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Physicochemical aspects of drug release. XV. Investigation of diffusional transport in dissolution of suspended, sparingly soluble drugs

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Summary

The dissolution rates of sparingly soluble, fine particulate, suspended drugs have been studied using a Coulter Counter Model TAII. For two sieve fractions of oxazepam the dissolution rates were monitored in media with varying viscosities brought about by the addition of glycerol, while for griseofulvin the change in the medium's viscosity was induced by changing the temperature. By calculating the dissolution rate, and compensating for differences in particle surface area and media solubility, it was shown that the dissolution rate was diffusion controlled. After additional normalization for the diffusion coefficient, it was suggested that the so-called apparent diffusional distance decreased substantially with particle size. The effect of particle size was more limited above approx. 15 μm.

Introduction

The dissolution of most pharmaceutical compounds, is assumed to be diffusion controlled (Nogami et al., 1966; Carstensen, 1972; Grijseels et al., 1981). Accordingly, the dissolution rate can be described by a combination of Noyes-Whitney (1897), Nernst (1904) and Brunner (1904) theories to give the equation:

$$\frac{dw}{dt} = \frac{D}{h_D} S_c (C_s - C_t) \quad (1)$$

where dw/dt is the rate of increase of the amount of material in solution, D denotes the diffusion coefficient, h_D is the thickness of an assumed stagnant diffusion boundary layer, whose definition will be discussed in more detail below, S_c represents the interfacial surface area taking part in the dissolution process, C_s is the equilibrium solubility and C_t corresponds to the concentration of dissolved drug in the bulk medium.

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Basically, there are three potential rate-limiting factors: the diffusional transport, the interfacial surface area and the equilibrium solubility. The diffusional transport of dissolved molecules away from the solid surface to the bulk solution is of major importance and is related to the diffusion coefficient (D) and to the distance (h_D) over which diffusion is the dominant transport mechanism (Levich, 1962). Diffusional transport is dependent on several parameters, such as agitation intensity, liquid viscosity, temperature of the medium and particle size of the dissolving particles. This initial transport phase is often claimed to be rate limiting as discussed below. For highly soluble material, the slow initial transport is the rate-limiting step, while for sparingly soluble materials it is sometimes claimed that the solvation is rate limiting (Higuchi, 1967).

The interfacial surface area taking part in the dissolution process for suspended compounds is sometimes difficult to quantify, e.g. for strongly agglomerating materials, using the surface area of the primary particles leads to an overestimation of the effective solid surface area participating in the dissolution (Finholt and Solvang, 1968). The use of gas adsorption techniques to characterize this surface area is especially dangerous (Hoelgard and Møller, 1973; Florence and Salole, 1976).

In order to mimic the in vivo situation and to standardize the test procedure, most dissolution experiments are conducted under conditions where C_t never exceeds 10% of the equilibrium solubility (C_s), i.e. sink conditions. Under these conditions, the dissolution rate is directly proportional to the equilibrium solubility (Hamlin et al., 1965; Nicklasson and Brodin, 1984), provided other factors are held constant.

Diffusion as a rate-limiting step in the dissolution process

Due to a reduction in the velocity of the liquid caused by friction, solid particles dispersed in a liquid medium under agitation are surrounded by some zones of less movable liquid, i.e. a hydrodynamic boundary reflecting a velocity gradient between the bulk fluid and the surface of the solid. The thickness of the hydrodynamic boundary layer is often defined as the distance from the surface of the solid to the point where the tangential velocity attains a value equal to 90% of the main stream velocity (Levich, 1962; Grijseels et al., 1981). The fraction of the hydrodynamic boundary layer where liquid motion is almost absent and diffusion dominates is often known as the effective diffusion boundary layer (Grijseels et al., 1981). This cannot be evaluated easily from dissolution experiments, but has to be calculated from hydrodynamic data, e.g. using rotating disk experiments (Levich, 1962). The thickness of this layer has been claimed to have a value about 10 times smaller than the hydrodynamic boundary layer thickness (Grijseels et al., 1981). In studies where the hydrodynamic properties are not readily definable, the so called stagnant diffusion boundary layer thickness is often estimated from the observed (surface specific) dissolution rate, according to Eqn 1. This represents a somewhat simplified approach, but involves fewer assumptions when a complex system, such as an agitated suspension is studied. The stagnant diffusion boundary layer, as such, has no physical relevance, since it does not exist in reality. The term apparent diffusional distance is thus used in this study as a simplified measure of the distance over which diffusion dominates and is calculated according to Eqn 1. Furthermore, the denotation of this parameter in Results and Discussion will be h_{APP} rather than h_D as used in Eqn 1.

