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Dissolution of a particle system at the fluid/fluid interface

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Summary

Dissolution behaviour of a particle system (acetaminophen) at a liquid paraffin/water interface is investigated under conditions of natural convection. Mass flow, the number of particles present in steady-state and their size during dissolution have been measured. Theoretically the minimum and maximum number of particles that can be present at an interface, is derived. Experimentally it was found that the actual number of particles present at the interface is within these extreme values. Dissolution via the pores in between the particles, causes a particle size distribution in steady state, ranging from the initial size of the particle to zero. A particle freshly substituted into the dissolving layer is having its initial maximum size, occupying an area (s_0) of the interface. Multiplying the counted number of particles in steady state with the area s_0, a value is found that is equal to the total available interfacial area, as if a tablet is dissolving with zero porosity. It is shown in this study that this is the result of a limit on number of dissolving particles that can be present at an interface.

Introduction

The mechanism of drug release from fatty suppositories is characterized by the presence of a lipid/water interface between the molten base and the rectal fluid. As most drugs used in rectal therapy are slightly soluble or even insoluble in the lipid base, transport of these drugs through the base and across the interface is a transport of particles. In the aqueous phase the situation is entirely different as the particles are dissolving in water attached to the interface, so drug transport in the rectal fluid is a convective-diffusional flow of solute. The effect of particle size and dosage on release rate in vitro and in vivo could be explained by a two-phase model (Schoonen et al., 1979).

Release rate is determined by the particle transport in the base if the drug dissolves rapidly in water, whereas dissolution at the aqueous side of the interface is the rate limiting step if the drug dissolves slowly in water (Schoonen et al., 1979a, 1980; Crommelin and De Blaey, 1980; Fokkens and De Blaey, 1982; Stuurman-Bieze et al., 1978; Moolenaar et al., 1979).

If dissolution of the drug particles in water is rate limiting, mass flux of drug in the usual range of particle sizes (< 125 μm) from an interface is almost equal to mass flux from a tablet of the same material (Schoonen et al., 1979b; Crommelin and De Blaey, 1980). Intuitively, this sounds rea-

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sonable, as the convective diffusional flow of solute is rate-limiting for both systems. However, the area of interface covered by dissolving particles is 40–50% whereas a tablet may be considered to have a low porosity. The interfacial area with pores therefore should have an equal mass flux as the area covered with particles. It is not readily seen, why this should be so. Investigating the release of sodium salicylate particles across a liquid paraffin/water interface (as a model of drug release from suppositories) a similar phenomenon was observed: the porosity of a particle layer dissolving at an interface was calculated to be exactly zero, whereas particles in a layer cannot be packed with a porosity less than 30%.

In an attempt to explain these phenomena the present study was performed in which a single layer of a slowly dissolving drug (acetaminophen) was investigated theoretically and experimentally.

Theory

Mass flow across a fluid/fluid interface

Consider a lipid/water interface at which uniformly sized particles with mass, m_p, are substituted at regular time intervals. Particles are insoluble in lipid, so mass flow onto the direction of the interface; ϕ_{in} is:

$$\phi_{in} = f \cdot m_p \tag{1}$$

where: f = frequency of substitution. Arriving at the interface a particle is wetted by the aqueous phase and dissolution will proceed until the particle has dissolved completely in time T (T = lifetime of a particle). For n_i particles present at the interface, mass flow of solute away from the interface is:

$$\phi_{out} = n_i \cdot m_p / T \tag{2}$$

(1) If the available interfacial area, S_b, is not a limiting factor, ϕ_{out} increases after substitution has started, until $\phi_{out} = \phi_{in}$ and a steady-state has been reached. In steady-state the number of particles dissolving at the interface: n_i = constant; T = constant and total area of the particles; $\sum_1^{n_i} s$ = constant. (s = area of interface, occupied by one dissolving particle). (2) If S_b is a limiting factor, ϕ_{out} increases until the interface is fully covered with particles.

$$\sum_1^{n_i} s = \beta \cdot S_b \tag{3}$$

where: β = fraction of interface covered with particles (porosity $p = (1 - \beta)$).

Then ϕ_{out} is at a maximum and $\sum_1^{n_i} s$, n_i and T are also constant. Particles are accumulating in the lipid phase where dissolution is impossible. In this way a multilayered system is developing in which particles are substituted from the second layer into the dissolving layer, each time a pore has been formed by dissolution that is large enough for a particle to enter, so mass flow across the interface is determined by dissolution.

The number of particles present in steady-state

If an interfacial area S_b is completely occupied by uniformly sized particles at $t = 0$, it can be written:

$$N \cdot s_0 = \beta \cdot S_b \tag{4}$$

where s_0 = interfacial area occupied by one particle at $t = 0$ and N = the calculated number of particles with area s_0 that can be present in area $\sum_1^{n_i} s$; $N = \sum_1^{n_i} s / s_0$.

