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Research Papers

Diffusion of a dispersed solute in a polymeric matrix

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Summary

A theoretical model for the diffusion study of a molecule in suspension in a continuous medium is presented. This model provides a realistic representation of the release by diffusion of a drug in a polymeric matrix at a concentration C_0 above its solubility C_s in the medium, in the case where the molecule diffuses into the receptor, similar to what occurs with the donor. The release kinetics is a function of $t^{1/2}$. It contains a numerical parameter β which is a function of the ratio C_0/C_s. The table of values of β is given. A variant of the method of analysis is also presented which has the advantage of not requiring knowledge of the solubility of the molecule in the system, which is often hard to measure in practice. In the experimental section, the theoretical models are validated using the diffusion of testosterone in suspension in a silicic acid gel.

Introduction

Controlled delivery of drugs using polymeric matrices has now become widespread (inert matrices for oral administration, implants, ocular systems, bioadhesive systems, transdermal systems, etc. (Chien, 1982; Buri et al., 1985; Langer and Peppas, 1983)). These systems are often characterized by the low solubility of the relevant molecules. The investigation of the properties of these systems for a dispersed solute is thus of considerable interest. There have been numerous descriptions of such release by diffusion into an ideal receptor. The first, Higuchi (1960, 1961) produced a first pseudo-steady-state model, which has afterwards been generalized (Higuchi, 1963). Paul and McSpaden (1976) have given an exact mathematical description of the problem, and an improvement of Higuchi's model has been reported by Lee (1980).

However, these theoretical models only predict the quantities released by such systems if the receptor is one of total elimination (zero concentration and perfect sink conditions). Although such conditions can be set up in vitro, for pharmaceutical systems, the conditions found in vivo are often far from ideal (Touitou and Friedman, 1984; Chien et al., 1975). Frequently, the migration of solute into regions in direct contact with

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the system is itself of a diffusional nature. The diffusion coefficient in the receiving medium may be of the same order of magnitude as the diffusion coefficient in the system, and even comparable in magnitude if the two media are similar (e.g. for implants (Davis, 1974)) or if diffusion takes place via a common solvent (inert matrices (Bamba et al., 1979), bioadhesive systems (Peppas et al., 1984; Illum et al., 1987)). Clearly in such systems, models of release for a perfect sink are not accurate. A model of release into a receiving medium which is initially at zero solute concentration but which has similar diffusional properties to that of the donor system would be more realistic.

In addition, the study of the diffusion alone of suspended solutes in a polymeric matrix is also interesting. On the one hand, controlled release systems are now available in which the drug is concentrated in the centre of the systems (Lee, 1984; Olanoff et al., 1979; Ishida et al., 1982); before its final release from the system, it has to first pass through peripheral zones where its concentration is initially zero. On the other hand, the in vitro optimisation of polymeric matrix systems requires knowledge of the intrinsic interactions between the drug and the matrix; many studies have shown the limitations of experiments on release into a receptor medium in the attempt to obtain a diffusion coefficient that accurately characterizes the matrix/drug interaction alone. This is essentially due to perturbations stemming from the presence of a liquid receptor phase (Petropoulos and Tsimboukis, 1986; Colton et al., 1971). For this case, characterization of the diffusion within the medium is required. For this, analysis of diffusion profiles is accurate, as numerous reports show for dissolved solutes (Muramatsu and Minton, 1988; Zierenberg, 1983).

The present study was designed to provide, in a first part, a theoretical framework for studying the diffusion of a drug in suspension in a continuous medium. This could correspond to an approximate realistic model of in vivo conditions, or an exact model of a technological situation (e.g. a multilayer system), or a model for in vitro characterisation of the diffusion of a molecule dispersed in a polymeric matrix. The second part of the study is devoted to an experimental investigation of diffusion of a dispersed drug in a polymeric matrix, having recourse to the same method that we have used for characterization of diffusion of dissolved solute. The aim of this part is to demonstrate the value of such a method for determination of the diffusion of a drug dispersed in a matrix and to validate the theoretical relationships derived in the first part.