In a dissolution process, where no reaction exists between solvent and solute molecules, the transport of dissolved molecules from the surface of the solid to the bulk medium is considered to be the rate-limiting step in the dissolution process (Nogami et al., 1966; Carstensen, 1972). From dissolution studies, De Smidt (1990) concluded that the dissolution kinetics could be diffusion controlled for sparingly soluble drugs as well. He formulated a tentative rule from his data which stated that, for drugs with solubilities greater than 10 mg/l, diffusion controlled the rate of the dissolution process. The results of experimental studies conducted by Nyström et al. (1985b), Bisrat and Nyström (1988) and Anderberg and Nyström (1990) suggest that even for compounds with aqueous solubilities lower than 10 mg/l, diffusion is still the rate-limiting step in the dissolution

process. The findings of De Smidt and these authors are thus in direct contrast to the possibility that the dissolution rate of sparingly soluble drugs is surface reaction controlled rather than diffusion controlled.

Relationship between particle size and diffusion boundary layer

For relatively narrow size fractions, Niebergall et al. (1963) showed that the surface specific dissolution rate increases as a function of time, i.e. with the decrease in particle size of the dissolving materials. They concluded that the hydrodynamic boundary layer thickness is a function of the square-root of the diameter of the dissolving particle. Using very fine particulate sparingly soluble drugs, Nyström et al. (1985b), Bisrat and Nyström (1988) and Anderberg et al. (1988) have also demonstrated that the thickness of the diffusion layer is a function of the particle size of the materials tested. An enhancement of the surface specific dissolution rate is especially pronounced when the particle size is below approx. 5 μm. It was also shown that the surface specific dissolution rates of particles < 5 μm are not significantly affected by increased agitation intensities, while a sieve fraction of the same compound in the range 25–35 μm is affected (Bisrat and Nyström, 1988).

Higuchi and Hiestand (1963) have stated that the diffusion boundary layer thickness is comparable to or greater than the particle radius. The interdependence of particle size and the diffusion boundary layer thickness was also taken into consideration by Hintz and Johnson (1989). They used a calculated diffusion layer thickness to simulate the dissolution profile of a polydispersed powder. The diffusion layer thickness was taken to be equal to the radius of the particle up to the value of 30 μm, above which it was assumed to be constantly 30 μm. This assumption fitted their simulated dissolution profile well.

The importance of diffusional transport in dissolution kinetics has been studied in a variety of ways. Several studies (King et al., 1935; Braun and Parrot, 1972; Nelson and Shah, 1987) have shown that the viscosity of the medium affects the dissolution kinetics of drugs. Apart from increasing the viscosity, the addition of viscosity enhancing agents affects solubility, diffusibility and thus even the diffusion layer thickness. The diffusion layer thickness is affected by both the direct increase in viscosity and the change in the diffusion coefficient due to the addition of viscosity enhancing agents.

This current work represents further studies on the importance of diffusional transport on the dissolution kinetics of sparingly soluble, fine particulate drugs by changing both the particle size of the drug and the viscosity of the dissolution medium by the addition of glycerol and changes in temperature.

