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A Theoretical Model for the Calculation of the Drug Distribution Profile in Matrices of Different Shape to Achieve the Desired Drug Release Kinetics

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ABSTRACT

The drug release kinetics from a matrix is often affected by the matrix geometry. To compensate for the influence of the matrix geometry on the drug release, a nonhomogeneous drug distribution has been suggested. Keeping in mind this approach, a theoretical mathematical model to calculate the drug distribution profile according to the matrix geometry is proposed. This approach could be useful in achieving the desired drug release kinetics without varying the matrix geometry.

INTRODUCTION

Drug release from an inert matrix occurs owing to the transport of the solvent in the matrix. In fact, the solvent penetration causes the dissolution of the drug, permitting its diffusion in the release medium.

According to the requirement of the therapy a diffusion-controlled or a zero-order controlled drug release matrix could be prepared. But, unfortunately the desired drug release kinetics is often difficult to achieve, depending on the matrix geometry. Several approaches have been proposed to modify the geometrical shape of the matrix in order to obtain the requested drug release kinetics (1-4). To compensate for the effect of the geometrical shape of the matrix on the drug release process, an interesting approach suggested by Lee (5,6) is to realize a nonhomogeneous drug distribution in the matrix.

Based on these premises, this work proposes a mathematical model to calculate the drug distribution profile in the matrix according to the geometrical shape in order to design drug delivery systems with desired drug release kinetics.

MATHEMATICAL MODEL

A few assumptions have to be postulated. It is necessary to suppose that the drug dissolution is not the limiting step of the release process; that is, that the penetration and dissolution fronts are at the same boundary retreat distance. It must also be hypothesised that the different concentrations of the drug in the matrix do not affect the penetration kinetics of the solvent.

Regardless to the matrix geometry, the power law expression allows the calculation of the kinetics of the penetrant front (7). The power law expression can be written as follows:

$$s = s_\infty t^{n'} \tag{1}$$

where $0 \le t \le 1$, n' is the kinetic exponent of the penetrant front, and s and s_∞ are the thickness of the matrix penetrated (penetration path length) at time t and at the time approaching the infinity, respectively. Considering the penetration path length along all the dimensions of the matrix, the volume of the penetrated matrix at the time t (V_t/V_∞) is given by an expression having a cubic form:

$$V_t/V_\infty = G_1 t^{n'} + G_2 t^{2n'} + G_3 t^{3n'} = \sum_1^3 {}_i G_i t^{in'} \tag{2}$$

where G_1 and G_2, and G_3 are geometrical parameters depending on the matrix shape.

Equation (2) can be considered as the generalized form of the one proposed by Cobby et al. (8). These authors derived their equation from the Higuchi law (square root law) (9).

If the volume of the penetrated matrix is related to the penetration path length (s), instead of the time t Eq. (4) can be rewritten as follows:

$$V_s/V_\infty = \sum_1^3 {}_i G_i (s/s_\infty)^{in'} \tag{2a}$$

where

$$\sum_1^3 {}_i G_i = 1$$

as, obviously, $V_t/V_\infty = 1$ for $s = s_\infty = 1$ ($t = t_\infty = 1$).

On the basis of the power law expression (10,11) proposed for the study of the drug release process:

$$M_t = M_\infty t^n \tag{3}$$

where M_t is the mass of the drug released at time t, M_∞ is the mass released at the time approaching the infinite time, and n the kinetic exponent of the drug release, the concentration distribution of the drug required to achieve the desired release kinetics could be calculated according to the matrix geometry. In fact, as:

$$M_t = \bar{\rho}_t V_t \tag{4}$$

where $\bar{\rho}_t$ is the mean drug concentration in the volume of the matrix penetrated at the time t, obviously:

$$\bar{\rho}_t = M_t/V_t \tag{5}$$

Substituting from Eqs. (1) and (3) into Eq. (5) gives:

$$\bar{\rho}_t = M_\infty t^n / V_\infty \sum_1^3 {}_i G_i t^{in'} = \rho_m t^n / \sum_1^3 {}_i G_i t^{in'} \tag{5a}$$

defining $\rho_m = M_\infty/V_\infty$ the mean drug concentration in the volume of the matrix penetrated at the time t approaching the infinity, that is, the drug concentration in the matrix.

