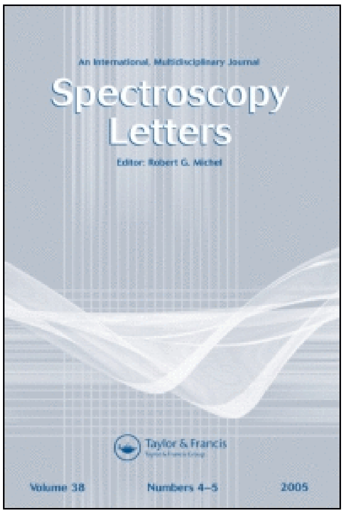

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A TURBIDITY STUDY OF THE RATE OF DISSOLUTION OF ZINC-MONOGLYCEROLATE IN AQUEOUS SOLUTION

Key words: Turbidity, zinc complex, dissolution, mass spectroscopy, NMR

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ABSTRACT

The turbidity of suspensions of polymeric zinc monoglycerolate (ZMG) has been used to determine dissolution rates in aqueous solution. The rate was found to be first order with respect to the concentration of undissolved ZMG and of order 1/2 with respect to the hydrogen ion concentration in the pH range 4.1 - 5.8 and a temperature range of 20°C - 45°C. The temperature dependence at constant pH obeys the Arrhenius equation and the activation energy of the dissolution process was found to be near 35 kJ mol^{-1}.

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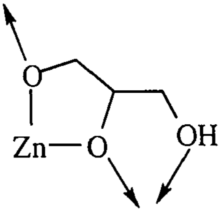
INTRODUCTION

Zinc monoglycerolate [1,2,3-propanetriolato zinc(II), hereafter referred to as ZMG] is a two-dimensional polymeric material constructed from the monomeric unit:



As revealed by an X-ray crystal structure analysis,[1] the coordination geometry about the zinc centre is approximately trigonal bipyramidal owing to the pentadentate mode of coordination of the dinegative glycerolate ligand. The aliphatic hydrogen atoms are orientated so as to occupy the regions between successive layers, an observation that accounts for the hydrophobic nature of the material as well as other chemical properties such as lubricity.[1,2] Particular interest in ZMG arises from its potential use as a medium for the slow/contolled release of zinc in both agricultural and pharmaceutical applications;[2-5] other applications relate to its use as a lubricant and talc substitute.[2] ZMG has been reported to have low solubility in neutral aqueous solution, however, except for an essentially preliminary report, quantitative experimental data are not available for the aqueous dissolution or solubility of ZMG under the various conditions such as pH, ionic strength and temperature.[2] A program has been initiated to gather information on the dissolution characteristics of ZMG in order to provide the necessary background knowledge required[6] for the inclusion of this material in pharmaceutical formulations.

Turbidity measurements may be used as a convenient method to follow the dissolution of ZMG particles dispersed in solution under various conditions. It has been found that the turbidity decay fits well a single exponential. This report describes the experimental procedures used in the study and shows that rates of dissolution may be determined with satisfactory precision as long as the half-life of the turbidity decay is not less than around 0.05 s. In addition, ZMG has been characterised by mass spectroscopic techniques and its solid state ^{13}C NMR spectrum recorded.

EXPERIMENTAL

Instrumentation:

Spectrophotometric measurements were made on a Cary 2200 double-beam spectrophotometer fitted with a MGW Lauda thermostat. Scanning Electron Microscopic (SEM) data were obtained on a Philips XL20 SEM. Cross-polarised magic angle spinning ^{13}C magnetic resonance data were measured on a Varian Unity 200 spectrometer operating at 50.309 MHz with hexamethylbenzene as the reference. Fast atom bombardment mass spectra were recorded on a VG ZAB-2HF spectrometer using 3-nitrobenzyl alcohol as matrix, exciting gas argon, FAB gun voltage 7 kV, current 1 mA and accelerating potential 8 kV.

Materials:

A sample of ZMG was provided by Dr M.J. Story of Bellara Medical Products Limited; the material was purified by solvent extraction with analytical grade 2-propanol. A SEM study showed that the particles of ZMG are aggregates of ZMG crystallites and are up to 80 μm in size but normally < 20 μm. A turbidimetric titration of ZMG with 0.01 M HCl showed that complete dissolution was effected by the addition of two molar equivalents of the acid per mole of zinc; this indicates that dissolution leads to the dissociation of the polymer into glycerol molecules and Zn^{2+} ions and that, consequently, control of pH is essential in ZMG dissolution studies. Phthalate buffer solutions (100 cm^3) were prepared to the required pH using potassium hydrogen phthalate (Ajax). Ionic strength was moderated using KCl (Ajax) or KNO_3 (BDH).

