Table VII—Physiological Availability of Ascorbic Acid from Tablets Containing Silica Gel—6-hr. Test

Subject	Dose (about 450 mg.) Excreted, %: Standard Ascorbic Acid	Lot No. 73-69/1 (33% E Adsorbate) Initial	Lot No. 73-69/1 (33% E Adsorbate) 3 mo./45°	Lot No. 73-69/3 (60% E Adsorbate) Initial
BM	28	27	27	17
MO	35	25	27	28
RG	18	26	26	37
JS	23	33	28	29
ED	26	29	28	24
Average	26.0	28.0	27.2	26.8
Availability ±*SE*, %		108 ± 13	105 ± 11	103 ± 17

Experiences with wet granulation formulations containing ascorbic acid or sodium ascorbate indicate that excellent stability can be achieved if the wet granulation is dried to about 10% moisture within a few hours and to the final, low moisture content within 24 hr.

Order of mixing of ingredients and especially the mode of addition of water can be important. The vitamin C stability may be influenced by the presence of adsorbents that bind water or soluble ingredients that serve as emulsifiers or influence the solubility or reactivity of vitamin C.

Availability Studies in Men—The results of bioavailability tests in men of ascorbic acid in tablets containing silica gel have been calculated on the basis of 24-hr. excretions of test doses. These results are summarized in Table VI. Both lots of tablets show complete bioavailability of the ascorbic acid, and this was not changed by storage for 3 months at 45°. In order to provide information on the question of whether or not silica gel reduces the rate of absorption of ascorbic acid *in vivo*, calculations of physiological availability also were made on the basis of urinary excretions in the first 6 hr. after dose. These data are given in Table VII. Again, the results show complete availability of ascorbic acid in all three tablet trials, indicating that the ascorbic acid is absorbed normally in the presence of silica gel.

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Interfacial Barriers in Interphase Transport II: Influence of Additives upon the Transport of Diethylphthalate Across the Hexadecane-Gelatin-Water Interface

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

Abstract □ The authors recently described a novel method for investigating the effects of an interfacial barrier in interphase transport. The procedures, both theoretical and experimental, were applied to the study of the effects of an adsorbed gelatin at the hexadecane-water interface upon the transport of diethylphthalate between the two phases. The present paper describes the influences of surfactants, electrolyte type, and concentration upon the permeability coefficient for the interfacial barrier. Experiments were conducted as before, employing diethylphthalate as the solute. The transport data were analyzed by the physical model described earlier. The results showed that the two ionic surfactants, sodium lauryl sulfate and dodecylpyridinium chloride, markedly decreased (2 to 12 times) the interfacial barrier even at low concentration (0.001–0.10% in the stock emulsion). Furthermore, the analysis showed that neither the electrolyte type nor concentration influenced the permeability coefficients, although they significantly altered the interphase transport rates themselves by changing the partition coefficients. These findings are particularly interesting as they may represent types of nonspecific situations that give rise to important barriers in *in vivo* drug transport.

Keyphrases □ Transport, interphase—interfacial barriers □ Diethylphthalate transport—hexadecane-gelatin-water interface □ Electrolyte effect—diethylphthalate transport, hexadecane-gelatin-water interface □ Surfactant effect—diethylphthalate transport, hexadecane-gelatin-water interface □ Permeability coefficients, interfacial barriers—surfactant, electrolyte type, concentration effect.

Recent studies from these laboratories (1, 2) involving the use of a novel method for investigating interfacial barriers in interphase transport have shown that substances adsorbed at the oil-water interface may control the interphase transport rates of solutes. Gelatin adsorbed at the hexadecane-water interface has been shown (1) to give an interphase transport rate for diethylphthalate that is about 1×10^4 times slower than diffusion controlled. A significant reduction in the aqueous to lipid transport rate of cholesterol by an

Table I—Oil Droplet Size Distribution Taken from Fig. 2 Photograph (for 3 ml. Stock Emulsion)

i	Channels	Mean Radius, μ	Total No. of Particles $\times 10^{-8}$	Total Volume $\times 10^{-10}$, μ^3
1	0–40	1.03	27.19	1.22
2	40–80	1.48	4.12	0.56
3	80–120	1.75	23.07	5.21
4	120–160	1.96	35.43	11.20
5	160–200	2.13	23.89	9.71
6	200–240	2.28	15.66	7.77
7	240–280	2.41	11.53	6.77
8	280–320	2.52	9.06	6.14
9	320–360	2.64	8.24	6.32
10	360–400	2.74	6.59	5.65
11	400–440[a]	2.83	4.12	3.91
12	440–480[a]	2.92	2.47	2.56

[a] Obtained by extrapolation.

adsorbed polysorbate 80 film has also been observed (2). These findings have suggested that such barriers, which are probably nonspecific in nature from the biopharmaceutical standpoint, may play important rate-determining roles in the transport of drug molecules across biological membranes and into tissues.

