ACKNOWLEDGMENTS AND ADDRESSES

Received March 24, 1969, from *Department of Pharmaceutical Chemistry, College of Pharmacy, St. John's University, Jamaica, NY 11432*

Accepted for publication May 7, 1969.

Abstracted in part from a dissertation submitted by L. W. Gerencser to the Graduate Division, College of Pharmacy, St. John's University, in partial fulfillment of Masters' of Science degree requirements.

The authors thank Dr. H. Eisen for his valuable suggestions during the preparation of this manuscript and Mr. J. Patel for his technical assistance.

A part of this work was presented at the First American Peptide Symposium, Yale University, New Haven, Conn., August, 1968, and communicated by A. Kapoor, L. W. Gerenscer, and W. R. Koutnik, *J. Pharm. Sci.*, **58**, 281(1969).

Release Rates of Salicylates from Cocoa Butter I

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Abstract □ The release of *N*-methyl salicylamide, methyl salicylate, and salicylic acid across a hydrophobic membrane from cocoa butter to an aqueous layer was studied at a temperature of 37°. The release of the drugs at the interface was diffusion-controlled. The Higuchi model was modified to account for the fact that the release rates were not constant, but varied inversely with the respective partition coefficients. Since the transference across the interface was a function of the partition coefficient, it was found that as the partition coefficient decreased, the release rate appeared to approach a limiting value.

Keyphrases □ Salicylates—release rates, cocoa butter □ Partitioning salicylates—cocoa butter–water □ Release rates, salicylates—continuous flow cell □ UV spectrophotometry—analysis

Cocoa butter has long been used as a base for suppositories, but the manner by which drugs are released from this base has not been shown. In the absence of a suitable model, several empirical relationships (1, 2) have been developed for the determination of the safe and efficacious amount of drug to be incorporated into the base; yet none has proven to be totally satisfactory.

The continuous release of salicylic acid, *N*-methyl salicylamide, and methyl salicylate from cocoa butter was tested for the applicability of the Higuchi model (3) to these systems. These compounds were chosen because (*a*) the difference between their respective diffusion coefficients should be insignificant, and (*b*) they have a range of solubilities in the cocoa butter. The partition coefficients of these drugs were studied to determine any effect on the release pattern of this system.

EXPERIMENTAL

Measurement of Partition Coefficients—A direct method was used to determine the partition coefficient of the drugs between cocoa butter and water. The aqueous phase was adjusted to a pH at least two units below the pKa value of the drug to limit the form of the partitioning drug to a single species. Deionized water was used for methyl salicylate, while *N*-methyl salicylamide and salicylic acid required HCl-adjusted solvents to pH 4 and 1, respectively.

Equilibrium was attained in from 24–48 hr.; however, with time, some of the cocoa butter became dispersed in the water phase resulting in a cloudy appearance. Therefore, contact time of the two phases should be minimized. The portion of drug which was expected to be in each phase upon reaching equilibrium was dissolved in the cocoa butter and water separately. The two immiscible solutions were combined and shaken well. The two phases quickly separated and were then maintained for 12–15 hr. in a constant-temperature gyrotory water bath[1] at 37 ± 0.1°. After equilibration, the phases were placed in separate containers and assayed for drug content.

As much cocoa butter as possible was removed from the aqueous layer which was placed in a conical flask, covered with a polyethylene film to limit evaporation, and allowed to remain at 20° for 5 hr. A pipet (T.C.), with its tip covered with fine glass wool, was used to withdraw a sample of solution. The sample was discharged into a 100-ml. volumetric flask and the pipet washed repeatedly with the appropriate solvent directly into the flask which was then filled to volume. The solutions were then analyzed at 302 and 360 mμ spectrophotometrically.[2] Two wavelengths were required to correct the drug analysis for the cocoa butter. This was accomplished by taking the absorbance at 360 mμ, where only cocoa butter absorbed light, and from a predetermined calibration curve for cocoa butter alone obtaining its absorbance contribution at 302 mμ where the drugs also absorbed light. By difference, the absorbance due to the drug was obtained at 302 mμ. The absorptivities using the Beer-Lambert equation for a 1-cm. cell were 0.2349 for methyl salicylate, 0.2039 for *N*-methyl salicylamide, and 0.5170 for salicylic acid. The concentration was expressed in mg./100 ml.

