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Dissolution at porous interfaces

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Summary

The occurrence of turbulence at a depression in a dissolving solid surface is assumed to be an important factor increasing the dissolution rate of the surface. To confirm this hypothesis experimentally, the dissolution rate of tablet surfaces, wherein cylindrical pores are drilled, is determined. The experiments are performed in a centrifugal stirrer system. An effort is made to describe the hydrodynamics inside the centrifugal stirrer system by comparing it with a tornado vortex generator used in tornado studies on laboratory scale. The similarity between both apparatuses is striking. The thickness of the hydrodynamical boundary layer along the tablet surface appears to be an important parameter: it seems to be correlated to the minimal pore diameter, above which the pore has an increasing effect on the dissolution rate of the surface, and besides it affects the extent of this increase.

Introduction

Studying dissolution of compressed non-disintegrating discs, it was observed that pores in the disc surface do not influence the mass transport rate (Parrott et al., 1955; Shah and Parrott, 1976). Only at very high porosities, i.e. about 20%, a marked increase in dissolution rate was observed (de Blaey and van der Graaff, 1977), which was ascribed to an increased effective surface area owing to the distortion of the so-called stagnant diffusion layer.

Pores in the surface of a compressed tablet are very small, i.e. mostly below 15 μm (Dees, 1980). For 1 mm pores, artificially drilled in a tablet, Wurster and Seitz

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(1960) observed an increase of the dissolution rate provided the inner pore surface was properly wetted. The shape of the pores changed during dissolution from cylindrical to conical. Van der Graaf et al. (1979) reported on the influence of the diameter of wetted pores on the dissolution rate and estimated that in their experimental set-up only above about 225 μm the pores contribute to the dissolution process.

This latter phenomenon might be of interest to understand release processes from systems in which large pores occur, i.e. in matrix-type sustained release tablets (Fessi et al., 1978) or from systems such as suspension suppositories where drug particles dissolve at a liquid–liquid interface (Crommelin and de Blaey, 1980; Schoonen et al., 1979 and 1980). Understanding of mass transport from interfaces and thus also from porous interfaces seems to require an approach based on hydrodynamics rather than on the classical stagnant layer theory. The relevant theory has been reviewed recently (Grijseels et al., 1981) and will be treated here only briefly and applied to porous systems. Essentially it implies that hydrodynamic factors cannot be overlooked when the dissolution from porous systems is concerned. The theory that the so-called stagnant layer curves into the pore, thus increasing the effective surface area, is a too simple representation of the facts. In reality in a convective dissolution system no stagnant layer exists, but both a hydrodynamic and a (much smaller) diffusion boundary layer develop along the surface of the dissolving solid. Under conditions of laminar flow along a flat plate the thicknesses of both layers increase with the square-root of the distance from the leading edge of the surface. Besides, the thicknesses are inversely proportional to the square-root of the liquid velocity along the plate. This finds expression in the measured dissolution rate of the surface, since when the diffusion boundary layer becomes thicker implicitly the diffusional flux (i.e. the local dissolution rate) decreases (cf. Grijseels et al., 1981).

Turbulence effects in the boundary layer cause a drastic decrease of the effective diffusion layer thickness. Turbulence arises when a critical Reynolds number is exceeded. The presence of a depression in a surface (Fig. 1) may lead to the occurrence of turbulence. Levich (1962) states that the dimensions of such a depression should be at least comparable with the thickness of the hydrodynamic

