Table II—Suppression of Apomorphine-Induced Pecking Syndrome by Chlorpromazine (CPZ) and Methdilazine (MDZ) Assayed by Two Methods

Statistic	Method	
	Visual	Instrument
ID_{50} (CPZ)[a]	2.05 (1.10–3.80)	1.65 (0.90–2.95)
ID_{50} (MDZ)	29.8 (24.0–37.0)	27.1 (20.9–34.6)
Slope (CPZ)[b]	84.9 ± 67.5	92.9 ± 29.1
Slope (MDZ)	71.6 ± 47.4	82.6 ± 30.7
Common slope (CPZ) + (MDZ)	90.11	78.43
Relative potency[c]	0.072 (0.046–0.100)	0.063 (0.043–0.96)

[a] Median inhibiting dose (95% confidence limits); in unit of micromoles of base per kilogram body weight. [b] Slope of the dose–response line ± 95% confidence limits; in units of percent/log dose. [c] Potency of MDZ (95% confidence limits) relative to CPZ.

activity obviates deriving CPR values by curve plotting and area computing manipulations. And, finally, the comparatively unsophisticated device can be fabricated with standard and readily available components.

It seems clear from the results summarized in Tables I and II that the instrument monitor provides data as accurate and as reliable as those provided by the more tedious visual method. The results of the inhibitor potency assay, particularly, demonstrate the utility and applicability of the instrument method for such experiments.

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Drug Permeation through Thin Model Membranes I: Development of a Polymeric Model Biomembrane

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Abstract □ The development of a polymeric nonporous model membrane, containing natural membrane components, and its use in a two-compartment transport cell are reported. Consideration was given to the polymer used to form the polymer matrix, membrane thickness, the amount and type of biological material incorporated, and the effect of nonbiological additives. The effect of these changes on the transport properties of the various membranes were monitored in terms of k_d, the rate of disappearance constant of salicylic acid, from the pH 2.0 compartment of the transport cell. As a result of these studies, a standard model biomembrane was designed, containing 44% ethylcellulose, 44% biological materials, and 12% mineral oil, dry weight of the membrane. From the lack of solvent flux under experimental conditions and the first-order disappearance of salicylic acid, it appears that the polymer membrane mimics the functionality of natural membranes insofar as passive diffusion is concerned.

Keyphrases □ Biomembrane model, polymeric—drug permeation □ Membrane, nonporous—natural membrane components □ Drug absorption, passive—model membranes □ Transport rates—drugs through model membranes

Model membranes have been employed in attempts to develop *in vitro* model systems whose transport characteristics correlate with *in vivo* passive drug absorption. In addition to permitting systematic study of the many variables affecting the *in vivo* process, these model systems also act as a potential tool for assessing the ability of new medicinal agents to cross the gastrointestinal membranes and similar barriers. Although considerable work has been reported concerning a number of models, significant accomplishments are yet to be made in elucidating the transport process occurring *in vivo* and in producing *in vitro* models that more closely reflect the functionality of biological membranes.

The following properties may be considered desirable in any model system for passive drug absorption:

1. The membrane should be thin, with a low volume ratio of membrane to surrounding aqueous media. This elimination of the membrane "volume" significantly reduces drug retention within the membrane phase.

2. Transport selectivity of the drug(s) in question should be based on solubility in a homogeneous barrier rather than on dialysis through a microporous structure.

3. The membrane should be sufficiently durable to withstand extended experimental procedures without loss of integrity which might lead to changes in the transport characteristics of the membrane.