Mathematical model

The theoretical model is designed to characterize the diffusion of a molecule in a continuous medium from a region of initial concentration $C_0 > C_s$ (C_s = the solubility of the solute in the medium) to a region of initially zero solute concentration in a planar geometry. Under these conditions, the concentration of the drug in the medium can be characterized in a single dimension, as illustrated in Fig. 1, where the abscissa refers to the plane of the discontinuity in concentration at time $t = 0$. At time $t > 0$, diffusion takes place into the initially unloaded region ($x > 0$) and into a fraction of the initially loaded region where the concentration comes below the solubility C_s. This is reflected at time t by the backwards movement of the solubility front which is at distance δ from its initial position.

For a dissolved solute in this geometry, the resolution of the Fick's second equation leads to

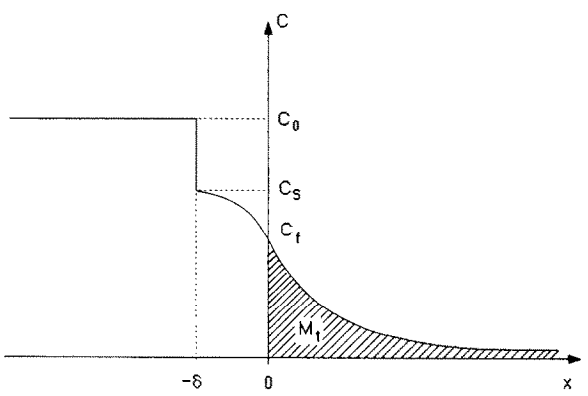

Fig. 1. Concentration profile of the theoretical model at time $t > 0$.

the classical expression for the concentration profile in the general form (Crank, 1975):

$$C(x, t) = k \operatorname{erfc}\left(\frac{x}{2\sqrt{Dt}}\right) \tag{1}$$

where erfc = (1 − error function) and D is the diffusion coefficient in the system. The constant k is determined by the initial conditions. Here it is:

$$k = C_0/2$$

or

$$C(x, t) = \frac{C_0}{2}\operatorname{erfc}\left(\frac{x}{2\sqrt{Dt}}\right) \tag{2}$$

This equation leads to the classical expression for the amount released per unit surface area into the unloaded region for a dissolved solute (Baker and Lonsdale; 1974):

$$M_t = C_0\frac{\sqrt{Dt}}{\sqrt{\pi}} \tag{3}$$

For a solute initially in the dispersed state, Fick's second equation must be integrated in the diffusion region, i.e. where the solute concentration is below C_s, i.e. the range $[-\delta, +\infty]$. This can be compared to the classical case described above providing moving boundary conditions are applied. Thus the solution can be given by Eqn. 1 where the factor k is determined by the moving boundary condition:

$$t > 0 \quad x = -\delta: \quad C(x, t) = C_s \tag{4}$$

This leads to the following expression for the concentration profile in the region $[-\delta, +\infty]$:

$$C(x, t) = C_s\frac{\operatorname{erfc}\left(\frac{x}{2\sqrt{Dt}}\right)}{\operatorname{erfc}\left(\frac{-\delta}{2\sqrt{Dt}}\right)} \tag{5}$$

This solution satisfies the boundary condition (4), and converges to the same boundary expression as Eqn. 2 when $C_0 \to C_s$ ($\delta \to \infty$):

$$C_0 = C_s: \quad C(x, t) = \frac{C_s}{2}\operatorname{erfc}\left(\frac{x}{2\sqrt{Dt}}\right) \tag{6}$$

It should be noted that Eqn. 5 is not an explicit expression of the function $C(x, t)$ since the parameter δ is an implicit function of time. To characterize this time dependency, the solution (5) must verify that the quantity of molecules crossing plane $x = -\delta$ is conserved. The calculation producing the fundamental relationship (7) is given in the appendix:

$$\frac{C_s}{C_0 - C_s} = \frac{1}{C_0/C_s - 1} = \sqrt{\pi}\left(\frac{\delta}{2\sqrt{Dt}}\right)\operatorname{erfc}\left(\frac{-\delta}{2\sqrt{Dt}}\right)\exp\left[\left(\frac{\delta}{2\sqrt{Dt}}\right)^2\right] \tag{7}$$