Experimental

Materials

Micronized oxazepam (Wyeth, Germany) was used because of its low aqueous solubility and relatively wide particle size distribution, thus making it possible to obtain different wet sieve fractions. Griseofulvin (fine particulate, Glaxo, U.K.) was also used because of its low solubility

TABLE 1

Primary characteristics of test materials

Materials	Density (g/cm^3)	Aqueous solubility at 23°C ($\mu g/ml$)	External surface area (cm^2/cm^3)	Surface shape factor (^{a}s, d_v)	Diffusion coefficient at 23°C (cm^2/s) ($\times 10^6$)
Oxazepam	1.48	22.0	13.400	6.7	7.67
Griseofulvin	1.44	8.9	31.000	5.1	4.86

TABLE 2

Size fractions of oxazepam and griseofulvin

Materials	Wet sieve fraction (μm)	Size distribution [b] by weight	
		d_v (μm)	S.D. (μm)
Oxazepam	< 5	3.24	1.87
	25–35	24.45	4.86 [c]
Griseofulvin	– [a]	3.51	1.63 [c]

[a] Untreated.
[b] Measured by Coulter counter TAII. Arithmetic mean values and S.D. are presented.
[c] Log-normal distribution characterized by geometric mean and geometric S.D. (dimensionless).

and since it has been well characterized in earlier studies (e.g., Nyström et al., 1985a).

Methods

Primary characterization of test materials

The primary characteristics of the untreated test materials are listed in Table 1.

Density. The density was measured with an air comparison pycnometer (Beckman Model 930, U.S.A.). The results are mean values of three determinations.

External specific surface area. The external surface areas were determined by permeametry, using a Blaine apparatus (Blaine, 1943). Due to the fine particulate materials used, the calculations of the surface area involved a correction for 'slip flow' (Alderborn et al., 1985). The results given are mean values of three determinations.

Particle size distribution. Particle size was measured using a Coulter Counter TAII, as described earlier (Nyström et al., 1985a). The results are shown in Table 2.

Particle shape. The surface shape factor, based on volume diameter and volume-specific external surface area measured by permeametry, was calculated according to Nyström et al. (1985b).

Preparation of wet sieve fractions

Oxazepam was wet sieved (precision test sieve with circular openings, Veco, The Netherlands) and sieve fractions in the range < 5 μm and 25–35 μm were prepared (Bisrat and Nyström, 1988). The particle size distributions of the sieve fractions are presented in Table 2.

Properties of oxazepam in aqueous glycerol mixtures

Solubility. The aqueous solubility of oxazepam was determined by adding an excess of the drug to 1 l of dissolution medium. The suspensions were shaken mechanically for 48 h at a constant temperature of 23 ± 0.2°C. After centrifugation the supernatant was assayed spectrophotometrically (Zeiss PMG, Germany) at 238 nm (Table 1). The solubility of oxazepam in 10, 20, 30 and 40% w/v of glycerol in water mixtures was determined by adding excess quantities of the drug to 500 ml of each mixture. The suspensions

TABLE 3

Solubility and diffusion coefficient of oxazepam in aqueous-glycerol mixtures and some properties of the mixture

Amount glycerol (%)	Kinematic viscosity (cSt)	Density (g/cm^3)	Dynamic viscosity (cP)	Solubility C_s (μg/ml)	Diffusion coefficient (cm^2/s) ($\times 10^6$)
0	0.935 [a]	0.998 [a]	0.933 [a]	22.0	7.67
10	1.223	1.023	1.251	35.0	5.72 [b]
20	1.717	1.046	1.796	45.5	3.99 [b]
30	1.947	1.075	2.093	65.8	3.44 [b]
40	2.592	1.096	2.841	90.43	2.52 [b]

[a] Data taken from Weast (1987).
[b] Calculated according to the Stokes-Einstein equation.

were then treated and analyzed as described above (Table 3).

Viscosity of dispersion media. The kinematic viscosities (ν) of the different glycerol-water mixtures were measured at 23 ± 0.2°C using a Cannon Fenske viscometer (Germany). The results are mean values of three determinations (Table 3). The densities (ρ) of the mixtures were determined using a pycnometer. The dynamic viscosity (η) was obtained from the equation $\nu = \eta/\rho$.

