Such small D_0 values are of the same order of magnitude as those values found when the rat gastrointestinal absorption data were treated (1, 2) and when data on drug transport across the hydrated *stratum corneum* were recently analyzed (19) by means of the physical model approach.

In summary, the physical model approach has been shown to be extremely successful in analyzing the buccal absorption data involving the alkanoic acids from C_4 to C_8. The mechanistic conclusions based upon the analysis appear to be very firm, because the agreement between the appropriate physical model and experiments was very good.

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[5] In Fig. 10 of *Reference 1*, the diffusion efficiency coefficient T should read T^2.

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Steroid Release from Silicone Elastomer Containing Excess Drug in Suspension

J. HALEBLIAN, R. RUNKEL, N. MUELLER, J. CHRISTOPHERSON, and K. NG

Abstract □ The *in vitro* release from a matrix consisting of silicone elastomer was studied for the purpose of testing release theories. The micronized steroid was suspended in silicone elastomer, and the release from a controlled surface area into an aqueous "sink" was experimentally determined. After a certain time period, the release from the matrixes displayed the predicted time and concentration dependencies. An initial period of apparent linear release was observed. The duration of this period was concentration and particle-size dependent. The amount released assumed square root of time dependency after the initial linearity period terminated. The observed results are inconsistent with the equations developed to describe the release of solutes from ointment bases and matrix systems. The concentration and particle-size effects on the duration of the linear release suggest that the release is dissolution rather than diffusion controlled.

Keyphrases □ Silicone elastomer—steroid release, *in vitro* □ Chlormadinone acetate release mechanism—silicone elastomer matrix □ Membranes, silicone elastomer—steroid transport rates □ Particle-size effect—steroid release from silicone matrix □ Colorimetric analysis—spectrophotometer

The behavior of simple diffusional processes is generally mathematically described in an adequate fashion by an equation containing a series of exponentials (1, 2). Diffusion of solutes through silicone elastomer membranes has recently been evaluated, and good predictive ability was achieved assuming that the drug solute diffused according to Fick's law (3–5). *In vitro* release of a solute dissolved in ointment bases was predicted by W. Higuchi (6) by applying equations similar to those used by Jost (2) and by restricting flux to a single direction. The mathematics of these processes is quite complex; for the formulator of ointment bases or similar drug delivery systems, a more practically usable equation was developed by T. Higuchi (7).

By assuming that diffusion is the slow step in the overall release process, Eq. 1:

$$Q = \sqrt{DC_s(2A - C_s)t} \qquad \text{(Eq. 1)}$$

was derived by T. Higuchi (8) to describe drug release from ointment systems into a receptor sink when excess drug is suspended in that system. The Q is the amount released at time t/square centimeter of surface contact with the receptor sink; D is the diffusion constant of the drug molecule in the ointment or matrix system, A is the concentration of drug in the ointment given in amount/cubic centimeter, and C_s is the solubility of the drug in the ointment expressed in amount/cubic centimeter.

This paper is a report of the results of release experiments from a drug–matrix system analogous to the one described previously (8). The validity of Eq. 1 is tested.

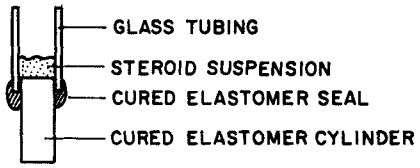

Figure 1—*Apparatus used for determination of solubility of chlormadinone acetate in silicone elastomer.*

The release dependencies on the time, concentration, and surface area parameters are examined.

THEORETICAL CONSIDERATIONS

The three rate processes necessary for drug depletion from the drug–matrix system are: (*a*) dissolution of the drug in the matrix; (*b*) diffusion of the solute to the matrix–receptor interface; and (*c*) transfer of the solute across the interface.

Equation 1 assumes that the diffusion process ultimately controls drug release. Two other possibilities exist. (*a*) Release may be controlled by the rate of drug dissolution into the matrix. In such a case, the surface area of the suspended drug particles affects the release. (*b*) The rate of solute transfer across the matrix–receptor interface may control the release. In such a situation, constant release rates are observed.