Sample Preparation, Turbidity Measurements:

Typically, measurements involved dispersing 0.5 mg of ground ZMG in 3 cm^3 buffer in a 1 cm quartz curvette. The suspension was shaken manually and placed in the spectrophotometer. The pH was monitored routinely, before and after dissolution, to ensure that the buffer capacity was not exceeded. The 0.5 mg mass was chosen as the optimum initial amount of ZMG over the pH range studied.

RESULTS AND DISCUSSION

Turbidity:

The turbidity, τ, was determined as the apparent absorbance at the wavelength of 500 nm. The forward scattering of light may be taken to be proportional[7] to the number of particles, N, and to the square of their volume, $<V^2>$:

$$\tau \propto N<V^2> \tag{1}$$

Typically, measurements involved dispersing 0.5 mg of ground ZMG in 3 cm^3 of buffer solution corresponding to a volume fraction of less than 2×10^{-4}. Experimental measurements in this range confirm the linerity of the turbidity, τ, with the particles in suspension; this is shown in Figure 1.

The turbidity decays with time as a single exponential to a very high precision as is shown in Figure 2 (obtained in a pH 5.5 buffer at 20°C at 0.5 M ionic strength at an initial ZMG particle concentration of 0.5 mg cm^{-3}). The digital output corresponded to a sampling rate of 12 measurements per second. The calculated curve is the least-squares fit of the first 2000 points of the experimental data to the equation:

$$\tau = \tau_0 \exp\{-k_\tau t\} - b \tag{2}$$

where t is the time and the three fitting parameters are τ_0, the turbidity at time zero, k_τ, the first order rate constant and b, a small base-line correction. The mean values of these parameters and their standard deviations in this instance were found to be $k_\tau = 2.660 \pm 0.001\ s^{-1}$, $\tau_0 = 1.074 \pm 0.001$, and $b = 7.67 \times 10^{-3} \pm 0.02 \times 10^{-3}$, where τ_0 and b have absorbance units.

The relationship between k_τ and the more conventional pseudo-first order rate coefficient is readily obtained if one approximates the root-mean-square value of the particle volume by the mean:

$$<V> \approx <V^2>^{1/2}$$

Then, by equation (1), $\tau^{1/2}$ is proportional to $<V>$ or to the volume concentration of the particles, C_V,

$$\tau^{1/2} \propto C_V$$

since, writing V_{total} for the total volume, $C_V = N<V>/V_{total}$ where N/V_{total} is a constant. Disregarding the small base-line correction and taking the square root of equation (2)

$$C_V = C_V^{\circ} \exp\{-k_\tau t/2\}$$

so that k_V', the pseudo-first order rate coefficient in terms of the volume concentration of the particles is related to k_τ by

$$k_V' = k_\tau/2$$

If one were to make the further assumption that the average volume, $<V>$, to the

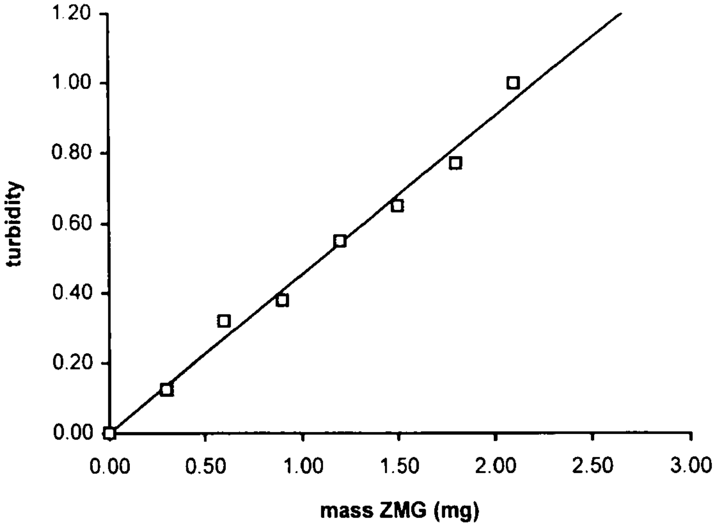


Figure 1. A plot of turbidity *vs* initial mass (mg) of ZMG in 3 cm^3 of water. Turbidity is determined as the absorbance extrapolated to zero time.

