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Shape modelling of dissolution profiles by non-integer kinetic orders

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Abstract

A model for the characterization of in-vitro dissolution profiles is presented. The basis is a mathematical expression designated 'the Order Model' which incorporates four parameters: the kinetic order, a rate constant, a gradual introduced lag-time and the assay level. Data fitting is performed by non-linear regression using standard PC software. It is emphasized that the order need not be an integer which will enhance the applicability of the model. Interpretation and applicability of the model are discussed in relation to different release systems. The cube-root law is a special case of the Order Model with the order = 2/3. The high degree of fitting possible with the Order Model is illustrated on three products: individual pellets, ensembles of pellets and tableted pellets. Arguments are provided that an increased inhomogeneity of the ensemble of pellets will lead to a higher kinetic order.

Keywords: Controlled release; Dissolution profile; Ensemble effects; Kinetic order; Mathematical modelling; Multiparticulate; Power Law

1. Introduction

The fitting of in-vitro dissolution data to mathematical expressions has formed the basis of a number of publications, including reviews (Koch, 1984; Stricker, 1985). The major advantage of fitting observed data to such expressions is that dissolution properties can be treated and analysed by statistical and mathematical methods (Jørgensen and Jacobsen, 1992).

In spite of the general attention paid to characterizing dissolution profiles, there are only few examples of attempts to use the release kinetic order as a fitting parameter (Flaig, 1974; Rey-Bellet, 1981; Keserü et al., 1988, 1989). Nevertheless, the kinetic order has a considerable potential as a shape parameter for release profiles as it is related to the release mechanisms. Furthermore the use of the kinetic order facilitates interpretation and

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communication of dissolution results. Finally, the order will be the obvious parameter to optimize when pre-formulating controlled release systems, especially when zero order is the aim.

The term 'order' is frequently used in other mathematical models for parameters that do not have much in common with the order parameter known from kinetics. For instance the exponent in the Power Law (Ritger and Peppas, 1987) has been denoted as the order (Franz et al., 1987). In this paper the term order is used in consistency with the reaction kinetic order. Traditionally, the release kinetic order has been considered an integer, but it is essential to avoid this limitation when used to characterize release profiles.

For the sake of completeness it should be noted that the square-root law (Higuchi, 1961) is not related to any order.

The aim of this paper is to show how the Order Model is derived, how its parameters may be interpreted, and how the mechanisms of different release systems are related to it. The versatility of the Order Model as an empirical and semi-empirical model is illustrated by the application of the model to the release profiles from individual pellets, ensembles of pellets and tableted pellets of a multiparticulate product.

2. Materials and methods

2.1. Test product

The product used for the dissolution tests is Ibumetin Retard® 300 mg multiparticulate controlled-release tablets and the untableted pellets from the same formulation. The pellets were manufactured by extrusion-spheronization of cores subsequently spray coated with an ethyl cellulose based coating.

2.2. Dissolution methods

The dissolution from ensembles of pellets and from tablets was tested according to the USP/Ph.Eur. basket method (Sotax AT 7), run at 100 rpm in 900 ml of pH 7.2 phosphate buffer. Quantitative determination was made spectrophotometrically at 221.8 nm, using a 1 mm cuvette in a fully automatic apparatus (Perkin Elmer). Measurements were made every 30 min for 48 h.

For the dissolution testing of individual pellets the same method was used except that a specially made vessel holding 100 ml was utilised, and the size of the cuvette was 1 cm.

2.3. Data fitting

The observed data were fitted to the Order Model extended by the lag-time function as expressed below in Eqs. (8) and (7), respectively. The parameters of the model were estimated using non-linear regression in Statgrafics Plus 6.0 (minimizing the sum of squares using a Marquardt search procedure). The programme calculates standard errors for the four parameters based on partial derivation of the standard error of the fitted $m(t)$-values. Furthermore, the coefficient of determination,

$$\frac{\sum (Y_{\mathrm{obs},i} - \bar{Y}_{\mathrm{obs}})^2 - \sum (Y_{\mathrm{obs},i} - Y_{\mathrm{fit},i})^2}{\sum (Y_{\mathrm{obs},i} - \bar{Y}_{\mathrm{obs}})^2}$$

is calculated.

