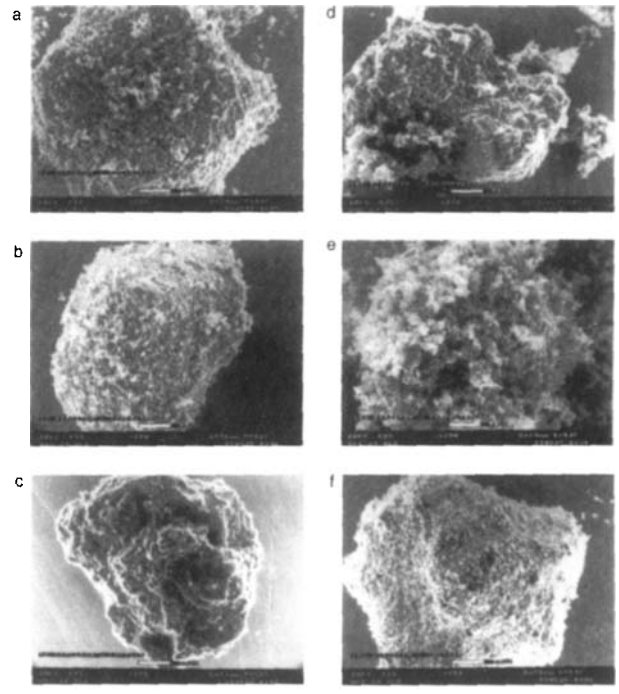

FIG. 2. Scanning electron micrographs of interactive mixtures containing 1·0 and 10·0% micronized diazepam on emcompress, compactrol and starch-lactose-povidone carriers. a, b and c represent 1% diazepam and d, e and f represent 10% diazepam on emcompress, compactrol and starch-lactose-povidone carriers, respectively.

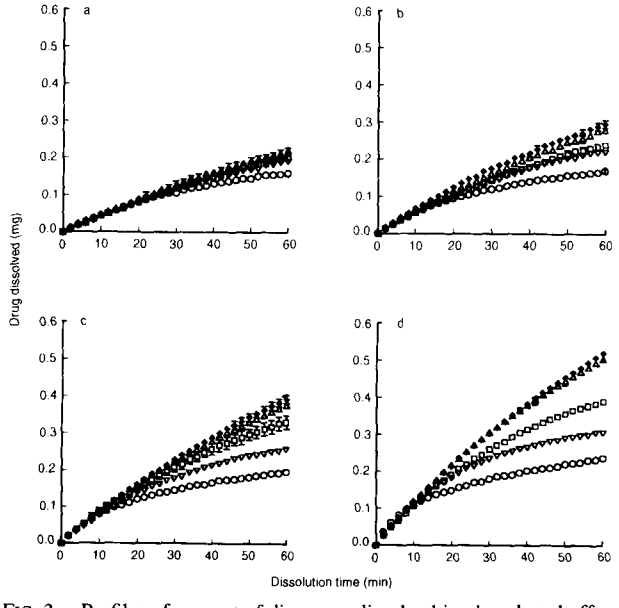

FIG. 3. Profiles of amount of diazepam dissolved in phosphate buffer (pH 5, μ = 0.5, 37°C) against time for interactive mixtures containing 1·0 (○), 2·5 (▽), 5·0 (□) and 15% (△) of diazepam on compactrol. The dissolution of pure diazepam (◆) is also shown. Each point is the average of six replicate measurements. Paddle speeds of 25 (a), 50 (b), 100 (c) and 200 (d) rev min^{-1} are shown.

with the negative deviations from the dissolution profile of pure diazepam being related to diazepam load in the mixtures. While the rank order of the negative deviations followed the increased diazepam load, the point at which the deviations occurred was not quantitatively related to load. For example, at 200 rev min^{-1}, deviations from linearity at 1% load occurred at approximately 0·1 mg of diazepam dissolved whereas at 10% load the deviations occurred at about 0.35 mg diazepam dissolved rather than at the theoretically expected 1.0 mg. The complexity of the interactive mixture with non-uniform surface coverage and aggregate formation on the surface at high concentration and its behaviour during compression, including possible interactive unit segregation, will make quantitative predictions difficult. In addition, partial dissolution of the calcium sulphate carrier in the disc might expose underlying pockets of diazepam to the dissolution medium, inflating the dissolution of diazepam in the low concentration mixtures.

