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Determination of some parameters influencing the dissolution rate of famotidine

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Summary

Equilibrium solubility studies of famotidine were conducted at different pH values in order to determine its macroscopic dissociation constant, K_a, pK_a and intrinsic solubility [B]. Famotidine dissolution studies were conducted at different stirring rates, pH values and temperatures for the determination of its diffusion coefficient, D, hydrodynamic layer thickness, h, and activation energy of dissolution E_a. The adherence of the dissolution data at pH 6.4 to the Noyes-Whitney and Levich equations together with the value of E_a indicated that the dissolution process is diffusion controlled. The kinetics of the dissolution process were zero-order at pH 6.4 and 7.8 and pseudo zero-order at acidic pH values.

Introduction

Famotidine is a new H_2-receptor antagonist that is a highly potent inhibitor of gastric acid secretions in humans (Takagi et al., 1982; Pendleton et al., 1983). It is poorly water soluble (Suleiman et al., 1989; Hassan et al., 1990) and hence its bioavailability is expected to be dissolution rate limited. Therefore, knowledge of the mechanism of its dissolution process and factors which influence such a process is of paramount importance in improving its bioavailability from oral dosage forms.

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Background

The dissolution of drugs is considered to be dependent on a number of factors which include equilibrium solubility, C_s, diffusion coefficient, D, pK_a, hydrodynamic layer thickness, h, pH and viscosity of the hydrodynamic layer, the bulk viscosity and the dissolution rate constant, K.

Several equations have been developed in order to correlate these factors to the dissolution rate of drugs. The equation of Noyes and Whitney (1897) is considered to be one of the earliest equations developed for this purpose. For diffusion-controlled dissolution processes this equation can be written as:-

$$J = KA(C_s - C) \quad (1)$$

where J denotes the dissolution rate per unit

surface area, A, and C is the drug concentration in the dissolution medium at a particular time.

The dissolution rate constant, K, according to diffusion layer theory (Serajuddin and Jarowski, 1985a,b) is given by

$$K = \frac{D}{h} \tag{2}$$

Under sink conditions $C_s \gg C$, thus Eqn 1 reduces to

$$J = \frac{DAC_s}{h} \tag{3}$$

Therefore, for diffusion-controlled dissolution processes, J is directly related to D and inversely related to h.

In order to calculate both D and h, Levich (1962) developed the following two equations:

$$J = 0.62 D^{2/3} \nu^{-1/6} \omega^{1/2} C_s \tag{4}$$

$$h = 1.612 D^{2/3} \nu^{1/6} \omega^{-1/2} \tag{5}$$

where ν is the kinematic viscosity of the dissolution medium and ω is the angular speed of rotation. According to Eqn 4, therefore, a plot of J vs $\omega^{1/2}$ would be linear with a slope equivalent to:

$$\text{slope} = 0.62 D^{2/3} \nu^{-1/6} C_s \tag{6}$$

hence D and h can be calculated.

In this work, Eqns 1–6 were used to study the dissolution kinetics of famotidine in order to determine its mechanism of dissolution and calculate the values of parameters which determine its dissolution rate.

Materials and Methods

Materials

Anhydrous citric acid, famotidine and KCl were obtained from Sigma (U.S.A.). Na_2HPO_4 was obtained from BDH (U.K.).

Methods

Determination of the equilibrium solubility An excess of famotidine was shaken in screw-capped vials for 24 h with 20 ml of McIlvain buffer of the required pH and adjusted to an ionic strength of 0.5 with KCl at 37 °C. The samples were then filtered through a 0.3 μm filter unit (Millipore, London, U.K.). The concentration of famotidine was determined spectrophotometrically using a Shimadzu 240 spectrophotometer (Shimadzu, Koyoto) at a wavelength of 280 nm against an appropriate blank. Samples were run in triplicate and the average values were taken.

