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Review

Modeling and comparison of dissolution profiles

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Abstract

Over recent years, drug release/dissolution from solid pharmaceutical dosage forms has been the subject of intense and profitable scientific developments. Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. The pharmaceutical industry and the registration authorities do focus, nowadays, on drug dissolution studies. The quantitative analysis of the values obtained in dissolution/release tests is easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used. In some cases, these mathematic models are derived from the theoretical analysis of the occurring process. In most of the cases the theoretical concept does not exist and some empirical equations have proved to be more appropriate. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or $Q = f(t)$. Some analytical definitions of the $Q(t)$ function are commonly used, such as zero order, first order, Hixson–Crowell, Weibull, Higuchi, Baker–Lonsdale, Korsmeyer–Peppas and Hopfenberg models. Other release parameters, such as dissolution time ($t_{x\%}$), assay time ($t_{x\ \mathrm{min}}$), dissolution efficacy (ED), difference factor (f_1), similarity factor (f_2) and Rescigno index (ξ_1 and ξ_2) can be used to characterize drug dissolution/release profiles.

Keywords: Drug dissolution; Drug release; Drug release models; Release parameters

1. Introduction

In vitro dissolution has been recognized as an important element in drug development. Under certain conditions it can be used as a surrogate for the assessment of Bioequivalence. Several theories/kinetics models describe drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where f_t is a function of t (time) related to the amount of drug dissolved from the pharmaceutical dosage system. The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of a generic equation that mathematically translates the dissolution curve in function of some parameters related with the pharmaceutical dosage forms. In some cases, that equation can be deduced by a theoretical analysis of the process, as for example in zero order kinetics. In most cases, with tablets, capsules, coated forms or prolonged release forms that theoretical fundament does not exist and some times a more adequate empirical equations is used. The kind of drug, its polymorphic form, cristallinity, particle size, solubility and amount in the pharmaceutical dosage form can influence the release kinetic (Salomon and Doelker, 1980; El-Arini and Leuenberger, 1995). A water-soluble drug incorporated in a matrix is mainly released by diffusion, while for a low water-soluble drug the self-erosion of the matrix will be the principal release mechanism. To accomplish these studies the cumulative profiles of the dissolved drug are more commonly used in opposition to their differential profiles. To compare dissolution profiles between two drug products model dependent (curve fitting), statistic analysis and model independent methods can be used.

2. Mathematical models

2.1. Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

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$$W_0 - W_t = Kt \quad (1)$$

where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at time t and K is a proportionality constant. Dividing this equation by W_0 and simplifying:

$$f_t = K_0 t \quad (2)$$

where $f_t = 1 - (W_t/W_0)$ and f_t represents the fraction of drug dissolved in time t and K_0 the apparent dissolution rate constant or zero order release constant. In this way, a graphic of the drug-dissolved fraction versus time will be linear if the previously established conditions were fulfilled.

This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs (Varelas et al., 1995), coated forms, osmotic systems, etc. The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$Q_1 = Q_0 + K_0 t \quad (3)$$

where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant.

2.2. First order kinetics

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner (1969). This model has been also used to describe absorption and/or elimination of some drugs (Gibaldi and Perrier, 1982), although it is difficult to conceptualise this mechanism in a theoretical basis. Kitazawa et al. (1975, 1977) proposed a slightly different model, but achieved practically the same conclusions.

The dissolution phenomena of a solid particle in a liquid media implies a surface action, as can be seen by the Noyes–Whitney Equation:

$$\frac{dC}{dt} = K(C_s - C) \quad (4)$$

where C is the concentration of the solute in time t, C_s is the solubility in the equilibrium at experience temperature and K is a first order proportionality constant. This equation was altered by Brunner et al. (1900), to incorporate the value of the solid area accessible to dissolution, S, getting:

$$\frac{dC}{dt} = K_1 S(C_s - C) \quad (5)$$

where k_1 is a new proportionality constant. Using the Fick first law, it is possible to establish the following relation for the constant k_1:

$$k_1 = \frac{D}{Vh} \quad (6)$$

where D is the solute diffusion coefficient in the dissolution media, V is the liquid dissolution volume and h is the width of the diffusion layer. Hixson and Crowell adapted the Noyes–Whitney equation in the following manner:

$$\frac{dW}{dt} = KS(C_s - C) \quad (7)$$

where W is the amount of solute in solution at time t, dW/dt is the passage rate of the solute into solution in time t and K is a constant. This last equation is obtained from the Noyes–Whitney equation by multiplying both terms of equation by V and making K equal to k_1V. Comparing these terms, the following relation is obtained:

$$K = \frac{D}{h} \quad (8)$$

In this manner, Hixson and Crowell Equation [Eq. (7)] can be rewritten as:

$$\frac{dW}{dt} = \frac{KS}{V}(VC_s - W) = k(VC_s - W) \quad (9)$$

where $k = k_1 S$. If one pharmaceutical dosage form with constant area is studied in ideal conditions (sink conditions), it is possible to use this last equation that, after integration, will become:

$$W = VC_s\left(1 - e^{-kt}\right) \quad (10)$$

This equation can be transformed, applying decimal logarithms in both terms, into:

$$\log (VC_s - W) = \log VC_s - \frac{kt}{2.303} \quad (11)$$

The following relation can also express this model:

$$Q_t = Q_0\, e^{-K_1 t} \quad \text{or} \quad \ln\left(\frac{Q_t}{Q_0}\right) = K_1 t \quad \text{or} \quad \ln q_t = \ln Q_0 K_1 t$$

or in decimal logarithms:

$$\log Q_t = \log Q_0 + \frac{K_1 t}{2.303} \quad (12)$$

where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_1 is the first order release constant. In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices (Mulye and Turco, 1995), release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminish.

2.3. Weibull model

A general empirical equation described by Weibull (1951) was adapted to the dissolution/release process (Langenbucher, 1972). This equation can be successfully applied to almost all kinds of dissolution curves and is commonly used in these studies (Goldsmith et al., 1978; Romero et al., 1991; Vudathala and Rogers, 1992). When applied to drug dissolution or release from pharmaceutical dosage forms, the Weibull equation expresses the accumulated fraction of the drug, m, in solution at time, t, by:

$$m = 1 - \exp\left[\frac{-(t - T_i)^b}{a}\right] \quad (13)$$

In this equation, the scale parameter, a, defines the time scale of the process. The location parameter, T_i, represents the lag time before the onset of the dissolution or release process and in most cases will be zero. The shape parameter, b, characterizes the curve as either exponential ($b = 1$) (Case 1), sigmoid, S-shaped, with upward curvature followed by a turning point ($b > 1$) (Case 2), or parabolic, with a higher initial slope and after that consistent with the exponential ($b < 1$) (Case 3). This equation may be rearranged into:

$$\log[-\ln(1 - m)] = b \log(t - T_i) - \log a \quad (14)$$

From this equation a linear relation can be obtained for a log–log plot of $-\ln(1-m)$ versus time, t. The shape parameter (b) is obtained from the slope of the line and the scale parameter, a, is estimated from the ordinate value ($1/a$) at time $t = 1$. The parameter, a, can be replaced by the more informative dissolution time, T_d, that is defined by $a = (T_d)^b$ and is read from the graph as the time value corresponding to the ordinate $-\ln(1 - m) = 1$. Since $-\ln(1 - m) = 1$ is equivalent to $m = 0.632$, T_d represents the time interval necessary to dissolve or release 63.2% of the drug present in the pharmaceutical dosage form. To pharmaceuticals systems following this model, the logarithm of the dissolved amount of drug versus the logarithm of time plot will be linear.

Because this is an empiric model, not deducted from any kinetic fundament, it presents some deficiencies and has been the subject of some criticism (Pedersen and Myrick, 1978; Christensen et al., 1980), such as:

- There is not any kinetic fundament and could only describe, but does not adequately characterize, the dissolution kinetic properties of the drug,
- there is not any single parameter related with the intrinsic dissolution rate of the drug and
- it is of limited use for establishing in vivo/in vitro correlations.

2.4. Higuchi model

Higuchi (1961, 1963) developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid matrixes. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. To study the dissolution from a planar system having a homogeneous matrix, the relation obtained was the following:

$$f_t = Q = \sqrt{D(2C - C_s)C_s t} \quad (15)$$

where Q is the amount of drug released in time t per unit area, C is the drug initial concentration, C_S is the drug solubility in the matrix media and D is the diffusivity of the drug molecules (diffusion constant) in the matrix substance.

This relation was first proposed by Higuchi to describe the dissolution of drugs in suspension from ointments bases, but is clearly in accordance with other types of dissolution from other pharmaceutical dosage forms. To these dosage forms a concentration profile, which may exist after application of the pharmaceutical system, can be represented (Fig. 1). The solid line represents the variation of drug concentration in the pharmaceutical system, after time, t, in the matrix layer normal to the release surface, being all the drug rapidly diffused (perfect sink conditions). The total drug concentration would be expected to show a sharp discontinuity at distance h and no drug dissolution could occur until the concentration drops below the matrix drug solubility (C_s). To distances higher than h, the concentration gradient will be constant, provided $C \gg C_s$. The linearity of the gradient over this distance follows Fick's first law. At a time t the amount of drug release by the system corresponds to the shaded area in Fig. 1. It is then evident that dQ, the amount of drug released, is related to dh, the movement of the release front:

$$dQ = C dh - 1/2(C_s\, dh) \quad (16)$$

But, in accordance to the Fick first law ($dQ/dt = DC_s/h$) the following expression is obtained:

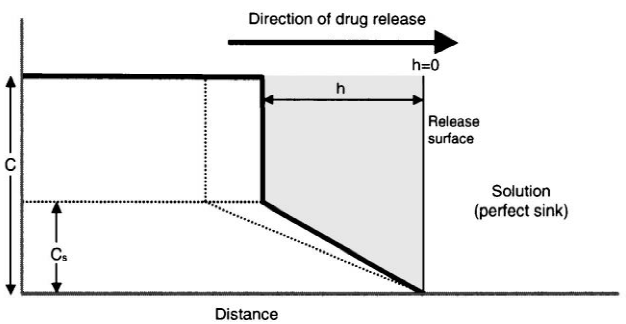

Fig. 1. Drug theoretical concentration profile of a matrix system in direct contact with a perfect sink release media.

$$\frac{(C\,\mathrm{d}h - 1/2(C_s\,\mathrm{d}h))}{\mathrm{d}t} = \frac{DC_s}{h}$$

or

$$\frac{h(C\,\mathrm{d}h - 1/2(C_s\,\mathrm{d}h))}{DC_s} = \mathrm{d}t$$

$$\frac{h(2C - C_s)\,\mathrm{d}h}{2DC_s} = \mathrm{d}t$$

Integrating this equation it becomes:

$$t = \frac{h^2}{4DC_s}(2C - C_s) + k'$$

where k' is an integration constant and k' will be zero if time was measured from zero and then:

$$t = \frac{h^2}{4DC_s}(2C - C_s) \quad \text{or} \quad h = 2\sqrt{\frac{tDC_S}{2C - C_S}}$$

Q (amount of drug released at time t) is then:

$$Q = hC - 1/2(hC_s) \quad \text{or} \quad Q = h(C - C_s)$$

Replacing in this equation h by the expression obtained:

$$Q = 2\sqrt{\frac{tDC_s}{2C - C_s}}(C - C_s)$$

and finally

$$Q = \sqrt{tDC_s(2C - C_s)} \tag{17}$$

This relation is valid during all the time, except when the total depletion of the drug in the therapeutic system is achieved. Higuchi developed also other models, such as drug release from spherical homogeneous matrix systems and planar or spherical systems having a granular (heterogeneous) matrix. To study the dissolution from a planar heterogeneous matrix system, where the drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix, the obtained relation was the following:

$$f_t = Q = \sqrt{\frac{D\varepsilon}{\tau}(2C - \varepsilon C_s)C_s t} \tag{18}$$

where Q is the amount of drug released in time t by surface unity, C is the initial concentration of the drug, ε is the matrix porosity, τ is the tortuosity factor of the capillary system, C_s is the drug solubility in the matrix/excipient media and D the diffusion constant of the drug molecules in that liquid. These models assume that these systems are neither surface coated nor that their matrices undergo a significant alteration in the presence of water.

Higuchi (1962) proposed the following equation, for the case in which the drug is dissolved from a saturated solution (where C_0 is the solution concentration) dispersed in a porous matrix:

$$f_t = Q = \sqrt{2C_0\varepsilon\frac{Dt}{\tau\pi}} \tag{19}$$

Cobby et al. (1974a,b) proposed the following generic, polynomial equation to the matrix tablets case:

$$f_t = Q = G_1K_rt^{1/2} - G_2(K_rt^{1/2})^2 + G_3(K_rt^{1/2})^3 \tag{20}$$

where Q is the released amount of drug in time t, K_r is a dissolution constant and G_1, G_2 and G_3 are shape factors.

These matrices usually have continuous channels, due to its porosity, being in this way above the first percolation threshold (in order to increase its mechanical stability) and bellow the second percolation threshold (in order to release all the drug amount), allowing us to apply the percolation theory (Leuenberger et al., 1989; Hastedt and Wright, 1990; Bonny and Leuenberger, 1991; Staufer and Aharony, 1994):

$$f_t = Q = \sqrt{D_BC_st[2\phi d - (\phi + \varepsilon)C_s]} \tag{21}$$

where ϕ is the volume accessible to the dissolution media throughout the network channels, D_B is the diffusion coefficient through this channels and d is the drug density. In a general way it is possible to resume the Higuchi model to the following expression (generally known as the simplified Higuchi model):

$$f_t = K_Ht^{1/2} \tag{22}$$

where K_H is the Higuchi dissolution constant treated sometimes in a different manner by different authors and theories. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems (Costa et al., 1996) and matrix tablets with water soluble drugs (Desai et al., 1966a,b; Schwartz et al., 1968a,b).

