for 12 hr and refrigerated overnight. The precipitate was filtered and washed with dry ether, and the filtrate was evaporated *in vacuo*, leaving an oil. This oil was distilled at 165–170°/0.2 mm, giving 3.8 g (25%) of a solid, mp 42–45°; IR (potassium bromide): 3300 (NH), 1520 (NO_2), 1335–1375, and 1125–1150 (SO_2) cm^{-1}; $[\alpha]_D^{30}$ +37.0° (c = 1, ethyl acetate).

Anal.—Calc. for $C_{10}H_{11}F_3N_2O_4S$: C, 38.46; H, 3.53; N, 8.97; S, 10.26. Found: C, 38.7; H, 3.8; N, 9.2; S, 10.3.

(+)-*N*-Trifluoromethanesulfonyl-1-methyl-2 - (4 - trifluoroacetylaminophenyl)ethylamine (XIV)—A solution of 3.12 g (0.01 mole) of V in 150 ml of tetrahydrofuran with 0.4 g of platinum dioxide was hydrogenated at 3 atm. After 48 hr, the solution was filtered and the solvent was removed *in vacuo*. The residual viscous liquid was dissolved in 250 ml of benzene; to this solution was added, with stirring, 2.1 g (0.015 mole) of trifluoroacetic anhydride. The mixture was refluxed for 3 hr, allowed to cool, and refrigerated overnight. The resulting solid was filtered, washed with water, and dried *in vacuo*. Recrystallization from aqueous ethanol gave 0.8 g, mp 143–145°; IR (potassium bromide): 3350, 3230 (NH), 1700 (C=O), 1200, and 1150 (SO_2) cm^{-1}; $[\alpha]_D^{29}$ +20° (c = 1, ethyl acetate).

Anal.—Calc. for $C_{12}H_{12}F_6N_2O_3S$: C, 38.10; H, 3.17; N, 7.41; S, 8.47. Found: C, 38.2; H, 3.2; N, 7.7; S, 8.1.

Antiobesity Test—Rats were trained over 2 weeks to eat their daily food ration[4] in only 5 hr. After training, either vehicle (controls) or drug was administered orally by gastric intubation daily for 5 days. One hour after drug, tared food cups containing the food ration were presented. The cups were weighed after 1 hr of feeding and again after 5 hr of feeding. Water was available *ad libitum*. Rats were weighed daily before drug administration.

[4] Ground Purina Laboratory Chow.

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[x] To whom inquiries should be directed.

Release of Drugs from Ointment Bases II: *In Vitro* Release of Benzocaine from Suspension-Type Aqueous Gels

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Abstract □ The *in vitro* release of benzocaine, suspended in an aqueous gel, through silicone rubber membranes was studied to test an extension of existing mathematical models. The theoretical treatment proposed is intended for experimental systems involving release, through a nonporous membrane, of a drug whose concentration is a few times (≥3) greater than its solubility in the vehicle. For either micronized (2 μm) or macrosize (125 μm) drug, the Q (amount released) *versus* $t^{1/2}$ (time$^{1/2}$) plots were not linear until substantial time had elapsed. Excellent agreement was found between the experimental points and theoretical plots, generated by a computer fit to experimental data of an equation derived from a reported vehicle-boundary diffusion layer model. The values of the solubility and of the diffusion coefficient of benzocaine in the gel, calculated by the present mathematical treatment from release data, were in agreement with literature data. The particle size of released benzocaine did not influence the release pattern, thus confirming release in the present conditions to be diffusion rather than dissolution controlled. The present method is applicable for determining the solubility and diffusion coefficient of drugs in vehicles in cases not contemplated in current release theories.

Keyphrases □ Drug release—benzocaine from aqueous gels through silicone rubber membranes *in vitro*, mathematical models extended □ Benzocaine—release from aqueous gels through silicone rubber membranes *in vitro*, mathematical models extended □ Models, mathematical—extended to fit *in vitro* drug release system where drug concentration is greater than solubility in vehicle □ Solubility—benzocaine in aqueous gel vehicle, calculations derived from mathematical drug release models □ Diffusion coefficients—benzocaine in aqueous gel vehicle, calculations derived from mathematical drug release models

The *in vitro* release of drugs from topical vehicles, in spite of its limited correlations with *in vivo* absorption, may offer useful information on some physicochemical factors involved in the latter process. Such important parameters as the diffusion coefficient and the solubility of a drug in a vehicle can be calculated by relatively simple equations, derived from mathematical models describing the process of *in vitro* release of drugs dissolved (1–3) or

suspended (1, 4–7) in ointment bases. In practice, these equations are used rarely, since their use is restricted by theoretical requirements whose fulfillment is difficult to realize and to verify in most experimental systems (3, 8–10).

