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Review

Higuchi equation: Derivation, applications, use and misuse

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ABSTRACT

Fifty years ago, the legendary Professor Takeru Higuchi published the derivation of an equation that allowed for the quantification of drug release from thin ointment films, containing finely dispersed drug into a perfect sink. This became the famous Higuchi equation whose fiftieth anniversary we celebrate this year. Despite the complexity of the involved mass transport processes, Higuchi derived a very simple equation, which is easy to use. Based on a pseudo-steady-state approach, a direct proportionality between the cumulative amount of drug released and the square root of time can be demonstrated. In contrast to various other "square root of time" release kinetics, the constant of proportionality in the classical Higuchi equation has a specific, physically realistic meaning. The major benefits of this equation include the possibility to: (i) facilitate device optimization, and (ii) to better understand the underlying drug release mechanisms. The equation can also be applied to other types of drug delivery systems than thin ointment films, e.g., controlled release transdermal patches or films for oral controlled drug delivery. Later, the equation was extended to other geometries and related theories have been proposed. The aim of this review is to highlight the assumptions the derivation of the classical Higuchi equation is based on and to give an overview on the use and potential misuse of this equation as well as of related theories.

Contents

1. Introduction

One of the most important and challenging areas in the drug delivery field is to predict the release of the active agent as a function of time using both simple and sophisticated mathematical models (Gurny et al., 1982; Korsmeyer and Peppas, 1983a; Korsmeyer et al., 1983; Peppas, 1983; Peppas and Franson, 1983; Franson and Peppas, 1983). The importance of such models lies in their utility during both the design stage of a pharmaceutical formulation and the experimental verification of a release mechanism (Peppas, 1984a,b; Harland et al., 1988a; Siepmann et al., 2006; Siepmann and Siepmann, 2008).

In order to identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. It is therefore clear that only a combination of accurate and precise data with models accurately depicting the physical situation will provide an insight into the actual mechanism of release (Korsmeyer and Peppas, 1983b; Peppas, 1984c,d; Lustig and Peppas, 1985; Siepmann and Peppas, 2000).

The vast majority of theoretical models is based on diffusion equations (Ritger and Peppas, 1987a,b; Siepmann and Peppas, 2001; Siepmann and Goepferich, 2001). The phenomenon of

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diffusion is intimately connected to the structure of the material through which the diffusion takes place thus the morphology of the polymeric materials should be accounted for in a successful model (Peppas and Gurny, 1983; Franson and Peppas, 1983; Gurny et al., 1983; Lustig and Peppas, 1984; Harland et al., 1988b; Peppas and Sahlin, 1989). There has been a limited number of reviews that have addressed these aspects of controlled release formulations. The mechanisms of drug release offer a convenient way to categorize controlled release systems into: (i) diffusion-controlled (Peppas and Lustig, 1985; Peppas and Segot-Chicq, 1985); (ii) swelling-controlled (Korsmeyer et al., 1982; Peppas et al., 1984; Davidson and Peppas, 1984, 1985; Peppas, 1987); and (iii) chemically controlled.

While the Higuchi equation addressed important aspects of drug transport and release from planar devices, it has been misinterpreted and misused in many occasions. It is instructive to return to the original derivation and examine how Higuchi's and other "popular" release equations were developed.

2. Derivation of the Higuchi equation

In his seminal contribution Takeru Higuchi considered the release of a drug from a thin ointment film into the skin (Higuchi, 1961). He considered the following conditions:

(1) Drug transport through the ointment base is rate limiting, whereas drug transport within the skin is rapid.
(2) The skin acts like a "perfect sink": The drug concentration in this compartment can be considered to be negligible.
(3) The initial drug concentration in the film is much higher than the solubility of the drug in the ointment base.
(4) The drug is finely dispersed within the ointment base (the size of the drug particles is much smaller than the thickness of the film).
(5) The drug is initially homogeneously distributed throughout the film.
(6) The dissolution of drug particles within the ointment base is rapid compared to the diffusion of dissolved drug molecules within the ointment base.
(7) The diffusion coefficient of the drug within the ointment base is constant and does not depend on time or the position within the film.
(8) Edge effects are negligible: The surface of the ointment film exposed to the skin is large compared to its thickness. The mathematical description of drug diffusion can be restricted to one dimension.
(9) The medium (ointment base) does not swell or dissolve during drug release.

