Two-Phase Method for the Investigation of Interphase Transport II: Experimental Aspects

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Abstract □ A series of experiments were conducted to demonstrate the validity of the baseline considerations presented in the accompanying communication and the usefulness of the combined experimental and theoretical approach in more complex situations. The experimental apparatus consisted of a water-jacketed chamber with controlled agitation. The lipid sink was prepared by saturating a filter with either dibutyl sebacate, hexadecane, or a combination of these oils with a polymer. A lipid sink made from a polymer-oil gel without the filter matrix was also used. A number of solutes which included diethyl phthalate, dinitrotoluene, and cholesterol were employed. The experimental results were found to be consistent with the predictions of theory. All solutes followed first-order behavior when the oil-water partition coefficient was large. For moderate partition coefficient values it was necessary to account for the solute buildup in the oil at the interface. In order to explain the absorption of cholesterol from a 0.10% aqueous polysorbate 80 solution of cholesterol, an interfacial barrier was proposed.

Keyphrases □ Interphase transport—experimental aspects □ Aqueous-to-lipid transport—experimental methods □ Diagram—interphase transport determination apparatus □ Scintillometry—analysis □ UV spectrophotometry—analysis

In Part I (1) of this series the theoretical aspects of a two-phase diffusion controlled model designed to study aqueous-to-lipid transport was discussed. The equations describing this model were developed and computations were made which predicted the effects of the various parameters involved. In this report experiments are described which demonstrate the validity and usefulness of the model.

EXPERIMENTAL

Materials—Cholesterol[1] labeled with ^{14}C or ^{3}H was received as a benzene solution. It was placed into aqueous solution (see *Procedure* section), and the assay of this solution was effected by means of a liquid scintillation system.[2] The scintillation cocktail for aqueous assay consisted of 7 g. 2,5-diphenyloxazole (PPO),[3] 100 g. naphthalene,[4] and spectroquality *p*-dioxane[5] added to a liter of total volume. Approximately 10 ml. of this cocktail was added for each milliliter of cholesterol solution assayed.

The diethyl phthalate[4] was used as supplied. Assay from the aqueous solution was done by utilizing a spectrophotometer[6] at a wavelength of 239 mμ. Using this same instrument at a wavelength of 251 mμ, the dinitrotoluene solutions were assayed. The 2,4-dinitrotoluene was recrystallized from a 75% ethanol solution before use. Reagent grade dibutyl sebacate[4] and spectroquality reagent hexadecane[5] were used as supplied.

The filters used in the lipid phase were epoxy filters[7] with a pore size of 0.9 μ. The gels were made using poly *n*-butyl methacrylate[8] high molecular weight polymer which was washed with water and dried under a vacuum.

Polysorbate 80 USP was used as supplied and sodium cholate was prepared by the reaction of recrystallized cholic acid with reagent grade sodium hydroxide. The unreacted cholic acid was extracted by the use of chloroform.

Apparatus—Figure 1 is a schematic diagram of the experimental apparatus used in all of the pickup experiments described. The lipid phase of the system consists either of an oil saturated filter or a lipid-poly *n*-butyl methacrylate gel. Both of these lipid systems have been designed to resist emulsification and interfacial changes even in the presence of enough stirring to maintain an aqueous diffusion layer in the 100-μ range.

The lipid phase is placed at the bottom of a glass beaker, water-jacketed at 30°. A piece of glass tubing, which is labeled "insert," of approximately 5 cm. in length, fits snugly into the 38-mm. beaker. This insert is used to push down the filter and hold it in place. In the case of the gel, the insert prevents gel on the side of the beaker from taking part in the pickup of the solute.

The beaker is covered by a plastic mount which prevents evaporation and supports a synchronous motor.[9] Two holes have been drilled in the mount, one of which permits sampling and the other of which permits a four-blade glass stirring rod to be inserted into the beaker.

This apparatus provides constant stirring at a fixed geometry and therefore the hydrodynamic conditions were expected to remain constant for a given beaker from run to run.

Procedure—As previously mentioned, the lipid phase of the model consisted of either an oil-saturated filter or a lipid gel. The

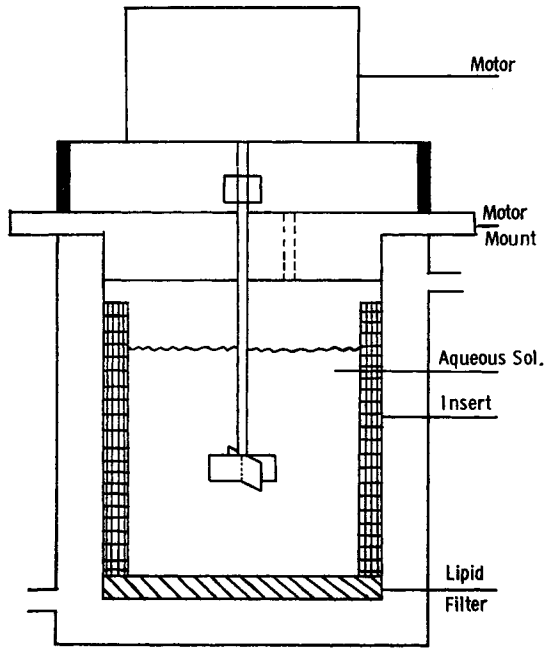

Figure 1—*Schematic diagram showing the apparatus used for the pickup experiments.*