In order to better understand the nature of these barriers, the present studies were undertaken. This article describes the results of the experiment on the effects of the different gelatin fractions of Pharmagel A,[1] the influences of electrolyte types and concentration, and the effect of surfactants on the transport rate of diethylphthalate. The data have been mechanistically analyzed and reported in terms of the permeability coefficients for the interfacial barriers.

EXPERIMENTAL

Consideration in the Design of the Experiment—A discussion o. the basic design and the advantages of the multiparticulate dispersion technique has already been given (1, 3). In the present study the same general approach was essentially employed.

The previous procedure for preparing the emulsion system was slightly modified in the direction of greater flexibility. Instead of preparing stock hexadecane-in-water emulsions near the interfacial coacervation point (1, 4) of gelatin sodium sulfate, lower electrolyte concentrations were used and the temperature was kept at 40° for the whole period of equilibration of the emulsion systems. This provided the means for varying the concentrations of the additives used in these studies without droplet-droplet aggregation taking place.

Materials—The gelatin used was Pharmagel A. Fractionation of the gelatin was accomplished (5) by adding successive amounts of ethanol to the gelatin solution adjusted to pH 7 at 40°. The hexadecane[2] was purified (6) and the diethylphthalate[3] was used without further purification. Sodium sulfate,[4] sodium chloride,[5] calcium chloride dihydrate,[4] magnesium chloride hexahydrate,[6] and magnesium sulfate[4] were used without further purification. Pure samples of sodium lauryl sulfate[7] and polysorbate 80[8] were used. Dodecylpyridinium chloride[3] was purified by recrystallizing three times from acetone. Spectroquality cyclohexane[9] was used in the UV analysis.

[1] Wilson's U-Cop-Co., Calumet City, Ill.
[2] Aldrich Chemical Co., Milwaukee, Wis.
[3] "Eastman grade," Eastman Kodak Co., Rochester, N. Y.
[4] Allied Chemicals, Industrial Chemical Division, Morristown, N. J.
[5] Mallinckrodt Chemical Works, New York, N. Y.
[6] Baker Chemical Co., Phillipsburg, N. J.
[7] Supplied by Dr. K. J. Mysels, Reynolds Tobacco Co., North Carolina.
[8] Supplied by Dr. P. Becher, Atlas Chemical Industries, Delaware.
[9] Matheson, Coleman & Bell, East Rutherford, N. J.

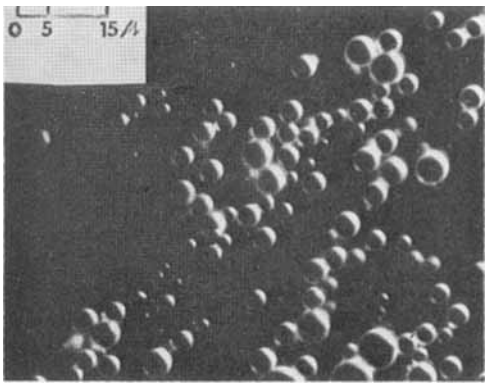

Figure 1—*Dark field photomicrograph of a typical emulsion system used in the release experiments.*