Determination of dissolution rate The dissolution rate of famotidine was determined in triplicates at 37 °C at the required stirring rate and pH of the dissolution medium using a USP dissolution apparatus. The dissolution medium consisted of 500 ml of McIlvain buffer at the required pH and of ionic strength 0.5 adjusted with KCl. The disc in its mould was attached centrally on the surface of the upper part of the USP dissolution basket apparatus leaving a lower surface area of 1.53 cm^2 available for dissolution. The pH of the dissolution medium was monitored throughout the experiment and was found to remain constant. Samples of 5 ml were withdrawn at the designated time intervals and immediately replaced with a similar volume of fresh dissolution medium. The samples were transferred to a syringe and rapidly filtered through the 0.3 μm membrane filter unit. The samples were then spectrophotometrically assayed for drug contents as described above.

Results and Discussion

The total solubility, S, of a basic drug such as famotidine is related to its intrinsic solubility, [B], and macroscopic dissociation constant, K_a, by the equation (Krebs and Speakman, 1945; Zimmermann, 1983)

$$S = [B] + \frac{[B][H^+]}{K_a}$$

Hence, a plot of S vs $[H^+]$ would be linear with an intercept of [B] and a slope of B/K_a. Such a plot for famotidine was linear ($r = 0.9986$, $n = 4$). The intercept of this plot when divided by the slope gives the value of K_a. Accordingly, under

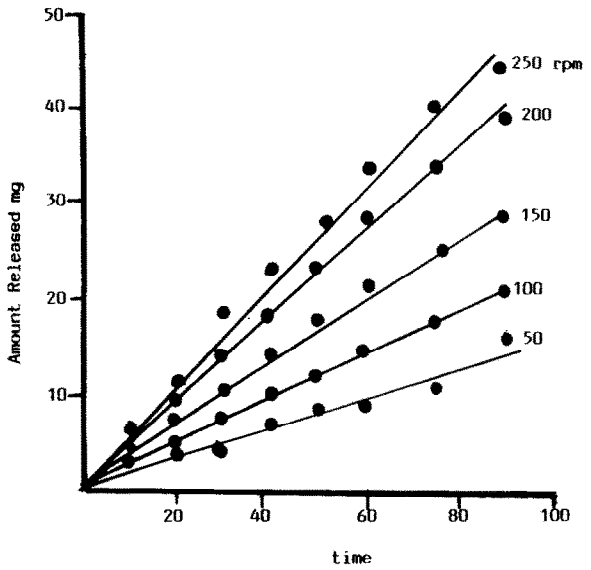

Fig. 1. Dissolution of famotidine at different stirring rates (abscissa scale: min).

these experimental conditions, the value of K_a for famotidine is 3.54×10^{-7} and hence the pK_a is 6.45 and its intrinsic solubility is 0.278 mg ml^{-1}.

Fig. 1 shows the amount of famotidine dissolved as a function of time from constant surface area discs at different stirring rates at pH 6.4. The figure indicates that at all stirring rates a linear relationship was obtained; however, higher release rates resulted when the stirring rates were increased. The linearity of these plots suggests that the dissolution data adhere to the Noyes-Whitney equation and therefore that the dissolution process is diffusion controlled. The linearity of the plots also indicates that the dissolution kinetics are zero order in nature, showing that a constant dissolution rate is achieved which is independent of concentration. Fig. 1 also indicates that with increasing stirring rate, the dissolution rate is increased. This could be due to the reduction in the thickness of the hydrodynamic layer which occurs with increasing stirring rate as indicated in Eqn 5 (Levich, 1962).

The slopes of the lines in Fig. 1 when divided by the exposed surface area of the disc give the flux J. When J was plotted against the square root of the angular speed of rotation, $\omega^{1/2}$, a linear relationship was obtained ($r = 0.986$, $n = 5$) with a slope of 1.13×10^{-3}. The linearity of the plot is indicative of the adherence of the dissolution rate to the Levich equation (Eqn 4). This therefore suggests that a true diffusion-type mechanism operates in the dissolution of famotidine. The value of the slope was used to calculate the diffusion coefficient of famotidine (Eqn 6) which was found to be 6.728×10^{-6} cm^2 s^{-1}.