Considering the penetration path length s instead of the time t, this equation can be written as follows:

$$\bar{\rho}_s = \rho_m (s/s_\infty)^{n/n'} / \sum_1^3 {}_i G_i (s/s_\infty)^i \tag{6a}$$

For each volume of the matrix penetrated dV_s, corresponding to each penetration path length ds:

$$\bar{\rho}_s = \int_0^s \rho_s dV_s / \int_0^s dV_s = \left(\int_0^s (\rho_s dV_s)/V_s \right) \tag{6b}$$

where ρ_s is the drug concentration at the distance s from the matrix surface. Hence:

$$\int_0^s \rho_s dV_s = \bar{\rho}_s V_s \tag{7}$$

from which ρ_s results:

$$\rho_s = (d\bar{\rho}_s/ds)\,[V_s/(dV_s/ds)] + \bar{\rho}_s \tag{8}$$

and

$$d\bar{\rho}_s/ds = (\bar{\rho}_s/s_\infty) \left[\sum_1^3 {}_i (n/n' - i) G_i (s/s_\infty)^{i-1} \right] / \sum_1^3 {}_i G_i (s/s_\infty)^i$$

Hence:

$$\rho_s/\rho_m = \left[(s/s_\infty)^{n/n'} / \sum_1^3 {}_i G_i (s/s_\infty)^i\right] \left\{\left[\sum_1^3 {}_i (n/n' - i) G_i (s/s_\infty)^{i-1} / \sum_1^3 {}_i i G_i (s/s_\infty)^{i-1}\right] + 1\right\} \quad (9)$$

where ρ_s/ρ_m is the ratio between the drug concentration at the distance s from the matrix surface and the mean drug concentration in the matrix.

The value of the geometrical parameters G_1, G_2, and G_3 can be calculated from Eq. (2) according to the matrix shape. The value of the kinetic exponent of the penetrant transport (n') can be experimentally measured (12). Therefore, applying Eq. (9) it is possible to calculate the drug concentration distribution profiles in the matrix for desired release kinetic exponent (n).

According to Eq. (9) the drug concentration depends on the ratio n/n'. At the matrix surface ($s = 0$) three cases can be obtained:

$$n/n' < 1.0 \qquad (\rho_s/\rho_m)_{s=0} \to \infty$$

$$n/n' = 1.0 \qquad (\rho_s/\rho_m)_{s=0} = 1/G_1$$

$$n/n' > 1.0 \qquad (\rho_s/\rho_m)_{s=0} = 0$$

and in the matrix core ($s = 1.0$):

$$(\rho_s/\rho_m)_{s=s_\infty} = (n/n')/\sum_1^3 {}_i i G_i$$

when

$$\sum_1^3 {}_i i G_i \neq 0$$

SOLUUTION OF THE MATHEMATICAL MODEL FOR VARIOUS MATRIX GEOMETRY

Cylindrical Matrix

In a cylindrical matrix of arbitrary aspect ratio a ($a = h/2r$), the solvent penetration takes place both in the radial direction from the lateral surface and in the axial direction from the bases. The corresponding kinetic exponents of the penetrant transport (n'_r and n'_a) and the penetration rate along the radial and axial directions could be the same or different.

Same Rate and Kinetics of Penetration Along the Axial and Radial Directions

If the solvent penetration in a cylindrical matrix occurs at both the same rate and kinetics from the lateral surface and from the bases, the penetration path length (s) and time t would be the same in the radial (s_r) and the axial (s_a) direction. Considering the matrix cross section, the vertices of the theoretical nonpenetrated cylinder formed during the penetration process are along a straight line having an angle $\alpha = 45°$ with the cylinder bases (Fig. 1). Below we define as "trajectory" the path followed by the vertices of the nonpenetrated cylinder in the time. The volume dV penetrated for each increase of the penetration path length ds can be described by the equation:

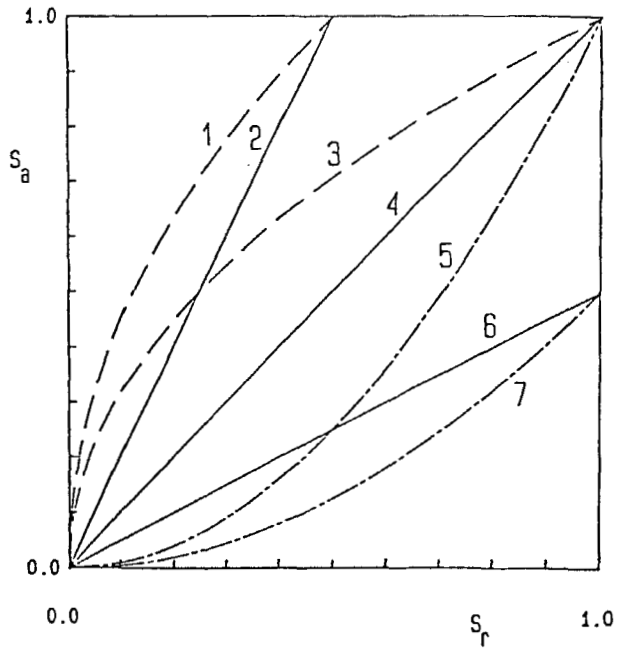

Figure 1. Propagation lines of the vertices of the nonpenetrated fraction of cylindrical matrices according to the penetration rate and kinetics. Key: 1, $n'_r/n'_a = 2.0$ and $s_{r\infty}/s_{a\infty} = 0.5$; 2, $n'_r/n'_a = 1.0$ and $s_{r\infty}/s_{a\infty} = 0.5$; 3, $n'_r/n'_a = 2.0$ and $s_{r\infty}/s_{a\infty} = 1.0$; 4, $n'_r/n'_a = 1.0$ and $s_{r\infty}/s_{a\infty} = 1.0$; 5, $n'_r/n'_a = 0.5$ and $s_{r\infty}/s_{a\infty} = 1.0$; 6, $n'_r/n'_a = 1.0$ and $s_{r\infty}/s_{a\infty} = 2.0$; 7, $n'_r/n'_a = 0.5$ and $s_{r\infty}/s_{a\infty} = 2.0$.

$$dV = 2\pi\,(r - s)\,(h + r - 3s)\,ds$$

which upon integration yields the solution of Eq. (2):

$$V_t/V_\infty = (2s_\infty/r + 2s_\infty/h)t^n - (4s_\infty^2/rh + 2s_\infty^2/r^2)t^{2n} + 2s_\infty^3/r^2h)t^{3n} = \sum_1^3 {}_i G_i t^{in'}$$

The values of the geometrical parameters G according to the aspect ratio (a) of the cylinder are reported in Table 1.

Figures 2 and 3 show the theoretical drug concentration distribution profiles calculated from Eq. (9) for different n/n' ratios.

Different Rates and Kinetics of Penetration Along the Axial and the Radial Directions

In a matrix cross section, the penetration process towards the matrix core can have two theoretical behaviors (Fig. 1).

The kinetic exponent of the radial penetration (n'_r) could be different from the kinetic exponent of the axial penetration (n'_a). Therefore, the "trajectories" are not linear. However, it is reasonable to presume that the penetration kinetics are the same in both directions.

Whenever the values of the radial and the axial kinetic exponents are the same ($n'_r = n'_a$), the "trajectories" follow a linear path, forming an angle $\alpha = \text{arctg}(s_{a\infty}/s_{r\infty}) \neq 45°$ with the bases of the matrix, since of course, $sa_\infty \neq sr_\infty$.

It has to be noted that $a/tg\alpha = a$ when $\alpha = 45°$ as $tg\ 45° = 1$. Therefore, the G values are the same as previously reported, but substituting a with $a/tg\alpha$ (Table 2).

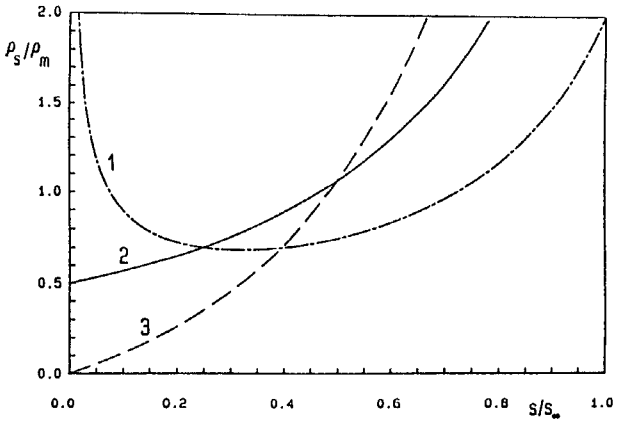

Figure 2. Distribution concentration profiles in cylinders according to the n/n' ratio (a or $a/tg\alpha = 0.5$). Key: 1, $n/n' = 0.5$; 2, $n/n' = 1.0$; 3, $n/n' = 2.0$.

