vert the chlorohydrin into the more toxic metabolic product, chloroacetaldehyde, or may simply be less sensitive to its effects and therefore can tolerate relatively higher concentrations of ethylene chlorohydrin.

Toxic Liability to Chlorohydrin—The results of the acute toxicity experiments reported here contribute additional evidence that ethylene chlorohydrin can be dangerous to life when inhaled or when the liquid comes in contact with skin. Small amounts of ethylene chlorohydrin falling on the skin may lead to systemic toxicity without showing significant signs of local irritation. If the dermal LD_{50} for rabbits (Table I) could be extrapolated to man, a volume slightly more than a teaspoonful could be lethal to the average (70 kg.) man if it contacts the skin and is not washed off immediately.

Plastic Devices—It is now well established that in the presence of chlorides, ethylene oxide sterilization of plastic medical devices can generate, as one of the reaction products, the highly toxic ethylene chlorohydrin. A potential local and systemic toxic hazard might thus be created if sufficient chlorohydrin or ethylene oxide is present in the device and is released to tissue or biological fluids (25). Proper degassing procedures for a plastic device after ethylene oxide sterilization can generally remove all of the residual ethylene oxide present in the device but this may not be the case for ethylene chlorohydrin (if present). To ensure safety to the patient, all ethylene oxide-sterilized devices should be biologically tested for possible toxic reaction products prior to their release for patient use. In most instances, manufacturers of plastic medical and dental devices are performing toxicity tests on their devices. Unfortunately, in many hospitals this type of testing program is not being conducted when "inhospital" ethylene oxide sterilization is performed on "reusable devices."

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Effects of Interaction with Surfactants, Adsorbents, and Other Substances on the Permeation of Chlorpromazine through a Dimethyl Polysiloxane Membrane

MASAHIRO NAKANO

Abstract □ Effects of the nature of two membranes, hydrogen-ion concentration, and some additives on the *in vitro* permeation of chlorpromazine were examined at 37° employing the diffusion technique. Disappearance of chlorpromazine from one compartment of a diffusion cell to the other through a dimethyl polysiloxane membrane appeared to be a partition-controlled process over the pH range 4.1–6.4 and a diffusion-controlled process over the pH range 6.8–7.4. Decreased permeation of the drug in the presence of surfactants and bile salts was attributed to micellar effect and insoluble complex formation. Reduction in permeation in the presence of activated carbon, kaolin, and talc was rationalized on the basis of the adsorption of the drug on solid surfaces. Caffeine, riboflavin, and saccharin also decreased the permeation of the drug; their effect was interpreted to be due to soluble complex formation with the drug. Retarding effects of milk and gastric mucin may be ascribable to protein binding.

Keyphrases □ Chlorpromazine permeation—dimethyl polysiloxane membrane □ Adsorbents, surfactants, interaction with chlorpromazine—membrane permeation effect □ Diffusion cell—chlorpromazine membrane permeation determination

Ingested drugs have to dissolve in gastrointestinal fluids and pass through a succession of membranes before they reach the circulating bloodstream. The physiological availability of drugs will be influenced by, among other factors, how the presence of various substances in the gastrointestinal lumen modifies the

