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Journal of Pharmaceutical and Biomedical Analysis 39 (2005) 900–907
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
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A new approach in the prediction of the dissolution behavior of suspended particles by means of their particle size distribution

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Received 15 March 2005; received in revised form 29 April 2005; accepted 11 May 2005
Available online 14 July 2005

Abstract

Though various attempts have been made in literature to model the particle size distribution of an active pharmaceutical ingredient (API) in function of the required release profile of the pharmaceutical product, so far one has not succeeded to develop a universal approach in the correlation of particle size distribution and in vitro dissolution data. In this publication, a new approach is presented on the use of particle size distribution data in the prediction of the in vitro dissolution profile of a suspension formulation. For this purpose, various theoretical experiments were done simply on paper and based on the Noyes–Whitney [A.A. Noyes, W.R. Whitney, J. Am. Chem. Soc. 19 (1897) 930–934] equation, the normalized dissolution profiles of various imaginary size distributions were calculated. For each size distribution, its weighted mean diameters were then calculated. Based on these theoretical data, a model could be developed which scientifically explains the dissolution profile of a suspension in function of its volume-weighted mean particle size (D[4, 3]). The applicability of this correlation model could experimentally be confirmed by evaluation of laser diffraction and in vitro dissolution data as they were obtained for different batches of a suspension formulation. This new approach in the correlation between particle size and dissolution may be an important analytical tool in the engineering of the particle size distribution of drug substance, and more precisely monitoring the D[4, 3] volume-weighted mean diameter may allow one to model the dissolution profile of a suspension formulation and thereby its in vivo release profile.

Keywords: Particle size distribution; Volume-weighted mean diameter; Laser diffraction; Dissolution; Correlation

1. Introduction

In pharmaceutical industry, the development of new drugs is not only related to the discovery of new pharmaceutical active ingredients (API), but also to the (chemical) development of a stable form of the API and the (pharmaceutical) development of an effective pharmaceutical dosage form. The latter should most of all be considered as a dosing device to enable the accurate and repetitive dosing of the API. However, a dosage form is far more than a simple drug carrier, since it may affect the absorption rate of the API, and thereby its effectiveness in the patient. As a result, one can state that the development of a pharmaceutical dosage form is an essential part in the entire drug development process. One of the objectives in the development of a pharmaceutical dosage form is to link what goes in the formulation in terms of ingredients and manufacturing conditions, and what comes out in the patient in terms of bioavailability, therapeutic activity and side effects. Once this relationship is known, the tools are available for the development in a shorter period of time of a better pharmaceutical dosage form with an improved therapeutic activity.

One of the aspects of the pharmaceutical dosage form, which may affect the effectiveness of the drug, is the particle size of the API [1,2]. The latter can readily be understood, since the dissolution rate of the API may highly depend on its particle size (distribution). As a means to mimic the disintegration and dissolution behavior of solid oral dose formulations in the gastro-intestinal tract of a patient, various in vitro dissolution techniques are available. Though in many cases in vitro dissolution testing is used as a quality control

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doi:10.1016/j.jpba.2005.05.014

parameter to monitor the constant manufacturing of a product, it can also be used as a basis for correlation of the in vitro dissolution profile and in vivo pharmacokinetic data (IVIVC). For innovative pharmaceutical R&D organizations IVIVC is regularly applied as an important analytical tool to design effective solid oral dosage forms. Various attempts have been made as well to correlate the particle size of the API with in vitro dissolution data [3–7]. However, so far these attempts did not succeed in a universal approach for the modeling of the in vitro dissolution profile of a pharmaceutical dosage form based on the particle size characteristics of the API.

The correlation between the particle size (distribution) of an API and the dissolution profile of its solid oral dose formulation is generally quite complex, since any relationship may depend not only on the dissolution of the API, but also on the disintegration of the dosage form itself. To keep things simple, the study as described here has initially been limited to particles that are already in suspension. For the correlation between two physical or physiological parameters (e.g. particle size distribution versus in vitro dissolution profile), one may use either a statistical or a scientific model. A statistical approach can be very effective and has the advantage that the chemistry and/or physics not necessarily need to be known. However, unlike a statistical model once the chemistry and physics are known, based on a scientific model analytical data can more readily be interpreted to better understand (or predict) the behavior of the product. As will appear from this publication, the dissolution behavior of particles in function of their particle size distribution can be estimated quite well if some basic fundamentals are taken into account. In the following sections, it is shown in more detail how a theoretical model on the dissolution of suspended particles can be derived by the performance on paper of some theoretical experiments. This theoretical model is at the end empirically verified for a series of suspension formulations by the determination of both the in vitro dissolution and the particle size distribution profile.