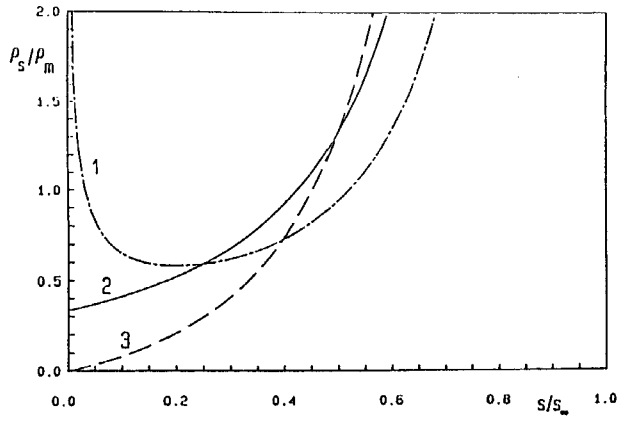

Figure 3. Distribution concentration profiles in cylinders according to the n/n' ratio (a or $a/tg\alpha = 1.0$). Key: 1, $n/n' = 0.5$; (spheres) 2, $n/n' = 1.0$; 3, $n/n' = 2.0$.

Table 1

Values of the Geometrical Parameters G for Cylinders According to the Aspect Ratio (a) for the Same Rate and Kinetics of Penetration Along the Axial and the Radial Directions

	$a < 1.0$	$a > 1.0$	$a = 1.0$	$a \to \infty$ (Rod)	$a = 0$ (Flat Disk)
G_1	$2a + 1$	$2 + (1/a)$	3	2	1
G_2	$-(2a + a^2)$	$-(2/a) - 1$	-3	-1	0
G_3	a^2	$1/a$	1	0	0

Table 2

Values of the Geometrical Parameters G for Cylinders According to the Aspect Ratio (a) for Different Rates of Penetration Along the Axial and the Radial Directions

	$a < tg\alpha$	$a > tg\alpha$	$a = tg\alpha$	$a \to \infty$	$a = 0$
G_1	$(2a/tg\alpha) + 1$	$2 + (tg\alpha/a)$	3	2	1
G_2	$-(2a/tg\alpha) - (a^2/tg^2\alpha)$	$-(2tg\alpha/a) - 1$	-3	-1	0
G_3	$a^2/tg^2\alpha$	$tg\alpha/a$	1	0	0

Figures 2 and 3 report the theoretical drug concentration distribution profiles obtained from Eq. (9) for cylinders for which $a/tg\alpha = 0.5$ and $a/tg\alpha = 1.0$, respectively.

Spherical Matrix

The volume dV penetrated in a spherical matrix can be derived from:

$$dV = 4\pi(r^2 - s)ds$$

which upon integration gives:

$$V_t/V_\infty = 3t^n - 3t^{2n} + t^{3n} = \sum_1^3 {}_i i G_i t^{in'}$$

Therefore, the geometrical parameters (G) (Table 1) and the concentration profiles of the drug (Fig. 3) are the same as those calculated for cylinders of aspect ratio $a = 1.0$.

CONCLUSION

The proposed mathematical model allows calculation of drug concentration distribution profiles to achieve appropriate release kinetics of drugs from different-shaped matrix geometries. Although further experimental tests are certainly necessary, it can be concluded that the application of the proposed model would be useful in overcoming the influence of the geometrical shape on the release process.

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REFERENCES

1. J. P. Cleave, J. Pharm. Pharmacol., 17, 698 (1965).
2. D. S. T. Hsieh, W. D. Rhine, and R. Langer, J. Pharm. Sci., 72, 17 (1983).
3. S. Béchard and J. N. McMullen, J. Pharm. Sci., 77, 222 (1988).
4. J.-P. Hsu, C. Ting, and M.-J. Lin, J. Pharm. Sci., 81, 866 (1992).
5. P. I. Lee, Polymer, 25, 973 (1984).
6. P. I. Lee, J. Pharm. Sci., 73, 1344 (1984).
7. S. Ségot-Chicq and N. A. Peppas, J. Controlled Release, 3, 193 (1986).
8. J. Cobby, M. Mayersohn, and G. C. Walker, J. Pharm. Sci., 63, 725 (1974).
9. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).
10. P. L. Ritger and N. A. Peppas, J. Controlled Release, 5, 23 (1987).
11. P. L. Ritger and N. A. Peppas, J. Controlled Release, 5, 37 (1987).
12. F. Carli, I. Colombo, L. Simioni, and R. Bianchini, J. Pharm. Pharmacol., 33, 129 (1981).