Analysis of Data on the Medicament Release from Ointments

By W. I. HIGUCHI

An analysis of some recently published data on the sodium radioiodide release from hydrophilic ointment bases is presented and discussed. The release dependence on time and the value for the effective diffusion coefficient are compared with theoretical predictions. The generally good agreement between theory and data demonstrates the potential usefulness of the theoretical relationships in both experimental design and data evaluation. The simplicity of some of the theoretical equations is indicated.

RECENT THEORETICAL investigations (1, 2) of drug release from ointments resulted in equations which were expected to be useful in describing ointment release rates. Because of the lack of availability of suitable data at the time, the applicability of these mathematical relationships to real situations was not experimentally demonstrated. Recently, however, Patel, Banker, and DeKay reported (3) results of some studies on sodium radioiodide release from hydrophilic ointment bases. Because an examination of their data with the appropriate theoretical relationships appeared to add to the better basic understanding of ointment behavior, this report was prepared for presentation at this time.

Higuchi deduced (1) the following equation for the amount of drug released from (one side of) a layer of ointment in which the drug is initially uniformly dissolved

$$Q = hC_0 \left[1 - \frac{8}{\pi^2} \sum_{m=0}^{\infty} \frac{1}{(2m+1)^2} \exp \left(- \frac{D(2m+1)^2 \pi^2 t}{4h^2} \right) \right] \quad \text{(Eq. 1)}$$

where Q = amount of drug released per unit area of application, h = thickness of layer, C_0 = initial concentration of drug in ointment, D = diffusion coefficient of drug in the ointment, t = time after application, m = integer, as indicated, goes from 0 to ∞.

The per cent released, R, is then simply

$$R = \frac{100Q}{hC_0} = 100 \left[1 - \frac{8}{\pi^2} \sum_{m=0}^{\infty} \frac{1}{(2m+1)^2} \exp \left(- \frac{D(2m+1)^2 \pi^2 t}{4h^2} \right) \right] \quad \text{(Eq. 2)}$$

Equation 1 is a solution to Fick's law of diffusion which is extensively described in a number of textbooks (4, 5). The main assumptions involved in Eq. 1, in practical language, are (*a*) that only a single drug species is important in the ointment, (*b*) that D must be constant with respect to both time and position in the ointment layer, (*c*) that only the drug is able to diffuse out of the layer, i. e., components of the vehicle cannot diffuse out (or evaporate), and finally (*d*) that the drug reaching the receptor side of the ointment layer is removed rapidly (means the same as the boundary condition: concentration of drug = 0 at receptor-ointment boundary for $t > 0$).

The experimental method described by Patel, Banker, and DeKay appears to conform approximately to all of the above requirements for the applicability of Eq. 1. Thus, a direct comparison of their data with Eq. 1 would seem to be justified. The difficulty with the idea of attempting a direct quantitative test is that the value of D is difficult to estimate for such complex systems as those studied by Patel, Banker, and DeKay. Therefore, the most profitable approach would be to consider first only the time-dependent part of the equation by selecting a value for D which gives the best overall fit for each set of data. Thus for each set of data one must choose the best single D value, which when placed into Eq. 2, will give the best agreement between the particular set of data and Eq. 2. This means effectively forcing a fit between data and theory at one point for each set of data. The agreement of the rest of the data for a particular set would constitute a test of the time-dependent portion of the theory. Then these chosen D values could be examined independently in light of the expected structure of the vehicle and with the mathematical relationships for D in heterogeneous systems (2).

TIME DEPENDENCE

In Fig. 1 representative sets of data taken from the work of Patel, Banker, and DeKay are given (circles). The different sets of data refer to sodium radioiodide release from bases[1] containing different surfactants or different amounts as indicated in the figure. The curves represent values predicted by Eq. 2 with a single value of D for each set of data.

The agreement of the time-dependent portion of Eq. 2 with the data is highly satisfactory indicating that the idealized conditions had been well approximated by the experimental method. These results support the assumptions (under assumption *d* above) that the Visking membrane in these experiments contributed negligibly to the release resistance and that stirring in the solution on the other side of the membrane was rapid enough to prevent buildup of a liquid diffusion layer of any

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[1] The reader is referred to the original work (3) for complete description of ointment bases. Except for the surfactant used, each base contained essentially the same ingredients and the same amounts of them as those in the official hydrophilic ointment U.S. P. XVI.