3. Derivation of the Order Model

In reaction kinetics the order describes the degree of correlation between the rate of formation of one component and the concentration of another (or several other) component(s). In a dissolution system there will not typically be a chemical reaction but a physicochemical change in phase or change of compartment. If a dissolution profile can be described by an order, there is one correlation between the release rate and the amount of drug not yet released at any point of the release period.

If the amount of drug dissolved at time, t, is denoted $m(t)$, and the total content of drug in the formulation is denoted m_∞, then the fraction of drug, $Y(t)$ dissolved at time, t, is defined as

$$Y(t) = \frac{m(t)}{m_\infty} \quad (1)$$

with $Y(t)$ denoting concentration, the definition of the kinetic order is:

$$\frac{dY(t)}{dt} = k(1 - Y(t))^n \quad (2)$$

where n is the kinetic order and k is the rate constant.

The kinetic order, n, is thus defined by the simple differential Eq. (2), which for $dY(t)/dt \neq 0$ can be solved analytically by solving the reciprocal function with respect to t, so that

$$\frac{dt}{dY(t)} = \frac{1}{k}(1 - Y(t))^{-n} \quad (3)$$

from which follows (for $n \neq 1$) that

$$t = -\frac{1}{k(1-n)}(1 - Y(t))^{1-n} + C \quad (4)$$

where C is the integration constant found to be given by

$$C = \frac{1}{k(1-n)} + t_0 \quad (5)$$

in Eq. (5) a quantity, t_0, is introduced, which is the value of t when $Y(t) = 0$. Normally this quantity is denoted lag-time. When re-writing Eqs. (4) and (5),

$$Y(t) = 1 - (1 - (1-n)k(t - t_0))^{1/(1-n)} \quad (6)$$

is obtained. In the following Eq. (6) is called the Order Model.

The Order Model, Eq. (6), has the following limitations: (a) $n \neq 1$, (b) $t \geq t_0$, (c) $t \leq (1-n)^{-1} k^{-1} + t_0$ (if $n < 1$).

Limitation (a) does not constitute a practical problem because n estimated from a data fit only very rarely equals unity (for $n = 1$ the traditional first order expression, $Y(t) = 1 - \exp(-k(t - t_0))$ is valid. Both (b) and (c) however do cause problems when data are fitted. Limitation (b) may be counteracted by letting the lag-time take effect gradually so that the profile always starts in (0.0). This may be accomplished by substituting t_0 by a function, $f(t_0)$, given by

$$f(t_0) = t_0(1 - e^{-t/\mathrm{abs}(t_0)}) \quad (7)$$

alternatively, $Y(t)$ may be put at zero for $t < t_0$.

Problems with (c) can be avoided by substituting Eq. (6) by $Y(t) = 1$ when t exceeds the limit.

As measured dissolution data will be related to the quantity, $m(t)$, and not the fraction, $Y(t)$, of dissolved drug, Eq. (6) must be combined with Eq. (1) for the expression to be applicable in model fitting. The fitting expression will then appear as:

$$m(t) = m_\infty(1 - (1 - (1-n)k(t - t_0))^{1/(1-n)}) \quad (8)$$

the parameters, n, k and t_0 are exactly the same in Eqs. (6) and (8). The use of Eq. (8) for model fitting implies that four parameters have to be estimated, i.e. n, k, t_0 and m_∞.

4. Interpretation of the parameters

As appears from Eq. (8) four parameters are needed to characterize a dissolution profile. They are listed below:

(1) n, the kinetic order, is the correlation between release rate, $dY(t)/dt$, and the undissolved fraction of drug, $1 - Y(t)$. The value of n will reflect the release mechanism in the test system. From a mathematical point of view n is a so-called shape parameter, independent of scaling and consequently n is dimensionless. From Fig. 1 it is clearly seen that for low t-values the order is of little importance for the release profile while for later t-values n becomes very important. This means that an exact estimate of the order for a given process requires data from the last part of the profile.

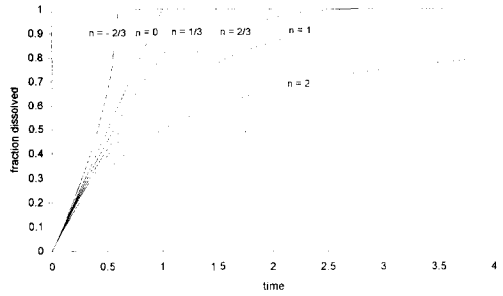

Fig. 1. Dissolution profiles for different values of the kinetic order, n with $k = 1$ and $t_0 = 0$ generated by the Order Model, Eq. (6).