2.5. Hixson–Crowell model

Hixson and Crowell (1931) recognizing that the particle regular area is proportional to the cubic root of its volume, derived an equation that can be described in the following manner:

$$W_0^{1/3} - W_t^{1/3} = K_st \tag{23}$$

where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and K_s is a constant incorporating the surface–volume relation. This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial

geometrical form keeps constant all the time. Eq. (23) can be rewritten:

$$W_0^{1/3} - W_t^{1/3} = \frac{K' N^{1/3} D C_s t}{\delta} \quad (24)$$

to a number N of particles, where K' is a constant related to the surface, the shape and the density of the particle, D is the diffusion coefficient, C_s is the solubility in the equilibrium at experience temperature and δ is the thickness of the diffusion layer. The shape factors for cubic or spherical particles should be kept constant if the particles dissolve in an equal manner by all sides. This possibly will not occur to particles with different shapes and consequently this equation can no longer be applied. Dividing Eq. (23) by $W_0^{1/3}$ and simplifying:

$$(1 - f_t)^{1/3} = 1 - K_\beta t \quad (25)$$

where $f_t = 1 - (W_t/W_0)$ and f_t represents the drug dissolved fraction at time t and K_β is a release constant. Then, a graphic of the cubic root of the unreleased fraction of drug versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the pharmaceutical dosage form diminishes proportionally over time. When this model is used, it is assumed that the release rate is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix. This model has been used to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution (Niebergall et al., 1963; Prista et al., 1995).

2.6. Korsmeyer–Peppas model

Korsmeyer et al. (1983) developed a simple, semi-empirical model, relating exponentially the drug release to the elapsed time (t):

$$f_t = at^n \quad (26)$$

where a is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism, and the function of t is M_t/M_∞ (fractional release of drug).

The drug diffusion from a controlled release polymeric system with the form of a plane sheet, of thickness δ can be represented by:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \quad (27)$$

where D is the drug diffusion coefficient (concentration independent). If drug release occurs under perfect sink conditions, the following initial and boundary conditions can be assumed:

$t = 0 \quad -d/2 < x < d/2 \quad c = c_0$

$t > 0 \quad x = \pm d/2 \quad c = c_1$

where c_0 is the initial drug concentration in the device and c_1 is the concentration of drug at the polymer–water interface. The solution equation under these conditions was proposed initially by Crank (1975):

$$\frac{M_t}{M_\infty} = 2\left(\frac{Dt}{\delta^2}\right)^{1/2}\left[\pi^{-1/2} + \sum_{n=1}^{\infty}(-1)^n \, i\,erfc\frac{n\delta}{2\sqrt{Dt}}\right] \quad (28)$$

A sufficiently accurate expression can be obtained for small values of t since the second term of Eq. (28) disappears and then it becomes:

$$\frac{M_t}{M_\infty} = 2\left(\frac{Dt}{\delta^2}\right)^{1/2} = at^{1/2} \quad (29)$$

Then, if the diffusion is the main drug release mechanism, a graphic representing the drug amount released, in the referred conditions, versus the square root of time should originate a straight line. Under some experimental situations the release mechanism deviates from the Fick equation, following an anomalous behaviour (non-Fickian). In these cases a more generic equation can be used:

$$\frac{M_t}{M_\infty} = at^n \quad (30)$$

Peppas (1985) used this n value in order to characterise different release mechanisms, concluding for values for a slab, of $n = 0.5$ for Fick diffusion and higher values of n, between 0.5 and 1.0, or $n = 1.0$, for mass transfer following a non-Fickian model (Table 1). In the case of a cylinder, $n = 0.45$ instead of 0.5, and 0.89 instead of 1.0. Eq. (29) can only be used in systems with a drug diffusion coefficient fairly concentration independent. To the determination of the exponent n the portion of the release curve where $M_t/M_\infty < 0.6$ should only be used. To use this equation it is also necessary that release occurs in a one-dimensional way and that the system width–thickness or length–thickness relation be at least 10. This model is generally used to analyse the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved.

A modified form of this equation (Harland et al., 1988; Ford et al., 1991; Kim and Fassihi, 1997; El-Arini and Leuenberger, 1998; Pillay and Fassihi, 1999) was de-

Table 1
Interpretation of diffusional release mechanisms from polymeric films

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
$0.5 < n < 1.0$	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero order release
Higher than 1.0	Super Case-II transport	t^{n-1}

veloped to accommodate the lag time (l) in the beginning of the drug release from the pharmaceutical dosage form:

$$\frac{M_{(t-l)}}{M_\infty} = a(t-l)^n \tag{31}$$

or, its logarithmic version:

$$\log\left(\frac{M_{(t-l)}}{M_\infty}\right) = \log a + n \log (t-1) \tag{32}$$

When there is the possibility of a burst effect, b, this equation becomes (Kim and Fassihi, 1997):

$$\frac{M_t}{M_\infty} = at^n + b \tag{33}$$

In the absence of lag time or burst effect, l and b values would be zero and only at^n is used. This mathematical model, also known as the Power Law, has been used, very frequently, to describe the drug release from several different pharmaceutical modified release dosage forms (Lin and Yang, 1989; Sangalli et al., 1994; Kim and Fassihi, 1997).