This transcendent equation fixes the dependence of δ on t and on the ratio C_0/C_s, which thus completely determines the equation for the concentration profile (Eqn. 5). However, the concentration profile is not obtained in a simple way, and only numerical simulation by computer can provide the profile at any time for a given experimental condition (ratio C_0/C_s). For a convenient exploitation of this theoretical analysis, it is better to consider the quantity of solute M_t which has diffused per unit surface area into the unloaded region ($x > 0$). This quantity released by diffusion is the practical parameter which will be used to characterize real systems represented by the model. The flux J across the area of relase ($x = 0$) can be calculated from Eqn. 5. This gives:

$$J = -D\left(\frac{\partial C}{\partial x}\right)_{x=0} = C_s\sqrt{\frac{D}{\pi t}} \cdot \frac{1}{\operatorname{erfc}\left(\frac{-1}{2\sqrt{Dt}}\right)} \tag{8}$$

Summation of the flux from time 0 to t gives the

expression for the quantity M_t. This integration is simple, since in Eqn. 7 the second term is just a function of the parameter $\delta/(2\sqrt{Dt})$ which so only depends on the ratio C_0/C_s and is thus independent of time. This gives:

$$M_t = \frac{2C_s}{\operatorname{erfc}\left(\frac{-\delta}{2\sqrt{Dt}}\right)} \cdot \frac{\sqrt{Dt}}{\sqrt{\pi}} \tag{9}$$

expression which can be written as:

$$M_t = \beta \cdot C_0 \cdot \frac{\sqrt{Dt}}{\sqrt{\pi}} \tag{10}$$

with

$$\beta = \frac{2C_s}{C_0 \operatorname{erfc}\left(\frac{-\delta}{2\sqrt{Dt}}\right)} \tag{11}$$

The coefficient β can be calculated after finding the solution $\delta/2\sqrt{Dt}$ from Eqn. 7.

As mentioned above, the coefficient β is a constant which only depends on the ratio C_0/C_s. The release kinetic (Eqn. 10) is thus a function of $t^{1/2}$. Table 1 lists values of β, which provide a convenient way of obtaining theoretical values for the released quantities from Eqn. 10.

By definition, the coefficient β tends to 1 when C_0 tends towards C_s ($\delta \to \infty$), which from Eqn. 10 gives the classical expression for M_t (Eqn. 3) for a dissolved drug.

Fig. 2 enables comparison of the amount released by diffusion at any time as a function of the initial concentration in the donor region, for both a dissolved and dispersed drug. For $C_0 < C_s$, the released amount is proportional to the concentration in the donor. On the other hand, above saturation, the curve in Fig. 2 flattens and tends towards the boundary value defined by Eqn. 12:

$$C_0 \gg C_s \Rightarrow M_t \simeq 2C_s \frac{\sqrt{Dt}}{\sqrt{\pi}} \tag{12}$$

The coefficient β is required, before the use of the fundamental relationship of this model (Eqn.

TABLE 1

Values of parameter β versus C_0/C_s

$\frac{C_0}{C_s}$	β
1.00	1.000
1.05	0.991
1.10	0.979
1.15	0.965
1.20	0.950
1.25	0.935
1.30	0.919
1.40	0.888
1.45	0.872
1.50	0.857
1.60	0.827
1.70	0.799
1.80	0.771
1.90	0.745
2.00	0.721
2.20	0.676
2.40	0.635
2.60	0.599
2.80	0.567
3.00	0.537
3.50	0.475
4.00	0.426
4.50	0.385
5.00	0.352
5.50	0.324
6.00	0.300
6.50	0.279
7.00	0.261
7.50	0.245
8.00	0.231
9.00	0.207
10.00	0.188

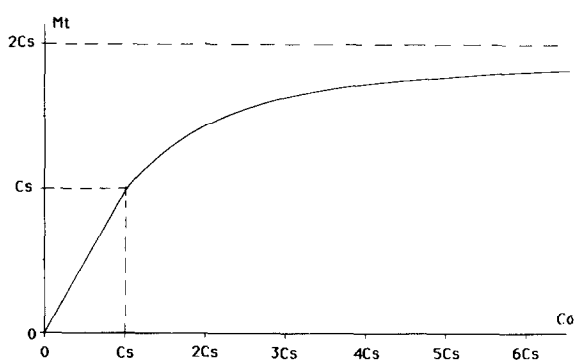

Fig. 2. Amount released by diffusion versus the initial concentration in donor, at time $t > 0$ ($Dt/\pi - 1$).

