Slow Dissolution of Implanted Beds of Spherical Particles as a Method for Prolonged-Release Medication

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There are many types of human ailments which do not involve serious immobilization of the individual but which do require long-term, fairly uniform administration of medicine. In such cases, oral ingestion of medication on a routine basis is normally prescribed. Another possibility is the implantation into the body of some type of cartridge of medicine in solid or encapsulated form, with the formulation providing for a slow and reasonably uniform dissolution and transfer of the medicine to the body over a period of time. Various types of prolonged release dosage forms have been proposed in the past. However, most of these attempt to extend the period of medication from a few hours to perhaps a day or two.

We are concerned here with much longer term devices which would release medication over durations ranging from a few weeks to months. For such durations, semipermanent implants consisting of single particles or of multiparticle cartridges might be used. Implantation could be made into suitable body tissues or into some fluid-filled channel (e.g., arteries, veins, etc.). For implants placed into tissue, diffusion of the medication through the tissue largely determines the overall medication rate. Diffusion-limited cases such as these have been considered several times in the pharmacological literature.

PURPOSE OF STUDY

The present analysis will be devoted solely to implants connected into fluid streams, where interfacial solubility of the medication plays the determining role in the overall transfer process. Specifically considered will be systems such as a small cylindrical cartridge connected into an artery or vein or into an arterio-venous shunt. The primary advantages of long-lived implanted cartridges over oral medication would be the much greater uniformity of administration with respect to time and the fact that the patient would not be required to remember and regulate his program of medication. Some of the obvious disadvantages include the necessity of cannulation and possible clot formation in such a device. The purpose of this paper is, however, not to debate these points but primarily to present an analysis of such devices and their operation.

We will assume that our system consists of a bed of spherical particles of compounded medicine contained in a cartridge through which blood is coursing in laminar flow. These particles are assumed to be dissolving slowly into the blood. The main objective of our analysis will be to determine how the dissolution rate can be maintained as nearly constant in time as possible. The rate of dissolution of any species i from a spherical surface may be written (*1*) as

$$W_i - X_{i0} \sum_{j=1}^{n} W_j = k_{xmi}\,(\pi d_p^2)\,(X_{i0} - X_{i\infty}) \qquad (1)$$

where n is the total number of species in the system.

The slowly dissolving spheres of compounded medicine are regarded as consisting of two components, the medicinal component A and the inert carrier B. We then write Equation (1) for each component on a pseudo steady state basis, neglecting counterdiffusion of plasma toward the surface of the spheres, and eliminate W_B between the two resulting equations. This gives, for the dissolution rate W_A of the active component

$$W_A\left[1 - \frac{X_{A0}\,X_{B0}}{(1 - X_{A0})(1 - X_{B0})}\right] = k_{xmA}\,(\pi d_p^2)\,\frac{(X_{A0} - X_{A\infty})}{(1 - X_{A0})} + \frac{k_{xmB}\,(\pi d_p^2)\,(X_{B0} - X_{B\infty})\,X_{A0}}{(1 - X_{A0})(1 - X_{B0})} \qquad (2)$$

For cases of practical interest, the equilibrium interfacial solubilities will have to be quite low, otherwise the life of the implanted cartridge would be impractically short. With X_{A0} and X_{B0} small, Equation (2) reduces to

$$W_A \cong k_{xmA}\,(\pi d_p^2)\,(X_{A0} - X_{A\infty})/(1 - X_{A0}) \qquad (3)$$

For packed beds, k_{xm} may be estimated from the correlation (*4*) as

$$k_{xm}/cv = 0.84\,Re^{-0.5}\,Sc^{-2/3} \qquad (4)$$

for $0.01 < Re < 50$. From the definition of the Reynolds number, $Re = [\epsilon v \rho d_p/6\,(1 - \epsilon)\mu]$, and from systemic circulation flow data available in standard physiology texts (*3*), it is easy to prove that this correlation must apply to any practical choices of implantation sites and sphere sizes. For constant physical properties, flow velocity, and total molar concentration, this correlation, when inserted into Equation (3), gives

$$W_A \cong K\,d_p^{3/2}\,(X_{A0} - X_{A\infty})/(1 - X_{A0}) \qquad (5)$$

It should be mentioned that $X_{A\infty}$ will normally be nearly zero because transfer of medication from the blood to the rest of the body and its subsequent metabolization will keep the concentration of medication in the blood at very low levels. This result states that the dissolution rate will progressively decrease as the particles dissolve and become smaller. Clearly, this behavior goes against the objective of achieving a uniform medication rate.