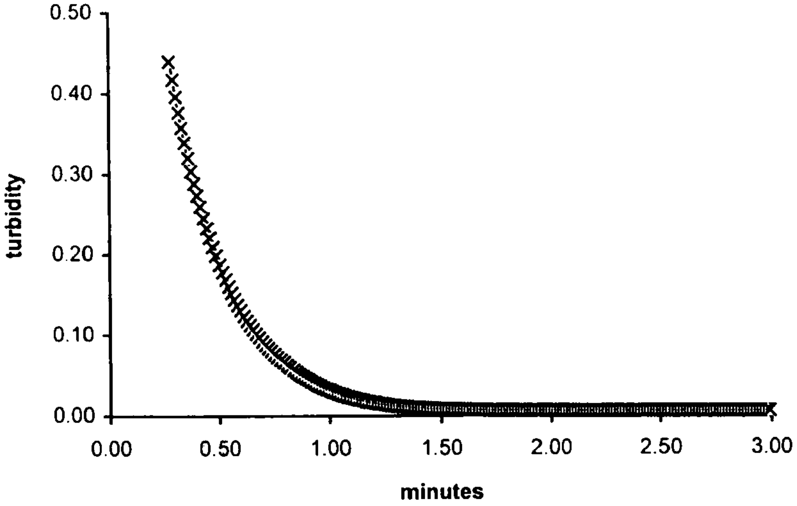


Figure 2. A plot of turbidity (as absorbance) *vs* time (s). The smooth line shows the fit, experimental points are shown by crosses; in order to avoid overcrowding the plot includes every tenth point only.

average surface area, <S>, of the particles is approximated by the corresponding ratio for spheres, $\langle S \rangle = \langle V \rangle^{2/3}$, then, in terms of the surface area of the N suspended particles, the pseudo-first order rate coefficient, k_S', is related to k_τ as

$$k_S = k_\tau/3$$

With the above assumptions and depending on the choice of the concentration unit for the undissolved ZMG in suspension, the rate law for the dissolution at constant pH is

$$\text{rate} = k_V' \, C_V$$

$$\text{rate} = k_S' \, C_S$$

The form of the above rate laws have been confirmed by showing under several conditions that the pseudo-first order rate coefficients did not change when the initial solid ZMG concentration was varied between 0.1 and 0.67 mg cm^{-3}.

Effect of External Conditions on the Rate of Dissolution of ZMG:

Using the procedures outlined above, the dissolution rate of suspended particles of ZMG were investigated in phthalate buffer solutions of varying ionic strengths in the pH range 4.1 to 5.8, and in the temperature range of 20 to 45°C. A brief summary of the key results of this on-going study follows.

The influence of ionic strength of the rate of dissolution was monitored in the concentration range 0.1 to 0.5 M adjusted with either KCl or KNO_3. No significant dependence of k_τ on either the concentration or the electrolyte was observed. By constrast, a small but measurable dependence of k_τ on the concentration of the phthalate buffer solution at constant ionic strength was detected. When under the following conditions of pH 5.2, temperature 25 °C and ionic strength 0.5 M (KCl), the buffer concentration was varied from 0.1 to 0.5 M, k_τ varied from 6.90 ± 0.03 (0.5 M) to 6.01 ● 0.02 (0.3 M), 5.69 ± (0.2 M) and 4.64 ± 0.03 s (0.1 M); extrapolation to [phthalate] = 0.0 M yielded a value for k_τ of 4.47 ± 0.03 s^{-1}.

A marked pH effect is detected in the rate of dissolution of suspended ZMG particles, with the rate increasing with decreasing pH. This is illustrated in Figure 3 which shows a graph of $\log_{10}k_\tau$ vs pH for the temperatures 20, 25, 30, 37 and 45 °C at 0.5 M ionic strength.

