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# Characterization of calcium fenoprofen:
# 3. Mechanism of dissolution from rotating discs

B.A. Hendriksen

*Pharmaceutical Research Department, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU20 6PH (U.K.)*

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## Summary

The mechanism of dissolution of an unmodified production batch has been investigated from compressed rotating discs in the range 11–37 °C and 50–150 rpm. The intrinsic dissolution rate ($G$) from centrically mounted discs into pure water is a linear function of $\sqrt{\omega}$ ($\omega$ = angular velocity), as predicted by the Levich equation, and is indicative of a diffusion-controlled mechanism under these conditions. The observed gradient leads to an estimate of the diffusion coefficient which, at 25 °C, agrees well with that independently calculated from conductivity data. Conductivity is thus shown to be a conveniently simple and valid means of estimating the diffusion coefficient of this pharmaceutical electrolyte. The limiting intrinsic dissolution rate at infinite rotational speed can be estimated from plots of $1/G$ against $1/\omega$, and these have yielded estimates in the temperature range 11–37 °C. Similar extrapolations from eccentrically mounted discs agree well provided the disc is not mounted near the outer edge of the plate, where some turbulence may be expected. The temperature dependence of both the diffusion process and the processes pertaining at infinite rotational speed lead to activation energies of about 20 kJ mol$^{-1}$. Dissolution into several electrolyte solutions is always slower than into pure water, although estimated diffusion coefficients are similar. In some cases, e.g., $CaCl_2$, this is because of lower solubility, but in phosphate solutions there appears to be a combination of precipitation onto the surface, and the building-up of an electrical double layer, either or both of which hinder further dissolution. Under these conditions the dissolution becomes surface controlled.

## Introduction

In the absence of complicating reactions, dissolution involves the sum of several processes. Molecules or ions must leave the solid phase and enter solution in the vicinity of the surface, where shear forces are relatively low and a 'stagnant' boundary layer builds up. This layer is relatively viscous and concentrated. Molecules or ions must then diffuse within this layer down the concentration gradient to the bulk liquid phase. The boundary layer has a notional thickness which at equilibrium will become smaller as the flow rate of bulk liquid past it increases. The overall dissolution process may be limited by the rate of initial dissolution from the solid surface (surface control) or by diffusion from the boundary layer (diffusion control), and both types of control may be observed for a given substance as the conditions are varied (Prakongpan et al., 1976).

The degree to which a system conforms to the

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*Correspondence:* B.A. Hendriksen, Pharmaceutical Research Dept, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU20 6PH, U.K.

linearity predicted by the Levich equation (see below) is generally taken as an indicator of which mechanism predominates. Low shear rates tend to favour diffusion control, under which conditions good linearity is observed, and these rates can be measured without difficulty (e.g., Friedman and Asherov, 1981). Measurement of the surface-controlled dissolution rate is less straightforward. Nicklasson and Brodin (1984) have suggested experimental arrangements involving rotating discs, both centrically and eccentrically mounted, which when extrapolated to infinite rotational speed, equivalent to boundary layers of zero thickness, yield estimates of the surface-controlled process.

The present series of studies on calcium fenoprofen [part 1: Hendriksen (1990); part 2: Hendriksen and Williams (1991)] is largely concerned with the dissolution properties of batches made in a variety of ways from powders, tablets and compressed discs, into water and into phosphate buffer solutions. It is important to know what mechanisms apply under varying conditions, and particularly important to obtain reliable baseline data on the dissolution of a representative unmodified production batch. Using therefore only one batch, data have been generated from centric and eccentric compressed rotating discs in pure water under a variety of temperatures and rotation rates, and from these the parameters of the two dissolution mechanisms have been estimated. Additionally, the effects of dilute electrolytes (buffers) and more concentrated electrolyte solutions upon the mechanism of dissolution have been briefly investigated. An adjunct of these studies is the independent evaluation of the diffusion coefficient, and as calcium fenoprofen is an electrolyte, these have been determined by a conductivity method.

## Experimental

### *Materials*

#### *Compressed discs*

One batch of calcium fenoprofen was used consistently throughout the present studies; it was from a production line and was referred to in part 1 (Hendriksen, 1990) as P6. Active ingredient below 75 $\mu$m ($\approx 0.24$ g) was compressed on an Apex laboratory hydraulic press to a pressure of 40 bar. No excipients were present and no lubricants were used. Each face of the disc had an area of 1.19 cm$^2$.