If pores between particles are too small to participate in the dissolution process, s_0 = constant and dissolution can proceed only in a vertical direction as is the case for a tablet surface situated horizontally, so in this case: $n_i = N$.

If pores are contributing to the dissolution process, s is decreasing during the lifetime of a particle and n_i should increase for a constant $\beta \cdot S_b$. So for a given system, N may be considered as the minimum number of particles that is present at an interface.

In the case that s is decreasing isometrically with a constant dissolution rate σ, it is easy to calculate how many particles will be present at an area $\beta \cdot S_b$ in a steady-state situation. It is convenient to use a diameter d instead of an area s in the equation, therefore d is defined as: $d = (s/\in)^{0.5}$ in which $\in$ is a shape factor for the particles under investigation.

Dissolution rate σ is constant, so $\Delta d = d_0/n_i$ is constant. At $t = 0$: $d = d_0$, so:

$$\sum_{1}^{n_i} s = \in \left\{ d_0^2 + (d_0 - d_0/n_i)^2 + (d_0 - 2d_0/n_i)^2 + \ldots + (d_0 - (n_i - 1)d_0/n_i)^2 + (d_0 - n_i d_0/n_i)^2 \right\}$$

$$= \in \cdot d_0^2/n_i^2 \left\{ n_i^2 + (n_i - 1)^2 + \ldots 2^2 + 1^2 \right\} \quad (5)$$

Since by definition $\in d_0^2 = s_0$: The sum of the arithmetical series in parentheses is:

$$\text{SUM} = 1/6n_i(n_i + 1)(2n_i + 1) \quad (6)$$

so:

$$\sum_{1}^{n_i} s = s_0 \cdot n_i(n_i + 1)(2n_i + 1)/6n_i^2 \quad (7)$$

For an interface fully covered with particles, according to Eqns. 3 and 4 the equation can be written as:

$$Ns_0 = n_i s_0 (2n_i^2 + 3n_i + 1)/6n_i^2 \quad (8)$$

rearranging and defining $F = n_i/N$:

$$F = n_i/N = \frac{6n_i^2}{2n_i^2 + 3n_i + 1} \quad (9)$$

and

$$\lim_{n \to \infty} F = 3 \quad (10)$$

So under the assumptions stated, 3 times as many particles may be present in steady-state, as compared with the minimum value ($n_i > 25$). However, it is highly unlikely that these assumptions will be fulfilled at an interface:

(1) Particles are in contact with each other, so at these points dissolution rate is zero. Consequently the assumption of an isometric retreat of area s_0 cannot be attained (Fig. 1a).

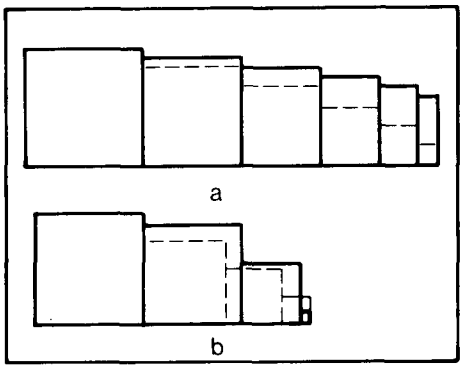

Fig. 1. a: effect of particles dissolving non-isometrically with a constant rate σ, on the interfacial area covered with particles, as compared to particles dissolving isometrically (broken lines). b: effect of particles dissolving isometrically with an increasing rate σ on the interfacial area covered with particles, also compared with particles dissolving isometrically with σ = constant (broken lines).

(2) A particle freshly substituted will have relatively small pores around it, as compared with particles that have been dissolving for some time. It may be expected that dissolution rate will increase with increasing pore size (Wurster and Seitz, 1960; Graaf et al., 1979; Grijseels and De Blaey, 1981; Grijseels et al., 1983a and b), so the assumption of a constant dissolution rate is also not satisfied (Fig. 1b).

Fig. 1 illustrates that both effects are resulting in a larger particle area for an equal number of particles, or a lower n_i for a constant β. It is concluded therefore, that the value $F = 3$ should be considered as a maximum and the number of particles at an interface may vary between $1N$ and $3N$, depending on the dissolution profile of a particle.

Materials and Methods

The acetaminophen (paracetamol) crystals used (Ned. Pharm. Ed. VI) are commercially available. Size fractions are obtained by sieving.

Analysis of size fraction: $\bar{d}_g = 7.28 \times 10^{-2}$ cm; $\sigma_g = 1.09$. Mean weight of a particle (m_p): 2.376×10^{-4} g. Mean area of a particle (s_0): 4.46×10^{-3} cm. The fluid/fluid system as well as the apparatus used have been described previously (Schoonen et al., 1979b).