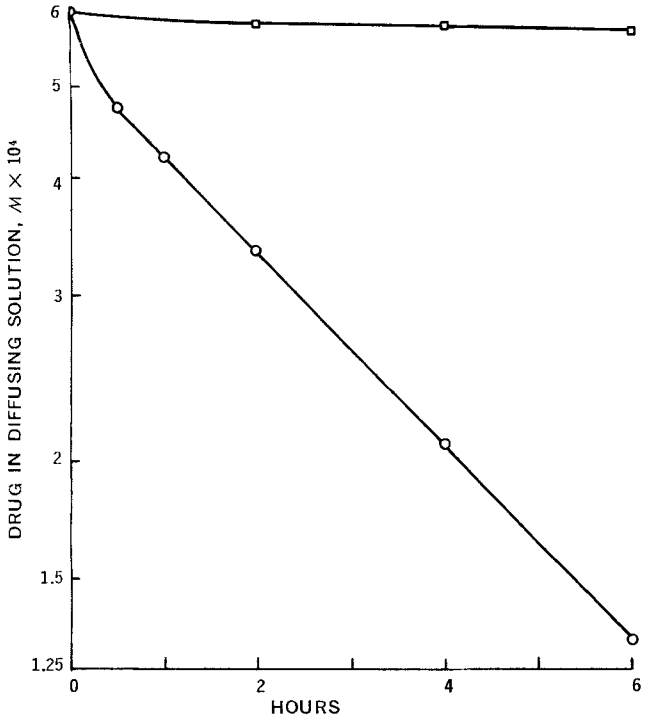

Figure 1—*Disappearance of chlorpromazine from the diffusing solution (in pH 6 citric acid buffer) through a 0.6-mil nylon membrane (□) and 5-mil dimethyl polysiloxane membrane (○) to the desorbing solution (5 × 10⁻³ N HCl) at 37°.*

permeation of drugs through such membranes. To approach this problem, it seems desirable to assess the physicochemical factors that would control this physiological process in the absence of biochemical factors.

This report is concerned with studies of the influences of a wide variety of substances such as surfactants, endogenous substances, dietary substances, adsorbents, and tablet excipients on the permeation of a drug through a model membrane. The choice of the diffusion technique for this purpose was based upon the belief that the absorption of drugs is a rate process and can best be studied kinetically. Silicone rubber membranes, which were chosen for this study, have been successfully used (1, 2). Chlorpromazine was selected as a model drug since it represents not only phenothiazine-type tranquilizers but also a good number of drugs with an aromatic group and an aliphatic amino side chain. Although chlorpromazine has been widely used for psychiatric treatment, only a few physicochemical studies on the interactive nature of this drug have been made. These include interfacial properties (3, 4), effects of adsorbents on gastrointestinal absorption (5–9), protein binding (10–12), and complex formation (13).

The objectives of the present work were to follow the time course of drug accumulation in the desorbing solution[1] and to discuss the effects of various interactions taking place in the diffusing solution[1] in the presence of various substances. Under these conditions, the influence of substances present in the diffusing solution on the permeative behavior of the drug through the synthetic membrane should mimic to a certain extent the effect of these substances on the absorption of the drug from gastrointestinal tracts. Some physiological effects of these substances, however, cannot be accounted for by this physicochemical model. It has been reported (14–16) that the submicellar concentrations of surfactants modify the permeability of biological membranes. Synthetic membranes, however, do not appear to have this property (17). In addition, the effect due to metabolic changes of the drug in the membrane has to be taken into account with live membranes.

[1] In this paper, a solution containing chlorpromazine at time zero is referred to as a diffusing solution, and a solution on the other side of the membrane is referred to as a desorbing solution.

EXPERIMENTAL

Materials—Chlorpromazine hydrochloride[2] was used without further purification. The following substances, which might interact with the drug and so affect its permeation, were examined: polysorbate 80[3], sodium lauryl sulfate[4], gastric mucin[5], sodium glycocholate[6], sodium taurocholate[4], caffeine[7], skim milk[8], saccharin sodium[9], riboflavin phosphate sodium[10], kaolin[6], activated charcoal[11], a sulfonic acid-type cation-exchange resin[12], lactose[6], gelatin[4], and talc[6]. Most of these materials were used as received. Buffers used in studies on the effect of pH were citric acid[7] buffer over the pH range 4.1–6.0 and 3,3-dimethylglutaric acid[13] buffer over the pH range 6.4–7.4 (18). The cation-exchange resin was washed several times with pH 6 citric acid buffer until no change in pH was observed.