For suspended systems, zero concentration of the drug at the interface separating the donor and the receiving phase is required in the vehicle-controlled model proposed by Higuchi (4), while Roseman and Higuchi's (6) vehicle–interfacial barrier-controlled model applies only to systems where the solubility of the drug is negligible with respect to the concentration in the vehicle. Neither model adequately fits some common experimental systems such as those involving release through a nonporous membrane of a drug whose concentration is only a few times greater than its solubility in an ointment.

The purposes of the present work are to describe and to assess an extension of the existing quantitative treatments that might be useful in similar cases. As a practical test of the theory, the release of benzocaine from suspension-type aqueous gels through silicone rubber membranes was investigated.

THEORETICAL

The matrix–boundary layer model proposed by Roseman and Higuchi (6) for the release of drugs suspended in planar matrixes may be extended to any homogeneous solid or semisolid vehicle separated from a receptor sink by a planar diffusional barrier. Accordingly, the following equation describing the pattern of the amount of drug released *versus* time can be derived:

$$Q^2 + 2D_vRAQ = 2D_vAC_st \qquad \text{(Eq. 1)}$$

where Q is the amount of drug released per unit area; D_v is the effective diffusivity of drug in the vehicle; A and C_s are the total concentration and the solubility, respectively, of drug in the vehicle; and R is the diffusional resistance of the barrier interposed between the vehicle and the receiving phase[1].

The following assumptions were made in the derivation of Eq. 1: (*a*) a quasi-steady state (11) exists, (*b*) the drug particles are small when compared to the average distance of diffusion, (*c*) the concentration of drug in the vehicle is much greater than its solubility in the vehicle ($A \gg C_s$), (*d*) the diffusion coefficients in the vehicle and in the barrier are constant, (*e*) diffusion rather than dissolution is the rate-controlling step, (*f*) the diffusion process occurs through the continuous phase rather than through pores or channels within the medium, and (*g*) the receiving solution is a perfect sink.

Equation 1 is essentially valid for all times in which the suspended phase is present, less than the initial lag time, corresponding to the time necessary for establishment of a quasi-stationary state and for the average distance of diffusion to overwhelm particle dimension [see conditions (*a*) and (*b*)].

When $Q^2 \gg 2D_vRAQ$, *i.e.*, when $Q/A \gg 2D_vR$, Eq. 1 reduces to Eq. 2, previously derived by Higuchi (4) for the entirely vehicle-controlled process:

$$Q = \sqrt{2AC_sD_vt} \qquad \text{(Eq. 2)}$$

Under these conditions, any appreciable resistance to diffusion at the vehicle-receiving phase interface, where the drug concentration drops to negligible values, no longer exists.

Where C_s is not negligible with respect to A, the vehicle-controlled model is described by (3):

$$Q = \sqrt{(2A - C_s)C_sD_vt} \qquad \text{(Eq. 3)}$$

The conditions for validity of Eq. 3 are the same as for Eq. 2, except that the total drug concentration (A) is only a few (3–4) times greater than the solubility in the vehicle (C_s). The application of Eq. 3 to the determination of the diffusivity and solubility of drugs in solid or semisolid vehicles was reported previously (12). However, Eq. 3 is only applicable when zero concentration exists at the vehicle-receiving phase interface. This condition is well approximated only in cases of very little diffusional resistance of the interfacial barrier compared with that of the vehicle. The more general Eq. 1, although not limited by this condition, is only valid when C_s is negligible with respect to A [condition (*c*)], so its use for the determination of D_v and C_s is limited in cases of high C_s values due to considerable experimental difficulties in attaining the $A \gg C_s$ condition.

The applicability of Eq. 1 can be extended to experimental systems in which A is but a few times (≥ 3) greater than C_s if it is modified as follows:

$$Q^2 + 2D_vRA^*Q = 2D_vA^*C_st \qquad \text{(Eq. 4)}$$

where:

$$A^* = A - \frac{(C_s + C_v)}{2} \qquad \text{(Eq. 5)}$$

and C_v represents the concentration of drug in the vehicle at the interface with the barrier. According to the assumptions made in the *Appendix*, where details of the derivation of Eq. 4 are discussed, A^* seems to be comparatively little influenced by the variation of C_v with time and may be considered as constant. For small values of R and/or large values of time, Eq. 5 reduces to $A^* = A - C_s/2$ (*cf.*, Eq. 8) and Eq. 4 reduces to Eq. 3.

Equation 4 should lend itself to the determination of the solubility and diffusivity of drugs in ointments through release data when either Eq. 1 or 3 is inapplicable. Therefore, it is convenient to put Eq. 4 in the form:

$$Q = -a + \sqrt{a^2 + b(t - q)} \qquad \text{(Eq. 6)}$$

where $a = D_vRA^*$, $b = 2D_vC_sA^*$, and q is a correction term which depends on the lag time.

