Mechanism of Sustained-Action Medication

Theoretical Analysis of Rate of Release of Solid Drugs Dispersed in Solid Matrices

By T. HIGUCHI

Theoretically expected rates of release of solid drugs incorporated into solid matrices have been derived for several model systems. Mathematical relations have been obtained for cases (a) where the drug particles are dispersed in a homogeneous, uniform matrix which acts as the diffusional medium and (b) where the drug particles are incorporated in an essentially granular matrix and released by the leaching action of the penetrating solvent. Release from both planar surface and a sphere is considered. The unidimensional release rates are shown to follow our earlier equation derived for release from ointment bases. Release rates from spherical pellets by both model mechanisms are shown not to followfi rst-order relationships. The analyses suggest that for the latter system the time required to release 50 per cent of the drug would normally be expected to be approximately 10 per cent of that required to dissolve the last trace of the solid drug phase in the center of the pellet.

THE PRESENT COMMUNICATION is concerned with the results of a theoretical analysis of mathematical relationships governing the rate of release of solid drugs randomly dispersed in solid matrices. Systems of this type have been widely studied and utilized recently as bases for dosage forms which provide more or less continuous release of medicaments over relatively long periods (1). Both Wiegand and Taylor (2) and Wagner (3) showed that per cent released time data reported in the literature for many sustained-release preparations give linear pseudo (or apparent) first-order rates over the terminal portions of the data from about 0.5 hour to the time the test was completed. The present study is an effort in relating the rate of release of drugs from such systems to the pertinent physical constants based on simple laws of diffusion.

Two geometric systems have been considered: (*a*) unidirectional leaching or extraction from a simple planar surface, and (*b*) three dimensional leaching or extraction from a spherical pellet. This would correspond most closely to the release process from an insoluble tablet matrix or certain sustained-action pellets.

Two mechanisms of release from these systems have been treated. (*a*) Extraction of the medicament by a simple diffusional process through and from an enveloping, homogeneous matrix. The drug is presumed to go successively from the crystal surfaces into the uniform matrix and out into the bathing solvent which in turn acts as a perfect sink. (*b*) Leaching of the medicament by the bathing fluid which is able to enter the drug-matrix phase through pores, cracks, and intergranular spaces. The drug is presumed to dissolve slowly into the permeating fluid phase and to diffuse from the system along the cracks and capillary channels filled with the extracting solvent. Intragranular diffusion is assumed, in this instance, to be insignificant. The two mechanisms are depicted schematically in Fig. 1.

It should be explicitly pointed out that the analyses reported here relate to these particular model systems, whereas the analyses of Wiegand and Taylor (2) and of Wagner (3) related to release data derived from formulated sustained-release or prolonged-action formulations. Actual dosage systems may be complicated by (*a*) simultaneous break-up of the matrix, (*b*) partial dissolution of the matrix substances, (*c*) one fraction of the dose being in a matrix form and the remainder of the dose being in a different, nonmatrix and readily available form, and (*d*) drug on the surface being released more rapidly than drug in the matrix. Where such complications are absent, the treatments under *Theoretical Analysis* are believed to yield the correct relationships.

THEORETICAL ANALYSIS

Release from a Planar System Having a Homogeneous Matrix.—The amount of total drug released from such a system into a bathing medium acting essentially as a perfect sink would be determined by the relationship

$$Q = \sqrt{Dt(2A - C_s)C_s} \qquad \text{(Eq. 1)}$$

where Q = the amount of drug released after time t per unit exposed area, D = the diffusitivity of the drug in the homogeneous matrix media, A = the total amount of drug present in the matrix per unit volume, and C_s = the solubility of the drug in the

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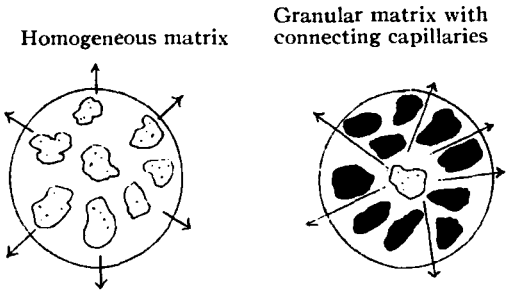

Fig. 1.—Two methods of drug release from the pellets.

matrix substance. We initially derived this equation for release from an ointment base containing finely dispersed drugs (4), but it is evident that it would be equally applicable for release from a sustained-action matrix of this type.