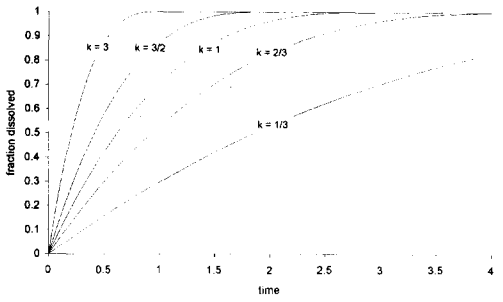

Fig. 2. Dissolution profiles for different values of the rate constant, k with $n = 2/3$ and $t_0 = 0$ generated by the Order Model, Eq. (6).

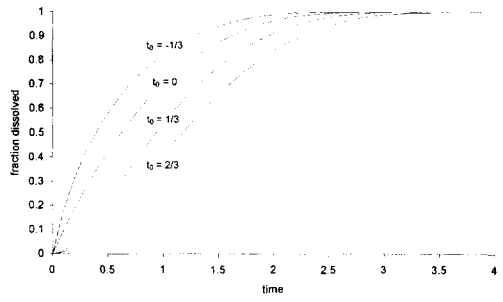

Fig. 3. Dissolution profiles for different values of the gradually introduced lag-time, t_0 with $n = 2/3$ and $k = 1$ generated by the Order Model, Eq. (6) extended by the lag-time function, Eq. (7).

(2) k, the rate constant, is the intrinsic dissolution rate. For $n \geq 0$ it is approximately the maximum release rate of the system, $\max\{dY(t)/dt\}$, which will be the situation when $t = t_0$ provided $t_0 > 0$ (however, the use of Eq. (7) causes that the $\max\{dY(t)/dt\}$ appears some time after t_0). If $t_0 \approx 0$, k will be given by the initial slope of the release profile and can then be estimated on the basis of few data at the start of the process (up to approx. 10% dissolved). The unit for k is reciprocal to the time unit (i.e. min^{-1} or h^{-1}) and causes k $(t - f(t_0))$ to become dimensionless.

Another way k can be interpreted is in relation to the geometry of the tested preparation. As appears from Eq. (9) k is proportional to the actively releasing specific surface area at the start of the release process (provided no lag-time):

$$k = Y'(0) = \frac{m'(0)}{m_\infty} = \kappa \frac{A_0}{V_0} \tag{9}$$

where $Y'(0)$ is $dY(t)/dt$ for $t = 0$, $m'(0)$ is $dm(t)/dt$ for $t = 0$, A_0 is the release area of the system (for $t = 0$), and V_0 is the volume of the system. The scaling factor, κ, between k and A_0/V_0 will depend on the release mechanism. Fig. 2 illustrates different degrees of retardation achieved by the same mechanism.

(3) t_0, the lag-time, is the time it takes the initial processes to establish the transport routes and reach a pseudo steady state in the release system. Disintegration and wetting are two of the most important lag-time processes. Negative lag-times may also occur, reflecting instant releasing, i.e. a burst effect. An estimate for t_0 will normally contain elements from both effects. In Fig. 3 the effect of t_0 is illustrated.

(4) m_∞, assay of the drug in the release system, is the end level attained by the dissolution profile. When estimating this parameter in Eq. (8), it is important to include late data points so that m_∞ can be estimated from the dissolution profile. If an expected content (e.g. declared amount or a similar quantity) is used instead, deviations from the real value will result in erroneous estimates for the other parameters.

5. Relations between order and release mechanism

There are various release systems whose mechanisms are related to a kinetic order.

(1) $n = 0$. The best known systems are the zero-order systems characterized by a constant release rate, $dY(t)/dt = k$, which can be seen by setting $n = 0$ in Eq. (2). Erodible systems with constant surface area and membrane-controlled diffusion systems with constant concentration gradient over the membrane will give zero-order release profiles.

