International Journal of Pharmaceutics, 49 (1989) 261–268
Elsevier

IJP 01675

Dissolution of acetaminophen in a single pore and its relevance for dissolution of tablets

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(Received 9 May 1988)
(Accepted 12 July 1988)

Key words: Acetaminophen (paracetamol) crystals; Dissolution; Single pores

Summary

Dissolution of acetaminophen from single pores is investigated in which the pore walls are prepared from specially grown crystals of acetaminophen. Dimensions of pores are measured during dissolution. It is found that a minimum pore size is needed to start pore growth. Above this minimum size, pore growth is proportional to pore width and an increasing height decreases pore growth. There is an effect on pore growth for different orientations of crystal faces constituting the pore wall, and pore shape can change to a cylindrical form. Crystals forming high and narrow pores dissolve with the highest rate at the entrance of the pore, whereas low and wide pores grow with the highest rate at their closed end. It is concluded from these results that centrally in the pore there is an ascending flow of fresh fluid and a descending flow of solute near the pore walls. It is the resistance to flow of the ascending fresh fluid in the pore that determines pore growth. It is shown that the postulated flow regimen for pores may also have some relevance for dissolution behaviour of tablets.

Introduction

Usually the effect of pores on dissolution rate is studied on disks prepared by compression or by a melt process. Results from these studies show a negligible influence of small pores on the dissolution rate up to porosities of 20% (Parrott et al., 1955; Shah and Parrott, 1976; De Blaey and Van der Graaff, 1977). Larger pores ($> 2 \times 10^{-2}$ cm) contribute to the dissolution process, but to a lower extent than is expected from a calculation of their surface area (Wurster and Seitz, 1960; Van der Graaf et al., 1979).

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Grijseels and De Blaey (1983) and Grijseels et al. (1981, 1983a, b and c) investigated the problem in depth in a series of papers and found for all kinds of flow regimens, including natural convection, that turbulent flow is induced by pores, if they exceed a certain minimum size. Turbulent flow creates troughs downstream of the pore that are responsible for the higher dissolution rate. So in these cases it is not the increase in surface area of the pore walls that is contributing to a higher dissolution rate, but it is the pore, acting as an obstacle, that increases dissolution rate. Pore size appeared to be linearly related to wake length and dissolution rate, whereas pore depth only has an effect with shallow pores. Crommelin and De Blaey (1980), Fokkens and De Blaey (1982) and Schoonen et al. (1979, 1980) studied release of drug particles across liquid paraffin/water inter-

faces as a model system for drug release from fatty suppositories.

These interfacial particle systems have a porosity of about 50%. The dissolution rate enhancing effect of pores as obstacles creating turbulent flow downstream is not likely for the interfacial systems. Therefore in this study the effects of pore size and shape on dissolution rate of acetaminophen are investigated for single pores under the same experimental conditions as used for the interfacial particle systems.

Materials and Methods

Materials

Crystals of acetaminophen (paracetamol) were obtained by recrystallization in an isothermal fashion from distilled water. Commercially obtained acetaminophen was dissolved in hot distilled water. After cooling, the saturated solution was filtered through a previously wetted filter in a large Petri dish (diameter 22 cm), covered with a thin polyethylene foil, to a height of about 0.75 cm. In a few days large crystals were grown. For the experiments on pore growth 3 crystals of equal height (± 20 μm) were selected. One of the crystals was cleaved under an angle of 90° with the aid of a razorblade. In this way two new and equal faces were created. These cleaved crystals fitted exactly between the other two crystals. Therefore a square pore was formed with two opposite walls under an angle of 90° with the horizontal and two opposite walls under an angle of $62° \pm 1°$ and $180° - 62° = 118°$ with the horizontal (Fig. 1).

