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# Testing the applicability of classical diffusional models to polydisperse systems

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**Abstract**

The purpose of this work is the study of the applicability of the classical dissolution models to a suspension of multisized particles. The dissolution profiles were obtained with the Coulter Multisizer, using three microsieved fractions of indomethacin (5–15, 15–25 and 25–35 $\mu$m). This instrument enables the dissolution process to be followed with regard to size, size distribution and number of the undissolved particles, as a function of time. This information is crucial for the discussion of the model-associated assumptions. It was concluded that most of the premises on which the models are based are not valid for the present experimental conditions. An alternative model was then proposed which takes into account the polydisperse nature of the particles and their number variation throughout dissolution. A remarkably good agreement was achieved between the simulated and the experimental profiles, indicating that the methodology adopted here is most suitable for the study of multiparticulate polydisperse systems.

*Keywords:* Dissolution rate; Particle size distribution; Coulter counter method; Indomethacin; Polydispersity; Dissolution modelling

## 1. Introduction

The dissolution rate plays an important role in the bioavailability of sparingly soluble drugs as it is considered the rate limiting step in drug absorption (Abdou, 1989). The use of drug powders in suspension is, most certainly, a more realistic in vivo approach for the measurement of dissolution rates than the commonly used disk method (Levich, 1962).

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Table 1
Commonly used dissolution models

| Assumptions | Basic equation | Dissolution constant |
|---|---|---|
| $h$ = constant | $W_0^{1/3} - W_t^{1/3} = K_{1/3}^t$ | $K_{1/3} = \frac{1}{3} N^{1/3} \frac{D}{h} \rho \left(\frac{6}{\rho\pi}\right)^{2/3} C_s$ (2) |
| $h = kd$ | $W_0^{2/3} - W_t^{2/3} = K_{2/3}^t$ | $K_{2/3} = \frac{2}{3} N^{2/3} \frac{D}{k} \rho \left(\frac{6}{\rho\pi}\right)^{1/3} C_s$ (3) |

$h$ = diffusion layer thickness; $d$ = particle diameter; $k$ = proportionality constant; $W_0$ = initial solids weight; $W_t$ = solids weight at time $t$; $\rho$ = particle density; $N$ = number of particles; $D$ = diffusion coefficient; $C_s$ = solubility.

To date, the dissolution of fine powders is assumed to be a diffusion controlled phenomenon (Cartensen and Musa, 1972; Grijseels et al., 1984), being currently described by the well-known modified Noyes and Whitney equation (Brunner, 1904):

$$-\frac{dW_t}{dt} = \frac{DS}{h}(C_s - C_t) \quad (1)$$

where $W_t$ represents the suspended solids weight at time $t$, $S$ the interfacial surface area, $D$ the drug diffusion coefficient, $h$ the diffusion layer thickness and $(C_s - C_t)$ the driving force in terms of concentration—$C_s$ corresponding to the solute saturation value and $C_t$ to its concentration in the main part of the solvent at time $t$.

The application of Eq. (1) to multiparticulate systems requires the knowledge of the particles surface area at any time, which in turn can be related to the weight (or volume) of suspended solids. Besides, assumptions have to be made regarding the value of the diffusion layer thickness.

The dissolution data used in this work were obtained experimentally as described in a previous paper (Simões et al., 1996). The main purpose was to investigate the effect of the primary particle size on the dissolution rate of indomethacin. For that, three microsieved fractions of indomethacin were sized and dissolution tested with the Coulter Multisizer II. This apparatus provides detailed information about important variables, like number and size of particles remaining in suspension throughout time, which are crucial for a better understanding of the dissolution phenomenon.

The present work aims, on the one hand, at the study of the applicability of the classical dissolution models to the previously obtained data and, on the other hand, at utilizing a new model, more adequate to simulate the behaviour of polydisperse systems.

