or rectal tracts since all of the models studied showed fairly good agreement. More knowledge of the structure and microenvironment of the membrane as well as drug interactions with cellular substances is necessary before modification of the physical models can be made. Furthermore, the models generally have more quantitative parameters in detail which the usual *in situ* experiments alone cannot provide. However, the physical model approach to drug transport studies is being further investigated.

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Interfacial Barriers in Interphase Transport III: Transport of Cholesterol and Other Organic Solutes into Hexadecane–Gelatin–Water Matrices

ABDEL-HALIM GHANEM, W. I. HIGUCHI, and A. P. SIMONELLI

Abstract □ The purpose of this study was to quantitate the transport behavior of several organic solutes in matrix systems composed of micron-size hexadecane droplets dispersed in an aqueous gelatin gel where the oil–water interfacial barrier to transport was expected to play an important role. Two interrelated experiments were conducted. The first was the one-dimensional aqueous uptake of the solute by the matrix which was a continuous layer placed at the bottom of a beaker. The other experiment was solute uptake and release from aggregates of oil droplets suspended in an aqueous medium. Solutes investigated were ^{14}C-labeled cholesterol, diethylphthalate, ^{14}C-labeled octanol, and ^{14}C-labeled progesterone. The data have been analyzed by various physical models. It was found that cholesterol transport essentially was controlled by the oil–water interfacial barrier in both kinds of experiments—even when the matrix thickness was as large as 3.7 mm. For the other solutes, the oil–water interfacial barriers were found to be controlling in the experiments with aggregates (10–1000 μ). However, in the experiments with the continuous matrix layers, bulk matrix diffusion factors as well as the oil–water interphase transport were found to be important for these solutes. The techniques developed in this investigation should be useful: (*a*) in the quantitation of interfacial barriers in oil–water interphase transport of solutes, and (*b*) in the separation of various bulk diffusional resistances from interfacial resistances in complex multiphase matrices.

Keyphrases □ Interphase transport—interfacial barriers □ Hexadecane–gelatin–water matrix—organic solute transport □ Matrix layer—solute uptake □ Aggregated gelatin encapsulated hexadecane droplets—solute transport □ Electrolyte, polysorbate 80, concentration effects—interphase transport

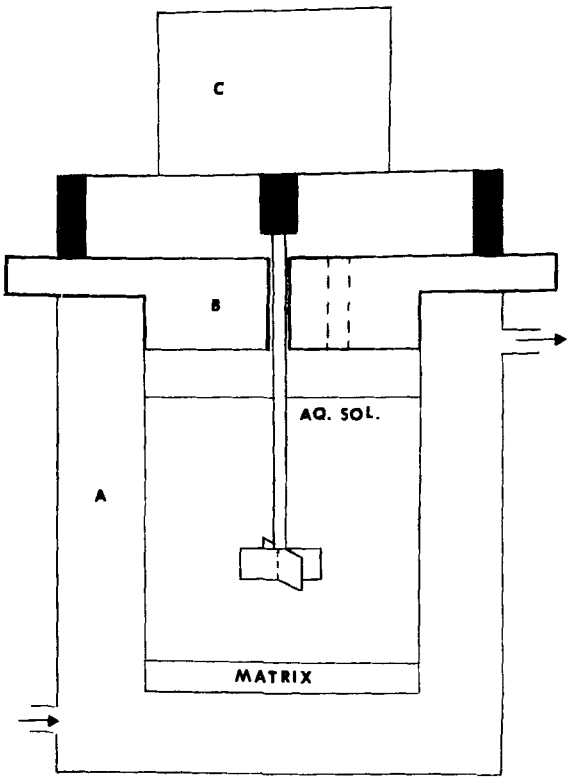


Figure 1—*Schematic diagram showing the apparatus used for the continuous matrix layer (CML) uptake experiments.*

Recent studies in these laboratories have been aimed at the mechanistic understanding of various factors influencing the interphase transport of drugs and other biologically interesting substances. These investigations (1–4) have considered, for example, the simultaneous multiphase interactions involving pH and the buffer parameters, the oil–water partition coefficients, and the diffusion coefficients. More recently (5–8), utilizing a novel technique, the existence and the importance of the

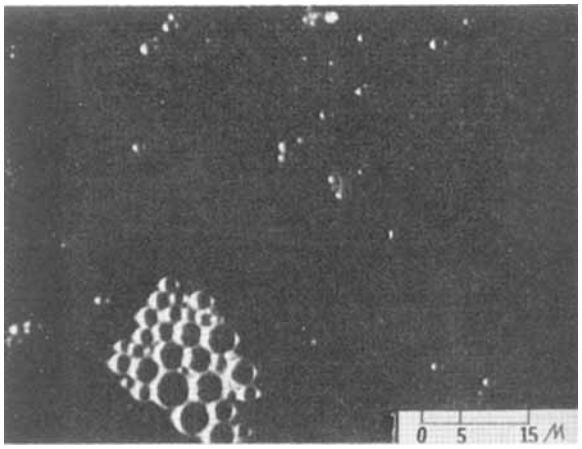


Figure 2—*Dark-field photomicrograph of aggregates before treatment with formaldehyde solution.*

oil–water interfacial barriers have been quantitated for several systems.

The present communication describes the results of experiments on the transport of solutes into and out of gelatin matrices in which micron-size droplets of hexadecane were dispersed. The findings of this study have been correlated with the previous research in these laboratories and demonstrate when an oil–water interfacial barrier is rate determining (5–7) and when bulk matrix diffusional factors are dominant (1–3).