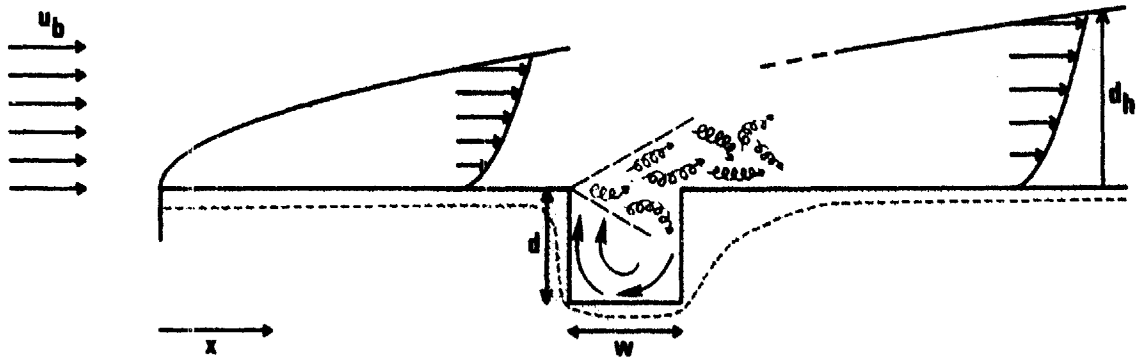

Fig. 1. Disturbance of the hydrodynamic laminar boundary layer present along a semi-infinite plate in the vicinity of a depression.

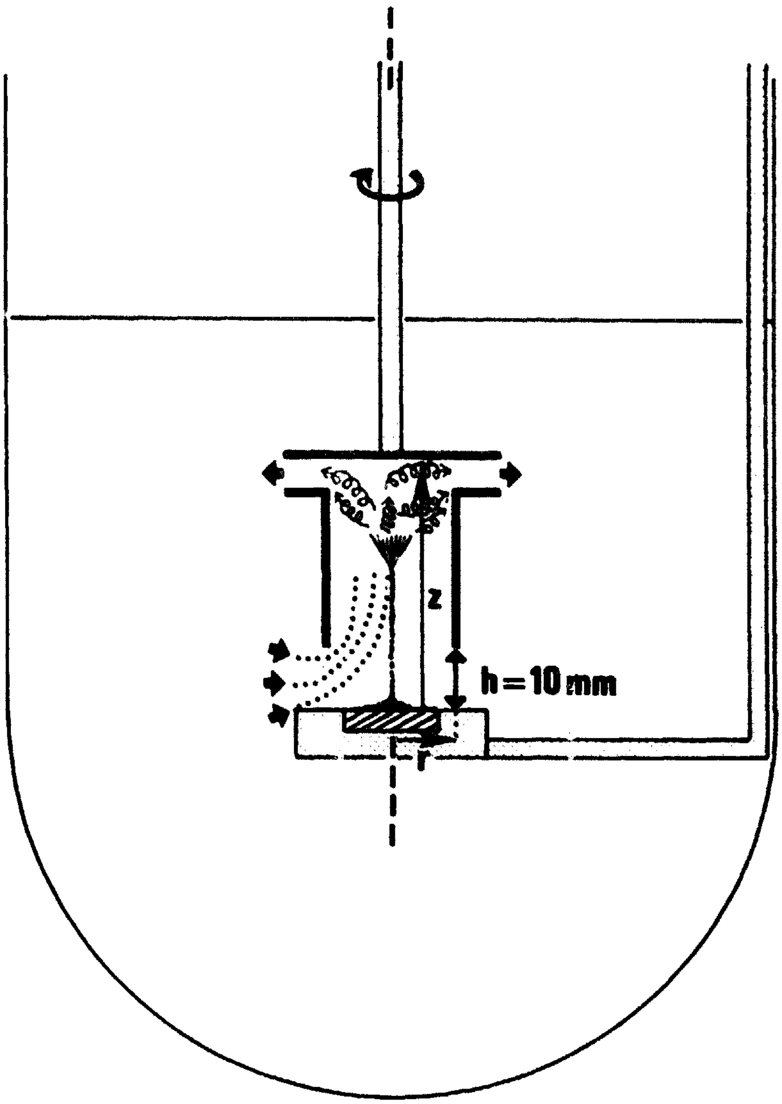

Fig. 2. The centrifugal stirrer dissolution rate apparatus (see text for explanation).

boundary layer. In that case even at small Reynolds numbers, separation of the streamlines above such a pore is noticed, while inside it a reversed flow is present. Their interaction causes an irregular, turbulent flow pattern (Sykes, 1980). The turbulent zone extends not only in and above the depression, but also in the region immediately downstream from it. There the turbulence is dampened gradually and the laminar boundary layer recurs. In the turbulent zone a higher dissolution rate is found (Davies, 1977), which will result in a faster retreat rate of the dissolving surface. The increase of the dissolution rate will depend on the liquid velocity, the kinematic viscosity of the solvent as well as on the dimensions, the shape and the position of the pore.