### 1.1. Classical diffusional models

Hixson and Crowell (1931) were the first investigators to present an integrated form of Eq. (1). Though primarily derived for a single spherical particle, it was later extended to multiparticulate powders by assuming a system of $N$ equal-sized particles (i.e. monodisperse), considering $N$ constant. Relating the particles surface area to their volume (or weight), through a geometrical shape factor (and density), and assuming a constant diffusion layer thickness and sink conditions, the integration of Eq. (1) results in Eq. (2), presented in Table 1. This equation is known as the cube root law and has been successfully applied to describe the dissolution process of some sparingly soluble drugs (Cartensen, 1980; Nikolic et al., 1992).

Nevertheless, other authors (e.g. Higuchi and Hiestand, 1963) considered the diffusion layer thickness dependent on particle size (and, consequently, on time), which seems intuitively more realistic. Eq. (3), also shown in Table 1, is the result of the integration of Eq. (1), assuming $h$ to be proportional to the particle diameter ($h = kd$, Table 1).

Good agreements (Pedersen and Brown, 1977) as well as significant deviations (Swarbrick and Diana, 1981) have been reported in the literature for both models. The main reason for this apparent contradiction may be attributed to the differ-

ent particle size ranges tested. In fact, the applicability of the cube root law has been questioned more often for the fine particles than for the coarser ones. Moreover, some investigators (Hintz and Johnson, 1989) who adopted a linear relationship between the film thickness and the particle size also recognized that there is a limit beyond which $h$ remains constant. This might explain why good agreements are generally found for large particles using the cube root law whereas, for the finest ones, the exponent 2/3 (Eq. (3)) usually gives better fits.

Additionally, it should be pointed out that the exact relationship between $h$ and $d$ is usually not determined from the experimental dissolution data. Indeed, from the dissolution profile, only the corresponding dissolution constant is evaluated which lumps together several parameters, namely the particle shape factor and the diffusion layer thickness (Table 1). However, the actual values of each one of these parameters have to be known when simulation studies are to be conducted.

In order to understand the limits and capabilities of the existing models it is essential to carry out a thorough investigation of the main variables which influence the release kinetics. With this in mind, the Coulter method was used to assess not only the drug dissolution profile, but also the number, area and size distribution of the suspended particles throughout the process.

## 2. Material and methods

### 2.1. Sample characterization

Indomethacin (Sigma lot 60H 448), originally supplied with a broad size distribution, was subsequently microsieved in order to obtain narrow fractions. The sieved fractions were fully characterized regarding particle size, specific surface area, solubility and density. The experimental details are described elsewhere (Simões et al., 1996), being briefly mentioned here.

The primary particle size distribution of each fraction was determined using the Coulter counter method (Coulter Multisizer II) on a drug saturated solution containing 0.9% NaCl (to increase the system conductivity) and 0.01% Tween 80 (added as a wetting agent) as suspending medium. The knowledge of the size distribution is needed not only to test the efficiency of the sieving process, but also to use in dissolution modelling, as described later.

Solubility studies (essential to know $C_s$) were conducted in phosphate buffer solutions (pH 6.2, also with 0.9% NaCl and 0.01% Tween 80) since these were further used to evaluate the dissolution profiles. An excess of material was added to these solutions which were shaken at room temperature and subsequently centrifuged, the supernatant being assayed by HPLC.

The material specific surface area was determined by B.E.T. method, employing krypton as adsorbate, and used to calculate the particles shape factor, $\alpha_{s,d_v}$, required to convert particle diameter ($d_v$) to surface area (Nyström et al., 1985).

The true solids density was calculated by dividing an accurate weight of sample by its volume, measured by gas (helium) pycnometry.

### 2.2. Dissolution profiles

The fractions were dissolution tested at ambient temperature ($23 \pm 1$°C) using the previously mentioned phosphate buffer solutions. The selection of these solutions resulted from a compromise between the required sink conditions—low solid concentration—and the need to sample a statistically valid number of particles.

The Coulter Multisizer II was utilized to monitor the volume of suspended solids as well as the particles number and size distribution, as a function of time. Knowing the material density and the volume of undissolved particles, the remaining solids weight ($W_t$) can be calculated and, consequently, the dissolved fraction given by $(W_0 - W_t)/W_0$. The dissolution profiles can thereby be evaluated.

All the experiments were performed five times for each size fraction.