Using intrinsic dissolution rates from the initial linear profiles in Fig. 3, Levich plots of intrinsic dissolution rates against square roots of speed of rotation were constructed (Fig. 4). The intrinsic dissolution rate of the 1·0% mix at 200 rev min^{-1} was not included because of the unreliable estimation of slope from the three data points on the linear portion of the profile. The dissolution behaviour of the compressed interactive mixtures over the linear portion of the profile was similar to that of pure diazepam, i.e. the Levich plots for the mixes showed no significant deviation from linearity and the slopes of the Levich plots for the interactive mixtures and pure diazepam were not significantly different. For pure diazepam the dissolution mechanism was diffusion-controlled. Non-zero intercepts were obtained for the interactive mixtures also. Although examination of the profiles in Fig. 3 showed little difference between the dissolution behaviour of the interactive mixtures and pure diazepam, statistical analysis of the data in the Levich plot revealed significant differences between the intrinsic dissolution rate of the mixtures and pure diazepam at each speed of rotation (Kruskal-Wallis non parametric method with one-way analysis of variance; $P = 0{\cdot}05$). In general, the intrinsic rate constants for the interactive mixtures were higher than for pure diazepam, indicating that the carrier enhanced the dissolution rate. Given that the mechanism appeared to be diffusion-con-

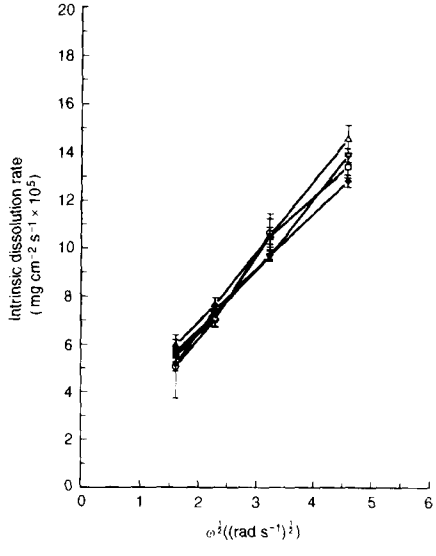

FIG. 4. Levich plot of the intrinsic dissolution rate constant against the square root of angular velocity for interactive mixtures containing 1·0 (○), 2·5 (▽), 5·0 (□) and 15·0% (△) diazepam on compactrol and for pure diazepam (◆) in phosphate buffer (pH 5, μ = 0·5) at 37°C.

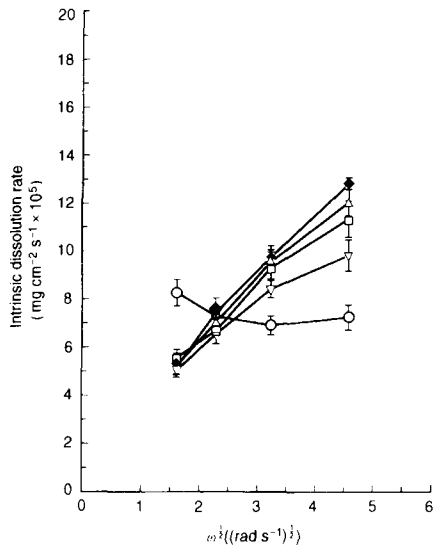

FIG. 5. Levich plot of the intrinsic dissolution rate constant against the square root of angular velocity for interactive mixtures containing 1·0 (○), 2·5 (▽), 5·0 (□) and 15·0% (△) diazepam on emcompress and for pure diazepam (◆) in phosphate buffer (pH 5, μ = 0·5) at 37°C.

trolled, the presence of compactrol must, in some way, change the properties of the diffusion layer or the effective surface area of the disc. It was possible that some dissolution of compactrol might have occurred in the initial stages of the dissolution of the interactive mixture disc because of the non-uniform surface coverage of the drug. Suppression of the saturation solubility of diazepam or increased diffusion-layer viscosity owing to dissolved compactrol were unlikely as this would have contributed to reduced intrinsic dissolution rate constants. Dissolution of compactrol might have exposed more diazepam in the internal layers of the disc and effectively increased the disc surface area.

