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Dissolution kinetics of ketanserin tartrate, the salt of a weakly basic drug

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Summary

The rotating disc method was used to study the dissolution kinetics of ketanserin tartrate, the salt of a weakly basic drug. Both solubility and dissolution rate decrease exponentially with increasing pH of the dissolution medium. A plot of the logarithm of the ratio of dissolution rate to solubility vs the bulk solution pH shows increasing ratios with increasing pH. This phenomenon is attributed to a self-buffering action of the drug within the diffusion layer at the solid-solvent interface.

Introduction

The release of a drug from a solid programmed release dosage form is mostly related to the solubility of the drug. Weak acids and weak bases exhibit pH-dependent solubilities and will thus show release profiles which may vary greatly in the gastrointestinal pH range. Incorporation of weakly basic drugs such as ketanserin and mianserin in the programmed release megaloporous system indeed showed strongly inhibited release rates in neutral media as compared to acidic media (Van der Veen et al., 1991). Knowledge of the solubility and dissolution behaviour of these type of drugs is consequently presumed for the design of solid programmed release dosage forms. This knowledge is particularly indispensable when the dosage form is supposed to release its drug at a well-defined rate in both acidic (the stomach) and neutral environments (the small intestine).

The mechanism of dissolution of a solid in a nonreactive solvent under mild to high agitation conditions is primarily described by the diffusion layer model, in which it is postulated that there is a static film adjacent to the solid interface (Levich, 1962). The reaction at the solid-liquid interface is assumed to be rapid, so that the rate of dissolution is governed entirely by diffusional transport of the solute molecules through the liquid film. This diffusion layer model predicts that:

$$dW/dt = A \cdot D/h \cdot (C_s - C) \quad (1)$$

where W is the mass of dissolved solid at time t, A the surface area of the dissolving solid, D the diffusion coefficient of the dissolved molecules, h the effective diffusion layer thickness, C_s the sat-

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uration solubility of the solid, and C the concentration of dissolved solid at time t in the dissolution medium.

Most methods of measuring and interpreting dissolution rates have been performed using compressed (rotating) discs at constant surface area A of the dissolving solid. In this way dissolution has indeed been found to be mainly diffusion-controlled (Wagner, 1970; Nelson and Shah, 1975; Shah and Nelson, 1975; Nicklasson et al., 1982).

The present study was performed according to the rotating disc method in order to determine the effect of the pH of the medium on the solubility and dissolution behaviour of ketanserin tartrate, the salt of a weakly basic drug.

Materials and Methods

Chemicals

Ketanserin tartrate is the salt of a weakly basic drug (Fig. 1). Ketanserin has a pK_a of 7.50. The drug was kindly supplied by Janssen Pharmaceutica (Beerse, Belgium).

Solubility profiles

Buffer solutions of different pH values were composed of 0.5 M citric acid monohydrate (pro analysi, Merck, Darmstadt, Germany) and 1 M Na_2HPO_4 (pro analysi, Merck, Darmstadt, Germany). Excess of drug was shaken with the buffer solutions over a period of 2 days at room temperature and subsequently for one night at 37°C. The saturated solutions were filtered through a 0.2 μm micropore filter (Schleicher and Schuell) and appropriately diluted. Drug concentrations were determined spectrophotometrically (PU 8720, Philips, Eindhoven, The Netherlands) at 245 or 310 nm against a blank run under the same conditions. The solubilities were determined in triplicate and are given as mean values. The pH values were measured for the filtered saturated drug solutions.

Dissolution rate measurements

Dissolution rate measurements were performed according to the rotating disc method as reported by Lagas (1980). Non-disintegrating discs

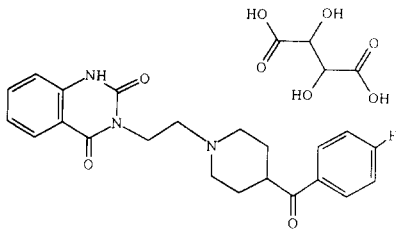

Fig. 1. Structural formula of ketanserin tartrate.

were prepared by compression of 400 mg ketanserin tartrate at 30 kN compression force into dies with a constant surface area of 1.32 cm^2. All dissolutions were performed under sink conditions at a temperature of 37°C in 1 l deaerated water and in buffer solutions of different pH values, respectively. The buffer solutions were composed of 0.1 M citric acid monohydrate and 0.2 M Na_2HPO_4. The rotation speed of the disc was 110 rpm for the buffer solutions; the measurements in water were performed at various speeds of rotation. Concentrations were determined spectrophotometrically. The dissolution rate measurements were performed in duplicate. Dissolution rates (μmol min^{-1} cm^2) were calculated by linear regression analysis.