### *Methods*

#### *Compressed disc dissolution*

Compressed discs were fitted into purpose-made stainless-steel holders similar to those described by Nicklasson and Magnusson (1985). The holders with a centric cavity have been described in part 2 (Hendriksen and Williams, 1991); the eccentric holders had a much larger radius (44.9 mm) in order to accommodate a cavity whose displacement from the central axis was 17.75 mm (small radius) or 35.75 mm (large radius). Dissolution rates were studied in the Hansen dissolution bath, using 100 ml of dissolution medium, which was usually distilled water, but at times included various electrolyte and buffer solutions. A variety of rotational speeds (50–150 rpm, sometimes up to 400 rpm) and temperatures (11–37 °C) were employed. Concentration with time was followed by UV absorbance at 220 nm. In some semiquantitative tests, the metallic faces of the disc were insulated with adhesive tape, and an electrical potential was applied from a d.c. source; the opposite electrode comprised a steel strip placed at the edge of the dissolution beaker.

#### *Solubility and conductivity*

Solubility of pure, recrystallised calcium fenoprofen was determined by adding an excess to doubly distilled water or to other salt solutions, and stirring in a thermostatted water-bath over a range of temperatures in a closed vessel, to exclude carbon dioxide. Supernatant was filtered after 18 h, diluted and assayed by UV absorption.

Conductivities were determined with a Radiometer CDM3 meter. A known weight of pure recrystallised calcium fenoprofen was dissolved in doubly distilled water (conductivity 3.1 $\mu$S at 25 °C); other concentrations were made by dilution. Conductivity values were determined at several temperatures in the range 16.3–30.0 ° C, and as a function of concentration down to 15 $\mu$M. Conductivities, as equivalent conductivities, were extrapolated to infinite dilution, using the relation given by Shedlovsky (1932).

*Zeta potential*

A Zetasizer 11 was used to determine the zeta potential of small calcium fenoprofen particles in buffer solutions of various strengths. The constraints imposed by the conductivity cell precluded the use of full-strength buffer solutions in these studies. The results are referred to in the Discussion.

## Results

*Centric discs in water*

Intrinsic dissolution rates are listed in Table 1 at three temperatures and three rotation speeds. Each is the mean of determinations; the standard deviation values are also given.

Plots of dissolution rate against $\sqrt{\omega}$ ($\omega$ = angular velocity) are shown in Fig. 1 at each temperature; in each case the relationship is linear and gradients may be directly determined.

TABLE 1

*Intrinsic dissolution rate in water from centrically mounted rotating discs as a function of temperature and rotation speed*

| Temperature (° C) | Rotation speed (rpm) | Intrinsic dissolution rate (mg/s per cm$^2$) ($\times 10^4$) |
|---|---|---|
| 11 | 50 | 18.9 ± 2.3 |
| 11 | 75 | 24.7 ± 0.9 |
| 11 | 100 | 28.5 ± 2.9 |
| 11 | 150 | 35.4 ± 1.6 |
| 25 | 50 | 27.8 ± 3.4 |
| 25 | 75 | 38.6 ± 2.5 |
| 25 | 100 | 42.7 ± 3.6 |
| 25 | 150 | 49.6 ± 0.6 |
| 36.5 | 50 | 39.7 ± 4.3 |
| 36.5 | 75 | 48.4 ± 3.8 |
| 36.5 | 100 | 60.8 ± 4.3 |
| 36.0 | 150 | 70.5 ± 3.0 |

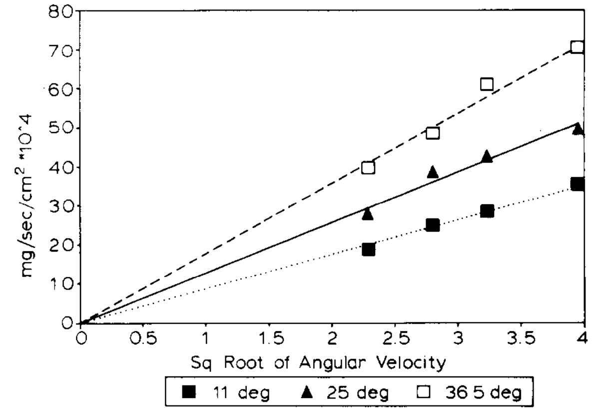

Fig. 1. Intrinsic dissolution rate from centric discs into water, as a function of temperature and of angular velocity, $\sqrt{\omega}$. (■) 11° C, (▲) 25° C, (□) 36.5° C.