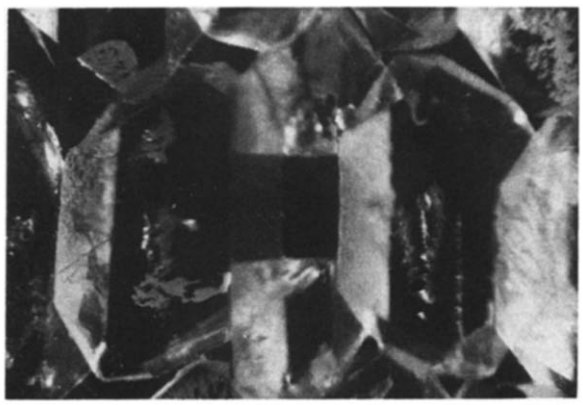

Fig. 1. A square pore made from 3 crystals of acetaminophen, surrounded by other crystals to prevent fast dissolution of the outer faces of the pore crystals.

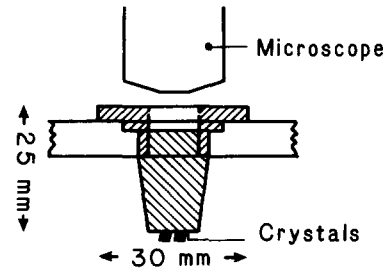

Fig. 2. Dimensions of perspex holder for crystals.

Apparatus

A dissolution flow cell was used as described previously (Schoonen et al., 1979b) with a few modifications.

(1) The crystals were not suspended from a liquid paraffin interface, but were fixed with liquid paraffin to a holder made of methacrylate polymer (perspex) (Fig. 2).
(2) Through this holder the crystals were photographed from above by a camera mounted on a microscope (Olympus).

Measurement

Dimensions of crystals and pores were measured with a microscope. To measure the retreat rate of each crystal face in the pore by dissolution and to notice a possible displacement of the crystals, which would destroy an accurate measurement, some fixed reference points were needed. The crystals were marked with small spots of white dye. With the aid of these marks, fixed lines, parallel to the crystal faces, could be drawn on the photographs, taken during an experiment. In this way distances of each crystal face relative to these lines could be measured.

To measure the enlargement of the photographs exactly, two parallel lines were etched on the perspex holder at the place where the crystals were fixed. The crystals constituting the pore were surrounded with other acetaminophen crystals to prevent fast dissolution of the outer faces of the

pore crystals (Fig. 1). The holder with crystals was lowered carefully into the dissolution cell after stabilisation of flow rate and temperature (37 °C).

In the experiments reported here mass flow of solute was not measured, so the drainage tube was positioned as low as possible ensuring free convection around the crystals. The applied flow was only used to maintain sink conditions in the dissolution cell.

Usually every 3 or 4 min during dissolution, the pore dimensions at the closed end of the pore against the holder were photographed from above with the aid of the microscope. At the end of an experiment the holder was taken out of the cell to measure dimensions of the open end of the pore, if this was possible. Retreat rate of the fastest dissolving crystal face (118° with the horizontal), measured at 10 min from the start of an experiment, was taken as the rate of pore growth.

Tablets ($\varnothing = 1.00$ cm) containing a mixture of acetaminophen (sieve fraction 100/120 μm) and dicalcium phosphate dihydrate (Emcompress; sieve fraction 75/125 μm) without any lubricant were prepared with the aid of a manual press at 20 kN. The die and punch assembly made of stainless steel was also suited for use in the dissolution cell, allowing dissolution of one tablet surface.

Results and Discussion

Single crystal dissolution was investigated earlier for potassium ferricyanide (Schoonen et al., 1979b). Dissolution of the crystal causes density differences between the solution close to the crystal faces and the bulk of the surrounding fluid. Under conditions of natural convection, a convective flow of solute downwards is generated. Fresh fluid flows radially in the direction of the crystal. Therefore the highest dissolution rate is found at the vertical crystal faces. This maximum dissolution rate under conditions of natural convection is also constant. Dissolution of the horizontal crystal face proceeds at a much lower rate and increases as the crystal dissolves to smaller sizes.

