in the degree of hysteresis. These facts suggest a substantial increase in the cohesive forces operating between particles of the high viscosity gel and a decrease in the level of cohesion for the low viscosity gel.

Alteration of the degree of particle–particle cohesion due to changes in the level of particle charge was established previously (17). It was shown that additional charge provides sufficient coulombic repulsion to overcome the van der Waals attraction forces so that the apparent viscosity decreases. Examination of the rates of acid neutralization by the two aluminum hydroxycarbonate gels (Fig. 7) indicates a significant decrease in the rate of acid neutralization of the low viscosity gel but no appreciable change for the high viscosity gel. This behavior indicates that crystallinity develops in the low viscosity gel, eventually leading to the formation of a crystalline form of aluminum hydroxide such as gibbsite, which is free of carbonate (5, 18). The transformation to a carbonate-free aluminum hydroxide results in an increased zero point of charge (17) and, therefore, a buildup of charge on the low-viscosity gel. Thus, the apparent viscosity, gel structure rigidity, and resistance to water flow would be expected to decrease as was observed. With the high viscosity gel, the relatively stable rate of acid neutralization during the time period studied indicates that no buildup of charge occurs so that the natural tendency of a gel to form the most stable arrangement of particles with the maximum degree of particle–particle linking is observed. Thus, an increased apparent viscosity, an enhanced gel structure rigidity, and a decreased capillary conductivity are consistent with the proposed mechanism.

CONCLUSIONS

The tension cell is useful for examining the physical state of a gel, especially when compared to other methods such as viscosity measurement where large inputs of mechanical energy in the form of shear stress may disrupt the gel structure. The tension cell is capable of providing meaningful data with a firm basis provided by thermodynamic and kinetic theory. The data reported here were obtained with considerable difficulty because of the necessity for position readjustment of the tension cell to maintain a constant tension, the long duration of the experiments, and the frequent tabulations of data required for the dynamic measurements. Early experiments, in which adjustments to maintain a constant tension during water outflow were not performed, did not produce satisfactory data. The manual adjustment of cell position to maintain a constant tension was essential in obtaining meaningful results. However, some of the scatter observed in Figs. 3 and 4 may have been due to unavoidable mechanical disturbances of the gel structure through the manual repositioning of the tension cell. Consequently, various methods for automating the tension cell are being tested so that acquiring the necessary data will be more convenient and more precise data may be obtained.

Future experiments are planned with the tension cell to give insight into various roles played by particle charge, size, and shape. The effects of surface charge and particle size on the compressibility of aluminum hydroxycarbonate gel are examined specifically in a subsequent report.

REFERENCES

(1) D. Swartzendruber, in "The Flow of Water in Unsaturated Solids," R. J. M. De Weist, Ed., Academic, New York, N.Y., 1969, chap. 6.

(2) N. J. Kerkhof, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, **66,** 1533 (1977).

(3) S. M. Beekman, U.S. pat. 3,773,917, (Nov. 20, 1973).

(4) S. L. Nail, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, **64,** 1166 (1975).

(5) C. J. Serna, J. L. White, and S. L. Hem, *ibid.*, **67,** 1144 (1978).

(6) N. J. Kerkhof, R. K. Vanderlaan, J. L. White, and S. L. Hem, *ibid.*, **66,** 1528 (1977).

(7) L. A. Richards, *Soil Sci.*, **68,** 95 (1949).

(8) C. B. Tanner and D. E. Elrick, *Soil Sci. Soc. Am. Proc.*, **22,** 575 (1958).

(9) R. J. Reginato and C. H. M. van Bavel, *ibid.*, **26,** 1 (1962).

(10) D. M. Anderson and P. F. Low, *ibid.*, **22,** 99 (1958).

(11) P. F. Low, *Adv. Agron.*, **13,** 269 (1961).

(12) P. F. Low, *Soil Sci.*, **93,** 6 (1962).

(13) J. D. Oster and P. F. Low, *Soil Sci. Soc. Am. Proc.*, **28,** 605 (1964).

(14) I. Ravina and P. F. Low, *Clays Clay Miner.*, **20,** 109 (1972).

(15) H. A. Ruiz and P. F. Low, in "Proceedings of the 50th International Conference on Colloid Interface Science," M. Kerker, Ed., Academic, New York, N.Y., 1976, pp. 503–515.

(16) R. J. Kunze and D. Kirkham, *Soil Sci. Soc. Am. Proc.*, **26,** 421 (1962).