Each drug in the cocoa butter was assayed by a nonaqueous titration procedure similar to the one described by Fritz (4) and previously shown to be accurate to within 1%. To remove the water which remained in the liquefied cocoa butter, anhydrous sodium chloride was added and the mixture was shaken and centrifuged. The oleaginous layer was decanted and powdered anhydrous sodium sulfate added. This was shaken for a period of 2 min., centrifuged, and placed in a 40° oven for 1 hr. The cocoa butter was finally decanted into a tared flask and weighed. Ninety milliliters of pyridine was added for the titrimetric determination of methyl salicylate and *N*-methyl salicylamide, using azo-violet as the indicator. In the case of salicylic acid, 100 ml. of chloroform was added with thymol blue as the indicator. In all cases standardized sodium methoxide (0.1 *N*) was used as the titrant. The concentration of drug in the base was calculated in terms of mg. of drug/g. of drug-cocoa butter solution.

Release Rate Determination—A continuous-flow method similar to that of Sjogren and Ervik (5) was utilized to study the release rate of each drug from cocoa butter. A continuous-flow cell[3] was used in the monitoring spectrophotometer. The partitioning cell[4] (Fig. 1) and a pump (model T-8 Sigma) were connected to the continuous-flow cell by means of tubing [Tygon, 0.635-cm. (1/4-in.) i.d.].

[1] Model G-76, New Brunswick Scientific Co., New Brunswick, N. J.

[2] Beckman DK-2 recording spectrophotometer.

[3] Beckman model No. 92522 continuous-flow cell.

[4] Loaned from the Sandoz Pharmaceutical Corp., Hanover, N. J.

In the partitioning cell, the sample was separated from the aqueous phase by a membrane. The membrane found most suitable was a hydrophobic fluorinated vinyl[5] of 0.45-μ pore size. Water was unable to penetrate the membrane; however, the drug passed through readily. This allowed the area in contact between the phases to be held constant.

Sufficient water (138 ml.), adjusted to a specific pH, was placed in the system so that the membrane barrier was submerged to a 1-cm. depth. A rotating stirring bar in the lower chamber of the partition cell was used to prevent a stagnant layer of drug from forming at the membrane interface. The sample of liquefied cocoa butter containing dissolved drug was introduced on top of the membrane barrier after 1 hr. of pre-equilibration time at 37 ± 0.1°.

RESULTS AND DISCUSSION

Partition Studies—A linear distribution coefficient isotherm of *N*-methyl salicylamide, salicylic acid, and methyl salicylate between cocoa butter and water was established. The partition coefficient, K, is defined as:

$$K = \frac{(C_{cb})^n}{C_{aq}} \qquad \text{(Eq. 1)}$$

where C_{aq} is mg. of drug/ml. of water, C_{cb} is mg. of drug/g. of drug-cocoa butter solution, and n is the degree of association of the drug in the cocoa butter. Taking the logarithm and rearranging, Eq. 1 becomes:

$$\log C_{cb} = \frac{1}{n} \log C_{aq} + \frac{\log K}{n} \qquad \text{(Eq. 2)}$$

A representative log-log plot for C_{cb} *versus* C_{aq} is shown in Fig. 2. Using the method of least squares (6), the degree of association was found to be 0.8787 ± 0.1126 (*SD*), 0.9958 ± 0.1176, and 0.9932 ± 0.3827, for *N*-methyl salicylamide, salicylic acid, and methyl salicylate, respectively. Considering the experimental error involved and the fact that any value less than one would have no physical meaning, the degree of association was taken to be 1.0, thus indicating no dimerization.

The partition coefficient used is the mean of the individual values obtained when the concentration in the cocoa butter is divided by the concentration in the water. These values are 4.90 ± 0.148 (*SD*), 30.1 ± 0.95, and 280 ± 25.5, for *N*-methyl salicylamide, salicylic acid, and methyl salicylate, respectively.

Release Rate Studies—T. Higuchi (3) derived an equation for the release rate of drugs from an ointment base. W. Higuchi (7) subsequently simplified the equation to:

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

where Q is the amount released/100 ml., C_0 is the initial concentration of drug in mg./g. of solution, and D is the diffusion coefficient of the drug in the base. The simplified equation applies when less than 30% of the contained drug is released. This model is based on the assumption that: (*a*) only a single drug species is important in the base; (*b*) the diffusion coefficient is constant with respect to both time and position in the base; (*c*) the drug alone is allowed to diffuse out of the base; and (*d*) the drug is rapidly removed upon reaching the interface. All assumptions should be valid for the system in this study.

Furthermore, the model also assumes that the phase receiving the drug is a "perfect sink." The experimental system used in this study complied with this stipulation since at no time did the concentration of drug in the bulk phase exceed 0.002%.

The system also complied with the restriction imposed above in order to simplify the equation since the maximum amount of drug released at any time was less than 1% of the total amount in the base.

Before the model could be tested to see if it applied to this system, the effect of the rate of flow of solvent had to be determined. A preliminary study showed that the release rate increased slightly when the flow rate was changed from the slowest to the fastest setting on the Sigma pump. It was observed visually that the pulsating flow of the solvent due to the Sigma pump caused the membrane to move up and down. The movement was greatest at the center since the membrane was fixed at the perimeter. It was thought that the movement of the pulsating membrane might have produced a constant rate of exchange of components at the interface which would account for the dependence of the rate of release of drug on the flow rate. Therefore, the rate of flow of the system was arbitrarily set at 75 ml./min.