If a second crystal is situated in the neighbourhood of a particular crystal, dissolution of both crystals is slowed down. The vertical faces forming the slit between both crystals have a lower dissolution rate due to the hindered radial flow of fresh fluid into the slit. Fig. 3 shows series of photographs of dissolving acetaminophen crystals. The bottom series shows 2 crystals viewed side-on and the upper series shows another set of 2 crystals from above. In the bottom series it can be clearly seen that the flow regimen is moulding the shape of the crystals.

Notice the rounding-off effect at the edges of the horizontal faces of both crystals. Although at these points the hydrodynamical boundary layer is partly saturated, the necessary change in direction of the flow here creates a thin boundary layer where dissolution rate is even higher than at the leading edge of the vertical faces at the perspex holder. It can also be seen that the shape of crystals is changing considerably due to a low dissolution rate of the horizontal face. In the upper series the hindered radial penetration of fresh fluid into the slit can be judged from the changing shape of the slit.

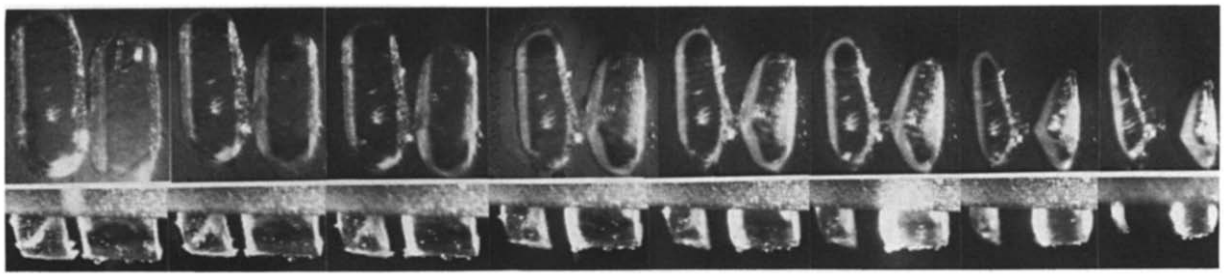

Fig. 3. Dissolution of 2 crystals of acetaminophen placed at a small distance from each other. Upper series: photographed from above through the perspex holder. Bottom series: photographed side on.

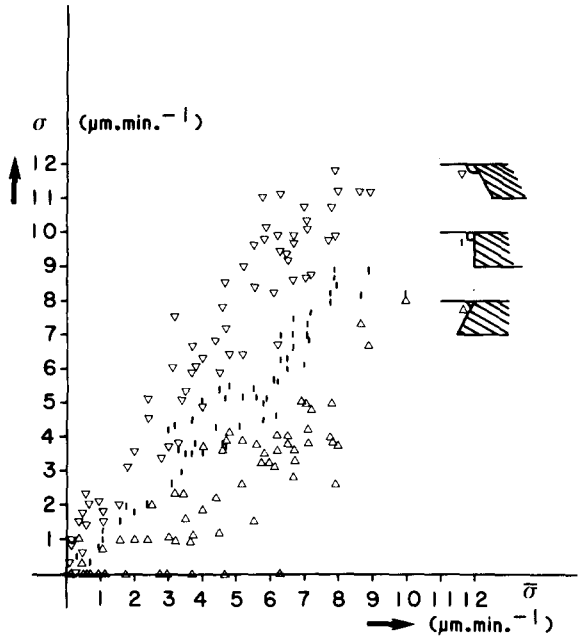

Fig. 4. Dissolution rate, σ, of a crystal face with one of 3 possible orientations in the pore versus mean dissolution rate.

Results so far suggest that the availability of fresh fluid has an important effect on dissolution rate. If a dissolving surface is freely accessible for fresh fluid, the dissolution rate is constant and maximum under conditions of natural convection (vertical faces in single particle dissolution). If surfaces are not freely accessible for fresh fluid, the dissolution rate decreases. This is the case for the vertical faces in the slit and also for the horizontal faces of crystals where transport of fresh fluid is prevented by the falling 'curtain' of solute from the vertical faces.