10). This can be obtained either from Table 1 or by using Eqn. 11 after numerical resolution of Eqn. 7 by computer. In either case, the solubility C_s of the drug in the system must be known. Unfortunately, the exact experimental determination of this parameter in polymeric matrix systems is not easy. In such a case, Eqn. 10 can be modified as follows: As mentioned above, the parameter $\delta/2\sqrt{Dt}$ is a constant, and so Eqn. 5 shows that concentration in $x = 0$ is a constant C_f (cf. Fig. 1) of value:

$$C_f = C_{x=0} = \frac{C_s}{\operatorname{erfc}\left(\frac{-\delta}{2\sqrt{Dt}}\right)} \tag{13}$$

The concentration in the plane initially separating the loaded region from the unloaded region is thus a constant ($C_f < C_s$) which is a characteristic of the system. Using the definition of β, this gives:

$$\beta = 2\frac{C_f}{C_0} \tag{14}$$

and this value inserted in Eqn. 10 gives:

$$M_t = 2C_f\frac{\sqrt{Dt}}{\sqrt{\pi}} \tag{15}$$

Thus when an experimental method enables determination of the characteristic concentration C_f (see Experimental) it is possible to predict the amounts released in a relatively simply way without knowledge of the solubility C_s, in contrast to using Eqns. 10 and 11.

Experimental

The polymeric system tested consists of a silicic acid gel (Aérosil R972, Degussa, Neuilly-sur-Seine, France) at 8 wt.% in propylene glycol dipelargonate (DPPG, Gattefossé, St. Priest, France). The tracer is [^{14}C]testosterone (CEA, Gif-sur-Yvette, France) added to a known quantity of unlabelled testosterone (Sigma Chemical Co., St. Louis, U.S.A.) at a level of 37 kBq/g gel (1 μCi/g). The final testosterone concentration in the gel is 2.0 wt.%. The solubility of testosterone in the gel $C_s = 1.6$ wt.%.

The diffusion cell (Fig. 3) is a hemicylinder (12 cm long, 1.5 cm wide). A 4 cm region in the centre is filled with loaded gel, while the lateral regions are filled with unloaded gel. Three cells of different lengths of the central loaded regions ($2h$ = 4.14, 4.03 and 4.14 cm) are studied. Release by diffusion takes place in each half of the cell with a thickness h of loaded gel.

A radiochromatogram (cf. Fig. 3) is obtained using a multichannel linear ionisation counter providing good spatial resolution (1024 channels over 20 cm) (Berthold, Wildbad, F.R.G.). The ionisation chamber of the counter is placed horizontally along the top side of the test cell. The chromatogram, representing the distribution of β^- activity in the cell, is assumed to represent the state of diffusion of all the testosterone. The analysis data are obtained by computer and automatically corrected for the random and multidirectional emission of the β^- particles. This methodology has been described in a previous publication for the characterization of a non-saturated system (Conrath et al., 1989). After application of the corrections, the chromatogram represents the experimental concentration profile of the testosterone in the cell. The computer program also calculates the area under the concentration profile in the initially unloaded regions. Since this area is propor-

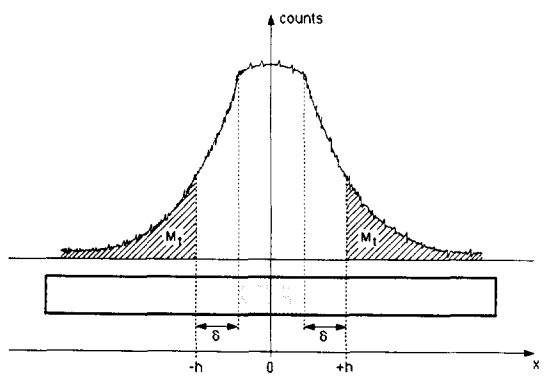

Fig. 3. Scheme of diffusion cell and associated radiochromatogram. Grey zone in cell = region with suspended solute at time $t > 0$; hatched zones in chromatogram = released amounts at time $t > 0$.