Diffusion coefficient. The diffusion coefficient measurements were carried out using a shear cell as described by Sundelöf (1982). The apparatus consists of four cylinders, each with two cells. Each cell consists of an upper (receiver) and a lower (donor) compartment which in the operative position will form one chamber. The cells were filled and allowed to equilibrate at room temperature for a few hours. The experiments were performed in a temperature-controlled room at 23 ± 0.1°C. All cells were made operative at nominally the same time but were stopped individually at predetermined times. Samples were then drawn from the receiving compartments for further spectrophotometric analysis of the amounts diffused. The diffusion coefficient values are given in Table 1 and were calculated according to Sundelöf (1982). From this value, the values of the diffusion coefficient of oxazepam in the different glycerol-water mixtures were calculated according to the Stokes-Einstein equation (Table 3).

Properties of griseofulvin in aqueous media at different temperatures

Solubility. The solubility of griseofulvin was determined using the spectrophotometer. Suspensions containing 400 mg/l (40°C), 300 mg/l (20, 30°C) and 200 mg/l (10°C) of griseofulvin in dissolution media were equilibrated for 24 h. The suspensions were filtered through a 0.6 μm standard Nucleopore polycarbonate membrane filter (Nucleopore, U.S.A.) into temperature-stabilised spectrophotometer cells, and the concentrations were determined immediately at 295 nm. The results presented are mean values of three determinations (Table 4).

Viscosity of dispersion media. The viscosity values of water at 10, 20, 30 and 40°C were taken from the literature (Weast, 1987) and are listed in Table 4.

TABLE 4

Solubility and diffusion coefficients for griseofulvin at different media temperatures and the corresponding viscosities

Temperature (°C)	Dynamic [a] viscosity (cP)	Aqueous solubility (μg/ml)	Diffusion [b] coefficient (cm^2/s) ($\times 10^6$)
10	1.307	4.8	3.32
20	1.002	6.4	4.48
30	0.798	9.4	5.82
40	0.653	14.6	7.34

[a] Data taken from Weast (1987).

[b] Diffusion coefficients calculated according to the Stokes-Einstein equation from experimentally measured value at 23°C (Table 1).

Diffusion coefficient. The diffusion coefficient measurements were carried out as described above and are given in Table 1. Using these values and the viscosity values of water from the literature, the diffusion coefficients of griseofulvin at the different temperatures were calculated (Table 4) as for oxazepam.

Determinations of surface specific dissolution rate

Particle size as a function of dissolution time. A Coulter Counter Model TAII fitted with a 50 μm aperture tube was used for griseofulvin, while 30 and 100 μm tubes were used for oxazepam sieve fractions < 5 and 25–35 μm, respectively. These aperture tubes were chosen in order to adequately cover the entire size distribution by weight.

Stock suspensions were prepared using particle-free distilled water containing 0.9% NaCl and 0.01% polysorbate 80. This electrolyte solution was also used as the dissolution medium in the experiments studying the effect of temperature. In the experiments where a viscosity enhancing agent was added, the dissolution medium was 4% NaCl, 0.01% polysorbate 80 and 10, 20, 30 or 40% glycerol.

The number of particles in 14 size classes was recorded simultaneously and calculations were carried out on a Hewlett Packard 9825T computer.

Calculation of surface specific dissolution rates. According to earlier equations (Nyström, 1985a), both the weight dissolved (μg) and the remaining external surface area (cm^2) were calculated as a function of time (min^{-1}). These calculations are based upon the material density, initial particle shape and specific surface area (Table 1). The calculations are further based upon the assumption that the particles dissolve in an isometric fashion, i.e. that the particle shape is not substantially changed during dissolution (Carstensen, 1980). From the amount dissolved and the mean external surface area, the surface specific dissolution rate ($\mu g\ min^{-1}\ cm^{-2}$) can be calculated for specific time intervals during the dissolution process.