At low pH and higher temperatures the rate was too fast to be measured realiably using the technique employed in the present study. It is noted that

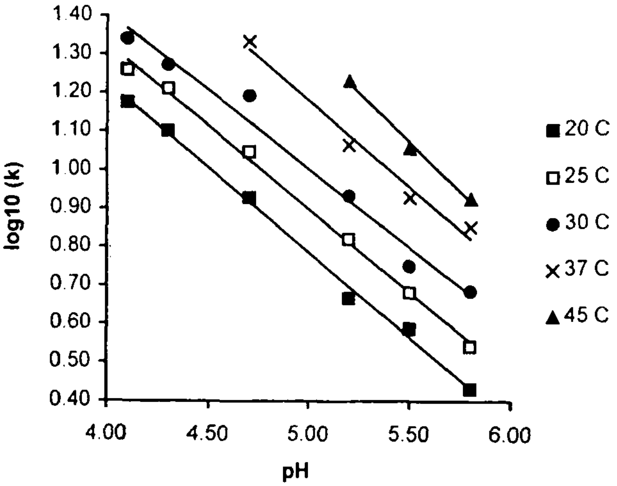


Figure 3. A plot of the first order rate constant (expressed as $\log_{10}$) as a function of pH at various temperatures

$\log_{10}k_{\tau}$ depends linearly on pH in this range and the slope of the dependence is close to -0.5 at the five temperatures studied. It seems, accordingly, that the rate of dissolution depends on the square root of the hydrogen ion concentration:

$$\text{rate} \propto [H^+]^{1/2}$$

This square root dependence contrasts with the consumption of two moles of hydrogen ion per mole of $[Zn(C_3H_6O_3)]$ for the degradation of ZMG (see *Materials*).

The temperature dependence of k_{τ} at fixed pH values appears to conform to the Arrhenius equation:

$$k_{\tau} \propto \exp\{E_a/RT\}$$

where E_a is the activation energy of the dissolution process. The $\ln k_{\tau}$ *vs* T^{-1} plots are shown in Figure 4.

The plots are linear within experimental error with similar slopes indicating that the mechanism of the dissolution process does not depend on the pH. From the slopes an average activation energy of $E_a = 35.1 \pm 5.5$ kJ mol^{-1} is obtained.

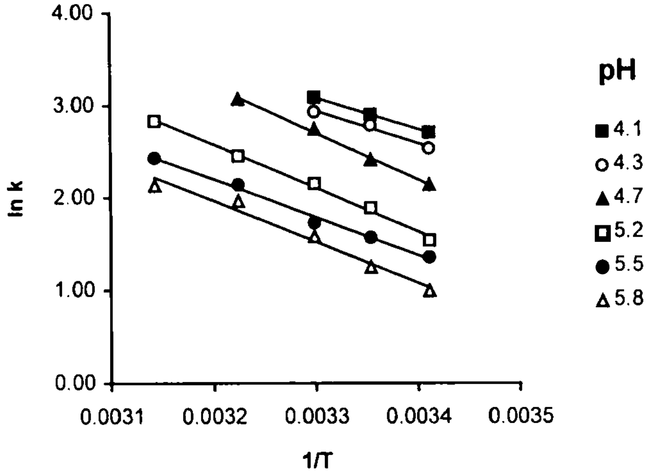


Figure 4. A plot of the natural log of the first order rate constant as a function of 1/T (K^{-1}) under various conditions of pH

Spectroscopic Characterisation:

The ^{13}C solid state NMR spectrum of ZMG showed three resonances only, at δ 70.8, 67.8 and 63.7 ppm in the ratio 1:1:1, consistent with the crystallographic result.[1] In the fast atom bombardment mass spectrum, a technique that has proved useful in the characterisation of polymeric materials,[8] evidence was found for $[Zn(C_3H_6O_3)]_4$ as the major fragment by comparing the observed and calculated isotopic distributions; there was no other zinc-containing fragment at higher m/e. Other significant zinc-bearing fragments included $[Zn(C_3H_6O_3)]_3$ (relative abundance 75%), $[Zn(C_3H_6O_3)]_2$ (35%) and the monomer $[Zn(C_3H_6O_3)]$ (70%). Additional ions, which differed from the above species by varying amounts of O and/or CH, were also observed.

CONCLUSIONS

1. The decrease in turbidity, as measured in an absorption spectrophotometer, may be used to follow the kinetics of dispersed solid particles.

2. The rate of the dissolution of ZMG depends on the concentration of the solid dispersion and, very likely, on the square root of the hydrogen ion concentration

$$\text{dissolution rate} \propto [ZMG_{solid}][H^+]^{1/2}$$

3. The activation energy is independent of the pH in the range studied implying that the mechanism of the dissolution process is also independent of the pH.

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