Table 2
Primary characterization of the indomethacin fractions

| Sample | $d_{50}^{a}$ ($\mu$m) | $d_{sv}^{b}$ ($\mu$m) | Solubility ($\mu$g/ml) | $\alpha_{s,d_v}{}^{c}$ | Density (g/cm$^3$) |
|---|---|---|---|---|---|
| 5–15 $\mu$m | 13.38 ± 0.3 | 13.26 ± 0.4 | 87 ± 6.6 | — | — |
| 15–25 $\mu$m | 17.98 ± 0.7 | 19.20 ± 0.5 | 72 ± 9.9 | — | — |
| 25–35 $\mu$m | 29.79 ± 0.7 | 30.91 ± 0.7 | 68 ± 5.0 | 3.7 | 1.375 ± 0.0012 |

[a] Mass median diameter obtained with the Coulter Multisizer.
[b] Defined as $\Sigma n_i d_{vi}^3 / \Sigma n_i d_{vi}^2$.
[c] Calculated (Simões et al., 1996).

### 2.3. Surface specific dissolution rates

The surface specific dissolution rate (Nyström et al., 1985), $G_t$, defined as the amount of solids dissolved per unit time and area, was calculated as:

$$G_t = \Delta W_t / (\bar{S}_t \cdot \Delta t) \quad (4)$$

where $\Delta W_t$ is the amount of drug dissolved during the time interval $\Delta t$ and $\bar{S}_t$ is the corresponding mean surface area. $\bar{S}_t$ was directly computed by the Coulter (assuming the particles to be spherical) and subsequently corrected using the particles shape factor ($\alpha_{s,d_v}$), experimentally determined for the indomethacin (Simões et al., 1996).

## 3. Results and discussion

### 3.1. Sample characterization

The results of the primary characterization of the different size fractions are summarized in Table 2. The fractions size distributions are quantified in this Table by their mass median diameter, $d_{50}$, and the surface volume diameter (Allen, 1990), $d_{sv}$, defined as $\Sigma n_i d_{vi}^3 / \Sigma n_i d_{vi}^2$ where $n_i$ and $d_{vi}$ are, respectively, the number and mean volume diameter of size class $i$. Although $d_{sv}$ is considered more appropriate for dissolution studies (Lieberman et al., 1990), both $d_{50}$ and $d_{sv}$ are similar, as expected for the relatively narrow distributions tested (Simões et al., 1996).

The shape factor, $\alpha_{s,d_v}$, was only determined for the 25–35 $\mu$m fraction (due to insufficient amounts of the remaining fractions) and assumed constant for the others. The actual value of this parameter (3.7) is close to that of the sphere ($\pi$) leading to the conclusion that the particles tested are not far from spherical.

### 3.2. Dissolution profiles

The dissolution profiles displayed in Fig. 1, in terms of dissolved fraction ($(W_0 - W_t)/W_0$) versus time, denote a strong effect of the fraction initial particle size distribution. As stated before, each curve is the mean of five independent dissolution tests, the SD values being lower than 5%.

### 3.3. Applicability of the classical diffusional models

Fig. 2 shows the data plots according to the theoretical equations listed in Table 1, using linear regression analysis. As can be seen, besides the nonlinear behaviour shown by all fractions, the deviations systematically increase with fraction size. Furthermore, no improvements have been

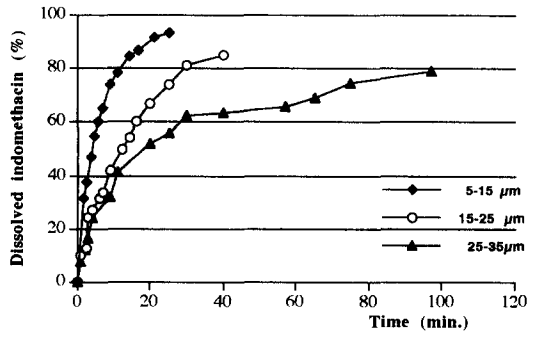


Fig. 1. Dissolution profiles of different fractions of indomethacin, obtained by the Coulter counter method.

