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Physicochemical aspects of drug release

X. Investigation of the applicability of the cube root law for characterization of the dissolution rate of fine particulate materials

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Summary

The dissolution of some sparingly soluble drugs has been studied to evaluate the cube root law in dissolution testing, especially regarding the applicability of the law for fine particulate materials with varying degrees of polydispersity. It has earlier been shown that the thickness of the diffusion boundary layer around dissolving particles decreases with a decrease in particle size during dissolution. A continuous decrease in mean particle size during dissolution could then be expected to produce a deviation from the cube root law. In contrast to what has been assumed in the literature, the results in this study show that the decrease in mean particle size for fine particulate polydispersed powders is limited during dissolution. Consequently, the dissolution of these materials follows the cube root law. However, it is suggested that the law will not be applicable to strictly monosized materials, for which a continuous decrease in particle size will occur.

Introduction

Dissolution rate theory

In most cases the dissolution of drugs is assumed to be diffusion-controlled (Carstensen, 1972; Grijseels et al., 1981). Equations have been suggested that take a diffusion boundary layer into account, but in these cases the presence of a homogeneous stagnant liquid layer probably represents an oversimplification.

The dissolution rate (dc/dt) of a suspended solid can then, based on the theories of Noyes and Whitney (1897), Nernst (1904) and Brunner (1904), be described by the well-known equation:

$$\frac{dc}{dt} = \frac{D}{V \cdot h} \cdot S_c (C_s - C_t) \qquad (1)$$

where D is the diffusion coefficient; S_c is the effective solid surface area taking part in the dissolution process; h is the thickness of an assumed stagnant diffusion boundary layer, whose definition will be discussed in more detail below; V is the volume of solvent; C_s is the saturation con-

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centration of the solid and C_t is the concentration of solute in the main part of the solvent.

If the dissolution experiment is conducted under near sink conditions, it is normally assumed that the dissolution rate is directly proportional to the equilibrium solubility and the effective solid surface area taking part in the dissolution process. This means that for a specific compound the amount of solid dissolved should be directly related to the remaining surface area of the solid.

Cube root law

The cube root law was first proposed by Hixson and Crowell (1931a) as a means of representing dissolution rate that is normalized for the decrease in solid surface area as a function of time. Provided there is no change in shape as a suspended solid dissolves, its surface decreases as the two-thirds power of its weight. This relation has been used by Hixson and Crowell in the derivation of the cube root law. When sink conditions are applied, the cube root law can be written as:

$$w_t^{1/3} = w_0^{1/3} - K \cdot t \tag{2}$$

where w_t denotes the remaining weight of solid at time t, w_0 is the initial weight of solid at time $t = 0$, and K represents the dissolution rate constant (weight$^{1/3} \cdot$ time^{-1}). A plot of $w_t^{1/3}$ vs t should yield a straight line with intercept $w_0^{1/3}$ and slope K.

The assumptions made for the validity of the law by Hixson and Crowell can be summarized as follows:

(1) The law is claimed to be valid ideally for monodispersed, predominantly spheroidal, materials, i.e., the solid is in the form of a single unit or all units have identical properties regarding size, shape, surface and volume characteristics.

(2) The dissolution takes place normal to the surface. The difference in rates at different crystal faces is negligible and the effect of agitation of the liquid against all parts of the surface is essentially the same.

(3) The liquid is agitated intensely in order to prevent significant stagnation in the neighbourhood of the dissolving particle resulting in a slow rate of diffusion.

In the first assumption the cube root law is defined as valid only for monodispersed materials, but the law has also been claimed to be applicable for log-normally polydispersed units (Carstensen and Musa, 1972; Brooke, 1973, 1974; Carstensen and Patel, 1975). In these works, the authors have assumed that the mean particle size for log-normally distributed powders decreases linearly with time, while the number of particles stays constant until the so-called 'critical time' is reached, when the smallest particles begin to disappear. This gives rise to a biphasic cube root plot.