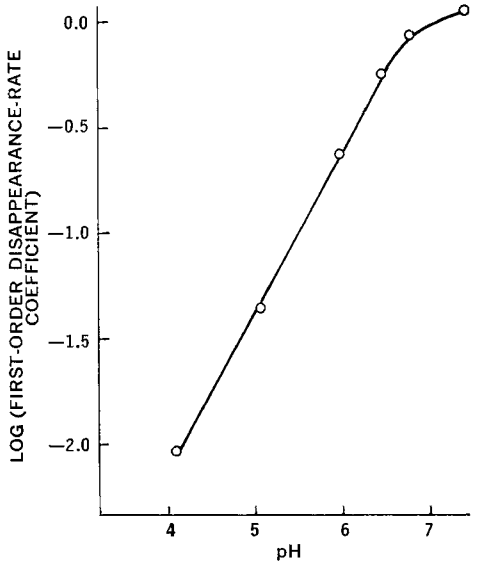

Figure 2—*pH profile of first-order disappearance-rate coefficient of chlorpromazine from the diffusing solution at 37°. Chlorpromazine concentration was 0.6 mM except at pH 7.4 where a 0.3 mM solution was used. Buffers were 0.05 M citric acid buffer over the pH range 4.1–6.0 and 0.05 M 3,3-dimethylglutaric acid buffer over the pH range 6.4–7.4. The desorbing solution was 5 × 10⁻³ N with respect to HCl.*

[2] Poulenc, Montreal, Canada.
[3] Tween 80, Atlas Chemical Industries, Wilmington, Del.
[4] Fisher Scientific Co., Chemical Manufacturing Div., Fair Lawn, N. J.
[5] Nutritional Biochemical Corp., Cleveland, Ohio.
[6] Merck & Co., Montreal, Canada, and Rahway, N. J.
[7] British Drug Houses, Toronto, Canada.
[8] Borden Co., Toronto, Canada.
[9] Abbott Laboratories, North Chicago, Ill.
[10] Sigma Chemical Co., St. Louis, Mo.
[11] Darco G-60, Anachemia Chemicals, Montreal, Canada.
[12] Dowex 50W-X12, 50–100 mesh, Dow Chemical Co., Midland, Mich.
[13] Eastman Organic Chemicals, Rochester, N. Y.

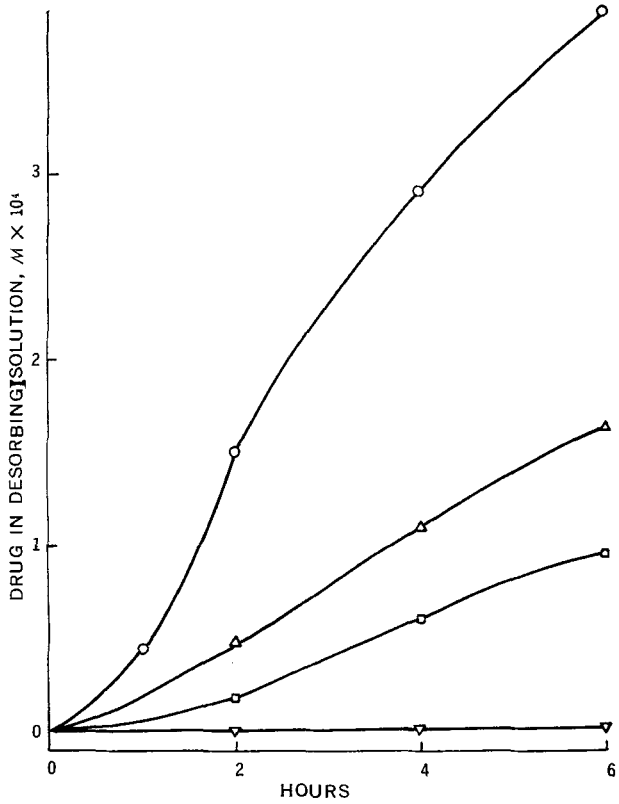

Figure 3—*Effect of surfactants on the permeation of chlorpromazine at 37°. Key: ○, no additive; △, 1% polysorbate 80; □, 0.6 mM sodium lauryl sulfate; and ▽, 2 mM and 6 mM sodium lauryl sulfate. Initial concentration of chlorpromazine was 0.6 mM in 0.05 M pH 6 citric acid buffer, and the desorbing solution was 5 × 10⁻³ N with respect to HCl. A point at 1 hr. in the control experiment was included to show sigmoidal increase in drug concentration in the desorbing solution.*

Diffusion Cell—A diffusion cell, similar to that of polymethy methacrylate described by Patel and Foss (19), was employed with the following modifications: (*a*) stainless steel was used instead of polymethyl methacrylate to avoid possible adsorption of the drug to the cell material (20); and (*b*) the height of the cell was increased by 2 cm. so that the openings on the top were still above the water level when the main part of the cell was immersed in a constant-temperature shaker water bath[14]. The overall dimensions were 10.0 × 7.7 × 3.8 cm.; each compartment occupied about 12 ml.; and the area available for diffusion was 9.4 cm.^{2}. The diffusion membrane employed was medical grade dimethyl polysiloxane sheeting[15] in a labeled thickness of 5 mil. The nylon membrane[16] used for preliminary work was 0.6 mil in thickness.