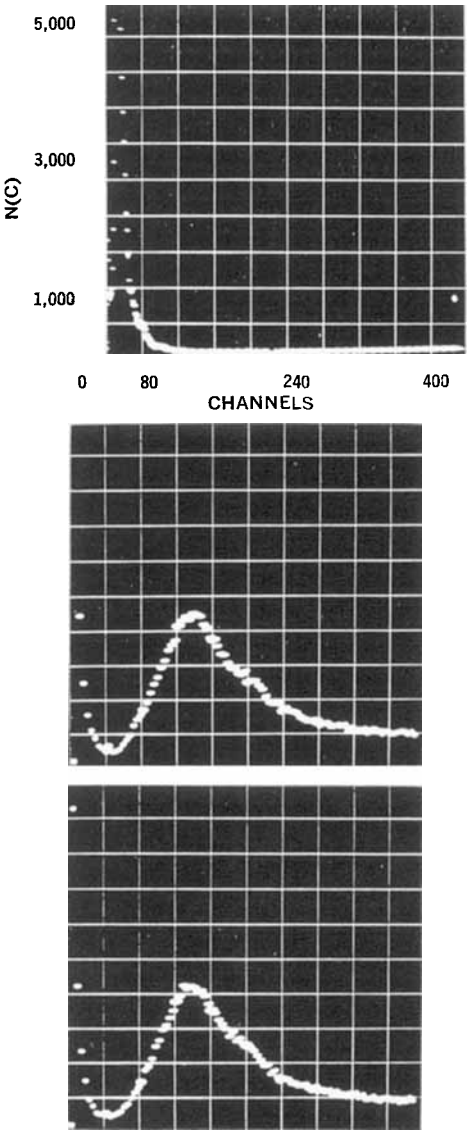

Figure 2—*Droplet size distribution data obtained with a Coulter counter and multichannel analyzer. First photograph shows calibration data obtained with 2.051-μ diameter polyvinyltoluene latex.* N(C) *is the concentration of particles in Channel* C. *Second photograph shows a typical droplet distribution in the release medium taken 1 min. after the beginning of a release experiment. Third photograph shows the droplet distribution after 15 min. in the release medium.*

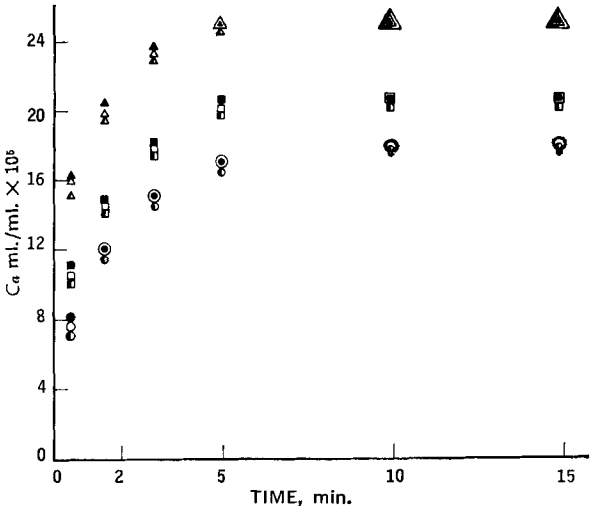

Figure 3—*Experimental results of diethylphthalate release obtained with three fractions of gelatin.* C_a *is amount of diethylphthalate released, ml./ml.,* versus *time in minutes. At zero time 3.0 ml. of emulsion system pretreated with 0.352* M *sodium sulfate was added to 100 ml. of aqueous medium at 23°. Using whole gelatin the aqueous media are: Key: ◐, 0.352* M *sodium sulfate; ◧, 0.176* M *sodium sulfate; ◭, water. Using the second gelatin fraction: ○, 0.352* M *sodium sulfate; □, 0.176* M *sodium sulfate; △, water. Using the third gelatin fraction: ●, 0.352* M *sodium sulfate; ■, 0.176* M *sodium sulfate; ▲, water.*

Experimental Procedure—The procedure for preparing the initial emulsion was exactly the same as before (1). The emulsion system was then treated with specified additives for 24 hr. Temperature during the treatment period was kept at 40°. Figure 1 shows a dark-field microphotograph of the oil droplets of a typical emulsion system used in these studies. Figure 2 gives a typical particle size distribution display obtained with a Coulter counter[10] and a multichannel analyzer.[11] Table I presents the results of the analysis of the particle size distribution taken from the Fig. 2 photograph. This information was used in the calculation of the permeability coefficients.

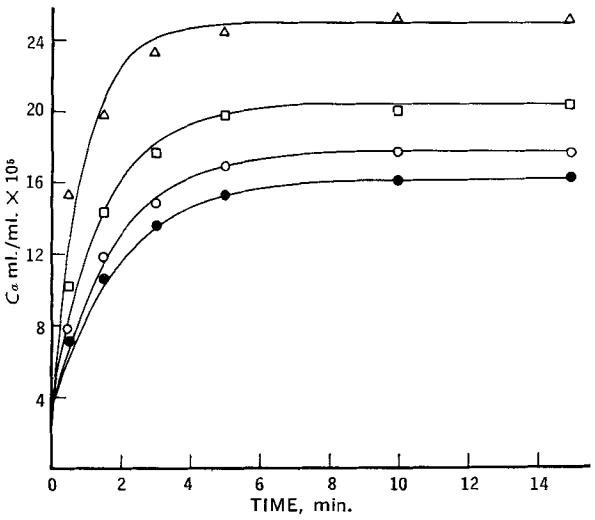

Figure 4—*Influence of electrolyte and the comparison of experimental release data with the theoretically computed ones.* C_a *is the amount of diethylphthalate released, ml./ml.,* versus *time in minutes. A 3.0-ml. aliquot of the emulsion system pretreated with 0.352* M *sodium sulfate was added to 100 ml. of aqueous medium at 23°. Key: experimental points, ●, 0.493* M *sodium sulfate; ○, 0.352* M *sodium sulfate; □, 0.176* M *sodium sulfate; △, water. Curves are theoretical values computed using Eqs. 1 and 2 with* $P = 5 \times 10^{-5}$ *cm./sec.*

[10] Coulter Electronics, Chicago, Ill.
[11] RIDL 400, Radiation Instrument Development Laboratory, Inc., Melrose Park, Ill.