Based on the Noyes–Whitney equation, for a product its dissolution profile can exactly be calculated, provided that the solubility of the drug (c_s) and the rate constant of dissolution (k) are known. This publication will however show that the exact values of c_s and k do not need to be known if only the correlation between the dissolution profile and the particle size distribution is aimed for. In Fig. 1, a schematic presentation is given on the stepwise approach, which is followed in the modeling of dissolution profiles based on particle size data. This approach as schematically outlined here can be used as a basis in the correlation of particle size characteristics and other physical or physiological aspects of a drug.

As a first step in the modeling of dissolution and particle size data, its theoretical basis will be discussed by means of a systematic explanation of:

a. the Noyes–Whitney equation;
b. the rate constant of dissolution (k) in function of the diameter (D) of a single particle;
c. the average rate constant of dissolution ($\bar{k}$) for a number of particles not necessarily having the same particle size.

As one can expect, the dissolution profile of a product relates to the cumulative contribution of all individual particles present in the product. For spherical particles, the theory according to Noyes–Whitney implies that if the dissolution behavior is known for a single particle with a certain size, the dissolution profile of other particles with known sizes is automatically known as well.

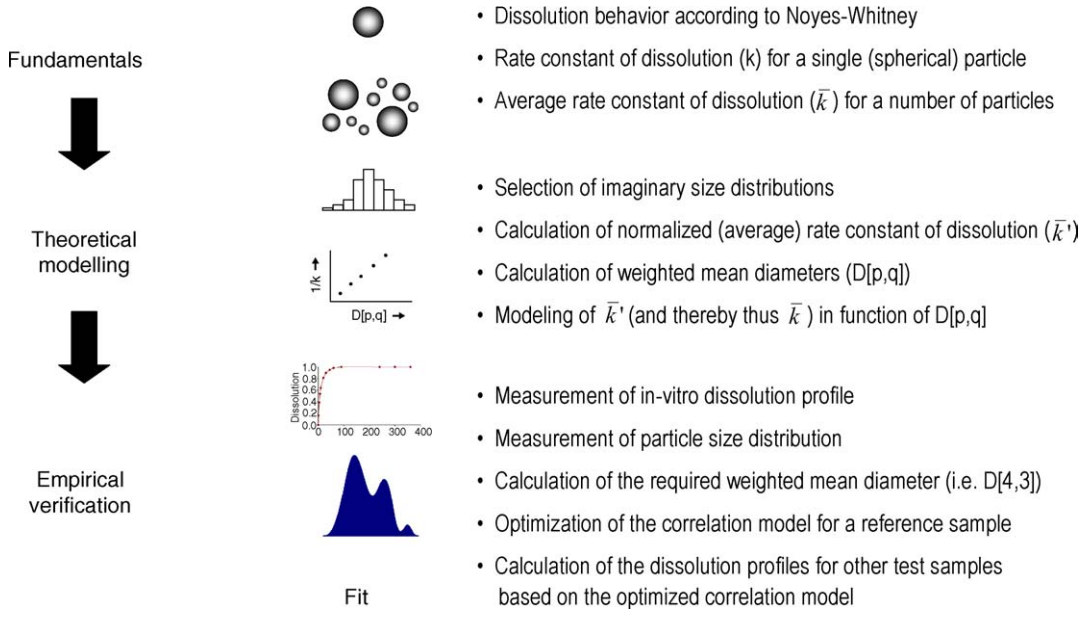

Fig. 1. A schematic presentation of the stepwise approach in the empirical modeling of the in vitro dissolution profile based on the particle size distribution profile of a suspension.

As a second step for a series of imaginary size distributions the theoretical modeling of the dissolution profile based on $\bar{k}$ will be discussed. For this purpose, size distributions were designed simply on paper by defining their size classes and the number of particles per size class. For the theoretical modeling, the following assumptions have been made:

a. sphericity of the particles;
b. dissolution of the particles according to Noyes–Whitney;
c. constant total volume (V) of the particles;
d. normalization of the solubility of the drug (i.e. $c_s = 1$).

For all the imaginary size distributions meant above $\bar{k}$ has been calculated together with the various weighted average diameters ($D[p, q]$) [8]. Based on these data it is then demonstrated how to determine the $D[p, q]$ which has the best correlation with $\bar{k}$, and which thus can best be used in the modeling of in vitro dissolution profiles based on particle size distribution data.

As a third and last step, the applicability of the new correlation concept will be demonstrated by the empirical modeling for a series of real-life samples of which the in vitro dissolution and the particle size distribution profiles have experimentally been determined. More precisely, this empirical approach will be discussed by means of a systematic explanation of:

a. correlation of $\bar{k}$ and $D[4, 3]$ according to $\frac{1}{\bar{k}} = \varphi \times D[4, 3]$;
b. optimization of φ such that the experimentally determined and normalized dissolution profile of a reference product corresponds to its empirically modeled dissolution profile;
c. calculation of the dissolution profile of other samples (for comparison with their experimentally determined dissolution profiles) based on their volume-weighted mean diameter ($D[4, 3]$) and φ;
d. fine tuning of the empirical model for broad(er) size distributions.

