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Physicochemical aspects of drug release. VIII. The relation between particle size and surface specific dissolution rate in agitated suspensions

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Summary

A Coulter Counter Model TAII was used to study the effect of particle size on the initial surface-specific dissolution rates of some fine particulate, sparingly soluble drugs. For all the materials studied, the surface-specific dissolution rate and the ratios of this value to the equilibrium solubility, increased with a decrease in particle size. This was especially pronounced when the particle size was below approximately 5 μm. No significant effect of agitation intensity on surface-specific dissolution rate was recorded for the finest particles while higher values were obtained for the coarser fractions when the agitation intensity was increased. The results were explained by a reduction in the diffusion boundary layer thickness with the decrease in particle size.

Introduction

In earlier reported work on agitated suspensions (Nyström et al., 1985a and b) it was observed, that the surface-specific dissolution rate (G) (e.g. in $\mu g \cdot min^{-1} \cdot cm^{-2}$), was relatively independent of agitation intensity. This was probably due to the very fine particulate nature of the materials tested. For such materials the diffusion boundary layer thickness (h_D) is relatively small; therefore the influence of a diffusional process is also relatively small and less important than for coarser particulate materials. In these studies it was shown that the initial surface-specific dissolution rate determined was affected by the particle size of the materials tested (Nyström et al., 1985a; Nyström and Bisrat 1986). These earlier results support the idea that the diffusion boundary layer thickness is a function of the drug particle size in an agitated suspension. Such suggestions have also been made by Niebergall and coworkers (1963) for coarser crystalline materials. They reported that experimentally obtained dissolution data, for relatively narrow size fractions of some materials, did not fit the cube-root law according to Hixson and Crowell (1931), but that the surface-specific dissolution rate increased as a function of time, parallel with the decrease in particle size of the dissolving materials. They concluded that the diffusion boundary layer thickness (h_D) was a function of the square-root of the diameter of the dissolving particle. However, it should be noted

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that their discussion mainly deals with parameters of importance for the hydrodynamic boundary layer thickness (h_H). Also other observations of similar deviations from the fit of the cube-root law have also been reported (Carstensen, 1980).

The effect of particle size on diffusion layer thickness and thus on dissolution rate is of special interest for very fine particulate materials, and especially for sparingly soluble drugs, where it is often necessary to improve their dissolution rates. Normally, the material is size reduced by milling and it is then assumed that the improvement in dissolution rate is due to the increase in specific surface area. Increases in material solubility, due to a partial amorphorization of the solid structure have been reported (Florence and Salole, 1976). The importance of diffusion layer thickness in this context has not been discussed in the literature. Improved experimental evidence of this effect would also be useful in understanding the dissolution rate of small drug particles attached to larger units (Westerberg et al., 1986). The earlier published interpretations (Nyström et al., 1985a; Nyström and Bisrat, 1986) regarding the influence of drug particle size on surface-specific dissolution rate was based on a comparison of different materials having different degrees of fineness. The objective of this paper is to evaluate in more detail the relation between particle size and surface-specific dissolution rate by using several size fractions of two fine particulate, sparingly soluble drugs.

Dissolution rate testing

Dissolution testing of drug compounds and preparations is of fundamental importance in the design and development of pharmaceutical products. Dissolution rate is normally described by some simple differential equation (e.g. Noyes and Whitney, 1897; Nernst and Brunner, 1902). The most common equation citated in pharmaceutical literature is the following:

$$dW/dt = D/h_D \cdot S_c \cdot (C_s - C_t) \quad (1)$$

where the dissolution rate (dW/dt) at time t is a function of 3 types of material or experimental parameters, namely surface area (S_c), concentration gradient ($C_s - C_t$) and diffusional transport D/h_D.

Surface area (S_c). The interfacial surface area (S_c) participating in the process between the dissolving compound and the dissolution media is sometimes difficult to quantify. For suspended, strongly agglomerating materials, the value could be substantially smaller than the total surface area of the primary particles as measured by permeametry or light-extinction (Finholt and Solvang, 1968; Nyström and Westerberg, 1986). Even in the case of well-dispersed suspensions, the particular surface characterization technique that best reflects the surface area taking part in the dissolution process should be chosen carefully. The use of gas adsorption techniques for some materials may produce a substantial overestimation in this context (Hoelgaard and Møller, 1973; Florence and Salole, 1976). A better approach is probably to use techniques measuring an external surface area of the primary particles (Hoelgaard and Møller, 1973; Nyström et al., 1985b; Nyström and Westerberg, 1986).