METHODS AND MATERIALS

Solubility in Silicone Elastomer—Cylinders of solid silicone elastomer[1], cured with stannous octoate[2], were prepared by drawing the fluid material into a 4-mm. (inner diameter) glass tube. The elastomer cylinders were removed from the tubes, sectioned into 2-cm. lengths, and partially inserted into a short length of empty glass tubing (Fig. 1). An aqueous suspension of tritium-labeled chlormadinone acetate[3] (6-chloro-17α-hydroxypregna-4,6-diene-3,20-dione acetate) was layered over the exposed elastomer surface in the tube. Several of these glass tubes were sealed in small glass vials and held at 37°. Thin slices of the protruding silicone elastomer cylinder were assayed periodically. The experiment continued until the assay values indicated that the concentration was constant. The thin sections of silicone elastomer (containing the tritium-labeled drug) were placed in 10 ml. of scintillation fluid. The fluid consisted of 4 g. of 2,5-diphenyloxazole[4] and 0.1 g. of 1,4-bis-[2-(4-methyl-5-phenyloxazoylyl)] benzene[4] in 1 l. of toluene. The samples were then counted on a liquid scintillation counter[5].

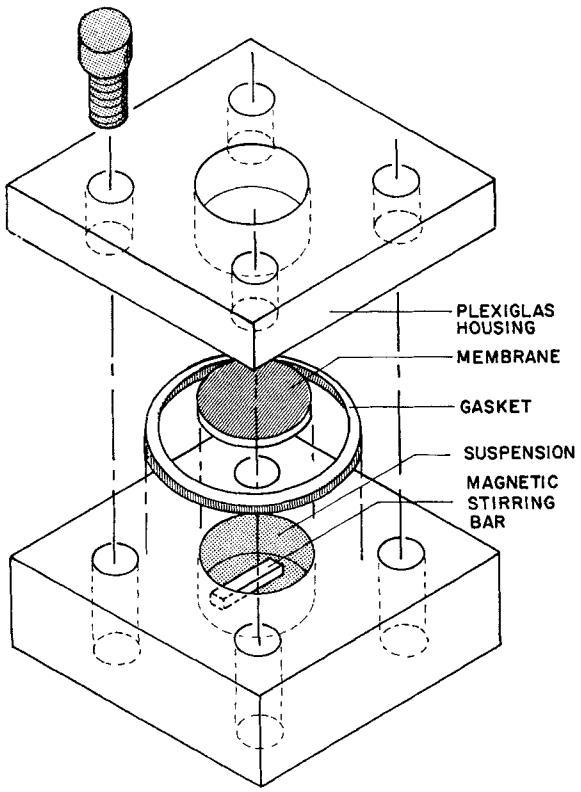

Figure 2—*Apparatus used for determination of transport rates of chlormadinone acetate across silicone elastomer membrane.*

Preparation of Matrixes—The drug–matrix release systems were prepared by levigating chlormadinone acetate into a silicone elastomer. The appropriate amount of stannous octoate was then levigated into the dispersion. The resulting fluid was then poured into tared glass petri dishes. The following systems were studied in triplicate:

1. Matrixes of 0.2, 2, 10, 20, and 40% chlormadinone acetate having the same depth and exposed surface area.
2. Matrixes of 2% chlormadinone acetate having the same depth but with 3.88, 7.15, and 59.7 cm.^{2} of exposed surface area.
3. Matrixes of 2% chlormadinone acetate with the same surface area but having depths of 0.635 and 1.91 cm.
4. Matrixes of 10% chlormadinone acetate with the same depth and exposed surface area as in System 1 but using macrocrystals. The macrocrystals were approximately 100–300 μ in length.

Release Experiments—The petri dishes were placed in beakers containing distilled water. The volumes and sampling times were such that the concentration of chlormadinone acetate never exceeded 10% of its solubility in water. The experiments were conducted in a water bath at 37°.