[1] New England Nuclear Corp., Boston, Mass.
[2] LS-200B, Beckman Instruments, Inc., Fullerton, Calif.
[3] Packard Instrument Co. Inc., Downers Grove, Ill.
[4] Eastman Organic Chemicals, Distillation Products Industries, Rochester, N. Y.
[5] Matheson Coleman and Bell, Division Matheson Co., Inc., Norwood, Ohio.
[6] Hitachi Perkin-Elmer 139 UV-vis, Hitachi, Ltd., Tokyo, Japan.
[7] Gelman 37-mm. diameter Versapor TM 6429, Gelman Instrument Co., Ann Arbor, Mich.
[8] Elvacite 2044, E. I. du Pont de Nemours, Inc., Wilmington, Del.
[9] Hurst model CA, Hurst Manufacturing Corp., Princeton, Ind.

former, being the simpler and purer system, was used for each of the experimental conditions described in the results, while the latter was used in only a limited number of situations.

The saturation of the filters was achieved by first placing steel paper clips on the filters. The filters were then suspended from the top of a vacuum desiccator by means of an external magnet bar. The lipid was placed on the bottom of the desiccator in a Petri dish. Using a water aspirator, a vacuum was maintained in the desiccator for approximately 30 min. With the vacuum still being applied, the magnet was removed and the filters fell into the lipid. After about 10 min. the vacuum was released and the filters were allowed to soak for at least 6 to 12 hr. The filters were then removed from the desiccator and the excess oil was removed by wiping with lens paper. Two filters were placed together, rough sides touching, wiped, and then pushed down into the beaker with the insert.

The gels were made by pipeting dibutyl sebacate into a Petri dish, and then adding 5 ml. of a 10% poly *n*-butyl methacrylate in acetone solution. The beakers were placed in an oven at approximately 50° for 3 days. A glass insert was forced down into the gel to prevent the gel, adsorbed on the sides of the beaker, from participating in the experiment.

After the lipid phase and the insert were in place, the stirrers were inserted and the 30 ml. of the aqueous solutions were then added. When the solute was either diethyl phthalate or dinitrotoluene, 2-ml. samples were taken. When cholesterol was used as the solute, 1-ml. samples were removed. In all cases, no replacement was made for the removed samples.

The 0.01% v/v diethyl phthalate solutions and the 0.01% w/v dinitrotoluene solutions were prepared by stirring for 24 hr. The ^{14}C labeled cholesterol solutions, on the other hand, were prepared by first transferring the appropriate amount of a cholesterol stock solution into a volumetric flask. The stock solution of cholesterol-^{14}C consisted of 3.75×10^{-3} mg./ml. cholesterol and the ^{3}H labeled cholesterol stock consisted of 7×10^{-5} mg./ml. cholesterol in 15% ethanol and 85% benzene. The ethanol and benzene were evaporated by passing nitrogen gas into the flask. Then 2 ml. of 95% ethanol was added for each liter of solution. This was done in order to ensure solution of the cholesterol. After approximately 30 min., water or aqueous surfactant solutions were added to volume. Each solution was allowed to stand approximately 1 day in the dark before use.

Aqueous diffusion coefficient experiments were carried out in the two-flask, magnetically stirred, apparatus described by Desai (2) and modified by Goldberg (3).

Oil-water partition coefficients were obtained using the following procedures. Twenty milliliters of a 0.1-mg./ml. dinitrotoluene or dibutyl sebacate water solution was added to 5 ml. of hexadecane in a test tube, and 20 ml. of water was added to 5 ml. of a 20-

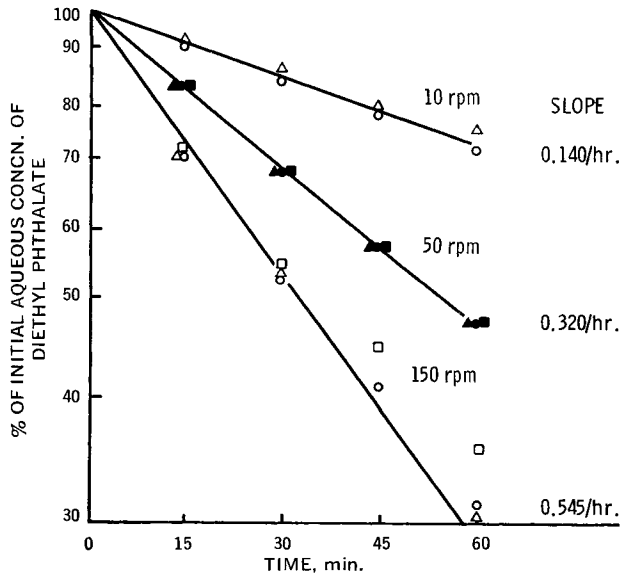

Figure 2—*Experimental semilog plot of percent initial concentration of diethyl phthalate in water as it goes into filters filled with dibutyl sebacate* versus *time in minutes. There were eight separate apparatus used.*