(17) J. R. Feldkamp, D. N. Shah, S. L. Meyer, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, **70,** 638 (1981).

(18) S. L. Nail, J. L. White, and S. L. Hem, *ibid.*, **65,** 231 (1976).

ACKNOWLEDGMENTS

Supported in part by a David Ross Fellowship to E. A. Lipka.

This report is Journal Paper 8071, Purdue University Agricultural Experiment Station, West Lafayette, IN 47907.

The authors thank Professor D. Swartzendruber for stimulating this research.

Effect of Complex Formation between 4-Hexylresorcinol and Ethyl Myristate on Release Rate of 4-Hexylresorcinol from Petrolatum Base

KATSUMI IGA, ANWAR HUSSAIN ˣ, and TOSHIO KASHIHARA

Received April 7, 1980, from the *College of Pharmacy, University of Kentucky, Lexington, KY 40506.* Accepted for publication February 5, 1981.

Abstract □ The effect of ethyl myristate on the release rate of 4-hexylresorcinol from petrolatum base was studied at pH 7.4 and 37°. 4-Hexylresorcinol was analyzed spectrophotometrically at 278 nm. The release rate of hexylresorcinol from the ointments was directly proportional to the square root of time and depended on the percentage of ethyl myristate in the ointment base. For 0, 0.5, 1, 3, and 5% of ethyl myristate, the release rates were 29.6, 35.4, 38.3, 55.7, and 70.0 $\mu g/hr^{1/2}/cm^2$, respectively. The solubility of hexylresorcinol in the petrolatum base was determined as a function of ethyl myristate using partitioning techniques. The enhancement in hexylresorcinol solubility was rationalized on the basis of 1:1 and 1:2 complexes between hexylresorcinol and ethyl myristate. The complexation constants of these complexes were estimated to be 10 M^{-1} and 206.1 M^{-2}, respectively. The diffusion coefficient of hexylresorcinol in the petrolatum base was estimated to be 1.31×10^{-8} cm^2/sec.

Keyphrases □ Release rate—effect of ethyl myristate on release of 4-hexylresorcinol from petrolatum, quantitative analysis □ Ethyl myristate—effect on release rate of 4-hexylresorcinol from petrolatum, quantitative analysis □ 4-Hexylresorcinol—effect of ethyl myristate on release rate from petrolatum, quantitative analysis

Percutaneous absorption depends on both drug release from the vehicle and drug permeability through the skin. Drug release depends on physicochemical factors, such as the drug's solubility and diffusion coefficient in the vehicle.

0022-3549/81/0800-0939$01.00/0

Table I—Composition of the Ointments Used in the Release Rate Study

Ingredient	Percent of Ethyl Myristate				
	0.0	0.5	1.0	3.0	5.0
White petrolatum, g	10	10	10	10	10
Hexylresorcinol, mg	200	200	200	200	200
Ethyl myristate, mg	—	50	100	300	500

Simplified equations describing drug release from suspension (1) and solution (2) vehicles have been reported, and numerous studies (3–10) attempted to relate vehicle composition to the *in vitro* release rate. There is, however, relatively little quantitative information correlating the release rate with variations in physicochemical parameters produced by a compositional change in the vehicles. This investigation quantitatively and mechanistically examined the effect of ethyl myristate on the release rate of 4-hexylresorcinol from petrolatum.

EXPERIMENTAL

Ointment Preparation—Table I shows the amounts of hexylresorcinol[1], ethyl myristate[2], and white petrolatum[3] used in ointment preparation. The ointments were prepared by warming hexylresorcinol and ethyl myristate at 40° in a 20-ml beaker. White petrolatum then was added, and the mixture was kept at 40° for 5 min until a homogeneous fluid mixture was obtained. A 5-ml sample of the liquid mixture was poured into a 20-ml polyethylene syringe from which the upper portion had been removed by cutting around the barrel at the 15-ml mark. The ointments were left in the syringe overnight at room temperature.

Release Rate Measurements—The half-syringe containing the ointment was attached to the USP dissolution apparatus and was immersed in a 60-ml glass tube containing 40 ml of 0.1 *M* phosphate buffer, pH 7.4, as shown in Fig. 1. The release rate of hexylresorcinol from the ointments was studied at 37° at a rotation speed of 50 rpm. At each sampling interval, the entire 40 ml of the dissolution medium was taken and replaced with 40 ml of fresh buffer. The hexylresorcinol concentration was determined spectrophotometrically[4] at 278 nm using a 10-cm cell.