Under these conditions, Higuchi could derive his surprisingly simple equation, allowing for the quantification of drug release from this rather complex type of drug delivery system. The basic ideas of the derivation of this famous equation are detailed in the following.

Upon exposure to perfect sink conditions, drug molecules dissolved in the ointment base diffuse into the skin. Initially, this occurs only close to the surface of the ointment film. Since drug dissolution is rapid and a large excess of drug is provided, the molecules that leach out of the system are rapidly replaced by the (partial) dissolution of non-dissolved drug particles located in this region. Thus, the concentration of dissolved drug molecules within the ointment base remains constant as long as non-dissolved drug excess is provided (saturated solution). Only when all drug particles located in the region next to the surface are finally dissolved, the concentration of dissolved drug molecules in this region falls below saturation concentration. Due to concentration gradients subsequently also dissolved drug molecules located further away from the film's surface diffuse through the ointment base into the skin. Importantly, the concentration of dissolved drug molecules in this newly concerned region remains constant (saturation concentration) as long as non-dissolved drug excess is provided in that region.

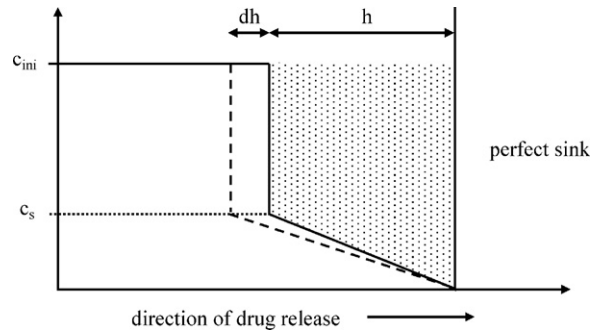

Fig. 1. Schematic presentation of the drug concentration–distance-profile within the ointment base after exposure to perfect sink conditions at time t (solid line) and at time $t+dt$ (dashed line). The variables have the following meanings: c_{ini} and c_s denote the initial drug concentration and drug solubility, respectively; h represents the distance of the front, which separates ointment free of non-dissolved drug excess from ointment still containing non-dissolved drug excess, from the "ointment-skin" interface at time t; dh is the distance this front moves inwards during the time interval dt.

After a given time t, the drug concentration–distance-profile represented by the solid line in Fig. 1 is obtained in the ointment film. On the y-axis, the drug concentration is plotted, on the x-axis the distance. The diagram can be seen as a cross-section through the ointment film and the skin (located on the right hand side and providing perfect sink conditions). Note that only for visibility reasons the illustrated drug solubility, c_s, is relatively high compared to the initial drug concentration c_{ini}. Ideally, c_{ini} should be much larger than c_s (by a factor of 10 or more). As it can be seen, parts of the ointment have been depleted of drug at this time point (illustrated by the dotted area). At a certain distance from the surface a sharp front can be observed, at which the drug concentration steeply increases from saturation concentration to "initial concentration". This front separates the part of the ointment, which still contains non-dissolved drug particles (left hand side) and the part of the ointment, which is free of non-dissolved drug excess (right hand side). This front is located at the distance h from the film's surface and is sometimes called "diffusion front". In order to be able to calculate the amount of drug released from the ointment film at this time point t, the drug concentration–distance-profile within the part of the ointment depleted of drug excess must be known.

In order to describe the drug concentration gradient in the ointment zone located between the "diffusion front" and the skin, Higuchi used a *pseudo-steady-state approach*, which is valid for systems containing initially a large excess of drug (drug loading $\gg$ drug solubility). The idea is the following: If the initial drug concentration is much higher than drug solubility in the ointment base (ideally, by factor 10 or more), it takes a long time to dissolve all drug excess at the distance h from the film's surface. Thus, the concentration at this position can be considered *constant* during a certain time period. In addition, perfect sink conditions are provided at the film's surface. Since the ointment base does not swell or dissolve, pseudo-steady-state conditions are provided for drug diffusion: a saturated drug solution on the one hand side, perfect sink on the other hand side and a constant distance in-between. Using Fick's second law of diffusion, it can be shown that under these conditions, the drug concentration–distance-profile between the surface of the film and the "diffusion front" is linear (solid line in