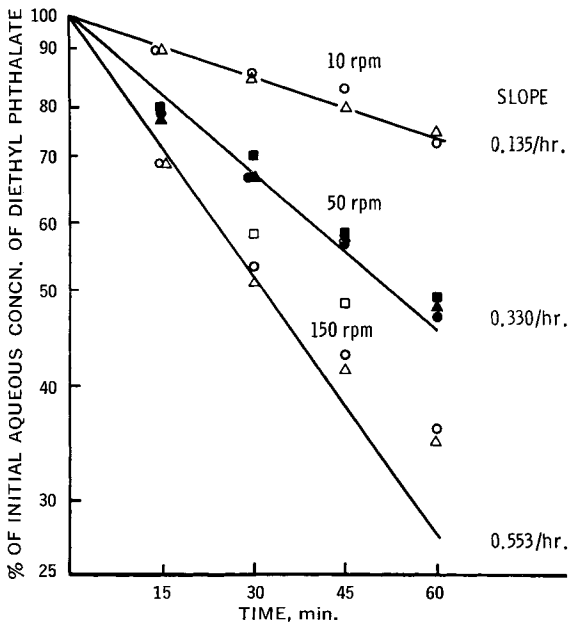

Figure 3—*Experimental semilog plot of the percent initial concentration of diethyl phthalate in water as it goes into 2:1 dibutyl sebacate–poly n-butyl methacrylate gel-saturated filters* versus *time in minutes.*

mg./ml. solution of either diethyl phthalate or dinitrotoluene in dibutyl sebacate. These tubes were shaken and centrifuged at 8000 r.p.m. for 30 min. The aqueous portion was sampled and assayed. The partition coefficients involving cholesterol were obtained by adding 50 ml. of the aqueous cholesterol solution described earlier to 5 ml. of the desired oil in a 100-ml. volumetric flask. After stirring with Teflon-coated stirring bars, 10-ml. samples were taken and centrifuged at 5000 r.p.m. for 2 hr. Both the oil and water phases were assayed using liquid scintillation spectrometer.

Modification of the Equations—In order to correct for the volume changes caused by the removal of samples, Method II in the previous paper (1) was modified. The aqueous volume term V_w was adjusted at each different sampling time. Comparison of the modified to the nonmodified computations showed little difference. Methods I and III do not lend themselves to such a modification and were not used in the D_0 calculations given in the following section.

RESULTS

The first series of experiments conducted were for the high partition coefficient case. Figure 2 shows a plot of the log of the percent of the original concentration of a 0.1-mg./ml. diethyl phthalate solution as a function of time when the lipid sink was dibutyl sebacate. The oil–water partition coefficient was determined to be 598 ± 3.5%. Eight separate experimental setups were used and each symbol in Fig. 2 represents a different apparatus. These experiments were repeated using filters saturated with a 2:1 dibutyl sebacate–poly *n*-butylmethacrylate gel. The results are shown in Fig. 3 and the initial slopes compare favorably with those in the pure dibutyl sebacate case. A pure 50:50 gel, without a filter matrix, was used as a sink with diethyl phthalate as the solute. The results obtained with this system, as shown in Fig. 4, correlate fairly well with the gel filters.

Figure 5 is a similar plot for dinitrotoluene going into dibutyl sebacate, the partition coefficient being 525 ± 4%. As with the diethyl phthalate, these experiments were repeated using a 2:1 gel of dibutyl sebacate–poly *n*-butyl methacrylate, and these results are shown in Fig. 6. Just as in the case of diethyl phthalate, the initial rates for the gel filter system were essentially the same as those when the pure lipid filter was used as the sink.

As predicted by theory (1) first-order aqueous diffusion control governs the pickup in the above situation since the partition coefficients are relatively high. Deviations from the first order,

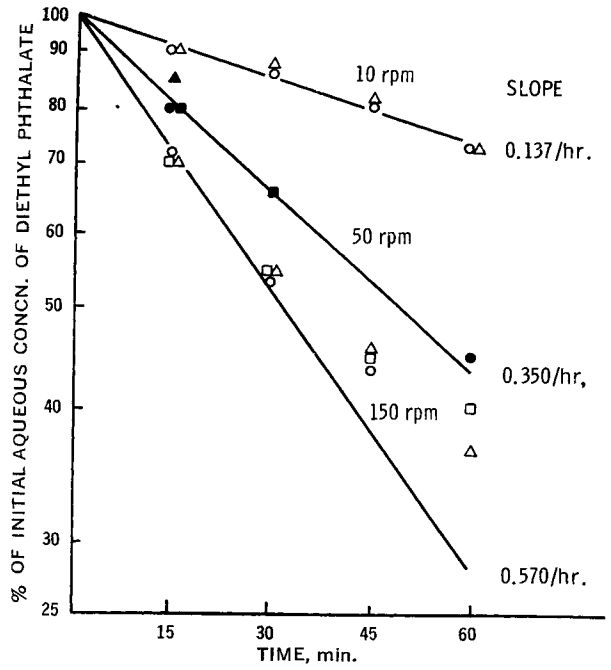

Figure 4—*Experimental semilog plot of percent initial concentration of diethyl phthalate in water as it goes into 1:1 dibutyl sebacate-poly n-butyl methacrylate gels with no filter matrix present* versus *time in minutes.*