The third assumption for the validity of the cube root law must be read in the light of Hixson and Crowell's disbelief in the existence 'of a layer of saturated solution or anything of that nature' next to the solid surface. Consequently, they avoided making any assumptions concerning the mechanism whereby dissolved molecules are transported away from the solid surface. As, in practice, the liquid around dissolving particles does stagnate, it is surprising that few authors seem to have paid any attention to the existence of the third assumption when discussing the cube root law and its validity. Examples of authors who have considered this requisite in their papers are Niebergall et al. (1963) and Mauger and Howard (1976).

Stagnant diffusion boundary layer

The stagnant diffusion boundary layer, h in Eqn 1, was proposed by Nernst (1904). The value for h cannot be predicted theoretically, but could be seen as a mathematical parameter, which could be determined for Eqn 1 by dissolution experiments.

In reality, no simple homogeneous stagnant layer exists. Instead, solids dispersed in a liquid medium under agitation are surrounded by some zones of less movable liquid, i.e., a hydrodynamic boundary, reflecting a velocity gradient between the bulk fluid and the surface of the solid (Bisrat and Nyström, 1988). Thus, saturation of the liquid will be attained only in the vicinity of the surface, where liquid motion is almost absent (Grijseels et al., 1981).

In spite of this, we have used the simplified concept of a stagnant diffusion boundary layer for the discussion of experimental data in this study, although such a parameter can be criticized. The relationship between this stagnant diffusion boundary layer and the so-called effective diffusion boundary layer and the hydrodynamic boundary layer, which can both be calculated from hydrodynamic data, is not quite clear (Grijseels et al., 1981), but it was not within the scope of this paper to investigate the exact nature and definition of diffusion boundary layer models.

Relation between particle size and diffusion boundary layer thickness

Recently, it has been demonstrated that the thickness of the diffusion boundary layer will decrease as a function of particle size for sparingly soluble fine particulate materials (Nyström et al., 1985b; Anderberg et al., 1988; Bisrat and Nyström, 1988). Similar statements have been made and experimentally evaluated for coarser materials by Niebergall et al. (1963). The effect of the decreasing boundary layer thickness on the surface specific dissolution rate (G) is especially pronounced with particle sizes of less than 3–5 μm (Anderberg et al., 1988). As pointed out by Niebergall et al. (1963), Hixson and Crowell themselves (1931b), when testing their theory, experimentally obtained rate constants (K in Eqn 1) that increased as dissolution proceeded. As Hixson and Crowell dissolved cubic crystals, Niebergall et al. concluded that the observed phenomenon could be due to a dependence on the boundary layer of particle size, rather than an effect of changes in particle shape.

A deviation from the cube root law may then be expected for the dissolution of monosized, especially very fine, particulate materials, because a decrease in mean particle size as a function of time during dissolution will produce an increase in dissolution rate greater than would be expected from the change in surface area alone. However, with few exceptions (such as Niebergall et al., 1963), the cube root law has frequently been reported to fit experimental data. To some extent this could be due to the fact that coarse particulate materials have usually been investigated, for which the effect of particle size on diffusion boundary layer thickness is probably limited. Furthermore, most of the reported experiments have been conducted on polydispersed samples, for which a change in mean particle size is not a simple process, rather than on monodispersed or nearly monodispersed materials.

The objective of the present study was therefore to monitor changes in mean particle size during dissolution by using well defined suspensions of fine particulate, sparingly soluble materials and to investigate the subsequent impact on the applicability of the cube root law, in particular to monosized materials.

Experimental

Materials

Felodipine (unmicronized quality, Hässle AB, Sweden) was wet sieved to obtain the 20–25 μm fraction (precision test sieves with circular openings, Veco, The Netherlands).

Griseofulvin (fine particulate, Glaxo, U.K.) was used both as supplied and as a 5–10 μm wet-sieved fraction (precision test sieves with circular openings, Veco).

Sample preparation

A stock suspension containing 150 mg/l was prepared for griseofulvin, as supplied, by suspending it in distilled, particle-free water containing 0.9% sodium chloride and 0.01% polysorbate 80. An ultrasonic bath was used to disperse the material.

To obtain griseofulvin in the 5–10 μm fraction, 0.2 g of griseofulvin, as supplied, was suspended in 300 ml of the medium described above and wet sieved. The resultant suspension had a concentration of 23.4 mg/l.