A few modifications in the apparatus are introduced:

(1) The measurements were made at $37 + 0.1°C$ and to avoid air bubbles in the continuous flow system the distilled water from the reservoir was boiled continuously in an extra vessel before the water was allowed to enter the system.

(2) In the top of the dissolution cell a tube was mounted, made of metacrylate polymer (perspex) with a length of 1.01 cm and an internal diameter of 1.5 cm to study single particle layers. In some experiments also a tube was used with a diameter of 1.01 cm. The particle layers could be photographed from above through the lipid phase by a camera mounted on a microscope (Olympus).

In a steady-state measurement, particles were allowed to fall through the liquid paraffin at a constant frequency (f) during the experiment. After individual wetting by the aqueous phase the crystals moved to the particles already wetted as the interface was slightly bent downwards by the weight of particles. For acetaminophen crystals the equilibrium position is similar to that of potassium ferricyanide (Schoonen et al., 1979b). Thus only the upper crystal faces are in contact with the lipid phase.

After some time the mass flow of solute measured spectrophotometrically stabilized at a constant value, and the steady-state had been reached: the weight of particles per unit time approaching the interface equals the mass of solute per unit time transported away from the interface. Photographs of the dissolving particle layer were taken and analysed on the number of particles (n_i). The area of the particles was measured with a particle size analyser (Zeiss, TGZ 3). At least 5 photographs were made during the steady-state, so the values for n_i and $\Sigma_1^{n_i} s$ are mean values of at least 5 measurements.

Suspensions of acetaminophen in liquid paraffin were also measured in the continuous flow recording apparatus. In the apparatus a weight of acetaminophen particles was added to the lipid phase that was sufficient for at least 4 layers. Tablets of acetaminophen were made in a holder ($D = 1.01$ cm) with the aid of a manual press (force: 11.76 kN), without any additives. Before mounting the holder in the dissolution cell, position of the tablet was adjusted, until the surfaces of tablet and holder were exactly in one plane.

Results and Discussion

A circular interface with a diameter of 1.5 cm provided a sufficiently large area to investigate single layers of acetaminophen particles up to a substitution frequency of 4 per minute. For each substitution frequency n_i, $\Sigma_1^{n_i} s$ and ϕ_{out} were measured; $N = \Sigma_1^{n_i} s / s_0$ was calculated so F could also be calculated (Table 1). Fig. 2 shows the F-values from Table 1 together with the theoretical curve according to equation 9. Comparing these plots, two kinds of deviations can be noted: (1) the actual value is about 2/3 of the theoretical value. (2) The shape of the experimental curve is different. The first effect was expected as it is unlikely that particles are dissolving isometrically with a constant dissolution rate (see Theory). The latter effect appeared to be correlated with the influence of the outer edge of the particle system.

At the circumference of a particle system, dissolution rate is at a maximum and equal to the rate of single crystals ($1.5 \times 10^{-5} \pm 0.2 \times 10^{-5}$ cm/s; $n = 10$), so particles situated at the edge are dissolving with a constant and high rate at least on one side.

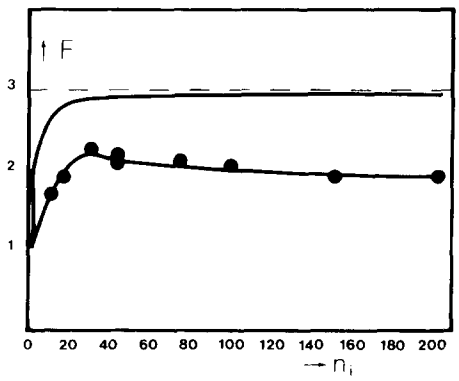

Fig. 2. Plot of the ratio $F = n_i / N$ versus n_i. Upper curve is theoretical curve drawn according to Eqn. 9.

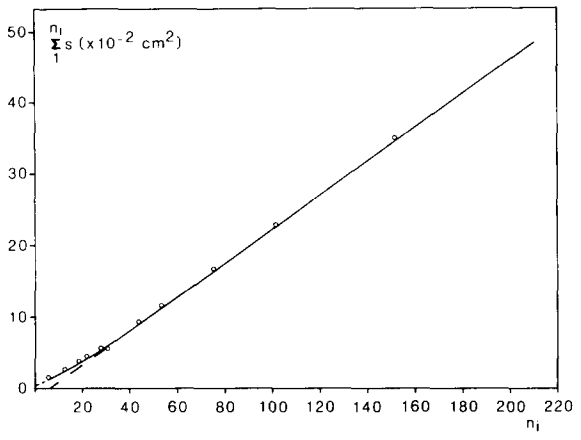

Fig. 3. Plot of the interfacial area covered with particles ($\Sigma_1^{n_i} s$) vs the number of particles present on the interface (n_i).