Table 1 lists the values of the hydrodynamic layer thickness calculated at different stirring rates using Eqn 6. The data indicate that increasing the stirring rate decreases the thickness of the hydrodynamic layer. This could be due to the fact that, with increase in stirring rate the Reynold's number of the fluid moving adjacent to the particle surface is increased, changing from laminar flow to stream line and at very high stirring rates to turbulence flow. As this occurs, the amount of liquid adhering to the solid surface is decreased and therefore the thickness of the hydrodynamic layer decreases.

Fig. 2 shows the dissolution of famotidine at various pH values. The figure indicates that the release of drug was inversely related to pH. This is to be expected, since famotidine is a basic drug and therefore its degree of ionization and hence solubility increase with pH decrease. It can be observed from Fig. 2 that for pH 6.4 and 7.8, a linear relationship existed between the amount released and time, suggesting that the kinetics of the release process is zero order and diffusion controlled. For lower pH values, however, a curvilinear relationship was obtained. This suggests that the kinetics of the release process is pseudo zero order in nature. The initial linear portion of the graph indicates that the release is independent of concentration, due to the presence of a suffi-

TABLE 1

Variation in hydrodynamic layer thickness (h) with stirring rate

Stirring rate (rpm)	h (μm)
50	1.10
100	0.78
150	0.64
200	0.55
250	0.49

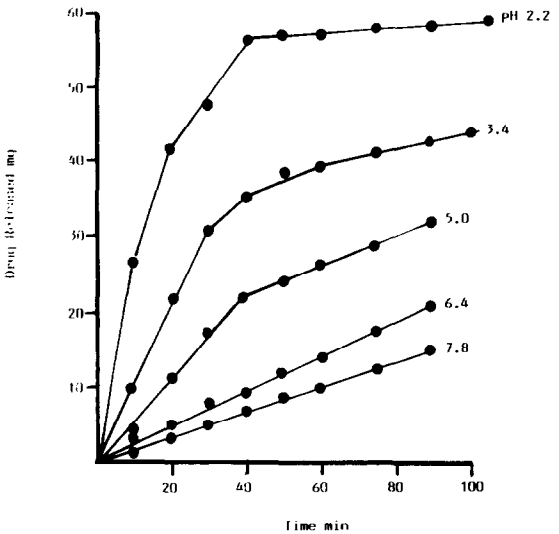

Fig. 2. Dissolution of famotidine at different pH values.

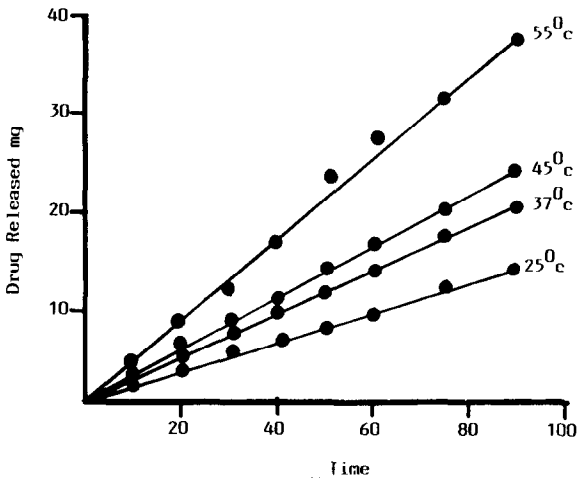

Fig. 4. Dissolution of famotidine at different temperatures (abscissa scale: min).

cient amount of drug to maintain a constant release rate. The time at which negative deviation from linearity occurs (θ) suggests that the amount of drug remaining is insufficient to maintain a constant release rate. The time at which this deviation occurs decreases with pH decrease. This variation in the kinetics of the release process with pH could be due to the change in the degree of ionization and hence solubility of the drug with pH. At higher pH values, i.e. pH 6.4 and 7.8, the degree of ionization is low, therefore the release rate is low and hence the amount of drug remaining undissolved is sufficient to maintain a constant release rate. At lower pH values, the degree of ionization is increased, therefore the rate of transfer of drug to the dissolution medium is increased and hence the drug reservoir which is