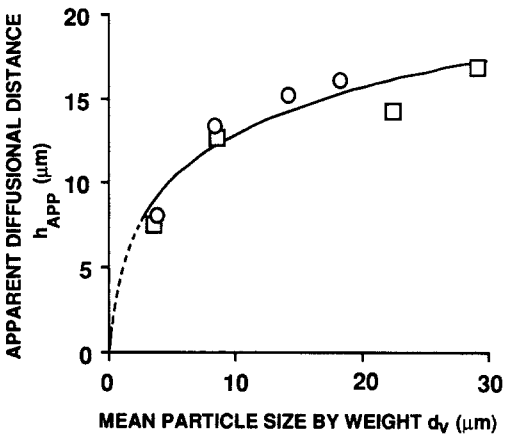

Fig. 2. Effect of particle size on apparent diffusional distance (h_{APP}); values obtained by calculation according to Eqn 2. Symbols as in Fig. 1.

Results and Discussion

The effect of particle size on dissolution rate and apparent diffusional distance

In Fig. 1, data taken from a previous study (Bisrat and Nyström, 1988), the surface-specific dissolution rates of digoxin and oxazepam, are plotted against the corresponding mean volume diameters by weight of the respective materials. This figure shows that the surface-specific dissolution rate for digoxin and oxazepam increases with a decrease in particle size of the materials. Since the parameters which affect the diffusion layer thickness such as temperature, viscosity and agitation were kept constant, the result can be explained by the effect of particle size on the thickness of the distance over which diffusion is the dominating transport mechanism.

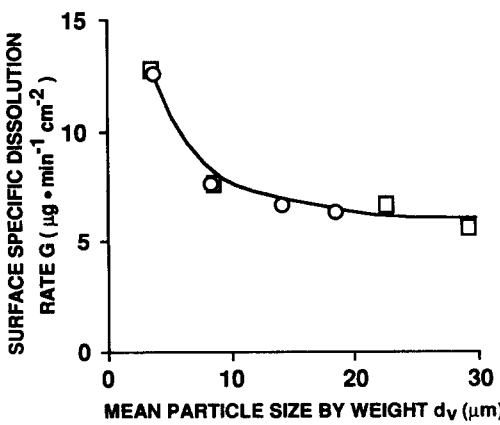

Fig. 1. Effect of particle size on surface specific dissolution rate (G) of (□) digoxin and (○) oxazepam.

To obtain an assessment of the numerical value of the thickness of the diffusion boundary layer, which is a rate-limiting step for the dissolution kinetics of digoxin and oxazepam since molecular diffusion to the bulk medium is retarded, it is necessary to correct the surface specific dissolution rate for both the solubility and the diffusion coefficient values. This was performed according to the Noyes-Whitney and Nernst-Brunner equations.

Since all the terms in Eqn 1 except the apparent diffusional distance, h_{APP} were determined experimentally, h_{APP} can be calculated by rearranging the equation to:

$$h_{APP} = \frac{DC_s}{G} \qquad (2)$$

Fig. 2 shows the plots for these corrected values (the apparent diffusional distances) for both materials, vs their mean particle sizes by weight. The diffusion coefficient value for digoxin substituted in Eqn 2 was determined to be 5.72×10^{-6} $cm^2\ s^{-1}$ and was measured as described above. The figure clearly demonstrates that a decrease

in particle size corresponds to a reduced diffusion layer thickness, i.e. a shorter diffusional distance for dissolved molecules. It is interesting to observe that the increase in the diffusion layer thickness is less pronounced for particles exceeding 10–15 μm in size. As the particle size increases, the diffusion layer thickness becomes small relative to the particle size and tends to level off to a constant value. Hintz and Johnson (1989) produced simulated dissolution rate profiles using diffusion layer thicknesses which when plotted vs the particle size had a profile approximately the same as those in this study.

The effect of viscosity on dissolution rate and apparent diffusional distance

For the concentrations studied (0–40% w/v glycerol), the viscosity varied from approx. 0.9 to 2.8 cP and the solubility of oxazepam in the glycerol-aqueous mixtures from 22 to 90 μg/ml, respectively (Table 3).