The gradients may alternatively be calculated from the Levich relation:

$$G = 0.61 \times D^{2/3} \times \nu^{-1/6} \times C_s \times \sqrt{\omega}$$

where $G$ is the intrinsic dissolution rate, $D$ is the diffusion coefficient, $\nu$ is the kinematic viscosity, and $C_s$ is the solubility. Diffusion coefficients were back-calculated from the Levich equation using the experimentally determined values for $G$ and $C_s$, and literature values for $\nu$. These values and the resultant estimates of the diffusion coefficients are summarised in Table 2.

TABLE 2

*Data used in the Levich equation and the resulting estimates of the diffusion coefficient as a function of temperature*

| | Temperature (° C) | | |
|---|---|---|---|
| | 11 | 25 | 36.5 |
| Gradient ($\times 10^4$) | 8.78 ± 0.12 | 12.89 ± 0.32 | 17.90 ± 0.34 |
| Kinematic viscosity | 0.012715 | 0.008930 | 0.007029 |
| Solubility | 2.074 | 2.502 | 2.881 |
| Diffusion coefficient ($\times 10^6$) | 6.14 ± 0.13 | 7.55 ± 0.28 | 9.41 ± 0.27 |
| Units: gradient | mg cm$^{-2}$ s$^{-0.5}$ | | |
| kinematic viscosity | cm$^2$ s$^{-1}$ (Stokes) | | |
| solubility | mg cm$^{-3}$ | | |
| diffusion coefficient | cm$^2$ s$^{-1}$ | | |

TABLE 3

*Intrinsic dissolution rates in water from eccentrically mounted rotating discs as a function of temperature, rotational speed, and radius of eccentricity*

| Rotation speed (rpm) | Temperature (° C) | Dissolution rate small radius (mg/cm$^2$ per s) (×10$^4$) | Rotation speed (rpm) | Temperature (° C) | Dissolution rate large radius (mg/cm$^2$ per s) (×10$^4$) |
|---|---|---|---|---|---|
| 50 | 24 | 40.0 ± 2.4 | 50 | 24 | 48.6 ± 2.9 |
| 75 | 24 | 50.7 ± 1.6 | 75 | 24 | 56.1 ± 1.2 |
| 100 | 24 | 51.2 ± 2.1 | 100 | 24 | 61.6 ± 2.2 |
| 150 | 24 | 64.1 ± 0.9 | 150 | 24 | 74.1 ± 1.9 |
| 50 | 37 | 52.7 ± 2.0 | 50 | 37 | 66.5 ± 3.7 |
| 75 | 37 | 67.0 ± 2.4 | 75 | 37 | 79.2 ± 2.7 |
| 100 | 37 | 71.9 ± 5.6 | 100 | 37 | 87.1 ± 4.1 |
| 150 | 37 | 86.5 ± 5.0 | 150 | 37 | 104.9 ± 3.7 |

*Eccentric discs in water*

The measured intrinsic dissolution rates for each temperature, rotational speed and radius of eccentricity are shown in Table 3. Each value shown is the mean of three to six determinations; the standard deviations are also given.

Dissolution rate may be plotted against $\sqrt{\omega}$ in the same way as for centrically mounted discs; Levich theory may not strictly apply to this configuration but nevertheless linear plots are obtained at each temperature and radius of eccentricity, and the gradients are tabulated below.

Small radius, 24 °C $16.64 \pm 0.45 \times 10^{-4}$ mg cm$^{-2}$ s$^{-0.5}$
Small radius, 37 °C $22.52 \pm 0.40 \times 10^{-4}$ mg cm$^{-2}$ s$^{-0.5}$
Large radius, 24 °C $19.40 \pm 0.44 \times 10^{-4}$ mg cm$^{-2}$ s$^{-0.5}$
Large radius, 37 °C $27.29 \pm 0.48 \times 10^{-4}$ mg cm$^{-2}$ s$^{-0.5}$

These are larger than the equivalent centric gradients, reflecting the greater shear rates experienced by these samples.