Felodipine powder, 0.25 g, was suspended in 25 ml of distilled particle-free water containing 0.9% NaCl and 0.005% polysorbate 80. The 20–25 μm fraction was prepared by wet sieving and the resultant suspension had a concentration of 305 mg/l.

Determination of mean particle size and particle size distribution

The number of particles in 14 size classes were recorded using a Coulter Counter TAII and from these values the mean particle sizes and the particle size distributions for each test material were calculated (Nyström et al., 1985a). Sample concentrations substantially exceeding the equilibrium solubility were chosen while limiting the coincidence error to less than 5%. The Coulter Counter was fitted with an aperture tube of 30 μm (griseofulvin), 70 μm (griseofulvin, sieve fraction 5–10 μm) or 140 μm (felodipine, sieve fraction 20–25 μm). The tubes were chosen to cover adequately the entire size distribution by weight. Results presented are mean values of at least three determinations.

To obtain both the mean particle size and weight frequency distributions as a function of time, the results from the dissolution rate experiments described below were used. The remaining particles were counted in the same manner as mentioned above at special time intervals during the dissolution process and the mean particle sizes and particle size distributions were calculated for each specific time (Nyström et al., 1985a).

Determination of surface specific dissolution rate

The Coulter Counter was used to determine the weight of the amount dissolved (μg) and the mean external surface area (cm^2) at specific time intervals during the dissolution process and from the values obtained the surface specific dissolution rate G (μg min^{-1} cm^{-2}) was calculated (Nyström, 1985a; Anderberg et al., 1988). The values quoted represent mean rates calculated for the dissolution period up to 85% of the initial weight amount was dissolved. The dissolution media were 0.01 and 0.05% w/v polysorbate in saline for griseofulvin and felodipine, respectively. The temperature was 22 ± 1° C. All experiments were performed under sink conditions and the results presented are mean values of three determinations.

The reason for the addition of polysorbate 80 to the dissolution medium is different for the two drugs used in this study. In the case of griseofulvin, the surfactant is added purely to prevent agglomeration of the drug particles, but in the case of felodipine it is added also to increase the drug solubility. The solubility enhancement is necessary to record the dissolution data for felodipine under sink conditions, as the Coulter Counter needs a minimum of counts to deliver reliable data. With 0.05% w/v polysorbate 80, the obtained G values for felodipine are directly related to the solubility in the medium (Anderberg et al., 1988). The solubility of felodipine with this concentration of surfactant is approx. 20 mg/l and the solubility of griseofulvin in 0.01% w/v polysorbate 80 is approx. 7 mg/l.

The drug concentrations used were 0.4, 0.7 and 1.1 mg/l for griseofulvin as supplied, griseofulvin wet sieved fraction and felodipine, respectively. In all experiments 300 ml of suspension, agitated at a rotational speed of 800 rpm, was analysed.

Results and Discussion

Primary characteristics of test materials

The results for all three materials are presented in Table 1 and Fig. 1. The griseofulvin microfine was used as supplied, representing a polydispersed, fine particulate material. The wet sieved fractions of griseofulvin and felodipine were prepared with the purpose of obtaining materials as close to uniform size as possible. As can be seen from Fig. 1 and Table 1 the wet sieved fractions have relatively narrow particle size distributions, but are still not totally within the sieve intervals.

Dissolution data according to the cube root function

In Fig. 2 the surface specific dissolution rates of a number of materials, corrected for differences in solubility, are plotted as a function of particle size. For these materials the surface specific dissolution rate increases as the particle size decreases, especially for particles of 3–5 μm or smaller. The increase in dissolution rate is probably due to a rapid decrease in the thickness of the stagnant diffusion boundary layer around this size range of particles (Anderberg et al., 1988; Bisrat and Nyström, 1988).

