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THEORETICAL RATIONALE FOR DRUG RELEASE FROM NON-IDEALISED, PLANAR, PERFORATED LAMINATES

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ABSTRACT

Methods of achieving the ideal of zero-order drug release kinetics are discussed with particular reference to the "multiple-hole approach". When considering this approach, certain assumptions are made concerning device geometry which may not hold in practice due to manufacturing procedures. The resultant non-conformity of device geometry requires modification of previously described equations of drug release from multiple hole devices. In this paper, a theoretical rationale for drug release from a non-idealised planar matrix surface exposed through multiple holes in an impermeable laminate is derived from first principles.

INTRODUCTION

Diffusion controlled matrices have been amongst the most widely used drug delivery systems for prolonged release, but a

common disadvantage is their inability to achieve the ideal of zero-order drug release kinetics[1,2]. Most matrix devices have been designed in the form of a rectangular slab where it has been observed that the cumulative amount of drug released, *in vitro* and *in vivo*, is proportional to the square root of time[3-7].

Laminating a rate controlling membrane to the releasing face of a matrix, where the membrane is less permeable to the drug than the matrix, provides the means of achieving zero-order drug release. Employing rate controlling membranes to achieve zero-order release kinetics requires the choice of a suitable membrane dependent on the solubility and diffusion coefficient of the drug in the membrane. Therefore, a specific membrane may be required for each different drug to be incorporated into the system.

An alternative method of controlling release kinetics from matrix systems is to change the matrix geometry. Although some geometries, in particular hemispherical geometries[8], can provide zero-order release kinetics, a special shape may be required which could be unsuitable depending on the end-use application of the system.

Kuu and Yalkowsky proposed a rationale for obtaining constant drug release by laminating an impermeable membrane, with multiple circular perforations at specific separation, onto a matrix slab[9]. The membrane was assumed to be impermeable to drug and so drug is released only through the holes.

The rate and duration of drug release can easily be modified by a simple alteration of hole size and spacial distribution, hole

configuration and hole number[9]. A general equation describes release:

$$J = 2N\pi DaC_s \qquad \text{equation 1}$$

where J is the diffusion rate, N is the total number of holes on the device, D is the diffusion coefficient of the drug in the matrix, a is the hole diameter (where $a = 2a_i$) and C_s is the solubility of the drug in the matrix. Therefore, the "multiple-hole approach" to obtaining zero-order release offers a greater degree of flexibility in the selection of a matrix material in that the rate and duration of drug release can be altered by easy adjustment of hole size and density. In addition, it allows for the release of macromolecules which will not pass through conventional rate controlling membranes.

However, the "multiple-hole approach" assumes that hemispherical holes are made into the polymer matrix[9]. In practice, the fabrication of laminates comprising an impermeable membrane perforated with regularly spaced holes which are continuous with planar holes in the membrane (as opposed to hemispherical holes) is anticipated. Consequently, such a modification of device geometry requires modification of the equation which describes drug release. In this work we have developed a theoretical equation for drug release from a planar matrix surface exposed through multiple holes in an impermeable laminate.

Theoretical - Development of the modified release equation.

A general expression describes the release of drug from inert matrices:

$$\frac{dQ}{dt} = \frac{DAdc}{dh} \qquad \text{equation 2}$$

where Q is the mass of drug being transferred, t is time, c is the drug concentration, D is the diffusion coefficient of the drug and A is the total cross-sectional area of the diffusion path at distance h, where h is the distance from the diffusion source to the release surface. Integrating equation 2 to give the diffusion rate yields:

$$\frac{dQ}{dt} = \frac{\Delta(C_s - C_a)}{\int_{h_o}^{H} \frac{dh}{A}} \qquad \text{equation 3}$$

where h_o is the initial boundary, C_s is the drug concentration at the dissolution surface, C_a is the drug concentration at the initial boundary and H is the distance to the receding boundary. Therefore, it is apparent that the diffusion rate is dependent upon the diffusion time, t, and, assuming that the initial drug concentration is much higher than the drug solubility, then:

$$J = \frac{dM}{dt} \qquad \text{equation 4}$$

where J is the diffusion rate and M is the total mass of drug dissolved in the diffusional path at anytime. Since the diffusion of the drug through the matrix is the rate controlling step, the concentration of the drug in the matrix at h=o is negligible. Therefore, substituting h_o=o and C_a=o into equation 3 and integrating gives equation 5 where the diffusion rate is shown to be inversely proportional to H:

$$J = \frac{ADC_s}{H} \qquad \text{equation 5}$$

where A is the surface area of the releasing face. Here we assume that the drug concentration in the dissolution medium is initially zero and that the partition coefficient of the drug between the dissolution medium and the matrix is unity.