2. Results and discussion

2.1. Step 1: fundamentals

The dissolution of a solid in a bulk liquid is a dynamic process, since molecules migrate from the solid particle into the diffusion layer that surrounds the particle. Then, these molecules diffuse from the diffusion layer into the bulk solution. Provided that during the dissolution of the particles so-called sink conditions are met, the dissolution kinetics are described by Eq. (1).

$$c(t) = c_s \times (1 - e^{-k \times t}) \quad (1)$$

With the so-called Noyes–Whitney equation [9], the concentration of the molecule in the bulk solution ($c(t)$) can be calculated from the concentration of the molecule in the diffusion layer or the so-called solubility of the drug (c_s), the time (t) and the rate constant of dissolution (k). The latter can be calculated by Eq. (2) from the surface of the particles (S), the diffusion coefficient of the dissolve molecule (ξ), the volume of the bulk solution (V_s) and the thickness of the diffusion layer (h).

$$k = \frac{S \times \xi}{V_s \times h} \quad (2)$$

For this study, the thickness of the diffusion layer is assumed to be constant for particles with a different size. However, one should know, that the latter is basically untrue since it is known that for particles in suspension the thickness of the diffusion layer generally decreases with a decrease in particle size [10,11] leading to a faster transport of the dissolved molecules from the particle surface into the bulk solution.

Finally, according to the Stokes equation (3), the diffusion coefficient (ξ) can be calculated from the Boltzmann constant (k_b), the temperature (T), the viscosity of the bulk solution (η) and the hydrodynamic radius of the dissolved molecule (r).

$$\xi = \frac{k_b \times T}{6\pi \times \eta \times r} \quad (3)$$

As the volume of the product (V) is considered to be a constant, the surface area of the product (S) is determined by the surface area of the particles (A) and substitution in (2) shows that for ideal particles the rate constant of dissolution (k) is inversely proportional to the diameter of the particle (D). The latter is demonstrated in Fig. 2 as for several particle sizes the relative dissolution rate is schematically presented, showing that (as one may expect) small particles will dissolve much quicker than bigger particles.

For (narrow) size distributions, a reasonable estimate of the dissolution profile of the product can be made based on the average rate constant of dissolution ($\bar{k}$). The latter can be calculated by weighting each rate constant of dissolution (k_i) for both its corresponding particle size (D_i), the volume of the corresponding particle $\sim D_i^3$, and the number of particles

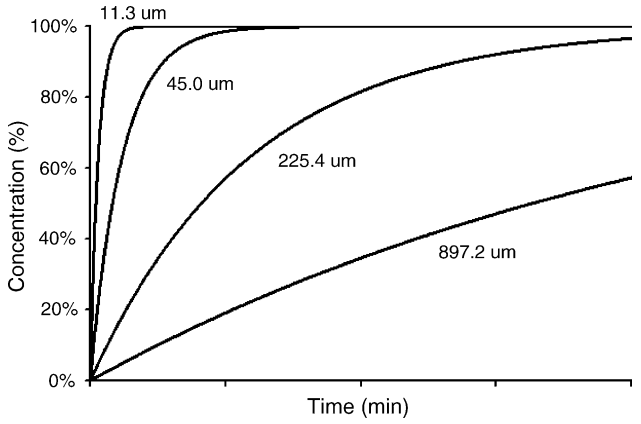

Fig. 2. A schematic presentation of the relative dissolution rate for particles with a different size (i.e. 11.3, 45.0, 225.4 and 897.2 μm).

per k_i (n_i) according to Eq. (4).

$$\bar{k} = \frac{\sum_i n_i \times d_i^4 \times k_i}{\sum_i n_i \times d_i^4} \quad (4)$$

In case the size distribution gets broader, the average rate constant of dissolution ($\bar{k}$) will become less accurate, thus leading to a less accurate prediction of the dissolution profile of the product.