The surface specific dissolution rates of oxazepam sieve fraction < 5 and 25–35 μm as a function of viscosity in glycerol-aqueous mixtures are shown in Fig. 3. In the concentration ranges studied, the increases in glycerol concentration, though increasing the solubility more than 4-fold, seemed to produce a slight decrease in the surface specific dissolution rate.

In this study the surface-specific dissolution rate value is a function of solubility, diffusion

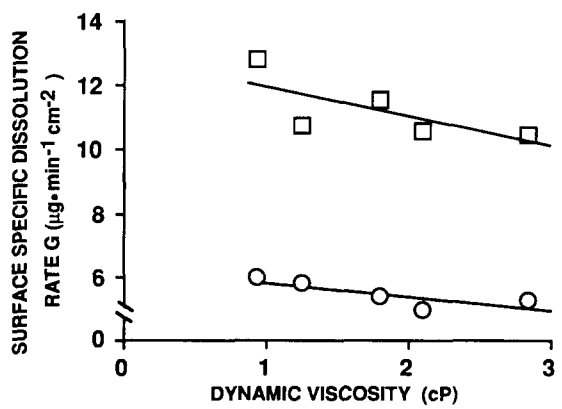

Fig. 3. Surface specific dissolution rate (G) of oxazepam with wet sieve fraction (□) < 5 μm and (○) 25–35 μm at different viscosity values.

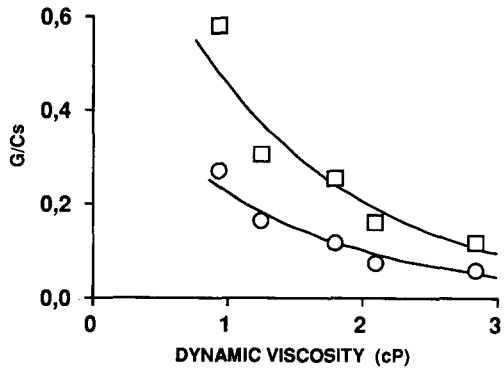

Fig. 4. Ratio of surface specific dissolution rate (G) to solubility (C_s) of oxazepam at different viscosity values. Symbols as in Fig. 3.

coefficient and diffusion layer thickness for the different particle sizes studied. The direct relationship between solubility and surface-specific dissolution rate is well documented in the literature (e.g., Hamlin et al., 1965; Nicklasson and Brodin, 1984). Since the solubility was greatly increased by the addition of glycerol, there is a need to correct for this increase by dividing the surface specific dissolution rate values by the corresponding solubility values in order to observe the effect of solubility on the dissolution (Fig. 4). This correction of the surface specific dissolution rate for solubility enables a decision to be made on whether or not the dissolution process is diffusion controlled. For a dissolution process where an interfacial reaction between the solid and liquid is the rate-limiting step, no difference would be expected in these corrected values for the different viscosity values. However, as seen from Fig. 4, the ratio between surface specific dissolution rate and solubility decreased with the increase in viscosity, showing that the diffusional process is of major importance in the dissolution process.

The other variable which has an influence in this dissolution study, especially in media with varying viscosities, is the diffusion coefficient. Thus, a further correction of the surface specific dissolution rate and solubility values for the diffusion coefficient values for the different aqueous-glycerol mixtures is necessary in order to obtain an indication of the apparent diffusional distance.

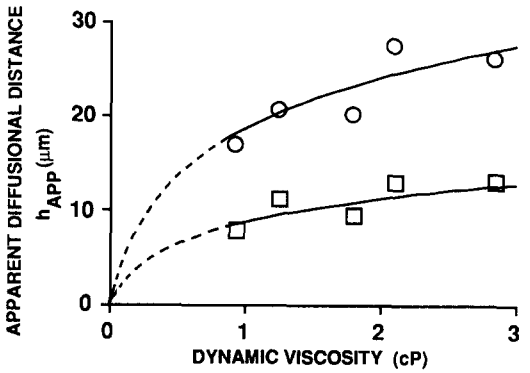

Fig. 5. Effect of viscosity on apparent diffusional distance (h_{APP}) of oxazepam, calculated according to Eqn 2. Symbols as in Fig. 3.

