Rate of Release of Medicaments from Ointment Bases Containing Drugs in Suspension

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An equation relating the rate of release of solid drugs suspended in ointment bases into perfect sinks is derived. The final expression is found to be surprisingly simple and convenient.

In an earlier publication (1) an equation was given relating the amount and rate of release of materials suspended in an ointment base to time and variables of the system

\[ Q = (2A - C_0) \sqrt[4]{\frac{D_i}{1 + \frac{2(A - C_0)}{C_0}}} \]

where \( Q \) = the amount absorbed at time \( t \) per unit area of exposure, \( A \) = the concentration of drug expressed in units/cm.\(^4\), \( C_0 \) = the solubility of the drug as units/cm.\(^4\) in the external phase of the ointment, and \( D \) = the diffusion constant of the drug molecule in the external phase.

The present communication is concerned with the theoretical derivation of this relationship. Normally, diffusional calculations are extremely complex and lead to unwieldy expressions. In the present instance, despite the obvious complexity of the type of system involved, the equation comes out rather simply and in a useful form.

The equation is derived for a system described as follows: (a) the suspended drug is in a fine state such that the particles are much smaller in diameter than the thickness of the applied in \( \tau \); (b) the amount of drug, \( A \), present per unit

volume is substantially greater than \( C \), the solubility of the drug per unit volume of the vehicle; (c) the surface to which the drug ointment is applied is immiscible with respect to the ointment and constitutes a perfect sink for the released drug.

All of the above conditions are evidently self-apparent, except possibly for the reference to a perfect sink. In the publication cited above it was pointed out that the rate of absorption of drug from an ointment could be effectively limited by any one of the three processes involved: (a) drug clearance below the "barrier layer," (b) passage through the "barrier layer," or (c) release by the ointment itself.

It was shown that in the cases where either of the first two processes were rate limiting, only the thermodynamic activity of the drug in the base was important. If the last process is of paramount importance, then we are tacitly assuming that the surface to which the ointment is applied acts as a perfect sink.

**DERIVATION OF THE EQUATION**

For such a system we can draw a concentration profile which may exist after the lapse of finite time after application of the ointment (Fig. 1). The solid line in the diagram would essentially represent the concentration gradient existing after time \( t \), in the ointment layer normal to the absorbing surface. The total drug concentration, as indicated in the drawing, would be expected to show a more or less sharp discontinuity at distance \( A \) from the surface, some of the suspended phase dissolving until the environmental concentration drops below \( C \). The sharpness of the break will be largely a func-
tion of the fitness and the state of dispersion of the solid phase. For the distance, $A$, above the absorbing surface the concentration gradient would be essentially constant, provided $A \gg h$. The linearity of the gradient over this distance follows under these conditions from Fick’s first law. The shift in the profile after additional interval of $\Delta t$ is shown as a dotted line in the diagram, corresponding to the extension of the zone of partial depletion by the distance $\Delta A$. It is evident, furthermore, that at time $t$, the amount of material absorbed or, equivalently, depleted from the ointment corresponds to the shaded area in the diagram.

It can be seen, based on the above diagram, that $dQ$, the amount additionally depleted by further movement of the front, by $A$, is related to other constants

$$dQ = A \Delta h - \frac{1}{2} C_d h$$

But according to Fick’s law

$$dQ/dt = D C / h$$

or

$$A \frac{dh}{dt} = \frac{1}{2} C_d \frac{dh}{dt} = D C / h$$

$$(2A - C) \frac{dh}{dt} = \frac{D C}{h}$$

Integrating both sides, we get

$$t = \frac{A^2}{4D C} (2A - C) + K$$

where $K$ is the integration constant.

It is apparent that $K = 0$ for $t$ measured from zero, or

$$t = \frac{A^2}{4D C} (2A - C)$$

and

$$h = 2 \frac{D C}{2A - C}.$$

From the diagram it is apparent that the amount of depletion $Q$, at time, $t$, is

$$Q = h A - \frac{h C}{2}$$

Substituting for $h$ from above we get

$$Q = (A - C) \sqrt{\frac{D C}{2A - C}}$$

These relationships will be essentially valid for all time less than that corresponding to complete depletion of the suspended phase. The initial lag time corresponding to the time necessary for establishment of a quasi-stationary state conforming to the equations would generally be less than

$$L = \frac{|mo|}{D_0}$$

where $a$ is the mean distance between the suspended particles and $m$ is of the order of 2 or 3. Since the interparticle distance is assumed to be extremely small for the model system relative to the layer thickness, the lag time is expected to be very short in comparison to the total depletion period.

Differentiating with respect to time, we obtain the instantaneous rate of absorption at time $t$.

$$\frac{dQ}{dt} = \frac{1}{2} \sqrt{D C (2A - C)}$$

For the common case of $C_3 \ll A$, the relationship simplifies to

$$Q = \sqrt{D A C}$$

and

$$\frac{dQ}{dt} = \frac{A D C}{2t}.$$

These relationships are identical with or equivalent forms of the earlier expressions.

According to these remarkably simple relationships, remarkable in view of the complexity of the situation treated, the amount of drug released from such suspension-type ointments ($C_3 \ll A$) is proportional to the square root of the amount of drug per unit volume, diffusion constant, drug solubility, and time. It is of interest to note that intuitively one might expect a direct relationship with concentration, but this is not the case.

It is evident that we can regulate the rate of release of drugs from such preparations by controlling $A$, $D$, and $C_3$. If partly aqueous base is employed, $C_3$ can be varied, for example, by changing the effective pH of the vehicles for insoluble acids and basic drugs. Or it can be altered by addition of complexing agent or coadvent. $D$, the diffusion coefficient, is inversely proportional to the microscopic viscosity of the vehicle and may be varied in this manner. $A$, the drug concentration, is, of course, susceptible to wide variation.

There are a number of other similar situations which have been solved dealing with diffusion flow where all of the gradient is in the applied phase. We have worked out cases involving both suspension-type ointments and ointments containing solid slivers such as zinc oxide. Nearly exact mathematical solutions to the behavior of these systems as drug sources are presently available.

REFERENCE