The value of H is obtained from equations 3, 4 and 5 by substituting V into equation 6:

$$M = V\rho \qquad \text{equation 6}$$

where V is the volume of the matrix in the diffusion region (equal to AH) and ρ is the weight of drug per unit volume of matrix. The value of H, therefore, is given by:

$$H = \left(\frac{2DC_s t}{\rho}\right)^{\frac{1}{2}} \qquad \text{equation 7}$$

The diffusion rate is then described by:

$$J = A\left(\frac{DC_s\rho}{2t}\right)^{\frac{1}{2}} \qquad \text{equation 8}$$

Equation 8 shows that the diffusion rate is inversely proportional to the square-root of time. Equation 8 can be compared with the one-dimensional model of Higuchi[3,4].

Having established the relationship between the distance to the receding boundary, H, and time, t (equation 7) it is possible to derive an equation which will describe drug release from a planar matrix surface exposed through multiple holes in an impermeable laminate. The releasing face will always be planar so, initially, release will follow square-root of time dependent kinetics. As the front of drug dissolution recedes into the polymer matrix, the presence of the impermeable membrane

surrounding each hole will influence the drug diffusion path. Figure 1 shows a schematic description of drug dissolution and release. The figure depicts the fronts of drug dissolution developing as a series of segments of circles of changing radius. On a three-dimensional scale, this becomes a series of segments of spheres of changing radius, r. From simple trigonometry, the area, A, of the segment of a sphere is described by the following relationship:

$$A = 2\pi rH \qquad \text{equation 9}$$

where r is the radius of the sphere and H is the height of the segment. Equation 9, therefore, enables a calculation to be made of the total surface area of each releasing face. The radius of each sphere is given by the equation:

$$r = \left(\frac{a^2 + 4H^2}{8H}\right) \qquad \text{equation 10}$$

where a is the length of the cord which cuts each segment (Figure 1) and which is calculated from the equation:

$$a = 2(a_i + H) \qquad \text{equation 11}$$

(where a_i is the radius of the hole). Therefore, the area of the segment of a sphere is given by the following equation:

$$A = 2\pi(\tfrac{1}{2}a_i^2 + a_iH + H^2) \qquad \text{equation 12}$$

H represents the height of the segment and, therefore, the distance to the receding boundary. The relationship between H and t has previously been determined (equation 7). Therefore, the total surface area available for release from a planar matrix