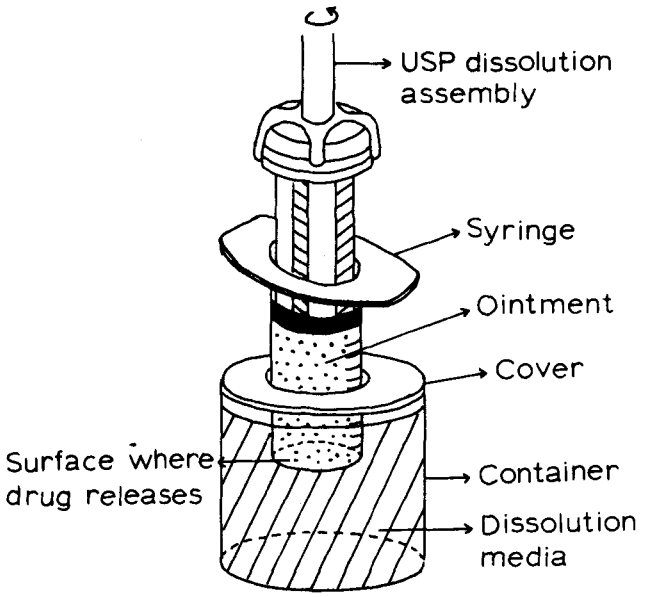

Figure 1—*Apparatus used for the determination of release rate of hexylresorcinol from ointment.*

[1] Curtin-Matheson, Cincinnati, Ohio.
[2] Sigma Chemical Co.
[3] Plough Inc.

Table II—Composition and Ratio of the Aqueous and Ointment Layers Employed in the Partition Coefficient Determination

Aqueous Solution of Hexylresorcinol, ml	White Petrolatum, g	Ethyl Myristate Added to White Petrolatum, mg	Percent of Ethyl Myristate
20	12	—	0
30	12	60	0.5
40	12	120	1
30	6	120	2
40	6	180	3
60	6	300	5

Partition Coefficient of Hexylresorcinol in pH 7.4 Buffer and in White Petrolatum Containing Different Amounts of Ethyl Myristate—Ethyl myristate and white petrolatum in the ratios shown in Table II were melted in a 200-ml beaker at 40° and were mixed thoroughly. An aqueous buffer solution containing 200 mg of hexylresorcinol in 500 ml of 0.1 *M* phosphate buffer, pH 7.4, also was prepared. Appropriate volumes of the hexylresorcinol solution (Table II) were added to the petrolatum–ethyl myristate mixtures, which were sonicated for 10 min in 200-ml beakers. The beaker then was shaken at 37° for 7 days, and the aqueous solution was filtered through a 0.45-μm filter[5]. Five milliliters of each filtrate was diluted to 50 ml with pH 7.4 phosphate buffer. The hexylresorcinol concentration was determined spectrophotometrically at 278 nm using a 10-cm cell.

The partition coefficient was calculated as follows:

$$\text{partition coefficient} = \frac{(\text{volume of aqueous layer})\,(\text{absorbance change, } A_0 - A, \text{ in aqueous layer})}{(\text{volume of ointment})\,(\text{absorbance in aqueous layer, } A)} \quad \text{(Eq. 1)}$$

where A_0 and A are the initial and final absorbances of the solution, respectively. The volume of the ointment was calculated from the density and weight of the ointment.

RESULTS AND DISCUSSION

The release profile of hexylresorcinol from the ointments is shown in Fig. 2 as a function of the ethyl myristate concentration. The release of hexylresorcinol from these ointments was proportional to the square root of time.

Higuchi (1) found that the release of drugs suspended in ointment bases obeys the following relationship:

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

where Q is the amount released at time t per unit area of exposure, A is the drug concentration expressed in units per cubic centimeter, C_s is the solubility of the drug in units per cubic centimeter in the external phase of the ointment, and D is the diffusion constant of the drug molecule in the external phase.

Singh *et al.* (11) found that the square root of time dependency also was observed for the release of two interacting drugs incorporated in an inert matrix. These authors found that the release of the individual compounds in benzocaine–caffeine systems, as well as the sum of the two compounds, followed a linear relationship with the square root of time.

It can be shown that the release of hexylresorcinol from ointment bases containing different amounts of ethyl myristate also follows a square root of time dependency (see Eq. A8 under *Appendix*).