The diffusion coefficient for oxazepam in saline solution (0% glycerol) was determined as described in Experimental and is given in Table 1. By using this value and the viscosity values for the different glycerol-aqueous mixtures (Table 3), the diffusion coefficient of oxazepam at the corresponding viscosities was calculated according to the Stokes-Einstein equation. An inverse relationship between the diffusion coefficient and the viscosity is obtained.

It can be seen from Fig. 5 that the apparent diffusional distance increases with the increase in viscosity for both sieve fractions of oxazepam. This increase was about 2-fold for the sieve fraction 25–35 μm compared to that of < 5 μm.

The results shown in Fig. 5 demonstrate the effect of particle size on the diffusion layer thickness in viscous media. Previous work by Bisrat and Nyström (1988), using aqueous media, has shown that a decrease in particle size leads to a decrease in the diffusion boundary layer. This was explained by Niebergall et al. (1963) using the Prandtl boundary layer equation:

$$h_H = K\frac{L^{1/2}}{V^{1/2}} \qquad (3)$$

which correlates the hydrodynamic boundary layer thickness (h_H) to the length of the surface in the direction of the flow (L) and the relative velocity of the flowing liquid vs the flat surface (V). Studying coarse particles, Niebergall et al. (1963) assumed that for a solid that is counteractively affected by L and V, dispersed in a liquid medium under agitation, the effect will be a decrease in h_H with a decrease in particle size. Since the experimental model utilized does not give mathematical values for V, we are unable to use V as a variable. The effect of V is minimized by controlling the agitation intensity.

Although the mathematical relationships between the relative velocity, viscosity and agitation are complex and beyond the scope of this study, the results in Fig. 5 showing a more limited increase in the diffusion layer thickness for the finer sieve fraction can be explained by the effect of viscosity on the relative velocity of the flowing liquid. It can be assumed that in the sieve fraction < 5 μm the particles are always surrounded by fluid moving in the same direction. Thus, the relative velocity of the flowing liquid vs these particles does not decrease proportionally with the increase in viscosity, as seems to be the case for the sieve fraction 25–35 μm. According to Prandtl's equation, this would then lead to a greater increase in the diffusion layer thickness for the coarser fraction with the increase in viscosity than for the fraction < 5 μm.

The effect of temperature on dissolution rate and apparent diffusional distance

Fig. 6 shows the effect of temperature on the surface specific dissolution rate of griseofulvin. As expected, and shown in the literature (Nogami

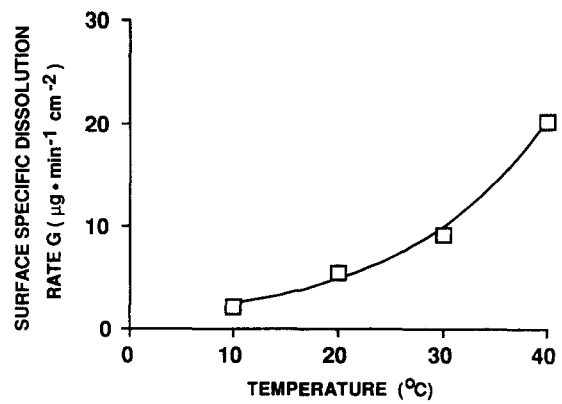

Fig. 6. Surface specific dissolution rate (G) of griseofulvin as a function of temperature.

et al., 1966; Tsuji et al., 1979), the dissolution rate increases with the increase in temperature. In the temperature range studied here (10–40°C), the surface specific dissolution rate increased 9-fold. The effect of temperature on the solubility of griseofulvin is shown in Table 4. With an increase in temperature from 10 to 40°C, the solubility of griseofulvin increased 3-fold.