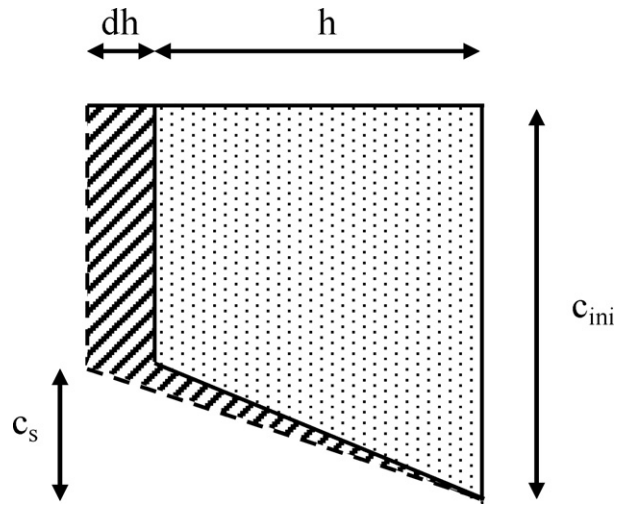

Fig. 2. Surfaces indicative for the amounts of drug released from the ointment base at time t (dotted trapezoid) and at time $t+dt$ (dashed trapezoid + dotted trapezoid). The variables have the following meanings: c_{ini} and c_s denote the initial drug concentration and drug solubility, respectively; h represents the distance of the front, which separates ointment free of non-dissolved drug excess from ointment still containing non-dissolved drug excess, from the "ointment-skin" interface at time t; dh is the distance this front moves inwards during the time interval dt.

Fig. 1). Consequently, the amount of drug released from the ointment film at time t can be represented by dotted trapezoid in Fig. 1. It has to be pointed out that under non-pseudo-steady-state conditions, the drug concentration gradient in the ointment zone free of drug excess is not linear and the resulting geometries are much more complicated.

Fig. 2 focuses on the dotted trapezoid representing the amount of drug released from the film at time t. Note that only a cross-section of the ointment film is illustrated in Figs. 1 and 2. Thus, the surface of the dotted trapezoid corresponds to the cumulative amount of drug released divided by the surface area of the film exposed to the skin, A. Due to the very simple geometry, it can easily be shown that the cumulative amount of drug released from the ointment film at time t, M_t, can be calculated as follows:

$$\frac{M_t}{A} = h\left(c_{ini} - \frac{c_s}{2}\right) \tag{1}$$

However, for the use of this equation h must be known. In order to express h as a function of other variables, Takeru Higuchi considered the drug concentration–distance-profile within the ointment film a certain time period (dt) later: at time $t+dt$. The dashed line in Fig. 1 illustrates this situation: The "diffusion front" separating ointment free of drug excess and ointment still containing drug excess moved the distance dh away from the surface. Importantly, the drug concentration gradient between the new front position $h+dh$ and the skin can again be considered linear, due to the high excess of drug (compared to the drug's solubility) and the pseudo-steady-state approach described above. Consequently, the cumulative amount of drug released per unit surface area dM/A in the time interval dt can be represented by the *dashed* trapezoid illustrated in Fig. 2. Again, due to the given, very simple geometries, it can easily be shown that:

$$\frac{dM}{A} = c_{ini}dh - \frac{c_s}{2}dh \tag{2}$$

In addition, Fick's 1st law of diffusion (Fick, 1855) can be used in order to quantify the amount of drug released from the ointment film in the time interval dt (considering a saturated drug solution at distance h from the surface and perfect sink conditions):

$$\frac{dM}{dt} = A\,D\,\frac{c_s}{h} \tag{3}$$

Importantly, combining Eqs. (2) and (3) allows to obtain the following expression for h:

$$h = 2\sqrt{\frac{D\,t\,c_s}{2\,c_{ini} - c_s}} \tag{4}$$

Substituting Eq. (4) into Eq. (1) and simplifying leads to:

$$\frac{M_t}{A} = \sqrt{(2c_{ini} - c_s)Dtc_s} \tag{5}$$

For a high initial excess of drug ($c_{ini} \gg c_s$), this equation can further be simplified to:

$$\frac{M_t}{A} = \sqrt{2\,c_{ini}D\,c_s\,t} \tag{6}$$

This is the classical Higuchi equation.