Release from a Planar System Having a Granular Matrix.—For the leaching type release mechanism occurring through diffusion movement utilizing intergranular openings, the above relation must be modified for the effective volume where diffusion can occur and the effective diffusional path. It can readily be seen for this system that

$$Q = \sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t} \qquad \text{(Eq. 2)}$$

where Q = the amount of drug released after time t per unit exposed area, D = the diffusitivity of the drug in the permeating fluid, τ = the tortuosity factor of the capillary system $\geqq 3$, A = the total amount of drug present in the matrix per unit volume, C_s = the solubility of the drug in the permeating fluid, and ϵ = the porosity of the matrix.

The derivation of the above expression is essentially the same as Eq. 1, except that the cross-sectional area of the diffusional path must be reduced by the porosity factor ϵ, and the apparent solubility of the drug in the total system per unit volume must also be decreased by the same factor. The tortuosity factor, τ, is introduced to correct, in the same sense used in the classical Kozeny equation, for the lengthened diffusional path caused by the necessary lateral excursions.

For both equations the derivation (4) is based on the existence of a pseudo steady state condition during the release process and on the assumption that the drug particles are quite small relative to the average distance of diffusion and are uniformly distributed in the matrix. The equations would be essentially valid for systems in which A is greater than C_s or ϵC_s by a factor of three or four. Of course, if $A < C_s$ or ϵC_s, the drug would no longer be present as a solid and a different equation would apply.

Since the porosity factor in Eq. 2 refers, of course, to the porosity of the leached portion of the pellet, it differs from the initial porosity of the initially formed matrix. The difference would correspond directly to the volume of free space previously occupied by the extracted component or components. Thus

$$\epsilon = \epsilon_o + KA$$

for systems where the drug is the only extractable component, K being introduced to convert A to its corresponding volume fraction. K is equal to the specific volume of the drug = 1/(density of the drug) if A is expressed in terms of grams of drug per milliliter. For those instances where the initial porosity, ϵ_o, is very small or where the fraction of the matrix volume occupied by the drug is relatively large $\epsilon \cong KA$ and Eq. 2 reduces to $Q = A\sqrt{DK/\tau(2 - KC_s)C_s t}$. Thus for these systems it would appear that the fraction of the drug released at anytime is essentially independent of A.

Release from a Spherical Pellet Having a Homogeneous Matrix.—Any attempt to derive an exact solution for a system of this type is, of course, impossible since it would require an exact coordinate description of the distribution pattern of the dispersed particles. A reasonably accurate and useful mathematical solution can be based on the same assumption which permitted solution of the two-dimensional system. We can again assume for the case $A \gg C_s$ that a pseudo steady state condition would exist during the leaching or extraction process and that a sharp front will be formed between the partly leached or extracted part of the sphere and the untouched portion. This state of affairs is shown in Fig. 2 where a_o = the radius of the whole pellet, a' = the radius of that part still unextracted, and a = the polar radius of any region under consideration, and the remaining symbols are the same as before.

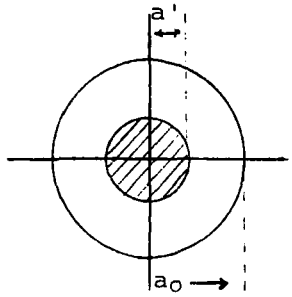

Fig. 2.—Schematic diagram of drug distribution in a partly extracted pellet.

It is evident in such a system that the concentration gradient is essentially zero for $a < a'$. The concentration in the region between a' and a_o will be a function of a and is assumed to be that fixed by Fick's first law.