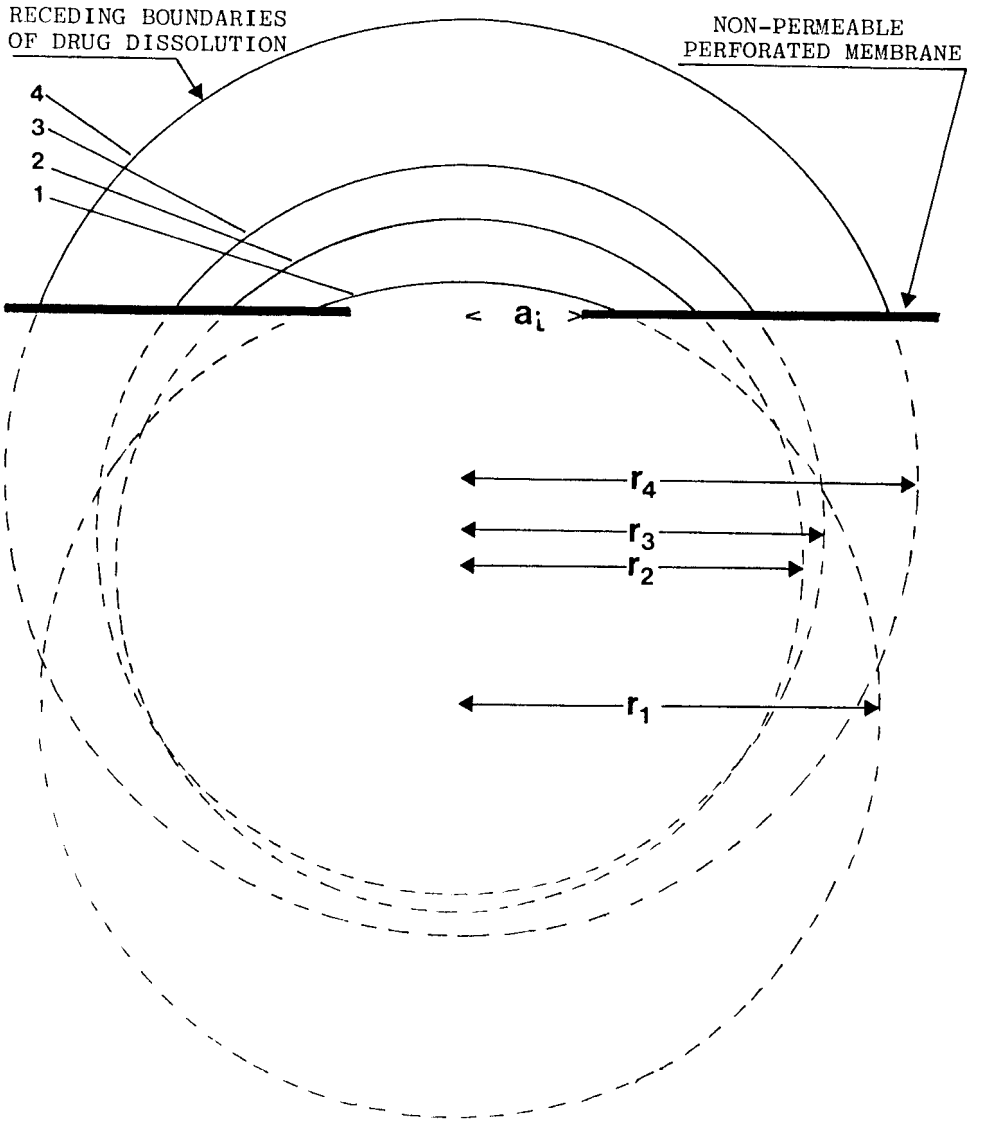

FIGURE 1

Schematic description of the formation of receding boundaries of drug dissolution from a planar hole.

exposed through a single hole in an impermeable laminate increases as a function of time according to the relationship:

$$A = 2\pi \left[\tfrac{1}{2}a_i^2 + a_i \left(\frac{2DC_s t}{\rho}\right)^{\frac{1}{2}} + \left(\frac{2DC_s t}{\rho}\right) \right] \qquad \text{equation 13}$$

From the Higuchi one-dimensional release model[3,4], release from a slab follows square-root of time dependent kinetics where the diffusion rate is inversely proportional to the square-root of time (equation 8). Substituting equation 13 into equation 8 gives:

$$J = \tfrac{1}{2}\pi a_i^2 (2DC_s)^{\frac{1}{2}} \rho^{\frac{1}{2}} t^{-\frac{1}{2}} + \pi a_i (2DC_s) + \pi (2DC_s)^{3/2} \rho^{-\frac{1}{2}} t^{\frac{1}{2}} \qquad \text{equation 14}$$

Integrating equation 14 gives the amount of drug release from a planar matrix exposed through a single hole in an impermeable laminate after time, t:

$$Q = \pi a_i^2 (2DC_s)^{\frac{1}{2}} \rho^{\frac{1}{2}} t^{\frac{1}{2}} + \pi a_i (2DC_s) t + {}^2/_3\pi (2DC_s)^{3/2} \rho^{-\frac{1}{2}} t^{3/2} \qquad \text{equation 15}$$

The amount of drug released through multiple holes after time, t, is described by:

$$Q_t = NQ \qquad \text{equation 16}$$

where N is the number of holes on the device. Thus the release of

drug from multiple-planar holes is predicted by a three parameter release model.

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