Obviously, one cannot violate the conditions on which Higuchi's derivation of his famous equation is based. In particular, the pseudo-steady-state approach needs to be valid, requiring a high initial excess of drug and a stationary "ointment–skin" interface (no swelling, no ointment base dissolution).

Obviously, the classical Higuchi equation can also be used to describe drug release from other controlled drug delivery systems than ointment films, e.g., thin patches for transdermal drug delivery or thin films for oral drug delivery. In the latter case, generally the two planar surfaces of the system are exposed to the release medium, which is a stirred bulk fluid (instead of skin). The Higuchi equation has later been extended to other geometries (e.g., Higuchi, 1963; Roseman and Higuchi, 1970). The reader is referred to the article of Lee of this special issue for more details (Lee, this issue).

Note that Eq. (6) can also be written in the following, more general form:

$$M_t = k\sqrt{t} \tag{7}$$

with

$$k = A\sqrt{2\,c_{ini}D\,c_s} \tag{8}$$

Thus, the classical Higuchi equation describes a "square root of time" release kinetics. However, it has to be pointed out that the constant k has a very specific and physically realistic meaning in the case of the Higuchi equation (Eq. (8)). Unfortunately, this is not always taken into account and in some reports the classical Higuchi equation is confused with other types of square root of time release kinetics. It has to be highlighted that other types of controlled drug delivery systems, which are governed by release mechanisms different from those considered by Higuchi can also be characterized by a proportionality between the cumulative amount of drug released and time. One example is described in the following.

3. Fickian diffusional release from a thin polymer sample

It is now instructive to consider also the simple derivation of a general solution of the diffusion equation for transport and release of drug from a one-dimensional object, in which the drug is initially homogeneously distributed at a concentration below the maximum solubility limit.

We consider one-dimensional, isothermal drug transport and diffusional release from a thin slab of a hydrophilic or hydrophobic polymer film or sheet of thickness L where the structure is initially maintained at a constant uniform drug concentration c_0, and perfect sink conditions are provided at the surfaces. This situation corresponds to the typical experimental conditions for a release experiment. For an assumed constant drug diffusion coefficient D

with one-dimensional diffusion in the x direction, Fick's second law, along with the appropriate initial and boundary conditions, may be written as:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \tag{9}$$

where

$$t = 0 \quad -L/2 < x < L/2 \quad c = c_0 \tag{10}$$

$$t > 0 \quad x = \pm L/2 \quad c = 0 \tag{11}$$

The solution to Fick's law in the form of a trigonometric series under the above specified conditions is (Crank, 1975):

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \cdot \pi^2} \cdot \exp\left(-\frac{(2n+1)^2 \cdot \pi^2}{L^2} \cdot D \cdot t\right) \tag{12}$$

where M_t is defined as the amount of drug released at time t, and M_∞ is the amount of drug released as time approaches infinity. An alternate solution to Eq. (12) that is useful for interpretation of short time behavior is given in the form of an error function series:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{L^2}\right)^{1/2} \left(\frac{1}{\pi^{1/2}} + 2\sum_{n=1}^{\infty}(-1)^n ierfc\frac{nL}{2\sqrt{Dt}}\right) \tag{13}$$

where *ierfc x* represents the integrated complementary error function of x. For 'small' times, Eq. (13) can be approximated by:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi L^2}\right)^{1/2} \tag{14}$$

As indicated by Eq. (14), Fickian diffusion in a thin polymer sample is characterized by an initial $t^{1/2}$-time dependence of the drug transport. The short time approximation is valid for the first 60% of the total drug release.

So, whether drug delivery is approached by the Higuchi equation or by the simple release from a polymer film using pure Fickian diffusion, the principal result is a $t^{1/2}$-time dependence of the drug transport.

4. Misunderstandings and misuse of the Higuchi and related equations

Several important assumptions have been implicitly incorporated in Eqs. (9)–(12). First, these equations describe the release of a drug from a carrier of a thin planar geometry, equivalent equations for release from thick slabs, cylinders, and spheres have been derived (Baker, 1987). It should also be emphasized that in the above written form of Fick's law the diffusion coefficient is assumed to be independent of concentration. This assumption, while not conceptually correct, has been largely accepted due to the computational simplicity.