Six beakers were stirred simultaneously at 50 r.p.m. by a multiple stirring apparatus[6]. The 7.5 × 2.5-cm. stirring blades were lowered halfway into the receptor phase. Aliquots of the distilled water were extracted with chloroform, passed through anhydrous sodium sulfate, and evaporated to dryness. The residue was dissolved in 5 ml. of an acidified methanol solution of 1% 4-aminoantipyrine hydrochloride[7]. The solutions were placed in the dark for 20 min. to allow color development. Each sample was read at 393 nm. against a methanol blank on a UV spectrophotometer[8], and the drug concentration was calculated from a standard reading.

Membrane Transport Rates—Membranes of silicone elastomer were cast in thicknesses of 0.132, 0.226, and 0.48 cm. The membranes were placed in Plexiglas housings (Fig. 2) in contact with an aqueous suspension of tritium-labeled chlormadinone acetate. The apparatus was placed in a beaker of distilled water, and conditions as described under *Release Experiments* were maintained. The magnetic stirring bar in the suspension chamber was rotated by a submerged water-driven motor. The distilled water was sampled at appropriate times, and aliquots were assayed as described under *Solubility in Silicone Elastomer*.

RESULTS

Solubility—The solubility of chlormadinone acetate in the cured silicone elastomer was determined to be 82 mcg./ml. at 37°. The solubility of chlormadinone acetate in distilled water at 37° is approximately 1 mcg./ml. The low aqueous solubility necessitated the use of large receptor volumes to maintain sink conditions at all times.

Release from Matrixes—The release profiles of the 0.2, 2, 10, 20, and 40% matrixes are shown in Fig. 3. The release data in Fig. 3 were plotted *versus* the square root of time, as suggested by the diffusion-controlled release model discussed earlier (Fig. 4). If the release of chlormadinone acetate from the matrixes is *via* the diffusion-controlled mechanism, the plot in Fig. 4 would be linear in all of the early times (*i.e.*, $t < t$ for complete depletion).

[1] Silastic Medical Grade Elastomer No. 382, Dow Corning Corp., Midland, Mich.
[2] Catalyst M, Dow Corning Corp., Midland, Mich.

[3] The authors wish to express their appreciation to Dr. W. Hafferl and Mr. Andre Hary of Syntex Research, Palo Alto, Calif., for supplying the radioactive tracer.
[4] Arapahoe Chemicals, Division of Syntex Corp., Boulder, Colo.
[5] Model 720, Nuclear Chicago Corp., Des Plaines, Ill.
[6] Phipps and Bird, Inc., Richmond, Va.
[7] Eastman Organic Chemicals, Distillation Products Industries, Rochester, N. Y.
[8] Beckman DU spectrophotometer, model 2407, Beckman Industries, Fullerton, Calif.

Table I—Release of Chlormadinone Acetate from 2% Silicone Elastomer Matrixes Having a Depth of 0.64 cm. (0.25 in.) into an Aqueous "Sink"

Hours	Release (Average of Three Experiments) mcg./cm.²	Variance	Cumulative Release, mcg./cm.²
8.0	46.6	(40.2–53.6)	47
14.5	52.3	(47.0–59.1)	99
30.5	65.6	(47.0–90.6)	165
38.5	45.4	(44.1–47.2)	210
54.5	60.6	(51.2–69.0)	270
70.5	62.9	(61.5–65.1)	333

Table II—Release of Chlormadinone Acetate from 2% Silicone Elastomer Matrixes Having a Depth of 1.9 cm. (0.75 in.) into an Aqueous "Sink"

Hours	Release (Average of Three Experiments) mcg./cm.²	Variance	Cumulative Release, mcg./cm.²
12	94.0	(86.5–101.0)	94
20	46.5	(41.8–50.8)	141
28	29.4	(26.3–33.9)	170
40	50.3	(44.6–57.0)	220
58	61.3	(49.3–79.1)	282
74.5	51.6	(45.2–60.5)	333

Release profiles were obtained with 2% matrixes having surface areas of 3.88, 7.15, and 59.5 cm.² exposed. As expected, the release was directly proportional to the area exposed.

Tables I and II present release data for the 2% matrixes having identical exposed surface areas but with thicknesses of 0.635 and 1.91 cm. Drug release is independent of the thickness of the matrix for the time period studied.