Particles situated more centrally are surrounded by pores that are relatively small when the particle has been substituted and starts to dissolve. During dissolution pores are growing and dissolution rate is increasing. As a result these particles occupy a larger mean area of the interface than particles at the circumference (Fig. 1). At low substitution frequencies most particles are at the edge. At higher frequencies however, relatively less particles are dissolving at the outer edge, as the interfacial area covered with particles is increasing as a quadratic function of the circumference. Fig. 3 shows this effect: for $n_i < 30$; $\Sigma_1^{n_i} s/n_i$ ($= N \cdot s_0/n_i$) is increasing (data from Table 1). In Fig. 2, F ($= n_i/N$) is plotted versus n_i,

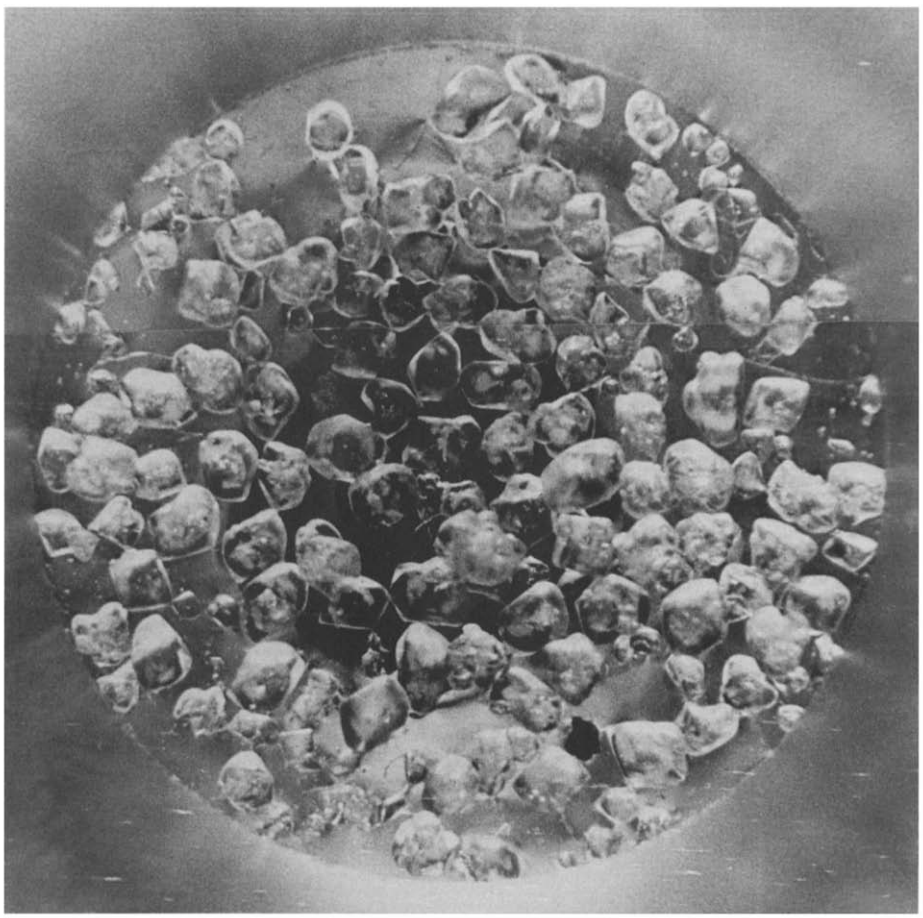

Fig. 4. Photographs of a single layer of particles paracetamol dissolving in steady-state at an interfacial area: $S_b = 0.8008$ cm^2 ($f = 3.4$).

TABLE 1

Measured and calculated data for systems at various frequencies of substitution

	Frequency f (min^{-1})								
	0.2	0.33	0.5	0.67	1	1.5	2	3	4
$\Sigma_1^{n_i}$ ($\times 10^{-2} cm^2$)	1.42 ± 0.06	2.72 ± 0.15	3.59 ± 0.17 4.37 ± 0.22	5.52 ± 0.31 5.61 ± 0.30	11.56 ± 0.35 9.35 ± 0.2	16.71 ± 1.44 16.32 ± 1.24	22.96 ± 1.07	35.05 ± 1.16	47.30 ± 1.00
n_i	6.63 ± 0.70	12.8 ± 1.4	18.7 ± 1.6 21.6 ± 1.0	31.1 ± 1.9 27.9 ± 1.7	53.7 ± 2.9 44.3 ± 2	76.3 ± 4.4	102.3 ± 3.3	151.8 ± 4.7	205.0 ± 1.4
ϕ_{out} ($\times 10^{-6} g \cdot s^{-1}$)	0.083	0.150	0.175 0.192	0.255	0.40 0.44	0.63	0.82	1.22 1.29	1.67
N	3.18	6.10	8.05 9.80	12.38 12.58	25.92 20.97	37.46 36.59	51.48	78.58	106.05
F	2.08	2.10	2.32 2.20	2.51 2.21	2.07 2.11	2.04	1.99	1.93	1.93