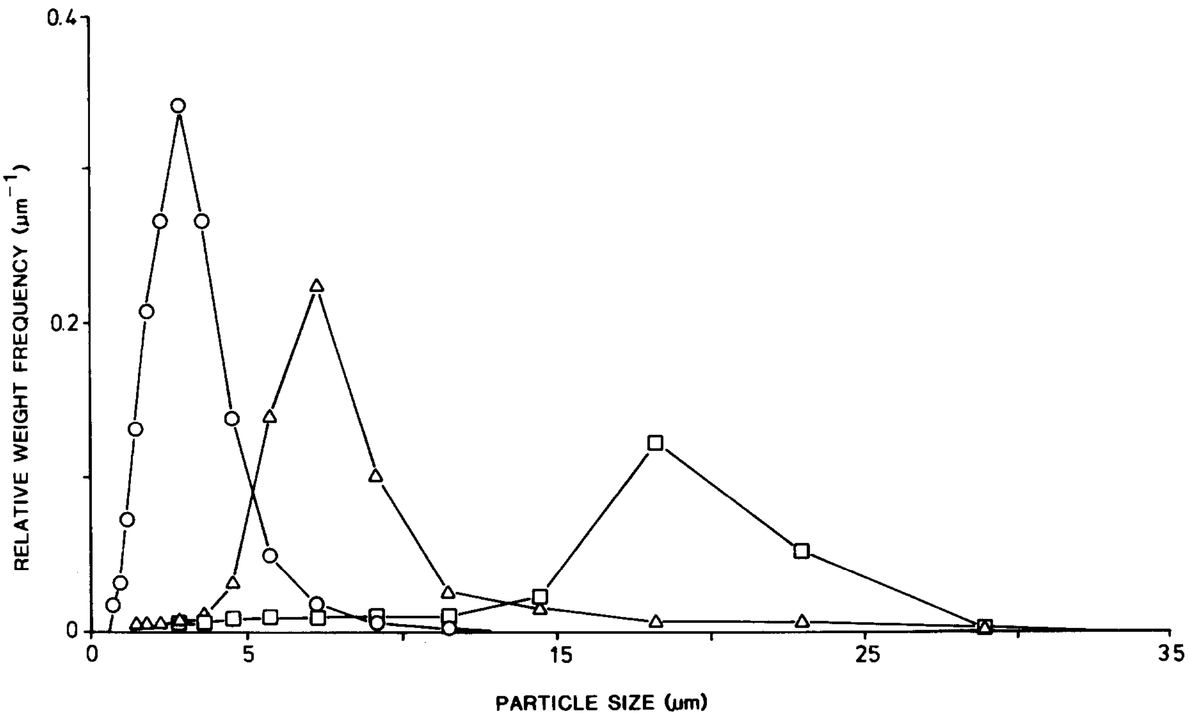

Fig. 1. Particle size distributions of (○) griseofulvin microfine, (△) griseofulvin sieve fraction 5–10 µm and (□) felodipine sieve fraction 20–25 µm.

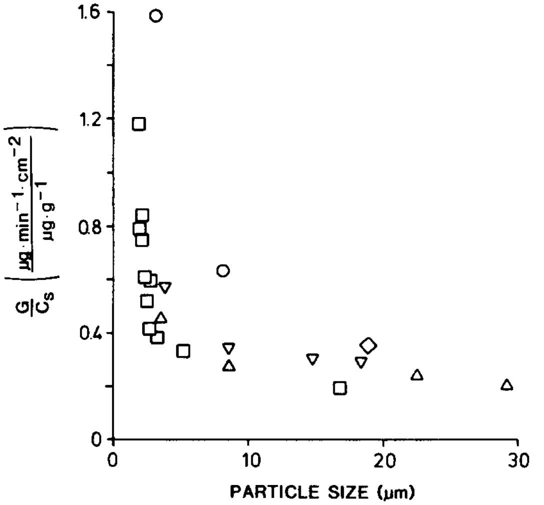

Fig. 2. Influence of particle size on the surface specific dissolution rate (G) corrected for solubility (C_s). (△) Digoxin (Bisrat and Nyström, 1988), (□) felodipine (Anderberg et al., 1988), (◇) felodipine, (○) griseofulvin, (▽) oxazepam (Bisrat and Nyström, 1988).