The values of a, b, and q can be obtained through a least-squares fit of Eq. 6 to experimental release data. By recalling Eq. 5, the following relationship between the parameter b and $(A - C_v/2)$ can be written:

$$b = 2D_vC_s\left(A - \frac{C_v}{2}\right) - D_vC_s^2 \qquad \text{(Eq. 7)}$$

For the same reasons indicated for Eqs. 4 and 5, Eq. 7 is supposed to hold with sufficient approximation for any value assumed by C_v in the time interval under study. Since linear concentration gradients are assumed, the value of C_v at any point of this interval can be obtained, once the diffusional resistance, R, is experimentally determined (*e.g.*, by steady- or quasi-steady-state permeation experiments), from the relationship (11):

$$C_v = R\frac{dQ}{dt} \qquad \text{(Eq. 8)}$$

where dQ/dt, the instantaneous release rate, can be obtained from Eq. 6 by differentiation. According to Eq. 7, it should be possible to construct a linear plot of b *versus* $(A - C_v/2)$ by carrying out experiments with varying drug concentrations ($A \geq 3C_s$) and calculating a single C_v value for each A at any time in the interval studied. The value of C_s equals twice the abscissa intercept of this plot.

Alternatively, C_s can be obtained from the averaged ratio of parameter b to parameter a (Eq. 6) once R is known:

$$C_s = (R/2)\overline{(b/a)} \qquad \text{(Eq. 9)}$$

Following the calculation of C_s, D_v can be calculated from the slope of the b *versus* $(A - C_v/2)$ plot utilizing Eq. 7. The accuracy of the results and its dependence on the C_v values used in the calculations will be evaluated later.

EXPERIMENTAL

Materials—Carbomer 934P, a carboxyvinyl polymer[2], was used as received; its sodium salt was prepared as described in the literature (13). Benzocaine[3] was crystallized to a constant melting point of 91.5°. Particles with an average diameter of 125 μm (geometric) were obtained using 100–140-mesh ASTM sieves. A sample was micronized[4], and the average diameter of the particles (microscopic analysis) was 2.0 μm (geometric).

[1] When more than one barrier is involved (*e.g.*, a membrane and the adjacent hydrodynamic layer), the resistance is the sum of the resistances of the individual barriers.

[2] Carbopol 934, B. F. Goodrich Chemical Corp., Cleveland, Ohio.
[3] Carlo Erba, Milano, Italy.
[4] Jet mill model JMRS-80, Fryma Maschinen AG, Rheinfelden, Switzerland.

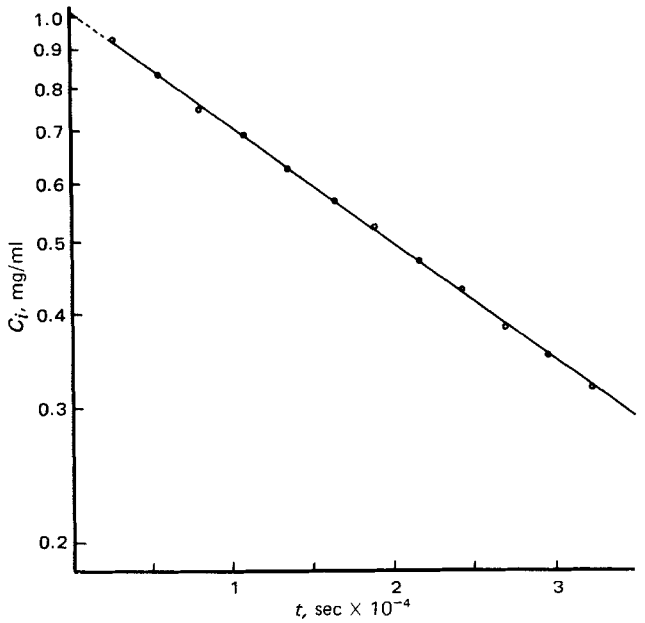

Figure 1—*Quasi-steady-state permeation plot of benzocaine through a silicone rubber membrane from an aqueous solution. Initial concentration* C_{i0} = *1.0 mg/ml.*

Silicone rubber[5] sheeting, labeled thickness of approximately 127 μm, was used as the membrane material.

Solubility Determinations—The water solubility of benzocaine at 30°, determined spectrophotometrically[6] (286 nm) on a sample equilibrated for 3 days, was 1.31 g/liter. The solubility in the gel was presumed to be the same, since gels containing 1.31 mg of benzocaine/ml were perfectly clear on microscopic[7] examination while suspended particles were visible in the gel kept at 30° several days after addition of 5% excess drug over the water solubility value.

Gel Preparation—The following procedure allowed preparation of homogeneous, air-free, suspension-type gels. To 100 ml of a saturated solution of benzocaine (0.13% w/v) in distilled water at 30° was added portionwise, while stirring, the sodium salt of the carboxyvinyl polymer (1.0 g, or 2.0 g in one case) together with the appropriate amount of either micronized or macrosize benzocaine. After the addition, the vessel was connected to a water pump; thorough stirring was continued until a bubble-free, clear gel formed.

After preparation, all gels were stored at 30° for future use. The benzocaine contents of the gels used, determined spectrophotometrically after appropriate dilution with water, were 2.59, 3.03, 3.70, 4.60, 5.10, and 10.90 mg/ml for micronized drug and 3.05, 4.12, and 4.92 mg/ml for macrosize drug.

