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TRANSPORT OF SOLUTES INTO POLYETHYLENE BOTTLES FROM AQUEOUS SOLUTIONS; EMPIRICAL RELATIONSHIPS OF THE DATA

A.E. POLACK *, L.J. NUNEZ and J. AUTIAN **

Materials Science Toxicology Laboratories, College of Pharmacy, University of Tennessee Center for the Health Sciences, Memphis, Tenn. 38163 (U.S.A.)

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SUMMARY

The interaction between a selected polyethylene container and solutes of aqueous solutions stored in the container was investigated. It was found that the solute disappearance from the solution follows either monoexponential or biexponential kinetics. It was shown that there is a rapid uptake stage followed by a slower (steady) disappearance phase during which the solute evaporates from the container to the atmosphere. The amount of solute in the container wall has been shown for the two principal solutes used in this work to remain constant until the concentration in solution drops to a predictable level. This constancy is attributed to the solubility of the solute in the plastic. The maximum amount of the solute dissolved in the container wall is related directly to the surface area of the container in contact with the solution. The effect of the polarity of a number of compounds on one of the characteristics of the interaction was investigated and a statistically significant correlation between the hexane–water partition coefficients of the compounds and their exponential disappearance rate constants was found.

INTRODUCTION

Much of the drug–plastic literature on diffusion and permeation consists of reports of fundamental studies performed in glass systems in which a polymeric film has been used as a barrier between a concentrated solution and a dilute solution. The effects of a number of physicochemical factors on the rate and extent of the movement of selected solute molecules into and through specific polymer films have been determined in this way. As a consequence of studies of this type many of the fundamental relationships have been developed to the point where pharmaceutical dosage forms, which incorporate a stage involving passage of a solute through a polymeric material, are now in use (Swarbrick, 1976). However, the literature on the processes which control the disappear-

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* School of Pharmacy, University of Tasmania, Hobart, Tasmania, Australia.
** To whom enquiries should be addressed.

ance of solute molecules from aqueous solutions in polyethylene containers is still relatively undeveloped. Numerous studies in which quantitative disappearance data appear have been published; however, the content of only a very small number of these is concerned, in the main, with the mechanisms which are responsible for the rate and extent of the uptake. It is important that an understanding of these mechanisms be developed so that we are better able to foresee this type of interaction and to prevent the undesirable consequences which may result. Two groups of authors have recently shown that there may be differences between the stated and actual concentrations of preservatives in ophthalmic solutions packaged in plastic containers (Richardson et al., 1977; Blackburn et al., 1978). Similarly, Sturek et al. (1978) and Crouthamel et al. (1978) have shown that nitroglycerin is removed from its aqueous solution stored in flexible infusion bags. The uptake of insulin by similar bags and by the delivery system attached to the bags has been reported by Hirsch et al. (1977).

The potential toxicity of materials leached from plastic containers and tubings into solutions which may be infused into patients is also a matter of concern (Autian, 1973; Petrick et al., 1977; Corley et al., 1977).

Some of the physicochemical factors which are important in determining the rate of disappearance of solutes from aqueous solutions in polyethylene have been identified (Polack et al., 1970; Roberts et al., 1979). These authors showed that the most important single factor controlling the rate of disappearance of the solute from the containers was the affinity between the solute and the polyethylene. It was shown that solutes with relatively high polyethylene–water partition coefficients disappeared by a biexponential mechanism; others disappeared by a monoexponential process.

The present study reports work directed towards an understanding of the processes responsible for the interactions between polyethylene containers and their aqueous solutions.

We have used nitrobenzene and acetophenone as the principal solutes because of their high affinity for polyethylene and because these substances have been used previously.

MATERIALS AND METHODS

Mathematics and data fitting

A computer program designated 'EXP FIT' fitted the experimental data expressed as the fraction of the amount of solute initially present in the solution as a function of time to either monoexponential or biexponential functions. The program utilized a non-linear parameter estimation method based on an algorithm of Donald Marquardt. The appropriate constants corresponding to a biexponential fit were accepted if improvement over a monoexponential fit could be demonstrated in the sum of squared error as tested by the *F* ratio at the 95% confidence level. If not, the monoexponential fit was accepted, provided the correlation coefficient was high and the sum of squared error was small. For biexponential fits the multiple correlation coefficient, *R* was also calculated. For some fits as many as 50 iterations were required but frequently excellent fits could be obtained in less than 20 iterations. Thus the constants in either of the following two equations were obtained from the computer:

$$F_s = 1.0\ e^{-kt} \tag{1}$$

and

$$F_s = Ae^{-\alpha t} + Be^{-\beta t} \tag{2}$$

where: F_s = fraction of solute remaining in solution;
k = monoexponential disappearance rate constant;
α,β = biexponential disappearance hybrid rate constants;
t = time in hours, and
$A + B = 1.000$

The computer program constrains A and B to sum to one. Eqn. 2 is a solution of the following pair of differential equations arrived at from a two-compartment model:

$$\text{SOLUTION} \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} \text{PLASTIC} \xrightarrow{k_{23}} \text{ATMOSPHERE}$$

where:

$$\frac{dF_s}{dt} = k_{21}F_p - k_{12}F_s \tag{3}$$

and

$$\frac{dF_p}{dt} = k_{12}F_s - (k_{21} + k_{23})F_p \tag{4}$$

where F_p = amount of solute in the plastic wall expressed as the fraction of the amount of solute initially present in the solution, and k_{12}, k_{21} and k_{23} are the appropriate rate constants.