The exposed surface area for the release of hexylresorcinol was calculated from the diameter of the syringe (2.0 cm) to be 3.14 cm^2. The release rate of hexylresorcinol per unit area from the different ointment bases can be calculated by dividing the slopes of the lines in Fig. 2 by 3.14 cm^2. These values are listed in Table III as a function of ethyl myristate. The data indicate that the release rate of hexylresorcinol increased as the percent of ethyl myristate in the ointment increased. Thus, it is apparent that the enhancement in the hexylresorcinol release rate was due to the increase in hexylresorcinol solubility.

To obtain insight into the effect of ethyl myristate on hexylresorcinol solubility in petrolatum and on the nature of the interaction between the two agents, the total solubility of hexylresorcinol was determined in

[4] Varian model 118.
[5] Millipore Corp., Bedford, Mass.

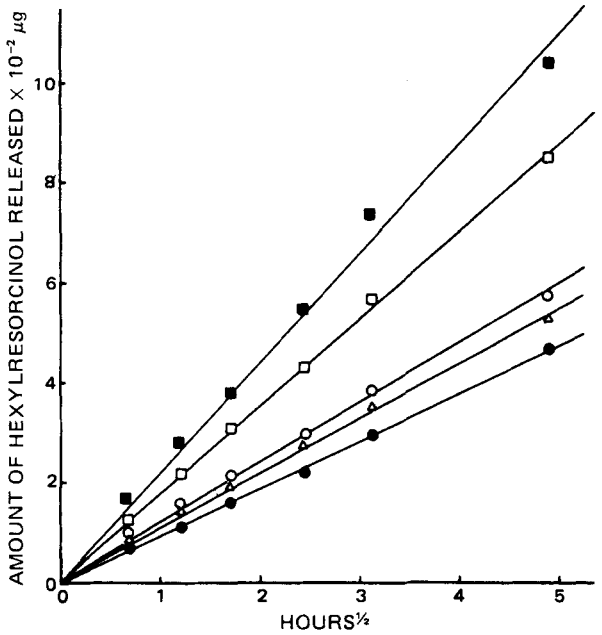

Figure 2—*Amount of hexylresorcinol released from ointment as a function of time*$^{1/2}$. *The amounts of ethyl myristate in the ointment were 0 (●), 0.5 (△), 1 (○), 3 (□), and 5 (■) %.*

petrolatum in the presence of ethyl myristate using partitioning. The partition coefficients of hexylresorcinol between the ointment bases and pH 7.4 buffer were calculated using Eq. 1 (Table IV and Fig. 3).

It is apparent from Fig. 3 that the partition coefficient of hexylresorcinol varied in a nonlinear fashion as a function of the ethyl myristate concentration. Previously, it was shown that the partition coefficient of hexylresorcinol between hexane containing various amounts of esters and pH 7.4 buffer also varied in a nonlinear fashion (12). Such behavior was rationalized on the basis of formation of 1:1 and 1:2 complexes between hexylresorcinol and the esters in hexane.

If a similar mechanism is operative in petrolatum, then the following relationships are valid:

$$HR_B \rightleftarrows HR$$

Scheme I

$$HR + EM \rightleftarrows HR\cdot EM$$

Scheme II

$$HR + 2EM \rightleftarrows HR\cdot EM_2$$

Scheme III

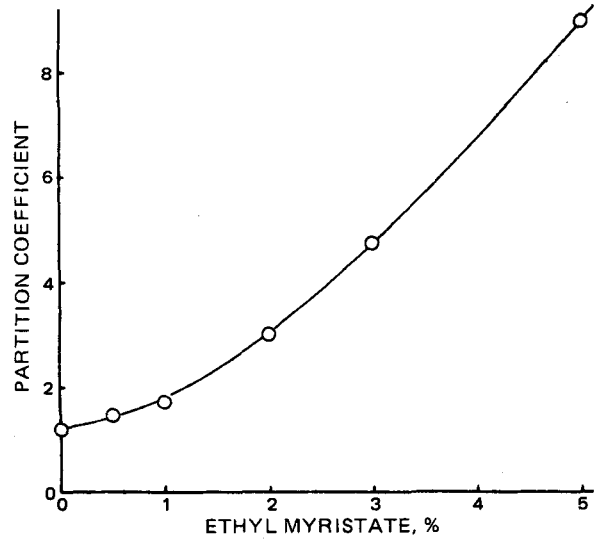

Figure 3—*Partition coefficient of hexylresorcinol between pH 7.4 buffer solution and ointment as a function of added ethyl myristate.*