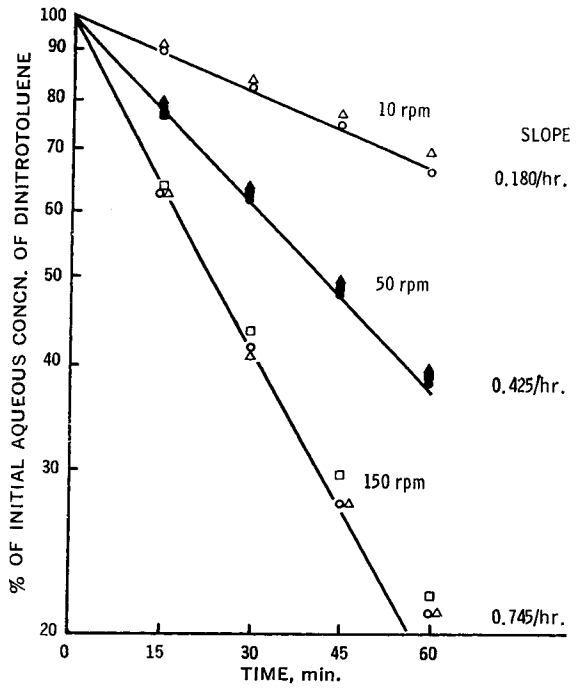

Figure 6—*Experimental semilog plot of the percent initial concentration of dinitrotoluene in water as it goes into filters filled with a 2:1 dibutyl sebacate-poly n-butyl methacrylate gel* versus *time in minutes.*

especially in the cases of 150 r.p.m. and in gel cases, may well be due to a low diffusion coefficient in the gel.

Using the average of the gel filter and the pure lipid filter results for each of the two solutes, the thicknesses of the Fick's diffusion layer (h) was calculated from the following formula:

$$h = \frac{D_w A}{(\text{slope}/3600) V_w \, 2.303} \qquad \text{(Eq. 1)}$$

For the 150 r.p.m. case, h was calculated to be 0.0083 cm. for diethyl phthalate and 0.0087 cm. for dinitrotoluene. For the 50 r.p.m. case, h was calculated to be 0.014 cm. for the diethyl phthalate and 0.0145 cm. for the dinitrotoluene. When the stirring speed was 10 r.p.m., h was calculated to be 0.033 cm. for diethyl phthalate and 0.034 cm. for dinitrotoluene. These calculations were carried out using the independently determined aqueous diffusion coefficients (D_w) of 7.85 × 10^{-6} cm.²/sec. for diethyl phthalate, and 1.1 × 10^{-6} cm.²/sec. for dinitrotoluene. These D_w values were considered

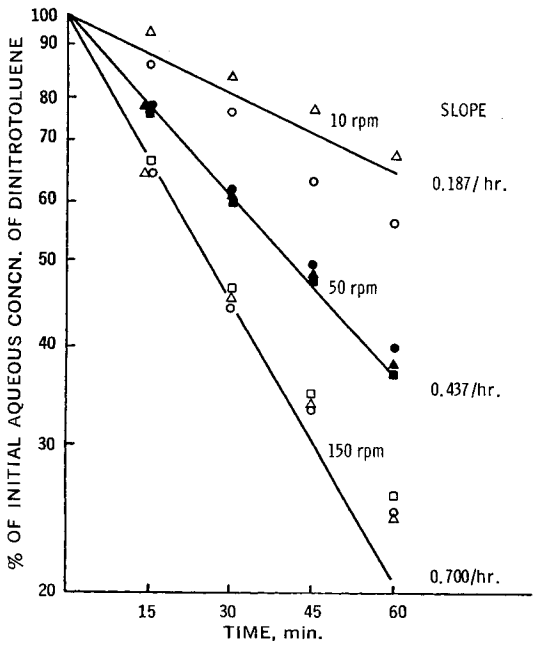

Figure 5—*Experimental semilog plot of percent initial concentration of dinitrotoluene in water as it goes into filters saturated with dibutyl sebacate* versus *time in minutes.*