According to Fig. 2, a single 5 µm particle should dissolve with an increasing surface specific dissolution rate, thus giving rise to a deviation from the straight line in the cube root graph predicted by Hixson and Crowell. Consequently, a dissolving material consisting of uniform sized particles should also result in a deviation from the cube root law.

As can be seen from Fig. 3, all three materials followed the cube root law fairly well. This is unexpected with reference to the decrease in stagnant diffusion boundary layer for fine particulate dissolving materials as discussed above. However, when the mean particle sizes for the materials are followed during dissolution, this unexpected obedience to the cube root law can be explained as follows.

Changes in mean particle size during dissolution

When following the mean particle size (geomet-

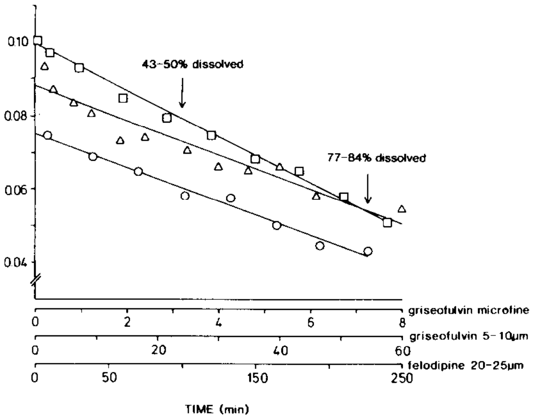

Fig. 3. Dissolution shown as cube root law graphs: (○) griseofulvin microfine, (△) griseofulvin sieve fraction 5–10 μm and (□) felodipine sieve fraction 20–25 μm.

ric mean volume diameter by weight and number) during dissolution for the two finest materials in the study (griseofulvin and griseofulvin sieve fraction 5–10 μm), no significant decrease in particle size was detected, even though up to 85% of the initial weight was dissolved (Fig. 4a, b). The relative weight frequency distributions in the beginning, in the middle and at the end of the dissolution process, further demonstrate that the size distributions of the powders remain relatively unchanged during dissolution (Fig. 5a, b).

It should be noted that relatively high statistical variations were obtained for the determination of size distributions, especially for the coarser size classes (e.g. Fig. 5a). This is obviously due to the small number of particles present in these classes. To demonstrate clearly that no growth or agglomeration of the discrete suspended particles has taken place, the change in absolute number of particles (0.05 ml samples) as a function of dissolution time is also presented for griseofulvin microfine (Fig. 6).

Since every individual particle diminishes during dissolution, one could expect that the mean particle size of a dissolving powder would decrease at the same time as the number of monitored particles gets smaller. However, in contrast to such reported suggestions (Carstensen and Musa, 1972), an almost constant particle size was observed in this study. As the mean particle size during dissolution did not change, obedience to the cube root law could be expected.

For the coarser material, felodipine, the mean particle size decreased from about 17 to 12 μm (geometric mean volume diameter by weight) (Fig. 4c), and the size distribution changed more than for the two griseofulvin samples (Fig. 5c). This decrease in mean particle size is too small in a relative sense to influence the surface specific dissolution rate, because the influence on the dissolu-