Table III—Dependency of the Release Rate of Hexylresorcinol on the Percentage of Ethyl Myristate Concentration in Petrolatum

Ethyl Myristate, %	Release Rate, $\mu g/hr^{1/2}/cm^2$
0.0	29.6
0.5	35.4
1.0	38.3
3.0	55.7
5.0	70.0

Table IV—Dependency of the Partition Coefficient of Hexylresorcinol between pH 7.4 Buffer and Petrolatum on the Percentage of Added Ethyl Myristate

Ethyl Myristate, %	Partition Coefficient
0	1.23
0.5	1.47
1	1.73
2	3.06
3	4.72
5	8.97

$$P_0 = \frac{(HR)}{(HR)_B} \quad \text{(Eq. 3)}$$

$$P = \frac{(HR)_T}{(HR)_B} \quad \text{(Eq. 4)}$$

$$K_{1:1} = \frac{(HR\cdot EM)}{(HR)(EM)} \quad \text{(Eq. 5)}$$

$$K_{1:2} = \frac{(HR\cdot EM_2)}{(HR)(EM)^2} \quad \text{(Eq. 6)}$$

$$(HR)_T = (HR) + (HR\cdot EM) + (HR\cdot EM_2) \quad \text{(Eq. 7)}$$

where P_0 and P are the partition coefficients of hexylresorcinol between the buffer solution and the ointments without ethyl myristate and with ethyl myristate, respectively; $K_{1:1}$ and $K_{1:2}$ are the complexation constants of 1:1 and 1:2 complexes, respectively; and (HR), $(HR)_B$, $(HR)_T$, (HR·EM), ($HR\cdot EM_2$), and (EM) are the concentrations of free hexylresorcinol in the ointments, free hexylresorcinol in the buffer solution, total hexylresorcinol in the ointments, 1:1 complex of hexylresorcinol in the ointments, 1:2 complex of hexylresorcinol in the ointments, and free ethyl myristate in the ointments, respectively. The combination of Eqs. 3–7 results in:

$$\frac{P - P_0}{P_0} = K_{1:1}(EM) + K_{1:2}(EM)^2 \quad \text{(Eq. 8)}$$

Since a very dilute aqueous solution of hexylresorcinol was employed in the partitioning study, the concentration of the complexes can be considered to be small in comparison with the concentration of free ethyl myristate. It follows that (EM) = $(EM)_T$. Rearranging Eq. 8 results in:

$$\frac{P - P_0}{P_0(EM)_T} = K_{1:1} + K_{1:2}(EM)_T \quad \text{(Eq. 9)}$$

Table V shows the values of the left side of Eq. 9 as a function of $(EM)_T$. A plot of $(P - P_0)/P_0(EM)_T$ *versus* $(EM)_T$ should result in a straight line with the intercept of $K_{1:1}$ and the slope of $K_{1:2}$ as shown in Fig. 4. The values of $K_{1:1}$ and $K_{1:2}$ were 10 M^{-1} and 206.1 M^{-2}, respectively. The apparent solubility of hexylresorcinol in the ointment bases can be estimated on the basis of the 1:1 and 1:2 complex formation from the values of the complexation constants ($K_{1:1}$, $K_{1:2}$) as follows.

Table V—Relationship between Total Ethyl Myristate, $(EM)_T$, and $(P - P_0)/P_0(EM)_T$

$(EM)_T$, M	$(P - P_0)/P_0(EM)_T$, M^{-1}
0.0×10^{-2}	—
1.53×10^{-2}	12.88
3.07×10^{-2}	13.29
6.14×10^{-2}	24.32
9.21×10^{-2}	30.89
15.31×10^{-2}	41.29

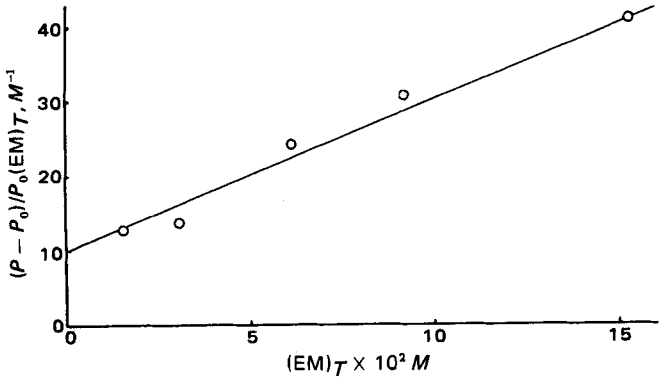

Figure 4—*Plot of* $(P - P_0)/P_0(EM)_T$ versus $(EM)_T$.