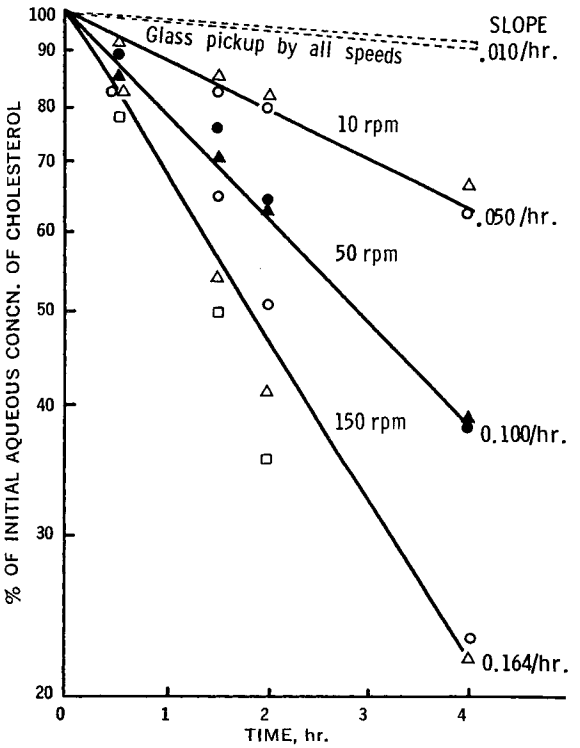

Figure 7—*Experimental semilog plot of percent initial concentration of cholesterol in water as it goes into dibutyl sebacate-saturated filters* versus *time in hours. The uppermost line is the result of this experiment with no lipid sink present. The dotted lines show the approximate scatter of data.*

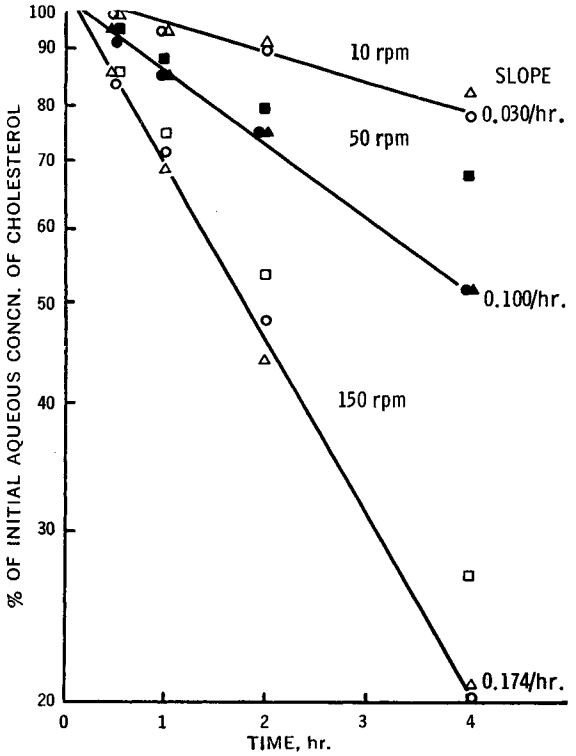

Figure 8—*Experimental semilog plot of percent initial concentration of ^{14}C labeled cholesterol in water as it goes into water-saturated filters* versus *time in hours.*

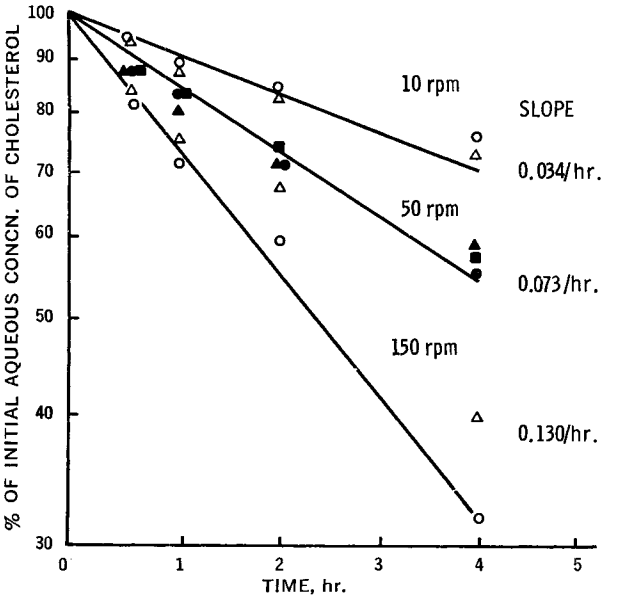

Figure 9—*Experimental semilog plot of percent initial concentration of ^{14}C labeled cholesterol in water as it goes into hexadecane-saturated filters* versus *time in hours.*

accurate to about ±10%, and therefore the calculated h values are well within experimental error. Thus, these experiments seem to show that for the simple high partition case, the model is reproducible and conforms to theory.

The results of experiments for the pickup of 1.5×10^{-8} g./ml. cholesterol-4-^{14}C into a dibutyl sebacate filter sink are shown in Fig. 7. The dotted line at the top of the figure is the control run at all the various stirring speeds when no filter or oil was present. Though there is appreciable variation in the data, the stirring effect is very obvious and is in approximately the same ratio as the previous diethyl phthalate and dibutyl sebacate experiments.

A solution containing ^{3}H labeled cholesterol and one containing ^{14}C labeled cholesterol were mixed and the two tags were run together. The results confirmed those previously mentioned. The total cholesterol in solution was again 1.5×10^{-8} g./ml. with approximately one tenth of that being tritiated sample. There seemed to be little to no glass pickup for the tritiated portion. It was found that the pure filters themselves adsorbed cholesterol. These filters saturated merely with water were used as a sink and the resulting pickup can be seen in Fig. 8. Hexadecane-saturated filters were also used as a sink and the results of these experiments are shown in Fig. 9.