2.2. Step 2: theoretical modeling

Since the dissolution behavior of a product is the result of the cumulative effect of all particles in the product, the mean particle diameter is expected to show a better correlation than typical statistical descriptors like, for instance, the 10% (d10), 50% (d50) and the 90% (d90) cumulative undersize [12]. For this reason, based on the so-called moment-ratio definition system for a particle size distribution several mean particle diameters [13] can be calculated according to Eqs. (5) and (6), where X_i is the centre of a size class and n_i is the number of particles per size class. The factors p and q are integers (i.e. 0, 1, 2, 3, etc.), and in practice often limited to a maximum value of ca. 5.

$$D[p,q] = \left[\frac{\sum_i n_i X_i^p}{\sum_i n_i X_i^q}\right]^{1/(p-q)}, \quad \text{with } p > q \quad (5)$$

$$D[p,q] = \exp\left[\frac{\sum_i n_i X_i^p \ln X_i}{\sum_i n_i X_i^p}\right], \quad \text{with } p = q \quad (6)$$

The particle size distribution that is measured with a certain particle sizing technique is dependent not only on the detected number of particles per size class, but also on the ability of the instrument to accurately monitor all particles in function of their size. The latter is quite regularly a serious matter of concern. For instance, in the case of laser diffraction it is known, that the technique may show an underestimation of a small portion of oversized particles [14]. Since a non-linear response of a particle size measurement system should not interfere with our initial attempt to correlate size distribution and dissolution data, it seemed better to initially define a series of imaginary particle size distributions and to simply calculate their theoretical dissolution profiles. For this pur-

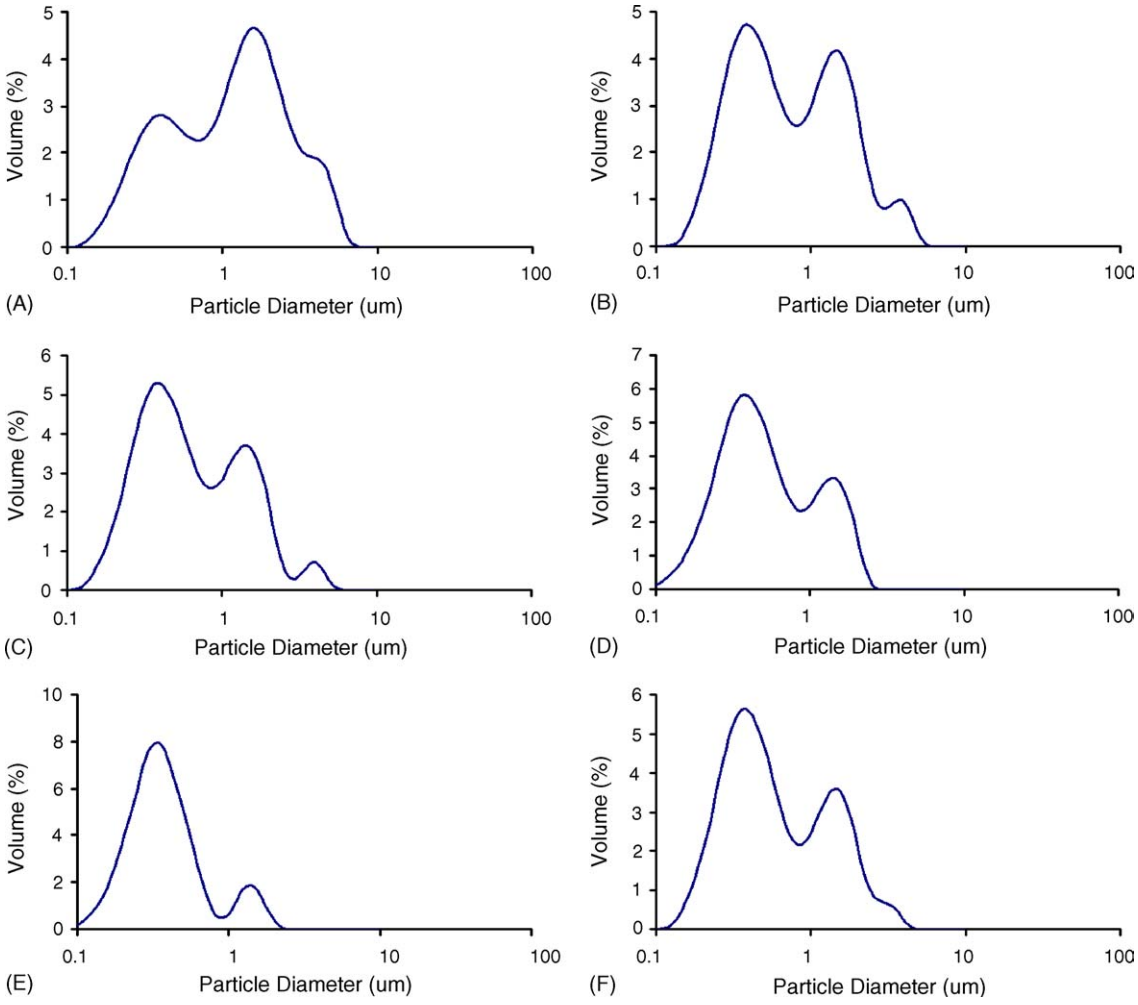

Fig. 3. The laser diffraction size distribution profiles as obtained for six suspension batches all originating from the same batch of drug substance.