(2) $n = 1$. In first order systems the release rate at any point is proportional to the remaining amount of drug. A first-order profile is expected in a membrane-controlled diffusion

system if the gradient is reduced due to decreasing concentration on the donor side in combination with sink conditions in the dissolution medium.

(3) $n = 2$. An example of second-order kinetics is found with dissolution profiles that may be fitted by a reciprocal plot where $Y(t)^{-1}$ depends linearly on t^{-1} (provided there is no lag-time).

(4) $n = 2/3$. Traditional reaction kinetics prefers to operate with integer orders (though pseudo first order, for example, actually means an order close to—but typically a little above—unity). This tradition may be part of the explanation why the cube-root law (Hixson and Crowell, 1931) has not earlier been connected with a kinetic order in the literature. With the previously used notation the cube-root law can be written in the following way:

$$1 - (1 - Y(t))^{1/3} = k_c t \tag{10}$$

where k_c is a constant. If Eq. (10) is rewritten so that $k = (1 - 2/3)k_c$ and $Y(t)$ is isolated, then Eq. (10) becomes a special case of Eq. (6), viz. when $n = 2/3$ and $t_0 = 0$. This means that the cube-root law expresses 2/3 order kinetics. The cube-root law is derived for erodible isometric geometries (e.g. spheres and cubes).

(5) $n = 1/2$. Expressions for cylinder shaped erodible preparations (Hopfenberger, 1976), are connected with an order of 0.5.

Interestingly Stricker (1985) has developed a general expression for erodible systems in which he uses a shape parameter that is identical with the kinetic order. However, he did not discuss any relation between the shape parameter and the kinetic order of the dissolution profile. In general erosion of a homogenous test preparation will follow a simple function of time as the release surface area, $A(t)$ is proportional to the release rate, $dY(t)/dt$ and the volume of the preparation, $V(t)$ is proportional to the undissolved fraction, $(1 - Y(t))$. Therefore, geometries following

$$A(t) = k_g V(t)^n \tag{11}$$

are characterized by a geometric constant, k_g that modifies the rate constant and a kinetic order, n. For example for a cube with side length, d Eq. (11) becomes $A(t) = 6V(t)^{2/3}$ as $A(t) = 6(d - k_d t)^2$ and $V(t) = (d - k_d t)^3$ where k_d is a proportionality constant between time and erosion rate. The order for an erodible cube thus will be 2/3.

If the Order Model, Eq. (8), is used for fitting dissolution profiles of a release system whose mechanism is not theoretically related to an order, the interpretation of parameters becomes less precise. However, knowledge of the actual system will often make it possible to deduce some qualitative meanings of the order as will be illustrated below.

6. Release kinetics for individual pellets and for ensemble of pellets

The relations between the release kinetics for ensembles and individual units have earlier been examined on the basis of extensive kinetics studies on individual micro capsules (Hoffman et al., 1986). In these studies the kinetics of individually tested micro capsules was very close to zero-order whereas the kinetics of the ensembles was approximately first-order. It has also been theoretically concluded (Gross et al., 1986) that an ensemble of zero-order releasing units under certain conditions will result in first-order kinetics. In the following a more generalized description of the change in kinetics from individual pellets to ensembles of pellets is attempted.

Assuming that an ensemble of pellets as well as individual pellets show release kinetics characterized by kinetic orders, the following relations can be established:

$$k_{ens} = \langle k_i \rangle_w \tag{12}$$

$$n_{ens} > \langle n_i \rangle_w \tag{13}$$

where the subscripts 'ens' and 'i' denote ensemble and individual pellets, respectively, and $\langle n_i \rangle_w$ and $\langle k_i \rangle_w$ are the—by pellet mass—weighted averages of the order and of the rate constant for pellets, respectively. For the sake of simplicity the lag-time parameter has been left out of consideration in this section, and it is assumed that $n_i < 1$ for all individual pellets.