TABLE 2

Measured and calculated data for systems dissolving at an area of $S_b = 0.80\ cm^2$

	$f = 3.4$	Suspension	Tablet
Φ ($\times 10^{-5}$ g·s^{-1})	1.36	1.375	1.015
S_b (cm^2)	0.8008	0.8008	0.8016
ϕ'' ($\times 10^{-5}$ g cm^{-2}s^{-1})	1.70	1.72	1.27
D (cm)	1.009	1.009	1.010
$\sum_1^{n_i} s$ (cm^2)	0.39		1 *
n_i	1.72		
$n_i \cdot s_0$ (cm^2)	0.77		0.802
$p = \left(1 - \frac{\sum_1^{n_i}}{S_b}\right)$	0.51		0
$p^a = \left(1 - \frac{n_i s_0}{S_b}\right)$	0.04		0
F	1.96		1 *
m_p ($\times 10^{-4}$ g)	2.375	2.375	
s_0 ($\times 10^{-3}$ cm^2)	4.46	4.46	
d_0 ($\times 10^{-2}$ cm)	7.30	7.30	
h_0 (h_{tab}) ($\times 10^{-2}$ cm)	4.12	4.12	4.12
T_{tab} ($\times 10^3$ s)			4.2

* Assumed to be 1.

so it is only the outer edge effect on N that causes the deviation in shape of the experimental curve.

The porosity problem

To investigate the dissolution rate-limited case, a known interfacial area, S_b, should be completely covered with particles. Experimentally this is rather difficult to achieve for a single layer of particles. It is now impossible to allow the substituted particle to move from the edge of the interface to the particles already dissolving. A particle should fall directly into a pore at the interface. Fig. 4 is a photograph of the system in steady-state and it shows that a few particles did not fall correctly into a pore, leaving too much room at the sites where they had to be substituted. In spite of this difficulty mass flow measured in this experiment is equal to mass flow from an ordinary suspension of particles (multilayered system) at the same interfacial area S_b (Table 2). From this it is concluded that a single layer of particles in steady-state is a good model for the multilayered system. All relevant parameters measured and calculated from these experiments are shown in Table 2.

The volume of acetaminophen dissolving in one lifetime T is equal to $n_i \times s_0 \times h_0$. It is shown in Table 2 that $n_i \times s_0 \simeq S_b$ (both values differ only 3.8%). So for the acetaminophen system an apparent porosity: $p^a = 0.04$ is calculated, whereas the actual value is: $p = 0.51$. This result is in agreement with the result found previously for sodium salicylate where also $p^a \simeq 0.0$ was found. In the theoretical section it is shown that the number of particles at an interface in steady-state (n_i) may vary between a minimum and a maximum as expressed in the relation: $1 \leqslant F \leqslant 3$.

As 172 particles are presented and $F = 1.96$ (Table 2), it can be calculated that n_i may vary between: $87 < n_i < 263$. So why is n_i fixed according to the relation $n_i s_0 = S_b$?

First the effect of mass flow from the interfacial pore area $(1 - \beta)S_b$, and particle area $(\beta)S_b$, on $n_i s_0 = S_b$ is evaluated:

$$\phi_{out} = \phi_{pore} + \phi_{part} = (1 - \beta)S_b\phi''_{pore} + (\beta)S_b\phi''_{part} \tag{11}$$

where: ϕ'' = mass flux.
According to Eqn. 2:

$$\phi_{out} = n_i m_p / T = n_i \rho s_0 h_0 / T \tag{12}$$

where: ρ = density
so:

$$n_i \rho s_0 h_0 / T = \rho(1 - \beta)S_b\tau_{pore} + \rho\beta S_b\tau_{part} \tag{13}$$

where: $\tau_{pore} = \phi''_{pore}/\rho$ and $\tau_{part} = \phi''_{part}/\rho$
In Eqn. 13 it is shown that $n_i s_0 = S_b$, if $\tau_{pore} = \tau_{part} = h_0/T$. An interfacial system with $\tau_{pore} = \tau_{part}$ is indistinguishable from a tablet of the same material. Such a tablet may be thought to consist of N_{tab} deformed particles with mass m_p and area s_0 without any pore:

$$\phi_{tab} = \rho N_{tab} s_0 h_0 / T_{tab} \tag{14}$$

If $\tau_{pore} = \tau_{part}$, pores do not generate a different mass flow, so diffusional convective flow of solute