pose, as a first assumption the particles were considered as being spherical, such that based on the diameter of the particles their surface area and volume can easily be calculated. As a second assumption the particles were considered to dissolve isotropically, i.e. meaning that the dissolution rate constant is the same at each location on the particle surface. Finally, as a third assumption the spherical shape of the particles was considered not to change during dissolution, i.e. meaning that the particles dissolve in an isometric way. According to these assumptions, a series of imaginary products was defined in terms of size classes (X_i) and the number of particles per size class (n_i), all being different with regard to the width and the modality of their particle size distribution, but all being equal with regard to the total volume (and thus the mass) of the particles (V).

For the imaginary particles per definition no true calculations can be made, since their physical parameters are not known. However, by just choosing an arbitrary value for the rate constant of dissolution (k_i) for one specific particle size (D_i), for the other particle sizes the relative value of $k_{j\neq i}$ can easily be calculated. Based on Eq. (4) the average rate constant of dissolution ($\bar{k}$) can now be calculated. Since it has been suggested in this document that an average effect of all particles together is responsible for the dissolution behavior of the product, the question now rises which mean diameter best correlates with the average rate constant of dissolution ($\bar{k}$). Since under Section 2.1 it has already been demonstrated that the rate constant of dissolution is inversely proportional to the particle diameter (D), $\bar{k}^{-1}$ has been plotted as a function of the various weighted mean particle diameters ($D[p, q]$), leading to the conclusion that from a theoretical point of view the so-called volume-weighted mean diameter ($D[4, 3]$) should have the best correlation with $\bar{k}^{-1}$. As long as the dissolution conditions remain constant, the slope of $\bar{k}^{-1}$ versus $D[4, 3]$ is believed to contain relevant information such as for instance on the thickness of the diffusion layer (h), and the relationship between k and $D[4, 3]$ is given by Eq. (7).

$$k = \frac{3 \times h \times V_s}{D[4,3] \times \xi \times V} \tag{7}$$

One may expect that the dissolution process is first of all controlled by the surface area of the product, as this is the region where the product interacts with the liquid and where molecules go into solution [15]. As long as the volume of the product (V) is constant, it is the surface area per volume of the product that will dominate the dissolution process. This so-called specific surface area (SSA) is inversely related to the diameter of the particles (D), and subsequent weighting for the volume of the particles ($\sim D^3$) leads to a D^4/D^3 relationship, which makes it ready to believe that a direct relationship exists between the $D[4, 3]$ volume-weighted diameter and the dissolution process.

A next step in the theoretical modeling of the dissolution profile in function of the particle size characteristics of the product is to calculate the (theoretical) dissolution profiles in two different ways. More precisely, for all imaginary size distributions the theoretical dissolution curves based on the cumulative contribution of all size classes ($\sum k_i$) (see Eq. (8)) were plotted together with the calculated dissolution curves based on the weighted rate constant ($\bar{k}$) (see Eq. (9)). The latter will from now on be referred to as the 1-k model, since only one single $\bar{k}$-value is used for calculation of the dissolution profile.

$$c(t) = \sum_i V_i \times (1 - e^{k_i \times t}) \tag{8}$$

$$c(t) = V \times (1 - e^{-\bar{k} \times t}) \tag{9}$$

Based on a visual evaluation of these data an excellent agreement between both curves is shown. However, it also appears from these calculations that if the volume distribution of the product becomes broader the predictive value of the 1-k model becomes limited. Therefore, it seems safe to assume, that for broad(er) volume distributions the predicted dissolution profile of the product will better agree with the true dissolution profile, if its particle size distribution is split in smaller sections each being considered as a separate size distribution. In line with the concept as explained above, for each section of the size distribution the corresponding $D[4, 3]_i$ volume-weighted mean diameter should then be calculated.

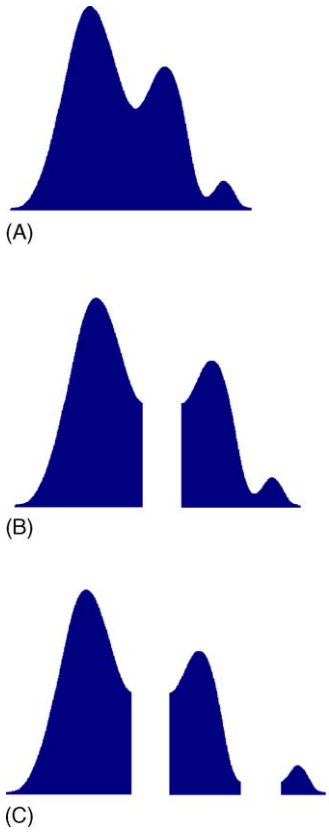

Fig. 4. A schematic presentation of the processing of the laser diffraction data in function of the choice for: (A) 1-k ($D[4, 3]$ with $V = 100\%$), (B) 2-k ($D[4, 3]_1$ with V_1; $D[4, 3]_2$ with V_2) or (C) 3-k ($D[4, 3]_1$ with V_1; $D[4, 3]_2$ with V_2; $D[4, 3]_3$ with V_3) correlation model.