Procedure—The two cavities of the assembled cell with the membrane were washed several times with water and methanol and then both compartments were filled with methanol overnight to facilitate the leaching of the drug absorbed within the membrane. They were washed thoroughly with water and filled with water until the cell was used. The water was completely removed prior to use, and the cell was placed in the shaker water bath maintained at 37° so that nine-tenths of the cell was immersed in water. A 10-ml. portion of a chlorpromazine solution (1.2 m*M*) in pH 6 citric acid buffer was mixed with an equal volume of an additive solution of appropriate concentration (see the figures). The mixture was placed in the water bath to equilibrate at 37°. A hydrochloric acid solution (5×10^{-3} *N*) was similarly warmed to the same temperature.

After equilibration, a 10-ml. portion of the hydrochloric acid solution was placed in one compartment of the cell to ionize the permeated drug so that the concentration of permeable species would be maintained at a zero value; thus, "sink" conditions apply. The same volume of the drug solution was placed in the other. Shaking was started immediately, and sampling (0.5 ml.) from the diffusing and desorbing solutions was made at 2, 4, and 6 hr. of incubation. When the effect of hydrogen-ion concentration was examined, sampling (0.2 ml.) was made at appropriate time intervals, depending on the rate of permeation of the drug at each pH. The shaking rate was maintained at 95 ± 2 oscillations/min. with the length of the stroke 2.4 cm. The concentrations of the drug were determined spectrophotometrically at 255 nm. (or 308 nm. when additives interfered with the assay at 255 nm.) after appropriate dilution. Although the decrease in volume due to sampling reached 10% of the original volume, no volume correction was made because the main interest in this study was centered on the relative effects of interactive species rather than the calculation of a permeability constant in the presence of each interactive species. Because of the photochemical instability of the drug, appropriate precautions were taken during the experiments.

RESULTS AND DISCUSSION

Choice of Membrane—Although a nylon film has been reported to be permeable to chlorpromazine (*21*), preliminary diffusion studies with a nylon membrane in a labeled thickness of 0.6 mil indicated rather slow permeation of the drug through this membrane in the pH range below 7.4 (Fig. 1). A dimethyl polysiloxane membrane in a labeled thickness of 5 mil, on the other hand, was found to be about 60 times more permeable to the drug than the nylon membrane. This observation as well as the lipidlike nature of the silicone rubber led to the use of the dimethyl polysiloxane membrane for the present investigation of the permeative behavior of chlorpromazine and the effect of additives on the permeation of the drug. The permeation of a steroid through dimethyl polysiloxane was also noted by Kincl *et al.* (22) to be about 100 times faster than through a nylon membrane of comparable thickness.

Permeation Characteristics of Chlorpromazine—A plot of log chlorpromazine concentrations of the diffusing solution against time is shown in Fig. 1. It can be seen from the figure that the depletion of the drug from the diffusing solution followed first-order elimination except in the initial period of permeation. The