4. It should be possible to demonstrate a correlation between *in vitro* transport rates and *in vivo* absorption rates.

Model membranes can be conveniently classified into two groups. First, some membranes are essentially bio-

experimental models, whose principal research function has been elucidation of some of the biochemical and biophysical aspects of the ultrastructure of the biological membrane and determination of the role of the constituents in conducting the vital physiological functions accorded to the biomembrane. Such systems are invariably "constructed" on a molecular level, prime examples being monolayers (1), black (bimolecular) lipid membranes (2), and liposomes (3). The second group of model membrane systems are those employed primarily to study transport phenomena. Such systems are of particular relevance to *in vivo* drug-absorption processes. These membrane systems, employed to study this phenomenon on an *in vitro* basis, are termed biotransport models. Many variations of these models were utilized in the preceding decade to study the kinetics of drug transport and the many variables which are held to influence the *in vivo* process.

Biotransport model membrane systems may be divided into natural and artificial (nonliving) systems. The former include goldfish (4) or the everted sac technique (5), which has received recent attention in biopharmaceutical studies (6, 7). Skin sections stripped from hairless mice have been used as model systems to study chloramphenicol transfer (8). There are limitations to all of these approaches, although, understandably, a living system is to be preferred when experimental conditions permit.

Artificial (nonliving) membrane systems fall into two basic categories: those utilizing a liquid barrier and those employing a solid barrier. The liquid membrane system was one of the earliest model membrane systems applied to pharmaceutical research (9–11). The underlying principle of the model is the separation of the two aqueous phases, representing the plasma and the gastrointestinal lumen, by a liquid oil phase which simulates the lipid nature of the biological membrane. Much of the kinetic groundwork was carried out using these models, and their use continues today (12–14).

Procedures applying a solid barrier to separate two aqueous phases are currently being explored, not only by pharmaceutical and medical scientists but also in a wide variety of other disciplines. Whatever the application, the problem of mechanical strength of the membrane becomes significant when a certain cross-sectional dimension is exceeded. When extreme conditions are required to produce the requisite flux, such as in the case of pressurized reverse osmosis in desalination (15) or in pharmaceutical transport studies where the inherent mechanical strength of the particular polymer employed is absent (16), supports of various types are often required to maintain the physical integrity of the barrier. Nonsupported membranes appear to be better suited as biotransport model systems and, consequently, film strength is a necessary criterion upon which to evaluate potential membrane-forming materials.

Based on the mechanism of transport involved, it is possible to distinguish two types of solid barriers. In the first, the permeating molecule can penetrate through pores in the membrane, without actually being in solution within the membrane. The ability to be transported is largely dependent on the relative size of the barrier pore and the penetrant. An example of this system is dialysis, which has been used in the treatment of drug overdosage and poisoning (17) and in earlier artificial kidneys (18).

The second mechanism is that involving actual solution of the penetrant within the solid membrane. This requisite solubility, when coupled with diffusion, allows permeation across the barrier. Subsequently the penetrant is desorbed from the distal surface. Considering that prior to the solution process, sorption at the proximal membrane surface must occur, these processes parallel a model for liquid permeation proposed by Tuwiner (19). The entire mechanism depends primarily on the ability of the penetrant to dissolve in the membrane. As such, this type of solid barrier better resembles the functionality of the biological membrane with respect to passive diffusion of the uncharged drug species. Included in this category are "solid" barriers formed by the Millipore membrane dip technique, originally conceived by Tobias *et al.* (20, 21) and subsequently used by pharmaceutical investigators (8, 22). The inclusion of this type of barrier is based on the assumptions that the oil-impregnated "channels" of the porous pad constitute the effective membrane with regard to transport and that the size of this channel is much greater than the dimensions of the penetrating molecule. It is through these channels that the intramembrane flux occurs; as a result this model can be considered, along with nonporous polymer barriers, as a partition model system.

When the Millipore model is compared to the three-phase liquid partition models, it is seen that the volume ratio of the liquid phase to the aqueous phases employed has been drastically reduced. Although this diminution is significant, drug retention may still be considerable within the membrane during the time course of transport. Ideally, a model should exhibit negligible capacity for the permeating species. This requirement appears to be most adequately fulfilled by the use of polymeric film-forming agents from which solid, nonporous barriers of quite thin cross section can be made. Two sources exist: commercially prepared films or those extemporaneously formed by the experimenter. An advantage of the latter is that it permits experimental flexibility, especially in terms of membrane composition.