All this implies that dissolution studies aiming at mechanistical insight have to be done in a set-up where the hydrodynamics can be described.

For this purpose we have started our investigations on this subject using a centrifugal stirrer system, adapted from de Blaey and van der Graaff (1977), shown in Fig. 2. The fluid is sucked along the dissolving surface by rotating the stirrer. The flow dynamics in this system show a great resemblance to the tornado vortex generator modeled by Ward (1972) and further evaluated by e.g. Church et al. (1977) and Rotunno (1977, 1979, 1980), studying tornadoes on a laboratory scale.

Rotunno (1979, 1980) gives a description of the airflow dynamics in such a system. Depending on swirl ratio, α, the ratio of the rotational and the radial flow at distance, r, from the vertical axis, different situations can occur. With low α-values (0–0.2), inside the upward bulk flow a central core is present in which axial downflow occurs. At higher swirl ratios ($\alpha > 0.3$) this backflow in the centre does not occur; on the contrary, an axial jet-like flow upward arises which is in fact a continuation of the lower plate boundary layer into an axial boundary layer. In the lower boundary layer, towards which our interest is directed in the first place, in addition to the radial flow a rotational flow exists, of course. Moreover, related to the usual increase of the thickness of the laminar layer along a plate, a vertical velocity component is present in the boundary zone. This increase in thickness is even more intensified by an additional growth of the boundary layer as consequence of its ring-shape: the boundary layer ring is directed inward and hence is compressed since its circumference becomes shorter.

In our centrifugal stirrer system a waterflow instead of an airflow is concerned; viscosity is higher and due to friction effects the rotational flow will be faster and the radial flow somewhat slower, relative to each other. Hence α is rather large and it is not surprising that we, as illustrated later, observed an axial jet flow in the centrifugal stirrer system (Fig. 2).

An argument that might even strengthen the supposed similarity of this hydrodynamic system with the aerodynamic tornado generator is the occurrence of vortex breakdown. For larger swirl ratios (e.g. $\alpha = 0.4$) Rotunno (1979) found that above a certain height in the column axial downflow occurred, whereas below it the axial jet-like upflow was induced. The collision of these two flows appeared to be associated with vortex breakdown; this breakdown refers to the transition of the swirling, narrow laminar jet to a funnel-shaped flow that breaks down into a broad, chaotic turbulence with much reduced swirl and reversed (i.e. downward) flow (see Rotunno, 1979; his figure 2.2). Anticipating the results we already report here that the same phenomenon was noticed during our experiments with the centrifugal stirrer.

Materials and methods

For the dissolution rate experiments we used disodium tetraboratedecahydrate (Borax, Ph. Eur.) as test material. Tablets of pure borax with a diameter of 15.0 mm were made under sufficiently high compression to avoid large pores in the compacts. The consistency of this procedure was confirmed by the good reproducibility of the experiments (see Results and Discussion). From the dimensions and weight of the tablets and the density of the bulk material, as determined by means of an air comparison pycnometer, the tablet porosity was calculated as about 7%.

Cylindrical pores were drilled in the compacts at 2200 rpm with a diameter ranging from 0.20 to 2.00 mm. Next to the diameter, the number of the pores and their position in the tablet surface were varied. The pore depth always exceeded the diameter, so basically all pores had the same shape, viz. narrow and deep.

All dissolution rate experiments were carried out in the same vessel (Fig. 2) to avoid hydrodynamic differences due to vessel size or shape. The vessel was thermostatted at 20.0 ± 0.1°C.