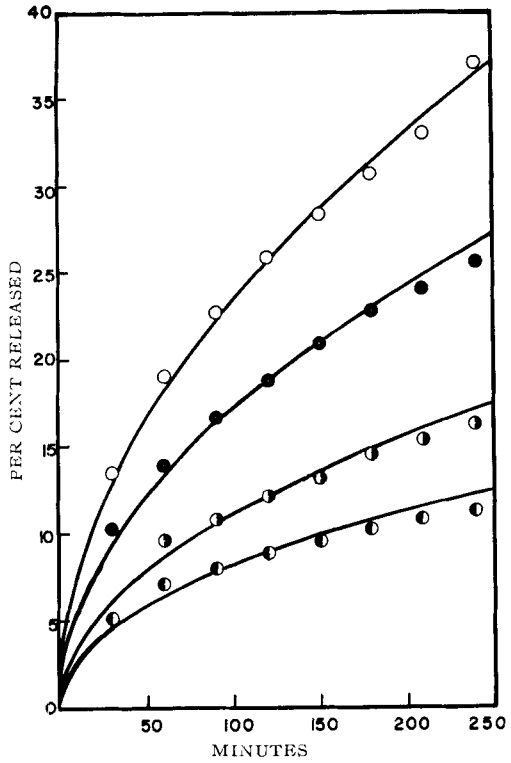

Fig. 1.—Comparison of data with theory for release from ointment base. Circles give data of Patel, Banker, and DeKay. Smooth curves obtained from Eq. 2 and a single adjustable parameter. ○, Sipon ES, 1%; ●, Sipon ES, 2%; ◑, Maprofix TLS, 3%; ◐, Catanac SN, 3%.

importance. If such were not the case, there would have been deviations of the data in the direction of less curvature than theory. Actually, the small deviations present are consistently in the opposite direction. The good agreement also supports the expected constancy of D (assumption b). This is reasonable in view of the diluteness of the sodium radioiodide in the vehicle.

It is worth while to point out at this time that for most practical applications of Eqs. 1 and 2, simplified forms of these equations may be used. When the per cent released, R, is not too large, i. e., for $R \lesssim 30\%$, it can be easily shown that

$$Q = 2\,C_0 \left(\frac{Dt}{\pi}\right)^{1/2} \qquad \text{(Eq. 3)}$$

and

$$R = 200 \left(\frac{Dt}{\pi h^2}\right)^{1/2} \qquad \text{(Eq. 4)}$$

These "square root" approximations should hold rather well for most studies of practical importance. The simplicity of Eqs. 3 and 4 makes the use of the theory very convenient.

EFFECTIVE OINTMENT DIFFUSION COEFFICIENTS

The values for the effective experimental diffusion coefficients derived from the data-theory fitting process described above are given in Table I.

Let us now see how these D values compare with the expected value based on our scanty knowledge

TABLE I.—EFFECTIVE DIFFUSION COEFFICIENTS OF SODIUM RADIOIODIDE IN OINTMENT BASES DETERMINED[a] FROM RELEASE DATA AT 37°

Base Designation	D (cm.^{2} sec.$^{-1}$)
Sipon ES, 1%	3.6×10^{-6}
Sipon ES, 2%	2.0×10^{-6}
Maprofix TLS, 3%	0.80×10^{-6}
Catanac SN, 3%	0.43×10^{-6}

[a] The value $h = 0.7$ cm. (3) was employed in these calculations.

of the detailed structure of these ointment bases. Since these hydrophilic bases are oil-in-water emulsions, the external phase is aqueous and presumably should represent about 40 to 50% of the total volume [corresponding to the 37% water and 12% propylene glycol by weight used (3)]. On the basis of what we know we could make both an upper limit estimate and a less exact "probable value" estimate of the effective diffusion coefficient.

For the upper limit estimate we assume that (a) sodium radioiodide is distributed only in the aqueous phase, that (b) it is able to diffuse only in the aqueous phase (i. e., zero diffusion coefficient in the internal phase), and that (c) the diffusion coefficient in the aqueous phase is the same as that in pure water. Note that assumption c makes this estimate an upper limit one. We may then write a relationship (2) for the effective diffusion coefficient in heterogeneous system where the internal phase may be considered to be impenetrable spheres

$$D_e = \frac{1.61 D_1}{3 - 1.39 V_1} \qquad \text{(Eq. 5)}$$

where D_e is the effective diffusion coefficient, D_1 is the diffusion coefficient in the external phase, and V_1 is the volume fraction of the external phase. Equation 5 appears to be a relatively good relationship for diffusion data (2) on suspensions of glass spheres, powders, sand, etc. For our calculation, if we take $V_1 \approx 0.45$, Eq. 5 gives $D_e \approx 0.7 D_1$. Now the literature value (6) for the diffusion coefficient of sodium iodide in water at 25° is 1.5×10^{-5} cm.^{2} sec.$^{-1}$. At 37° the value would be[2] about 1.9×10^{-5} cm.^{2} sec.$^{-1}$. Therefore, at 37°, $D_e \approx 1.3 \times 10^{-5}$ cm.^{2} sec.$^{-1}$, which is only about 3.6 times greater than the largest D value in Table I.