2.7. Baker–Lonsdale model

This model was developed by Baker and Lonsdale (1974) from the Higuchi model and describes the drug controlled release from a spherical matrix, being represented by the following expression:

$$\frac{3}{2}\left[1-\left(1-\frac{M_t}{M_\infty}\right)^{2/3}\right] - \frac{M_t}{M_\infty} = \frac{3D_m C_{ms}}{r_0^2 C_0} t \tag{34}$$

where M_t is the drug released amount at time t and M_∞ is the amount of drug released at an infinite time, D_m is the diffusion coefficient, C_{ms} is the drug solubility in the matrix, r_0 is the radius of the spherical matrix and C_0 is the initial concentration of drug in the matrix.

If the matrix is not homogeneous and presents fractures or capillaries that may contribute to the drug release, the following equation (Seki et al., 1980) is used:

$$\frac{3}{2}\left[1-\left(1-\frac{M_t}{M_\infty}\right)^{2/3}\right] - \frac{M_t}{M_\infty} = \frac{3D_f C_{fs}\varepsilon}{r_0^2 C_0 \tau} t \tag{35}$$

where D_f is the diffusion coefficient, C_{fs} is the drug solubility in the liquid surrounding the matrix, τ is the tortuosity factor of the capillary system and ε is the porosity of the matrix. The matrix porosity can be described by (Desai et al., 1966a,b,c):

$$\varepsilon = \varepsilon_0 + KC_0 \tag{36}$$

where ε_0 is the initial porosity and K is the drug specific volume. If ε_0 is small, Eq. (35) can be rearranged as:

$$\frac{3}{2}\left[1-\left(1-\frac{M_t}{M_\infty}\right)^{2/3}\right] - \frac{M_t}{M_\infty} = \frac{3D_f K C_{fs}}{r_0^2 \tau} t \tag{37}$$

In this way a graphic relating the left side of the equation and time will be linear if the established conditions were fulfilled and the Baker–Lonsdale model could be defined as:

$$f_t = \frac{3}{2}\left[1-\left(1-\frac{M_t}{M_\infty}\right)^{2/3}\right] - \frac{M_t}{M_\infty} = kt \tag{38}$$

where the release constant, k, corresponds to the slope. This equation has been used to the linearization of release data from several formulations of microcapsules or microspheres (Seki et al., 1980; Jun and Lai, 1983; Chang et al., 1986; Shukla and Price, 1989, 1991; Bhanja and Pal, 1994).

2.8. Hopfenberg model

The release of drugs from surface-eroding devices with several geometries was analysed by Hopfenberg who developed a general mathematical equation describing drug release from slabs, spheres and infinite cylinders displaying heterogeneous erosion (Hopfenberg, 1976; Katzhendler et al., 1997):

$$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{k_0 t}{C_0 a_0}\right]^n \tag{39}$$

where M_t is the amount of drug dissolved in time t, M_∞ is the total amount of drug dissolved when the pharmaceutical dosage form is exhausted, M_t/M_∞ is the fraction of drug dissolved, k_0 is the erosion rate constant, C_0 is the initial concentration of drug in the matrix and a_0 is the initial radius for a sphere or cylinder or the half-thickness for a slab. The value of n is 1, 2 and 3 for a slab, cylinder and sphere, respectively. A modified form of this model was developed (El-Arini and Leuenberger, 1998) to accommodate the lag time (l) in the beginning of the drug release from the pharmaceutical dosage form:

$$\frac{M_t}{M_\infty} = 1 - [1 - k_1 t(t-l)]^n \tag{40}$$

where k_1 is equal to $k_0/C_0 a_0$. This model assumes that the rate-limiting step of drug release is the erosion of the matrix itself and that time dependent diffusional resistances internal or external to the eroding matrix do not influence it.

2.9. Other release parameteres

Other parameters used to characterise drug release profile are $t_{x\%}$, sampling time and dissolution efficiency. The $t_{x\%}$ parameter corresponds to the time necessary to the release of a determined percentage of drug (e.g., $t_{20\%}$, $t_{50\%}$, $t_{80\%}$) and sampling time corresponds to the amount of drug dissolved in that time (e.g., $t_{20\ \mathrm{min}}$, $t_{50\ \mathrm{min}}$, $t_{90\ \mathrm{min}}$). Pharmacopoeias very frequently use this parameter as an acceptance limit of the dissolution test (e.g., $t_{45\ \mathrm{min}} \geq 80\%$).

$$D.E.(\%) = \frac{SA}{R} \times 100$$

SA – Shaded area

R - Rectangle area ($y_{100} \times t$)

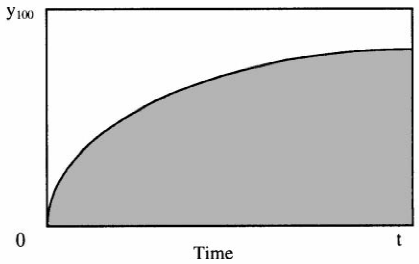

Fig. 2. Dissolution of a drug from a pharmaceutical dosage form.