MEMBRANE COMPOSITION

Monoconstituent Membranes—Membranes that consist entirely of film-forming materials, alone or in combination, are termed monoconstituent or pure membranes. Regardless of the method used to produce these membranes, this type of barrier has received the most attention. Water-vapor transmission through polymeric films has been studied both in terms of the free film (23) and when the film is applied to tablets (24). Moisture uptake increased with increasing hydrophobicity of the barrier, and the transmission characteristics of the free film differed from that of the applied film. Permeation studies using polyethylene allowed the computation of apparent diffusion coefficients, permeability constants, and solubility coefficients of six aromatic compounds, the majority of which were nonelectrolytes (25). As an alternative to conventional separation methods of azeotropic binary mixtures of organic liquids, selective diffusion through polymer membranes has been employed by Carter and Jagannadhaswamy (26) as the rationale behind their extraction procedure. Termed pervaporation, the permeating component of the mixture vaporizes on the receiving side of the membrane and is subsequently collected in a cold trap.

Biomedical applications of pure films also have received attention. Extracorporeal hemodialysis efficiency has heretofore been extremely limited for large molecular volume solutes such as urea when employing cellophane-type membranes. Recently, attempts to fabricate a membrane applicable to "hemodialysis," whose mechanism of selectivity is based *not* upon dialysis but upon partition phenomena, have centered around a block copolymer system (27). Furthermore, with the upsurge in plastic packaging of a wide variety of pharmaceutical products, investigations of drug–polymer interactions continue (28), as workers attempt to elucidate the mechanisms of interaction based upon the study of kinetic and thermodynamic parameters.

There have been limited reports concerning drug transfer from one aqueous environment across a polymeric barrier into a second receiving compartment, also aqueous in nature. Johnson (29) used crosslinked thiolated gelatin films to study ionic and nonionic drug diffusion. Rummel *et al.* (30) separated an acid medium from an alkaline medium with several different polymeric membranes and noted that transport was unidirectional, favoring the unionized species. Garrett and Chemburkar (31–33) reported extensive experimentation utilizing dimethylsiloxane polymer sheeting. The silastic membranes proved to be impermeable to ions, and Fick's law was shown to apply for the diffusing species.

Composite Membranes—Flexibility of membrane composition, as an experimental variable, provides considerable potential for investigation. As a consequence, several researchers have attempted to alter the permeation properties of polymer membranes by the addition of compatible materials. Experimentally, this is most often accomplished by incorporating the additives into the membrane solution prior to casting, resulting in a composite membrane. Recently (34) a patent for a paraffin oil additive to polyethylene was awarded. The resultant film was said to have good vapor permeability and was suitable as a packaging material for fresh fruits and vegetables. Dupeyrat and Schreiber (35) studied the electrical properties of an oleic acid–collodion membrane which separated aqueous solutions of electrolytes. These properties were altered when the additive was omitted from the collodion matrix. A lipid-permeable collodion membrane, in which mineral oil was incorporated, was employed to study cholesterol transfer which was then used as a measure of serum lipoprotein–cholesterol complex dissociation (36).

Weatherby (37, 38) was one of the first to construct polymeric membranes comprised of materials distinctly biochemical in nature. He qualitatively demonstrated a relationship between pH of the bathing solution (distilled water was used in the receiving chamber) and the transport of some organic electrolytes. Ionic impermeability was attributed to like-charge repulsion arising from the exposed ionizable groups of the incorporated biochemicals on the membrane surface. Later, Weatherby (39) expanded this original work while employing phospholipids of determined composition. At about the same time, Goldman (40) prepared and studied the electrical characteristics of parlodion (purified collodion) and polystyrene membranes, some of which contained added phospholipid material. More recently, Lakshminarayanaiah (41) studied the resistance and capacitance of parlodion membranes containing stearic acid, phosphatidyl-L-serine, and cholesterol.