The availability of fresh fluid is further investigated in pores that are made by inserting two more crystals at both ends of the slit (Fig. 1). In this way a pore was created with well-defined dimensions (length equal to width). In a vertically oriented pore as shown in Fig. 1, fresh fluid has to flow upwards in the center of a pore to replace the downward flow of the solute, close to the pore walls. Retreat rate of a crystal face constituting

Fig. 5. The modeling of a square pore to a cylindrical shape during pore growth.

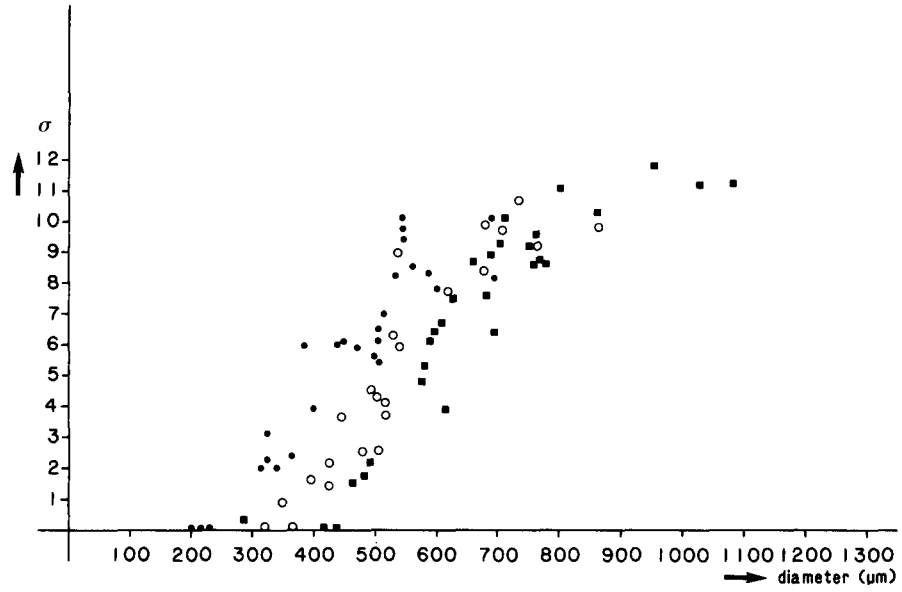

Fig. 6. Plot of pore growth, σ (retreat rate of the fastest dissolving crystal face) versus pore diameter at $t = 0$. Mean height of pore is: ●, 300 μm; ○, 500 μm; ■, 700 μm.

the pore, was measured separately. As was to be expected, different orientations of faces in the pore have an effect on dissolution rate. Fig. 4 is a plot of these differences, measured at the closed end of the pore against the perspex holder. The pore wall with an angle of 118° with the holder is dissolving about twice as fast as the pore wall which has an angle of 62°, whereas the vertical