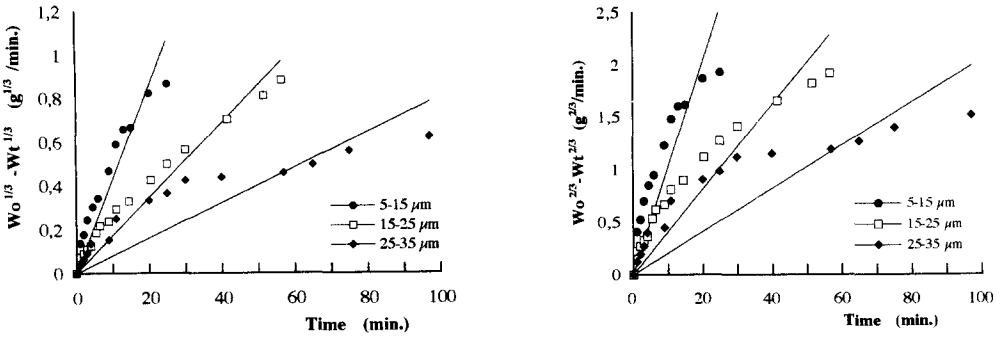


Fig. 2. Fitting of the experimental data to the classical diffusional models (Table 1).

found when using a time dependent diffusion layer (Eq. (3)). It can thus be concluded that, independently of $h$, the assumptions on which the classical diffusional models are based are not valid for the present experimental conditions.

### 3.4. Surface specific dissolution rates

The surface specific dissolution rates, $G_t$ (Eq. (4)), were also calculated for one minute time intervals during the first ten minutes. The average values are plotted in Fig. 3 as a function of $d_{sv}$. Being a surface specific parameter, $G_t$ was supposed to be independent of particle size however, as shown in Fig. 3, it decreases as the fraction mean diameter increases. Similar findings were also reported by (Bisrat and Nyström, 1988) for digoxin and oxazepan.

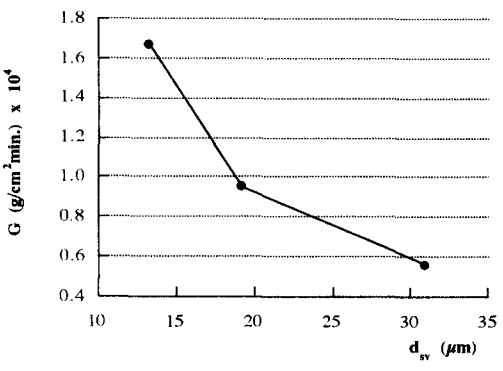


Fig. 3. Influence of particle size ($d_{sv}$) on the surface specific dissolution rate ($G_t$).

Since Eq. (4) was directly derived from Eq. (1), just assuming that $C_s$, $D$ and $h$ were constants, and since no significant changes in solubility were found (Table 2) and the diffusion coefficient was shown to be invariable (Anderberg and Nyström, 1990), the dependence of $G_t$ on $d_{sv}$ can only be explained if $h$ varies with particle size. Thereby, the increase in the dissolution rate verified for the finest fractions can not only be attributed to an increase in the particles surface area but also to a decrease in the diffusion layer thickness, as also discussed by Bisrat and Nyström (1988).

This result is apparently in contrast to the conclusions drawn from Fig. 2 which show that the fits are equally bad for both model. However, it should be remembered that assumptions other than simply the dependence of $h$ on $d$ are involved in these models. As a matter of fact, the invariability of the number of suspended particles during dissolution and the monodispersity of the powder, assumed by the models, when not observed can justify the lack of fit. These points will be examined in detail in the next sections.

### 3.5. Changes in particle number and median size

As mentioned before, one of the advantages of using a particle counter is that it allows the number of suspended particles to be evaluated as a function of time. Fig. 4 shows these results in a dimensionless form, $N/N_0$ ($N_0$ being the initial number of particles), for the various fractions. Each point is the average of five independent

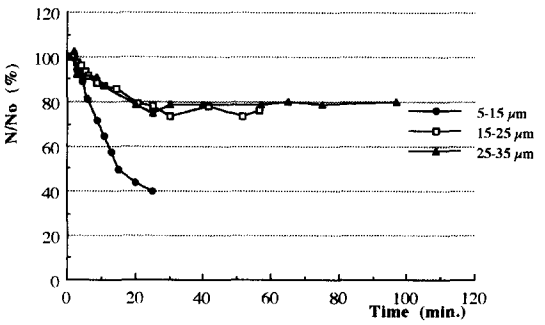


Fig. 4. Relative variation of the number of suspended particles measured by the Coulter as a function of time.

measurements, the SD values being lower than 5%.