The constants of Eqn. 2, obtained from the computer fit of the data, are related to the constants of Eqn. 3 and Eqn. 4 by the following expressions:

$$\alpha\beta = k_{12}k_{23} \tag{5}$$

$$\alpha + \beta = k_{12} + k_{21} + k_{23} \tag{6}$$

$$A = \frac{k_{21} + k_{23} - \alpha}{\alpha - \beta} \tag{7}$$

$$B = \frac{\beta - k_{21} - k_{23}}{\beta - \alpha} \tag{8}$$

Another equation is also obtained:

$$F_p = \frac{k_{12}}{\beta - \alpha}(e^{-\alpha t} - e^{-\beta t}) \tag{9}$$

Eqn. 9 represents a solution of the differential equation associated with the two-compartment model. Computer evaluation of the constants of Eqn. 2 allows F_p of Eqn. 9 to be calculated as a function of time.

F_p of Eqn. 9 goes through a maximum. When the derivative is taken with respect to time and set equal to zero, the following relationships are found to hold:

$$(F_p)_m = \frac{k_{12}}{\alpha}(e^{-\beta(t)_m}) \tag{10}$$

and:

$$(t)_m = \frac{\ln(\alpha/\beta)}{\alpha - \beta} \tag{11}$$

where $(F_p)_m$ = maximum value of F_p and $(t)_m$ = time corresponding to maximum value of F_p.

All computer operations were performed on a PDP-15 computer.

Compounds

The compounds used in this study were as follows: acetophenone, Fisher, high purity reagent, Lot 790716; n-amyl alcohol, Fisher, high purity reagent, Lot 711331; benzaldehyde, Mallinckrodt, analytical reagent, Lot NRE; 1-butanol, Baker, laboratory reagent, Lot 33106; hexane, Burdick and Jackson, U.V. quality, Lot AB905; 4-methylacetophenone, Eastman, laboratory reagent; p-methoxyacetophenone, Aldrich, laboratory reagent, Lot LB091577; nitrobenzene, Fisher, high purity reagent, Lot 793455; 4-nitroacetophenone, Matheson, laboratory reagent, Lot 10.

All compounds were used as received without further purification. All compounds were used throughout the study as aqueous solution.

Containers

The polyethylene containers used were manufactured by Nalgene Labware Division, Rochester, N.Y. and are described by the manufacturer as 'Nalgene Linear Polyethylene Narrow Mouth Bottles'. The containers are designed for the use of a screw cap; they are described by the manufacturer as being of 4 oz./125 ml capacity and are defined by Catalog Number '2002-004' (Nalgene Catalog 1977, page 8). 'Linear Polyethylene' is described in the same catalog as 'high density polyethylene' and is stated to have a specific gravity of 0.95. The container dimensions are as follows: brim capacity, 137 ml; height, without closure, 3.9 in.; outside diameter, 2.0 in. (Nalgene Catalog, 1977, p. 20). The vertical sides of the bottle were measured to be approximately 0.037 in. thick and our measurements indicate the base to be approximately 0.065 in. thick. We determined the average weight of the container, without screw cap, to be 16.9 g. The average (dry) weight of that part of the container which was in contact with liquid when 100 ml was placed in the container, was determined in preliminary experiments to be 9.8 g.

The internal surface area of the bottle in contact with liquid was calculated from a knowledge of the simple geometry of the bottle, measurements of the internal dimensions of the bottle and measurements of the height of the liquid surface above the base of the bottle. Since the geometry of the bottle was simple, its area was taken as the sum of a plane circle, cylindrical walls and a conic section.

Analytical methods

The concentrations of all compounds other than n-amyl alcohol and benzaldehyde were determined in their aqueous solutions by ultraviolet spectrophotometry, using 1 cm cells, on a Hitachi Perkin Elmer 139 UV-Vis Spectrophotometer at the previously determined wavelength of maximum absorption for each compound. Plots of optical density against concentration at that wavelength were linear for all compounds.

n-Amyl alcohol was analyzed using a flame ionization detector on a Varian 2100 gas chromatograph fitted with a 5 ft. X 0.25 in. metal column containing Poropak Q. The oven temperature was 220°C; the injector was set at 240°C and the detector at 250°C. The flow rate of the carrier (helium) was 34 ml min^{-1}; that of hydrogen 30 ml min^{-1} and that of air, 300 ml min^{-1}. The concentration of n-amyl alcohol was determined from a peak height ratio–concentration ratio plot previously prepared using 1-butanol as the internal standard. This plot was linear through the origin. Retention times under the conditions used were as follows: 1-butanol, 3.1 min; n-amyl alcohol, 6.0 min. Concentration in solution was calculated using the mean peak height ratios of 4 injections. The coefficient of variation using this method was generally within 5%.

Benzaldehyde was determined in exactly the same manner as n-amyl alcohol, using a metal column (of the same dimensions) of 3% OV 17 on 100/120 VarAport 30 [1]. The column temperature was 90°C, that of the injector 180°C and that of the detector 190°C. Flow rates of the gases were as follows: carrier, 22 ml min^{-1}; hydrogen, 30 ml min^{-1}; air, 300 ml min^{-1}. Benzaldehyde concentration in solution was determined in the same way as that of n-amyl alcohol, in this determination acetophenone being used as the internal standard. Retention times of the substances under these conditions were as follows: benzaldehyde, 1.6 min; acetophenone, 3.2 min.

Rate studies

Storage experiments were carried out in hot air ovens at the stated temperature. All ovens used were equipped with a small orifice in the roof. This orifice remained open throughout all experiments.

All temperatures stated in this work were controlled to ±1°C.

Polyethylene containers and solutions were brought to temperature independently by being allowed to equilibrate in the oven overnight prior to the solution being poured into the container (at time zero).

All experiments other than those involving the determination of the effect of concentration were conducted (at least) in duplicate. In all experiments the initial volume in the container was 100 ml unless otherwise indicated.