The diffusion coefficient of cholesterol could not be obtained from the two-flask membrane system used for the other two solutes due to adsorption of cholesterol on all of the membranes used. Thus another possible use for this model might be the approximation of aqueous diffusion coefficients for insoluble materials when these values cannot be obtained by conventional methods.

The average slopes of the results of all of the cholesterol experiments were used to calculate the D_w of cholesterol for each (h) thickness obtained from the dinitrotoluene experiments. The D_w calculated for cholesterol at a stirring speed of 150 r.p.m. is 2.2×10^{-6} cm.^{2}/sec., for 50 r.p.m. 2.15×10^{-6} cm.^{2}/sec., and 2.0×10^{-6} cm.^{2}/sec. for 10 r.p.m. The similarity of these values shows that the stirring dependence is the same as that of the dinitrotoluene and diethyl phthalate cases. The values were lower than the Stokes-Einstein approximation for cholesterol (4.1×10^{-6} cm.^{2}/sec.).

When the partition coefficient is sufficiently low, pickup is no longer first-order and aqueous diffusion controlled. Diffusion in the oil becomes very important. The symbols in Fig. 10 show the pickup of a 0.1-mg./ml. diethyl phthalate solution into hexadecane, the o/w partition coefficient being 45 ± 5%. Figure 11 shows the pickup of a 0.1-mg./ml. dinitrotoluene solution by hexadecane, the o/w partition coefficient being 20 ± 10%. The solid theoretical curves were obtained by a curve-fitting technique in which the appropriate aqueous diffusion coefficients, partition coefficients, and diffusion layer thicknesses were substituted into the equations of the modified Method II previously mentioned. Then the best value for D_0, the diffusion coefficient in the oil, was used to give the fit shown with the experimental results. The best fit occurred for the same D_0 value for each stirring speed and by this method an approximate effective diffusion coefficient of 10^{-6} cm.^{2}/sec. for diethyl phthalate in the hexadecane sink and a value of 2×10^{-6} cm.^{2}/sec. for dinitrotoluene in the hexadecane sink were obtained. The dotted curves in the two figures are for 150 r.p.m., and in Fig. 10 for a D_0 of 1.5×10^{-6} cm.^{2}/sec., and in Fig. 11 for a D_0 of 2.5×10^{-6} cm.^{2}/sec. These dotted curves demonstrate that the method is fairly sensitive for the conditions used. If, however, the thickness

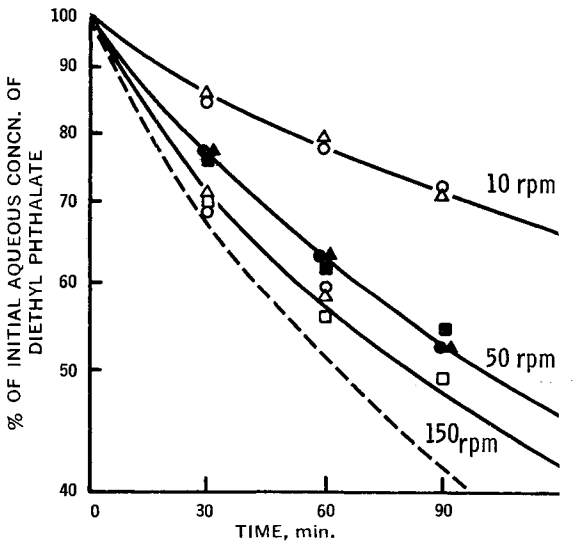

Figure 10—*Experimental semilog plot of percent initial concentration of diethyl phthalate in water as it goes into hexadecane-saturated filters* versus *time in minutes. The symbols are the experimental points. The solid curves are theoretical computations where $D_0 = 1 \times 10^{-6}$ cm.^{2}/sec. The dotted curve is the theoretical calculation for 150 r.p.m. and $D_0 = 1.5 \times 10^{-6}$ cm.^{2}/sec.*

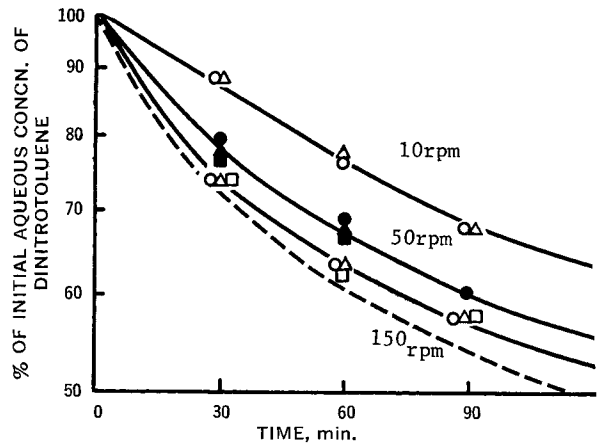

Figure 11—*Experimental semilog plot of percent initial concentration of dinitrotoluene in water as it goes into hexadecane-saturated filters* versus *time in minutes. The symbols are the experimental points. The solid curves are theoretical calculations where* $D_0 = 2 \times 10^{-6}$ *cm.²/sec. The dotted curve is the theoretical calculation for 150 r.p.m. and* $D_0 = 2.5 \times 10^{-6}$ *cm.²/sec.*

of the sink is cut in half, theoretical calculations show that this sensitivity no longer exists in the dinitrotoluene case due to backup. There is no doubt, however, that this system may be a possible method for determining the effective diffusion coefficients in lipid filters. Such filters have been used and may be used in future three-phase model studies.