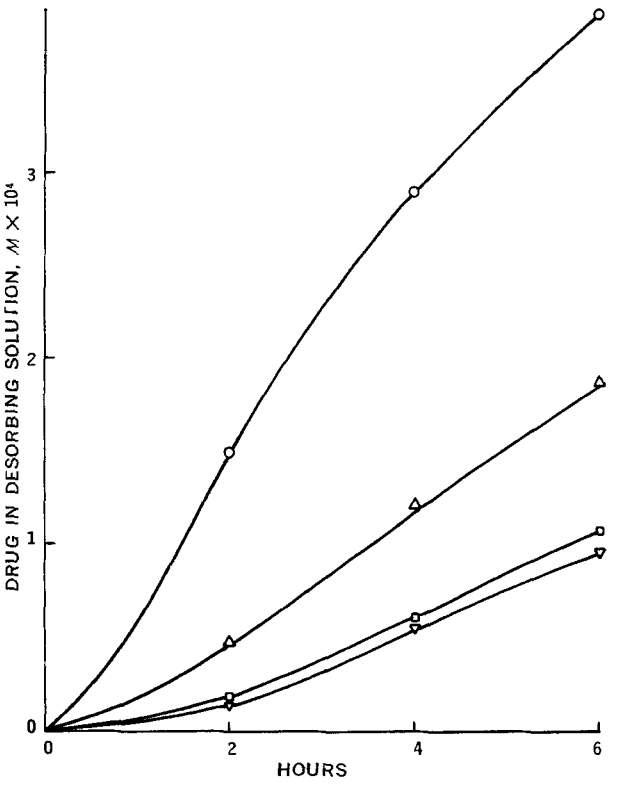

Figure 4—*Effect of endogenous substances on the permeation of chlorpromazine at 37°. Key: ○, no additive; △, 1% gastric mucin; □, 10 mM sodium glycocholate; and ▽, 10 mM sodium taurocholate.*

[14] Model MSB-1122A-1 constant-temperature shaker bath, Blue M. Electric Co., Blue Island, Ill.

[15] Silastic, Medical Products Div., Dow Corning Corp., Midland, Mich.

[16] Capran 77C, Allied Chemical Canada, Belleville, Ontario, Canada.

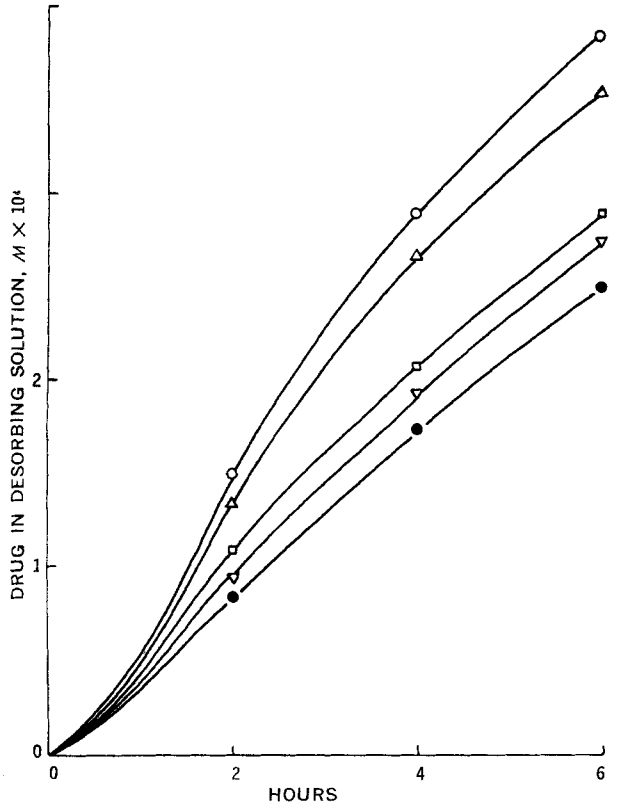

Figure 5—*Effect of dietary substances on the permeation of chlorpromazine at 37°. Key: ○, no additive; △, 10 mM saccharin sodium; □, 2.5% skim milk; ▽, 20 mM caffeine; and ●, 10 mM riboflavin phosphate sodium.*

initial sudden decrease in drug concentrations was attributed by some workers (21, 23) to the initial build-up of the drug in the membrane.

The change in first-order disappearance-rate coefficient[17] of the drug from the diffusing solution through the membrane to the desorbing solution over the physiological pH range is presented in Fig. 2. An essentially linear relationship was obtained between log rate coefficient and pH over pH 4.1–6.4. Beyond pH 6.8, there was deviation from the linear relationship. Among factors that control the permeation rate of the drug through the membrane, the partition coefficient is considered to influence the rate-limiting step in the pH range 4.1–6.4. Chlorpromazine with a pKa of 9.3 (24, 25) has an extremely high oil–water partition coefficient when the aqueous phase is alkaline (26). In this pH range, as the pH of the diffusing solution is increased, the proportion of unprotonated molecule increases and partition would then be favored. This factor is likely to be responsible for the observed linear relationship in the pH range 4.1–6.4. At higher pH values, however, the partition coefficient may no longer influence the rate-limiting step; instead, diffusion through the bulk solution–membrane interfacial diffusion layer (27) or through the membrane may limit the permeation rate.