The dissolution efficiency (DE) of a pharmaceutical dosage form (Khan and Rhodes, 1972; Khan, 1975) is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. It is represented in Fig. 2, and can be calculated by the following equation:

$$D.E. = \frac{\int_0^t y \times \mathrm{d}t}{y_{100} \times t} \times 100\% \quad (41)$$

where y is the drug percent dissolved at time t.

3. Release profiles comparision

The parameters described above contribute with a little information to clarifying the release mechanism and should be used associated with each other or with some of the models previously referred.

Some methods to compare drug release profiles were recently proposed (CMC, 1995; Shah and Polli, 1996; Ju and Liaw, 1997; Polli et al., 1997; Fassihi and Pillay, 1998). Those methods were classified into several categories, such as:

- Statistical methods (Tsong and Hammerstrom, 1996) based in the analysis of variance or in t-student tests
  - Single time point dissolution
  - Multiple time point dissolution
- Model-independent methods
- Model-dependent methods, using some of the previously described models, or lesser used models such as the quadratic, logistic or Gompertz model.

The methods based in the analysis of variance can also be distinguished in one-way analysis of variance (ANOVA) and multivariate analysis of variance (MANOVA). The statistical methods assess the difference between the means of two drug release data sets in single time point dissolution (ANOVA or t-student test) or in multiple time point dissolution (MANOVA).

Model-independent methods can be further differentiated as ratio tests and pair-wise procedures. The ratio tests are relations between parameters obtained from the release assay of the reference formulation and the release assay of the test product at the same time and can go from a simple ratio of percent dissolved drug ($t_{x\%}$) to a ratio of area under the release curve (AUC) or even to a ratio of mean dissolution time (MDT). The mean dissolution time can be calculated by the following expression:

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}_j \, \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad (42)$$

where j is the sample number, n is the number of dissolution sample times, $\hat{t}_j$ is the time at midpoint between t_j and t_{j-1} (easily calculated with the expression $(t_j + t_{j-1})/2$) and ΔM_i is the additional amount of drug dissolved between t_i and t_{i-1}.

The pair-wise procedures includes the *difference factor* and the *similarity factor* (Moore and Flanner, 1996) and the *Rescigno index* (Rescigno, 1992).

The difference factor (f_1) measures the percent error between two curves over all time points:

$$f_t = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100 \quad (43)$$

where n is the sampling number, R_j and T_j are the percent dissolved of the reference and test products at each time point j. The percent error is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles.

The similarity factor (f_2) is a logarithmic transformation of the sum-squared error of differences between the test T_j and reference products R_j over all time points:

$$f_2 = 50 \times \log\left\{ \left[1 + (1/n) \sum_{j=1}^{n} w_j |R_j - T_j|^2 \right]^{-0.5} \times 100 \right\} \quad (44)$$

where w_j is an optional weight factor. The similarity factor

fits the result between 0 and 100. It is 100 when the test and reference profiles are identical and tends to 0 as the dissimilarity increases. This method is more adequate to dissolution profile comparisons when more than three or four dissolution time points are available. Eq. (43) can only be applied if the average difference between R and T is less than 100. If this difference is higher than 100 normalisation of the data is required (Moore and Flanner, 1996).

This similarity factor has been adopted by the Center for Drug Evaluation and Research (FDA) and by Human Medicines Evaluation Unit of The European Agency for the Evaluation of Medicinal Products (EMEA), as a criterion for the assessment of the similarity between two in vitro dissolution profiles and is included in the ''Guidance on Immediate Release Solid Oral Dosage Forms; Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation'' (CMC, 1995), commonly called SUPAC IR, and in the ''Note For Guidance on Quality of Modified Release Products: A. Oral Dosage Forms; B. Transdermal Dosage Forms; Section I (Quality)'' (EMEA, 1999). The similarity factor (f_2) as defined by FDA and EMEA is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test and the reference products:

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{j=1}^{n}|R_j - T_j|^2\right]^{-0.5} \times 100\right\} \tag{45}$$

This equation differs from the one proposed by Moore and Flanner in the weight factor and in the fact that it uses percent dissolution values. In order to consider the similar dissolution profiles, the f_1 values should be close to 0 and values f_2 should be close to 100. In general, f_1 values lower than 15 (0–15) and f_2 values higher than 50 (50–100) show the similarity of the dissolution profiles. FDA and EMEA suggest that two dissolution profiles are declared similar if f_2 is between 50 and 100. In addition, it requests the sponsor uses the similarity factor to compare the dissolution treatment effect in the presence of at least 12 individual dosage units.