At each sampling time the container was removed from the oven and an aliquot (usually 0.2 ml) removed for analysis. The container was immediately returned to the

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[1] Varian Aerograph, Walnut Creek, Calif.

oven. The volume removed was not replaced. The effect of the temperature on the volume of the sample was disregarded. In the experiments in which the containers were covered with aluminum foil, the covered containers were equilibrated in the same way. In these cases the container was covered with at least three layers of aluminum foil which covered the entire container (i.e. up to the neck). The screw cap and neck were covered with a separate piece of foil which was removed at each sampling time and replaced immediately thereafter. At each sampling time the container and contents was gently swirled for a short time; the container remained stationary in the oven in the period between each sampling time.

Stability determination

The extent of decomposition of each compound was examined at the highest temperature used by placing 100 ml of a solution of the compound into a 100 ml glass stoppered volumetric flask and allowing it to remain in the oven for the duration of the experiment (usually 216 h). The flask was removed from the oven and allowed to cool and the concentration of the compound determined.

Sorption

The rate and extent of solute uptake by the container was carried out as follows: the container was placed in 375 ml of the stated solution in a glass container. The top of the glass container was covered with aluminum foil prior to the screw cap being placing in position. Under these conditions the polyethylene container protruded through the surface of the solution. The containers were stored in the ovens for the required period; with the exception of the controls the containers remained unopened until the required period had elapsed. During this period the containers and their contents were shaken vigorously at regular intervals. The interior of the container was kept full during the storage period.

Partition coefficients

The hexane–water partition coefficients of n-amyl alcohol and 4-methylacetophenone were determined as follows: 5 ml of a solution of known concentration of the solute in water (previously saturated with hexane) was pipetted into a glass tube. Five ml of hexane (previously saturated with water) was added to the solution. The tube was stoppered and allowed to stand at 24.5°C for 7 days. During this period the tube was shaken vigorously at regular intervals. Each determination was performed in triplicate. Only one concentration was used for n-amyl alcohol; for 4-methylacetophenone two concentrations were used and the partition coefficient was taken as the mean of the two values.

Permeation cells

Each cell was constructed from a 16 oz. screw cap glass jar by boring a hole in the screw cap (bakelite) of a size such that the screw cap of the polyethylene container (in the closed position) fitted very tightly into the orifice. A seal was effected by means of silicone adhesive. A smaller hole was drilled into the screw cap of the polyethylene container. This hole, which served as a sampling port, was closed by means of a rubber stopper lined with aluminum foil. The cell is shown diagrammatically in Fig. 1.

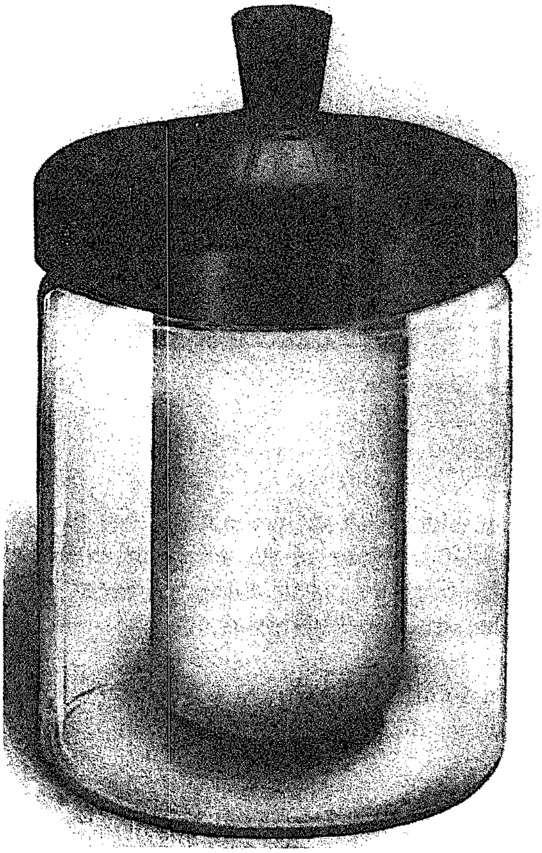

Fig. 1. Diagrammatic representation of permeation cell.

The inside of the bakelite screw cap was completely lined by aluminum foil throughout the period of any rate studies using the cell.

At each sampling time (usually 24 h) the entire contents of the outside chamber was replaced with water. The volume of water used in the outside chamber was 300 ml (unless otherwise stated) which was sufficient to cover the polyethylene to a level higher than that of the solution inside the polyethylene.

Apart from gentle swirling of the entire cell immediately prior to each sample being taken the cell remained stationary throughout the period between each sampling time.

Differential equilibrium sorption

This procedure is used for determining the amount of solute present in the walls of the container, F_p of Eqn. 9, and is performed as follows.

After a specific elapsed time of normal storage, the container was emptied, rinsed rapidly twice with distilled water, then immersed in a nitrobenzene solution of known strength in a glass container at 54.5°C. The procedure described under Sorption was then followed. Therefore:

$$A_e = A_p + A_u$$

where A_e = amount in plastic equilibrium;
A_p = amount in plastic at specific elapsed time; and
A_u = amount transferred from the sorption solution to the plastic.

$$F_p = \frac{A_p}{I}$$

where I = initial amount of solute in the storage experiment.

RESULTS AND DISCUSSION

None of the solutions used (other than benzaldehyde) showed any change in concentration after storage in glass at 71°C for 240 h. None of the solutions extracted materials which absorbed in the ultraviolet range from the plastic during storage at 71°C for 240 h. The amount of water lost under the same conditions was negligible and has been disregarded.