In the solubility system, $(HR)_T$ and (HR) can be written as:

$$(HR)_T = S_T \quad \text{(Eq. 10)}$$

$$(HR) = S_0 \quad \text{(Eq. 11)}$$

where S_T and S_0 are the apparent and the original solubility of hexylresorcinol, respectively. Therefore, the total concentration of ethyl myristate and S_T can be written as:

$$(EM)_T = (EM) + K_{1:1}(EM)S_0 + 2K_{1:2}(EM)^2S_0 \quad \text{(Eq. 12)}$$

$$S_T = S_0 + K_{1:1}(EM)S_0 + K_{1:2}(EM)^2S_0 \quad \text{(Eq. 13)}$$

Elimination of the $(EM)^2$ form gives an equation for the concentration of free ethyl myristate:

$$(EM) = \frac{1}{1 - K_{1:1}S_0}[(EM)_T - 2(S_T - S_0)] \quad \text{(Eq. 14)}$$

The combination of Eqs. 13 and 14 gives:

$$S_T = S_0 + \frac{K_{1:1}S_0}{1 - K_{1:1}S_0}[(EM)_T - 2(S_T - S_0)] + \frac{K_{1:2}S_0}{(1 - K_{1:1}S_0)^2}[(EM)_T - 2(S_T - S_0)]^2 \quad \text{(Eq. 15)}$$

The apparent solubility of hexylresorcinol in the ointment base can be estimated by using the determined values of $K_{1:1}$ and $K_{1:2}$ and S_0, which can be estimated as:

$$S_0 = P_0 \times S_B \quad \text{(Eq. 16)}$$

where S_B is the solubility of hexylresorcinol in the buffer solution. The results shown in Table VI strongly suggest that the apparent solubility of hexylresorcinol in the ointment base increases in the presence of ethyl myristate and is due to the complex formation between hexylresorcinol and ethyl myristate.

Table VI—Apparent Solubility of Hexylresorcinol in the Ointment Bases as a Function of Ethyl Myristate

Ethyl Myristate, %	Solubility of Hexylresorcinol in Ointments, $\mu g/cm^3$
0.0	0.680×10^3
0.5	0.801×10^3
1.0	0.987×10^3
2.0	1.479×10^3
3.0	2.121×10^3
5.0	3.753×10^3

Table VII—Relationship between Added Ethyl Myristate and $\sqrt{C_s(2A - C_s)}$

Ethyl Myristate, %	$\sqrt{C_s(2A - C_s)}$, $\mu g/cm^3$
0.0	4.578×10^3
0.5	4.976×10^3
1.0	5.488×10^3
3.0	7.894×10^3
5.0	10.203×10^3

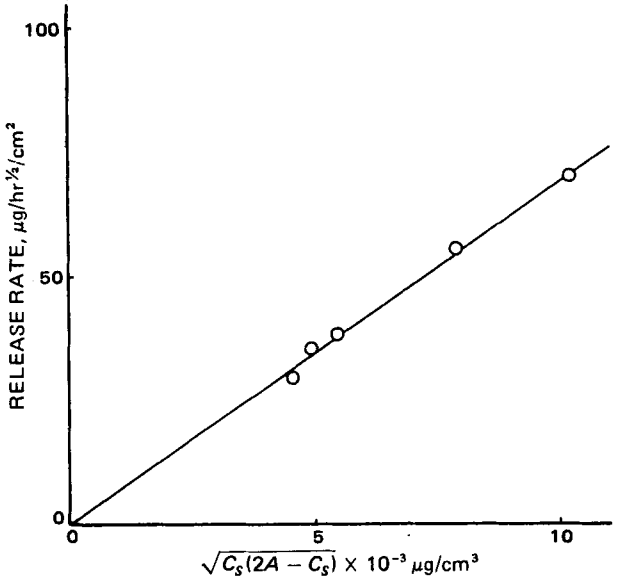

Figure 5—*Plot of release rate of hexylresorcinol from ointment* versus $\sqrt{C_s(2A - C_s)}$.