Under pseudo steady state conditions as described above the total amount of material, SdQ, being released per unit time, dt, will be given by Fick's first law as

$$\frac{SdQ}{dt} = -4\pi a^2 D\frac{dC}{da} \qquad \text{(Eq. 3)}$$

where S is the diffusional area for $a' \leqq a \leqq a_o$. Integrating this from a to a_o we obtain

$$\left(\frac{SdQ}{dt}\right)_t\left(\frac{1}{a} - \frac{1}{a_o}\right) = 4\pi DC_a$$

where C_a = concentration at a or

$$\left(\frac{SdQ}{dt}\right)_t = \frac{4\pi DC_a}{\left(\frac{1}{a} - \frac{1}{a_o}\right)} = \frac{4\pi DC_s}{\left(\frac{1}{a'} - \frac{1}{a_o}\right)} \qquad \text{(Eq. 4)}$$

since $C_a = C_s$ at $a = a'$ and $C_a = 0$ at $a = a_o$ and

$$C_a = C_s \frac{a'}{a} \frac{(a_o - a)}{(a_o - a')} \quad \text{(Eq. 5)}$$

an expression which relates concentration to a in the region $a' < a < a_o$.

It is apparent that the total amount of the drug contained by the pellet at time = t is the sum of that in the unleached portion ($a < a'$) and that in the region no longer saturated with the drug ($a' < a < a_o$). Or the total residual amount of drug equals

$$\frac{4}{3}a'^3\pi A + \int_{a'}^{a_o} 4\pi a^2 C_a da \quad \text{(Eq. 6)}$$

$$= \frac{4}{3}\pi a'^3 A + \int_{a'}^{a_o} 4\pi a^2 C_s \frac{a'}{a}\frac{(a_o - a)}{(a_o - a')} da$$

$$= \frac{4}{3}\pi a'^3 A + \frac{4}{6}\pi C_s \frac{a'}{a_o - a'}(a_o^3 - 3a_o a'^2 + 2a'^3)$$

$$= 4\pi\left[\frac{a'^3}{3}A + \frac{C_s}{6}a'(a_o^2 + a'a_o - 2a'^2)\right] \quad \text{(Eq. 7)}$$

The change in the residual drug concentration corresponding to a change $-da'$ would then be

$$= 4\pi\left[Aa'^2 + \frac{C_s}{6}(a_o^2 + 2a'a_o - 6a'^2)\right](-da') \quad \text{(Eq. 8)}$$

This should in turn be equal but opposite in sign to the total flux over the period involved

$$\left(\frac{SdQ}{dt}\right)dt = \frac{4\pi DC_s}{\left(\frac{1}{a'} - \frac{1}{a_o}\right)}dt =$$

$$4\pi\left[Aa'^2 + \frac{C_s}{6}(a_o^2 + 2a'a_o - 6a'^2)\right]da'$$

$$DC_s dt = \left(\frac{a_o - a'}{a_o a'}\right)\left[Aa'^2 + \frac{C_s}{6}(a_o^2 + 2a'a_o - 6a'^2)\right]da' \quad \text{(Eq. 9)}$$

Integrating from a_o to a' we obtain

$$A(a_o^3 + 2a'^3 - 3a_o a'^2) +$$

$$C_s\left(4a'^2 a_o + a_o^3 \ln\frac{a_o}{a'} - a_o^3 - a_o^2 a' - 2a'^3\right) = 6DC_s a_o t \quad \text{(Eq. 10)}$$

For $C_s \ll A$ the above reduces to

$$a_o^3 - 3a'^2 a_o + 2a'^3 = \frac{6a_o}{A}DC_s t \quad \text{(Eq. 11)}$$

Equation 10 represents a general solution to the proposed problem since it permits determination of a' as a function of time, t, if the constants of the system, a_o, A, C_s, and D are known. Since the residual amount of drug at any time is already expressed by Eq. 7 in terms again of a', the total amount of drug released as a function of time can be readily calculated. Since any attempt to convert Eq. 10 into an explicit solution for a' as a function of t would result in a cumbersome relationship, it is more feasible in practice to obtain t as a function of a' and the amount of release also as a function of a' from Eq. 7 and then correlate the two dependent variables.