It is obvious from these graphs that the number of particles does not remain constant during the dissolution process. As can be noticed, there is a constant and pronounced decrease in particle number for the finest fraction, in agreement with the results reported by (Anderberg and Nyström, 1990) for fine particles ( $< 10$ $\mu$m). Concerning the coarser fractions (15–25 and 25–35 $\mu$m), the number of particles decreases mainly at the initial stages of dissolution tending to become constant afterwards. This is most probably due to the complete dissolution, and subsequent disappearance, of a small amount of very fine particles which are present in these fractions as a result of some limitations of the wet sieving process.

Although negligible in volume (or mass), the number of these fine particles is significant and its change may well explain the variation over the time of the median sizes ($d_{50}$), evaluated from the number-based and volume- (or mass-) based cumulative size distributions (Fig. 5). In fact, while the number median diameter continuously diminishes, the reduction in the mass median diameter is considerably less. All these apparent contradictions anticipate difficulties when trying to analyse results obtained by other investigators in different testing conditions (namely, particle size ranges and size distributions).

### 3.6. Fractions polydispersity

As mentioned earlier, the classical models are based on the presumption that particles are monodisperse. However, truly monosized systems do not exist in practice and rules have to be followed which account for the polydisperse nature of the real powders.

Attempts have been made to develop models to describe these systems (Higuchi and Hiestand, 1963; Cartensen and Musa, 1972; Brooke, 1973; Pedersen, 1977). Besides being mathematically complex, these models are frequently based on the premise that particle size distributions follow a log-normal law (Brooke, 1974; Pedersen, 1977; Lu et al., 1993) which, in many cases, represents an oversimplification. As a matter of fact, in the present work, the actual size distributions approximate better to a normal than to a log-normal distribution confirming, therefore, that these assumptions can not be made a priori.

In order to overcome the above limitations, a new methodology was adopted in this study, which intends to be valid for particles having any initial size distribution. It was based on the Coulter Multisizer channelizing principle, that subdivides the particle size distribution into many size classes.

Eq. (3) was applied to each of these size classes. Two reasons justify the choice of this dissolution equation: first, the results obtained for the surface specific dissolution rate (Section 3.4) suggest that $h$ varies with particle size; and second, this approach seems to be physically more realistic, especially for small particles (Hintz and Johnson, 1989).

The large number of classes considered (256) ensures that the particles in every class can be considered monosized, thus following one of the model-associated assumptions. On the other hand, the time intervals used in the calculations were sufficiently short to assume $N$ constant. The number of particles in each size class was constantly updated by taking into consideration that every time the particle diameters fall below a given limit (set to be equal to the minimum size detectable by the Coulter) the particles are considered dissolved. At specified time intervals, the