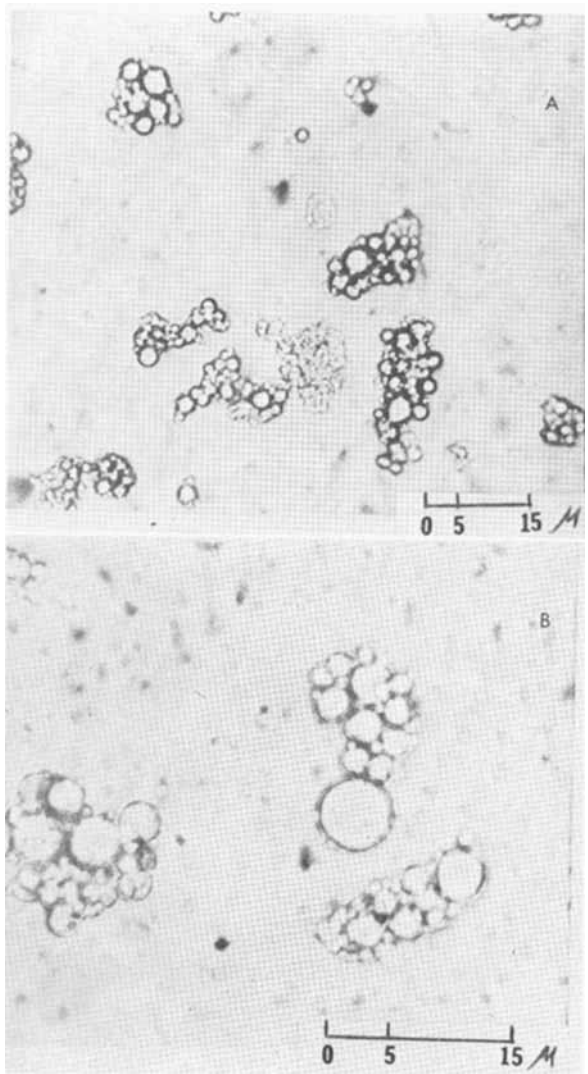


Figure 3—*Photomicrograph of the aggregates after treatment with an 18.5% formaldehyde solution.*

EXPERIMENTAL

General Considerations—Essentially two kinds of interrelated experiments were conceived. The first of these was the one-dimensional aqueous uptake of the solute by a dispersion of oil droplets in a continuous gelatin matrix layer polymerized with a formaldehyde solution. The second type of experiment was the determination of the uptake and release of solute from an aqueous suspension of aggregates of the oil droplets prepared by first treating the gelatin stabilized oil-in-water emulsion with concentrated sodium sulfate (5) and then with a formaldehyde solution. As will be seen, this combined approach provides the means to determine the relative importances of oil–water interfacial barriers and bulk diffusion in complex heterogeneous matrices of this type.

Materials—The gelatin, hexadecane, sodium sulfate, and diethylphthalate employed in these studies were previously described

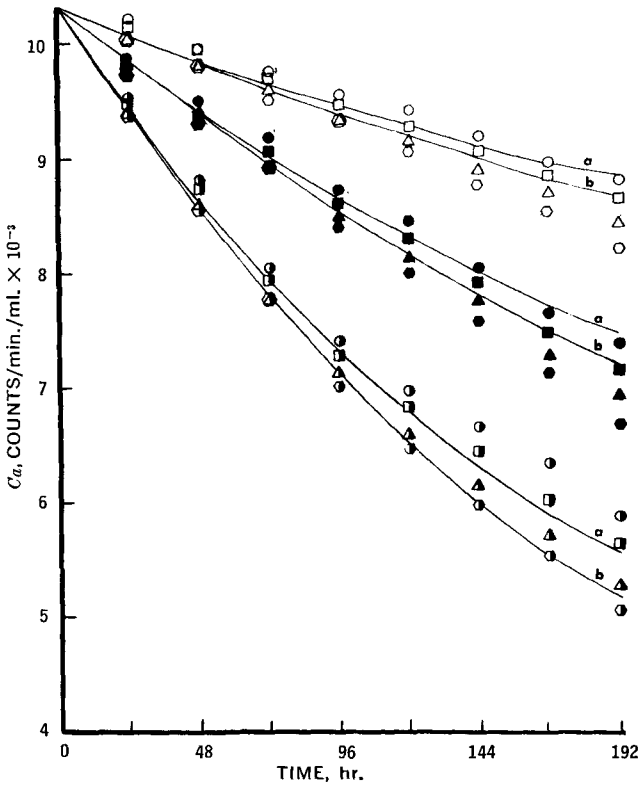


Figure 4—*Comparison of experimental ^{14}C-labeled cholesterol uptakes (CML and AGE techniques) with theoretically computed values based upon the interfacial barrier model as a function of oil volumes and polysorbate 80.* C_a *is counts/min./ml. of solute in the aqueous polysorbate 80 remaining* versus *time in hours. Initial* (t = 0) ^{14}C*-4-cholesterol concentration was* 3.4×10^{-8} *g./ml. and initial aqueous volumes were 50 ml. in all experiments. Key:*

Oil Volume, ml.	*0.1% Polysorbate 80 Solution (a)*		*0.05% Polysorbate 80 Solution (b)*	
	CML	*AGE*	*CML*	*AGE*
0.2	○	□	△	⬡
0.4	●	■	▲	⬢
0.8	◑	◨	◭	◑

Curves are theoretically computed values using K = *140 for Curve (a),* K = *250 for Curve (b), and* P = 5×10^{-9} *cm./sec.*