In general terms, the dissolution behavior of a product with a broad volume distribution is expected to behave according to Eq. (10), whereas the partial volume of the particles (V_i) and the volume-weighted mean diameter ($D[4,3]_i$) for each section of the size distribution determine the overall dissolution behavior of the product.

$$c(t) = V_a \times (1 - e^{-k_a \times t}) + \sum_{b \neq a} V_b \times (1 - e^{(D[4,3]_a / D[4,3]_b) \times k_a \times t}) \quad (10)$$

2.3. Step 3: empirical verification

Now that a theoretical approach on the correlation of particle size distribution and dissolution data seems to be available, the new concept has been tested for a set of experimental data. Since the disintegration of tablet formulations may lead to results that are difficult to interpret, the experi-

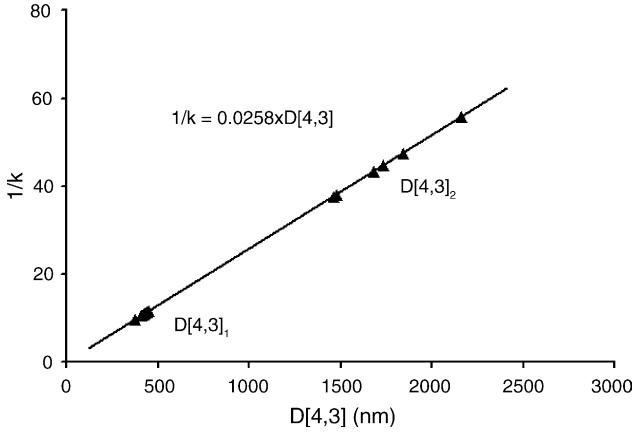

Fig. 5. Based on a bimodal processing of the laser diffraction data, the calculation of the rate constant of dissolution based on an arbitrary slope for $1/k$ vs. $D[4,3]$ for six batches of a suspension formulation.