MEDICINE COMPOUNDED ON AN INERT CORE

One way of attaining a reasonably uniform medication rate would be to use the cartridge for only a limited period of time during which the change in particle diameter (and thus the dissolution rate) would be small. Since the cartridge would be discarded after use, it would be economical to make the discardable "cores" out of an inert material, i.e., with no medicine compounded into it. The original particles would thus consist of inert cores surrounded by "shells" of compounded medicine.

Figure 1 shows the net decrease in dissolution rate that would be experienced during a change in particle diameter from the original diameter down to the inert core diameter. Also shown is the amount of mass of the usable shell relative to the total original particle mass. For example, if a 15% decrease in medication rate can be accepted as tolerable, 27.5% of the mass of the particle will be usable for medication. It thus appears that the "shell and core" configuration might not be too inefficient.

Some consideration should be given to the possibility of using a cylindrical or flat-plate (or disk) geometry for the medication, as the surface areas of these types change less rapidly with dissolution than do spheres. In particular, it is clear that flat disks might be quite desirable, for their near constancy of surface area during dissolution is obvious.

USE OF ENCAPSULATED LIQUIDS AS MEDICATION

There are certainly many medicines which either have to be, or are most easily, formulated in liquid form. The present type of system can be used for liquids by employing the microencapsulation techniques developed by Chang (2) and others. Membranes of controllable porosity and thickness are polymerized around beads of the liquid previously dispersed in another insoluble liquid. Pure liquids, slurries, and dissolved enzymes are a few of the many formulations encapsulated to date.

For systems consisting of medicines encapsulated in 100% liquid form, the equations describing the dissolution process are the same as before except that no terms $(1 - X_{i0})$ appear; in liquid systems counterdiffusion of solvent on roughly an equimolal basis occurs. Note, however, that in liquid systems d_p will remain constant, for the polymer shell will remain relatively rigid, and so

$$W_A \cong K' X_{A0} \qquad (6)$$

will characterize the system for low $X_{A\infty}$ values.

As mass transfer occurs, X_{A0} will (unlike in the solid case) decrease steadily with time. Thus, if a cartridge of microcapsules is allowed to remain until a 15% decrease in rate has been reached, only 15% of the original compounded medicine in the microcapsules can be utilized. From this standpoint, the formulation of medicine in solid form is seen to be preferred over liquid formulation.