Plots of the fraction of solute remaining in solution, F_s, against time at 54.5°C for p-methoxyacetophenone and 4-methylacetophenone illustrating mono- and biexponential

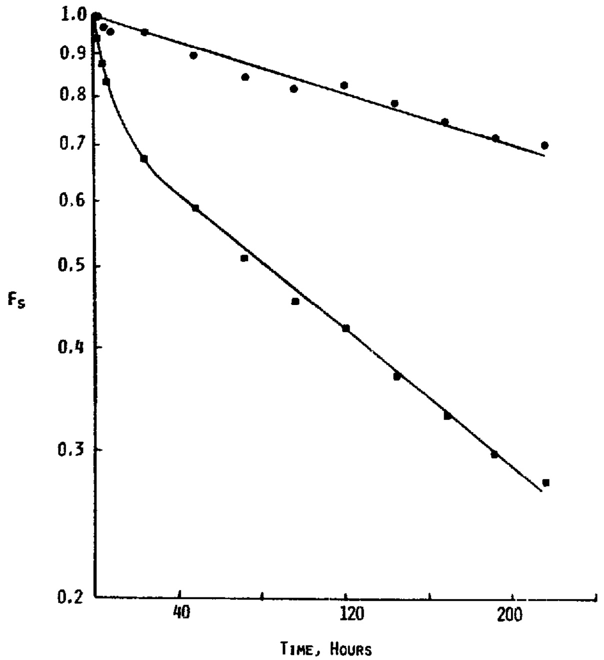

Fig. 2. Fraction of solute remaining in solution (F_S) against time at 54.5°C. ●, p-methoxyacetophenone; ■, 4-methylacetophenone.

fits respectively, are shown in Fig. 2. The lines are the computer fitted curves of Eqns. 1 and 2, respectively, for the experimentally determined points.

Repetitive determinations exhibit a wide range of values for the computer-determined constants α, k_{12} and k_{21}, whereas the constants B, β and k_{23} are in closer agreement. This is a direct consequence of the nature of the biexponential plot and the extreme sensitivity of the curve-fitting procedure used. This point is illustrated in Table 1 in which the computer-determined constants are presented for two individual containers containing acetophenone at 63°C. The values of α, k_{12} and k_{21} should be regarded as representative of a range and not as specific values. Four replicate determinations were obtained for acetophenone at 71°C yielding a standard deviation of about 18% for the constant α and 6.5% for the constant β.

The effect of heat in so far as it may be responsible for a change in the integrity of the container was also investigated. Four replicate determinations were made at 71°C with acetophenone using bottles preheated at 71°C for 18 days prior to initiation of the experiment. The values of the computer-determined constants of Eqn. 2 were similar to those of the untreated containers. We conclude, therefore, that heat does not significantly alter the integrity of the container at the highest temperature used in this work.

The fraction of solute F_s, remaining at any time during the disappearance of acetophenone and nitrobenzene from their aqueous solutions, has been found to be independent of initial concentration. This result is consistent with a previous report (Roberts et al., 1979).

The experimental data for nitrobenzene give good fits to the biexponential Eqn. 2 for all temperatures studied. The values of the constants are presented in Table 2 along with the multiple correlation coefficient, R. Each constant in the table is obtained from a computer fit of average values of duplicate determinations. Plots of these data are presented in Fig. 3. The trend of more rapid decrease of the nitrobenzene in the solution with increasing temperature is readily apparent. This same trend was observed in smaller sized bottles by other workers (Roberts et al., 1979). Plots of the logarithms of the hybrid rate constants against the reciprocal of absolute temperature are presented in Fig. 4. Least squares lines are presented in the figure and it can be seen that the lines are nearly parallel. Since these plots are linear over the limited range studied, the lines may be

TABLE 1

KINETIC CONSTANTS DERIVED FROM THE DATA FOR ACETOPHENONE AT 63°C

Constants	Container 1	Container 2
B	0.889	0.883
α, h^{-1}	0.125	0.0725
β, h^{-1}	0.0046	0.0046
k_{12}, h^{-1}	0.0180	0.0125
k_{21}, h^{-1}	0.0795	0.0381
k_{23}, h^{-1}	0.0319	0.0265
R	0.998	0.998

TABLE 2

CONSTANTS FOR NITROBENZENE [a]

	Temperature (°C)			
	46	54.5	63	71
B	0.739	0.740	0.733	0.706
α, h^{-1}	0.146	0.277	0.540	1.180
β, h^{-1}	0.00356	0.00650	0.0114	0.0178
k_{12}, h^{-1}	0.0408	0.0769	0.153	0.360
k_{21}, h^{-1}	0.0960	0.184	0.358	0.780
k_{23}, h^{-1}	0.0127	0.0235	0.0405	0.0583
R	0.999	0.999	0.999	0.999

[a] Each constant is obtained from a computer fit of average values of duplicate determinations.

extrapolated to a 1/T value of 32.2×10^{-4} which corresponds to 37°C. A plot of the constant B versus temperature (not shown) is also linear and may be extrapolated to 37°C.

Thus all the constants required for Eqn. 2 are now available to predict F_s as a function of time at 37°C, i.e.

$$F_s = (0.243)e^{-(0.060)t} + (0.757)e^{-(0.00189)t} \qquad (12)$$

Such a plot is presented in Fig. 5. The smooth curve represents values calculated from

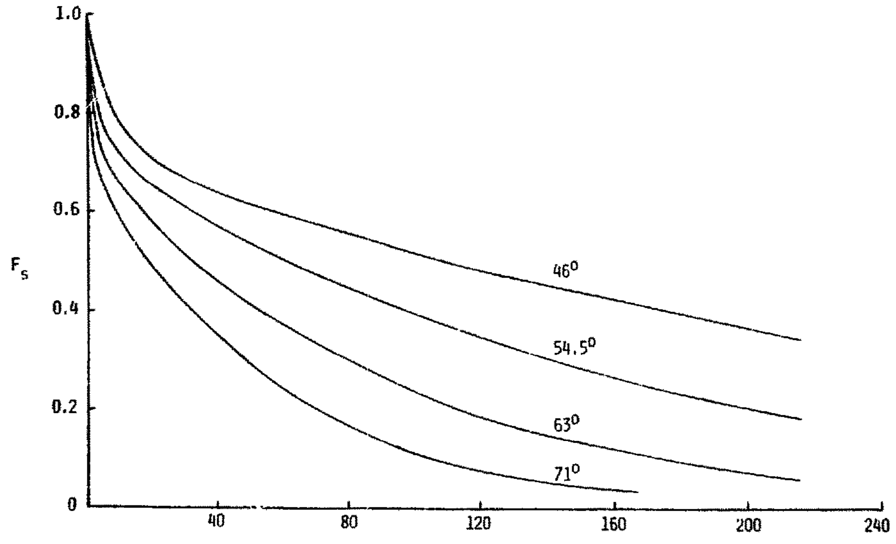

Fig. 3. The effect of temperature on the disappearance of nitrobenzene.