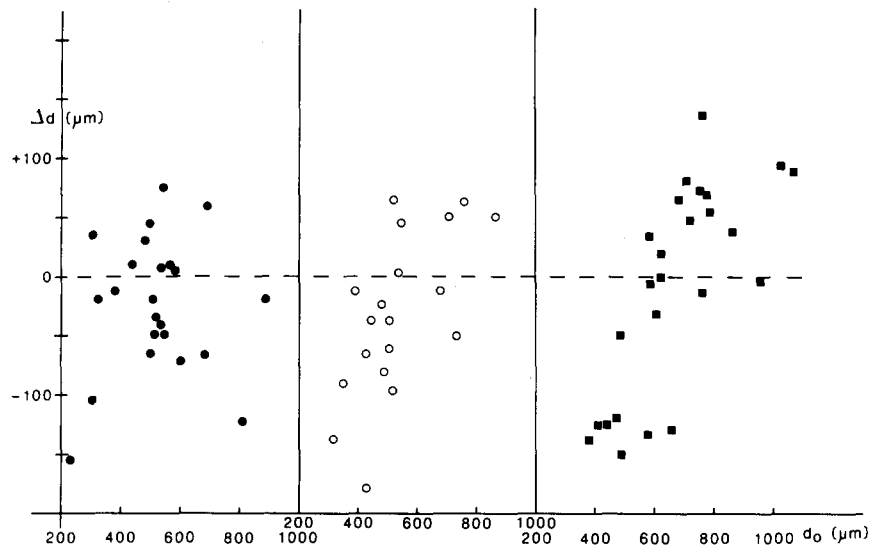

Fig. 7. Plot of difference in pore diameters at the entrance and the closed end of a pore (Δd) versus pore diameter at $t = 0$, for a pore height of: ●, 300 μm; ○, 500 μm; ■, 700 μm.

pore walls are roughly dissolving at the mean dissolution rate. The fast dissolving pore wall is better available for the inflowing fluid; therefore a proportionally larger amount of fresh fluid is directed to this wall.

The same phenomenon is seen in the series shown in Fig. 5, which is a representative example. The pore wall is remodeled into a cylinder by the upward-flowing fresh fluid, since the availability of the mid-points of the crystal faces for the inflowing fluid is better than for the corners.

The effect of pore dimensions on dissolution of its wall were investigated by measuring pore width and length at successive time intervals. Dissolution rate increases during pore growth, but the first 8–10 min dissolution rate is practically constant, so retreat rate of the fastest dissolving crystal face during the first 10 min was plotted versus pore width at time $t = 0$ (Fig. 6).

The effect of pore height on pore growth is shown by clustering the values in 3 classes with a mean height of about 300, 500 and 700 μm.

As a first approximation it is concluded that: (1) pore growth increases rather proportionally with pore width; (2) an increasing height decreases pore growth for all points in a cluster by about the same amount; (3) there is a maximum rate of pore growth that equals maximum dissolution rate of a single crystal (11–12 μm/s); and (4) a minimum pore size for each height is needed to start pore growth.

At first sight a vertical pore with dissolving walls closed at the upper side seems to be a simple enough concept to deduce analytically the pore growth and solute flow under natural convection from basic equations for mass transfer. However, the most complicated case solved under conditions of natural convection up to now is the case of a dissolving vertical plate (Levich, 1962). A pore in which the incoming fluid is hindered is a case much more complicated; therefore we have to be satisfied with the description given above.

If the flow of ascending fluid is the rate-limiting step in the dissolution process of crystal faces in a vertical pore, there should also be differences

Fig. 8. Independent growth of 3 pores at a small distance from each other.

in the dissolution rate at the entrance of the pore and at the closed end of the pore. Smaller and higher pores should dissolve faster at the entrance since the ascending fluid cannot reach the closed end of the pore or only with difficulty. If the ascending fluid, however, reaches the closed end of the pore, the edges of the crystals at the closed end are in contact with fresh fluid, whereas the edges at the entrance are in contact with a more saturated solution. Therefore larger and shorter pores should grow faster at the closed end. In Fig. 7 the differences in pore diameter at the entrance and the closed end of a pore after finishing the dissolution process are plotted for the 3 clusters versus pore diameter at time zero.

For pores with a height of 300 μm, the assumed effect is not measured within the investigated range of pore diameters. For the higher pores (500 μm, 700 μm) the effect was clearly measured. Smaller pores grow faster at the entrance whereas larger pores grow faster at the closed end.

This study shows that under conditions of natural convection, flow patterns in pores with walls of a soluble material are characterized by an ascending column of fresh fluid centrally in the pore and a descending flow of solute with higher density along the pore walls. It is the resistance to flow of the ascending fresh fluid in the pore that determines dissolution rate of the pore wall.