As solvent medium, about 1000 ml of demineralized water was used. The tablets were mounted in a perspex holder, exposing only one flat surface to the solvent, whereby they could be so positioned that at the start of every experiment the upper surfaces of the tablet and holder lay in one plane. Then the removable holder was fixed under the centrifugal stirrer in a position as shown in Fig. 2. The stirring rate was 100 or 200 rpm respectively, which provided a thorough mixing of the solvent in the vessel.

During the experiments the borax concentration in the solvent was measured continuously by means of a conductometer. In the range used, a linear correlation was observed between concentration and conductivity. To calibrate the conductometer 10.0 ml of a 8.0 mg/ml borax solution was added to the solvent prior to every dissolution rate experiment and the increase in conductivity was recorded. This pre-addition of borax to the dissolution medium has two advantages: (1) the system is re-calibrated before every experiment, whereby the exact solvent volume does not have to be known. The solubility of borax in demineralized water was determined as 48.8 mg/ml (20.0°C), so at the start of any experiment the concentration was less than 0.2% of the solubility. At the end the concentration never exceeded 1% of the saturation concentration, consequently sink conditions are assured; and (2) the pH of the solvent remains constant over the whole duration of the experiments. During several experiments with undrilled tablet surfaces we measured pH and conductivity simultaneously. Indeed no variation in bulk pH nor in dissolution rate was recorded: the pH retained continuously its value of 9.1, and all conductivity vs time curves were straight (the standard error of estimate, computed by a microprocessor that was connected to the conductometer parallel with the recorder, never exceeded 0.3% of the mean conductivity during an experiment).

Before every experiment the drilled pores were filled with saturated borax solution by means of an injection syringe analogously to the method used by van der Graaff et al. (1979). When necessary, prior to the dissolution experiment, the remaining air bubbles were carefully removed from the pores with the aid of an injection needle cleaning wire. Experiments were performed at least in triplicate.

Results and Discussion

Intact tablet surface

In the first place dissolution rate experiments were performed with tablet surfaces of different batches in which no artificial pores were drilled. We found a good

TABLE 1

	100 rpm	200 rpm
$\bar{R}$ (mg/s)	0.1324	0.1846
s (mg/s)	0.0014	0.0044
cv (%)	1.0	2.4
n	12	16

The mean dissolution rate ($\bar{R}$) of intact tablet surfaces ($S = 176.7\ mm^2$) at two stirring rates; n = number of experiments, s = standard deviation and cv = coefficient of variation (symbols are listed at the end of the article).

reproducibility of the dissolution rate values with a variation coefficient of about 1–2% (Table 1). From visual observation of the dissolving tablet in the centrifugal stirrer system an attempt was made to give a qualitative description of the hydrodynamics. In all cases a tornado-like plume was noticed, starting at the central zone of the tablet surface and rising up in vertical direction where it broke down at certain height (depending on the stirring rate) above the surface. This plume was visible thanks to the difference in refractive indices of the bulk solvent and the more concentrated borax solution coming from the surface.

The dissolution rate of the intact tablet surface increased proportionally with the square-root of the rotation speed of the stirrer (Table 1), which is a strong indication that a laminar boundary layer flow is present along the surface, since in the case of a turbulent boundary layer the dissolution rate is expected to depend on the rotation speed to a power of about 0.9 (Grijseels et al., 1981). With a stirring rate of 100 rpm the mean retreat rate of the intact surface was calculated at about 0.27 mm in 10 min. Near the edge we measured with a micrometer a retreat of 0.40 ± 0.05 mm; this confirmed the impression obtained by visual inspection of the surface, that the centre of the tablet dissolved slower than the edges, according to the convective diffusion theory for laminar flow along a plate.