Concentration gradient ($C_s - C_t$). This is the relationship between equilibrium solubility (C_s) and the existing concentration of dissolved drug in the bulk of the dissolution media (C_t). It is normally assumed that the concentration in the proximity of the solid material is equal to the saturation concentration. The thickness of this layer cannot be easily calculated nor determined experimentally.

In most laboratory tests a situation close to the so-called sink conditions is required, to mimic the in vivo situation or to improve the standardization of the test procedure. Strict sink conditions mean that the term C_t is zero. In practice it is normally regarded as satisfactory if C_t is 10% or less compared to C_s.

Diffusional transport (D/h_D). The influence of a relatively slow, diffusional transport of dissolved drug molecules away from the solid surface to the bulk solution is of major importance. In an agitated system the dominating transport mechanism in the bulk is by convection. The relative importance of diffusional transport is then described by the diffusion coefficient (D) and a parameter describing the distance (h_D) over which

diffusion is the dominant transport mechanism (Levich, 1962). The thickness of such a layer, is mainly related to the hydrodynamic boundary layer thickness (h_H) around the solid material, but may also be influenced by the drug solubility. The diffusion coefficient is normally regarded as a constant, while the thickness of a hydrodynamic boundary layer, and subsequently the diffusion distance (h_D) is dependent on several parameters, such as agitation intensity and liquid viscosity. To obtain reproducible results it is necessary to keep the agitation intensity constant or to create a situation where the effect of a diffusional process can be neglected. One technique, using the rotating disk method, has been to extrapolate the dissolution rate to infinite rotational speed or infinite specimen distance from the rotation axis (Nicklasson et al., 1982), when it is assumed that the diffusion layer thickness is close to zero.

For dissolution testing of pure drug compounds, a common feature is to obtain test procedures that are as independent as possible of the 3 parameters discussed. To reduce the effect of C_s, experiments are conducted under near sink conditions, and since the dissolution rate under sink conditions is directly proportional to C_s (Hamlin et al., 1965; Nicklasson and Brodin, 1984), it is preferable to express the dissolution rate in relation to the material solubility. To reduce the marked effect of variations in (h_D), experiments are standardized with respect to agitation intensity, while D normally is not affected by the experimental design. To reduce the effect of S_c, due to variations in amount or degree of fineness of the drug tested, the dissolution rate can be expressed as a surface-specific dissolution rate. This can be accomplished in several ways. The most common procedure is to keep the surface area constant by the use of compressed discs (Wood et al., 1965). Another technique, used for particulate suspensions, is to calculate the change in surface with dissolution time, from a knowledge of the change in weight dissolved. The well-known procedure of Hixson and Crowell (1931) assumes that the change in surface area is proportional to the change in weight raised to the power of 2/3. The proportionality constant is composed of density and particle shape properties. This concept has been claimed to be acceptable for nearly monodispersed materials and for polydispersed materials showing a log-normal size distribution (Higuchi and Hiestand, 1963). Another approach used to obtain a surface-specific dissolution rate characterization has been to directly measure the change in surface area as a function of time (Rubinstein and Bansal, 1987). Using a Coulter Counter TAII, this approach has been tested, especially for fine particulate, sparingly soluble materials (Nyström et al. 1985a and b; Nyström and Bisrat, 1986).

Experimental

Materials

Micronized oxazepam (Wyeth, F.R.G.) and digoxin (Boehringer Ingeheim, F.R.G.) were used. These materials were chosen because of their low solubility and their relatively wide particle size distributions, making it possible to obtain a number of different size fractions by wet sieving.

Methods

Primary characterization of test materials

The primary characteristics of the untreated test materials are given in Table 1.

Density. The density was measured with an air comparison pycnometer (Beckman Mod. 930, U.S.A.). The results are the mean values of 3 determinations (Table 1).

Solubility. The aqueous solubility of oxazepam was determined by adding an excess of the drug to 1 liter of dissolution medium. The suspensions were shaken mechanically for 48 h at a constant temperature of 23°C. After centrifugation, the supernatant was assayed spectrophotometrically (Zeiss PM 6, F.R.G.) at 238 nm, for the amount of drug. The results shown in Table 1 are the mean values of 3 determinations.