The literature does not appear to contain any reports of investigations utilizing a nonporous polymeric barrier, in which are incorporated additives of a biological nature, used expressly for the purpose of studying passive drug transport. Misra *et al.* (16), using collodion as the matrix material, combined lecithin into membranes cast on a mercury substrate and quantitated the permeation of several pharmaceutical substances. Analysis of the transport kinetics using such a model membrane system indicated that salicylic acid did not permeate the membrane in a fashion predicted by the pH-partition hypothesis. Moreover, nonlinearity of a semilogarithmic plot of concentration *versus* time depicting salicylic acid transport in the model system was observed and attributed to adsorption of the acid on the membrane.

It was, therefore, decided to investigate a composite model membrane system for its potential as a model biomembrane which would mimic some of the distinctive qualities of the biological membrane with regard to passive drug absorption. A prime consideration was the design of a membrane that would better fulfill the aforementioned criteria than model systems heretofore utilized. This preliminary report details the various parameters investigated in constructing such a model biomembrane.

EXPERIMENTAL

Materials—Solutions of lecithin (90% pure, bovine)[1] and cephalin (animal)[1] in chloroform were filtered through Whatman No. 2 filter paper to remove insoluble contaminants. The solvent was evaporated under ambient conditions, and the material collected was stored over a desiccant. The composition of the cephalin was taken to be 15% phosphatidylethanolamine and 85% phosphatidylserine (20). Cholesterol was similarly stored over a desiccant. The polymeric film-forming agents tested included ethylcellulose,[2] *n*-butyl methacrylate,[3] and a vinyl chloride copolymer.[4] Buffer components (sodium hydroxide, potassium phosphate monobasic, potassium chloride, and hydrochloric acid), salicylic acid,[5] and the polymer solvents employed were all of reagent grade. Light mineral oil NF[6] and sodium carboxymethylcellulose[7] were also used in this study. All chemicals, except where specified, were used as received.

Membrane Formation—Solutions of the chosen polymer (percent weight in volume ratio) and liquid paraffin (percent volume in volume ratio) in chloroform were made to contain twice the concentration desired for each component in the final membrane solution. To 5 ml. of this stock solution were added the requisite amounts of lecithin, cephalin, and cholesterol in chloroform, and the volume was brought to 10 ml. with chloroform.

The membrane was formed by a casting technique. Two milliliters of the solution containing the biological materials and the polymer was introduced into a glass ring (5.5 cm. i.d.) clamped onto a leveled glass plate approximately 12.5 cm. square. No seepage occurred at the ring-plate joint. The solvent was allowed to evaporate under controlled conditions at room temperature. This took 6–7 hr. The resulting polymer film containing the dispersed biochemicals was removed by soaking for 10 min. in distilled water at room temperature. The membrane was allowed to air dry and was stored in a glass culture dish until used.

Transport-Rate Studies—A 50-ml. Plexiglas dialysis cell, similar to that described by Patel and Foss (42) and consisting of two half-cells separated by the model membrane, was employed in the transport-rate studies. The cell was modified by the addition of two sampling ports, each having a 4.0-cm. extension of glass tubing (0.9 cm. i.d.) which permitted sampling while the cell remained submerged in a constant-temperature water bath. The sampling extensions were closed during agitation. The maximum area of contact between the membrane and solution was 11.34 cm.^{2}.

Twenty-five milliliters of a pH 7.4 buffer (43), used as the receiving medium, was introduced into one side of the cell. The unexposed surface of the membrane was inspected for leaks. The drug-containing pH 2.0 buffer solution (43) was then added to the other chamber. All solutions were previously equilibrated to 37° except where noted. The cells were immersed in the temperature-controlled water bath at 37° and shaken at 73 strokes/min. At appropriate time intervals, 1-ml. samples were withdrawn from both chambers and diluted with the respective buffer solutions; the absorbance was determined spectrophotometrically at 303 and 298 mμ, the wavelengths of maximum absorbance of salicylic acid in pH 2.0 and pH 7.4 buffer, respectively. The corresponding buffer was employed as the reference in each case. From a predetermined calibration curve, the unknown concentration of the test drug was determined. In most cases, the initial concentration of drug was 300 mg./l.