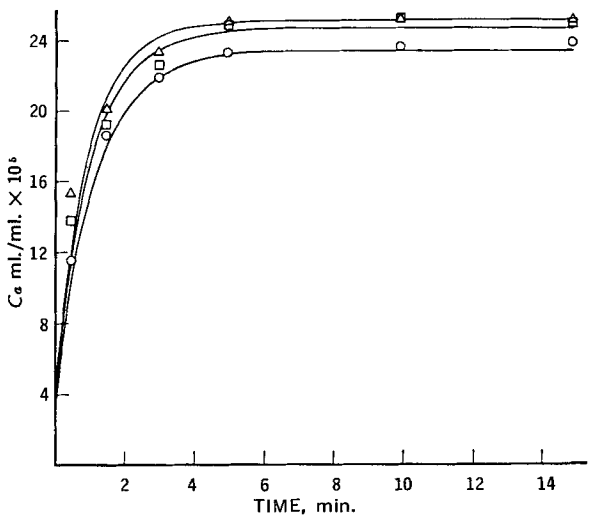

Figure 5—*Influence of electrolyte and the comparison of experimental release data with the theoretically computed ones.* C_a *is the amount of diethylphthalate released, ml./ml.,* versus *time in minutes. A 3.0-ml. aliquot of the emulsion system pretreated with 0.352* M *sodium chloride was added to 100 ml. of aqueous medium at 23°. Key: experimental points, ○, 0.352* M *sodium chloride; □, 0.176* M *sodium chloride; △, water. Curves are theoretical values computed using Eqs. 1 and 2 with* $P = 5 \times 10^{-5}$ *cm./sec.*

The hexadecane-water partition coefficients for diethylphthalate were determined in two ways as previously discussed (1) with and without gelatin present. Table II gives the partition coefficients obtained in different electrolyte media. It is clear that the partition coefficients obtained with and without gelatin at the interface are the same within the experimental error. However, the partition coefficients were found to be dependent on the nature and the concentration of the electrolytes used. This can be attributed to the salting-out effect (7).

The interphase transport experiments were carried out as described previously (1). A 3-ml. aliquot of the stock emulsion system containing the diethylphthalate was pipeted into 100 ml. of the aqueous release medium at zero time, and the amounts released to the aqueous phase were determined as a function of time.

EXPERIMENTAL RESULTS

Effect of Different Gelatin Fractions—Figure 3 gives the experimental results of diethylphthalate release obtained using whole

Table II—Partition Coefficients of Diethylphthalate[a] for Hexadecane-Aqueous Electrolyte Solutions at 23°C.

Media	Without Gelatin: Water	Without Gelatin: 0.176 *M*	Without Gelatin: 0.352 *M*	With Gelatin: Water	With Gelatin: 0.176 *M*	With Gelatin: 0.352 *M*
Water	54 ± 6[b]	—	—	—	—	—
Sodium sulfate	—	94 ± 6	130 ± 4	48 ± 7	96 ± 5	126 ± 7
Sodium chloride	—	55 ± 3	66 ± 3	50 ± 4	53 ± 3	63 ± 5
Calcium chloride	—	68 ± 3	92 ± 4	54 ± 6	67 ± 5	89 ± 4
Magnesium chloride	—	69 ± 2	92 ± 3	52 ± 3	66 ± 4	91 ± 4
Magnesium sulfate	—	89 ± 3	122 ± 5	49 ± 4	91 ± 5	118 ± 8

[a] The concentration of diethylphthalate was 0.05096 ml./ml. and in all experiments, 1.0 ml. of oil phase or equivalent amount of emulsion system was added to 100 ml. of the aqueous phase in a 250-ml. volumetric flask and shaken for 24 hr. [b] Standard deviations of triplicate or quadruplicate determinations.