Results and Discussion

Fig. 2 reflects the logarithm of the solubility of ketanserin tartrate, the salt of a weakly basic drug, vs the pH of the medium. It should be noted that high buffer capacities, composed of 0.5 M citric acid monohydrate and 1 M Na_2HPO_4, were necessary in order to counteract the pH effect of ketanserin tartrate and to create a range of medium pH. The pH-solubility profile shows two distinct parts. Down to a pH value of about 5, the drug shows an exponentially increasing solubility with increasing acidity of the medium, due to protonation of the diprotic tartrate. Below a pH value of 5, the weak base ketanserin is protonated, resulting in further increasing solubilities with increasing acidity of the medium. The drug thus shows high solubilities at low pH values but extremely low solubilities at more neutral pH values.

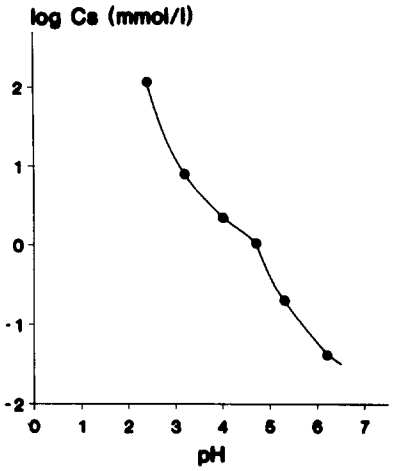

Fig. 2. Solubility (C_s) of ketanserin tartrate vs bulk solution pH at 37°C.

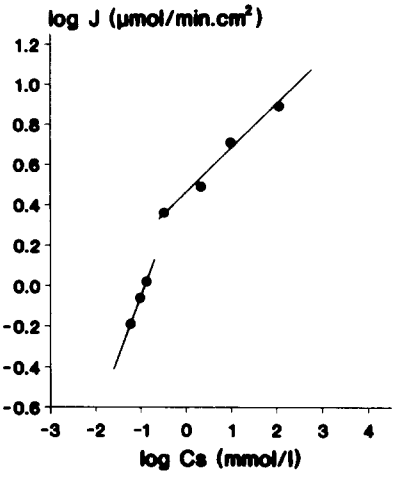

Fig. 4. Correlation between dissolution rate (J) and solubility (C_s) of ketanserin tartrate at various bulk solution pH.

The dissolution rates of ketanserin tartrate were determined by the rotating disc method. The measurements were performed in different media over a pH range as occurs in the gastrointestinal tract. It should be noted that lower buffer capacities of the dissolution media, 0.1 M citric acid monohydrate and 0.2 M Na_2HPO_4, were employed than necessary for the solubility measurements. As expected, the results show (Fig. 3) high (intrinsic) dissolution rates at low pH values, exponentially decreasing with increasing pH of the dissolution medium. It is evident that the pH-dissolution rate profile displays a shape similar to that found for the pH-solubility profile (Fig. 2).

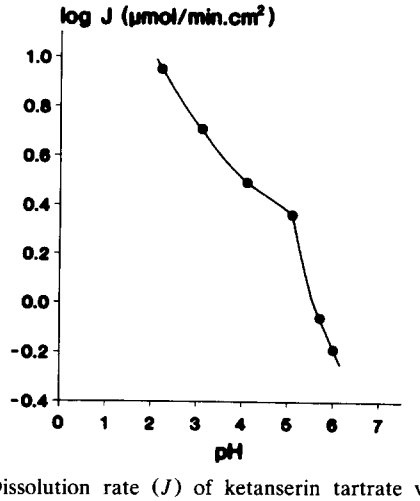

Fig. 3. Dissolution rate (J) of ketanserin tartrate vs bulk solution pH at 37°C.

The mechanism of dissolution of a solid from a rotating disc has been described by Levich (1962). Assuming laminar flow and a diffusion-controlled process, he derived the equation:

$$J = 0.62 \cdot D^{2/3} \cdot \nu^{-1/6} \cdot C_s \cdot \omega^{1/2} \qquad (2)$$

where J is the observed (intrinsic) dissolution rate of the solid (μmol min^{-1} cm^2), D the diffusion coefficient (cm^2/min), ν the kinematic viscosity (cm^2/min), C_s the aqueous solubility (μmol/cm^3) and ω the angular velocity (min^{-1}).