tional to the amount released, an interpretation of M_t in relative value is obtained by transformation of Eqn. 10, giving Eqn. 16:

$$\frac{M_t}{M_0} = \beta \cdot \frac{\sqrt{Dt}}{h\sqrt{\pi}} \tag{16}$$

The rate of release at time t (M_t/M_0) is determined from the ratio of the partial area (hatched area in Fig. 3) to the total area under the concentration profile. It should be noted that our cell does not correspond exactly to the infinite geometry of the theoretical model. This is not a limitation provided a central zone with suspended drug is present at all times within the cell ($\delta < h$), since the drug only diffuses into non-saturated regions. It can be shown that the limit of validity under these conditions, in our model of diffusion of suspended solutes, is independent of the thickness $2h$ of the loaded region, and only depends on the ratio C_0/C_s. We have calculated the boundary rates of release beyond which this model is no longer applicable. These values are given in Table 2, which thus determine the experimental conditions for the study.

The following procedure is used: the concentration profiles in the 3 cells are determined at times 0, 9.5, 25, 49, 80, 122, 177, 241 and 321 h, which are compatible with the above-mentioned domain of experimental validity ($M_t/M_0 < 0.35$ for $C_0/C_s = 1.25$; cf. Table 2). The cells are maintained at 34 °C throughout the experiments.

TABLE 2

Boundary rates of release versus C_0/C_s for validity of model

$\frac{C_0}{C_s}$	$(\frac{M_t}{M_0})_{limit}$
1.00	0.000
1.05	0.225
1.10	0.266
1.15	0.299
1.20	0.327
1.25	0.351
1.30	0.374
1.35	0.394
1.40	0.413
1.45	0.430
1.50	0.447
1.60	0.477
1.70	0.503
1.80	0.527
1.90	0.549
2.00	0.568
2.20	0.603
2.40	0.632
2.60	0.657
2.80	0.679
3.00	0.699
3.50	0.738
4.00	0.768
4.50	0.793
5.00	0.812
5.50	0.828
6.00	0.842
6.50	0.853
7.00	0.863
7.50	0.872
8.00	0.880
9.00	0.893
10.00	0.903

Results and Discussion

Table 3 lists the rates of the different times for the three cells. From Eqn. 16, the rates should be a function of $t^{1/2}$. The graphs of M_t/M_0 vs $t^{1/2}$ are plotted in Fig. 4 for the 3 cells, demonstrating the good agreement between the theoretical and experimental findings.

The slope of the linear regression lines of the experimental points is equal to $\beta \cdot (\sqrt{D}/h\sqrt{\pi})$, enabling calculation of the diffusion coefficient. For

TABLE 3

Experimental values of the ratio M_t/M_0

time (h)	cell 1 $2h$ = 4.14 cm	cell 2 $2h$ = 4.03 cm	cell 3 $2h$ = 4.14 cm
0	0	0	0
9.5	0.048	0.059	0.077
25	0.090	0.099	0.104
49	0.122	0.117	0.135
80	0.172	0.154	0.165
122	0.184	0.191	0.197
177	0.223	0.226	0.234
241	0.268	0.259	0.278
321	0.297	0.291	0.296

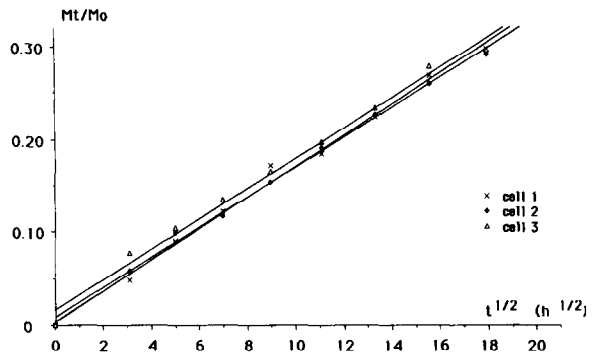

Fig. 4. Amount of testosterone released for the 3 cells versus $t^{1/2}$.

this system, the parameters appearing in Eqn. 11 are:

$$C_0/C_s = 1.25 \Rightarrow \beta = 0.935 \qquad (15)$$

Table 4 summarises the results for the 3 cells, namely the slope of the regression line of the plot of M_t/M_0 vs $t^{1/2}$, the correlation coefficient, and the calculated value of the diffusion coefficient of testosterone in the gel. The small scatter in the values of D provides an indication of the reliability and accuracy of the method.