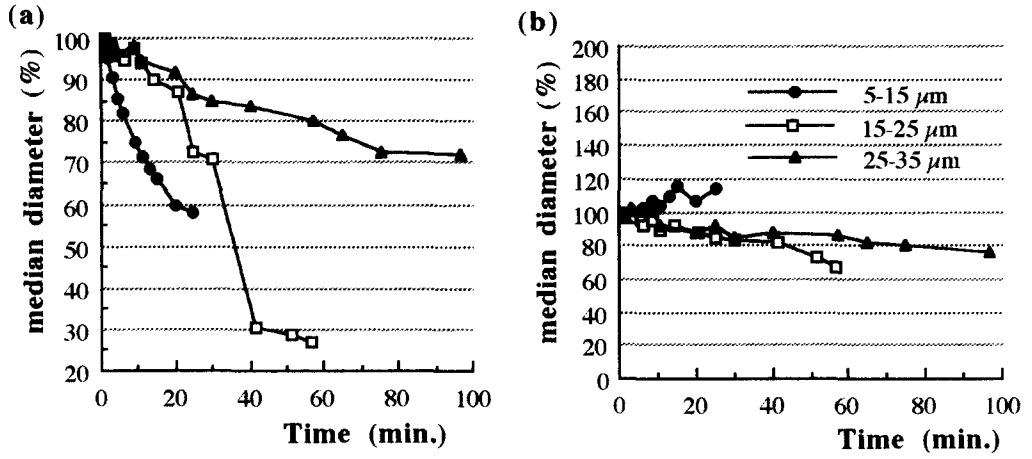


Fig. 5. Variation of the number (a) and mass (b) median diameters ($d_{50}$) throughout time, expressed as a percentage of the initial value, for the various fractions of indomethacin.

total mass of suspended solids was evaluated as the summation of the values calculated for each size class, and the dissolved fraction estimated.

Simulated dissolution profiles were then evaluated using the fractions primary size distribution and the drug physical characteristics specified in Table 2 (the actual particle shape factor, $\alpha_{s,d_v}$, substitutes $\pi$, only valid for spheres). The diffusion coefficient of $4.7 \times 10^{-6}$ $cm^2\ s^{-1}$ was also experimentally determined for the indomethacin particles (Pereira de Almeida et al., 1996). As the relationship between $h$ and $d$ was not known, several values of $k$ ($=h/d$) were tested, the best fit being obtained for $h$ equal to $d$.

Fig. 6 shows the comparison between the experimental and simulated dissolution profiles for one of the fractions (5–15 $\mu$m). As can be seen, an almost perfect agreement was achieved leading to the conclusion that this procedure is valid to accurately describe the dissolution kinetics of indomethacin, for the present experimental conditions.

The program used has been further refined in order to be sufficiently general to be applicable to other dissolution equations, size ranges and degrees of polydispersity, and will be explained in detail in a forthcoming publication.

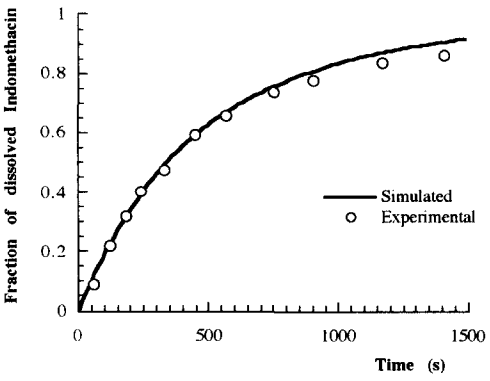


Fig. 6. Comparison between the experimental and simulated dissolution profiles for the 5–15 $\mu$m indomethacin fraction.

## 4. Conclusions

The present work clearly demonstrates that the classical dissolution models do not adequately describe the dissolution of the indomethacin particles under the study conditions. These models differ, basically, on the distinct relationships between the diffusion layer thickness and particle size. However, this is not the only assumption associated with these models and additional information is needed to understand the dissolution mechanism, especially that of multiparticulate polydisperse systems.

The use of a particle counter—the Coulter Multisizer II—proved to be an invaluable tool to follow the dissolution process of these systems, since it provides information about number, size, size distribution and surface area of suspended particles through time. In this way, it was possible to find out that the surface specific dissolution rate varied with particle size, leading to the conclusion that $h$ is not constant but is size (and time) dependent.

On the other hand, monitoring the number of particles remaining in suspension also showed that $N$ significantly decreases with time for the fractions tested. This is in contradiction to the models premises and could be responsible, at least partially, for the deviations encountered between the models and the experimental data.

Finally, the influence of polydispersity was also investigated. In fact, despite the narrowness of each size fraction, they can not be considered monosized which, consequently, contradicts another of the models assumptions.

To overcome these problems, a simulation program was developed which takes into account the polydisperse nature of the powders and the number of undissolved particles at any time. For that, an adequate dissolution equation was applied to each of a large number of size classes of the initial particle size distribution. This method has the great advantage of being straightforward, requiring only the knowledge of the primary characteristics of the drug powder. The perfect agreement between the experimental and simulated dissolution profiles suggests that the assumptions made are physically realistic.

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