According to this equation, the dissolution rate of a solid should be proportional to its saturation solubility. A plot of the dissolution rate at different solvent pH values vs the corresponding solubility of ketanserin tartrate shows, however, no single relationship over the whole pH range, but two distinct relationships (Fig. 4). This lack of single proportionality is suggested to be caused by changing dissolution kinetics at the solid-solvent interface.

Mooney et al. (1981a,b) examined the effect of solubility and bulk solution pH on the dissolution behaviour of three carboxylic acids from rotating compressed discs into both unbuffered and

buffered solutions. A theoretical model was derived which was found to predict the dissolution rates of these acids accurately as a function of the bulk solution pH. The model assumed that diffusion-controlled mass transport and simple, instantaneously established reaction equilibria existed across a postulated diffusion layer. The concept of a micro environment within the diffusion layer was used to explain the influence of several factors, such as bulk solution pH, pK_a, solubility and diffusivity, on the dissolution rate of the acids. Serajuddin and Rosoff (1984) studied the release of papaverine hydrochloride from sustained-release pellets consisting of a shellac-based matrix. The release rates at various pH values of the permeating solvent were found to be directly proportional to the solubility below the apparent pH at which precipitation of the papaverine base occurred (pH_{max}). The expected decrease in release rate based on the decreased solubility at $pH > pH_{max}$ was not observed. These results were explained by the self-buffering action of the drug and consequently the tendency to revert towards the apparent pH_{max} in the media of low buffer capacity. Serajuddin and Jarowski (1985a,b) continued their investigations to elucidate the mechanism of dissolution of pharmaceutical bases and their hydrochloride salts, and of acids and their sodium salts, by systematically correlating their pH-dissolution rate profiles with their pH-solubility profiles. Constant ratios between observed dissolution rates and saturation solubilities were obtained when the solubility values under pH conditions as the diffusion layer thickness approaches zero were used rather than solubilities under pH conditions of the bulk media.

As mentioned before, a plot of the logarithm of the intrinsic dissolution rate (J) vs the logarithm of the solubility (C_s) of ketanserin tartrate showed two distinct linear relationships (Fig. 4). At solubilities lower than 0.2 mmol/l the regression line was calculated to be: $\log J = 0.60 \cdot \log C_s + 0.55$, with a correlation coefficient of 0.999. At solubilities above 0.2 mmol/l, the regression line was: $\log J = 0.22 \cdot \log C_s + 0.46$, with $r = 0.990$. It should be noted that the increase in dissolution rate with solubility is about 3-fold higher when $C_s < 0.2$ mmol/l, as compared with

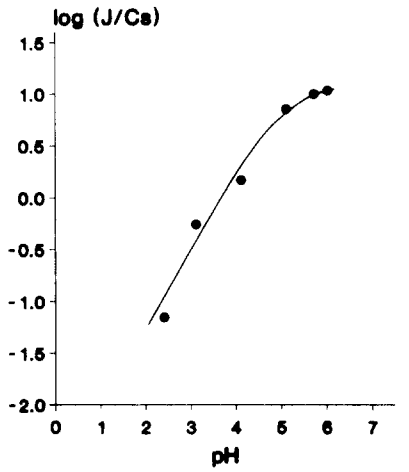

Fig. 5. Plot of the logarithm of the ratio of dissolution rate (J) to solubility (C_s) of ketanserin tartrate vs the bulk solution pH.

the increases found when $C_s > 0.2$ mmol/l. These two distinct regions in correlation between dissolution rate and solubility of the drug may be attributed to a difference in dissolution kinetics at the solid-solvent interface. In the region of low solubilities, corresponding with high pH values of the dissolution medium, the drug salt dissolves as a complex, whereas dissolution occurs by protonation of the weak base in the region of high solubilities, corresponding with low pH values of the solvent. It may consequently be assumed that changing pH profiles will be generated across the diffusion layer at the solid-solvent interface, as indicated in the cited literature. To express the difference between the dissolution kinetics and solubility mechanism of ketanserin tartrate, $\log (J/C_s)$ was plotted against the pH of the dissolution medium (Fig. 5). This result demonstrates increasing ratios of dissolution rate to solubility with increasing pH values of the solvent. Realizing that both dissolution rate and solubility of ketanserin tartrate decrease with increasing pH, dissolution is apparently less affected by the bulk solvent pH than the solubility. This observation may be attributed to a self-buffering action of the drug, generating lower pH values within the diffusion layer at the solid-solvent interface. Moreover, it should be borne in mind that 5-fold higher buffer capacities were