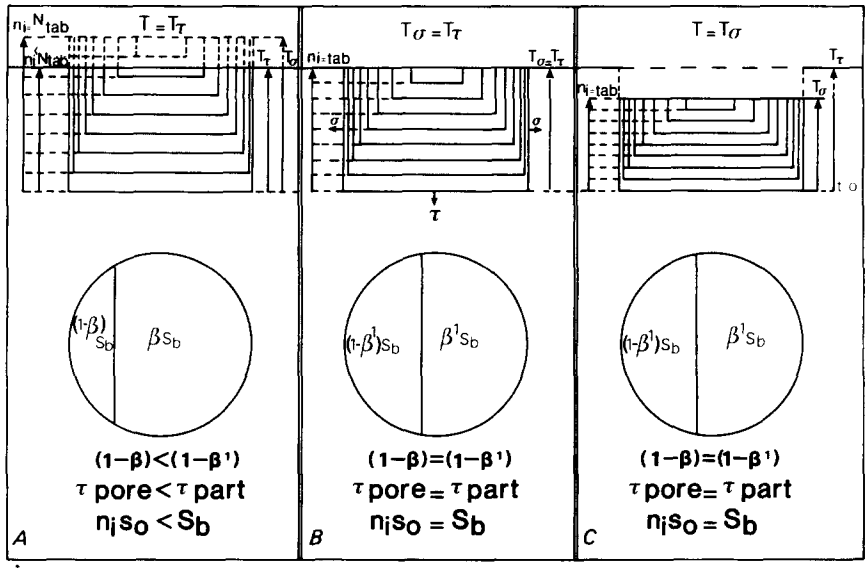

Fig. 5. Dissolution of a particle at an interface among other particles as (a) lifetime $T = T_{\tau\,\mathrm{part}}$ ($T_\sigma > T_{\tau\,\mathrm{part}}$); (b) the boundary case; lifetime $T = T_{\tau\,\mathrm{part}} = T_\sigma$; (c) lifetime $T = T_\sigma (T_\sigma < T_{\tau\,\mathrm{part}})$. Starting at $t = 0$ a particle grows smaller until it is completely dissolved at the end of its lifetime $t = T$. Dividing the time axis in n_i stages the particle area for a multiparticulate system, β, S_b, is obtained by summation of the n_i horizontal particle area. This area as part of the total interfacial area S_b is also depicted for the 3 cases.

away from the interface or tablet surface determines mass flow. Therefore, in this case:

$$n_i = N_{tab}; \quad T = T_{tab} \quad \text{and} \quad \phi_{out} = \phi_{tab}$$

For the tablet system N_{tab} and T_{tab} are constants, when hydrodynamical conditions do not change. Dissolution rate τ_{part} in the interfacial system may also be considered to be constant. Dissolution rate τ_{pore} however may vary, for instance with particle size. If this is the case n_i or T may change, but as will be shown below they will not change simultaneously. Thus, if an interfacial system with $\tau_{pore} = \tau_{part}$ is changed into a system with $\tau_{pore} \neq \tau_{part}$, only T may have another value. Than the condition $n_i s_0 = S_b$ still holds.

Summarizing, if $\tau_{pore} = \tau_{part}$, then the condition $n_i s_0 = S_b$ is always valid, but $n_i s_0 = S_b$ can also be true for $\tau_{pore} \neq \tau_{part}$.

Secondly, the effect of two dissolution rates: σ for the vertical particles faces and τ for the horizontal particle faces on n_i en T will be investigated.

It was previously shown (Schoonen et al., 1979b) that for single particles at an interface at least two different dissolution rates should be defined: a dissolution rate τ in vertical direction for the horizontal particle face and a rate σ in horizontal direction for the vertical faces. Therefore lifetime T can be determined by τ and the vertical dimension, h_0, of the particle: $T = T_\tau = h_0/\tau$ or by σ and the horizontal dimension, $1/2\ d_0$ ($= r_0$), of the particle: $T = T_\sigma = r_0/\sigma$. Dissolution of a single particle for both cases ($T = T_\tau$ and $T = T_\sigma$) and the boundary case ($T_\sigma = T_\tau$) is depicted in Fig. 5. For each particle a mean fraction of the area, $\beta \cdot s_0$, on which τ_{part} is working during time T and a mean fraction of pore area, $(1 - \beta)s_0$, can be calculated. If all dissolved mass from the vertical particle faces with rate σ is passing across the area, $(1 - \beta)s_0$, with rate τ_{pore}, the equation can be written as:

$$\phi_{particle} = \rho s_0 h_0 / T$$

$$= \rho\beta s_0 h_0/T_\tau + \rho(1-\beta)s_0 h_0/T_\sigma \qquad (15)$$

For the boundary case β will have a certain value: $\beta = \beta'$ and $T_\tau = T_\sigma$. And for an interfacial area s_0: $\tau_{part} = \tau_{pore}$ (Fig. 5b). It may be noted that this result has been obtained without knowledge of the value σ for various pore sizes.