The validity of Eq. (12) can be shown by means of Eq. (9) giving

$$k_{ens} = Y'_{ens}(0) = \frac{m'_{ens}(0)}{m_{ens}} = \frac{\sum m'_i(0)}{\sum m_i} = \frac{\sum k_i m_i}{\sum m_i}$$

$$= \langle k_i \rangle_w \quad (14)$$

the validity of Eq. (13) is based on the fact that the total release time for the ensemble will be dictated by the slowest individual pellet. As the rate constant is given by Eq. (12), the following is obtained by means of Eq. (6)

$$n_{ens} = 1 - \frac{1}{k_{ens}\, t_{\infty,ens}} = 1 - \frac{1}{\langle k_i \rangle_w \max\{t_{\infty,i}\}} \quad (15)$$

which again leads to Eq. (13) (according to the definition $\langle n_i \rangle_w = 1 - \langle (k_i\ t_{\infty,i})^{-1} \rangle_w$ and using general unequality relations it is found that $\langle (k_i\ t_{\infty,i})^{-1} \rangle_w \geq \langle k_i\ \ t_{\infty,i} \rangle_w^{-1} > (\langle k_i \rangle_w\ \ \max\{t_{\infty,i}\})^{-1}$ showing Eq. (13) by means of Eq. (15)).

It appears from Eq. (15) that with unchanged $\langle k_i \rangle_w$, n_{ens} increases when $\max\{t_{\infty,i}\}$ is increased. This will be the situation when the variation in release time increases, while the mean value is maintained. Thus the difference between the order of the ensemble and that of the individual pellets will reflect the degree of inhomogeneity in the system. Complete homogeneity, corresponding to $t_{\infty,i}$ being identical for all pellets, will consequently result in the two orders becoming identical. These relations can be briefly written as

$$n_{ens} \to \langle n_i \rangle_w \quad \text{for } \sigma(t_{\infty,i}) \to 0 \quad (16)$$

and

$$n_{ens} \to 1 \quad \text{for } \sigma(t_{\infty,i}) \to \infty \quad (17)$$

where $\sigma(t_{\infty,i})$ denotes the variation in total release time, $t_{\infty,i}$, for the individual pellets.

The validity of Eqs. (16) and (17) implies that a final release time, $t_{\infty,i}$, exists for all pellets. This is the case provided all $n_i < 1$, which we so far observed in all cases. However, if $n \geq 1$ for some of the pellets the same argument is valid using the time it takes to dissolve, e.g. 0.95%.

7. The Order Model used for release characterization of a multiparticulate product

The following three sections illustrate the use of the Order Model with experimental dissolution results for individual pellets, ensembles of pellets, and tableted pellets, respectively. The samples were taken during the manufacture of the product, Ibumetin Retard.

To illustrate the fitting ability of the Order Model all profiles were also fitted to the Power Law (Ritger and Peppas, 1987):

$$m(t) = m(\infty)(k(t - t_0))^p \quad (18)$$

the Power Law is a generalization of Higuchi's square-root law (corresponding to $p = 1/2$ in Eq. (18)). The Power Law has obtained general recognition, mainly because of its simple form. Basically, Eq. (18) was not developed for the description of complete profiles, but it has been found suitable for the description of the initial phase (up to approx. 60% dissolved). When it is nevertheless used in this section to describe complete profiles, the purpose is to make it comparable with the Order Model. An attempt to apply the lag-time function, Eq. (7) to the Power Law, Eq. (18) was abandoned, as the estimated lag times were large negative values, although no burst was seen. Instead $Y(t)$ has been set at 0 for $t < t_0$.

For both the Order Model and the Power Law the estimates were supplemented with two derived values illustrating the degree of retardation of the dissolution; the total release time, t_∞, and the mean dissolution time, MDT. For the Order Model these values are approximated by

$$t_{\infty,order} = \frac{1}{k(1-n)} + t_0 \quad (19)$$

$$MDT_{order} = \frac{1}{k(2-n)} + t_0 \quad (20)$$

(the expressions are valid with exactness if $t_0 \geq 0$ and the lag-time function, Eq. (7), is not used, but in all cases the approximation will be so good that the deviations are of no practical importance).