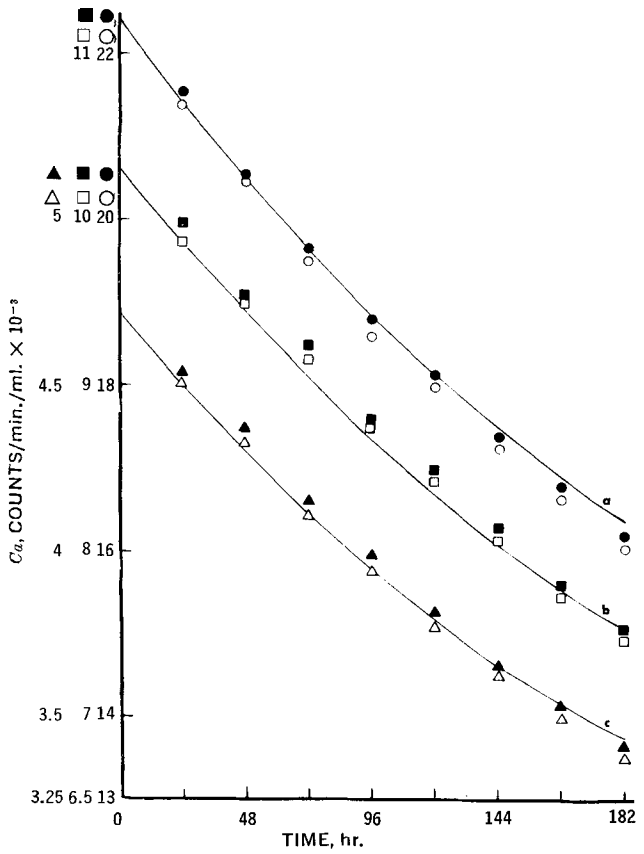


Figure 5—*Comparison of experimental ^{14}C-labeled cholesterol uptake (CML technique) with theoretically computed values (interfacial barrier model) at two stirring speeds and three ^{14}C-4-cholesterol concentrations in 0.1% polysorbate 80. C_a is counts/min./ml. of solute in the aqueous polysorbate 80 remaining* versus *time in hours. Oil volume was 0.4 ml. Initial aqueous volumes were 50 ml. Key:*

Stirring Speed, r.p.m.	*8.5 × 10^{-8} g./ml. (a)*	*3.4 × 10^{-8} g./ml. (b)*	*1.36 × 10^{-8} g./ml. (c)*
50	●	■	▲
150	○	□	△

Curves are theoretically computed values with K = *140 and* P = *5 × 10^{-9} cm./sec.*

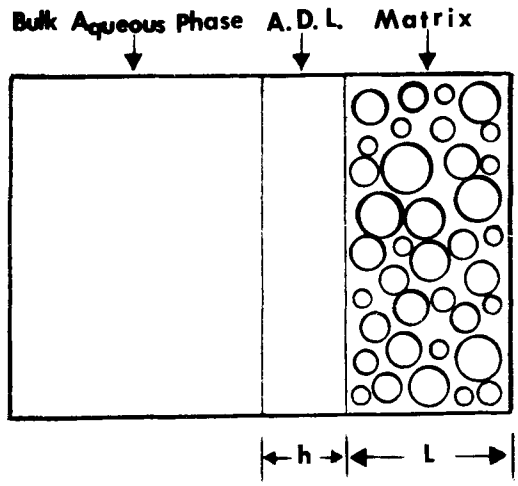
(5, 6). Formaldehyde AR grade[1] was used. Solutes other than diethylphthalate investigated in these studies were ^{14}C-4-cholesterol,[2] ^{14}C-4-progesterone,[3] and ^{14}C-1-octanol.[4]

Procedure for the Continuous Matrix Layer (CML) Uptake—Figure 1 shows a schematic diagram of the experimental apparatus which consists of a water-jacketed beaker (A) with a plastic cover (B) that prevents evaporation and supports a synchronous motor (C).[5] Two holes have been drilled in the cover, one for sampling and the other for a four-blade glass stirring rod.

A specified amount of the hexadecane-in-water emulsion stabilized with gelatin was prepared as previously reported (6). The emulsion at 40° was transferred to the beaker, and the temperature was immediately dropped to 10° by placing the beaker in an ice water bath for 1 hr. Then 25 ml. of a 3.7% formaldehyde solution (pH 9.0) at 10° was added to the beaker and allowed to interact with the gel for 1 hour at the same temperature. The formaldehyde was then leached out by washing with water several times over a period of 12–18 hr. In this manner, matrices of different thicknesses (volumes corresponding to 1, 2, 4, and 8 ml.) were prepared and were found to be stable in water or in polysorbate 80 solution (0.05–0.1%) over a period of 10 days.

The uptake experiments were carried out in the following manner. The aqueous solution of the organic solute was added to the beaker containing the prepared matrix system. Stirring was immediately initiated using either a 50 or a 150 r.p.m. synchronous motor. The temperature was kept at 23 ± 2°. Samples of 1.0 ml. were removed at predetermined time intervals for quantitative analysis.

Procedure for the Transport Studies with Aggregated "Gelatin-Encapsulated" Hexadecane Droplets (AGE)—Fifty grams of an 18% solution of sodium sulfate was added to 70 g. of the previously described (5) hexadecane–gelatin emulsion. The mixture was stirred for 6–8 hr. at 50° (5). The mixture was then transferred to an ice water jacketed Waring blender operating at a speed of 1500–2000 r.p.m. and cooled to 10°. Then 100 ml. of an 18.5% formaldehyde solution (pH 9.0, temperature 10°) was added to the mixture and allowed to react for 1 hr. with continuous stirring. The material was then washed with water and stored in water until use in the uptake experiment.