A general solution to Eq. 11 can be obtained in this implicit manner. For this it is more convenient to transform Eq. 11 into a dimensionless relationship

$$1 - 3\left(\frac{a'}{a_o}\right)^2 2\left(\frac{a'}{a_o}\right)^3 = \frac{6DC_s}{Aa_o^2}t = BT \quad \text{(Eq. 12)}$$

In this form the left hand expression in terms of a'/a_o is dimensionless and is independent of any units of measure employed. The factor, $B = 6DC_s/Aa_o^2$ is dimensionless except for time and can be calculated from the constants of the system. Since the fraction of drug remaining in the pellet for this system where $A \gg C_s$ would be

$$\text{Residual fraction of drug in pellet} = \left(\frac{a'}{a_o}\right)^3 \quad \text{(Eq. 13)}$$

we can readily prepare a plot of the residual fraction remaining in the pellet as a function of relative time. Actual time unit can be substituted in real systems where the constants comprising B are determinable. The results are shown for different (a'/a_o) values in Table I and are plotted in Fig. 3. It is evident

TABLE I.—CALCULATION OF RELEASE RATE FROM SPHERICAL PELLET $A \gg C_s$[a]

Time Scale		Drug Remaining (%) in Pellet
$\left(\frac{a'}{a_o}\right)$	Bt	$\left(\frac{a'}{a_o}\right)^3 \times 100$
1.00	0.0000	100.0
0.990	0.00030	97.03
0.980	0.001184	94.12
0.950	0.00725	85.70
0.90	0.02800	72.90
0.80	0.1040	51.20
0.70	0.2160	34.30
0.60	0.3520	21.60
0.50	0.5000	12.90
0.40	0.6480	6.40
0.30	0.7840	2.70
0.20	0.8960	0.800
0.10	0.9720	0.100
0.00	1.000	0.000

[a] Equation 11.

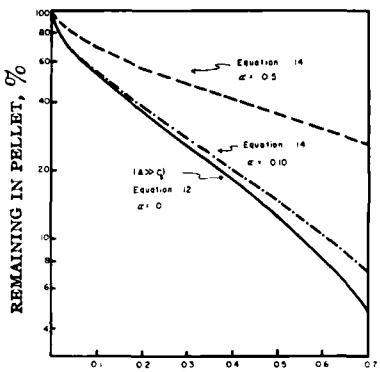

Fig. 3.—Influence of $\alpha = C_s/A$ values on rate of release.

from the table that the physical significance of B is that for the case $A \gg C_s$ its reciprocal corresponds to that time when the last trace of the solid drug dissolves into the matrix. Under these conditions the pellet can be considered to be totally exhausted. Also from the table it is apparent that the drug is very rapidly released at the beginning, approximately 50% of it being released at $t = 0.1 \times 1/B$.

The values shown in Table I have been plotted in Fig. 3 in the usual semilogarithmic fashion to show that the release rate predicted by this mechanism departs significantly from the first-order behavior. Aside from what appears to be a large initial surge of release, however, the plot yields a surprisingly linear relationship over a relatively wide range. This seems to arise from the fact that it is actually sigmoidal in nature and the apparent linear relationship observed (2, 3) may for some system be coincidental and for others be because of different overall mechanism.

In Fig. 4 the fraction of drug released from a sphere calculated from Eq. 11 is compared to that expected from Eq. 1 on the basis that the total exposed surface is $4\pi a_o^2$. The plot has been made as a function of $(Bt)^{1/2}$ since this affords a linear relationship for the two-dimensional system. It is evident that at the beginning the two equations predict a similar extent of release, as expected, since a plane of the same area would be a good approximation for the sphere in this phase. It is only beyond 50% release that significant deviation is evident between the two equations.