Of the total amount of drug present at the beginning of the experiments, approximately 2% was depleted. Attempts were made to determine concentration changes at various depths in the matrixes but they were unsuccessful. Apparently, the precision of the assay did not allow determination of minor changes in high concentrations.

The possibility that the dissolution rate of the drug in the matrix might affect the release prompted the experiment employing 10% chlormadinone acetate matrixes prepared with particles presenting vastly different surface areas. Figure 5 shows the release profiles for 10% chlormadinone acetate matrixes prepared with micro- (0.5–12 μ) and macro- (100–300 μ) particles. The particles were assumed to be spherical; by using average particle diameters, the surface area of the microparticles was estimated to be 60 times that of the macroparticles.

Membrane Transport—Drug transport across silicone elastomer membranes of various thicknesses was followed to a steady state. The lag time (1, 9, 10) was obtained from a plot of amount *versus* time. The diffusion coefficient was then calculated using Eq. 2:

$$L = \frac{l^2}{6D} \qquad \text{(Eq. 2)}$$

In this equation, L is the lag time in seconds, l is the membrane thickness in centimeters, and D is the diffusivity in square centimeters/second. The results listed in Table III represent the average of two experiments. The steady-state transport rates are roughly proportional to the inverse of the membrane thickness as predicted by Fick's first law. The numbers obtained for D are of the same magnitude as those calculated for the diffusion of radioiodide in petrolatum (6).

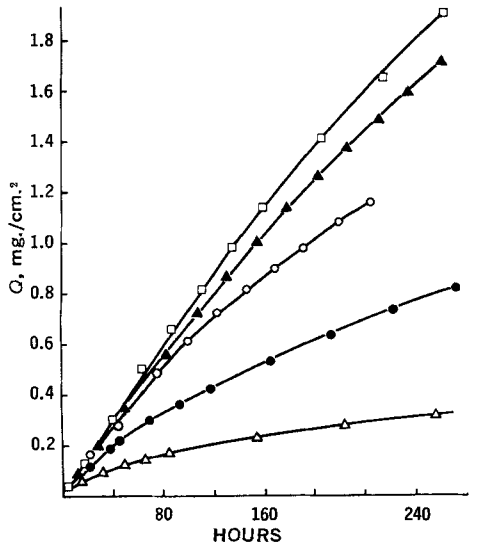

Figure 3—*Release of chlormadinone acetate (micronized) from several concentrations of silicone elastomer matrixes into an aqueous "sink." (Points indicate the average of three experiments.) Key: △, 0.2%; ●, 2%; ○, 10%; ▲, 20%, and □, 40%.*

DISCUSSION

Time Dependence—The release curves in Fig. 3 for 0.2 and 2% chlormadinone acetate appear to have the time dependency of a diffusion-controlled process. They are similar in shape to those reported by Patel *et al.* (11), for the release of radioiodide from an ointment solution, and later treated by W. Higuchi (6), who fitted the data to equations developed from diffusion theory. The release profiles for the 10, 20, and 40% matrixes, however, appear different enough that one might question whether the release mechanism is the same as that for the 0.2 and 2% matrixes. The release from the 40% matrixes was apparently linear with time for at least 140 hr. The release rates for the 10 and 20% matrixes were apparently constant also but for shorter times. Presumably, the 0.2 and 2% matrixes behave similarly, but assays would have to begin much earlier to detect the linear release period. Thus, there seems to be a maximum achievable release rate which is independent of total drug concentration.

A similar observation might have been made for the data reported by Whitworth and Becker (12) on the release of sulfacetamide and sulfathiazole from 5% ointments. Assuming that there was no receptor phase–solid drug contact, the initial part of the curves is difficult to rationalize within the diffusion-controlled model.