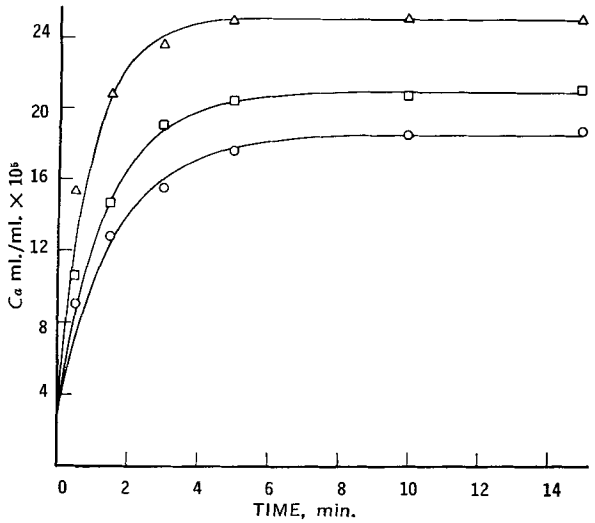

Figure 6—*Influence of electrolyte and the comparison of experimental release data with theoretically computed ones.* C_a *is the amount of diethylphthalate released, ml./ml.,* versus *time in minutes. A 3.0-ml. aliquot of the emulsion system pretreated with 0.352* M *calcium chloride was added to 100 ml. of aqueous medium at 23°. Key: experimental points,* ○, *0.352* M *calcium chloride;* □, *0.176* M *calcium chloride;* △, *water. Curves are theoretical values computed using Eqs. 1 and 2 with* $P = 5 \times 10^{-5}$ *cm./sec.*

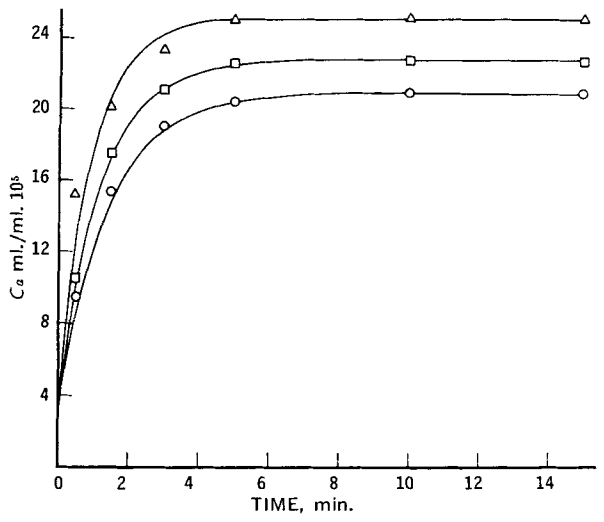

Figure 8—*Influence of electrolyte and the comparison of experimental release data with the theoretically computed ones.* C_a *is the amount of diethylphthalate released, ml./ml.,* versus *time in minutes. A 3.0-ml. aliquot of the emulsion system pretreated with 0.352* M *magnesium sulfate was added to 100 ml. of aqueous medium at 23°. Key: experimental points,* ○, *0.352* M *magnesium sulfate;* □, *0.176* M *magnesium sulfate;* △, *water. Curves are theoretical values computed using Eqs. 1 and 2 with* $P = 5 \times 10^{-5}$ *cm./sec.*

gelatin and two fractions of gelatin (second and third fraction) under similar conditions. These stock emulsions were pretreated with 0.352 *M* sodium sulfate for 24 hr. prior to the release experiments in the various electrolyte concentrations. The differences in the release-rate data among the three fractions of gelatin used were within experimental error.

Effect of Electrolytes—The experimental results obtained with five electrolytes—sodium sulfate, sodium chloride, calcium chloride, magnesium chloride, and magnesium sulfate—are shown in Figs. 4–8. In these runs an emulsion system of essentially the same particle size distribution was pretreated with a 0.352 *M* solution of the particular electrolyte for 24 hr. at 40°. The release medium was either 0.352 *M*, 0.176 *M* electrolyte, or water at 23°.

These experiments showed that both electrolyte type and concentration have significant influences upon the transport rate.

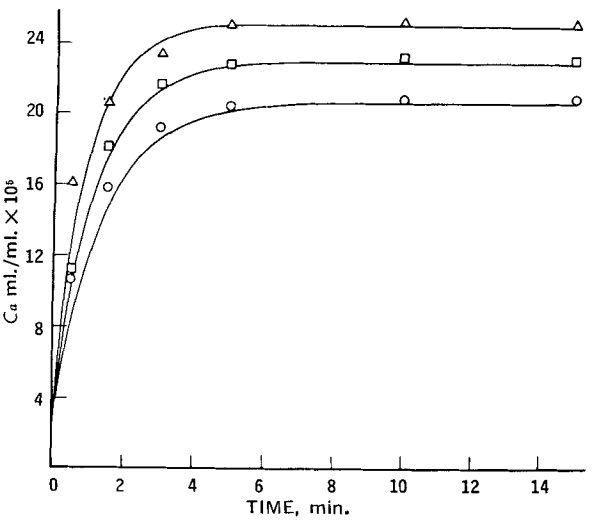

Figure 7—*Influence of electrolyte and the comparison of experimental release data with the theoretically computed ones.* C_a *is the amount of diethylphthalate released, ml./ml.,* versus *time in minutes. A 3.0-ml. aliquot of the emulsion system pretreated with 0.352* M *magnesium chloride was added to 100 ml. of aqueous medium at 23°. Key: experimental points,* ○, *0.352* M *magnesium chloride;* □, *0.176* M *magnesium chloride;* △, *water. Curves are theoretical values computed using Eqs. 1 and 2 with* $P = 5 \times 10^{-5}$ *cm./sec.*

However, as will be seen, the effects may be attributed entirely to the influences of salts upon the partition coefficient (see Table II) and not the permeability coefficients.