Effect of Additives on Permeation of Chlorpromazine—The analyses of desorbing solutions were used mainly in this study because the additives frequently interfered with the assay procedure in the diffusing solutions. The lack of concentration–time data for diffusing solutions, however, made simple calculations of permeation coefficients of the drug impossible because the concentrations of both diffusing and desorbing solutions are required for calculation of the rate coefficients for nonsteady-state permeations such as those of the present study. The effects of additives are, therefore, discussed on the basis of the graphical representation of the amount of drug permeated into the desorbing solution at time t. A pH of 6 was chosen for these experiments due to the convenient rate of permeation of the drug at this pH.

[17] A term "rate coefficient" is used in this paper instead of "apparent rate constant."

Surfactants—The effects of a nonionic surfactant, polysorbate 80, and an anionic surfactant, sodium lauryl sulfate, on the permeation of the drug are shown in Fig. 3. Both surfactants exhibited a rate-retarding effect. The effect of polysorbate 80 is most likely due to a micellar effect (14). The drug present in micelles would be expected to be less or unavailable for permeation. This surfactant, with a very small critical micelle concentration (CMC) of 0.0013% (28), is considered to be in micelle form in the concentration employed.

The effect of sodium lauryl sulfate is, on the other hand, likely to stem from both insoluble complex formation and micellar effect[18]. Sodium lauryl sulfate seems to form an insoluble complex with chlorpromazine below its CMC and soluble micellar aggregates above it. Solutions of chlorpromazine in 6 m*M* sodium lauryl sulfate (above CMC) were clear, but the drug was found to be almost unavailable for permeation. This could indicate that most of the drug was present in micelles and unavailable for permeation. The drug solutions in 0.6 and 2 m*M* sodium lauryl sulfate (below CMC) were cloudy, and the degree of turbidity depended upon the concentration of the surfactant. Furthermore, when a turbid mixture containing a small amount of the surfactant was warmed, it gave a clear solution. From these observations of concentration and temperature effects of the phenomenon, it would be safe to assume that the turbidity was indicative of the formation of a poorly soluble complex between chlorpromazine and the surfactant. The reasonably fast rate of permeation observed from the 0.6 m*M* sodium lauryl sulfate solution indicates that some portion of the drug was still uncomplexed and available for permeation. The percentages of complexed drug increased with increasing concentration of the lauryl sulfate. Practically none was available for permeation at the lauryl sulfate concentration of 2 m*M*, which is

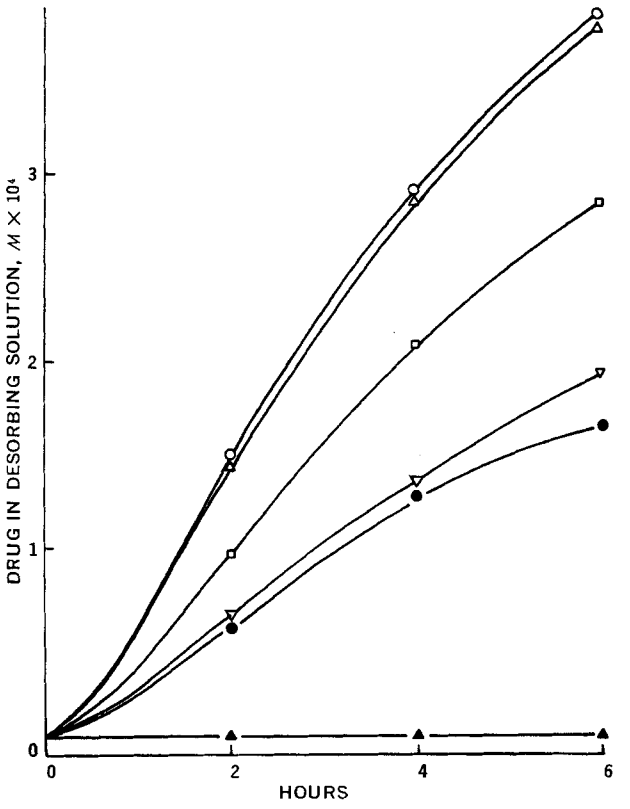

Figure 6—*Effect of adsorbents and tablet excipients on the permeation of chlorpromazine at 37°. Key: ○, no additive and 2% lactose; △, 1% gelatin; □, 1% talc; ▽, 1% kaolin; ●, 1% cation-exchange resin; and ▲, 1% activated charcoal.*