Now a "probable value" estimate can be made if it is permissible to assume that essentially all of the propylene glycol is in the aqueous phase. This consideration will make D_e smaller by about a factor of two[3] or so (with an uncertainty, say, about one-half of this).

The above analysis, although crude, clearly supports the expected mechanism of release. Sipon ES, 1%, represents a base with just about the maximum rate of release, i. e., further changes in surfactant or surfactant concentration should not increase the per cent release rate by a great deal. More independent information on these systems is needed before the dependence of D on surfactant type and surfactant concentration (see Table I) can be logically explained.

[2] Both Stokes-Einstein equation and data on similar systems predict this.

[3] Stokes-Einstein equation prediction (inverse proportionality with viscosity). Viscosity estimates inferred from other systems.

CONCLUSIONS

The analyses of the data of Patel, Banker, and DeKay by means of theory demonstrates the possible usefulness of the quantitative theory in future studies. Simple relations could be employed to help evaluate the proposed mechanisms. It would be of interest to investigate experimentally other types of ointments, e. g., the water-in-oil type, suspension type, bound drug type, etc., and compare results with appropriate theoretical relationships (1, 2).

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Synthesis of Some Monoamino Alkynes

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The preparation of a series of monoamino alkynes has been undertaken. A method of reduction of the substituted and unsubstituted quinolines to their corresponding tetrahydro derivatives is presented. Some of the monoamino alkynes showed weak fungicidal activity against *T. mentagrophytes*.

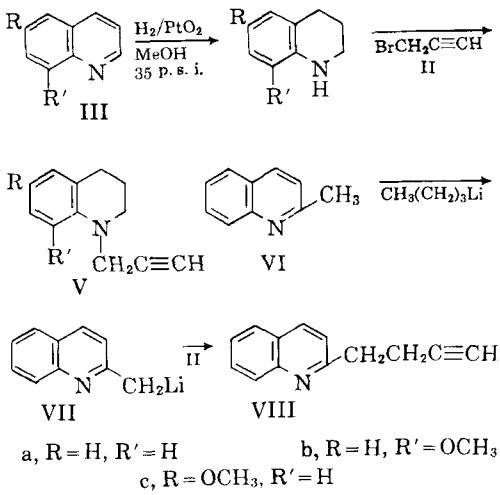
DURING THE COURSE of the investigation of a series of unsymmetrically alkylated acetylenic bis-quaternary ammonium compounds, it was necessary to prepare a series of monoamino alkynes (I)

$$RCH_2C{\equiv}CH$$
I

R = Pyrrolidino, diethylamino, 1,2,3,4-tetrahydroquinolino, 6-methoxy-1,2,3,4-tetrahydroquinolino, 8-methoxy - 1,2,3,4 - tetrahydroquinolino, 2 - quinolyl methyl

The structural similarity of certain of these intermediates to a series of 8-hydroxy-2-quinoline acrylic acids, prepared by Vaidya and Cannon (1), exhibiting fungicidal activity, prompted us to screen these compounds as potential fungicides. Preliminary screening against *T. mentagrophytes*, and *C. albicans* revealed that some of these compounds showed fungicidal activity against *T. mentagrophytes* at concentrations of 100–500 mcg./ml.

Propargyl bromide (II) was employed as the alkylating agent for the preparation of these compounds by the following routes.



a, R = H, R′ = H b, R = H, R′ = OCH_3

c, R = OCH_3, R′ = H

The catalytic reduction of quinoline and of the 6- and 8-methoxy-quinolines (III a, b, and c) was based on a method of Skita and Meyer (2) who reduced quinoline to decahydro- and tetrahydroquinoline with platinum chloride in glacial acetic acid. Employing platinum oxide (Adams) in methanol at 35 p.s.i., we successfully reduced the quinolines III a, b, and c to their respective tetrahydro derivatives in 80–96% yields. Propargyl bromide (II) was then treated with a 1-molar excess of the appropriate tetrahydroquinoline in isopropyl alcohol. The formation of quaternary propargyl halide salts was prevented by adding the propargyl bromide slowly to the amine. The alkynyl amines could be readily purified by fractional distillation

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