The more general Eq. 10 which takes into account the amount of drug remaining in the partly extracted region can be solved in an identical manner based on Eqs. 7 and 10. Setting $C_s = \alpha A$ and rearranging Eq. 10 we obtain

$$1 + 2\left(\frac{a'}{a_o}\right)^3 - 3\left(\frac{a'}{a_o}\right)^2 + \alpha\left[4\left(\frac{a'}{a_o}\right)^2 + ln\,\frac{a_o}{a'} - \frac{a'}{a_o} - 2\left(\frac{a'}{a_o}\right)^3 - 1\right] = \frac{6DC_st}{Aa_o^2}$$

or

$$1 - \alpha + 2(1-\alpha)\left(\frac{a'}{a_o}\right)^3 - (3 - 4\alpha)\left(\frac{a'}{a_o}\right)^2 - \alpha\left(\frac{a'}{a_o}\right) + \alpha\, ln\,\frac{a_o}{a'} = \frac{6DC_st}{Aa_o^2} \quad \text{(Eq. 14)}$$

Release behavior predicted by this equation for several values of α are also shown in Fig. 3. Residual fraction in these instances based on Eq. 7 would be

$$\text{Residual Fraction} = \left(\frac{a'}{a_o}\right)^3 + \frac{\alpha}{2}\left[\left(\frac{a'}{a_o}\right) + \left(\frac{a'}{a_o}\right)^2 - 2\left(\frac{a'}{a_o}\right)^3\right] \quad \text{(Eq. 15)}$$

Since in most real systems α is usually very small, any term containing it as a factor can normally be ignored.

Plots shown in Fig. 3 are, in a sense, universal relationships in that they permit estimation of the release behavior for all systems for given α values. They indicate that the relative release rates (*i.e.*, the fraction released per unit time) from pellets of this type would be inversely proportional to the square of the radius of the pellet and the drug concentration but directly proportional to the solubility and the diffusitivity of the drug. The plot shown for $\alpha = 0.5$ is less valid than the others since the assumed pseudo steady state condition requires A to be significantly larger than C_s. Actually α must be considerably smaller for the spherical three-dimensional system for the steady state situation to exist than for the planar system. This is especially true for higher states of depletion.

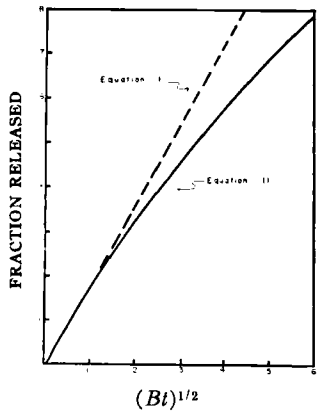

Fig. 4.—Comparison of Eqs. 1 and 11.

Release by Leaching from Granular Spherical Pellet.—The solution to the rate of leaching by external solvent (*e.g.*, gastric fluid) of solid drugs uniformly dispersed in granular spherical pellets can be developed exactly as in the preceeding case. It is evident that the dimensionless expression corresponding to Eq. 14 will take the form

$$(1-\alpha) + 2\left(\frac{a'}{a_o}\right)^3(1-\alpha) - \left(\frac{a'}{a_o}\right)^2(3 - 4\alpha) - \alpha\left(\frac{a'}{a_o}\right) + \alpha\, ln\left(\frac{a_o}{a'}\right) = \frac{6D\epsilon C_st}{\tau Aa_o^2} \quad \text{(Eq. 16)}$$

where $\alpha = \epsilon C_s/A$ and $\epsilon = \epsilon_o + KA$, and the remaining symbols the same meanings as before with D being the diffusitivity in the solvent. If as in the two-dimensional case we take the initial porosity, ϵ_o, as being negligible we obtain

$$(1-\alpha) + 2\left(\frac{a'}{a_o}\right)^3(1-\alpha) - \left(\frac{a'}{a_o}\right)^2(3 - 4\alpha) - \alpha\left(\frac{a'}{a_o}\right) + \alpha\, ln\left(\frac{a_o}{a'}\right) = \frac{6DKC_st}{\tau a_o^2}$$

For $\alpha \ll 1$, this reduces to

$$1 + 2\left(\frac{a'}{a_o}\right)^3 - 3\left(\frac{a'}{a_o}\right)^2 + \frac{6DKC_st}{\tau a_o^2} \quad \text{(Eq. 17)}$$

where the residual fraction $= (a'/a_o)^3$.