Release Experiments—The release of benzocaine from the gels through silicone rubber membranes was investigated using a previously described apparatus (14) with minor modifications. A new cell, made entirely of polymethyl methacrylate[8], was used in place of the metal cell. The metal cell released, to the acidic (0.1 *N* HCl) receiving solution, substances interfering with the spectrophotometric assays. The only metal parts were the screw shanks (*cf.*, Ref. 14, Fig. 1), whose contact with the external solution was prevented by polymethyl methacrylate cap nuts and silicone rubber gaskets. The transparent material also allowed inspection of the cell contents, so the development of a sharply defined depletion zone in the gels could be observed during the experiments.

The capacity of the cell was 19.60 ml, and the diameter of the available area for diffusion was 5.0 cm. The cell was filled with the gel, the excess was removed with a spatula to produce an even surface, and the membrane, which had been presoaked in water for at least 24 hr, was carefully placed and pressed on the gel. The upper part of the cell was then assembled. All of these operations were performed in a conditioned atmosphere (30° and 100% relative humidity). The cell was then placed into a jacketed beaker (full capacity of 1.5 liters) connected to a constant-temperature bath (30 ± 0.1°) and circulator.

[5] Silastic, Medical Products Division, Dow Corning Corp., Midland, Mich.
[6] Beckman DU spectrophotometer.
[7] Zeiss Zoom III stereomicroscope.
[8] Plexiglas, Rohm & Haas Co., Philadelphia, Pa.

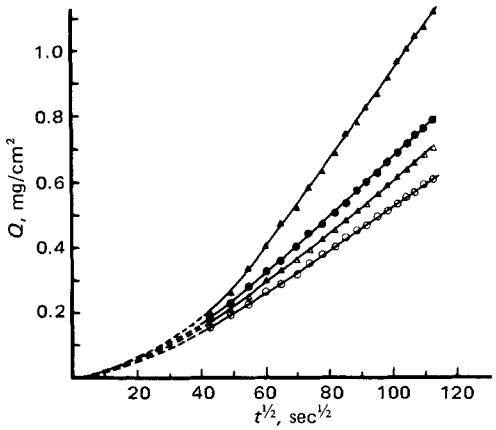

Figure 2—*Amount of benzocaine released from suspension-type gels prepared with micronized drug as a function of the square root of time. Key:* ▲, *10.9 mg/ml;* ●, *4.6 mg/ml;* △, *3.7 mg/ml; and* ○, *2.59 mg/ml. Two plots (5.10 and 3.03 mg/ml) were omitted for clarity.*

At t = 0, prewarmed 0.1 *N* HCl (0.5–1.0 liter, depending on the gel concentration) was introduced into the beaker, and stirring was immediately initiated using a two-blade propeller connected to a 300-rpm synchronous motor[9]. At appropriate intervals, measured volumes of the receiving phase were removed, diluted, if necessary, with 0.1 *N* HCl, and analyzed spectrophotometrically for benzocaine hydrochloride (227 nm). Blank runs demonstrated the absence in the external solution of materials that might interfere with the measurements.

Diffusional Resistance of Membrane—This value was determined by allowing benzocaine to permeate through the membrane under quasi-steady-state conditions. The experimental technique was described previously (15, 16). The permeation cell used had polymethyl methacrylate parts, instead of the stainless steel parts of the original cell, in contact with the external solution. The membranes were of the same type as in the release experiments and were presoaked in water for at least 24 hr. Both the internal and external stirring was performed by 300-rpm synchronous motors[9].

The available area for diffusion was 7.55 cm^2; the volume of the internal solution (benzocaine in distilled water, 0.1% w/v) was 25.0 ml. The experiments were carried out at 30°. Aqueous 0.1 *N* HCl (500 ml) was used as the external solution; the permeant content of this solution was determined at appropriate intervals, as in the release experiments. The concentration of the internal solution (C_i) at different times was calculated from the final drug concentration inside the cell and the amount that had appeared in the external solution. Blank runs demonstrated the absence, in the external solution, of materials that might interfere with the measurements.

Data Treatment—Each release and permeation experiment was performed at least four times, and the averaged data were used to draw the individual plots. With the linear plots, the data were fed to a desk electronic computer[10] fitted with a program for the computation of regression parameters and statistics. All linear regressions were highly significant ($p < 0.005$). Least-squares fits of Eq. 6 to release data were done with the aid of a digital computer, using an appropriate program[11].

RESULTS AND DISCUSSION

Diffusional Resistance of Membrane—In the present system, the diffusional resistance of the interfacial barrier, R, was only due to the silicone rubber membrane, since the diffusant was completely converted to a different species (its salt form) immediately after crossing the membrane. To obtain a more realistic value, R was determined by quasi-steady-state rather than by steady-state experiments. The conditions were thought to reproduce more closely those existing during release experiments, *i.e.*, a varying drug concentration at the membrane–donor phase interface.