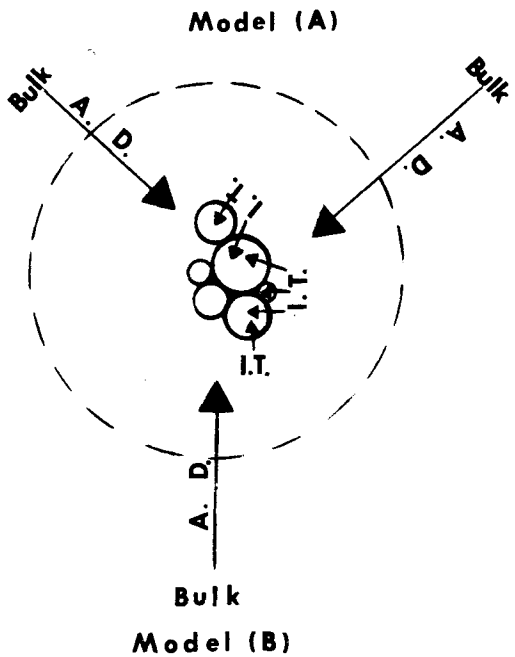


Figure 6—*The physical models that describe the uptakes of the solute from the aqueous phase to the CML, Model (A), and the AGE, Model (B). A.D.L. = aqueous diffusion layer. A.D. = aqueous diffusion. I.T. = interfacial transport.*

[1] Mallinckrodt Chemical Works, New York, N. Y.
[2] New England Nuclear Corp., Boston, Mass.
[3] Amersham/Searle Corp., Chicago, Ill.
[4] International Chemical and Nuclear Corp., City of Industry, Calif.
[5] Hurst Manufacturing Corp., Princeton, Ind.

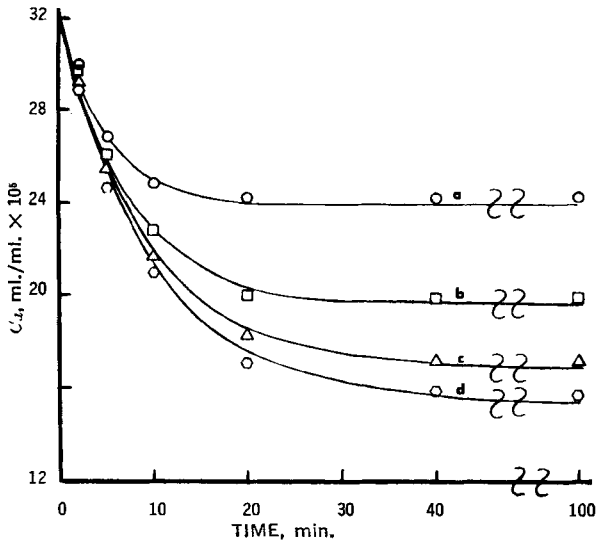


Figure 7—*Comparison of experimental diethylphthalate uptakes (AGE technique) with theoretically computed values (interfacial barrier model) and the influence of different sodium sulfate concentrations.* C_a *is ml./ml. of solute in the aqueous medium remaining* versus *time in minutes. To 1.5-g. aggregates was added 100 ml. of diethylphthalate in:* ○, *water (a);* □, *2.5% sodium sulfate (b);* △, *5% sodium sulfate (c); and* ⬡, *7% sodium sulfate (d). Curves are theoretically computed values with* K = *50, 95, 132, and 160 for (a), (b), (c), and (d), respectively; and* P = 1.0×10^{-5} *cm./sec.*

"Fine" aggregates of supramicron sizes were produced by this procedure and these were found to be stable in water for a month. These aggregates were also found to be stable in polysorbate 80 solution (0.05–0.1%) for at least 7 days. Figure 2 shows a dark-field photomicrograph of the aggregates before treatment with formaldehyde. Figure 3 shows a photomicrograph of the aggregates after treatment with formaldehyde solution. Visual examination of these aggregates showed that about 10% were singlets, about 20% were aggregates of 2–10, about 40% were from 10 to 20, 20% were from 20 to 100, and 10% from 100 to 200.

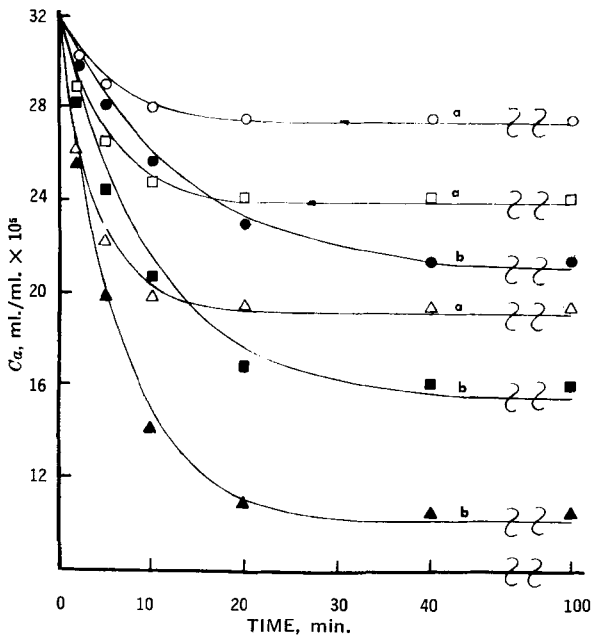


Figure 8—*Comparison of experimental diethylphthalate uptakes (AGE technique) with theoretically computed values (interfacial barrier model), and the effect of different aggregate weights in water and 7% sodium sulfate.* C_a *is ml./ml. of solute in the aqueous medium remaining* versus *time in minutes. Key:*

Medium, 100 ml.	*0.75 g.*	*1.5 g.*	*3.0 g.*
Water (a)	○	□	△
7% Sodium sulfate (b)	●	■	▲

Curves are theoretically computed values with K = *50 for Curve (a),* K = *160 for Curve (b), and* P = 1.0×10^{-5} *cm./sec.*