Experiments were conducted using 1.5×10^{-8} g./ml. ^{14}C-4-cholesterol, 0.1% sodium cholate solutions (buffered by phosphate buffer at pH 8) as the aqueous phase. Fig. 12 shows the pickup of cholesterol from such a solution when dibutyl sebacate saturated filters served as the lipid phase. The dotted lines at the top of the figure are the control runs at all the various stirring speeds when no filter or oil was present. Similar results were obtained when the solution was presaturated with dibutyl sebacate. The pickup rate seems to be slowed by the addition of the cholate and it is believed that this effect may be caused by association between the sodium cholate and cholesterol molecules despite the fact that the concentration of sodium cholate is well below the "limit one" described by Ekwall (4) where association takes place.

Experiments were also conducted using 1.4×10^{-8} g./ml. cholesterol-0.1% polysorbate 80 aqueous solutions as the aqueous phase and hexadecane saturated filters as the lipid phase. The results of one set of these experiments are reported in Fig. 13. The lack of good precision and also the nature of the curves make a detailed analysis of the data difficult.

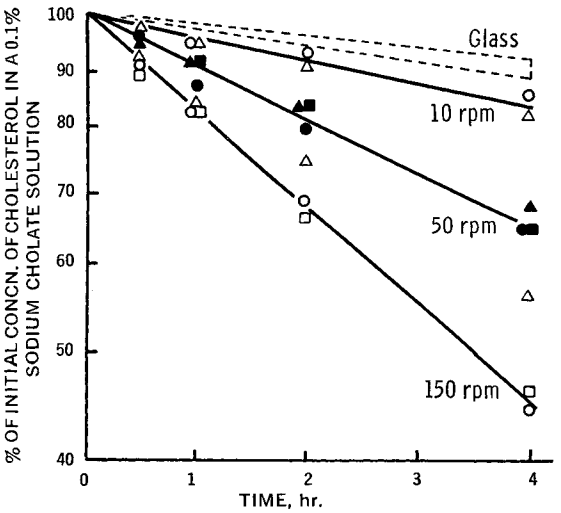

Figure 12—*Experimental semilog plot of percent initial concentration of cholesterol in a 0.1% aqueous sodium cholate solution as it goes into filters presaturated with dibutyl sebacate* versus *time in hours.*

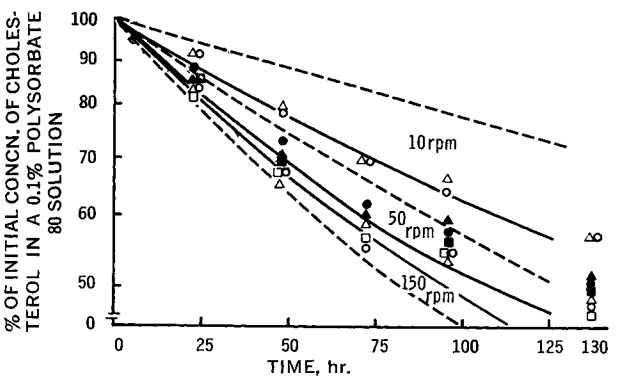

Figure 13—*Experimental semilog plot of percent initial concentration of cholesterol in a 0.1% polysorbate 80 solution as it goes into hexadecane-saturated filters* versus *time in hours. The solid curves are the theoretical computations when* $D_w = 2.4 \times 10^{-7}$ *cm.²/sec. and* $R = 0.15$ *cm. The dotted curves are the theoretical computations when an interfacial barrier is not considered and* $D_w = 0.7 \times 10^{-7}$ *cm.²/sec. In both cases* $D_0 = 0.5 \times 10^{-6}$ *cm.²/sec.*

All of these experiments, however, showed that the presence of polysorbate 80 slows the rate of pickup by about 40 times when compared to the pure cholesterol experiment. It was first thought that the expected low diffusion coefficient of the micelles formed and the low o/w partition coefficient might well combine to cause this effect. However, a theoretical analysis using Method III of the previous report (1) shows that the experimental results cannot be described on the basis of a purely diffusion-controlled process. First D_w and D_0 were varied until the theoretical curves were in the range of the experimental results. The dotted lines in Fig. 13 represent the theoretical computation when $D_w = 0.7 \times 10^{-7}$ cm.²/sec. and $D_0 = 0.5 \times 10^{-6}$ cm.²/sec. It is clear that the spread for the various stirring speeds is not at all consistent with that for the experimental results. It should also be mentioned that this aqueous diffusion coefficient value is probably much lower than what would be expected for the polysorbate-cholesterol micelles. It is very likely, therefore, that some other process is contributing to this reduction in the rate of pickup and that this may be some type of an interfacial barrier.