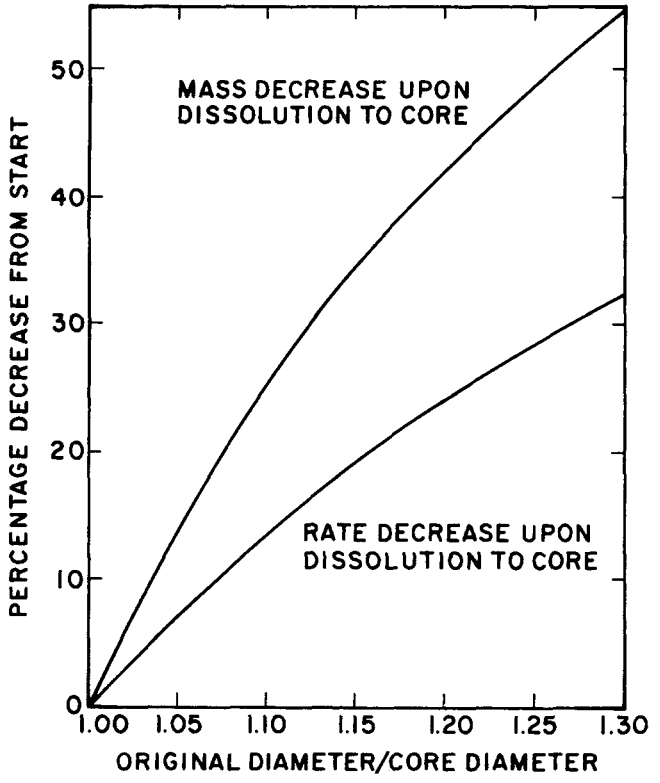

Fig. 1. Dissolution rate and mass loss for dissolving sphere.

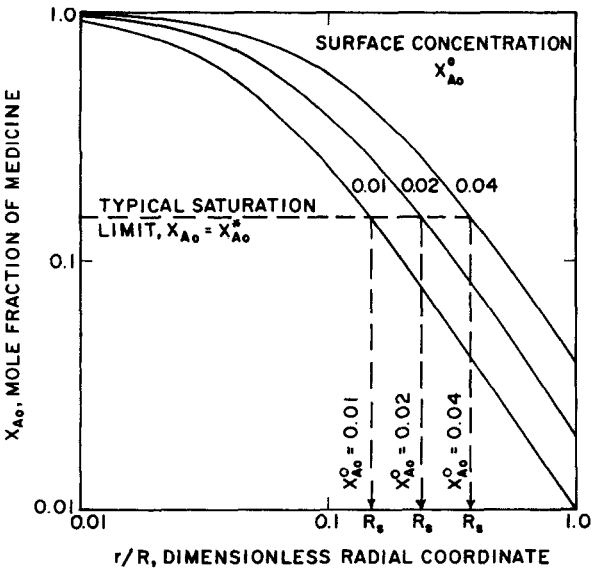

Fig. 2. Concentration versus sphere radius for constant rate of dissolution.

SOLID SPHERES WITH VARIABLE MEDICINE CONCENTRATION

From Equation (5) it may be deduced that one way to counteract the tendency of the solid dissolution rate to decrease with time would be to increase the surface concentration X_{A0} with time. That is, if $[X_{A0}/(1 - X_{A0})]$ could be made proportional to $d_p^{-3/2}$ (i.e., increase with a decrease in diameter), then W_A could be made constant and independent of d_p. Figure 2 shows how the concentration X_{A0} would have to vary as a function of particle radius in order to achieve this behavior. It should be noted that the original surface concentration X^0_{A0} is a parameter here. Because the mathematics indicate an infinite concentration at zero radius and because X_{A0} can be no larger than the value corresponding to the saturation solubility of A, X^*_{A0}, in the plasma at the prevailing temperature, then the cartridge would have to be removed when the radius R_s corresponding to $X_{A0} = X^*_{A0}$ is reached, for at this point the dissolution rate would begin to fall off.

The fabrication of such variable-concentration beads will not be discussed here. However, it is clear that, as the transfer rate for each particle will be the same and will be time-invariant, the dosage can be regulated by setting the number of particles contained in the cartridge; i.e., the number of particles would be equal to the desired dosage rate divided by the rate per particle. The longevity of the cartridge can be fixed by varying the initial size of the particles in the cartridge.

INERT ENCLOSING A MEDICINAL CORE

Another very different possibility for regular long-term administration of medication would be to coat active cores of fairly soluble medicine with outer shells of low solubility inert. During contact with flowing blood, the outer shell of a particle would slowly dissolve to nothingness, and the contained medicine would then be released as a small "dose" into the blood.

By varying the thickness of the inert shell, it is possible to vary the length of time that must lapse before the medicine is released. By providing a proper distribution of shell thicknesses it is therefore feasible to yield a fairly uniform sequence of release times. Obviously, a succession of small concentrated doses is not the same as continuous constant-rate dissolution of low concentration material,

but, in the limit of large numbers of particles and low dosage per particle, the effects are the same. This approach would seem to be desirable especially for highly soluble medications. Formulations based on this principle presently exist in crude form; however, quantitative analyses of their design and operation have not been reported.