To test the hypothesis that the diffusional migration of drug in the base is the rate-controlling step, the amount of drug released/100 ml. was plotted *versus* $\sqrt{t}$ as represented in Fig. 3 when methyl salicylate was used. The resulting curve was linear as long as no cocoa butter leaked through the membrane. This indicated that the application of this model appeared valid. When cocoa butter did leak through the membrane, the increase in the surface area in contact at the interface increased the release rate. This fact had to be accounted for in each release run since some leakage always

[5] Metricel VF-6, Gelman Instrument Co., Ann Arbor, Mich.

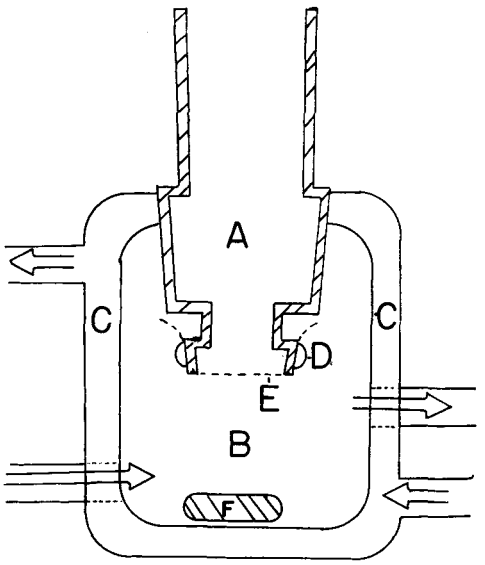

Figure 1—*Cross-sectional diagram of the partitioning cell. Key:* A, *upper chamber containing cocoa butter solution;* B, *lower chamber, "sink";* C, *water jacket;* D, *collar-holding membrane;* E, *membrane;* F, *stirring bar.*

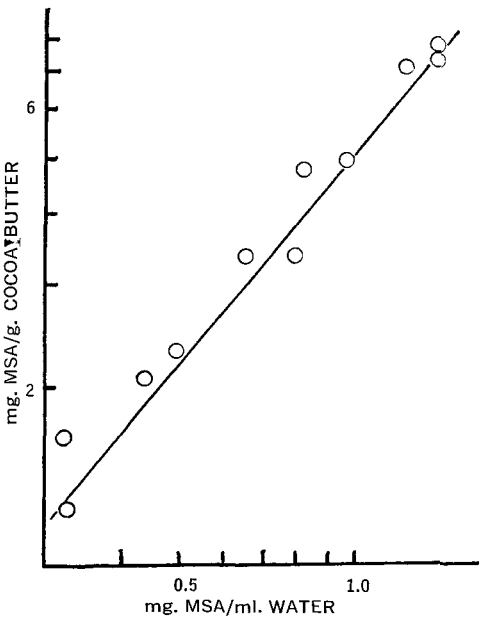

Figure 2—*Log-log plot of the concentration of* N*-methyl salicylamide in the cocoa butter (mg. MSA/g. cocoa butter)* versus *concentration in the aqueous phase (mg. MSA/ml. water).*

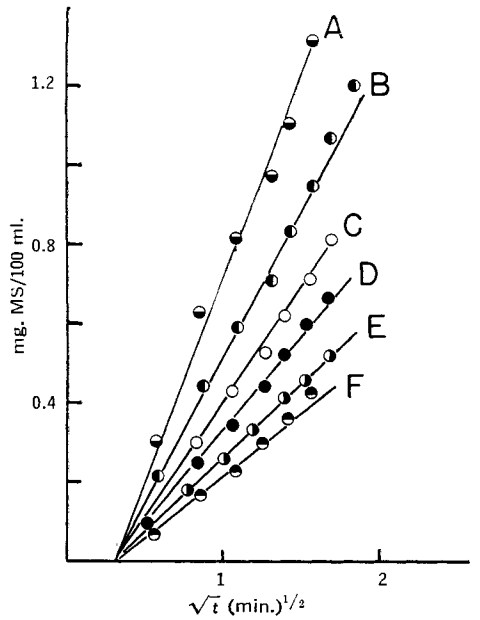

Figure 3—*Plot of the amount of methyl salicylate released (mg. MS/100 ml. water)* versus *the square root of time (min.$^{1/2}$). Key: initial concentrations (mg./g. cocoa butter solution):* A, *161.8;* B, *124.8;* C, *96.1;* D, *84.6;* E, 71.4; F, *61.7.*

eventually occurred. To negate the leakage effect, the lower points of the plots of concentration *versus* $\sqrt{t}$ were weighed more heavily in determining linearity. Similar linear release patterns were obtained for *N*-methyl salicylamide and salicylic acid.