The experiments of Laug *et al.* (13) showed that, over a time interval of 0–24 hr., there was no increase in the amount of mercury absorbed when ointments ranging from 4–50% were applied to the skin of rats. Absorption from a 0.9% ointment was lower, however. Strakosch and Clark (14) reported similar results for the penetration of sulfonamides into the intact skin of guinea pigs. Data from the present study parallel that of the above-mentioned investigators (13, 14). Drug release over the 0–40-hr. time interval was the same

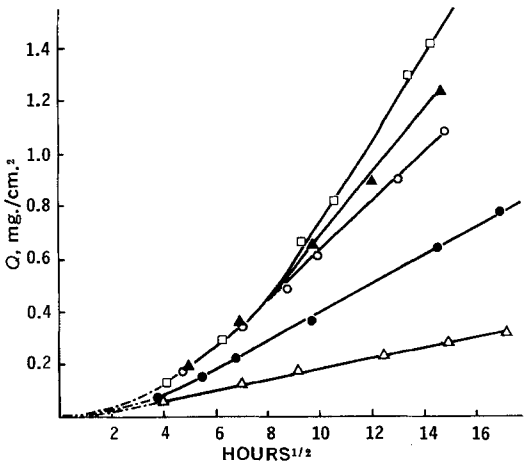

Figure 4—*Release of chlormadinone acetate (micronized) from several concentrations of silicone elastomer matrixes into an aqueous "sink" as a function of the square root of time. (Points indicate the average of three experiments.) Key: △, 0.2%; ●, 2%; ○, 10%; ▲, 20%; and □, 40%.*

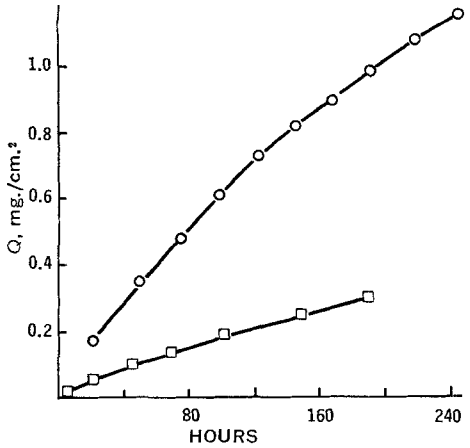

Figure 5—*Release of chlormadinone acetate from 10% silicone elastomer matrixes prepared with micronized and macrosize particles. (Points indicate the average of three experiments.) Key: □, macroparticles; and ○, microparticles.*

for 10, 20, and 40% matrixes but was lower for the 0.2 and the 2% matrixes.

Particle-Size Effect—The release profiles for 10% matrixes prepared with micro- and macrosize drug particles (Fig. 5) demonstrate the effect of surface area of undissolved drug. After 200 hr. the matrixes prepared with micronized chlormadinone acetate released approximately four times more than those prepared with macroparticles. This effect is probably due to a decreased dissolution rate because of the reduced total surface area of drug particles. The surface area effect is complicated because the matrix–drug system is not stirred and the net flux in that system is essentially unidirectional. Apparently, the surfaces actively involved in dissolution are some fraction of the total, and the depth (in the matrix) at which this process takes place increases with time.

The particle-size effect on release from ointments was demonstrated by a number of investigators, using various drugs. Barrett *et al.* (15) observed this effect in the *in vivo* release of fluocinolone acetonide from petrolatum ointments. Similar results were reported for salicylic acid (16) and for calomel (13, 17).

Equation 1 has failed to predict the release time dependence. This is graphically illustrated in Fig. 4 where definite curvature is seen in the early portions of the curves. Equation 1 further suggests that drug release should be proportional to the square root of the total concentration. The early portions of the curves in Fig. 3 display a release that is independent of concentration; these results are substantiated by the work of others (12–14). Finally, while it is true that Eq. 1 was developed for fine particles (8), this parameter is not reflected in the release equations, and changes in excess drug particle size do affect release.

The maximum release rate may be explained if the rate of desorption, from the matrix surface into the sink, controls the overall release process. Garrett and Chemburkar (4) considered such a case in their discussion of drug permeation through silicone membranes. They pointed out that if desorption controls the transport process, then the thickness of the membrane would have no effect on the steady-state transport rates. In the present experiments, the membrane thickness did affect those rates. The steady-state transport rate was roughly proportional to the inverse of the membrane thickness. The conclusion, therefore, is that the maximum release rate from the matrixes is not enforced by a limiting rate of desorption.