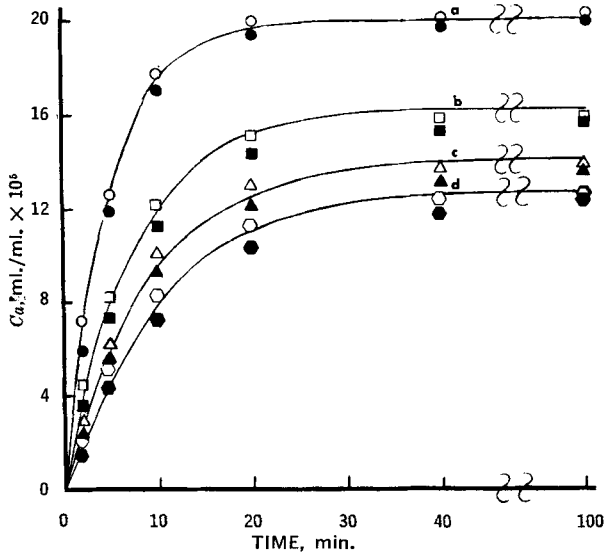


Figure 9—*Comparison of experimental diethylphthalate releases (AGE technique) with theoretically computed values (interfacial barrier model) and the influence of different sodium sulfate concentrations.* C_a *is ml./ml. of solute in the aqueous medium released* versus *time in minutes. Volume of the aqueous medium was 100 ml. Key:*

1.5-g. Aggregates	*Water (a)*	*2.5% Sodium Sulfate (b)*	*5% Sodium Sulfate (c)*	*7% Sodium Sulfate (d)*
Fine	○	□	△	⬡
Coarse	●	■	▲	●

Curves are theoretically computed values with the same parameters as previously mentioned under Fig. 7.

"Coarse" aggregates were also prepared in a similar manner but by using a 22% sodium sulfate solution instead of 18% as was used in the case of the "fine" aggregate preparation. Visual examination of this preparation indicated that about 10% were singlets, 20% were from 2 to 10, 20% from 10 to 50, 30% from 50 to 200, and 30% from 200 to 500.

The solute uptake experiments were carried out as follows. The stock aggregates in water were stirred for a few minutes, a portion was filtered, and then allowed to remain for 2 hr. on the filter. A predetermined amount (0.75, 1.5, or 3.0 g.) was transferred to a 150-ml. plastic beaker[6] which was found to resist sticking of the aggregates to the beaker wall—a problem encountered with glassware. Exactly 100 ml. of the aqueous medium containing the solute was then added to the beaker. Stirring was initiated immediately by means of a synchronous motor (150 or 300 r.p.m.) with a magnetic head coupling to a magnetic stirring bar. In order to achieve good dispersion of the aggregates, the magnetic head was placed slightly off-center of the beaker. The temperature was kept at 23 ± 2°. At different time intervals, a sample of 5 ml. was withdrawn by a 10-ml. syringe, and approximately half of it was filtered through a silver filter membrane[7] using a 10-mm. diameter stainless steel filter holder.[8] Part of this filtrate was used for analysis.

The diethylphthalate release studies with these aggregates were carried out in the same way except that the prepared aggregates were treated in the following manner. A suspension of about 60 g. of the aggregates in about 200 ml. of water containing 1.2 ml. of

[6] Nalgene, Nalge Co., Rochester, N. Y.
[7] Selas Flotronics, Spring House, Pa.
[8] Millipore Filter Corp., Bedford, Mass.

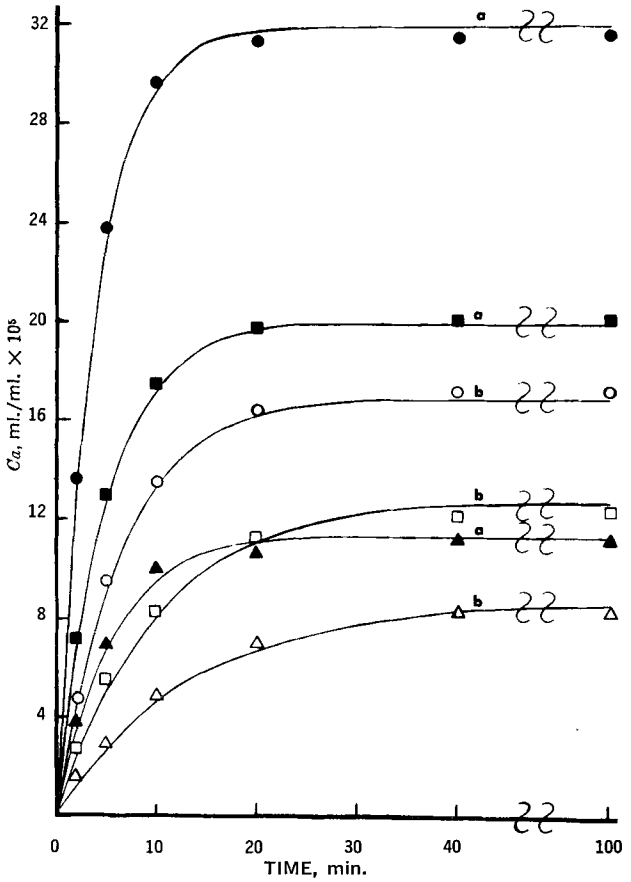


Figure 10—*Comparison of experimental diethylphthalate releases (AGE technique) with theoretically computed values (interfacial barrier model) and the effect of different aggregate weights in water and 7% sodium sulfate.* C_a *is ml./ml. of solute in the aqueous medium released* versus *time in minutes. Key:*

Medium, 100 ml.	*0.75 g.*	*1.5 g.*	*3.0 g.*
Water (a)	▲	■	●
7% Sodium sulfate (b)	△	□	○

Curves are theoretically computed values with the same parameters as previously mentioned under Fig. 8.

diethylphthalate was slowly stirred for 48 hr. with a magnetic stirrer. The mixture was then filtered, washed twice with 50 ml. of water, and stored in 200 ml. of a 0.03% diethylphthalate solution. The concentration of diethylphthalate in the encapsulated oil was determined by total extraction of diethylphthalate (5).