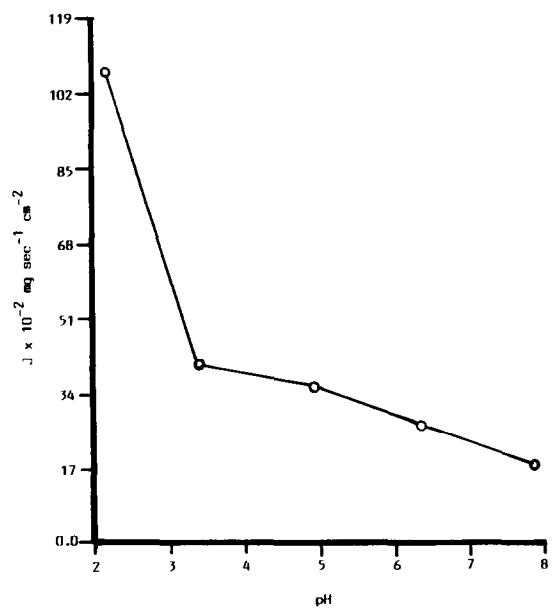

Fig. 3. Relationship between the relative dissolution rate (J_r) and pH.

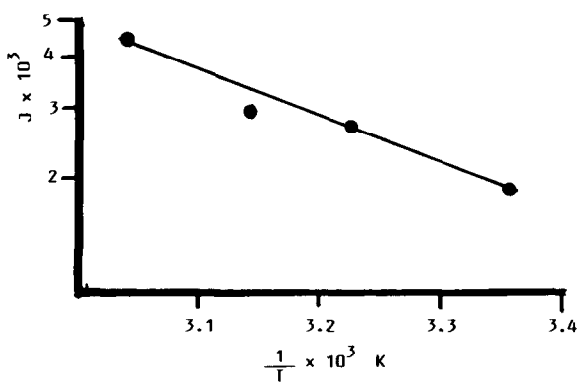

Fig. 5. Arrhenius plot showing the relationship between log J and the reciprocal of the absolute temperature.

necessary to maintain a constant release rate is depleted at time θ and the release rate falls off.

The effect of pH on the rate of dissolution, J, was studied by determining the variation of the relative dissolution rate, J_r, as a function of bulk pH. J_r is defined as the ratio of the dissolution rate at a particular pH, J, to that at a pH where ionization of the drug is negligible, J_0 and only the undissociated species is diffusant (Mooney et al., 1981a,b; McNamara and Amidon, 1986).

The values of J_r plotted as a function of pH are shown in Fig. 3. This figure indicates that J_r increases only slightly as the pH is reduced from 7.8 to 3.4. For pH below 3.4, J_r increases sharply. The sharp increase in J_r in acidic media below pH 3.4 has been attributed (Tsuji et al., 1978) to the back diffusion of hydrogen ions towards the solid surface, causing a high degree of ionization of the basic groups of the drug and therefore increasing J_r.

The effect of temperature on the dissolution of famotidine was determined by studying the dissolution at different temperatures. The results obtained are shown in Fig. 4. Fig. 4 indicates that increasing the temperature results in an increase in dissolution and a linear relationship exists between the amount of drug released and time. The temperature dependence of J was investigated by plotting log J against reciprocal absolute temperature in accordance with the Arrhenius equation, as shown in Fig. 5. The activation energy of dissolution calculated from the slope of the plot was 7.1 kcal deg^{-1} mol^{-1}. This value is in reasonable agreement with previously reported energies for diffusion-controlled dissolution processes (Tsuji et al., 1978).

In conclusion, the values of some of the parameters that might influence the dissolution of famotidine are presented in Table 2.

TABLE 2

Values of some of the parameters influencing the dissolution rate of famotidine

Parameter	Value
D	6.728×10^{-6} cm^2 s^{-1}
h at 100 rpm	0.78 μm
K_a	3.54×10^{-7}
pK_a	6.45
E_a	7.1 kcal deg^{-1} mol^{-1}
[B]	0.278 mg ml^{-1}

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