The required distribution of inert shell thicknesses for a uniform pattern of release times may be easily determined. Because the rate of decrease of particle mass may be equated to the rate of mass transfer to the surrounding fluid, then

$$-d(4\pi r^3/3)/dt \cong k_{xmA}\,(4\pi r^2)\,(X_{A0} - X_{A\infty})/(1 - X_{A0}) \tag{7}$$

For constant X_{A0}, and k_{xm} proportional to $r^{-1/2}$

$$dr^3/dt = E\,r^{3/2} \tag{8}$$

where E is a constant. This equation indicates that the time required for complete dissolution of a shell from an outer radius R to an inner radius R_c will be

$$\text{release time} = E'\,(R^{3/2} - R_c^{3/2}) \tag{9}$$

Assuming that the optimum situation is one in which each capsule carries the same dose, then R_c will be the same for all capsules, and the distribution times will depend only on the distribution of the outer shell radii R, as shown in the above result. For production purposes the easiest way to achieve the desired range of bead sizes (and, therefore, of release times) would probably be to make many single batches of uniformly sized beads and blend the batches. How many different bead sizes would be needed to give a close approach to a continuous-size-distribution is a subject which requires deeper analysis and will not be explored here.

Certainly serious qualifications concerning the desirability, practicality, and feasibility of the administration of medicine by the above methods may be raised. The purpose of this paper has been to give initial insight into the nature and requirements of these approaches. Whether or not these techniques will be adjudged to have great, moderate, or little merit remains to be shown.

NOTATION

A = the medicinal compound being transferred
B = the inert carrier compound
c = total molar concentration of fluid, mole/cc.
d_p = sphere diameter at any arbitrary time, cm.
E, E' = constants
i, j = arbitrary chemical species
k_{xm} = mean mass transfer coefficient from sphere, mole/sq.cm.-sec.
K, K' = constants
n = total number of species present
r = radial coordinate, cm.
R = radius of spheres at start of dissolution, cm.
R_c = inner radius of time capsule shell, cm.
R_s = radius of sphere corresponding to $X_{A0} = X^*_{A0}$
Sc = Schmidt number, dimensionless
t = time, sec.
v = fluid velocity, cm./sec.
W = mass transfer rate, mole/cc.
X_{A0} = mole fraction of A at sphere surface at any time
X^0_{A0} = mole fraction of A at sphere surface at start of dissolution
X^*_{A0} = mole fraction of A at sphere surface corresponding to saturation
$X_{A\infty}$ = mole fraction of A in bulk of fluid stream
ϵ = void fraction in bed of particles, dimensionless
μ = fluid phase viscosity, g./cm.-sec.
ρ = fluid phase density, g./cc.

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A Stable Explicit Method for Simultaneous Quasi-Linear Differential Equations

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Differential equations that are encountered in studies of transport phenomena, such as mass transfer with a chemical reaction (*1*) and the transfer of heat generated by a temperature sensitive chemical reaction (*2*), are often of the form

$$\frac{\partial U}{\partial t} = a_0 \frac{\partial^2 U}{\partial x^2} + a_1 \frac{\partial U}{\partial x} + a_2\,U \tag{1}$$

and

$$\frac{\partial V}{\partial t} = b_0 \frac{\partial^2 V}{\partial x^2} + b_1 \frac{\partial V}{\partial x} + b_2\,V \tag{2}$$

where a_0, a_1, a_2, b_0, b_1, and b_2 may be functions of x, t, U, and V.

The method described for simultaneously solving sets of partial differential equations is not limited to just two differential equations or to two independent variables. For simplicity, the method is described in terms of Equations (1) and (2). Equations of the form of Equations (1) and (2) are not readily solved by analytical methods. They are best solved by finite difference methods.

Implicit, finite difference methods are cumbersome because when they are applied to nonlinear partial differen-