For the Power Law the t_∞ and MDT are given by

Table 1
Results from the fitting of the dissolution profiles for three pellets tested individually

Parameters	Power law	Order model
Pellet A		
Shape, p or n	0.694 ± 0.015	0.448 ± 0.006
Scale, k (h^{-1})	0.0679 ± 0.0006	0.0974 ± 0.0006
Lag time, t_0 (h)	1.33 ± 0.08	0.83 ± 0.03
Coefficient of determination	0.998	0.99993
Release time, t_∞ (h)	16.1	19.4
Retardation, MDT (h)	7.4	7.4
Pellet B		
Shape, p or n	0.722 ± 0.013	0.338 ± 0.005
Scale, k (h^{-1})	0.0539 ± 0.0004	0.00708 ± 0.0003
Lag time, t_0 (h)	1.20 ± 0.09	0.41 ± 0.02
Coefficient of determination	0.999	0.99993
Release time, t_∞ (h)	19.8	21.7
Retardation, MDT (h)	9.0	8.9
Pellet C		
Shape, p or n	0.784 ± 0.019	0.409 ± 0.008
Scale, k (h^{-1})	0.0541 ± 0.0005	0.0781 ± 0.0007
Lag time, t_0 (h)	1.82 ± 0.13	2.08 ± 0.05
Coefficient of determination	0.998	0.99991
Release time, t_∞ (h)	20.3	23.7
Retardation, MDT (h)	9.9	10.0

The dissolution profiles were fitted to the Power Law and to the Order Model. The values of n, p, k and t_0 are shown with $\pm$ estimated standard error.

$$t_{\infty,\text{power}} = \frac{1}{k} + t_0 \tag{21}$$

$$\text{MDT}_{\text{power}} = \frac{p}{k(1+p)} + t_0 \tag{22}$$

7.1. Test of individual pellets

Table 1 and Fig. 4 show the release from the three pellets tested individually. Fig. 5 shows residual plots for the three profiles. For the sake of comparability the residuals have been calculated as the difference between fit and observed quantities in fraction of drug dissolved while Fig. 4 takes into account the difference in assay for the three pellets.

Table 1 as well as Figs. 4 and 5 clearly show that the Order Model yields the best fit to the release profiles observed.

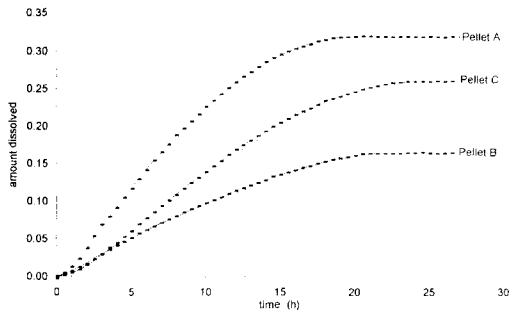

Fig. 4. Dissolution profiles for three individually tested pellets. The marks represent the observed values in an arbitrary unit whereas the solid lines are the fitted profiles using the Order Model and the dashed lines are the fitted profiles using the Power Law.

Table 1 also shows that the estimated release time, t_∞ is shorter with the Power Law than with the Order Model. This is in accordance with the recommended use of the Power Law up to about 60% released. Although remarkable, it is not a coincidence that the estimates for MDT are almost identical for the two dissolution profile models. The explanation of the identity is that MDT expresses the area between the fitted release profile and $Y(t) = 1$. Fitting by the least squares method means that the fitted profile will have equal negative and positive deviations from the observed profile. As the sampling points are equidistant in time, these deviations will also represent equal areas on each side of the observed profile. Therefore the total area between the fitted profile and $Y(t) = 1$ will be independent of the lack of fitting.

7.2. Ensembles of pellets

The results of the fitting of the ensembles of pellets are shown in Table 2 and Figs. 6 and 7. The difference in fitting ability between the Power Law and the Order Model is even more marked than for individual pellets.

In agreement with Eqs. (16) and (17) the release kinetic order for the ensemble (0.65) is larger than for the individual pellets (0.33–0.45) and smaller than unity.

Compared with the individually tested pellets it is remarkable that the release time, t_∞, is so much