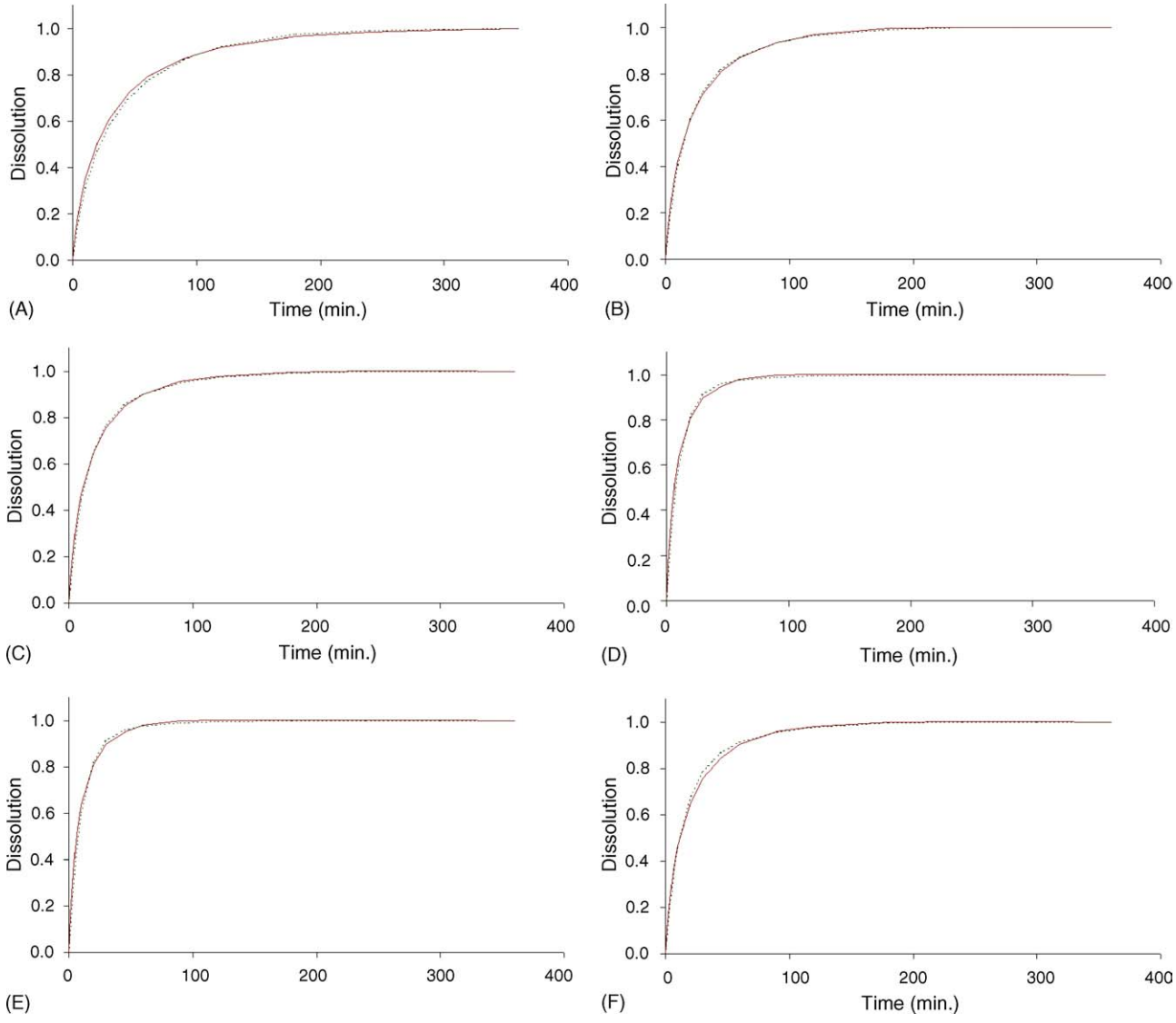

Fig. 6. For the six suspension products the 2-k modeled (- - -) vs. the measured (—) dissolution profiles are presented.

mental verification has initially been done for a suspension formulation containing particles in the high nanometer- and low micrometer-area. More precisely, different suspension formulations have been prepared all originating from the same batch of API, but with only a difference in their particle size distribution. For all these batches, the in vitro dissolution profiles were obtained, together with the size distribution data determined with laser diffraction. For the laser diffraction measurements, a Beckman Coulter LS230 instrument was used. The latter is relevant to mention here, since it is known that different types of laser diffraction equipment may lead to (serious) differences in particle size distribution. The latter may of course to some extent affect the correlation data, though the correlation between $1/k$ and $D[4, 3]$ is expected to occur independent of the measuring technique, and independent of the instrument brand. As one can see from Fig. 3, all suspensions are characterized by a rather broad and bimodal or trimodal size distribution.

Theoretical modeling as discussed in Section 2.2 explains that for broad(er) particle size distributions, the distribution profile cannot be modeled adequately using a 1-k model. For this reason, the laser diffraction data were processed as if the product was either unimodal, bimodal or trimodal. The $D[4, 3]_i$ volume-weighted mean diameters and the partial volumes (V_i) were obtained by manual processing of the data (see Fig. 4). In addition, calculation of the dissolution profile of the different products was done according to Eq. (11).

$$c(t) = V_1 \times (1 - e^{-k_1 \times t}) + V_2 \times (1 - e^{-k_2 \times t}) + V_3 \times (1 - e^{-k_3 \times t}) \quad (11)$$

In order to evaluate the quantitative capabilities of the laser diffractometer, the partial values V_1, V_2 and V_3 were taken from the printouts as such. In addition, the rate constants of dissolution k_1, k_2 and k_3 were calculated from the $1/k$–$D[4, 3]$ correlation plot using the $D[4, 3]_1$, and $D[4, 3]_2$ and (if applicable) the $D[4, 3]_3$ values (see Fig. 5). Since all batches of the suspension formulation originate from the same drug substance batch, the milled particles in suspension were expected to have the same physical characteristics (e.g. polymorphy and porosimetry, etc.). As a result, it was assumed that for all suspension batches except for $\bar{k}$ and $D[4, 3]$ all other parameters as indicated in Eq. (7) remain constant. The latter means, that if the equation for $\bar{k}$ versus $D[4, 3]$ is optimized for the modeling of one dissolution curve, it is automatically optimized for modeling of the others too. And the experimental data as obtained for this study indeed demonstrate, that for all suspension formulations the dissolution profiles can be modeled based on the use of just one single $1/k$–$D[4, 3]$ plot. The latter is illustrated in more detail by the 2-k modeling of the various dissolution curves (see Fig. 6). Finally, based on Fig. 7, the values for the residual sum of squares show, that if a 2-k modeling is applied the fit between the calculated versus the measured dissolution curve is better than a 1-k modeling approach. However, apparently a 3-k order modeling does not lead to a further improvement of the fit, thereby demonstrating a limited accuracy and as a result a limited quantitative applicability of the laser diffraction method.