The apparent rate constant, k_a, for the disappearance of salicylic acid from the chamber buffered at pH 2.0 was obtained from a semilogarithmic plot of the concentration of drug remaining on the pH 2.0 side of the membrane *versus* time. In all cases, the reported rate constant was derived from the statistically determined slope (method of least squares) of such a plot, using the first sample period (not zero time) in the computation. Correlation coefficients were not less than 0.97. Except where specified, triplicate runs were made.

[1] Nutritional Biochemical Corp., Cleveland, Ohio.
[2] Ethocel, supplied by the Dow Chemical Co., Midland, Mich.
[3] Elvacite 2044, supplied by E. I. du Pont De Nemours and Co., Wilmington, Del.
[4] Exon 400 XR-77, supplied by Firestone Plastics Co., Pottstown, Pa.
[5] Crystal, Baker and Adamson, Allied Chemical Corp., Morristown, N. J.
[6] Atlas Drug and Chemical Co., New York, N. Y.
[7] CMC 7HP, Hercules Powder Co., Wilmington, Del.

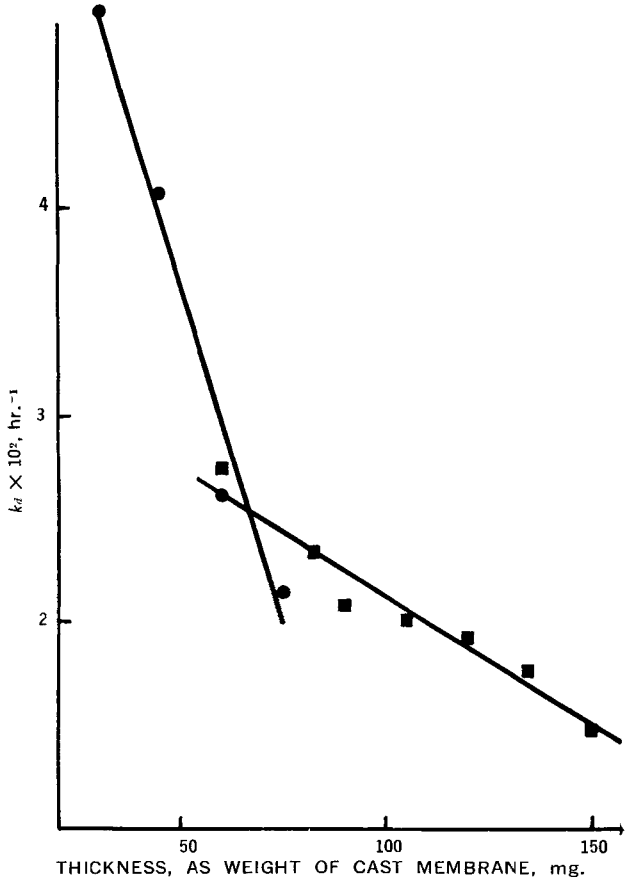

Figure 1—*Effect of the polymer forming the matrix and membrane thickness on the rate of salicylic acid disappearance. All membranes were prewashed for 4 hr. Key: ■, BMA; and ●, EC.*