It should be pointed out that in all cases, plots of amounts of drug released *versus* $\sqrt{t}$ did not pass through the origin as the theory for the model predicts. The model of Koizumi and Higuchi (8) also exhibited a lag time for the release of a drug across an artificial membrane. They were able to show mathematically that the lag time was partially due to the lower diffusion coefficient within the membrane as compared to the bulk phase. In the experimental system studied here the effective diffusion coefficient of the drug within the membrane should also be lower than in the bulk phase. Thus, as in the Koizumi-Higuchi model, the lag time of the system could be attributed to the presence of the membrane separating the bulk phase and sink. This is supported by the fact that the lag time is independent of pH of the receptor phase and the initial concentration of drug in the cocoa butter.

Partition Coefficient-Release Rate Relationship—Inspection of Eq. 3 shows that the T. Higuchi model is independent of the partition coefficient. This equation can be rearranged to:

$$\frac{Q}{C_0 t^{1/2}} = 2\left(\frac{D}{\pi}\right)^{1/2} \qquad \text{(Eq. 4)}$$

The left-hand side of Eq. 4 should remain constant regardless of the partition coefficient. To test this, the release "rate" ($Q/t^{1/2}$) divided by the initial concentration of drug in the cocoa butter (C_0) was plotted as a function of the inverse of the partition coefficient (Fig. 4). Rather than the straight line, with zero slope, which Eq. 4 predicts, a curved line was obtained which appears to approach a plateau at low partition coefficients. A review of the simplified Higuchi equation was required in an attempt to explain such behavior by this model.

In Eq. 4, the only variable not accounted for was the diffusion coefficient. However, the data indicates that it would have to increase by a factor of 3.7 to account for the variation in release rate between methyl salicylate and *N*-methyl salicylamide. This is unlikely, owing to the insignificant difference in size and shape of these molecules. Furthermore, this order of magnitude could not be accounted for by a difference in the degree of solvation of the molecules in the cocoa butter. Thus, it appears that this model is

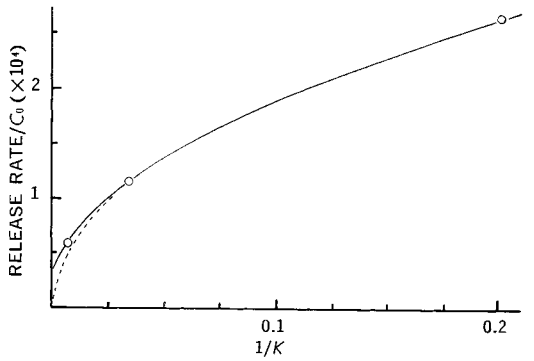

Figure 4—*Plot of the release rate*/C_0 versus *the inverse of the partition coefficient.*

not totally adequate to explain the mechanism of the release of drugs in this system.

In reviewing other possible models it was noted that the release rate was proportional to the partition coefficient when a diffusional barrier was present in the receptor phase (3). In the derivation of his equation for the diffusion of a drug to the interface, T. Higuchi assumed that upon reaching the interface the drug was rapidly removed. Thus, it appears that for the authors' experimental system the model of T. Higuchi must be modified to include a diffusional barrier in the aqueous phase. To aid in the understanding of the role of the partition coefficient, it may be looked upon as the ratio of the rate of release of solute from the oil into the water to the rate at which it returns. A small partition coefficient indicates that the first rate predominates as in the case of the rapidly released *N*-methyl salicylamide. The second rate would prevail for a drug with a high partition coefficient as is the case with methyl salicylate.

Support is given to this interpretation of the data by the relatively small increase in release of salicylic acid at a high pH. Since the reverse rate of *N*-methyl salicylamide is relatively small, eliminating this rate should increase the release rate only slightly. The release rate of salicylic acid increased from 1.1×10^{-4} to 3.1×10^{-4} when a phosphate buffer of pH 6.8 (9) was used as compared to 2.5×10^{-4} for *N*-methyl salicylamide. This could be accounted for by high dissociation constant of salicylic acid, thus effectively eliminating the return rate.

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ACKNOWLEDGMENTS AND ADDRESSES

Received February 6, 1969, from *Rutgers, The State University, College of Pharmacy, Newark, NJ 07014*

Accepted for publication May 2, 1969.

Abstracted in part from a thesis submitted by Aaron L. Weiss to the Graduate School of Rutgers, The State University, in partial fulfillment of the Master of Science degree requirements.

This study was supported in part by a grant from the Sandoz Pharmaceutical Co., Hanover, NJ 07936