Initial and boundary conditions, which are necessary for solving Eq. (9), allow for the appropriate description of the experimental conditions imposed upon the drug release device. The solutions of Eq. (9) are subject to a number of boundary conditions that can be applied to various in vitro and ex vivo experiments.

In order to improve the predictive power of the Fickian diffusion theory, a concentration dependent diffusion coefficient can be used in Fick's law. The latter is then rewritten and solved with the appropriate boundary conditions:

$$\frac{\partial c_i}{\partial t} = \frac{\partial}{\partial x}\left(D_{ip}(c_i)\frac{\partial c_i}{\partial x}\right) \tag{15}$$

In Eq. (15), $D_{ip}(c_i)$ is the concentration-dependent diffusion coefficient; its form of concentration dependence is affected by the structural characteristics of the polymer carrier.

Table 1
Different forms of non-constant diffusion coefficients (the variables are defined in the text).

Type of carrier	Eq.	Form of D_{ip}
Porous	16	$D_{ip} = \frac{\lambda^2 \nu}{6}$
Porous	17	$D_{eff} = D_{iw} K_p K_r \frac{\varepsilon}{\tau}$
Microporous	18	$\frac{D_{ip}}{D_b} = (1-\lambda)^2(1+\alpha\lambda+\beta\lambda^3+\gamma\lambda^5)$
Nonporous	19	$D_{ip} = D_o \exp\left\{-\frac{k}{v_f}\right\}$
Nonporous	20	$\frac{D_{2,13}}{D_{2,1}} = \varphi(q_s)\exp\left[-B\left(\frac{q_s}{V_{f,1}}\right)\left(\frac{1}{H}-1\right)\right]$
Nonporous (highly swollen)	21	$\frac{D_{2,13}}{D_{2,1}} = k_1\left(\frac{\bar{M}_c-\bar{M}_c^*}{\bar{M}_n-\bar{M}_c^*}\right)\exp\left(-\frac{k_2 r_s^2}{Q-1}\right)$

A selective summary of the various forms of the diffusion coefficient is provided in Table 1.

One of the earliest approaches of estimating the diffusion coefficient through a polymer carrier is that of Eyring (1936). In this theory, diffusion of a solute through a medium is presented as a series of jumps instead of a continuous process. Therefore, in Eq. (16) in Table 1, which comes from the Eyring analysis, λ is the diffusional jump of the drug in the polymer and ν is the frequency of jumping.

Fujita (1961) utilized the idea of free volume in polymers to estimate the drug diffusion coefficient and arrived at an exponential dependence of the drug diffusion coefficient on the free volume, u_f, which is given by Eq. (19) in Table 1. Yasuda and Lamaze (1971) refined the Fujita's theory and presented a molecularly based theory, which predicts the diffusion coefficients of drugs through a polymer matrix rather accurately (Eq. (20)). In their treatment the normalized diffusion coefficient, the ratio of the diffusion coefficient of the solute in the polymer, $D_{2,13}$, to the diffusion coefficient of the solute in the pure solvent, $D_{2,1}$, is related to the degree of hydration, H, and free-volume occupied by the swelling medium, $V_{f,1}$. In addition, φ is a sieving factor which provides a limiting mesh size impermeable to drugs with cross-sectional area q_s, and B is a parameter characteristic of the polymer. In Eq. (20), the subscripts 1, 2 and 3 refer to the swelling medium, drug and polymer, respectively.

Peppas and Reinhart (1983), Reinhart and Peppas (1984) and Peppas and Moynihan (1985) also developed a theoretical model based on a free volume of the polymer matrix. In their theory they assumed the free volume of the polymer to be the same as the free volume of the solvent and they arrived at Eq. (21) in Table 1. They related the normalized diffusion coefficient to the degree of swelling, Q, the solute radius, r_s, and the molecular weight of the polymer chains. More specifically, $\bar{M}_c$ is the average molecular weight of the polymer chains between adjacent crosslinks (Fig. 3), $\bar{M}_n$ is the average molecular weight of the linear polymer chains prepared under identical conditions in the absence of the crosslinking agent, and $\bar{M}_c^*$ is the critical molecular weight between crosslinks below which a drug of size r_s could not diffuse through the polymer network. In addition, k_1 and k_2 are constants related to the polymer structure. This theory is applicable to drug transport in highly swollen, nonporous hydrogels. Equations for moderately or poorly swollen (Peppas and Moynihan, 1985) and semi-crystalline hydrogels (Harland and Peppas, 1989) were also developed.