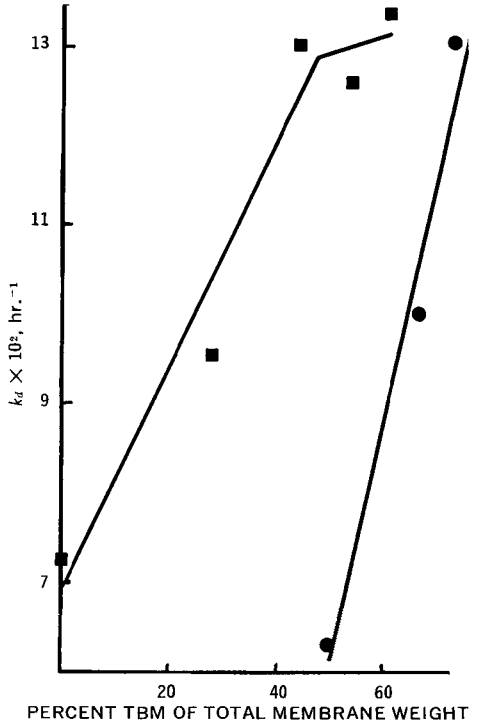

Figure 2—*Effect of TBM on the rate of salicylic acid disappearance. Key: ■, matrix solution was EC (1.5%) and MO (0.5%); and ●, matrix solution was EC (1.5%).*

RESULTS AND DISCUSSION

To represent the major biological components of membranes of animal origin (44, 45), two phospholipids, lecithin (phosphatidylcholine) and cephalin (phosphatidylethanolamine and phosphatidylserine), and the neutral lipid cholesterol were chosen. In subsequent discussions, this combination is referred to as the total biological mixture or TBM. The 1:1:2 molar ratio of cephalin, lecithin, and cholesterol, respectively, used in the majority of these initial studies represents a 1:1 molar ratio of *total* phospholipid to cholesterol and is based upon a comparable ratio found in the plasma membrane (46). A recent report (47) demonstrated that these materials are major components of the intestinal membrane and exist therein in this approximate ratio. As will be discussed, consideration was first given to the polymer used to form the supporting matrix. Attention was then directed toward the effect of increasing the TBM, both with and without additives of a nonbiological nature. Finally, the effect on transport rate of varying the ratio of the individual biological membrane components was studied.

Choice of Supporting Matrix—Several film-forming agents were chosen for their potential to create a lipophilic matrix. Only data associated with two of these materials [*n*-butyl methacrylate (BMA) and ethylcellulose (EC), 50 cps.] will be presented here. With BMA, membranes of constant-surface area were cast from a series of dilutions of a stock solution containing BMA (6.0%) and TBM (1.5%) in chloroform. In this manner, the weight of the membrane and hence the thickness varied while holding constant the ratio of polymer to TBM. A similar series of membranes was cast from dilutions of a stock solution containing EC (3.0%) and TBM (0.75%) in chloroform. The rate constants, k_d, for the transport of salicylic acid through these membranes are shown in Fig. 1 as a function of the weight per unit area (equivalent to thickness) of the cast membrane. It is apparent that the change in k_d with thickness was greater with the EC membrane than with the BMA membrane system, the rate constant increasing rapidly with the thinner membranes. The EC films possessed certain other advantages over the BMA membranes. The pliability of the BMA film limited its handling qualities and mechanical strength and these, in turn, limited the minimum thickness to which the membrane could be cast. Mechanical strength of the BMA membrane was also sensitive to small changes in TBM concentration. On this basis and because of the higher transport rates of thin EC membranes, all subsequent studies were conducted using this polymer as the film-forming agent.

Effect of TBM on k_d—Increasing amounts of TBM were added to solutions of 1.5% EC in chloroform in an attempt to potentiate transport across the resultant membrane. It was found, however, that above a certain concentration of TBM the aqueous phases in the transport system became turbid due to excessive washout of biological material from the membrane. To ensure that all such material had been removed, it was necessary to prewash the membrane for prolonged periods of time (up to 116 hr.).