If sink conditions are assured, the permeation of a drug from a stirred

[9] Crouzet SA, Paris, France.
[10] Olivetti Programma 101.
[11] IBM 370/158; Nonlinear Least-Squares Regression Program BMDX85 (W. J. Dixon, "Biomedical Computer Program, X-Series Supplement," University of California Press, Berkeley, Calif., 1970).

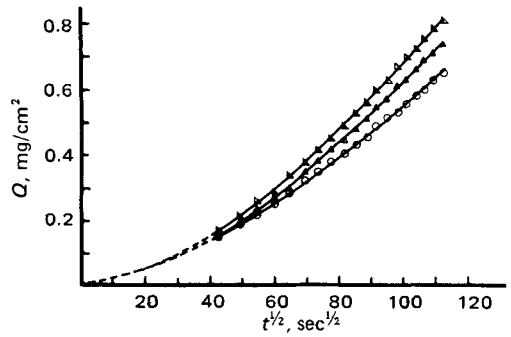

Figure 3—*Amount of benzocaine released from suspension-type gels prepared with macrosize drug as a function of the square root of time. Key: ◺, 4.92 mg/ml; △, 4.12 mg/ml; and ○, 3.05 mg/ml.*

solution across a membrane under quasi-steady-state conditions is described by (11):

$$\ln C_i/C_{i0} = \frac{S}{R'V_i}t \qquad \text{(Eq. 10)}$$

where C_i and C_{i0} are the concentrations of the donor solution at finite time t and at $t = 0$, respectively; V_i is the volume of the donor solution; S is the area of the membrane; and R' is the diffusional resistance of the membrane if contributions from nonstirred liquid layers adjacent to both sides of the membrane are insignificant, as assumed for the present experimental system.

The value of R (in release experiments) is related to R' (calculated from permeation experiments) through the following equation, which takes into account the difference existing between the donor phases in release and permeation experiments:

$$R = \frac{K_{m/w}}{K_{m/g}}R' \qquad \text{(Eq. 11)}$$

where $K_{m/w}$ and $K_{m/g}$ are the membrane–water and membrane–gel partition coefficients, respectively. In the present case, the drug solubility

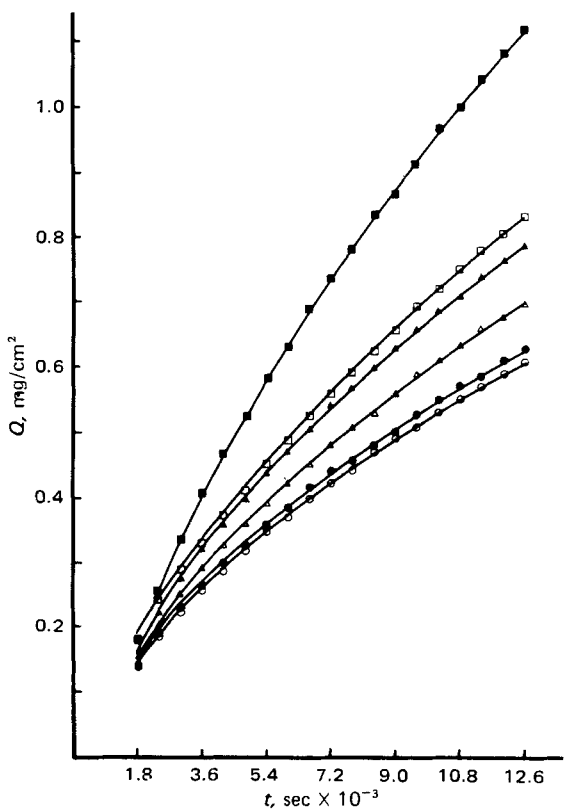

Figure 4—*Amount of benzocaine released from suspension-type gels containing different concentrations of micronized drug as a function of time. Symbols represent experimental data; curves are based on theoretical calculations. Key: ■, 10.9 mg/ml; □, 5.1 mg/ml; ▲, 4.6 mg/ml; △, 3.7 mg/ml; ●, 3.03 mg/ml; and ○, 2.59 mg/ml.*

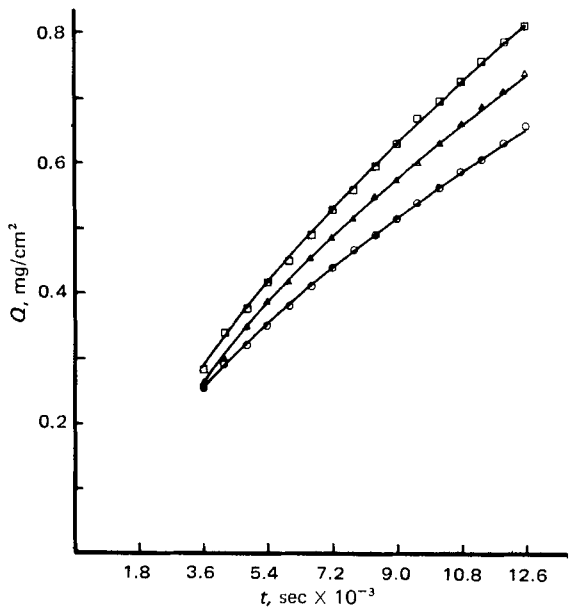

Figure 5—*Amount of benzocaine released from suspension-type gels containing different concentrations of macrosize drug as a function of time. Symbols represent experimental data; curves are based on theoretical calculations. Key: □, 4.92 mg/ml; △, 4.12 mg/ml; and ○, 3.05 mg/ml.*