The dissolution profiles of diazepam-emcompress interactive mixtures were determined for drug loadings between 1·0 and 15·0%. All profiles showed an initial linear increase in diazepam dissolved followed by negative deviations from linearity which were consistent with the drug load. Levich plots were constructed using the initial linear portion of the profile to determine the intrinsic dissolution rate constants (Fig. 5). The Levich plots for all interactive mixtures showed significant deviations from linearity. The deviations from linearity were more pronounced at high speeds of rotation and at lower drug concentrations. All mixtures showed lower intrinsic dissolution rate constants than did pure diazepam at a specific speed of rotation. The 1·0% mixture had a higher intrinsic dissolution rate constant at 25 rev min^{-1} and there was little variation of dissolution rate constant between 50 and 200 rev min^{-1}.

The behaviour of this interactive system contrasted with that of the diazepam-compactrol system which was similar to that of pure diazepam. The characteristics of the Levich plot strongly suggested that the dissolution was not totally diffusion-controlled and that some interfacial control was involved in drug dissolution. Examination of the SEMs in Fig. 2 showed that, whereas diazepam aggregation was observed in the interactive mixtures with emcompress, higher diazepam loads provided better surface coverage and, therefore, a more uniform diazepam layer on the disc surface than at lower drug loads. A reduction in effective surface area of diazepam in the disc might have occurred for the low diazepam concentration mixtures; such reductions should, however, have resulted in linear Levich plots with reduced slopes and this is clearly not so.

Another factor that could influence the mechanism of release of diazepam from the discs was the possible interaction of emcompress with the phosphate buffer. Emcompress, which is an insoluble calcium hydrogen phosphate, will ionize at the disc surface as follows:

$$CaHPO_4 \rightleftharpoons Ca^{2+} + HPO_4^{2-}$$

The calcium and hydrogen phosphate ion concentrations will be determined by the solubility product of emcompress. Diffusion of hydrogen phosphate ion in the buffer through the diffusion layer to the disc surface would reduce the solubility of the calcium hydrogen phosphate, resulting in precipitation of the dissolved carrier on to the disc surface, overlaying the diazepam layer and causing an effective reduction in disc surface area. Increased stirring speed would enhance this effect by reducing the thickness of the diffusional layer.

To test this hypothesis, the intrinsic dissolution of the same 1% diazepam-emcompress interactive mixtures was studied in water. The comparative dissolution behaviour in water and phosphate buffer is shown in Fig. 6. Dissolution rate constants increased in water at the higher speeds of rotation, giving some credence to the hypothesis, but a return to the diffusion-controlled behaviour of diazepam did not occur, suggesting that other mechanisms might also be influencing the interfacial activity. It was unlikely that pH effects contributed to the rate differences because the pH of the distilled water did not decrease below 6 and pH-independent dissolution was known to occur between pH 5 and 7 (Sangchantra 1995).

The dissolution profiles of diazepam in diazepam-starch-lactose-povidone (1·0-15·0%) were determined over 25–200 rev min^{-1}. The profiles of amount dissolved (mg) against time

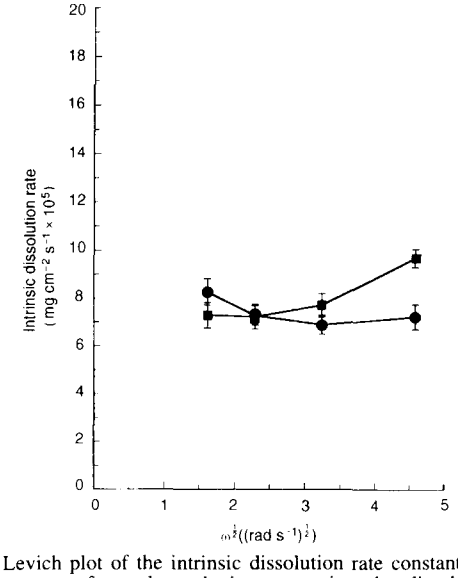

FIG. 6. Levich plot of the intrinsic dissolution rate constant against the square root of angular velocity comparing the dissolution of diazepam (1%)-emcompress interactive mixtures in phosphate buffer (●, pH 5, μ = 0·5) and distilled water (■) at 37°C.