Particle size distribution. These were carried out on each sieve fraction of the two materials using a Coulter Counter TAII, as described earlier (Nyström et al., 1985b).

TABLE 1

Primary characteristics of test materials

Material	Density (g/cm^3)	Aqueous solubility at 23° C ($\mu g/ml$)	External specific surface area [a] (cm^2/cm^3)	Surface shape factor [b] (α_{s,d_v})
Digoxin	1.28	28 [d]	6,800	4.4
Oxazepam	1.48	22	13,400	6.7
Griseofulvin [c]	1.44	8.9	31,000	5.1
Hydrocortisone acetate [c]	1.29	7.7	10,000	9.6
Calcium carbonate [c]	2.65	19	5,000	3.4

[a] Measured by permeametry as described in the experimental section.
[b] Calculated according to Heywood (1954).
[c] Earlier reported data (Nyström et al., 1985a).
[d] Data from Nyberg et al. (1974).

External surface area of primary particles. The external surface areas (in cm^2/cm^3) were determined by permeametry, using a Blaine apparatus (Blaine, 1943). Due to the fine particulate materials used, the calculations of the surface area involved a correction for 'slip flow' (Alderborn et al., 1985). The mean value of the 3 determinations is given in Table 1.

Preparation of sieve fractions. Both digoxin and oxazepam were wet sieved (precision test sieve with circular openings, Veco, The Netherlands) and sieve fractions in the range up to 45 μm were prepared. The particle size distributions of the sieve fractions of the two materials are presented in Table 2 and Figs. 1 and 2.

Coulter Counter measurement

Experimental design. A Coulter Counter Model TAII, fitted with a 30 μm aperture tube for the sieve fraction < 5 μm, a 100 μm aperture tube for the fractions in the range 10–35 μm, and a 140 μm tube for the 35–45 μm fraction were used. These aperture tubes were chosen in order to adequately cover the entire size distribution by weight of the different sieve fractions (Table 2).

Stock suspensions were prepared using a par-

TABLE 2

Size fractions of digoxin and oxazepam tested

Material	Wet sieve fraction (μm)	Size distribution by weight [a]		Aperture tube used (μm)	Size range covered (μm)
		$\bar{d}_v$ (μm)	(μm)		
Digoxin	< 5	3.50	1.37	30	0.63–12.8
	10–15	8.57	1.31 [b]	100	1.60–32.2
	25–35	22.48	4.02	100	1.60–32.2
	35–45	29.16	1.21 [b]	140	2.54–51.2
Oxazepam	< 5	3.80	1.46 [b]	30	0.63–12.8
	10–15	8.44	1.43 [b]	100	1.60–32.2
	15–25	14.17	3.82	100	1.60–32.2
	25–35	18.4	4.94	100	1.60–32.2

[a] Measured by Coulter Counter TAII. Arithmetic mean values and S.D. are presented.
[b] Log-normal distributions, here represented by geometric mean values and geometric S.D.s (dimensionless).

ticle-free distilled water containing 0.9% w/w NaCl and 0.01% w/w polysorbate (Tween) 80. This electrolyte was also used as dissolution medium in all experiments performed. All stock suspensions were treated in an ultrasonic bath to achieve an adequate dispersion.

In all the experiments, the volume of the final suspension after the addition of the required stock suspension was 300 ml. The sample volumes analyzed were 0.05, 0.5 and 2.0 ml for the 30, 100 and 140 μm aperture tubes, respectively.

The number of particles in 14 size classes were recorded simultaneously and used for further calculations on a Hewlett Packard 9825T computer.

Determination of remaining particle weight and surface area. Knowing the true density of the materials, the number of particles in each class per ml and the arithmetic mean volume diameter in the classes, the total weight of the remaining particles per ml of suspension can be calculated according to Nyström et al. (1985b).

From the knowledge of surface shape factor (based on volume diameter and the volume-specific external surface area), the total external surface area of remaining particles per ml of suspension was calculated as described by Nyström et al. (1985b).

These calculations are based upon the assumption that the materials' density did not vary with particle size nor with time and also that the shape of the particles did not change during dissolution, i.e. that the particles are dissolved in an isometric fashion (Carstensen, 1980).