Some relevant statistical issues of the similarity factor have been presented (Liu and Chow, 1996; Liu et al., 1997). Those issues include the invariant property of f_2 with respect to the location change and the consequence of failure to take into account the shape of the curve and the unequal spacing between sampling time points. The similarity factor is a sample statistic that cannot be used to formulate a statistical hypothesis for the assessment of dissolution similarity. It is, therefore, impossible to evaluate false positive and false negative rates of decisions for approval of drug products based on f_2. Simulation results also indicate that the similarity factor is too liberal in concluding similarity between dissolution profiles. In addition, the range of f_2 is from $-\infty$ to 100 and it is not symmetric about zero. All this shows that f_2 is a convenience criterion and not a criterion based on scientific facts.

These parameters, especially f_1, are used to compare two dissolution profiles, being necessary to consider one of them as the reference product. The drive to mutual recognition in Europe has led to certain specific problems such as the definition of reference products and will require the harmonization of criteria among the different countries. To calculate the difference factor, the same pair of pharmaceutical formulations presents different f_1 values depending on the formulation chosen as the reference. A modification of the formula (Costa, 1999) used to calculate the difference factor (f_1') could avoid this problem:

$$f_1' = \frac{\sum_{j=1}^{n}|R_j - T_j|}{\sum_{j=1}^{n}(R_j + T_j)\Big/2} \times 100 \tag{46}$$

using as divisor not the sum of the reference formula values, but the sum of the average values of the two formulations for each dissolution sampling point.

Rescigno proposed a bioequivalence index to measure the dissimilarity between a reference and a test product based on plasma concentration as a function of time. This Rescigno index (ξ_i) can also be used based on drug dissolution concentrations:

$$\xi_i = \left\{\frac{\int_0^{\infty}|d_R(t) - d_T(t)|^i\,dt}{\int_0^{\infty}|d_R(t) + d_T(t)|^i\,dt}\right\}^{1/i} \tag{47}$$

where $d_R(t)$ is the reference product dissolved amount, $d_T(t)$ is the test product dissolved amount at each sample time point and i is any positive integer number. This, adimensional, index always presents values between 0 and 1 inclusive, and measures the differences between two dissolution profiles. This index is 0 when the two release profiles are identical and 1 when the drug from either the test or the reference formulation is not released at all. By increasing the value of i, more weight will be given to the magnitude of the change in concentration, than to the duration of that change. Two Rescigno indexes are generally calculated ξ_1, replacing in the formula i by 1, or ξ_2, where $i=2$. A method to calculate the Rescigno index consists in substituting the previous definition with an equivalent definition valid for discrete variations of the $d_R(t)$ and $d_T(t)$ values at each time point j:

$$\xi_i = \left(\frac{\sum_{j=1}^{n} w_j|d_R(t_j) - d_T(t_j)|^i}{\sum_{j=1}^{n} w_j|d_R(t_j) - d_T(t_j)|^i}\right)^{1/i} \tag{48}$$

where n is the number of time points tested and w_j is an appropriate coefficient, optional, representing the weight to give to each sampling time point (as with the similarity factor).

The comparison of two drug dissolution profiles (Ju and Liaw, 1997) can also be made with the Gill split–plot approach (Gill, 1988) and Chow's time series approach (Chow and Ki, 1997).

Although the model-independent methods are easy to apply, they lack scientific justification (Liu and Chow, 1996; Ju and Liaw, 1997; Liu et al., 1997, Polli et al., 1997). For controlled release dosage forms, the spacing between sampling times becomes much more important than for immediate release and should be taken into account for the assessment of dissolution similarity. In vitro dissolution is an invaluable development instrument for understanding drug release mechanisms. The other major application of dissolution testing is in Quality Control and, besides the above limitations, these model-independent methods can be used as a very important tool in this area.

4. Conclusions

As it has been previously referred to, the quantitative interpretation of the values obtained in dissolution assays is easier using mathematical equations which describe the release profile in function of some parameters related with the pharmaceutical dosage forms. Some of the most relevant and more commonly used mathematical models describing the dissolution curves are shown in Table 2.

The drug transport inside pharmaceutical systems and its release sometimes involves multiple steps provoked by different physical or chemical phenomena, making it difficult, or even impossible, to get a mathematical model describing it in the correct way. These models better describe the drug release from pharmaceutical systems when it results from a simple phenomenon or when that phenomenon, by the fact of being the rate-limiting step, conditions all the other processes.