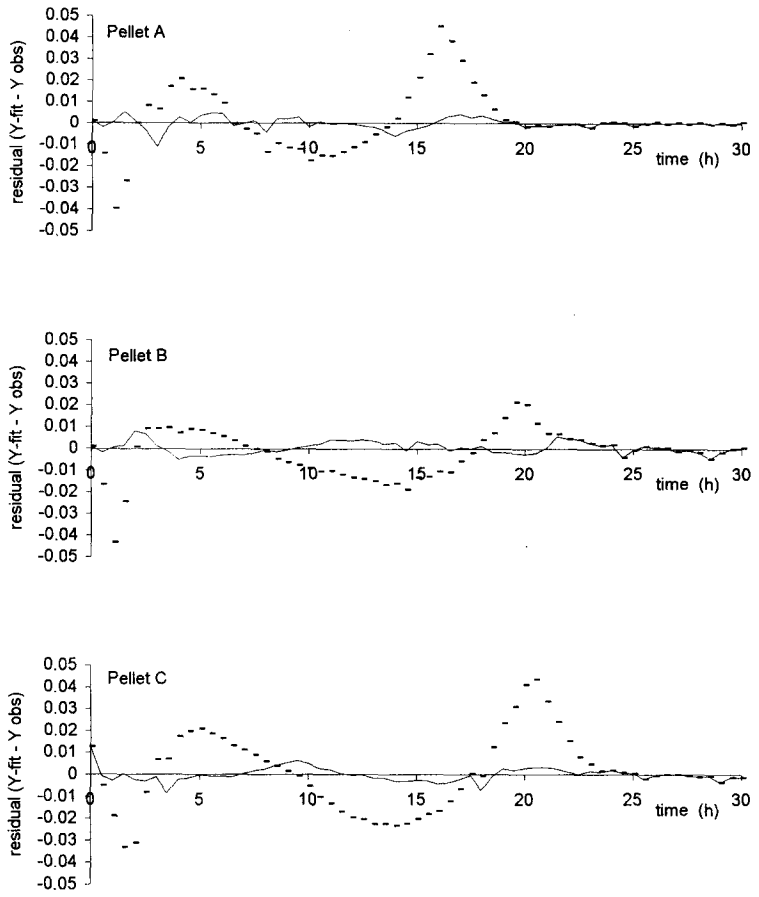

Fig. 5. Residual plots obtained by means of the profiles in Fig. 4. The curves show the differences between the fitted values and the observed values normalized to units of fractions released. The solid lines relate to the Order Model whereas the marks relate to the Power Law.

higher for the ensemble (45.4 h compared with 19.4–23.7 h for the individual pellets). The explanation is that the three pellets do not represent all of the variation in release time, and that the release time of the ensemble is determined by the slowest releasing pellet cf. Eq. (15). However, it cannot be precluded that the difference in dissolution method may contribute to the apparent difference.

7.3. Tableted pellets

The release profiles and residual plots obtained for the tableted pellets are shown in Figs. 8 and 9, and the equivalent parametric descriptions are shown in Table 3. Again the Order Model offers a much better fit than the Power Law.

The differences between the release profiles for ensembles of pellets and tableted pellets cannot be statistically assessed on the basis of the number of profiles given in the present paper. But these data show some typical tendencies which will be briefly interpreted here. This may in fact contribute to elucidating the meaning of the parameters in the Order Model (the same is not the case with the Power Law because of too poor profile fitting).

First, it is characteristic that a short positive lag-time for the ensemble of pellets is substituted by a negative value for the tablets denoting an initial burst. This burst effect is a result of damage

Table 2
Results from the fitting of the dissolution profile for the ensemble of pellets

Parameters	Power Law	Order Model
Shape, p or n	0.578 ± 0.013	0.652 ± 0.002
Scale, k (h^{-1})	0.0357 ± 0.0004	0.0634 ± 0.0001
Lag time, t_0 (h)	1.36 ± 0.11	0.11 ± 0.01
Coefficient of determination	0.994	0.99998
Release time, t_∞ (h)	29.4	45.4
Retardation, MDT (h)	11.6	11.8

The dissolution profiles were fitted to the Power Law and to the Order Model. The values of n, p, k and t_0 are shown with $\pm$ the estimated standard error.

to the membrane of some of the pellets during the tableting process.

Typically, the tableting will result in a higher order. The process will most probably increase the variation in release time for the individual pellets because of a larger number of very rapidly releasing pellets—which was also reflected in the lag-time parameter.

The total retardation determined by MDT is smallest for the tablets. In the light of the observed decrease in t_0 this is not surprising. However, t_∞ is not reduced because some of the slowest pellets are unaffected by the tableting process. Thus, the main reason for the decrease in MDT (and the increased order) is that some pellets have become very rapid. One explanation of this relationship is that pellets with a thicker coating will release their drug more slowly and proportionately with the coating thickness they will withstand the impact of the tableting process better.