Calculation of surface-specific dissolution rate. The surface-specific dissolution rate, G, ($\mu g \cdot min^{-1} \cdot cm^{-2}$) for a specific time interval was calculated from the amount dissolved (μg) and the mean external surface area (cm^2) (Nyström et al., 1985b). For all the sieve fractions of the materials, the final concentrations tested never exceeded 10% of the solubility (near sink conditions).

Aperture tube checking. As the determination of dissolution rate from Coulter Counter data is highly dependent upon the validity of the calculation of weight amounts of remaining undissolved particles, it was important to check if the use of 3 different aperture tubes introduced any increase in the total error. To test this a standardized suspension of calibration latex spheres (6.0 μm) was characterized by all 3 aperture tubes. Using a density value of 1.06 g/cm^3, the final weight concentration was calculated for each aperture tube. The aperture tubes were first calibrated with 2.02 μm or 8.06 μm latex spheres. A stock suspension of the 6.0 μm latex spheres in distilled particle-free water containing 0.9% NaCl and 0.01% polysorbate 80 was prepared. After a few minutes in an ultrasonic bath, a known volume from the latex stock suspension was added to the Coulter media. Since the latex particles were insoluble in the media, the number of particles analysed every minute for 5 min was recorded in the 14 size classes and mean values used to calculate the final concentration (Table 3).

TABLE 3

Comparative test of aperture tubes used

The 95% confidence interval for the mean are given in brackets.

Aperture tube (μm)	Concentration of 6.0 μm latex spheres (μg/ml)
30	0.632 ($\pm$0.024)
100	0.654 ($\pm$0.010)
140	0.642 ($\pm$0.012)

Results and Discussion

Aperture tube checking

The results from the check of the 3 aperture tubes and their capability to detect the same weight concentration of suspended latex spheres are presented in Table 3. No significant differences were obtained.

The accuracy of the Coulter Counter technique is also dependent on the amount of the characterized material outside the measurement range of the aperture tube being used. The larger the weight fraction of a material outside the limits, the less accurate is the result. The size ranges covered by the aperture tubes used together with the size distribution of the sieve fractions are given in Table 2. For all the sieve fractions of the two

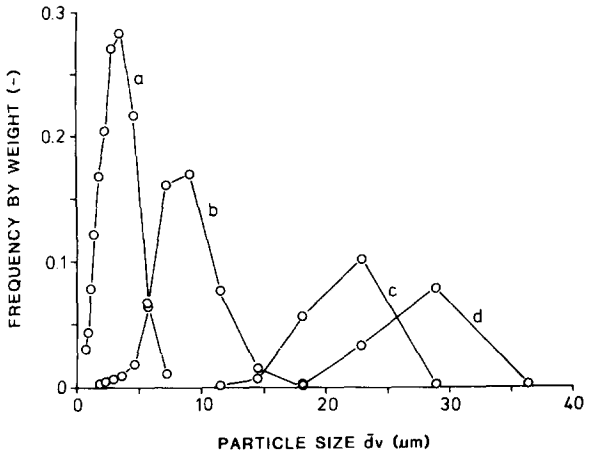

Fig. 1. Particle size distributions (obtained by the Coulter Counter TAII) for wet sieve fractions of digoxin: (a) < 5 μm; (b) 10–15 μm; (c) 25–35 μm; and (d) 35–45 μm.

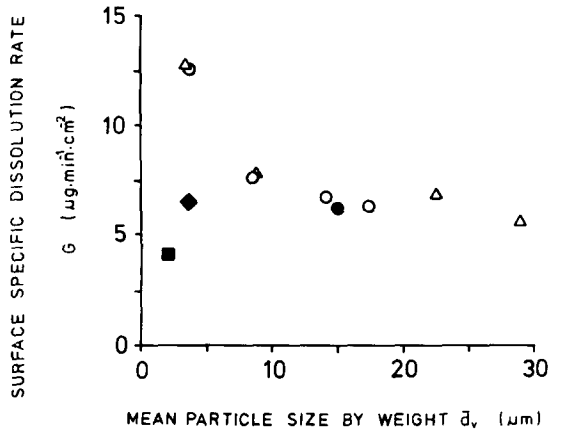

Fig. 3. Effect of particle size on surface specific dissolution rate (G) for test materials: △, digoxin; ○, oxazepam; ◆, griseofulvin; ■, hydrocortisone acetate; ●, calcium carbonate. Filled symbols denote that the data are taken from an earlier study (Nyström et al., 1985a).

materials, no or only negligible weight amounts were below the lower limit of the aperture tubes used. The choice of tubes were therefore considered appropriate.