Assay Procedure—Where radioactive-labeled materials were employed, the Beckman LS 200B liquid scintillation system[9] was used. In the diethylphthalate experiments, a spectrophotometric analysis[10] (λ = 273.5 mμ) was employed.

EXPERIMENTAL RESULTS AND THEORETICAL TREATMENT

^{14}C-Labeled Cholesterol Transport from Aqueous Polysorbate 80 Solution into the Hexadecane–Gelatin Matrix Layer (CML) and into Dispersed Aggregates (AGE)—The results of the ^{14}C-4-cholesterol uptake experiments using both techniques (CML and AGE) for three oil volumes and two polysorbate 80 concentrations[11] (0.05 and 0.1%) are presented in Figs. 4 and 5. The uptake rates were found to be generally slow and, for the CML as well as the AGE experiments, the rates were dependent strongly on the oil volumes in the system. Figure 5 presents the influence of the stirring rates and the aqueous ^{14}C-4-cholesterol concentration upon the CML uptake experiments. As can be seen, stirring had a negligible effect upon the rates. Also the uptake rates were found to be directly proportional (first order) to the cholesterol concentration.

The CML and the AGE uptake rates were found to be essentially identical when the mass of the oil phases were the same, as was the case for the experiments shown in Fig. 4. As the primary oil particle-size distributions were the same for the CML and AGE studies, this finding is particularly significant.

In order to explain these data, let us consider the various possible rate-determining mechanisms by referring to the models given in Fig. 6. In general, for the CML case there are three possible processes, any of which can be the rate-determining one. These are: (*a*) diffusion through the aqueous diffusion layer of thickness *h*, (*b*) diffusion through the matrix itself, or (*c*) interfacial barrier transport. For the AGE experiment these three processes may still apply, but the magnitudes of aqueous diffusion and the matrix diffusion resistances would be expected to be much smaller than for those in the CML situation. The interfacial barrier, however, would be expected to be about the same for both the CML and the AGE situations, even though the preparation procedures differed somewhat (see *Experimental*).

All of these experimental results for cholesterol uptake in both systems support the mechanism in which an interfacial barrier is rate determining. First, the absolute rates were essentially the same for the CML and the AGE experiments in every situation. Secondly, the rate of stirring had no influence on the CML uptake rates. Thirdly, the uptake rates showed a strong oil volume (or a layer thickness) dependence with the CML experiments. This would not have been expected if either transport in the aqueous diffusion layer or transport through the matrix itself was rate determining. Thus all of the data support the overwhelming importance of the interfacial process in both situations.

These conclusions justify the quantitative treatment based upon an interfacial barrier control developed previously (5). Thus employing the primary oil droplet size distribution data obtained earlier (6) and the independently determined partition coefficients, the theoretical uptake rates were calculated using different interfacial barrier permeability coefficients. These theoretical calcula-

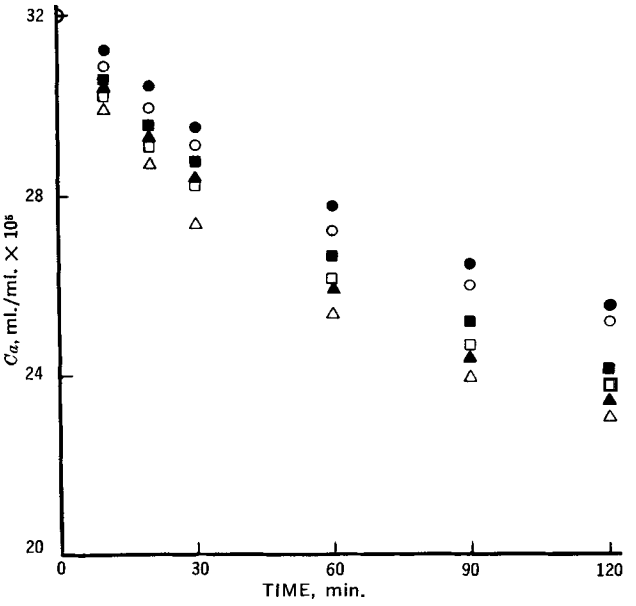


Figure 11—*Experimental diethylphthalate uptakes using the CML method as a function of matrix volume and stirring.* C_a *is ml./ml. of solute in the aqueous medium remaining* versus *time in minutes. Volume of the aqueous medium was 50 ml. of water. Key:*

Stirring Speed, r.p.m.	*2.0 ml.*	*4.0 ml.*	*8.0 ml.*
50	●	■	▲
150	○	□	△

[9] Beckman Instruments, Inc., Fullerton, Calif.
[10] Hitachi, Ltd., Tokyo, Japan.
[11] Preliminary experiments showed that in the absence of polysorbate 80, appreciable adsorption of cholesterol occurred on the beaker walls.