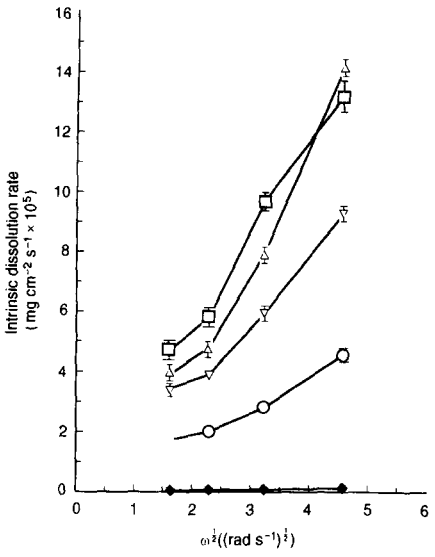

FIG. 7. Levich plot of the intrinsic dissolution rate constant against the square root of angular velocity for interactive mixtures containing 1·0 (○), 2·5 (▽), 5·0 (□) and 15% (△) diazepam and starch-lactose-povidone granules and for pure diazepam (◆) in phosphate buffer (pH 5, $\mu = 0{\cdot}5$) at 37°C.

were linear until the disc collapsed and showed rapid release of diazepam, i.e. the rates were about 100 times greater than those of the compactrol and emcompress interactive mixtures. Dissolution rate also increased with speed of rotation.

One important observation was a short lag-period, between 0 and 2 min, in the dissolution profiles. The lag-period was obvious at low speeds of rotation and high drug concentrations. For 1·0 and 2·5% diazepam, the lag period was found at 25 rev min^{-1} only, and for 5·0 and 15·0% diazepam, was observed up to 100 rev min^{-1}. This lag period was probably caused by slow wetting of the compressed disc owing to the hydrophobic surface coverage by micronized diazepam. At high drug-concentrations, the quantity of diazepam occupying the disc surface increased and the lag-time was more obvious as the initial surface coating dissolved. Once the diazepam surface coating dissolved, increased dissolution was facilitated because of the high water-solubility of the lactose carrier. The surface of the disc was, therefore, not static but retreated into the rotating die.

Intrinsic dissolution rates were calculated from the profiles and Levich plots were constructed (Fig. 7). In contrast with the compactrol and emcompress interactive mixtures, the dissolution rates for the lactose-starch-povidone mixture were much greater than those of pure diazepam. The high dissolution rates were attributed to rapid dissolution of the water-soluble carrier enabling further penetration of the dissolution medium into the disc and causing retraction of the disc surface and the exposure of the inner diazepam layers to the dissolution medium. Positive deviations from linearity were observed in the Levich plots and this might have been caused by the turbulent flow around the disc surface after particle dissolution and surface retraction (Touitou & Donbrow 1981). Studies on the 1% mixtures at 25 rev min^{-1} demonstrated a linear surface retraction of about 1·4 mm over a 24-min dissolution period. The surfaces were markedly pitted, contributing to the turbulence effect.

The dissolution rate increased with diazepam load except for the 15% diazepam mixture; the rate for this was less than that for the 5% mixture. Such behaviour might have been associated with the increasing hydrophobicity of the disc surface with an increase in the poorly soluble diazepam and a decrease in soluble lactose.

The effect of carrier on the dissolution of interactive mixtures can be related to specific intrinsic effects of the carrier on the drug and to secondary effects related to drug surface distribution and particle aggregation. Many of the previous studies have focussed on the secondary effects to explain differences in dissolution behaviour. The use of intrinsic dissolution methodology in this study was informative and provided some insight into the dissolution behaviour of interactive mixtures by enabling quantification of the dissolution rate and mechanistic effects. The most significant findings of this study were the dissolution-rate increases associated with lactose interactive mixtures and the mechanistic change found in the emcompress mixtures. Rate increases were large for lactose interactive mixtures, behaviour which was not a consequence of any intrinsic carrier effect but was a consequence of the water-solubility of the carrier, the subsequent penetration of the dissolution medium into the disc and the resulting dissolution of diazepam from the interior layers. A clear mechanistic change from diffusion to interfacial control was observed for the emcompress interactive mixture. The common-ion effect of hydrogen phosphate might be partially responsible but did not account for all of the observed deviation from linearity in the Levich plot. This mechanistic effect does not seem to be an artefact caused by surface area effects and might contribute to reduced dissolution in these types of system. The relative importance of this intrinsic effect in formulations will depend on the manner in which drug and carrier interact during dissolution processes.

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