[18] Although the CMC of sodium lauryl sulfate is reported to be 8 m*M* (0.23%) from conductivity measurement (29, 30), it appears to vary considerably in the presence of solubilizates. The CMC determined from solubility measurements of steroids is reported to be 2 m*M* (31). In the presence of 0.6 m*M* chlorpromazine, the CMC was estimated to be around 4 m*M* at 25° (17). The CMC estimated from the solubility diagram of prednisolone at 30° (32) is also around 4 m*M*.

still below its CMC[18]. The formation of a poorly soluble complex between chlorpromazine cation and lauryl sulfate anion may be similar to the formation of procaine penicillin between procaine cation and penicillin G anion.

Endogenous Substances—The rate-retarding effect of gastric mucin, sodium glycocholate, and sodium taurocholate is presented in Fig. 4. The effect of the mucin may be attributed to at least one of the following factors: protein binding and the increased viscosity of the drug solution. Increased viscosity was reported to retard the absorption rate of salicylic acid from the stomach of the rat (33). Bile salts, on the other hand, form micelles (34) and make the drug less available for permeation. Insoluble complex formation was also noted below the CMC's of the bile salts. At concentrations of the bile salts employed in this study, however, the effect may be attributed mainly to micelle formation. The CMC's of sodium taurocholate and sodium glycocholate are reported to be around 8 m*M* and 10 m*M*, respectively, at 37° (34). Increase in membrane permeability in the presence of bile salts in submicellar concentrations as observed in the everted rat intestine (35, 36) and in goldfish (37) appears to be absent in the silicone rubber membrane.

Dietary Substances—Results with caffeine, riboflavin, saccharin, and skim milk are shown in Fig. 5. All these substances reduced the permeation rate of the drug. The effect of caffeine and riboflavin may be attributed to complex formation, since they are known to be very good complexing agents (38, 39). These complexes, even though they are soluble, are reported to be less or not permeable (40). The observed permeation of the drug may thus be considered mainly due to the free (uncomplexed) drug. Riboflavin phosphate, although it is an anion, did not form an insoluble complex with chlorpromazine cation. The effect of saccharin is small but appears to be real since the data were reproducible. This effect may also be due to soluble complex formation, because the alternative of insoluble complex formation between saccharin anion and chlorpromazine cation was not observed. The effect of skim milk can be ascribed to protein binding, since the protein binding of phenothiazine tranquilizers by bovine serum albumin is well documented (10–12).

Adsorbents—Among adsorbents investigated, activated charcoal was found to be extremely effective in retarding the permeation rate of chlorpromazine (Fig. 6). The adsorption of phenothiazine derivatives by charcoal was reported (5, 8) to be more extensive than by kaolin. Adsorption to these solid materials may be presumed to be the reason why the drug permeated to a much less extent that it did in their absence. Chlorpromazine, which is mostly protonated at pH 6, would be adsorbed by the cation-exchange resin. This would cause the conversion of unprotonated species to a protonated form in order to maintain the equilibrium at this pH. Decrease in permeable unprotonated species can then be considered to render the drug less available for permeation in the presence of the cation-exchange resin than in its absence.

Tablet Excipients—Lactose, gelatin, and talc were selected from many possible excipients of tablets. Lactose did not appreciably modify the permeation of chlorpromazine (Fig. 6). It is reasonable to expect that other sugars such as sucrose and glucose also do not interact with the drug significantly. Gelatin also failed to modify markedly the permeation rate of the drug. This may be attributed to weak interactive properties of gelatin which lacks tryptophan and contains only small amounts of other aromatic amino acids (41). Aromatic amino acids may be considered to be a strong binding group within protein molecules if hydrophobic bonding plays a dominant role in protein binding (42), although the exact mechanism of protein binding has not been established. The rate-retarding effect of talc, on the other hand, may be explained by adsorption of the drug to the solid surface (5, 8).

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