In Eq. 2, if the effective diffusion coefficient of hexylresorcinol in the ointments is the same, then the release rate depends only on the amount of hexylresorcinol and its apparent solubility in the ointments:

$$\text{release rate} = K\sqrt{C_s(2A - C_s)} \quad \text{(Eq. 17)}$$

where K is a constant expressed as $\sqrt{D}$ and A is 15.748 mg/cm³ on the basis of proper dimension. The calculated values of $\sqrt{C_s(2A - C_s)}$ are shown in Table VII.

Plots of the release rate *versus* $\sqrt{C_s(2A - C_s)}$ according to Eq. 17 should result in a straight line with a zero intercept as shown in Fig. 5. It is apparent from Fig. 5 that the enhancement in the release rate of hexylresorcinol is due only to the increase in hexylresorcinol solubility in the presence of ethyl myristate.

The calculated value of the effective diffusion coefficient, D, of hexylresorcinol in the ointment base was estimated from the slope of the line in Fig. 5 to be 1.31×10^{-8} cm²/sec. By using the values of D and C_s, the release rates of hexylresorcinol as a function of ethyl myristate were calculated using Eq. 2. These data (Fig. 6) show that good agreement was obtained between the calculated and experimental values.

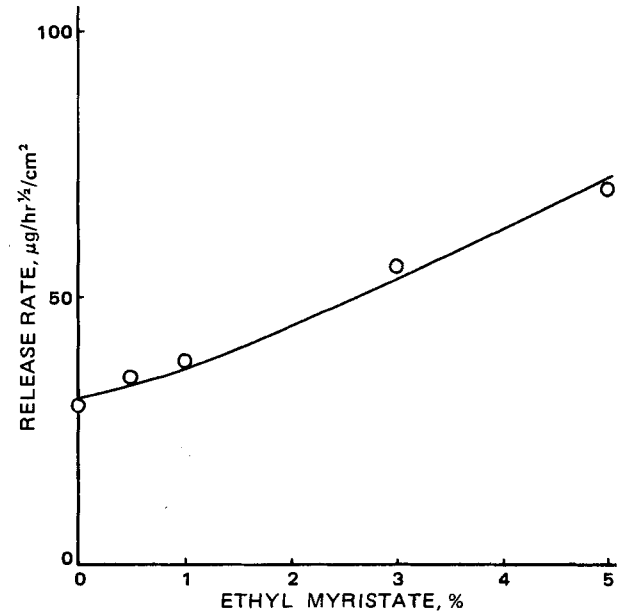

Figure 6—*Release rate of hexylresorcinol from ointment as a function of added ethyl myristate. Key:* O, *experimental values; and* —, *calculated values.*

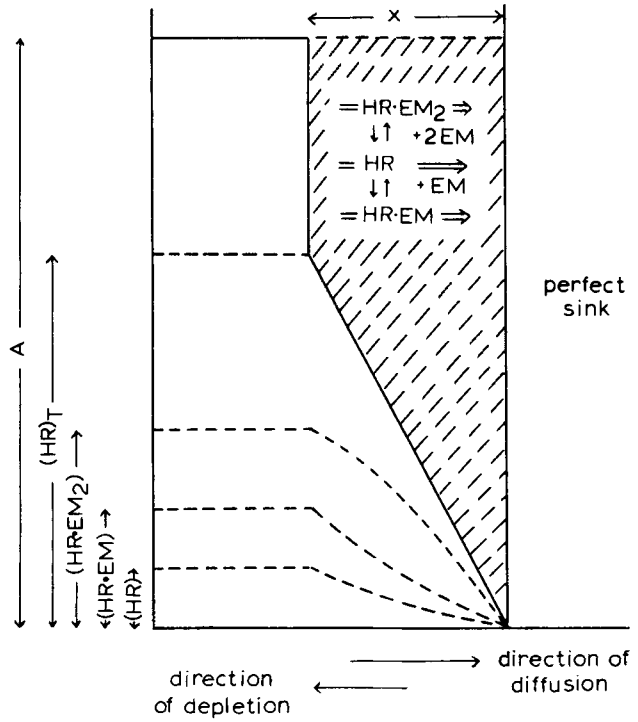

Figure A1—*Theoretical model describing the simultaneous release under sink conditions of HR, HR·EM, HR·EM$_2$, and (HR)$_T$ from petrolatum.*