An interfacial barrier can be treated, mathematically at least, as a barrier in series with the primary aqueous diffusion layer (h). Thus, the transport coefficient that is normally D_wA/h now can be written as $D_wA/(h + R)$, where R is the "effective" thickness of the interfacial barrier and is equal to D_w/P, where P is the permeability constant for the barrier and D_w is the diffusion coefficient of the micelle in water.

When D_w was given the value of 2.4×10^{-7} cm.²/sec., R the value of 0.025 cm., and D_0 the value of 0.5×10^{-6} cm.²/sec. the solid curves in Fig. 13 were obtained. These theoretical curves give fairly good agreement at least for the initial portion of the data. Both the values for the aqueous diffusion coefficient and the permeability constant that can be obtained from R are reasonable and agree fairly well with other experiments that have been conducted with a similar system.[10]

The cholate and polysorbate experiments demonstrate some of the possible situations and information that this model might be of use in handling. It is hoped that the model presented here will become a useful and successful tool for future experimental investigation.

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Chemical Modifications of Polymeric Film Systems in the Solid State I: Anhydride Acid Conversion

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Abstract □ Poly(methylvinyl ether/maleic anhydride) was employed as a pharmaceutical film coating employing new and unique film coating concepts. Films of this polymer, PVM/MA, have excellent gloss and clarity, are hard, demonstrate good abrasion resistance, and yet are flexible. Half esters of the polymer are reported to possess excellent enteric and prolonged-release properties. However the anhydride form of the polymer is soluble in organic solvents but is slowly soluble in water or gastric media, while the acid water-soluble form of the polymer is insoluble in common organic solvents. A method is described wherein the polymer is applied in the anhydride form from an organic solvent, after which the coated tablets are subjected to mild humidity conditioning treatment to partially convert the polymer to the more soluble acid form. Radiographic analysis in man indicated that the complete anhydride film disintegrated outside the stomach, in approximately 3–4 hr. after administration. Films partially converted to the poly-acid form disintegrated in the stomach or proximal jejunum in 30–45 min. compared to 10–30 min. for the uncoated tablets. The rate of water vapor transmission through the PVM/MA films was one-fourth that observed for a typical cellulosic film.

Keyphrases □ Poly(methylvinyl ether/maleic anhydride)—tablet film coating □ Polymer modification, solid state—anhydride to acid conversion □ Film solubilities, water vapor transmission rate—humidity pretreatment effects □ *In vitro* dissolution—film-coated tablets □ *In vivo* disintegration times, man—radiopaque, film-coated tablets

Film coating of solid dosage forms, as a means of promoting drug stability and esthetic appeal, is one of the more recent processes and dosage form modifications developed and employed by the pharmaceutical industry. Numerous advantages of film-coating techniques have been listed and contrasted to the time-honored technique or "art" of sugar coating (1, 2). There appears to be, however, one feature lacking related to film coating. Regardless of the application technique, polymer concentrations, and film additives used, coating by this method has been limited to a small group of polymer derivatives derived from cellulose.

Hydroxypropyl methyl cellulose, alone and in combination with ethyl cellulose, and cellulose acetate phthalate (CAP) with annealing agents, serve as the most widely, if not the only, systems used in the United States as soluble film-coating agents designed for substantially immediate drug release. Although systems of these types have been used for a number of years, they are not without disadvantages. The dissimilar solubilities of methyl and ethyl cellulose require that complex solvent systems be used to produce compatible film coating solutions which can be applied to tablets. These two polymers must be used in a balanced ratio to promote the desired film strength, coatability and yet retain the proper *in vivo* solubility characteristics.

Similarly, CAP, when used as a rapid-release coating, must be combined with high percentages of water soluble annealing agents for rapid film disintegration under gastric conditions (1). The soluble cellulosic films possess a low gloss index and therefore, are often combined with agents to produce gloss, or the final product must be polished to improve coat appearance and esthetic appeal. Yearly, the plastics industry produces numerous new and modified polymers, some of which may surpass the properties of cellulosic derivatives with regard to film coating. It would be advantageous, for example, to use a single polymer without the need for annealing agents and glossants, which could be prepared for coating using a single solvent. The applied film must comply with the intended film coating purposes, and serve to protect the drug against environmental conditions, yet be readily soluble at gastric conditions. This study was therefore undertaken to search for and develop simple, noncellulosic film-coating systems which would broaden the selection of materials currently available to the pharmaceutical industry. Of several classes of polymers investigated, poly(methylvinylether/maleic anhydride), co-polymer (PVM/MA), was shown to possess qualities which might meet the objectives.

Heretofore, this co-polymer, modified by partial esterification, has been studied as an enteric or sustained-release coating for tablets and granules. Lappas and McKeehan (3), studied a series of partial esters of PVM/MA and found that the ester chain length and