*Centric discs in other media*

Dissolution data at 25 °C were determined in several electrolytes (see Table 4). In some cases diffusion coefficients were estimated as in the previous section using literature viscosity data and experimental solubility data, but as the calculations are based on at best two rotational speeds only, they are less reliable than the corresponding water value.

TABLE 4

*Intrinsic dissolution rates in electrolyte solutions from centric discs, at 25 ° C, and estimates of diffusion coefficients*

| Dissolution medium | Intrinsic dissolution rate (mg/cm$^2$ per s) (×10$^4$) | | Estimates of diffusion coefficient (cm$^2$/s) (×10$^{-6}$) |
|---|---|---|---|
| | 50 rpm | 150 rpm | |
| NaCl (1.349 M) | 26.2 ± 1.4 | 48.3 | 6.87 |
| NaCl (2.698 M) | | 21.0 | |
| $CaCl_2$ (0.500 M) | 6.5 ± 1.0 | | 7.59 |
| $CaCl_2$ (1.349 M) | 1.96 ± 0.16 | 3.10 ± 0.19 | 5.55 |
| $BaCl_2$ (1.349 M) | | 14.3 | |
| $NaH_2PO_4$ (1.349 M) | | 4.7 | |
| Water | 27.8 ± 3.4 | 49.6 ± 0.6 | 7.55 |

### *Solubility*

Solubility data in four aqueous media, as a function of temperature, are summarised in Table 5.

The relationship between solubility and temperature may be approximated by

$$\ln S = \ln S_0 - (\Delta H / RT)$$

where $S$ is the solubility at temperature $T$ and $\ln S_0$ is a constant related to the entropy of solution (Hildebrand et al., 1970). When $\ln S$ is plotted vs $1/T$, a linear relationship is expected, the gradient of which is $-\Delta H/R$, and from which the enthalpy of solution, $\Delta H$, is directly estimated. Linear relationships were obtained in the present work, the principal use of which was the short extrapolation of solubilities to the temperatures of the rotating disc experiments, discussed below. Enthalpies of solution were determined in each medium and are also included in Table 5.

Enthalpies of solution are positive, in line with many inorganic hydrates; comparison between the above solutes is not possible because the final state (concentration) varies between them.

### *Conductivities*

Limiting equivalent conductivities (half the molar values in the present case) are shown in Table 6. Using the same units, the limiting equivalent ionic conductivity of $Ca^{2+}$ at 25 °C is 59.0 (Falkenhagen and Ebeling, 1971), from which the corresponding value for the fenoprofen ion may be calculated by subtraction as 28.56. The diffusion coefficient ($D$) can be calculated from the Nernst-Hartley equation when the final ($d \ln \gamma_\pm / d \ln c$) term is known.

$$D = \frac{(\nu_+ + \nu_-)(l_+^\circ l_-^\circ)}{\nu_+ |z_+|(l_+^\circ + l_-^\circ)} \cdot \frac{RT}{F^2}\left(1 + \frac{d \ln \gamma_\pm}{d \ln c}\right)$$

$\nu_+$, $\nu_-$ are numbers of cations and anions, $z_+$ is the cation valency, $l_+^\circ$, $l_-^\circ$ are the limiting equivalent ionic conductivities, $\gamma_\pm$ is the mean molar activity coefficient, $c$ is the electrolyte molarity, $F$ is the Faraday number, $R$ is the gas constant and $T$ is the temperature. At infinite dilution the ($d \ln \gamma_\pm / d \ln c$) term approaches zero, and $D = 7.69 \times 10^{-6}$ at 25 °C. In the present work, concentrations were low but not zero; e.g., rotating discs at 25 °C and 150 rpm gave solutions about 20 mM after 3 min, the period over which dissolution rates were measured. The term $d \ln \gamma_\pm / d \ln c$ at this concentration was estimated as $-0.18$ using the Güntelberg (1926) modification to the Debye-Hückel limiting law, suggesting that during this period the diffusion coefficient steadily reduces to 0.82 of its initial infinite dilution value, i.e., to about $6.31 \times 10^{-6}$. Kuu et al. (1989) employed a similar equation but without the ($d \ln \gamma_\pm / d \ln c$) term in their studies on variation of diffusion coefficient within the boundary layer.