The release models with major appliance and best describing drug release phenomena are, in general, the Higuchi model, zero order model, Weibull model and Korsmeyer–Peppas model. The Higuchi and zero order models represent two limit cases in the transport and drug release phenomena, and the Korsmeyer–Peppas model can be a decision parameter between these two models. While the Higuchi model has a large application in polymeric matrix systems, the zero order model becomes ideal to describe coated dosage forms or membrane controlled dosage forms.

Table 2
Mathematical models used to describe drug dissolution curves

Zero order	$Q_t = Q_0 + K_0 t$
First order	$\ln Q_t = \ln Q_0 + K_1 t$
Second order	$Q_t/Q_\infty(Q_\infty - Q_t)K_2 t$
Hixson–Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_s t$
Weibull	$\log[-\ln(1-(Q_t/Q_\infty))] = b \times \log t - \log a$
Higuchi	$Q_t = K_H\sqrt{t}$
Baker–Lonsdale	$(3/2)[1-(-1(Q_t/Q_\infty))^{2/3}] - (Q_t/Q_\infty) = Kt$
Korsmeyer–Peppas	$Q_t/Q_\infty = K_k t^n$
Quadratic	$Q_t = 100(K_1 t^2 + K_2 t)$
Logistic	$Q_t = A/[1+\mathrm{e}^{-K(t-y)}]$
Gompertz	$Q_t = A\ \mathrm{e}^{-e-K(t-y)}$
Hopfenberg	$Q_t/Q_\infty = 1-[1-k_0 t/C_0 a_0]^n$

But what are the criteria to choose the ''best model'' to study drug dissolution/release phenomena? One common method uses the coefficient of determination, R^2, to assess the ''fit'' of a model equation. However, usually, this value tends to get greater with the addition of more model parameters, irrespective of the significance of the variable added to the model. For the same number of parameters, however, the coefficient of determination can be used to determine the best of this subset of model equations. When comparing models with different numbers of parameters, the adjusted coefficient of determination (R^2_{adjusted}) is more meaningful:

$$R^2{}_{\text{adjusted}} = 1 - \frac{(n-1)}{(n-p)}(1-R^2) \tag{49}$$

where n is the number of dissolution data points (M/t) and p is the number of parameters in the model. Whereas the R^2 always increases or at least stays constant when adding new model parameters, R^2_{adjusted} can actually decrease, thus giving an indication if the new parameter really improves the model or might lead to over fitting. In other words, the ''best'' model would be the one with the highest adjusted coefficient of determination.

Besides the coefficient of determination (R^2) or the adjusted coefficient of determination (R^2_{adjusted}), the correlation coefficient (R), the sum of squares of residues (SSR), the mean square error (MSE), the Akaike Information Criterion (AIC) and the F-ratio probability are also used to test the applicability of the release models.

The Akaike Information Criterion is a measure of goodness of fit based on maximum likelihood. When comparing several models for a given set of data, the model associated with the smallest value of AIC is regarded as giving the best fit out of that set of models. The Akaike Criteria is only appropriate when comparing models using the same weighting scheme.

$$\text{AIC} = n \times \ln(\text{WSSR}) + 2 \times p \tag{50}$$

where n is the number of dissolution data points (M/t), p is the number of the parameters of the model, WSSR is the weighed sum of square of residues, calculated by this process:

$$\text{WSSR} = \sum_{i=1}^{n} [w_i(y_i - \hat{y}_i)^2] \tag{51}$$

where w_i is an optional weighing factor and y_i denotes the

predicted value of y_i. The AIC criterion has become a standard tool in model fitting, and its computation is available in many statistical programs.

Because analysing dissolution results with linear regression is a very common practice, it should be asked first whether it might make more sense to fit data with non-linear regression. If the non-linear data have been transformed to create a linear relationship, it will probably be better to use non-linear regression on the untransformed dissolution data. Before non-linear regression was readily available, the best way to analyse non-linear data was to transform it to create a linear graph, and then analyse this transformed data with linear regression. The problem with this method is that the transformation might distort the experimental error. Some computer programs were recently developed allowing the analysis of dissolution–release profiles, in a quick and relatively easy way, and to choose the model that best reproduces this process (Costa, 1999; Lu et al., 1996a,b).

To characterize drug release profile it is also possible to use other parameters, such as $t_{x\%}$, sampling time (a very used parameter by the generality of the Pharmacopoeias) and dissolution efficiency. As it has been said, the information obtained from these parameters to the knowledge of the release mechanism is a very limited one, and these parameters should be used associated between themselves or associated to some of the referred models.

The pair-wise procedures, like difference factor (f_1), similarity factor (f_2) and Rescigno index (ξ_i), also suffer from the same problem referred to above. Besides, these parameters are used to compare the release profiles of two different formulations, being necessary to consider one of them as the reference formulation. These pair-wise procedures reflect only the major or minor similarities between these two profiles, and can be considered as a good tool to judge its dissolution equivalence.

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