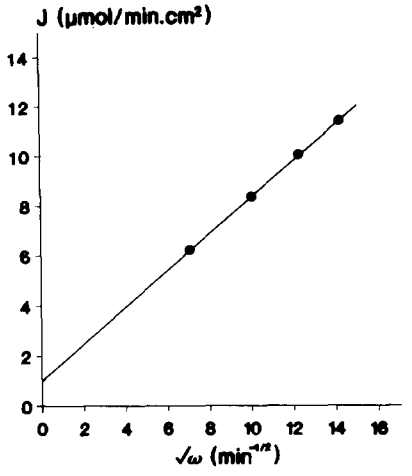

Fig. 6. Dissolution rate (J) of ketanserin tartrate in water from centrically rotating discs vs the square root of the angular velocity (ω).

necessary to perform the solubility determinations of ketanserin tartrate over a range of medium pH. The impact of the self-buffering effect of the drug is therefore stronger on the process of dissolution than on the equilibrium solubility.

To determine whether the dissolution process of ketanserin tartrate was diffusion controlled, dissolution rate measurements were finally determined at different rotation speeds. In Fig. 6 the observed dissolution rates are plotted vs the square root of the angular velocity of the disc. The plot shows a linear relationship with a correlation coefficient of 1.000. It may consequently be concluded that dissolution of the drug was indeed diffusion controlled. The linear relation shows, however, a small intercept, which is not consistent with the Levich equation. This slight deviation from theory might be caused by the observed phenomenon of a self-buffering action of ketanserin tartrate in the diffusion layer.

References

Lagas, M., Wettability and availability of drugs, Ph. D. Thesis, University of Groningen, Groningen (1980).

Levich, V.G., *Physicochemical Hydrodynamics*, Prentice-Hall, Englewood Cliffs, NJ, 1962 pp.1–80.

Mooney, K.G., Mintun, M.A., Himmelstein, K.J. and Stella, V.J., Dissolution kinetics of carboxylic acids. I: Effect of pH under unbuffered conditions. *J. Pharm. Sci.*, 70 (1981a) 13–22.

Mooney, K.G., Mintun, M.A., Himmelstein, K.J. and Stella, V.J., Dissolution kinetics of carboxylic acids. II: Effect of buffers. *J. Pharm. Sci.*, 70 (1981b) 22–32.

Nelson, K.G. and Shah, A.C., Convective diffusion model for a transport-controlled dissolution rate process. *J. Pharm. Sci.*, 64 (1975) 610–614.

Nicklasson, M., Brodin, A. and Sundelöf, L.-O., On the determination of true intrinsic rates of dissolution by means of a generalized rotating disk method. *Acta Pharm. Suec.*, 19 (1982) 109–118.

Serajuddin, A.T.M. and Jarowski, C.I., Effect of diffusion layer pH and solubility on the dissolution rate of pharmaceutical bases and their hydrochloride salts. I: Phenazopyridine. *J. Pharm. Sci.*, 74 (1985a) 142–147.

Serajuddin, A.T.M. and Jarowski, C.I., Effect of diffusion layer pH and solubility on the dissolution rate of pharmaceutical acids and their sodium salts. II: Salicylic acid, theophylline, and benzoic acid. *J. Pharm. Sci.*, 74 (1985b) 148–154.

Serajuddin, A.T.M. and Rosoff, M., pH-solubility profile of papaverine hydrochloride and its relationship to the dissolution rate of sustained-release pellets. *J. Pharm. Sci.*, 73 (1984) 1203–1208.

Shah, A.C. and Nelson, K.G., Evaluation of a convective diffusion drug dissolution rate model. *J. Pharm. Sci.*, 64 (1975) 1518–1520.

Van der Veen, J., Buitendijk, H.H. and Lerk C.F., The effect of acidic excipients on the release of weakly basic drugs from the programmed release megaloporous system. *Eur. J. Pharm. Biopharm.*, 37 (1991) 238–242.

Wagner, J.G., Biopharmaceutics 18. Rate of dissolution part III. Methods of measuring and interpreting in vitro rates. *Drug Intell. and Clin. Pharm.*, 4 (1970) 77–82.