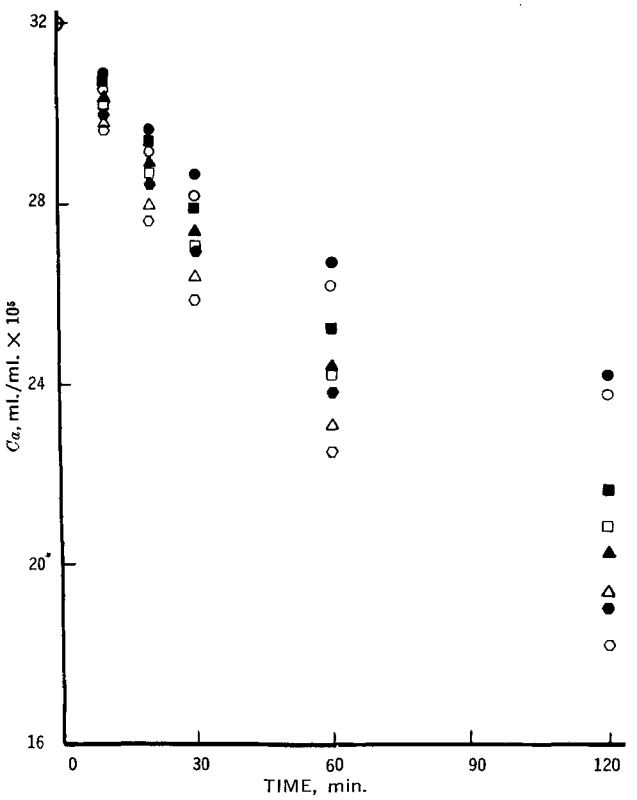


Figure 12—*Experimental diethylphthalate uptakes using CML method as a function of sodium sulfate concentrations and stirring.* C_a *is ml./ml. of solute in the aqueous medium remaining* versus *time in minutes. Matrix volume was 4.0 ml. and aqueous volume was 50 ml. Key:*

Stirring Speed, r.p.m.	*Water*	*2.5% Sodium Sulfate*	*5% Sodium Sulfate*	*7% Sodium Sulfate*
50	●	■	▲	●
150	○	□	△	○

tions have revealed that a single permeability coefficient value of $P = 5 \times 10^{-3}$ cm./sec. quantitatively describes all of the data (Figs. 4 and 5). The smooth curves presented in these plots correspond to the theoretical uptake calculations utilizing this P value. The agreement, as can be seen, is quite satisfactory.

Transport of Diethylphthalate into the Hexadecane–Gelatin Matrix Layer (CML) and into and out of Dispersed Aggregates (AGE)—The results of the diethylphthalate uptake experiments employing the AGE method are presented in Figs. 7 and 8. In Fig. 7, the influence of the electrolyte concentrations on the uptake rate is demonstrated. As can be seen, the significant effects are large at times, *i.e.*, near equilibrium. The initial rate appears to be relatively independent of the electrolyte concentration. In Fig. 8, comparisons of the uptake behavior are shown for three different concentrations of the aggregates in water and in 7% sodium sulfate. The strong dependence upon the oil volume is apparent.

The curves given in Figs. 7 and 8 are the theoretically computed values based upon the known primary particle distribution (6), the independently determined partition coefficients, and a permeability coefficient, $P = 1.0 \times 10^{-5}$ cm./sec. The good agreement of the experimental data with theoretical computations in regard to the time dependence and the oil volume dependence demonstrates that the interfacial barrier model (5, 6) is operative. Furthermore, this good correlation of the experiment with the theoretical calculations states that the electrolyte influence upon the uptake rate is a partition coefficient effect and not an effect upon the permeability coefficient, as was also found with the nonaggregated, nonencapsulated, hexadecane–gelatin–water systems (6).

Results of the diethylphthalate release rate experiments with the dispersed aggregates are given in Figs. 9 and 10. The effects of different electrolyte concentrations upon the release rate are shown in Fig. 9 for both the "fine" and "coarse" aggregate systems. Figure 10 presents the data on the oil volume effect for the release of diethylphthalate into water and 7% sodium sulfate.

The curves in Figs. 9 and 10 give the theoretically computed values for the release of diethylphthalate using the primary droplet size distribution data (6), the independently determined partition coefficient for each situation, and a P value of 1.0×10^{-5} cm./sec. The good agreement obtained for the uptake (Figs. 7 and 8) using the same P value clearly shows that the same interfacial barrier model is governing the transport of the solute in both situations. It is noteworthy that the aggregate size differences between the "fine" and "coarse" aggregates do not appear to be significant (Fig. 9). It was also found that experiments at 150 and 300 r.p.m. showed no differences in these experiments.

Results of some of the diethylphthalate uptake experiments employing the matrix layer method (CML) are presented in Figs. 11 and 12. Figure 11 shows the matrix volume and the stirring rate effects upon the solute uptake rates. Figure 12 presents the influence of electrolyte concentration on the diethylphthalate CML uptake rates.

In contrast to the cholesterol CML and AGE experiments (Figs. 4 and 5), in which the rates in both kinds of experiments were comparable and in good agreement with the interfacial barrier model, the diethylphthalate CML and AGE experiments show large differences in several respects. First, the diethylphthalate CML rates are generally much slower than the AGE rates. Secondly, there is an appreciable initial stirring rate effect in the diethylphthalate CML experiments. Finally, the CML matrix volume effects (Fig. 11) are relatively much smaller than those observed with the diethylphthalate AGE experiments and the cholesterol CML and AGE experiments. All of these findings dictate, that in the diethylphthalate CML experiments, the interfacial barrier is not, or at least not by itself, rate determining.