In membrane diffusion, steady state is defined as the condition where the rate of transport is constant because the concentrations in the first and last monolayers of the membrane are invariant with time. This definition assumes that the dimensions of the membrane do not change. If the concentration at the depot side monolayer is at a maximum for a given solute in a particular membrane, a maximum steady-state transport rate would be achieved. By applying this reasoning to the drug–matrix system, a maximum rate of release is not implausible since, regardless of the total drug concentration, C_s does not increase. The diffusing species are the solute molecules, not drug particles. What does change with concentrations (A), however, is the ability to maintain a concentration gradient across a diffusion barrier. The barrier here is the film of matrix material separating the embedded particles, nearest to the surface, from the aqueous receptor. All particles are assumed to be covered with silicone elastomer.

Table III—Steady-State Transport Rates and Calculated Diffusion Coefficients for Chlormadinone Acetate in Silicone Elastomer[a]

Membrane Thickness, cm.	Steady-State Transport Rates $\left(\frac{\text{mcg.}}{\text{cm.}^2/\text{hr.}}\right)$	L, hr.	D, cm.²/sec.
0.132	0.52	3	2.8×10^{-7}
0.226	0.34	8	3.0×10^{-7}
0.480	0.19	32	3.3×10^{-7}

[a] The transport rates are averages of two experiments.

This line of reasoning suggests that the chlormadinone acetate concentration was at a maximum at time zero in all the matrixes, all throughout the matrixes. Further, the initial rate of release was the same for all because the gradient initially established was the same. The more solid drug surface area exposed for dissolution, the longer the linear release period can be sustained. A decrease in the total concentration then shortens the linear release period but does not affect the initial release rate, provided excess solid drug is present initially.

There seems to be little doubt that the release model and the parameters affecting release are more complex than Eq. 1 indicates. The particle-size effect is inescapable. It is concluded that to describe adequately the release from these matrix systems, equations are needed that will reflect the effect of drug dissolution on the release.

SUMMARY

By employing distilled water as a receptor sink, release from several concentrations of chlormadinone acetate–silicone elastomer matrixes was studied. The 10% matrix was prepared with microparticles and macroparticles of chlormadinone acetate. Drug release from these systems was found to be a function of time, concentration, and surface area of the excess drug particles. Release from the 10% micronized matrixes was approximately four times that of the 10% macromatrixes, suggesting that the overall release process was controlled by the dissolution rate of the drug in the matrix. These results and their implications are pertinent to the analogous release system of an ointment containing excess suspended drug. The conclusion that drug dissolution rate affects release explains results in some early reports which previously could not be reconciled with the predictions of the accepted release equation. Equations are needed which will describe release and which will contain all the parameters that affect release.

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GLC Determination of Ethylene Chlorohydrin following Co-Sweep Extraction

JOSEPH WEINBERGER

Abstract □ A Co-Sweep extraction method was developed for removing and concentrating trace amounts of ethylene chlorohydrin from a variety of materials which were sterilized with ethylene oxide. Samples placed inside glass tubes were extracted in an apparatus with the aid of heat, solvents, and a continuous flow of carrier gas. The volatilized solvents were condensed in a cooling coil and swept into a collection tube. The entire extraction procedure was accomplished within 35 min. GLC was used to analyze the extract for ethylene chlorohydrin in the nanogram range. An ethylene chlorohydrin recovery study was performed in the microgram per gram range on different types of samples. The results indicate that the Co-Sweep technique is reliable, simple to operate, and potentially applicable to a wide variety of materials.