This conclusion is supported by the following observations:

(1) the existence of a minimum pore size needed to start dissolution of the pore walls;
(2) the effect of orientation of crystal faces on dissolution rate in the pore;
(3) the cylindrical deformation of a pore during dissolution;
(4) the differences in dissolution rate measured at the entrance of a pore and its closed end, for long, narrow pores versus short, wide pores.

If more pores are studied simultaneously (Fig. 8), it appears that there are as many ascending fluid columns generated as there are pores. Naturally ascending and descending columns of flow in pore are continuous with ascending and descending flows in the fluid beneath the layer of pores and crystals. Therefore it is of interest to know if the dissolution rate of larger areas such as tablets or particles at an interface, are determined by the resistance between ascending and descending flows of fluid.

In Fig. 9 the dissolution behaviour is shown for acetaminophen crystals compressed with the insoluble calcium diphosphate into tablets with an

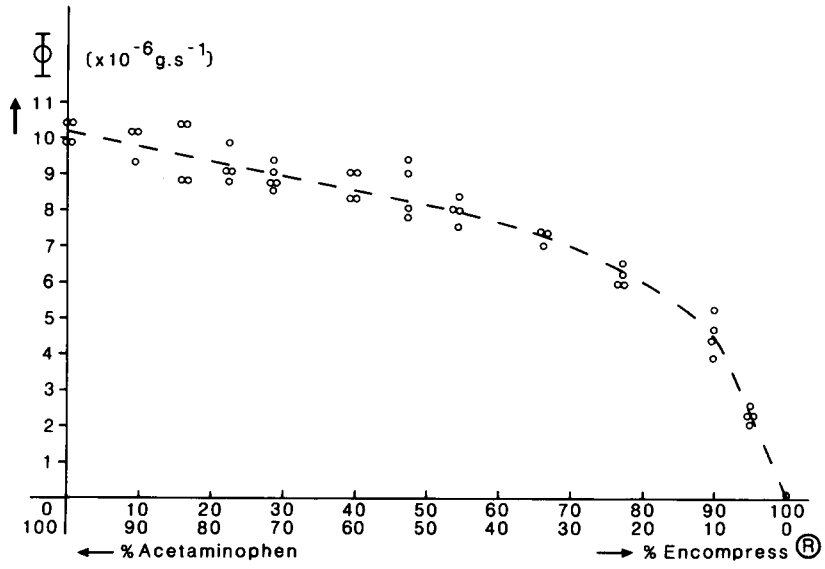

Fig. 9. Plot of dissolved acetaminophen flow from tablet faces with an increasing content of the insoluble Encompress (dicalcium phosphate dihydrate) and a decreasing content of acetaminophen.

increasing content of acetaminophen from right to left. If only a few crystals are dispersed on the tablet surface ($\leqslant 10\%$), the dissolution rate is high and constant. From 10% to 50%, dissolution rate decreases and above 50%, the dissolution rate is low and rather constant. This kind of dissolution behaviour can easily be interpreted if a flow regime of ascending and descending columns of fluid is postulated. At low acetaminophen content, dissolved acetaminophen flows downwards where a crystal is situated at the tablet surface. There is enough room for ascending and radially inflowing fresh fluid, so resistance between fresh fluid and solute flow is at a minimum. At a higher acetaminophen content resistance increases between ascending and descending columns of fluid, so mass flow per unit soluble area decreases. For slowly dissolving substances such as acetaminophen, probably the columns of convective fluid flow are also coalescing to form one column. Rapidly dissolving substances generate high density gradients, so convective fluid columns may remain separate. For tablets with a content of 50% acetaminophen or higher, the convective flow regimen is fully developed and resistance is at a maximum. Then the dependence of solute mass flow on surface area is a factor 12 weaker compared to the mass flow for tablets with a low acetaminophen content ($< 10\%$).

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