Figure 9 gives the results obtained employing different electrolyte concentrations in the pretreatment media prior to the release runs. As can be seen, little or no influence of the pretreatment was found. This suggested that, as far as salt interactions were concerned, essentially equilibrium conditions were present during the release period.

Effect of Surfactants—The influences of two ionic surfactants, sodium lauryl sulfate and dodecylpyridinium chloride, upon the release rate in sodium sulfate solutions are shown in Figs. 10–13. The effects of both of these surfactants were found to be similar

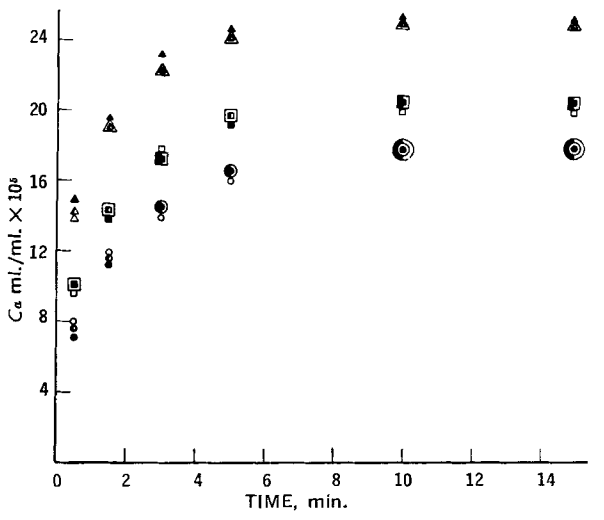

Figure 9—*Comparison of the experimental release of diethylphthalate from emulsion systems pretreated with different electrolyte concentrations. Three milliliters of emulsion system was added to 100 ml. of aqueous medium at 23°. Emulsion system was pretreated with 0.352* M *sodium sulfate and released in:* ●, *0.352* M *sodium sulfate;* ■, *0.176* M *sodium sulfate;* ▲, *water. Emulsion system was pretreated with 0.176* M *sodium sulfate and released in:* ◐, *0.352* M *sodium sulfate;* ◧, *0.176* M *sodium sulfate;* ◭, *water. Emulsion system was without electrolyte pretreatment and released in:* ○, *0.352* M *sodium sulfate;* □, *0.176* M *sodium sulfate;* △, *water.*

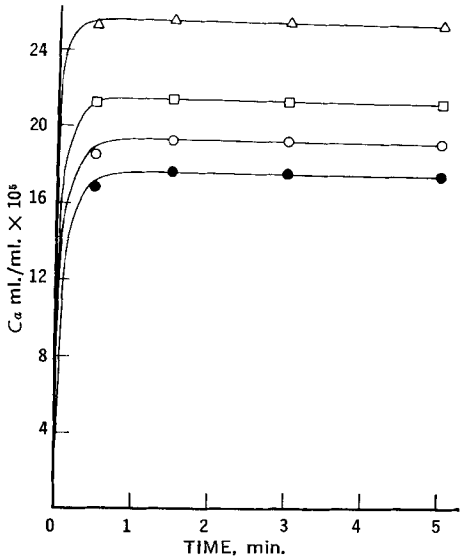

Figure 10—*Influence of sodium lauryl sulfate and comparison of the experimental release data with theory.* C_a *is amount of diethylphthalate released, ml./ml.,* versus *time in minutes. Three milliliters of emulsion system pretreated with 0.352* M *sodium sulfate and 0.1% sodium lauryl sulfate was added to 100 ml. of aqueous medium at 23°. Key: experimental points,* ●, *0.493* M *sodium sulfate;* ○, *0.352* M *sodium sulfate;* □, *0.176* M *sodium sulfate;* △, *water. The curves are theoretical values computed using Eqs. 1 and 2 and* P = 6 × 10^{-4} *cm./sec.*