Keyphrases □ Ethylene chlorohydrin—determination □ Ethylene oxide-sterilized materials—ethylene chlorohydrin extraction, determination □ Extraction, Co-Sweep—ethylene chlorohydrin □ GLC—analysis

Ethylene oxide is now being used extensively for the sterilization of foods, pharmaceuticals, and manufactured goods. Numerous researchers have reported on various aspects of ethylene oxide sterilization. Until 1965, the only residues found from the use of this epoxide were ethylene oxide *per se*, ethylene glycol, and diethylene glycol (1–8). Wesley *et al.* (9) showed that chlorohydrins could be formed in foods fumigated with ethylene oxide or propylene oxide in the presence of inorganic chloride. Methods for analyzing ethylene oxide-sterilized foods, plastic, and rubber materials for residual ethylene chlorohydrin (2-chloroethanol) were reported by various researchers (10–17). Spitz and Weinberger (18) recently reported on a GLC method for the determination of ethylene oxide and the simultaneous determination of ethylene chlorohydrin and ethylene glycol in cellulose-type materials.

A rapid method was developed for the extraction of trace amounts of ethylene chlorohydrin from fabrics, cellulose-type materials, and a conglomerate of various materials sterilized by ethylene oxide. An aqueous extraction of ethylene chlorohydrin was achieved with a Co-Sweep extraction apparatus using heat, solvent, and a continuous flow of nitrogen gas. The entire extraction procedure was completed within 35 min. The aqueous extract obtained was quantitatively determined for ethylene chlorohydrin by GLC analysis.

EXPERIMENTAL

Apparatus—A Kontes Sweep Co-Distiller[1] (No. K-500750) was employed for the extraction and was equipped with a four-bay manifold flowmeter (K-628100-000), Teflon connection tubing (K-500500-307), and specially made glass side-arm sample tubes (13 mm. o.d. × 11 mm. i.d. × 33 cm. in length, with a 4-mm. Luer joint[2]). The open end of the tube was wrapped with two turns of Teflon ribbon tape [1.27-cm. (0.5-in.) width] and sealed with a 13-mm. o.d. silicone septum and a 0.97-cm. (0.38-in.) stainless steel hex-nut (Swagelock). The extracts were collected in 4-ml. graduated concentrator or collection tubes with a 19/22 ground-glass joint connected to glass extenders[3]. The end of the Teflon coil was held at the bottom of the collection tube by passing the tubing through a one-hole silicone septum (6 mm. o.d. × 8 mm. in length) inserted into a medicine dropper which was clamped in the bracket above the cooling bath. A cylinder of compressed nitrogen gas was equipped with a two-stage regulator and a 5A molecular sieve. A gas chromatograph[4], equipped with a dual-flame ionization detector and a stainless steel column [0.318 cm. (0.125 in.) × 2.44 m. (8 ft.)] packed with 10% polyethylene glycol[5] on 60–80-mesh acid-washed diatomaceous silica[6], was employed for all the experiments. The GLC operating temperatures were: column, 115°; injector, 135°; and detector, 200°. The GLC gases and flow rates were: helium, 30 ml./min. at 40 psig.; air, 300 ml./min. at 29 psig.; and hydrogen, 45 ml./min. at 27 psig.

Procedure—Prior to starting the extraction, the oven was adjusted to the horizontal position and preheated to 140°; the collection tubes and Teflon cooling coils were immersed in ice water baths, and the nitrogen carrier gas flow was adjusted in each of the four bays of the manifold flowmeter to approximately 75–80 ml./min. at 10 psig. A soap bubble meter was used to adjust the flow.

Four samples were extracted simultaneously in the Co-Sweep apparatus. The sample materials to be extracted were cut, weighed, and placed inside the glass sample tubes. A hex-nut and silicone rubber septum were used to seal each tube. Approximately 1 ml. of purified water was injected into the sample tubes with a hypodermic syringe and needle. The sample tubes were placed inside the preheated oven (140°) and connected to the Teflon cooling coil and then to the nitrogen carrier gas flow. The extraction time was started at this point. After 15 min. of sweeping carrier gas through the

[1] Kontes Glass Co., Vineland, N. J.
[2] Drawing No. 002172-29, Kontes Glass Co., Vineland, N. J.
[3] Kontes No. K-570050-0425 and K-570100, part 355.
[4] F & M model 5750.
[5] Carbowax 20M, Union Carbide, New York, N. Y.
[6] Chromosorb W, Johns-Manville, New York, N. Y.