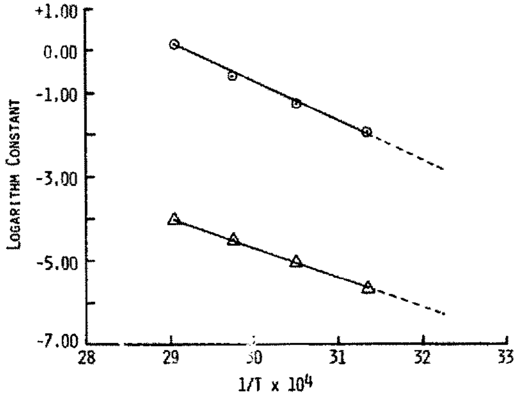

Fig. 4. The effect of temperature on the logarithms of two constants of Eqn. 2 for nitrobzene. o,α; △,β.

Eqn. 12. The points represent experimental data. It can be seen that agreement between experimental data and calculated data is good.

Computer fits to Eqn. 2 were obtained on nitrobenzene data from individual bottles for pairs of bottles at each of three different temperatures: 46, 63 and 71°C. The average deviation of the mean (expressed as %) for the pairs was 10.5% for α and 5.0% for β, the constants in Eqn. 2, showing again that there is a considerably larger variability in determining α than in determining β. A similar effect was observed at 54.5°C with data from 4 individual bottles obtained from different starting compositions of nitrobenzene: 0.06, 0.08, 0.10 and 0.12%.

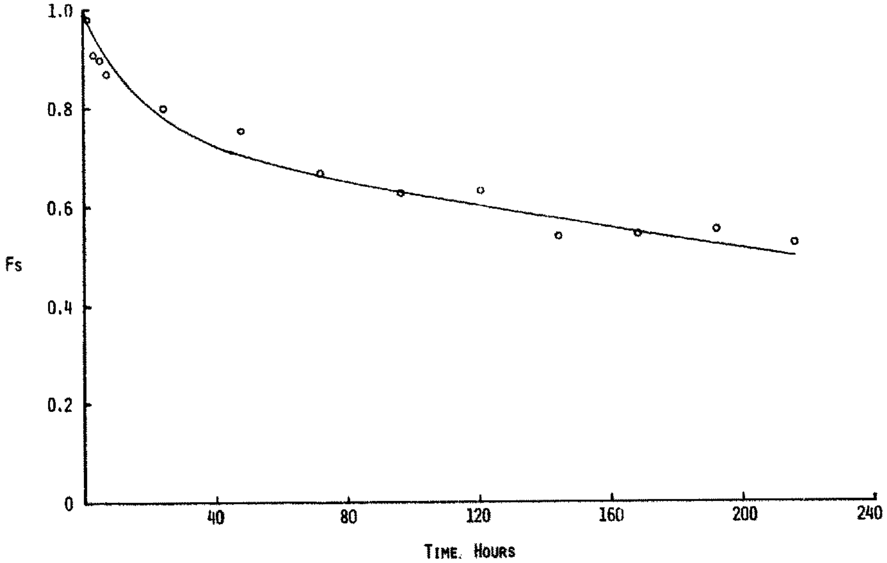

Fig. 5. The disappearance of nitrobenzene at 37°C. The line shows the fraction of solute remaining in solution (F_S) predicted by Eqn. 12. The points are experimentally determined (mean of 2 containers).

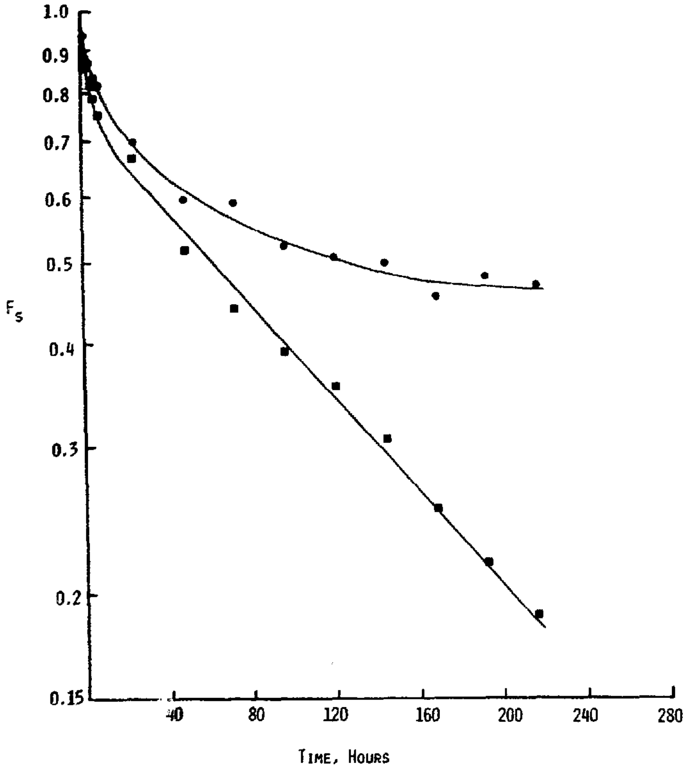

Fig. 6. Disappearance of nitrobenzene at 54.5°C. ●, container covered with aluminum foil (mean of 3 containers); ■, normal storage (mean of 4 containers).