We have previously reported (Conrath et al., 1989) an interpretation of the concentration profiles in the same system, but with an initial testosterone concentration of 5 mg/g which is below the solubility of this solute in this gel. Using a different theoretical model applicable to the diffusion of dissolved solute, we obtained an average value of diffusion coefficient of 9.8×10^{-7} cm^2/s. A similar value is found in the present study ($D_{ave.} = 1.1 \times 10^{-6}$ cm^2/s) indicating the validity of this interpretation under different conditions. As shown in the theoretical part, an interesting property of the concentration profiles is the existence of a constant concentration C_f at the planes of release. Our experimental set-up which determines radioactivity along the length of the cell, can use this property.

TABLE 4

Diffusion coefficients determined from Eqn. 16 ($\beta = 0.935$)

	$\beta\frac{\sqrt{D}}{h\sqrt{\pi}}$ ($s^{-1/2}$)	r	D (cm^2/s)
cell 1	2.792×10^{-4}	0.996	1.20×10^{-6}
cell 2	2.687×10^{-4}	0.998	1.05×10^{-6}
cell 3	2.715×10^{-4}	0.996	1.14×10^{-6}

TABLE 5

Experimental values of the ratio C_f/C_0

time (h)	cell 1 $2h =$ 4.14 cm	cell 2 $2h =$ 4.03 cm	cell 3 $2h =$ 4.14 cm
9.5	0.433	0.446	0.455
25	0.458	0.458	0.477
49	0.468	0.453	0.487
80	0.498	0.456	0.492
122	0.495	0.468	0.504
177	0.500	0.483	0.478
241	0.493	0.475	0.488
321	0.492	0.472	0.497

Measurement of radioactivity at a single point can only give a relative estimate of the concentration. For that, the values of C_f are expressed relative to the concentration C_0 in the centre of the cell. Eqn. 14 gives:

$$C_0/C_s = 1.25 \Rightarrow C_f/C_0 = \beta/2 = 0.467 \qquad (18)$$

Table 5 shows the average value of the ratio C_f/C_0 measured over the two release interfaces for each cell at different times. At time 0, this value is not determined because the concentration profiles are vertical at the planes of release.

It can be seen that the values of C_f/C_0 are similar, confirming the theoretical prediction that the concentration is constant at the planes of release. However, it should be noted that the values of C_f/C_0 (cf. Table 5) are more scattered at the shorter times, and more comparable at the longer times ($t > 80$ h). This is due to the inaccuracy in the determination of C_f for the first concentration profiles which have a steep slope at these times. The maximum difference between theoretical and experimental values from Eqn. 18 and Table 5 is 7%.

Aside from its theoretical interest, determination of C_f has practical significance, since it en-

TABLE 6

Diffusion coefficients determined from Eqn. 19

	$2\frac{C_f}{C_0}\frac{\sqrt{D}}{h\sqrt{\pi}}$ ($s^{-1/2}$)	$(\frac{C_f}{C_0})_{ave.}$	D (cm^2/s)
cell 1	2.792×10^{-4}	0.496	1.07×10^{-6}
cell 2	2.687×10^{-4}	0.471	1.04×10^{-6}
cell 3	2.715×10^{-4}	0.492	1.02×10^{-6}

ables calculation of the amount released without prior knowledge of the solubility. Eqn. 15 can be transposed into relative values giving Eqn. 19:

$$\frac{M_t}{M_0} = 2 \cdot \frac{C_f}{C_0} \cdot \frac{\sqrt{Dt}}{h\sqrt{\pi}} \tag{19}$$

Table 6 gives the various parameters derived from the plots of M_t/M_0 vs $t^{1/2}$ using Eqn. 19. For each cell, the ratio C_f/C_0 is the average of the most reliable determinations, i.e. those at $t > 80$ h (cf. Table 5). This method appears to be valid since it gives a diffusion coefficient of 1.0×10^{-6} cm^2/s which is close to the reference value of 9.8×10^{-7} cm^2/s obtained for the same drug in solution in the same system. The slight discrepancy with the value obtained by the first method can be attributed to inaccuracy in the determination of the solubility of testosterone in the gel which affects the calculations in the first method.