Yet, another approach for the prediction of the diffusion coefficient of a drug in a controlled-release device has been adopted from the chemical engineering field. More specifically, the transport phenomena in porous rocks, ion-exchange resins, and catalysis are of very similar nature to a drug diffusing through a macro- or micro-porous polymer. In these types of polymers the diffusion is assumed to be taking place predominantly through the water, or body fluid filled pores. The diffusion coefficient of a drug in a poly-

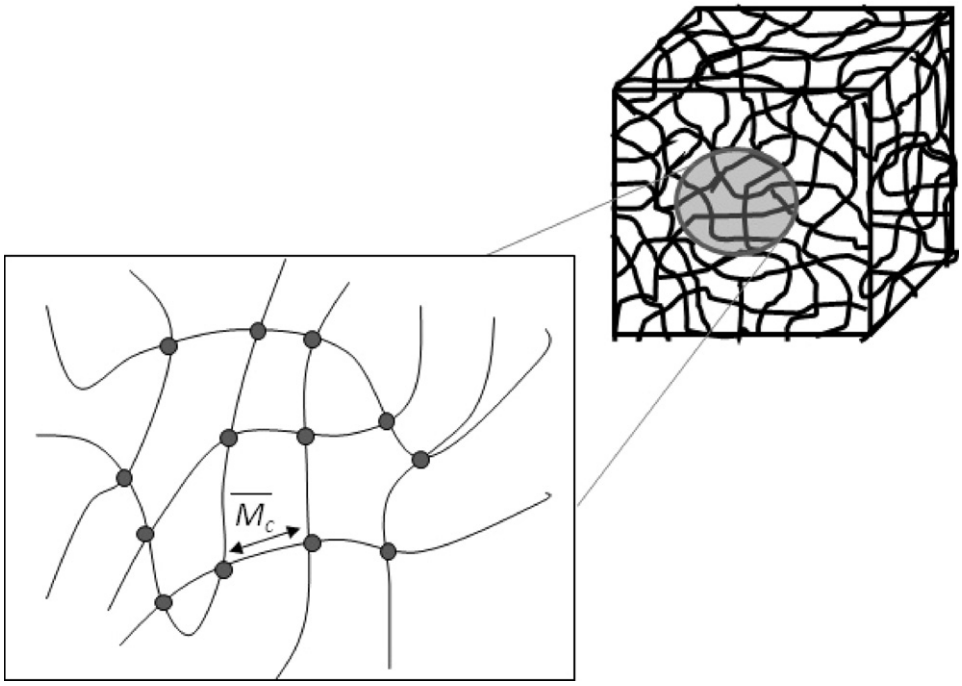

Fig. 3. Schematic illustration of a macromolecular network used to control the release rate of a drug. The average molecular weight of the polymer chains between adjacent crosslinks is denoted $\bar{M}_c$.

mer, D_{ip}, in Eq. (15) is replaced by an effective diffusive coefficient, D_{eff}, which is defined by Eq. (17) in Table 1. In Eq. (17), ε is the porosity, or void fraction, of the polymer, which is a measure of the volume of the pores available for diffusion and τ is the tortuosity, which describes the geometric characteristics of the pores. The term K_p is the equilibrium-partitioning coefficient, which is a parameter, needed when the drug is soluble in the polymer matrix, it is the ratio of the concentration inside of the pore to the concentration outside of the pore. The term K_r describes the fractional reduction in diffusivity within the pore when the solute diameter, d_s, is comparable in size to the pore diameter d_r. Eq. (18) in Table 1 is a semi-empirical relation proposed by Faxen (1923) for diffusion of spheres through porous media. In this equation, λ is the ratio of the drug radius, r_s, to the pore average radius, r_p, D_{ip} and D_b are the diffusion coefficients of the sphere through the pore and in bulk, respectively; and α, β and γ are constants. It is clear to see that as the size of the drug gets smaller with respect to the size of the pore, the ratio of D_{ip}/D_b approaches the limit of one.