in the gel was the same as in water. Therefore, $K_{m/w} = K_{m/g}$, and R could be calculated directly from the slope of the permeation plot according to Eq. 10. Figure 1 illustrates a typical permeation (log C_i/C_{i0} *versus* t) plot, whose linearity demonstrates the adherence of the experimental system to Eq. 10. An average value of 8.3×10^3 sec/cm resulted for R from the permeation experiments.

Release Experiments—Figures 2 and 3 illustrate the results of release experiments with micronized and macrosize benzocaine, respectively. The experiments were carried out over 3.5 hr at concentrations ranging from 2.59 to 10.9 mg/ml for micronized drug and from 3.05 to 4.92 mg/ml for macrosize drug. In no case was a linear relationship between Q and $t^{1/2}$ observed, at least until a substantial amount of time elapsed. Thus, the nonlinearity of the graphs appears to rule out the vehicle-controlled model described by Eq. 3. Since Eqs. 1 and 4 predict the presence of a nonlinear region during early release times, it is reasonable to assume that the vehicle–membrane-controlled model was operative in this case.

This assumption is confirmed by the graphs in Figs. 4 and 5, in which the experimental release plots of benzocaine (micronized and macrosize, respectively) are compared with theoretical plots, generated by a least-squares fit of Eq. 6 to experimental data, obtained with the aid of a digital computer. Since, as pointed out in the theoretical section, Eq. 6 is valid after the lag time, all data used for the interpretation were taken 30 min after the beginning of release experiments with micronized drug (60 min with macrosize drug). After these lapses of time, the thickness of the depletion zone, l, approximately estimated for each concentration from the amount of released drug ($l = Q/A$), was sufficiently great with respect to particle size and interparticulate distance for micronized and macrosize particles. The time required for establishment of a linear concentration gradient in the membrane should be negligible, as shown by the quasi-steady-state permeation graph in Fig. 1, whose ordinate intercept closely approaches the theoretical value, 1.00 mg/ml. Thus, it can be safely assumed that conditions (*a*) and (*b*) for the validity of Eq. 1 (and 6) were attained. The excellent agreement between calculated and experimental points indicates that Eq. 6 is well suited for describing the release pattern of micronized and macrosize drug.

The values of a, b, and q, estimated for each release experiment by the computer fit of Eq. 6 to release data, and the corresponding values of the concentration at the gel–membrane interface, calculated by Eqs. 6 and 8, at the lower (C_v^i) and the upper (C_v^f) ends of each time interval, are listed in Table I. The values of C_v^i and C_v^f are approximately 47–80 and 18–40%, respectively, of C_s, the solubility of benzocaine in the gel (1.31 mg/ml, see *Experimental*). These comparatively high values possibly account for the curvature of the Q *versus* $t^{1/2}$ plots (Figs. 2 and 3) and further support the application of Eq. 4, rather than of Eq. 3, to the present experimental system.

Table I—Values of Parameters *a*, *b*, and *q* (Eq. 6) and of C_v (Eq. 8) Calculated at the Lower ($C_v{}^i$) and Upper ($C_v{}^f$) Ends of the Time Interval for Each Release Experiment

Particle Size, μm	*A*, mg/ml	*a*	$b \times 10^4$	*q*	$C_v{}^i$, mg/ml	$C_v{}^f$, mg/ml
2.0	2.59	0.140	0.441	297	0.62	0.24
2.0	3.03	0.170	0.485	163	0.61	0.25
125.0	3.05	0.173	0.550	990	0.55	0.28
2.0	3.70	0.208	0.640	396	0.73	0.29
125.0	4.12	0.254	0.797	1170	0.65	0.33
2.0	4.60	0.260	0.852	378	0.81	0.34
125.0	4.92	0.325	0.995	945	0.68	0.37
2.0	5.10	0.330	1.005	360	0.83	0.36
2.0	10.90	0.720	2.330	405	1.05	0.53

Determination of Diffusion Coefficient and Solubility—In Fig. 6, *b* was plotted *versus* $(A - C_v{}^i/2)$ and $(A - C_v{}^f/2)$ (*cf.*, Eq. 7 and Table I). Since all points fell, within the range of experimental error, on the same line, all data were grouped to build up the regression line. The nonperfect alignment of the points in the line is due to wide variations of the parameter *b* with experimental error. However, the high value of the correlation coefficient (0.998) points to a significant linear relationship between *b* and $(A - C_v/2)$ as predicted by Eq. 7.