Drilled pores

Next, dissolution rate measurements were performed with tablets containing drilled cylindrical pores. The pores were so positioned in the surface that they formed a fairy ring around the centre of the tablet. The diameter of this ring was 10.0 or 5.0 mm, so the distance from the edge of the tablet to the pores was 2.5 mm and 5.0 mm, respectively. Although both the pore shape changed and the tablet surface retreated inwards into the holder during the experiments, all dissolution recordings were straight lines, apparent from the calculated standard error of estimate which was less than 0.5% of the mean conductivity during all experiments. Again a good reproducibility was found for identical experiments with variation coefficients ranging from 1 to 3%.

After a dissolution experiment the tablet surface was always inspected through a stereomicroscope; an interesting phenomenon was the presence of a kind of trough downstream from the pores (Fig. 3). Their orientation with respect to the pores could be qualified as being between radial and tangential; in fact just as the flow pattern along the surface is expected to be directed. It is likely the troughs arise as

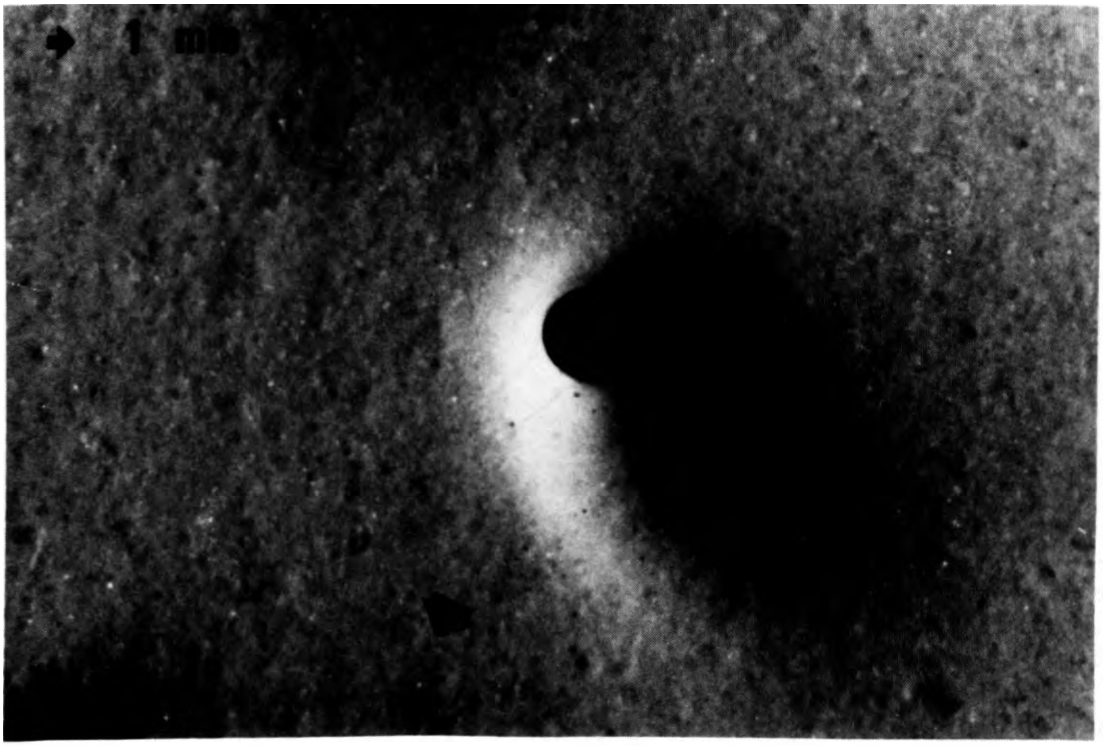

Fig. 3. Photograph of a trough, developed near a drilled 0.40 mm pore in the surface of a borax tablet during a dissolution experiment at 100 rpm. The arrow points to the centre of the tablet surface and does not indicate the flow direction.