Particle size distribution of test materials

The efficiency of the wet sieving separation is shown by the particle size distributions of the 4 fractions, respectively, for digoxin and oxazepam in Figs. 1 and 2. This could also be seen from mean particle sizes, presented in Table 2. All fractions contained substantial amounts of particles smaller than the lower size limits utilized. Therefore the mean particle sizes were close to or smaller than the lower nominal limits of each sieve fraction prepared.

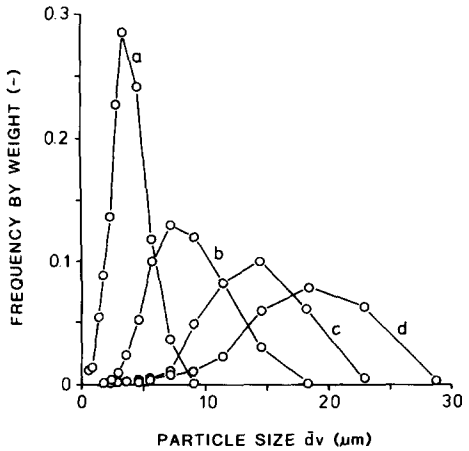

Fig. 2. Particle size distributions (obtained by the Coulter Counter TAII) for wet sieve fractions of oxazepam: (a) < 5 μm; (b) 10–15 μm; (c) 15–25 μm; and (d) 25–35 μm.

Surface-specific dissolution rate

In Fig. 3 the surface-specific dissolution rates of digoxin and oxazepam are plotted against the corresponding mean volume diameters by weight of the respective materials. In Fig. 3 the filled symbols denote data taken from a previous study (Nyström et al., 1985a). Fig. 3 shows that the surface-specific dissolution rate for digoxin and oxazepam increased with the decrease in particle size of the materials. However, a deviation from this pattern was obtained when including data from other materials.

The parameters which are widely known to affect the diffusion layer thickness (temperature, viscosity and agitation) were, in this study, kept constant. Agitation was induced by a rotating propeller from the Coulter Counter at a stirring rate of 800 rpm. Niebergall et al. (1963) showed for narrowly sized coarser materials that the diffusion layer thickness was proportional to the square-root of particle diameter. As can be seen from Fig. 3 the parameter which is found for

digoxin and oxazepam to affect the surface specific dissolution rate is the particle size of the dissolving materials.

It can be assumed that this is due to an effect of particle size on the thickness of the distance over which diffusion is the dominating transport mechanism, i.e. the rate-limiting factor for the dissolution process. Whereas Niebergall et al. (1963) used coarse particulate, nearly monodispersed materials, the materials used in this study were polydispersed, fine particulate and sparingly soluble.

Surface-specific dissolution rate related to solubility

The deviating results (Fig. 3) for griseofulvin, hydrocortisone acetate and calcium carbonate in the relation between mean particle size and G-values, can probably be related to their differences in equilibrium solubility (Table 1). Therefore the ratio of surface-specific dissolution rate to equilibrium solubility (G/C_s) for each material and fraction tested were plotted against particle size in Fig. 4. The results in Fig. 4 demonstrate the importance of solubility corrections when comparing different materials. The direct relationship between solubility and surface-specific dissolution rates is well documented in the literature (e.g. Hamlin et al., 1965; Nicklasson and Brodin, 1984). In Fig. 4, all the data obtained fit one single profile, describing

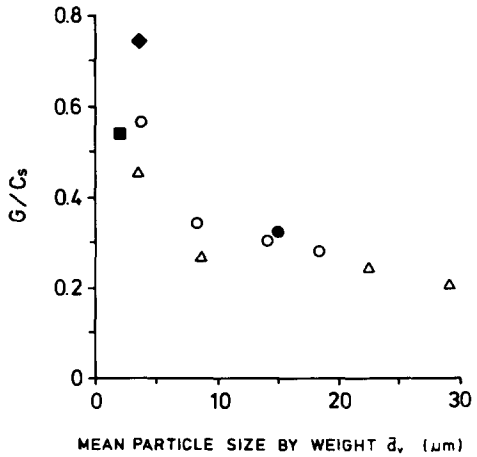

Fig. 4. Effect of particle size on surface-specific dissolution rate (G) corrected for aqueous solubility (C_s). Symbols as in Fig. 3.

the importance of particle size for surface-specific dissolution rate and probably diffusion boundary layer thickness.