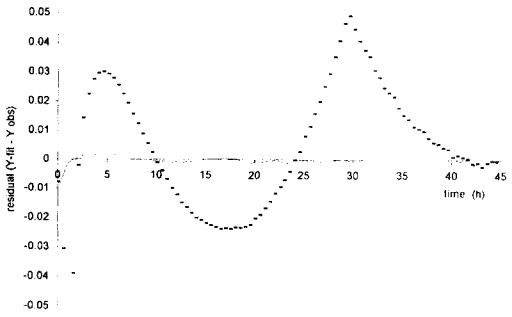

Fig. 7. Residual plot obtained by means of the profile in Fig. 6. The curve shows the differences between the fitted values and the observed values.The solid line relates to the Order Model whereas the marks relate to the Power Law.

8. Conclusion

The Order Model, a four parameter expression for the release of drug from a controlled release product has been established. It involves the release kinetic order, the rate constant, a lag-time parameter and the assay level. With the expression the release from individually tested pellets, ensembles of pellets and tableted pellets were fitted accurately. The same profiles cannot be fitted satisfactorily to the Power Law throughout the release time.

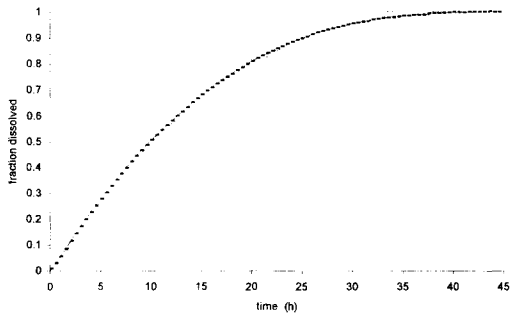

Fig. 6. The dissolution profile for the ensemble of untableted pellets. The marks represent the observed values whereas the solid line is the fitted profile using the Order Model and the dashed line is the fitted profiles using the Power Law.

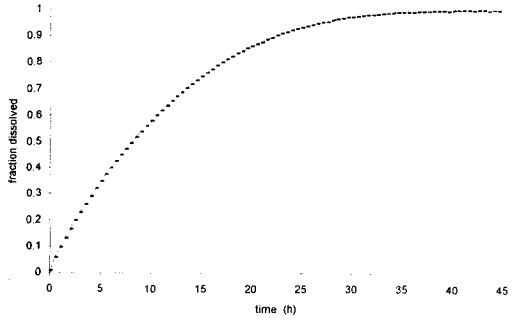

Fig. 8. The dissolution profile for the tableted pellets. The marks represent the observed values whereas the solid line is the fitted profile using the Order Model and the dashed line is the fitted profile using the Power Law.

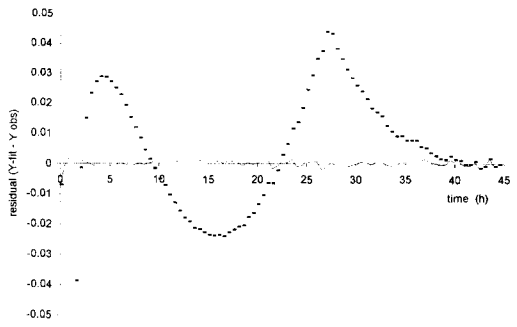

Fig. 9. Residual plot obtained by means of the profile in Fig. 8. The curve shows the differences between the fitted values and the observed values. The solid line relates to the Order Model whereas the marks relate to the Power Law.

Table 3
Results from the fitting of the dissolution profile for a multiparticulate tablet

Parameters	Power Law	Order Model
Shape, p or n	0.509 ± 0.013	0.710 ± 0.002
Scale, k (h^{-1})	0.0387 ± 0.0005	0.0740 ± 0.0001
Lag time, t_0 (h)	1.26 ± 0.11	-0.40 ± 0.01
Coefficient of determination	0.993	0.99999
Release time, t_∞ (h)	27.1	46.2
Retardation, MDT (h)	10.0	10.1

The dissolution profiles were fitted to the Power Law and to the Order Model. The values of n, p, k and t_0 are shown with $\pm$ the estimated standard error.

On the basis of the fine fitting properties obtained and because a number of mechanisms have been shown to be related to the kinetic order, the Order Model seems to offer a considerable potential for characterization of release profiles.

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