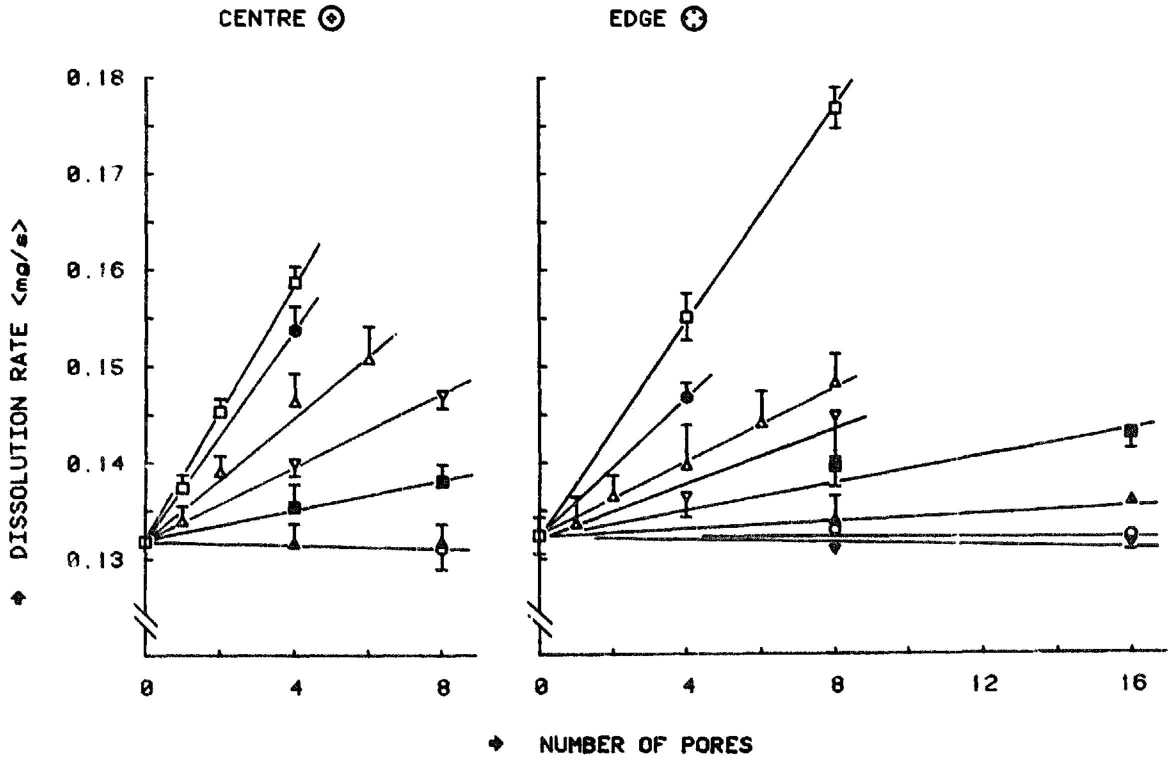

Fig. 4. Dissolution rate of a borax tablet surface with drilled pores at 100 rpm. Vertical bars represent the standard deviation of the mean dissolution rate. The points are connected by linear regression lines calculated by means of the least-squares method. Distance from pores to surface edge: (a) 5.0 mm (central position); (b) 2.5 mm (edge position). □, pore diameter 2.00 mm; ●, 1.50 mm; △, 1.00 mm; ▽, 0.70 mm; ■, 0.50 mm; ▲, 0.40 mm; ○, 0.30 mm; ▼, 0.20 mm.

TABLE 2

Pore diameter (mm)	100 rpm		200 rpm	
	Edge	Centre	Edge	Centre
0.20	−0.06±0.07		0.73±0.18	0.22±0.27 *
0.30	0.00±0.05	−0.09±0.17	0.94±0.19	0.85±0.31
0.40	0.19±0.07	−0.03±0.14 *	–	–
0.50	0.68±0.07	0.79±0.15 *	2.90±0.37	2.98±0.38
0.70	1.42±0.20	1.93±0.05 *	4.40±0.70	4.43±0.52
1.00	1.90±0.15	3.19±0.19 *	6.87±0.71	7.87±0.64 *
1.50	3.71±0.24	5.46±0.45 *	11.44±0.72	14.29±0.82 *
2.00	5.56±0.14	6.81±0.21 *	15.78±0.81	19.14±1.45 *

Increase per pore of the dissolution rate (μg/s) as function of the pore diameter (mm), pore position (Edge: 2.5 mm from the surface edge; Centre: 5.0 mm from the surface edge) and rotation speed of the stirrer. These values are calculated from the slopes of the lines in Fig. 4 (100 rpm) and the corresponding lines at 200 rpm. The standard deviation of the slopes are also given.