Roberts et al. (1979) suggested that the terminal phase of the biexponential plot of the fraction remaining against time represented the evaporation of the solute from the container wall to the atmosphere. We have attempted to eliminate such an event occurring by covering the container with aluminum foil (held in position by rubber bands) and then monitoring the fraction remaining in the solution with respect to time. Comparison of the results for nitrobenze at 54.5°C is shown in Fig. 6. Examination of this figure indicates that in the absence of an 'escape route' to the outside, the solute concentration in the solution (and therefore also in the container wall) appears to be approaching an equilibrium situation.

The equilibrium value determined in glass for nitrobenzene at 54.5°C and the polyethylene containers used in this work is 8.45 ± 0.54 S.D. based on 6 determinations. The partition coefficient is independent of concentration within the range studied. The time required for the system to reach equilibrium when all of the container is in contact with the solution was determined previously to be less than 168 h.

The plots in Fig. 6 (and similar results obtained using 130 ml in the container) indicate that the solute does evaporate to the atmosphere when the bottle is not covered with foil. This conclusion is supported by the pre-soaking data of Roberts et al. (1979) where it was shown that the initial rapid uptake phase of nitrobenzene (from aqueous solution) into

TABLE 3

COMPARISON OF 'CELL' AND 'NORMAL STORAGE' CONSTANTS FOR NITROBENZENE

	Temperature (°C)					
	37		46		54.5	
	Normal [a]	Cell [c]	Normal [a]	Cell [c]	Normal [b]	Cell [c]
B	0.805	0.805	0.739	0.739	0.735	0.772
α, h^{-1}	0.157	0.158	0.146	0.119	0.261	0.217
β, h^{-1}	0.00218	0.00227	0.00356	0.00443	0.00632	0.00599
R	0.999	0.999	0.999	0.998	0.999	0.999

[a] Mean of 2 containers.
[b] Mean of 4 containers.
[c] Measurements in a single cell.

polyethylene containers could be eliminated by 'saturating' the container prior to the commencement of the experiment. The subsequent rate of disappearance followed mono-exponential kinetics with a slope apparently the same as that found in the case of the untreated container. Other studies have also shown that solute molecules are capable of permeating through polyethylene containers from an external vapor phase to the aqueous solution within the container (Goss et al., 1968; Polack, 1975).

In the present work we have measured the fraction in the container wall, F_p, using the permeation cells described earlier. Within the 'cell' the external 'receptor' solution was changed daily to ensure maintenance of an adequate concentration gradient. Except for

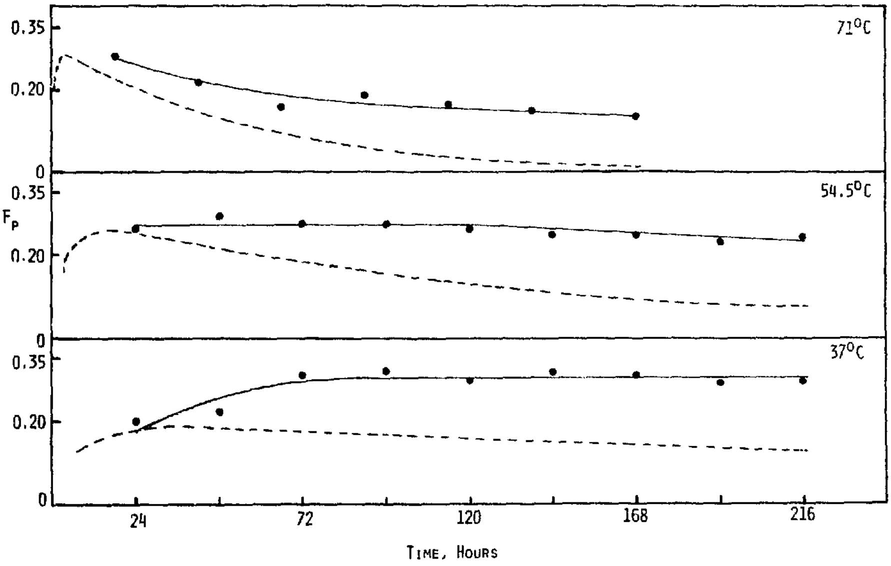

Fig. 7. Fraction of nitrobenzene in the container wall at three temperatures. ------, predicted by Eqn. 9; ●, experimentally determined from cell data.

some periods at 71°C the concentration in the external solution never exceeded 10% of that inside the container (i.e. of the internal solution).

The difference between the fraction of solute remaining in solution in the container housed inside the cell and that in a container stored in the normal way is shown in a representative set of data in Table 3. The variation in the values of B and β is within the range seen between containers.

The experimental values of F_p and the amounts predicted by Eqn. 9 for nitrobenzene at three temperatures are shown in Fig. 7. It is apparent that it is not possible to correctly predict the fraction in the wall by means of Eqn. 9. We have also measured the amount in the wall of individual containers following normal storage experiments by a procedure which we have described as differential equilibrium sorption (DES). This method (DES) is considered to be somewhat crude and the results are subject to large errors. Nevertheless, these data confirm that the amounts of solute in the container wall in the cell are comparable to the amounts found in the wall under normal storage conditions.