	Residual Sum of Squares		
	1-k model	2-k model	3-k model
Sample 1	7.1×E-02	7.7× E-03	3.9× E-03
Sample 2	5.2× E-02	3.8× E-03	4.1× E-03
Sample 3	5.5× E-02	5.9× E-03	5.8× E-03
Sample 4	1.8× E-01	8.7× E-02	n.a. (*)
Sample 5	4.2× E-02	1.5× E-02	n.a. (*)
Sample 6	4.1× E-02	5.8× E-03	6.4× E-03

(*) Due to the narrowness of the size distribution, the 3-k model has not been used.

Fig. 7. For the six suspension products the applicability of the correlation model is illustrated by means of the residual sum of squares (RSSQ) for the 1-k, 2-k and 3-k predicted dissolution profiles relative to the measured dissolution profiles (i.e. the lower the RSSQ, the better the fit).

For the suspension batches as investigated here, the linear plot of $1/k$ versus $D[4, 3]$ is the basis for the accurate prediction of the dissolution profile of the product. This linear relationship thereby demonstrates, that the thickness of the diffusion layer (h) is constant within the entire range of the particle size distribution of the product. The latter should probably be explained by the agitation in the dissolution vessel, leading to a dynamic situation where diffusional transport is not varying with particle size anymore.

3. Conclusions

Based on theoretical calculations the $D[4, 3]$ volume-weighted mean diameter of a size distribution is expected to correlate with the rate constant of dissolution (k) of the product. Since the dissolution profile of the product is determined by the cumulative contribution of all individual particles, this correlation seems more difficult to demonstrate when the size distribution gets broader. However, experimental verification shows that a better fit between the calculated and measured dissolution profile is obtained by splitting (broad) size distributions in smaller sections. For each section of the size distribution the $D[4, 3]_i$ volume-weighted mean diameter together with its partial volume (V_i) has than to be determined. For the Coulter LS230 laser diffractometer, the measured partial volumes appear to lead to an excellent fit, but only if a $1/k$–$D[4, 3]$ correlation plot is used for calculation of the rate constant of dissolution (k). One should therefore conclude, that laser diffraction is definitely able to quantitatively monitor the particle size distribution in function of the in vitro dissolution behavior of the product. Using an optimized $1/k$–$D[4, 3]$ correlation plot, any deviation of a calculated dissolution profile relative to its experimentally determined in vitro dissolution profile may indicate, that something has changed with regard to the particle characteristics, such as the morphology, porosity or polymorphy. As a result, this new approach for correlation of particle size and dissolution

rate is considered as a very powerful analytical tool in the chemical and pharmaceutical development of new products. More work needs to be done to investigate the effect of the shape of the particles on their dissolution behavior. Last but not the least, further research is needed into the area of direct compression formulations especially with regard to the effect of the disintegration process.

References

[1] A.J. Jounela, P.J. Pentikäinen, A. Sothmann, Eur. J. Clin. Pharmacol. 8 (1975) 365–370.
[2] A.S. Ridolfo, L. Thompkins, L.D. Bechtol, R.H. Carmichael, J. Pharm. Sci. 68 (1979) 850–852.
[3] J. Whang, D.F. Flanagan, J. Pharm. Sci. 88 (1999) 731–738.
[4] J. Whang, D.R. Flanagan, J. Pharm. Sci. 91 (2002) 534–542.
[5] S. Simões, A. Sousa, M. Figueiredo, Int. J. Pharm. 127 (1996) 283–291.
[6] L. Pereira de Almeida, S. Simões, P. Brito, A. Portugal, M. Figueiredo, J. Pharm. Sci. 86 (1997) 726–732.
[7] M.V. Dali, J.T. Carstensen, Drug Dev. Ind. Pharm. 24 (1998) 637–644.
[8] M. Alderliesten, Part. Part. Syst. Charact. 7 (1990) 233–241.
[9] A.A. Noyes, W.R. Whitney, J. Am. Chem. Soc. 19 (1897) 930–934.
[10] M. Bisrat, C. Nyström, Int. J. Pharm. 47 (1988) 223–231.
[11] R.J. Hintz, K.C. Johnson, Int. J. Pharm. 51 (1989) 9–17.
[12] M. Alderliesten, Part. Part. Syst. Charact. 21 (2004) 179–196.
[13] M. Alderliesten, Part. Part. Syst. Charact. 8 (1991) 237–241.
[14] F.M. Etzler, R. Deanne, Part. Part. Syst. Charact. 14 (1997) 278–282.
[15] C. Nyström, J. Mazur, M.I. Barnett, M. Glazer, J. Pharm. Pharmacol. 37 (1985) 217–221.