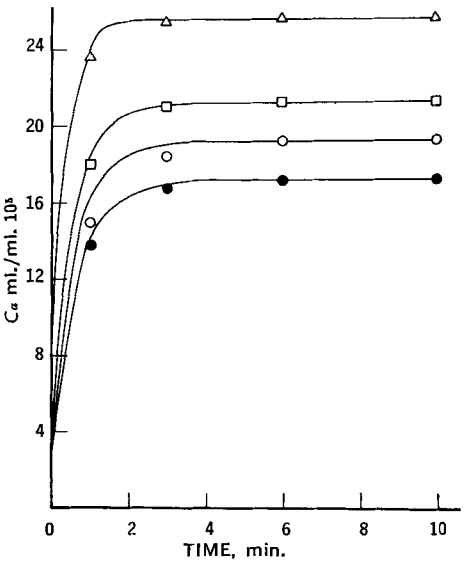

Figure 11—*Influence of sodium lauryl sulfate and comparison of the experimental release data with theory.* C_a *is amount of diethylphthalate released, ml./ml.,* versus *time in minutes. Three milliliters of emulsion system pretreated with 0.352* M *sodium sulfate and 0.01% sodium lauryl sulfate was added to 100 ml. of aqueous medium at 23°. Key: experimental points,* ●, *0.493* M *sodium sulfate;* ○, *0.352* M *sodium sulfate;* □, *0.176* M *sodium sulfate;* △, *water. The curves are theoretical values computed using Eqs. 1 and 2 and* P = 2.5 × 10^{-4} *cm./sec.*

and showed marked enhancement of the release rates at relatively low concentrations.

Experiments with polysorbate 80 were also attempted. However, the emulsions containing this material were found to be unstable with respect to coalescence. During the pretreatment stage, extensive cracking of the emulsion containing polysorbate 80 was observed.

TREATMENT OF THE DATA AND DISCUSSION

The experimental results presented in Figs. 4–13 may be analyzed by the theoretical methods discussed previously (1). Equations 1 and 2,

$$\frac{-dC_{0i}}{dt} = \frac{3DP(C_{0i}/K - C_a)}{a_i(D + a_iP)} \qquad \text{(Eq. 1)}$$

$$(C_a - E)\,V_a = \sum_{i=1}^{L} 4/3\pi\, a_i^3\, n_i\,(C_0^* - C_{0i}) \qquad \text{(Eq. 2)}$$

give the two basic relations that can be used in the treatment of the data obtained in these studies. Here C_{0i} is the solute concentration in the droplet of radius a_i, C_a is the aqueous concentration, D is the diffusion coefficient of the solute in water, P is the interfacial barrier permeability coefficient, C_0^* and E are the solute concentrations in the oil and aqueous phases at zero time, V_a is the volume of the aqueous phase, K is the oil-water partition coefficient for the solute, n_i is the number of droplets of sizes between a_i and a_{i+1}, and t is time. Equation 2 assumes (1) that no binding of the solute occurs at the oil-water interface. This assumption should be reasonable in view of the partition coefficient data in Table II which shows that the presence of gelatin at the interface does not significantly alter the experimental partition coefficients. In the previous study (1), because of the higher electrolyte concentrations used, adsorption of diethylphthalate was found to be significant, and a modified form of Eq. 2 was found to be necessary for explaining the experimental data.

Influence of Electrolytes—The results of theoretical computations employing Eqs. 1 and 2 and the computer program previously given (1) are presented as the curves in Figs. 4–8. The partition coefficients used were taken from Table II and the particle size distribution function, n_i (a_i), was taken from Table I. A value of 6 × 10^{-6} cm.^{2}/sec. was used for the diffusion coefficient. The theoretical release-time profiles were fitted to the experimental data by varying the parameter, P, the permeability coefficient for the interfacial barrier.

First it should be noted that the time-dependence agreement between experiment and theory is generally good in all cases (Figs. 4–8). The slight deviations are always in the direction of somewhat faster experimental release rates at early times.

The most significant aspects of the comparison of experiments with theory is that a single P value of 5 × 10^{-5} cm./sec. quantita-

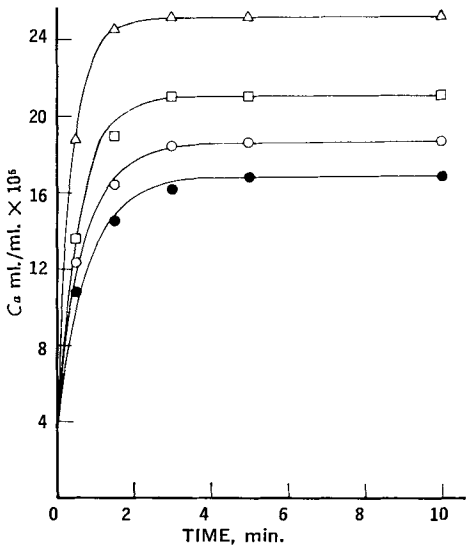

Figure 12—*Influence of sodium lauryl sulfate and comparison of the experimental release data with theory.* C_a *is amount of diethylphthalate released, ml./ml.,* versus *time in minutes. Three milliliters of emulsion system pretreated with 0.352* M *sodium sulfate and 0.001% sodium lauryl sulfate was added to 100 ml. of aqueous medium at 23°. Key: experimental points,* ●, *0.493* M *sodium sulfate;* ○, *0.352* M *sodium sulfate;* □, *0.176* M *sodium sulfate;* △, *water. The curves are theoretical values computed using Eqs. 1 and 2 and* P = 1.2 × 10^{-4} *cm./sec.*