* The asterisks indicate a significant difference ($P = 0.95$) between 'edge' and 'centre' position.

consequence of the turbulence induced by the pore, which causes a local increase of the diffusional flux and thus an extra erosion of the tablet surface. In the way the pores were positioned with regard to each other, in most cases a visible overlap of the troughs was absent.

Number and position of pores

Fig. 4 shows the dissolution rates at 100 rpm as a function of the number of pores, where each symbol represents one particular pore diameter. In the left part of the figure results of centrally positioned pores are drawn; pores with a diameter of 0.4 mm or less cause no significant increase of the dissolution rate (Student's t-test; $P = 0.95$). Larger pores, however, accelerate the dissolution rate of the tablet surface, this effect being more pronounced the larger the pore diameter.

The right part of Fig. 4 (pore position near the edge of the surface) shows that pores of about 0.3 mm or less have no noticeable influence on the dissolution rate, but, here too, with larger diameters an accelerating effect is observed.

Besides, it is clear from the straightness of the drawn lines (the linear regression lines computed by the least-squares method), that for all pore diameters investigated, a linear correlation exists between number of pores and dissolution rate, meaning that all pores dissolve independently on each other.

Pore size

The slopes of the lines in Fig. 4 express the increase in dissolution rate due to one pore of a particular diameter. These are summarized in Table 2, together with the corresponding data obtained at 200 rpm. In Fig. 5 these extra dissolution rates per