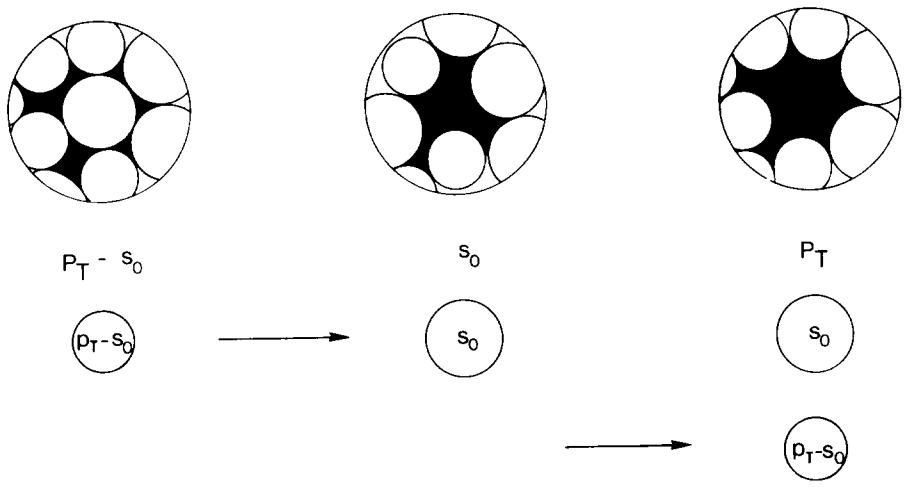

Fig. 6. Schematical representation of pore growth and particle dissolution. From left to right: at $t = 0$ a particle is substituted leaving pores $p_T - s_0$ outside the area s_0 to start dissolution (p_T depends on side and shape of the particles). A pore is growing and reaches size s_0: from that moment pore growth continues till pore p_T has been formed and a new particle with area s_0 can take its place among the other dissolving particles at an interface. Starting in the middle a pore grows from 0 to $(p_T - s_0)$ and from $(p_T - s_0)$ to s_0.

When a particle starts to dissolve at an interface at $T = 0$, there is a complication as pores outside the area s_0 are needed for dissolution of the vertical faces. Then for a single particle the assumption made for Eqn. 15 that all mass from the vertical walls is transported away through the area $(1 - \beta)s_0$ is not valid: $\tau_{pore} < \tau_{part}$, at $T_\sigma = T_\tau$. The scheme in Fig. 6 shows a multiparticulate system. A pore with an area p_T is needed for a particle to take its place among the other already dissolving particles, so pores with area $(p_T - s_0)$ remain after substitution at $T = 0$. In the case of a multiparticulate system the complication vanishes, as each particle needs pores $(p_T - s_0)$ at the area of neighbours to start. So the dissolved mass of a particle that is transported away outside the area s_0 is equated by the mass transport of neighbouring particles within the area s_0 of that particle.

The pore area $(1 - \beta')\ s_0$ for one particle is minimally needed for dissolution rate σ, to grow a pore from 0 to s_0 in time $T_\sigma = T_\tau$. Consequently for an interface with area S_b, the boundary case will be valid for all n_i particles present, if

$$(1 - \beta)S_b = (1 - \beta')s_0 \cdot S_b/s_0 = (1 - \beta')s_0 \cdot n_i \tag{16}$$

then:

$$(1 - \beta) = (1 - \beta') \quad \text{and} \quad n_i s_0 = S_b \tag{17}$$

A porosity of $(1 - \beta) < (1 - \beta')$, will be the result, if σ is too low to grow pores to a size s_0 in time $T_\sigma = T_{\tau\,part}$. Fig. 5a shows this case. Dissolution rate $\tau_{part} = h_0/T_{\tau\,part}$ is constant, so $T = T_{\tau\,part} =$ constant. According to Eqn. 13, only n_i in the left part of the equation is a variable, so ϕ_{out} is linearly related with n_i. In this case particle and pore distribution depend on σ and:

$$n_i s_0 < S_b \tag{18}$$

Fig. 5c shows the case that σ has a higher value than in the boundary case. Pore growth from 0 to s_0 is determined by σ in the same way as in the boundary case, only lifetime T in which the same pores grow is shorter: $T_\sigma < T_{\tau\,part}$. Therefore particle and pore distribution is constant: $(1 - \beta) = (1 - \beta')$ and ϕ_{out} is linearly related with $1/T$:

$$n_i s_0 = S_b \tag{19}$$

In this study $n_i = N_{tab}$ particles of acetaminophen could be counted, whereas in a previous study