TABLE 5

*Solubility and enthalpy of solution of calcium fenoprofen in various media (units: mg / ml)*

| | Temperature (°C) | | | Enthalpy of solution (kJ/mol) |
|---|---|---|---|---|
| | 25 | 36.1 | 43.95 | |
| Pure water | 2.51 | 2.81 | 3.125 | 8.99 ± 0.35 |
| NaCl (1.349 M) | 2.59 | 2.98 | 3.28 | 9.79 ± 0.08 |
| $CaCl_2$ (0.5 M) | 0.58 | 0.6 | 0.81 | 12.94 ± 1.27 |
| $CaCl_2$ (1.349 M) | 0.207 | 0.257 | 0.303 | 15.74 ± 0.59 |

TABLE 6

*Limiting equivalent conductivity of calcium fenoprofen as a function of temperature*

| Temperature (°C) | Conductivity ($\Omega^{-1}$ cm$^{-2}$ equiv.$^{-1}$) |
|---|---|
| 16.3 | 70.78 |
| 20 | 77.735 |
| 25 | 87.56 |
| 30 | 97.47 |

## Discussion

### *Water*

The linearity of intrinsic dissolution rate with $\sqrt{\omega}$ in the Levich plots (Fig. 1) indicates that the reaction is diffusion controlled under the conditions studied, both for centric discs and for the higher shear rates experienced by eccentric discs.

Intrinsic dissolution rates at infinite rotational speed ($G_\infty$) may be estimated by a number of extrapolation methods. Nicklasson et al. (1982) considered the case of an eccentrically mounted horizontal disc under conditions of laminar flow and suggested that $1/G$ would be a linear function of $1/R\sqrt{\omega}$, where $R$ is the radius of eccentricity. For a vertically mounted disc under turbulent conditions, they concluded $1/G$ would be a linear function of $1/\omega$. For the former case these authors also suggested the relationship $G \propto 1/R\sqrt{\omega}$ (Nicklasson and Brodin, 1984). In the present work, attempts were made to extrapolate data from both centric and eccentric discs to infinite rotational speed using the four combinations of $G$ and $1/G$ vs $1/\omega$ or $1/\sqrt{\omega}$. All in principle yielded estimates of $G_\infty$ but the following points should be noted.

(a) For centric discs the $1/G$ vs $1/\sqrt{\omega}$ relationship yielded negative values of $G_\infty$. It should be borne in mind, however, that this relationship was proposed for eccentric discs.
(b) For eccentric discs the $1/G$ vs $1/\sqrt{\omega}$ relationship yielded positive and high values of $G_\infty$, but the standard errors are so large (up to 50% of the values of $G_\infty$) as to render this extrapolation useless in practice.
(c) The two relationships $1/G$ vs $1/\omega$ and $G$ vs $1/\sqrt{\omega}$ give values not dissimilar from each other, and with standard errors and regression coefficients not unreasonably high.
(d) The fourth relationship, $G$ vs $1/\omega$, yields values in the same ranking order as (c) but about 25% lower.

It cannot be asserted from such an empirical examination which extrapolation is 'correct' or even 'best'. However, the values resulting from the $1/G$ vs $1/\omega$ extrapolation do at least give $G_\infty$ values from centric discs which are closely similar to those from eccentric discs and a small radius of eccentricity. In addition, it was the relationship used by Al-Janabi (1990) in his studies of three substances as centric discs. If Al-Janabi's data are plotted in any of the alternative ways described here, then the same comments could be made for his three substances as have been made for calcium fenoprofen.

TABLE 7

*Intrinsic dissolution rate in water of the surface-controlled reaction (units: mg / cm² per s) ( × 10⁴)*

| Temperature (° C) | From centric discs | From eccentric discs | |
|---|---|---|---|
| | | Small radius | Large radius |
| 11 | 61.4 | – | – |
| 24 | – | 85.3 | 94.2 |
| 25 | 86.6 | – | – |
| 36.5 | 117.1 | – | – |
| 37 | – | 123.7 | 139.7 |

The intrinsic dissolution rates at infinite rotational speed are estimated accordingly from plots of $1/G$ vs $1/\omega$ and are given in Table 7, for centric discs and for eccentric discs at two radii of eccentricity. Although such rates have been equated with those of the surface-controlled dissolution reaction (Nicklasson and Magnusson, 1985), it is perhaps safer to observe caution and interpret them as the 'limiting rate of dissolution for the given experimental conditions' (Nicklasson et al., 1982).