Over the past fifty years these equations have been used incorrectly to analyze drug transport, especially from tablets. Some of the common errors are

(1) Use of the equation with a constant diffusion coefficient when the drug delivery formulation is actually expanding due to swelling or contracting due significant dissolution and release of drug with associated pore formation and collapse of the pores created during the release.
(2) Use of a one-dimensional equation for release from three-dimensional formulations (such as tablets).
(3) Lack of appreciation of the importance of the lateral area of diffusion (especially for tablets) and treatment of the problem as a one-dimensional problem.
(4) While a formulation is swelling or dissolving, the equation used is one developed with stationary boundary conditions.
(5) Certain contributions ignore the importance of other components (e.g., fillers, disintegrants) and treat the drug delivery process as a one-component diffusion process when in reality it is a multi-component diffusional process.

An example for a system, which is highly unusual for application of Higuchi's law is illustrated in Fig. 4: Hydroxypropyl methylcellulose-based tablets containing diltiazem, which are partially coated with an impermeable layer [case 0 (square), case 1 (filled diamond), case 2 (open square), case 3 (open diamond), case 4 (filled square)]. The significant swelling of these systems along with the impermeable coating layers renders the tablets very specific and deviate from the Higuchi assumptions.

5. Drug delivery from swellable systems

Transport from swellable systems may often lead to release under conditions that do not agree with Higuchi's or the Fickian behavior (Korsmeyer et al., 1986a,b; Davidson and Peppas, 1986a,b; Peppas and Korsmeyer, 1987; Lustig and Peppas, 1987; Klier and Peppas, 1988). For example, a simple semi-empirical equation used to define water transport in glassy polymers has been proposed by us (Sinclair and Peppas, 1984). The same equation was further developed to analyze drug release from films that had both a diffusional and a relaxational component.

For Fickian diffusional release from a thin film, Eq. (14) above indicates that the first 60% of the normalized drug release at any time can be characterized by some constant multiplied by the square root of time. For the second limiting case, Case II water transport and relaxational swelling of a sample, the normalized water uptake at any time is linearly related to time. Most transport processes in glassy polymers fall between these two limiting cases; as such, they can be represented by a coupling of the Fickian and Case II transport mechanisms. A simple expression of this observation can be heuristically written by adding the diffusion-controlled and relaxation-controlled drug delivery:

$$\frac{M_t}{M_\infty} = k_1\sqrt{t} + k_2 t \tag{22}$$

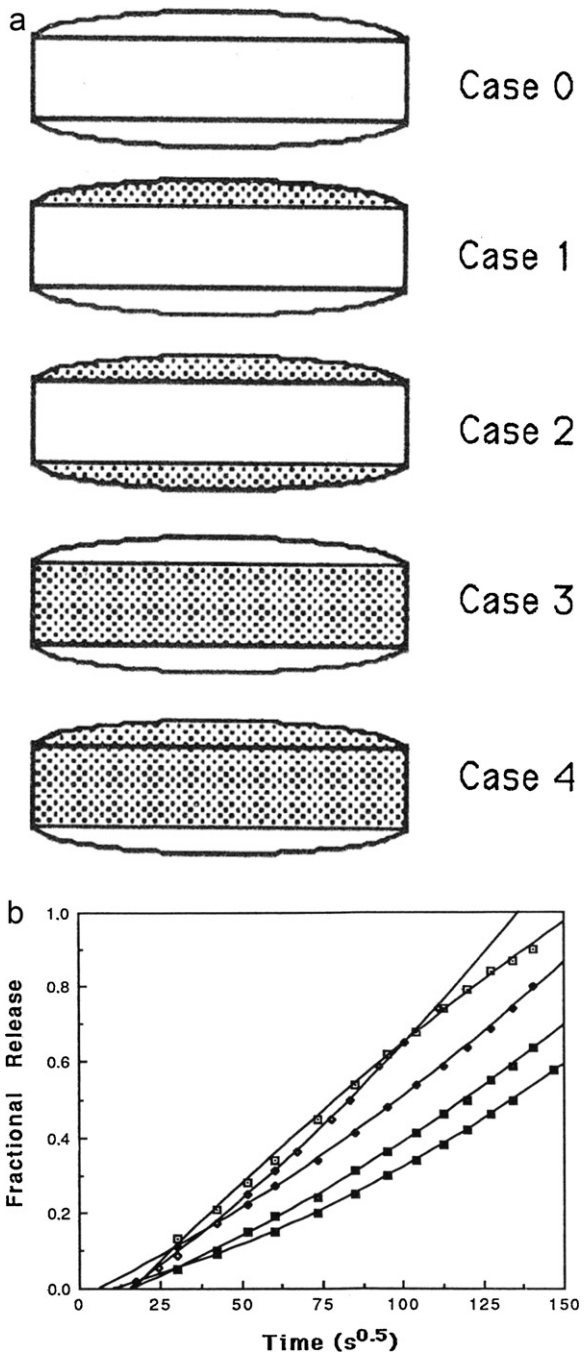

Fig. 4. Drug release behavior cannot always be fitted to Higuchi's law, when various defining conditions are violated. Here the fractional diltiazem release from hydroxypropyl methylcellulose-based tablets is presented versus the square root of release time. The significant swelling of these systems along with the deliberate partial coating of surfaces of the tablet make this system highly unusual for application of Higuchi's law. The open squares with a dot represent drug release from uncoated tablets (case 0), the filled diamonds represent drug release from tablets with one of the bases coated (case 1), the open squares represent drug release from tablets with both bases coated (case 2), the open diamonds represent drug release from tablets with the lateral surface coated (case 3), the filled squares represent drug release from tablets with the lateral surface and one of the bases coated (case 4).
Reprinted with permission from Colombo et al. (1992).

where k_1 and k_2 are constants. A generalized expression can be written as:

$$\frac{M_t}{M_\infty} = kt^n \quad (23)$$

Table 2
Exponent n of the Peppas equation and drug release mechanism from polymeric controlled delivery system for different geometries.

Thin film	Cylinder	Sphere	Drug release mechanism
Exponent, n			
0.5	0.45	0.43	Fickian diffusion
$0.5 < n < 1.0$	$0.45 < n < 0.89$	$0.43 < n < 0.85$	Anomalous transport
1.0	0.89	0.85	Case-II transport

where k is a constant incorporating characteristics of the macromolecular network or particle system that makes up the formulation, and n is the diffusional exponent which is indicative of the transport mechanism. This power law has first been introduced in the pharmaceutical field in 1985 (Peppas, 1985) and has become known as the "Peppas equation". It is valid for the first 60% of the normalized drug release. In the case of thin films with negligible edge effects, Fickian drug diffusion and relaxational drug transport are defined by n equal to l/2 and n equal to 1, respectively. Anomalous drug transport behavior is intermediate between Fickian and Case II; this is reflected by the fact that anomalous behavior is defined by values of n between l/2 and 1. For other geometries, different n-values are indicative for diffusion or polymer relaxation controlled drug release, as shown in Table 2.

In recent years, we have seen an explosion in the preparation and utilization of swellable controlled release systems from simple nasal, buccal and rectal administration applications to more complex bioadhesive uses. Whether in the form of microspheres, discs or the more conventional tablets, such systems have now found applications in various fields. Swellable tablets and related systems continue being of commercial interest. Several recent studies have been reported where the releasing area of these systems has been modified in order to achieve a desirable release rate. Prediction of release rates from such systems requires expressions of the Fickian or non-Fickian penetrant transport by an appropriate equation, and similar expression of the drug diffusion. In both cases, the problem must be solved in a three-dimensional form with appropriate initial and boundary conditions. This requires extensive numerical solutions as shown, for example, by Ritger and Peppas (1987b) or Lustig and Peppas (1989).

6. Conclusions

The classical Higuchi equation had a tremendous impact in the field of advanced drug delivery and still affects the work of numerous research groups all over the world. Takeru Higuchi can be seen as the "father" for a mechanistic understanding of controlled drug delivery systems. His equation allows for a very easy calculation of drug release from a rather complex type of system. However, caution should be paid not to violate any of the conditions, the derivation of this equation is based on.

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