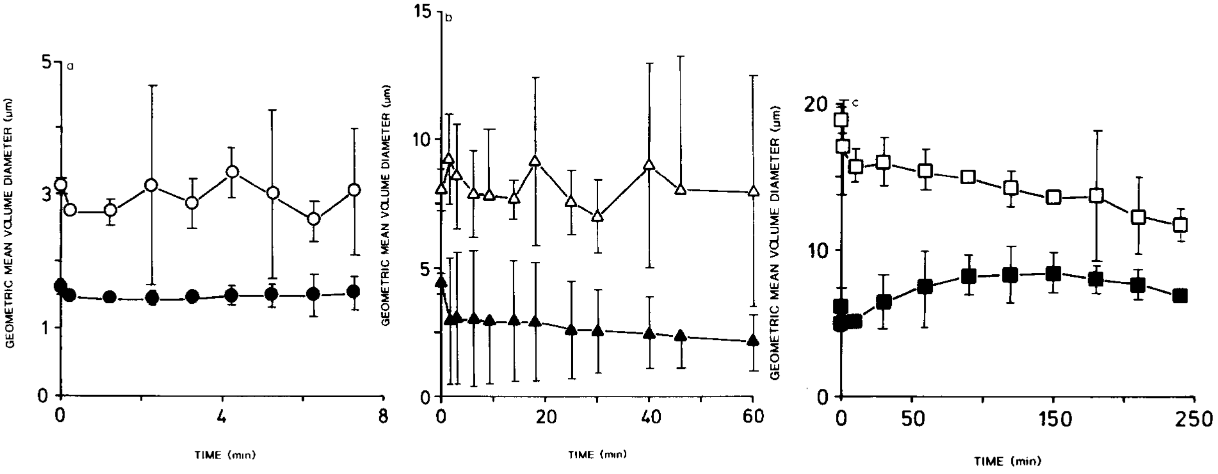

Fig. 4. Geometric mean volume diameter during dissolution. Closed symbols refer to diameter by number and open symbols correspond to diameter by weight. Error bars represent the 95% confidence interval for the mean. (a) Griseofulvin microfine. (b) Griseofulvin sieve fraction 5–10 μm. (c) Felodipine sieve fraction 20–25 μm.

TABLE 1

Primary characteristics of test materials

Material	Particle size distribution [a]		Specific surface area (m^2/g)	Surface shape factor
	Mean (μm)	S.D.		
Griseofulvin microfine	3.1 [b]	1.5	2.10 [c]	4.44 [f]
Griseofulvin, sieve fraction 5–10 μm	8.1 [b]	1.4	0.69 [d]	4.44 [g]
Felodipine, sieve fraction 20–25 μm	18.9 [b]	1.2	0.38 [e]	5.29 [f]

[a] Weight frequency distributions obtained by Coulter Counter TAII.

[b] Log-normal distribution characterized by geometric mean and geometric standard deviation.

[c] Measured by permeametry as described by Nyström et al. (1985a).

[d] Calculated from harmonic mean diameter by weight (Coulter Counter) and surface to volume shape factor of 8.49 (Heywood, 1954).

[e] Measured by a narrow angle photometer (EEL) according to Barnett et al. (1980).

[f] Calculated according to Nyström et al. (1985b).

[g] The surface shape factor for griseofulvin is assumed to be the same for the wet sieved fraction as for the raw material.

tion rate of the change in thickness of the hydrodynamic boundary layer is not pronounced at this particle size interval (Fig. 2).

Conclusions

As truly monosized materials cannot be prepared in practice, the cube root law has basically always been applied to polydispersed systems. Polydispersed materials had to be used in this study as well. All materials and size fractions tested dissolved in accordance with the cube root law.

During dissolution of polydispersed, fine particulate materials we have shown that, in contrast to what has been previously assumed (Carstensen and Musa, 1972), the particle size stays relatively constant. An explanation for this could be found in Fig. 2, which shows that the smallest particles