The extent of the deviation between the experimental and predicted values of F_p is apparently unchanged with increase of temperature above 37°C. This observation is substantiated by the data for acetophenone (Fig. 8). It can be seen (Figs. 7 and 8) that the amount of each solute in the wall remains constant in all cases (except nitrobenzene at 54°C and 71°C) once the initial 'time lag' has elapsed. The 'time lag' can be regarded as being the time required for the membrane to attain its maximum solute content (Jordan and Polack, 1972). The 'time lag' can be measured by plotting the cumulative amount permeated (i.e. into the receptor side) against time and extrapolating the linear portion of the curve to the time axis. The intercept gives the 'time lag' (Gonzales et al., 1967). Plots of this type for nitrobenzene are shown in Fig. 9. The measured 'time lags' for both

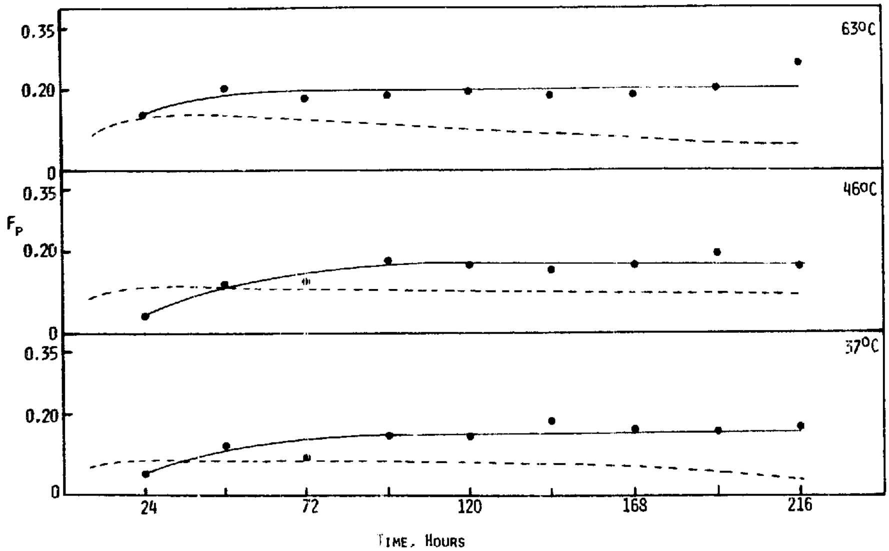

Fig. 8. Fraction of acetophenone in the container wall (F_p) at three temperatures. ------, predicted by Eqn. 9; ●, experimentally determined from cell data.

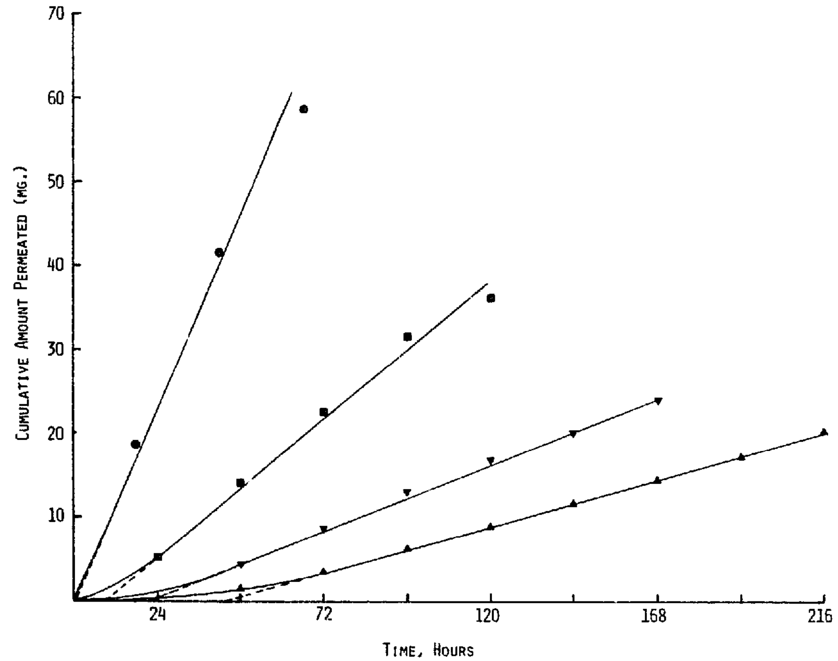

Fig. 9. Determination of time lags for nitrobenzene. ▲, 37°C; ▼, 46°C; ■, 54.5°C; ●, 71°C.

solutes were compared to the times at which the fraction in the wall, F_p, is predicted to reach a maximum (by Eqn. 11). In most cases agreement was poor.

Comparison of the values of the maximum fraction of nitrobenzene achieved in the container wall, predicted by the constant A of Eqn. 2 and the experimental value shows some agreement at the higher temperatures (Table 4). The maximum value of F_p calculated by Eqn. 10 is generally very close to the value of A.

The fact that F_p remains virtually constant with time (except for nitrobenzene at 54°C and 71°C) gives rise to the possibility that the solute is retained in the wall as a consequence of its solubility in polyethylene. The experimental values of F_p (Figs. 7 and 8) are consistent with results presented previously for the distribution of salicylic acid between water and cyclohexane (Doluisio and Swintosky, 1965) and the distribution of amidopyrine between the same solvents (Perrin, 1967) in analogous systems. In both of these cases, the amount of solute in the non-aqueous phase maintained a constant level for the duration of the experiments; the constant value was in each case attributed to the relatively high solubility of the solute in cyclohexane.