The mechanisms of this observation can be related to the hydrodynamics of an agitated system of a suspended solid body. Solids dispersed in a liquid media 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. For flow past a flat surface, the Prandtl boundary layer equation can be used to express the hydrodynamic boundary layer thickness (h_H).

$$h_H = k \cdot L^{1/2}/V^{1/2} \qquad (2)$$

where L is the length of the surface in the direction of flow and V is the relative velocity of the flowing liquid versus the flat surface. The application of Eqn. 2 to a system of suspended small particles is fairly complicated. A decrease in particle size for a given intensity of agitation, would probably result in a decrease in V, while the smaller particle corresponds to a smaller value of L. Although these two effects counteract each other, it has been assumed (Niebergall et al., 1963) that the nett effect is a decrease in h_H. It is thus believed that a difference in particle size or diameter could correspond to a difference in the parameter L in Eqn. 2. Therefore a decrease in particle size corresponds to a reduced distance over which frictional forces could act, leading to a thinner region in which there exist a velocity gradient. This would then correspond to a shorter diffusional distance for dissolved molecules. The fraction of the hydrodynamic boundary layer thickness (h_H) in which diffusion dominates, i.e. constitutes the diffusion boundary layer thickness (h_D) will probably vary between materials, depending on e.g. material solubility.

Effect of agitation intensity

Possible differences in solid structure between the particle size fractions tested may be used to explain the dissolution rates obtained.

Differences in solid structure and energy would correspond to differences in aqueous solubility. If such differences are used to explain the data, the

TABLE 4

Effect of agitation intensity on surface specific dissolution rate (G)

Material	Mean particle size by weight $\bar{d}_v$ (μm)	G-values in $\mu g \cdot min^{-1} \cdot cm^{-2}$ for different agitation intensities (rpm)		
		350	500	800
Digoxin	3.5	12.9	12.8	12.8 ns *
	22.5	–	5.9	6.7 $P < 0.01$
Oxazepam	3.8	12.3	12.4	12.5 ns *
	18.4	–	5.4	6.5 $P < 0.05$

* No significant difference.

effect of agitation intensity would be negligible. To test this hypothesis the following experiments were performed.

Dissolution measurements were made using stirring rates between 350 and 800 rpm for the size fractions < 5 μm and 500–800 rpm for the sieve fractions 25–35 μm (Table 4). 350 rpm could not be applied for the coarser material due to moderate sedimentation tendencies. The data in Table 4 indicate that the *G*-values for the fine particulate materials are not significantly affected by the difference in rotational speed in the range tested. But for the coarser sieve fractions of both digoxin and oxazepam the *G*-values obtained at the lower rotational speeds were significantly lower from those obtained at the higher speed. Considering the limited agitation range applied, an explanation is that the thickness of the diffusion layer around the fine particles is so small that the applied changes in stirring rate have no measurable effect on the *G*-values. For the coarser fraction, on the other hand, the diffusion distance is probably large enough to be sensitive for the variation in the applied agitational intensity.

Conclusions

The results in this study indicate that differences in particle size, for relatively fine, sparingly soluble drugs in suspended form, will affect the diffusion boundary layer thickness in a dissolution process. A change in particle size will, even if all other material and experimental properties are held constant, change the surface-specific dissolution rate. This interpretation of the data is supported by the following observations. For the sieve fraction 25–35 μm, the dissolution rate was influenced by agitation intensity. Secondly, one single profile was obtained for 5 different materials, possessing different physicochemical properties, and thirdly, for the finest sieve fractions tested, very high *G*-values were obtained. In fact, these values were as high as for the calculated values corresponding to infinite rotational speed (Nicklasson et al., 1982), where the thickness of the diffusion layer approaches zero. Additionally, for the finest fraction in this study, no effect of agitation intensity could be monitored.

The results in this study support the concept that the increase in dissolution rate of poorly soluble compounds due to micronization is achieved not only due to the increase in the surface area and possible changes in material solubility (Florence and Salole, 1976), but also due to the fact that the micronized particles have a smaller diffusion boundary layer thickness, resulting in a faster transport of the dissolved molecules from the particles surface.

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