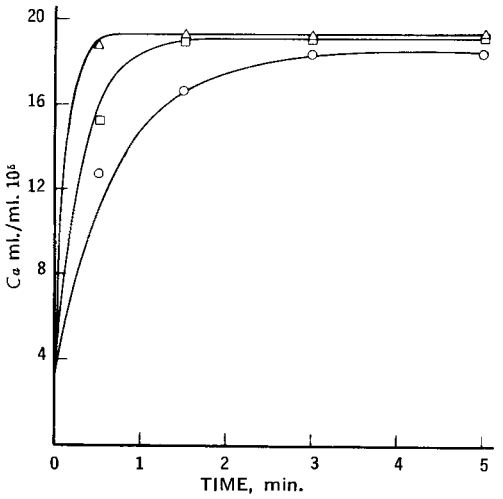

Figure 13—*Influence of dodecylpyridinium chloride (DDPCl) and the comparison of the experimental release with theory.* C_a *is amount of diethylphthalate released, ml./ml.,* versus *time in minutes. Three milliliters of emulsion system pretreated with 0.352* M *sodium sulfate and different concentrations of DDPCl was added to 100 ml. 0.352* M *sodium sulfate at 23°. Key:* △, *pretreated with 0.1%;* □, *pretreated with 0.01%;* ○, *pretreated with 0.001% DDPCl. The curves are theoretical values computed using Eqs. 1 and 2 and* P *values of* 6×10^{-4}, 2.5×10^{-4}, *and* 1.2×10^{-4} *cm./sec. for the three concentrations of DDPCl, respectively.*

tively describes the data. This was unexpected in view of the large differences in the rates found in the different electrolyte media. This can only mean that the observed differences in the rate may be attributed entirely to the effect of salts upon K, the partition coefficient. The K values given in Table II show that a significant salt effect upon K exists which may be explained on the basis of a salting-out effect (7).

The absence of the salt effect upon the permeability coefficient is somewhat surprising in view of the polyelectrolytic nature of gelatin. This effect may, however, be related in part to Veis' interpretation (8) of acid-precursor gelatin having a relatively compact structure and its configuration being less readily altered by environmental conditions. The absence of the salt effect may also be related to the concept that the main contribution to the interfacial barrier should arise from those interactions between gelatin, hexadecane, and water at the hexadecane side of the gelatin film. This effect may be enhanced by the possibility of surface denaturation (9) of the polymer at the oil interface.

Influence of Surfactants—The results of theoretical computations employing the same procedure previously mentioned are shown as the curves in Figs. 10–13. For these calculations the partition coefficients used were obtained from the terminal aqueous concentrations of the rate runs themselves. These values were generally slightly lower than those given in Table II.

First it should be noted that the shapes of the curves compare very well with the experimental results. The theoretical analysis of the surfactant effects was quite significant (Figs. 10–13). The P values obtained were 6×10^{-4}, 2.5×10^{-4}, and 1.2×10^{-4} cm./sec. for emulsion systems pretreated with 0.1, 0.01, and 0.001% surfactants, respectively. These P values were found to be independent of the electrolyte concentration.

The permeability coefficients obtained with sodium lauryl sulfate and dodecylpyridinium chloride were found to be about the same at the same percent surfactant concentration levels. Thus, it appears that both anionic and cationic surfactants operate by a similar general mechanism in influencing the permeability of diethylphthalate. These findings might be related to Pearson's studies (10, 11) which showed that cationic and anionic surfactants affect the surface viscosity of adsorbed protein films in a similar manner.

Biopharmaceutical Significance—It is noteworthy that these values for interfacial resistance are of the same order of magnitude as those observed (12) in lipid bilayer transfer studies and therefore generate the idea that biological membrane barriers might be largely of interfacial nature. Also, as pointed out by Ghanem *et al.* (1), the low apparent diffusion coefficient (10^{-9}–10^{-16} cm.^{2} sec.$^{-1}$) observed by Blank *et al.* (13) for the stratum corneum is of the same order of magnitude expected from the data obtained in these experiments. Other noteworthy results of this study are that the role of ionic surfactants in enhancing interfacial transport may closely parallel the influence of ionic surfactant in, for example, erythrocyte membrane permeability (14) or in enhancing transfer of drugs through the stratum corneum (15).

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