To overcome this disadvantage, 0.5% mineral oil (MO) was added to the chloroform solution of EC and TBM prior to casting. The membranes were then prewashed with pH 2.0 and pH 7.4 buffers on their respective sides of the membrane mounted within the transport cell for 3 hr., this now being sufficient time to remove the excess material. The effect of increasing TBM on k_d, for membranes with and without MO, is shown in Fig. 2. Several points are apparent. First, the addition of 0.5% MO to the casting solution acts to potentiate the transport rate of salicylic acid. Second, there is a certain capacity of the polymer matrix for TBM in the presence of MO. This is evidenced by the break in the left-hand curve in Fig. 2, indicating the failure of additional TBM to enhance k_d. The breakpoint is equivalent to a membrane containing 44% TBM, expressed as a percentage of the total weight of the dry membrane. It would appear that any TBM in excess of this concentration is removed in the prewash; as a result, k_d remains constant.

As a result of this study, the standard membrane used in all subsequent investigations consisted of 44% EC, 44% TBM, and 12% MO, expressed in terms of the dry weight of the membrane.

Effect of Biochemical Constituent Variation—To study the effect of variations in the three biological components of the membrane on k_d, a series of membranes was studied in which the percentage of lecithin was progressively increased. The remaining TBM requirement was divided equally between cephalin and cholesterol. The TBM was held constant at 44% of the membrane weight, which also contained 44% EC and 12% MO. The data are shown in Fig.

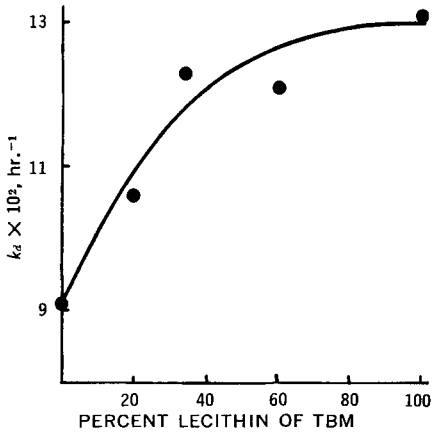

Figure 3—*Effect of lecithin as a percentage of TBM on the rate of salicylic acid disappearance. Membrane composition was 44% EC, 44% TBM, and 12% MO.*

3, where it is apparent that lecithin has a potentiating effect on the rate of salicylic acid transport. This rate increase may be attributed to the contribution of lecithin to the nonpolar character of the model biomembrane, hence increasing the passage of the lipid-soluble drug species. In contrast to both phosphatidylserine and phosphatidylethanolamine, phosphatidylchlorine has a greater alkyl moiety esterified to the common phosphatidic acid backbone. This is consistent with the effect observed with the incorporation of MO into the EC membrane (Fig. 2).

Determination of Solvent Flux—Employing the standard membrane, the effect of hydrostatic and osmotic pressure on solvent flux was investigated. Distilled water was placed on one side of the membrane and dialyzed against an equal volume of a 5% aqueous solution of sodium carboxymethylcellulose (CMC). After 6 days, there was no volume increase in the chamber containing the CMC. In another study, 25 ml. of distilled water was added to one chamber, the second chamber remaining empty. Although the membranes appeared slightly distended after 6 days, there was no evidence of leakage or the appearance of moisture on the distal side of the membrane. These observations lend support to the proposed mechanism for the transport of unionized drug molecules across polymeric barriers, wherein the permeating species moves across the membrane without the aid of the aqueous solvent.

SUMMARY

In summary, a polymeric membrane that incorporates biochemicals representing natural membrane constituents was fabricated by casting. The transport of salicylic acid through such a model followed apparent first-order kinetics and is represented by the disappearance-rate constant, k_a. Additionally, the lack of solvent flux indicates that this solid barrier is nonporous in nature. This property, coupled with approximately 2% salicylic acid retention (48), allows the model biomembrane to mimic the passive diffusion functionality of natural membranes. Lecithin potentiates transport, as does MO, both apparently contributing to the lipophilicity of the barrier.

As a result of these studies, a standard model biomembrane was prepared. The composition of this membrane is 44% EC, 44% TBM, and 12% MO, expressed as dry weight before prewashing. The transport characteristics of the standard membrane are presently being investigated and will be the subject of a future communication.

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