The value for the solubility of benzocaine in the gel, C_s, calculated from the abscissa intercept of the plot in Fig. 6, was 1.18 mg/ml; the value of C_s calculated by Eq. 9 was 1.29 mg/ml. Both values are in satisfactory agreement with the directly determined solubility value at 30°, 1.31 mg/ml. The values of the diffusion coefficient of benzocaine in the gel, calculated from the slope of the plot reported in Fig. 5 according to Eq. 7, are 1.00×10^{-5} and 9.14×10^{-6} cm²/sec, assuming $C_s = 1.18$ and 1.29 mg/ml, respectively. The agreement with the literature (17) value for the diffusion coefficient of benzocaine in water at 30° (9.9×10^{-6} cm²/sec) is satisfactory. This finding is indicative of the absence of interactions, mechanical and/or chemical, between diffusant and gel. Indeed, the pores in the gel network should be much larger than the molecular diameter of the diffusing drug, as indicated also by the observation that the rate of release of benzocaine was unaffected when the concentration of carboxyvinyl polymer in the gels was doubled. The occurrence of chemical interactions appears unlikely in view of the chemical nature of benzocaine and the carboxyvinyl polymer and because the solubility of benzocaine in the gel was the same as in water.

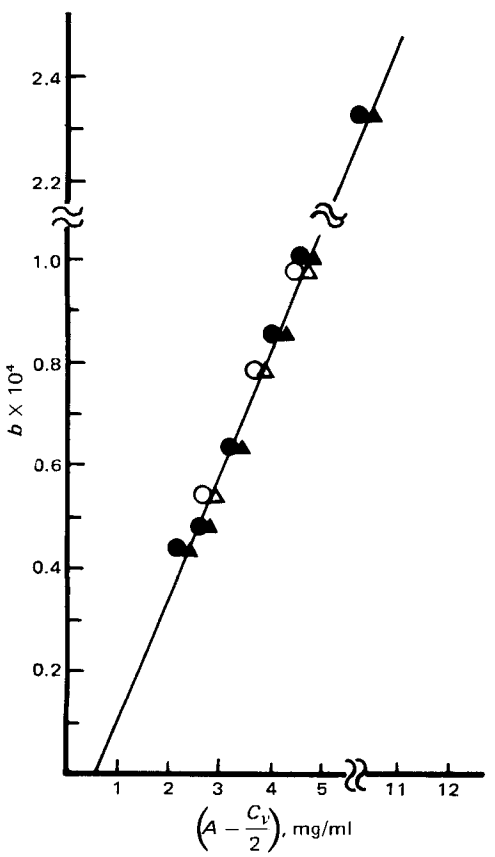

Figure 6—*Relationship between parameter* b *and* $(A - C_v/2)$. *Key:* ●, $(A - C_v{}^i/2)$, *micronized;* ○, $(A - C_v{}^i/2)$, *macrosize;* ▲, $(A - C_v{}^f/2)$, *micronized; and* △, $(A - C_v{}^f/2)$, *macrosize. See text for details.*

Influence of Particle Size—As stated earlier, the release pattern of benzocaine was unaffected by particle size; both micronized and macrosize drug were released according to Eq. 4 after a finite time from the beginning of the experiments. Indeed, the surface area of undissolved drug should not influence the release rate beyond the lag time, since Eq. 4 requires release to be diffusion rather than dissolution controlled. However, the lag time itself should be highly influenced by particle size insofar as it depends on the time necessary for the thickness of the depletion zone to overwhelm particle diameter. In effect, the correction factor *q* (Eq. 6), which is directly related to the lag time, was greater for macrosize than for micronized drug (Table I).

The observations do not disagree with the assumptions of Haleblian *et al.* (10), who found that the surface area greatly influenced the release rate of chlormadinone acetate from silicone elastomer matrixes. They attributed this effect to a dissolution-influenced release. Indeed, the thickness of the depletion zone of their experimental system, estimated (as the Q/A ratio) from the reported data, was at most about 100 μm, while the diameters of the macrocrystals used were in the 100–300-μm range.

CONCLUSIONS

Equation 1, applied previously to the release of drugs from solid matrixes at concentrations largely exceeding solubility, is valid in a modified form (Eq. 4) for the release of benzocaine from an aqueous gel at drug concentrations only a few times greater than solubility. Equation 4 lends itself to the determination of the solubility as well as of the diffusion coefficient of drug in a vehicle. The determined values are satisfactorily accurate, at least for practical purposes.

The present results are indicative of a method of potential utility for the study of the above parameters, particularly where the application of Eq. 3 is ruled out by the influence on release of the diffusional resistance of the barrier separating the donor and receiving phase and where the use of Eq. 1 is prevented by the practical impossibility of attaining the $A \gg C_s$ condition because of a high drug solubility in the ointment.