In these analyses it has been tacitly assumed that the time of extraction begins with the slightly porous pellet already permeated by the extracting solution. Since in practice such pellets (or "cores") will be taken dry there will be a short lag time corresponding to that required to wet the interior of the matrix. This time, however, should normally be relatively small compared to the duration of action of such medications.

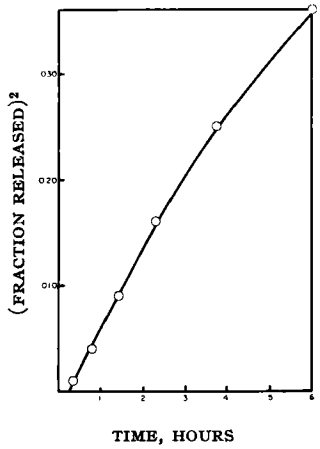

Fig. 5.—Comparison of Simoons' experimental data (5) with Eq. 17.

GENERAL DISCUSSION

The several solutions to the release behavior of the systems considered are believed to be essentially exact for the models employed. Experimental data available appear to substantiate these analyses (5).

In real systems, however, a number of other factors may come into play which may modify the total behavior. The models employed assume that the systems are neither surface coated, nor that their matrices undergo significant alteration in the presence of moisture. Since in real systems these play varying roles in modifying the release pattern of sustained-action dosage forms, any attempt to apply these equations must be made with this in mind.

Other serious deviations from the derived relationship may occur for systems which tend to differ significantly from the adopted models. For example, for pellets containing a relatively high percentage of drugs the leaching process would tend to weaken the matrix structure and produce erosion. This may play a significant role in altering the observed real rate. Another effect which is not considered in these treatments is the influence of solvent flow induced within the pellets by external agitation. This effect, however, will be important only with pellets of relatively high porosity.

In Fig. 5 data reported by Simoons in his interesting paper on experimental measurements of release rate of sustained-action medication (6) for relatively insoluble drug hard compressed (his Fig. 15) are plotted in the form of square of fraction released against extraction time. The extraction data show a short lag time probably corresponding to that required to wet the pellets. This is followed by a release pattern closely matching that predicted by Eq. 17, the smooth line representing the theoretical values and the points, the experimentally observed values reported by Simoons. The total theoretical curve was based on experimentally observed time for 50% release and the initial lag time.

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Dielectric Constants of Complex Pharmaceutical Solvent Systems I

Water-Ethanol-Glycerin and Water-Ethanol-Propylene Glycol

By D. L. SORBY, R. G. BITTER, and J. G. WEBB

Dielectric constants of water-ethanol-glycerin and water-ethanol-propylene glycol systems have been experimentally determined. The measured values were found to differ from values calculated according to simplification of the Onsager-Kirkwood equation, regardless of whether composition of the various solutions was expressed on the basis of weight percentage or volume percentage. Dielectric constant values presented in this paper are recommended for precise adjustment of solvent polarity in formulation work and data are presented to be of maximum use in this respect.

MOORE (1) HAS PRESENTED a method wherein manipulation of solvent dielectric constant is utilized to produce dissolution of a solute at a desired concentration and to blend pharmaceutical solvents to a predetermined degree of polarity. In this method, certain simplifying assumptions are made, one being that the dielectric constant of a complex solvent mixture may be calculated to a good approximation by taking the sum of the products of volume composition and dielectric constant for each individual component in the mixture. This method of calculating dielectric constants of complex mixtures is based on a simplification of the Onsager-Kirkwood

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