The CML data in Figs. 11 and 12 have been further theoretically treated employing a matrix-bulk diffusion model developed in these laboratories (3) using the mixture relationships (1, 2) that assume rapid equilibrium between the oil droplets and the gel matrix. The comparison of the experimental data with this theory has so far not been very satisfactory. Consequently, a model in-

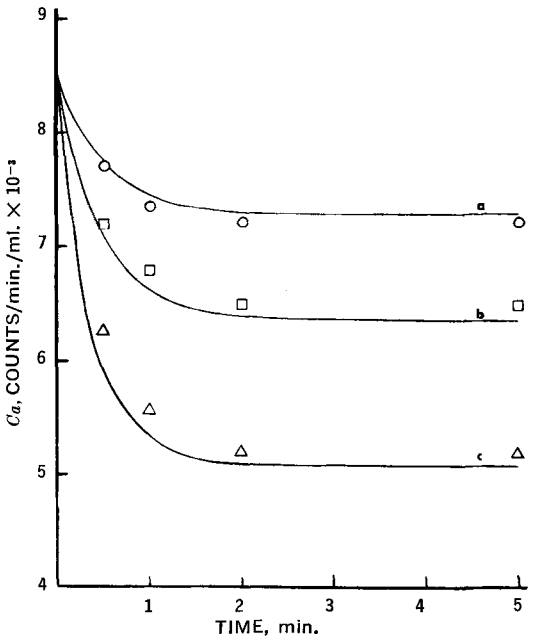


Figure 13—*Comparison of experimental* ^{14}C*-labeled octanol uptakes (AGE technique) with theoretically computed values (interfacial barrier model) as a function of aggregate weights.* C_a *is counts/min./ml. of the solute in water remaining* versus *time in minutes. One hundred milliliters of* ^{14}C*-1-octanol solution in water was added to:* ○, *0.75 g. (a);* □, *1.5 g. (b); and* △, *3.0 g. (c) of the aggregates. Curves are theoretically computed values with* K = *50 and* P = *1.0* × 10^{-4} *cm./sec.*

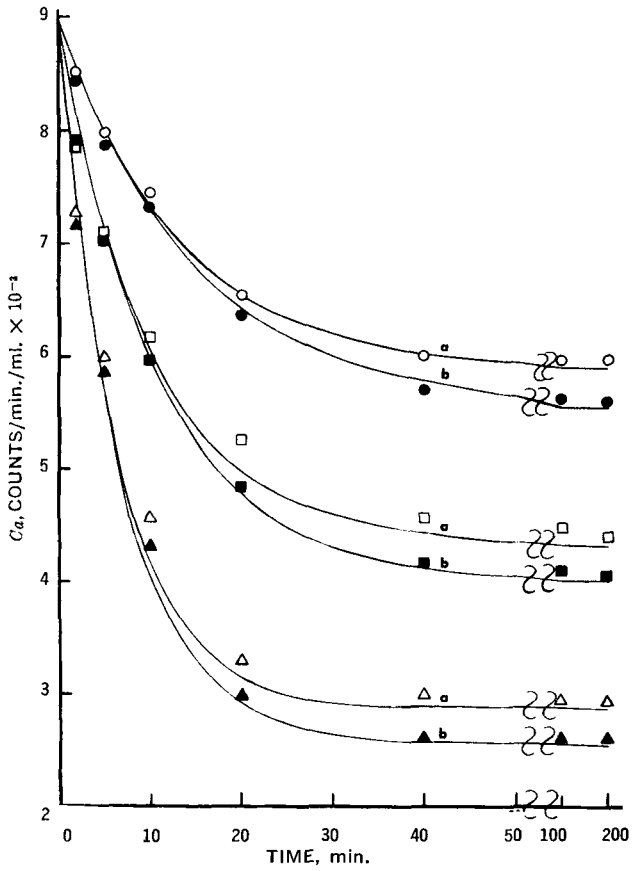


Figure 14—*Comparison of experimental* ^{14}C*-labeled progesterone uptakes (AGE technique) with theoretically computed values (interfacial barrier model) as a function of the aggregate weights and polysorbate 80 solutions.* C_a *is counts/min./ml. of the solute in the polysorbate 80 remaining* versus *time in minutes. Key:*

Medium, 100 ml.	*0.75 g.*	*1.5 g.*	*3.0 g.*
0.1% Polysorbate 80 (a)	○	□	△
0.05% Polysorbate 80 (b)	●	■	▲

Curves are theoretically computed values with K = *160 for Curve (a),* K = *185 for Curve (b), and* P = *1.0* × 10^{-5} *cm./sec.*

volving the simultaneous consideration of (*a*) the aqueous diffusion layer, (*b*) bulk gelatin-matrix diffusional parameters, and (*c*) the interfacial transport barrier of the oil droplets is being developed (9).

Transport Studies with Other Solutes Employing the AGE Technique—Uptake studies with ^{14}C-1-octanol and ^{14}C-4-progesterone are shown in Figs. 13 and 14, respectively. These experiments with octanol (Fig. 13) compare very well with the theoretically computed values using the primary droplet size distribution (6), independently determined partition coefficient, and a *P* value of 1 × 10^{-4} cm./sec. Figure 14 compares the experimental ^{14}C-4-progesterone uptake rates from polysorbate 80 solutions[12] by the aggregates with theoretically computed values employing the same primary droplet size distribution (6), the partition coefficients, and a *P* value of 1.0 × 10^{-5} cm./sec. The ^{14}C-labeled progesterone results which show good agreement with the theoretical calculations indicate that the polysorbate 80 concentration effect is primarily a partition coefficient effect rather than a permeability coefficient effect. More work is underway to distinguish whether the free solute, the micelle-solubilized solute, or both are involved in the interfacial event.

DISCUSSION

These techniques and their general applicability to various solute transport situations should be uniquely helpful in many biological and pharmaceutical problems. One aspect of the studies underway in these laboratories is aimed at the molecular mechanistic understanding of transport factors at biological membranes and tissues.

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[12] In the absence of polysorbate 80, appreciable adsorption of progesterone to the beaker walls was noticed.