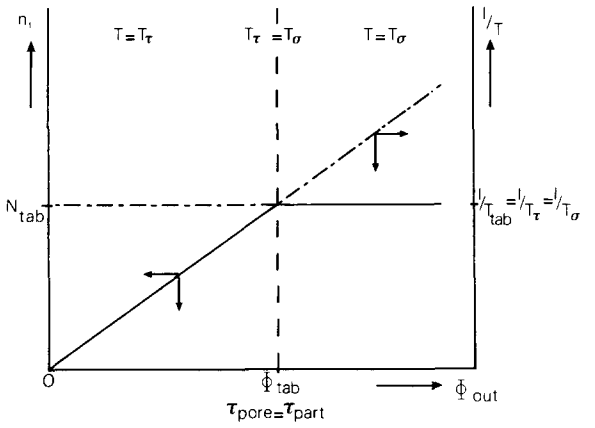

Fig. 7. Plot of mass flow from a multiparticulate system dissolving at an interface versus the number of particles present at steady state (n_i) and the reciprocal lifetime ($1/T$) respectively. For $T = T_\tau$, mass flow is linearly related with n_i; for $T = T_\sigma$, mass flow is proportional to $1/T$ and $n_i = N_{tab}$ = constant.

(Schoonen et al., 1980) an apparent porosity of zero could be calculated for sodium salicylate, which is an equivalent statement for $n_i s_0 = S_b$. Finally it was checked for the acetaminophen system, whether $1/T$ is proportional to mass flow in the region: $\phi_{out} > \phi_{tab}$.

$$\phi_{out}/\phi_{tab} = T_{tab}/T. \qquad (20)$$

ϕ_{out} and T could be measured independently. With the data from Table 2, where $n_i/f = T$ the left hand side of the equation is calculated to be 1.34. For the right hand side the value is 1.38, so the difference is only 3%.

In conclusion mass flow from a particle system at a fluid/fluid interface depends on the number of particles dissolving at the interface in steady state (n_i) and the lifetime of each particle (T). Two cases can be identified: one in which lifetime of particles is independent from pore growth (σ) and therefore constant and a second case in which lifetime is inversely proportional with pore growth: then the number of particles (n_i) is constant (Fig. 7).

This is a consequence of particle dissolution at an interface where for a single particle two rather independent dissolution rates can be defined: σ for the vertical faces and τ for the horizontal face. Only one of these rates can determine lifetime: $T = T_\sigma$ or $T = T_\tau$. It is shown for the boundary case: $T_\sigma = T_\tau$ that mass flux from a particle system equals mass flux from a tablet of the same material and the number of particles (n_i) is at a maximum (Fig. 7).

Symbols

r	particle radius (cm)
d	particle diameter (cm)
dg	geometrical mean diameter (cm)
D	diameter of interface (cm)
f	frequency of substitution
F	n_i/N
h	particle height, $h_0 = m_p/(\rho \cdot s_0)$ (cm)
m_p	mass of particle
n_i	number of particles dissolving at interface in steady-state
N	number of particles with area s_0 that can be present at the part of interface covered with particles
N_{tab}	number of particles with area s_0 that can be present at interface if porosity is zero (tablet)
p^a	apparent porosity
$p = (1-\beta)$	porosity
s	particle area (cm^2)
s_0	particle area at $t = 0$ (cm^2)
$\Sigma_1^{n_i} s$	total particle area in steady-state (cm^2)
S_b	interfacial area (cm^2)
T	particle lifetime (s)
T_σ	lifetime determined by σ (s)
T_τ	lifetime determined by τ (s)
T_{tab}	lifetime of particle in tablet model (s)
β	fraction of interface covered with particles
β'	fraction of interface covered with particles for the boundary case
$\in$	shape factor
ϕ	mass flow (g·s^{-1})
ϕ''	mass flux (g·cm^{-2}s^{-1})
ρ	density (g·cm^{-3})
σ	horizontal dissolution rate for vertical particle faces in the pores (cm·s^{-1})
σ_g	geometrical standard deviation
τ	vertical dissolution rate for horizontal particle faces (cm·s^{-1})
τ_{pore}	mean dissolution rate in vertical direction from pore area $(1-\beta)S_b$ (cm·s^{-1})
τ_{part}	mean dissolution rate in vertical direction from particle area $\beta \cdot S_b$ (cm·s^{-1})

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