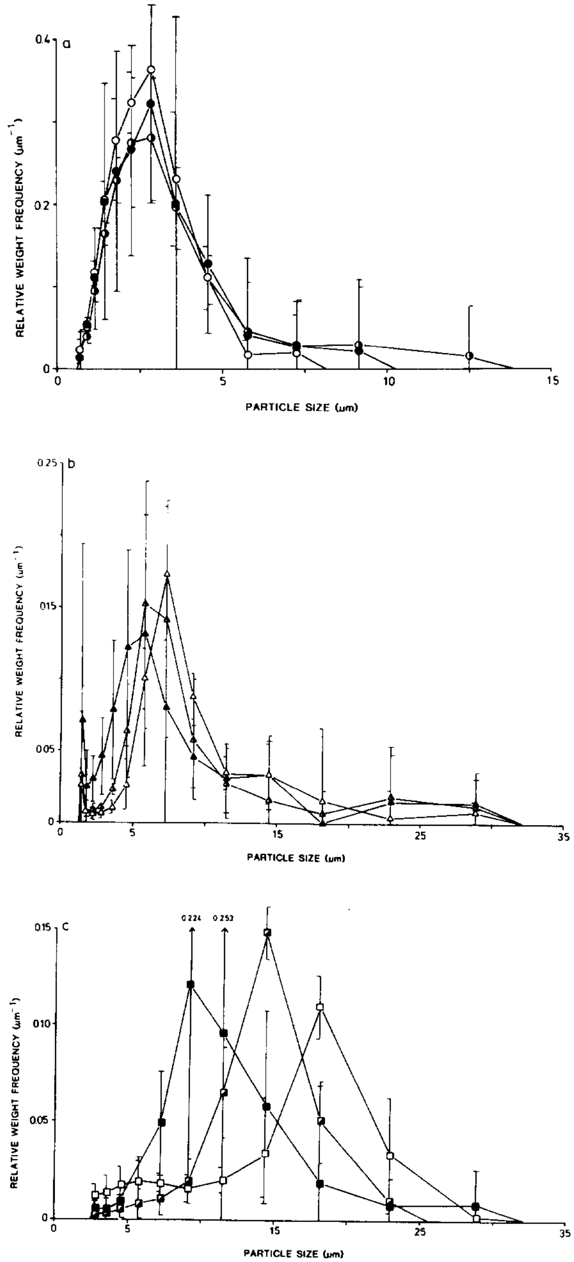

Fig. 5. Particle size distributions at the beginning, middle and end of dissolution. Error bars represent the 95% confidence interval for the mean. (a) Griseofulvin microfine after: (○) 0.25 min (1% dissolved), error bar ended by ⌉; (◑) 4.25 min (55% dissolved), error bar ended by ⌈; (●) 7.25 min (81% dissolved), error bar ended by ⊤. (b) Griseofulvin sieve fraction 5–10 μm after: (△) 1.5 min (0% dissolved), error bar ended by ⌉; (◭) 18 min (31% dissolved), error bar ended by ⌈; (▲) 46 min (72% dissolved), error bar ended by ⊤. (c) Felodipine sieve fraction 20–25 μm after: (□) 1 min (0% dissolved), error bar ended by ⌉; (◪) 120 min (59% dissolved), error bar ended by ⌈; (■) 240 min (86% dissolved), error bar ended by ⊤.

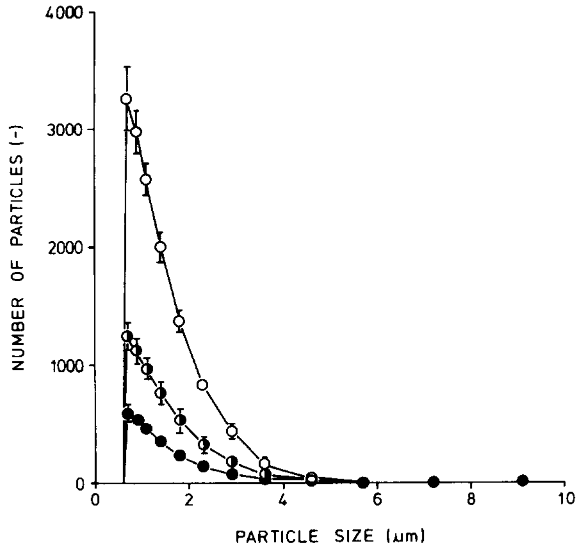

Fig. 6. Number of particles per 0.05 ml of suspension after: (○) 0.25 min (1% dissolved), (◑) 4.25 min (55% dissolved) and (●) 7.25 min (81% dissolved) for griseofulvin microfine. Error bars represent the 95% confidence interval for the mean.

dissolve and disappear faster than the coarser particles. It balances the mean particle size in such a way that it stays relatively constant during the dissolution process. It could also explain why polydispersed materials have been found experimentally to follow the cube root law, indicating that the law will not be applicable to strictly monodispersed samples.

In order to be able to prove in practice that the decrease in thickness of the hydrodynamic boundary layer, especially with very fine particles, can cause a deviation from the cube root law, particles with well-defined properties would be needed. Such particles would have to be truly monosized with a particle size preferably about 5 μm, they would have to be smooth and crystalline and their dissolution rate would have to be possible to detect with the Coulter Counter. It is very difficult, or impossible, in practice to obtain such ideal material by wet sieving or other methods known to us.

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