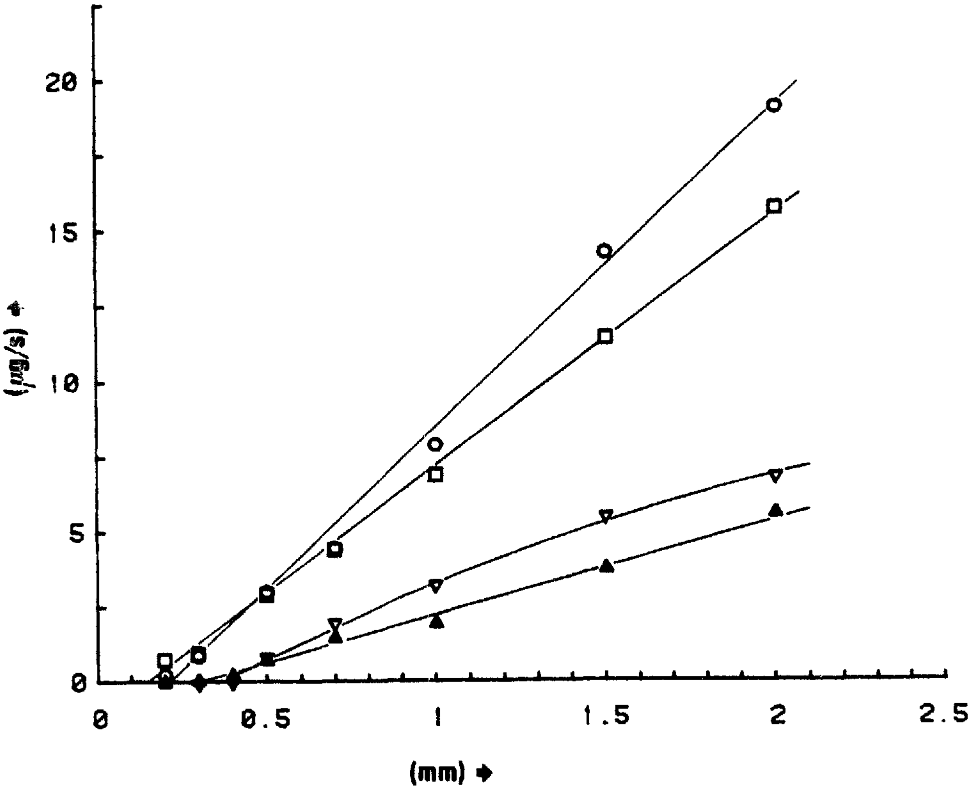

Fig. 5. Increase per pore of the dissolution rate as function of the pore diameter (cf. Table 2; for clarity standard deviations are not drawn). ▲, 100 rpm, edge; ▽, 100 rpm, centre; □, 200 rpm, edge; ○, 200 rpm, centre.

pore are drawn as function of the pore diameter. Obviously, both at 100 and 200 rpm, the centrally positioned pores tend to cause a bigger increase of the dissolution rate than the pores drilled near the edge of the surface.

Based on the boundary layer theory the following explanation can be offered: the laminar boundary layer has a greater thickness at the centre of a tablet than near the edges. The same holds for the diffusion boundary layer. The turbulence that is likely to occur in the surroundings of a pore decreases the thickness of these layers, thus increasing the local dissolution rate. In the centre this increase will be more pronounced since there is a relatively larger reduction of the diffusion layer thickness. This might explain why the lines of the pores in the central zone are steeper.

It is striking that the majority of the lines in Fig. 5 are straight, which indicates that the increase in dissolution rate depends on the pore diameter and not on the inner surface or the depth/diameter ratio of the cylindrical pore. Another interesting conclusion to be drawn from Fig. 5 is the existence of a so-called minimal pore diameter below which no positive influence on the dissolution rate is executed. The value of this critical diameter seems to depend on the flow velocity (actually the rotation speed of the stirrer) and on the position of the pore in the tablet surface. Table 3 contains the minimal pore diameters calculated by the least-squares method from the linear regression lines through the underlined points of Table 2. The minimal pore diameters found at 200 rpm are significantly ($P = 0.95$) smaller than

TABLE 3

	100 rpm	200 rpm
Edge	0.32 ± 0.05	0.16 ± 0.03
Centre	0.37 ± 0.06	0.23 ± 0.04

The minimal pore diameter (mm) (see text) as a function of the pore position and the stirring rate. The values and standard deviations are calculated from the least-squares regression lines through the underlined data in Table 2.

at 100 rpm. The same holds in the case of 200 rpm for pores near the edge compared to pores in the central region. No significant difference can be demonstrated between the two pore positions at 100 rpm, but in this case too the central position tends to be joined with a larger minimal pore diameter. All these findings seem to comply with the statement of Levich (1962) that a relationship exists between pore dimensions and the disturbance of the laminar boundary layer. Turbulence arises only when the pore diameter is large enough in relation to the hydrodynamic boundary layer thickness. As stated before, the boundary layer thickness is smaller near the leading edge of the surface or with a higher solvent velocity. The minimal pore diameter seems to follow the same trend. Qualitatively it varies just like the thickness of the hydrodynamic boundary layer. How far a quantitative relationship exists, however, is to be investigated during further dissolution rate studies that allow for an exact calculation of the thickness of the laminar boundary layer.

Abbreviations

cv	coefficient of variation
d	poredepth (mm)
d_h	thickness of the hydrodynamic boundary layer (mm)
h	distance between tablet holder and stirrer (mm)
n	number of experiments
P	probability
r	radius of the stirrer (mm)
$\bar{R}$	mean dissolution rate (mg/s)
s	standard deviation (mg/s)
S	tablet surface area (mm^2)
u_b	flow velocity in the bulk (m/s)
w	pore diameter (mm)
x	distance from the leading edge of the surface (mm)
z	distance normal to the surface (mm)
α	swirl ratio

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