The results for the first two data sets are in good agreement with each other but for the third are a little higher, probably because of turbulence near the edges of the mounting plate. Data from eccentrically mounted discs have reinforced the data from centric discs, but the latter are sufficient in themselves in the present system for extrapolating to the limiting dissolution rate, which is thus seen to be about 70% faster than the diffusion-controlled reaction at 150 rpm. Other substances can differ widely from this behaviour; the data of Nicklasson and Magnusson (1985) show wide variation in the ratios between diffusion-controlled rates at low rotational speeds and what they refer to as surface-controlled rates.

The temperature dependence of the diffusion-controlled reaction leads to an estimated activation energy of 20.4 (centric) or 19.0 (eccentric) kJ mol$^{-1}$, which is essentially the same as that similarly computed for the limiting rate at infinite rotational speed, 19.3 kJ mol$^{-1}$. Nicklasson et al. (1982, 1988) reported 20.3 kJ $mol^{-1}$ for the much more soluble substance referred to as HI-6, and values in the range 45–55 kJ $mol^{-1}$ for sulphamethizole, aspirin and alaproclate hydrochloride. Gardner and Nancollas (1975) reported 24.3 kJ $mol^{-1}$ for calcium oxalate. These activation energies do not correlate well with measured solubilities, and any connection there may be between them requires further study.

Diffusion coefficients calculated from electrical conductivity are in good agreement with those back-calculated from the Levich equation. Conductance may thus represent a convenient means of determining diffusion coefficients in water for pharmaceutical electrolytes. Many pharmaceutical substances whether electrolytes or not give diffusion coefficients of similar magnitude, e.g., Nicklasson and Magnusson (1985) report values in the range $4.3–12.3 \times 10^{-6}$ for eight substances whose solubilities vary over a range of 750 : 1.

Diffusion coefficients may be calculated from conductance data at temperatures other than 25 ° C in order to make comparisons with diffusion coefficients from rotating disc experiments at temperatures other than 25 ° C. Experimental conductivities were linearly extrapolated, and combined with limiting ionic conductivities interpolated from the literature (Falkenhagen and Ebeling, 1971). The Nernst-Hartley equation thus predicts diffusion coefficients at 11 and 36.5 ° C of 4.88 and $9.90 \times 10^{-6}$ at infinite dilution. These are of the right order but agree less well than the values at 25 ° C, possibly because of the extrapolations neccessarily involved; the conductance data were restricted to the range 16–30 ° C.

*Electrolyte media*

Dissolution rates in electrolyte media are understandably influenced by the varying solubilities, themselves a consequence of salting in or salting out, but it is notable that the calculated diffusion coefficients do not differ greatly from the value in pure water at 25 ° C, $7.55 \times 10^{6}$ $cm^2$ $s^{-1}$, in spite of the solubilities in these media being in some cases substantially different from the water solubility (see Table 4). The two slowest dissolution rates are in calcium chloride and sodium dihydrogen phosphate, but the causes are quite different. Calcium chloride salts out the solute by the common ion effect, a mechanism clearly not possible with the latter salt, whose low rate may be better understood from studies with a much more dilute phosphate buffer solution.

When dissolution experiments were attempted in the phosphate buffer used in the powder dissolution studies (0.039 M) (parts 1 and 2), rates were initially fast, but rapidly declined, this disparity becoming more pronounced at higher temperatures, concentrations or rotation rates.

Taking the initial period as 0–2 min and comparing with the rate during the 10–14 min period, this disparity reached 24 : 1 at 45 ° C and 400 rpm, which may be compared to 8 : 1 for buffer of 20% of normal strength (0.0078 M) or 1.8 : 1 for pure water. The rapid dissolution rates initially observed in buffer were hard to measure accurately but were generally about 3-times the initial rate in pure water.