The size of suspended particles is particularly important. Since the time necessary for attainment of the conditions of applicability of Eq. 4 is remarkably dependent on particle dimension, the use of macrosize powder might waste both time and materials.

APPENDIX

Equation 1 was derived by equating the rate of release and the rate of quasi-steady-state diffusion through the vehicle and the interfacial barrier. For the $A \gg C_s$ condition, the first parameter is directly proportional to the rate of increase of the thickness of the depletion zone, *l* (6):

$$dQ/dt = A\, dl/dt \qquad \text{(Eq. A1)}$$

When C_s is not negligible with respect to *A*, the proportionality fails as long as the time-dependent concentration at the interface with the barrier, C_v, must also be taken into account in the expression of the released amount per unit area and of the release rate:

$$Q = [A - (C_s + C_v)/2]l \qquad \text{(Eq. A2)}$$

$$dQ/dt = [A - (C_s + C_v)/2]\, dl/dt - 1/2l\, dC_v/dt \qquad \text{(Eq. A3)}$$

However, if the second term in the rate expression is negligible when compared with the first, the factor within brackets in Eq. A3 can be as-

sumed by approximation to be constant (*cf.*, Eq. 5). The consequent proportionality between dQ/dt and dl/dt should enable derivation of Eq. 4 in complete analogy with Eq. 1. That the condition for proportionality is generally satisfied also for values of A as little as $3C_s$ can be verified by expressing this condition through the ratio of the first to the second term in the expression of the release rate (Eq. A3):

$$\left|\frac{2A - C_s - C_v}{l} dl/dC_v\right| \gg 1 \qquad \text{(Eq. A4)}$$

and further substituting into this relationship the following expressions of C_v, dC_v, l, and dl:

$$C_v = R\, dQ/dt \qquad \text{(Eq. A5)}$$

$$dC_v = (R\, d^2Q/dt^2)\, dt \qquad \text{(Eq. A6)}$$

$$l = Q/(n - 1/2)C_s \qquad \text{(Eq. A7)}$$

$$dl = [1/(n - 1/2)C_s]\, dQ \qquad \text{(Eq. A8)}$$

where $n = A/C_s$. Equation 1, where $(n - 1/2)C_s$ is used in place of A, can be employed to obtain approximate expressions of Q, dQ, and d^2Q/dt^2.

Following calculation, the condition for proportionality between the release rate and the rate of increase of the thickness of the depletion zone can be written as follows:

$$\frac{2x^2(n - 1/2) - x}{x - 1} \gg 1 \qquad \text{(Eq. A9)}$$

where $x = \sqrt{1 + [2/(n - 1/2)D_vR^2]t}$.

It can be readily verified that the minimum value of the ratio is 18 for $n = 3$, while it increases with increasing n.

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Metabolism of *N*-Ethyl-3-piperidyl Benzilate in Rats

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Abstract □ The metabolic fate of *N*-ethyl-3-piperidyl benzilate (I) and its potential metabolites 3-piperidyl benzilate (II), *N*-ethyl-3-hydroxypiperidine (III), and 3-hydroxypiperidine (IV) was studied. Incubation of I with rat liver homogenates resulted in the formation of II and III. Only a trace of unchanged drug appeared in urine after intraperitoneal injection of I. Approximately 9% of the injected dose of I was excreted in urine as III and 2% in the form of metabolites that produced III after acid hydrolysis. After intraperitoneal injection of II in rats, 18% of the dose was excreted in urine as IV. Approximately 26% of the injected dose of III was present in urine as the unchanged drug, and 63% of the dose was excreted in the urine in the form of conjugates that produced III on acid hydrolysis. Urine of rats injected with IV contained approximately 50% of the injected dose as the unchanged drug and 50% of the dose in the form of a conjugate that produced IV on acid hydrolysis. The identity of the metabolites in extracts from urine was established by GLC–mass spectrometry. It is concluded that hydrolysis was one metabolic pathway for I and II. The major routes of elimination of these compounds are not yet known and may include excretion in feces or metabolic transformations resulting in the degradation of the piperidine ring.

Keyphrases □ *N*-Ethyl-3-piperidyl benzilate—metabolism in rats □ Metabolism—*N*-ethyl-3-piperidyl benzilate in rats □ Benzilates—*N*-ethyl-3-piperidyl ester, metabolism in rats

During studies to develop potent and selectively acting atropine substituents for the treatment of GI disturbances, numerous compounds were synthesized that were superior to atropine with respect to anticholinergic potency, antisecretory effects, and reduced incidence of side effects (1). Most of these compounds are glycolate esters of heterocyclic imino alcohols. In experimental animals, these drugs produced potent central nervous system (CNS) stimulation, as indicated by hyperactivity and other behavioral disturbance tests (2). In humans, they were potent and long-lasting hallucinogenic and psychotomimetic agents (3).

Some human subjects manifested a marked change in their basic mood and drive 1 or 2 days following a single