It is known from the literature (Hamlin et al., 1965; Nicklasson and Brodin, 1984) that there is a direct relationship between dissolution rate and solubility. Here, the increase in the dissolution rate of griseofulvin at the temperature intervals studied is greater than that expected from the increase in solubility (Fig. 7). This increase therefore cannot be explained solely by the increase in solubility, but must also be due to the effect of temperature on viscosity and thus on diffusional transport.

The viscosity is seen here to decrease with an increase in temperature (Table 4). The increase in temperature and the decrease in the viscosity of the media lead, according to the Stokes-Einstein equation, to an increase in the diffusion coefficient of griseofulvin (Table 4). The diffusion coefficient values given in Table 4 were calculated according to the Stokes-Einstein equation from an experimentally determined diffusion coefficient value for griseofulvin at 23°C (Table 1). By correcting the surface specific dissolution rate at the different temperatures for the corresponding diffusion coefficient and solubility values for

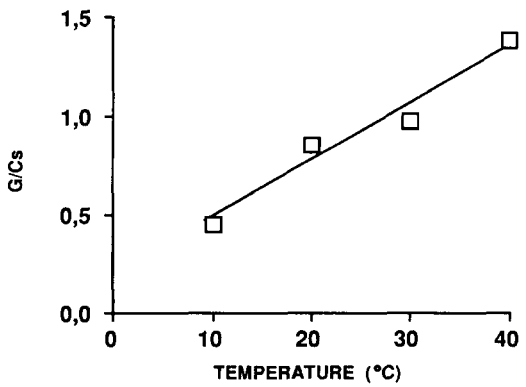

Fig. 7. Ratio of surface specific dissolution rate (G) to solubility (C_s) of griseofulvin as a function of temperature.

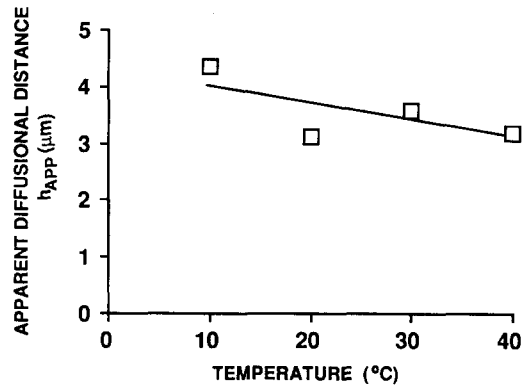

Fig. 8. Effect of temperature on apparent diffusional distance (h_{APP}) of griseofulvin, calculated according to Eqn 2.

griseofulvin (utilizing Eqn 2), we can obtain an indication of the apparent diffusion distance. These values were then plotted vs the temperature (Fig. 8). There is some indication that the increase in temperature caused a decrease in diffusional distance. However, the temperature range tested corresponds to a fairly limited viscosity range as compared to the studies on oxazepam. Thus, the effect of temperature on diffusional distance in this study is uncertain.

The strong influence of temperature on the surface specific dissolution rate of griseofulvin is attributed not only to the increase in solubility but also to a great extent to a decrease in the viscosity of the media. The decrease in viscosity leads to an increase in the diffusion coefficient for griseofulvin and probably to the limited decrease in the diffusional layer thickness.

Conclusions

The results of this study show that for sparingly soluble, fine particulate, suspended drugs, diffusional transport plays a major role in the dissolution kinetics. This was concluded by calculating the surface specific dissolution rate divided by compound solubility. The changes in media viscosity and temperature strongly affected the dissolution rate, independently of this solubility correction. The distance over which diffusion dominates as a transport mechanism is also seen

to be affected by both the particle size and the viscosity of the dissolution media. This was concluded after further correction of the dissolution rate for the diffusion coefficient values. It was thus demonstrated that the effects of particle size and viscosity still remained.

As a simplified representation of the diffusion dominated distance, a so-called apparent diffusional distance was calculated. This parameter is normally known as the stagnant diffusion boundary layer. Although it is obvious that a homogeneous stagnant layer has no physical relevance, it does represent a useful means for identifying the importance of formulation factors such as particle size, temperature and viscosity.

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