In seeking an explanation for the rapid decline, the possibility was considered that phosphate ions might adsorb or precipitate onto the surface, hindering subsequent dissolution of fenoprofen. To test this, three discs were soaked overnight in buffer. Compared to water as control, soaking in 1, 10 and 100% (0.039 M) buffer subsequently gave dissolution rates of 97, 13 and 72%, respectively, showing an erratic slowing down is taking place, consistent with precipitation being at least partially implicated. When initial dissolution rate in buffer was plotted vs $\sqrt{\omega}$, the relationship was certainly not linear, showing that this reaction differs mechanistically from that with water, in that it became surface rather than diffusion controlled. Soaking discs in pure water cannot give precipitation, but when thus presoaked for a few seconds and for 1 h, their initial dissolution rates in buffer declined to 92 and 80% of control, suggesting some different time-dependent mechanism.

The possibility was considered that an electrical double layer forms at the surface, in water and in buffers, to an extent that increases as the degree of dissolution increases, proportionately hindering further dissolution. Ho et al. (1984) have implicated a similar phenomenon in their studies on cholesterol monohydrate dissolution.

In a series of semiquantitative studies, a direct voltage was applied to the conducting disc holder, the opposite electrode being placed in the dissolution medium. When a negative potential of 6 V was applied, the dissolution rates increased over the control, by 6% (phosphate buffer), 38% (Tris buffer), or zero for water. A positive potential of 6 V reduced the dissolution rate by 27% (phosphate buffer), 6% (Tris buffer), or 13% (water). The data are consistent with a positive potential naturally forming during dissolution, which may be neutralised or exacerbated externally with measurable effects upon dissolution rate.

Zeta potentials of calcium fenoprofen particles were determined in water and in very dilute phosphate buffer solutions. In water, the particles developed a potential of −27 mV, while in phosphate buffer the potential was a function of concentration, being +3 mV at 1–2 mM, declining to zero at 4 mM and to −9 mV at 6–8 mM. These concentrations are lower than that of the buffer used in the dissolution experiments (39 mM), which was too conductive for the instrument cell, and the particles studied were of necessity very small ones, but overall the zeta potential data do suggest interaction between the surface and the buffer, the nature of which is concentration dependent. However, they do not support directly the above suggestion that a positive potential forms during dissolution. In view of the semiquantitative and limited nature of the applied potential studies, it is perhaps futile to seek a detailed mechanistic interpretation of the dissolution step at this stage, beyond stating the probable involvement of a combination of electrical forces and of phosphate adsorption or precipitation on the surface.

In conclusion, it is apparent that in pure water dissolution is a diffusion-controlled process. A slowing down is observed after a few minutes, and it is possible that this is caused by the initial preferential dissolution of one of the ions. This would lead to a surface charge of opposite sign from that of the ion in question, with a hindering of the dissolution of this ion and thus of the drug substance as a whole. An externally applied potential suggests this charge is positive, while zeta potential measurements indicate that it is negative. Clearly, further studies are needed to resolve this problem, but irrespective of the sign of the charge, it remains a plausible mechanism for the slowing down in pure water.

In dilute phosphate buffers, the slowing down is much more marked, particularly under conditions of rotation rate and of temperature that would naturally be expected to enhance dissolution rate. Surface charges could be responsible in these systems as for pure water: externally applied potentials caused an increase (when negative) or a decrease (when positive), consistent with a positive charge naturally forming. Zeta potential measurements are less useful in this system; they are a function of concentration, and the concentration of principal interest is not experimentally accessible. Nevertheless, surface charges of whatever sign are unlikely to account in full for the relatively large slowing down observed; neither can changes in diffusion coefficient which are seen to be very similar in a range of concentrated electrolytes. It seems likely that surface precipitation or absorption of phosphate ions is a major contributor to the slowing down, consistent with the rapid onset of surface control in phosphate buffers.

Surface precipitation, if accepted, would further clarify why some tablet formulations prepared from coarse active ingredient (part 2) give such a marked slowing down in the latter stages of dissolution. Coarse particles intrinsically have an unfavourable area/mass ratio, but, in addition, it is these particles that are likely to survive long enough for surface precipitation to commence, which will further slow down their dissolution in phosphate buffer.

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