Conclusion

The model described here enables a complete characterization of the diffusion of a drug in suspension in any continuous medium. In a pharmaceutical range, this would be of value in the study of polymeric matrix systems for the controlled delivery of drugs by diffusion. Under such conditions, the amounts released by the loaded region towards regions that are initially unloaded are expressed as a function of $t^{1/2}$, as for the release into a receptor obeying perfect sink conditions (model of Higuchi, or Paul and McSpaden). However, these kinetics differ by a numerical coefficient β. We have presented a table of values of β which enables the model to be exploited simply. In addition, this model can predict the rate of release for systems in which the drug is initially above its solubility in the medium without knowledge of the solubility of the drug in the medium. This is of particular interest for many polymeric systems where the solubility is often hard to measure. We also presented an experimental validation of the model by determining the concentration profile of a drug (testosterone) in a polymeric gel matrix. This model could also have application to situations outside the diffusional release of molecules of therapeutic interest. For example, such applications include diffusion study of pesticides, contaminations or impurities in the ranges of agricultural, food, pharmaceutical or plastic industry.

Appendix

The solution (5) can be written as:

$$C(x, t) = \gamma(t) \cdot u(x, t) \tag{A1}$$

with

$$\gamma(t) = \frac{1}{\operatorname{erfc}\left(\frac{-\delta}{2\sqrt{Dt}}\right)} \qquad u(x, t) = C_s \operatorname{erfc}\left(\frac{x}{2\sqrt{Dt}}\right) \tag{A2}$$

$C(x, t)$ verifies the Fick's second equation:

$$\frac{\partial C}{\partial t} - D\frac{\partial^2 C}{\partial x^2} = 0 \tag{A3}$$

By taking out the definitions A2, this gives:

$$\gamma(t)\left[\frac{\partial u}{\partial t} - D\frac{\partial^2 u}{\partial x^2}\right] + u(x, t)\frac{\partial \gamma}{\partial t} = 0 \tag{A4}$$

$u(x, t)$ is a fickian function (cf. Eqn. A2), so Eqn. A4 leads to:

$$\frac{\partial \gamma}{\partial t} = 0 \Rightarrow \frac{\delta}{2\sqrt{Dt}} = \text{Constant} \tag{A5}$$

The conservation of the quantity of molecules crossing plane $x = -\delta$ (cf. Fig. 1) for a displacement $d\delta$ of this plane, can be written as:

$$(C_0 - C_s)\frac{d\delta}{dt} = -D\left(\frac{\partial C}{\partial x}\right)_{x=-\delta} \tag{A6}$$

with (cf. Eqn. A5):

$$\frac{d\delta}{dt} = \frac{\delta}{2t} \tag{A7}$$

and (cf. Eqns. A1, A2, A5):

$$\left(\frac{\partial C}{\partial x}\right)_{x=-\delta} = \frac{-C_s}{\sqrt{\pi}\sqrt{Dt}} \frac{\exp\left[-\left(\frac{\delta}{2\sqrt{Dt}}\right)^2\right]}{\operatorname{erfc}\left(\frac{-\delta}{2\sqrt{Dt}}\right)} \tag{A8}$$

These expressions inserted in A6 give:

$$\frac{C_s}{C_0 - C_s} = \frac{1}{C_0/C_s - 1} = \sqrt{\pi}\left(\frac{\delta}{2\sqrt{Dt}}\right) \operatorname{erfc}\left(\frac{-\delta}{2\sqrt{Dt}}\right) \exp\left[\left(\frac{\delta}{2\sqrt{Dt}}\right)^2\right] \tag{A9}$$

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