APPENDIX

In the diffusion layer, the following relationships are valid:

$$HR + EM \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HR\cdot EM$$

Scheme AI

$$HR + EM_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} HR\cdot EM_2$$

Scheme AII

where k_1, k_{-1}, k_2, and k_{-2} are the rate constants for complexation. The combination of Fick's second law and reversible kinetic equations results in:

$$\frac{d(HR)}{dt} = D_1\frac{\partial^2(HR)}{\partial\chi^2} + k_{-1}(HR\cdot EM) + k_{-2}(HR\cdot EM_2) - k_1(HR)(EM) - k_2(HR)(EM)^2 \quad \text{(Eq. A1)}$$

$$\frac{d(HR\cdot EM)}{dt} = D_2\frac{\partial^2(HR\cdot EM)}{\partial\chi^2} + k_1(HR\cdot EM) - k_{-1}(HR\cdot EM) \quad \text{(Eq. A2)}$$

$$\frac{d(HR\cdot EM_2)}{dt} = D_3\frac{\partial^2(HR\cdot EM_2)}{\partial\chi^2} + k_2(HR)(EM)^2 - k_{-2}(HR\cdot EM_2) \quad \text{(Eq. A3)}$$

where D_1, D_2, and D_3 are the diffusion coefficients of HR, HR·EM, and HR·EM$_2$, respectively.

The mass balance equation for hexylresorcinol becomes:

$$(HR)_T = (HR) + (HR\cdot EM) + (HR\cdot EM_2) \quad \text{(Eq. A4)}$$

Differentiating with respect to time of Eq. A4 results in:

$$\frac{d(HR)_T}{dt} = \frac{d(HR)}{dt} + \frac{d(HR\cdot EM)}{dt} + \frac{d(HR\cdot EM_2)}{dt} \quad \text{(Eq. A5)}$$

The combination of Eqs. A1–A3 and A5 results in:

$$\frac{d(HR)_T}{dt} = D_1\frac{\partial^2(HR)}{\partial\chi^2} + D_2\frac{\partial^2(HR\cdot EM)}{\partial\chi^2} + D_3\frac{\partial^2(HR\cdot EM_2)}{\partial\chi^2} \quad \text{(Eq. A6)}$$

The diffusion coefficient of compounds is very insensitive to their molecular weights and only varies with $\sqrt[3]{1/\text{mol. wt.}}$. The molecular weights of hexylresorcinol, the 1:1 complex, and the 1:2 complex are 194, 440, and 716, respectively, and $\sqrt[3]{1/\text{mol. wt.}}$ values for the three compounds are 0.173, 0.131, and 0.112, respectively. Then $D_1 = D_2 = D_3 = D$, and Eq. A6 can be rewritten as:

$$\frac{d(HR)_T}{dt} = \frac{\partial^2(HR)_T}{\partial\chi^2} \quad \text{(Eq. A7)}$$

For such a system, the concentration profiles that may exist after the lapse of finite time can be drawn (Fig. A1).

As seen from Eqs. A1–A3 and A7 and Fig. A1, the concentration gradients of (HR), (HR·EM), and (HR·EM$_2$) do not give a straight line, but the concentration gradient of (HR)$_T$ gives a straight line and Eq. A8 can be used to calculate the release rate of hexylresorcinol in this system (1):

$$\text{release rate} = \sqrt{DC_s(2A - C_s)} \quad \text{(Eq. A8)}$$

REFERENCES

(1) T. Higuchi, *J. Pharm. Sci.*, **50**, 874 (1961).

(2) W. I. Higuchi, *ibid.*, **51**, 802 (1962).

(3) J. Surowiecki, *Diss. Pharm. Pharmacol.*, XXIV, **4**, 407 (1972).

(4) J. Ostrenga, J. Haleblian, B. Poulsen, B. Ferrell, N. Mueller, and S. Shastri, *J. Invest. Dermatol.*, **56**, 392 (1971).

(5) C. W. Whitworth, *J. Pharm. Sci.*, **57**, 1540 (1968).

(6) C. W. Whitworth and R. E. Stephenson, *ibid.*, **60**, 48 (1971).

(7) M. Nakano and N. K. Patel, *ibid.*, **59**, 985 (1970).

(8) C. W. Whitworth and C. H. Becker, *ibid.*, **54**, 569 (1965).

(9) B. J. Poulsen, E. Young, V. Coquilla, and M. Katz, *ibid.*, **56**, 928 (1967).

(10) Z. T. Chowhan and R. Pritchard, *ibid.*, **64**, 754 (1975).

(11) P. Singh, S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **56**, 1548 (1967).

(12) E. Akaho, Ph.D. thesis, University of Kentucky, Lexington, Ky, 1979.