It has been shown above that when evaporation to the atmosphere is blocked the levels of solute in the solution and in the wall approach an equilibrium situation. Thus the rate of evaporation is one of the factors which controls the level at which F_p becomes constant. Once the fraction F_p has become constant, the overall rate of disappearance of the solute from the solution becomes largely controlled by the constant β in Eqn. 2. This observation is consistent with that of Doluisio and Swintosky (1965) who found a similar change in the rate of disappearance of salicylic acid from water into cyclohexane in an analogous system. If evaporation from the container was the rate controlling step in this

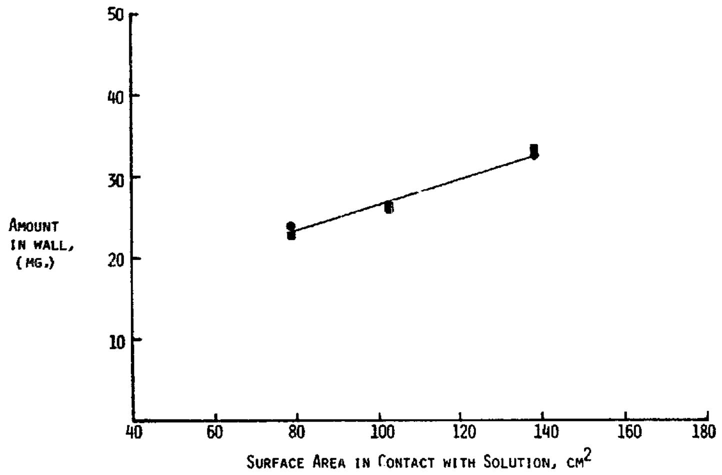

Fig. 10. Amount of nitrobenzene in the container wall when different volumes of solution are in the containers at 54.5°C. ■, from fraction in wall (F_p) determined in permeation cell at twenty-four hours. ●, from intercept 'A' of Eqn. 2 (mean of 2 containers).

stage of the process, the rate of disappearance from the solution would be zero-order. This is clearly not the case (Fig. 3).

A plot of the amount of solute in the wall, determined by two methods, against surface area in contact with the solution (Fig. 10) indicates that the amount in the wall increases linearly with surface area within the range studied. This is consistent with expectation and shows quite clearly that only the plastic in contact with the solution is involved in the uptake and that the solute diffuses only laterally while the interaction is

TABLE 4

MAXIMUM FRACTION OF SOLUTE IN THE CONTAINER WALL

	Temperature (°C)		Experimental[a]	Predicted	
				Intercept 'A'	Eqn. 10[b]
Nitrobenzene	37		0.307	0.195	0.194
	54.5	70 ml	0.351	0.342	0.323
		100 ml	0.276	0.265	0.258
		135 ml	0.276	0.241	0.236
	71		0.280	0.306	0.286
Acetophenone	37		0.152	0.085	0.086
	46		0.164	0.111	0.114
	63		0.175	0.115	0.136

[a] Measurement in a single cell. Value estimated by averaging measured values at times greater than experimentally determined time lag. For nitrobenzene at 54°C, for 70 ml and 100 ml: estimated by averaging measured values at times up to and including 48 h; at 71°C: measured value at 18 h only.
[b] Each value is the mean of the values in each container.

TABLE 5

FRACTION OF SOLUTE IN CONTAINER WALL AS A FUNCTION OF TIME UNDER VARIOUS CONDITIONS

	Temp., (°C)	Initial volume (ml)	Polyethylene–water partition coefficient (K_{pw})	Constant fraction in wall [c] (F_p)	Estimated frac. in solution (F_s) at which solubility coefficient [d] exceeds (K_{pw})	Time at which solubility coefficient exceeds (K_{pw}) [e] (h)
Nitrobenzene [f]	71	100	5.99 [a]	0.280	0.28	48
	54	70	8.45 [a]	0.351	0.41	65
		100	8.45 [a]	0.276	0.32	124
		135	8.45 [a]	0.276	0.28	>216
	37	100	9.00 [b]	0.307	0.21	>216
Acetophenone [g]	63	100	4.32 [a]	0.175	0.24	>216
	46	100	3.87 [a]	0.164	0.25	>216
	37	100	3.50 [b]	0.152	0.26	>216

[a] Experimentally determined.

[b] Estimated.

[c] From Table 8.

[d] Solubility coefficient = $\frac{\text{concentration in plastic}}{\text{concentration in solution}}$ (Gonzales, 1967).

[e] Estimated from F_s vs time plots.

[f] Initial concentration: approximately 0.100% v/v.

[g] Initial concentration: approximately 0.180% v/v.

in a dynamic state. In the equilibrium state, a different situation prevails and diffusion occurs throughout the wall.

It can be postulated that the amount in the wall will remain constant only until the concentration in the wall exceeds the concentration in the solution by a value greater than the equilibrium partition value (in the case of nitrobenzene at 54.5°C, 8.45). It can be seen that, in the case of nitrobenzene at 54.5°C, the experimentally determined constant value of F_p is approximately 0.276 (Fig. 7, Table 4). It can be shown that the concentration in the wall (276 mg in 10 g of plastic) will be 8.45 times greater than the concentration in the solution when the latter has dropped to 32.7 mg in 100 ml. This occurs at approximately 124 h (Fig. 6). It is apparent (Fig. 7) that the measured value of F_p is decreasing prior to 216 h. Similar reasoning can be applied to all the F_p plots and the results are shown in Table 5. The suggestion that F_p will fall only when the ratio of the concentration in the plastic to that in the solution exceeds the equilibrium value is supported in each case reported in Table 5.

We have attempted in this work to identify some of the factors which are important in the transport of solute molecules from their aqueous solutions into and through polyethylene containers. In previous work involving the use of polyethylene films many workers have shown that a linear relationship exists between the rate of permeation of a solute in the steady state and the hexane water partition coefficient of the particular

TABLE 6

RELATIONSHIP BETWEEN THE EXPONENTIAL CONSTANTS k AND β AT 54.5°C AND THE HEXANE–WATER PARTITION COEFFICIENTS OF THE COMPOUNDS

	Hexane–water partition coefficient at 25 ± 1°C	k [d] (h^{-1}) ×10^5	β [d] (h^{-1}) ×10^5	Nature of fraction of solute remaining against time plot
n-Amyl Alcohol	1.3 [a]	70.4		Monoexponential
4-Nitroacetophenone	5.3 [b]	158		Monoexponential
p-Methoxyacetophenone	8.6 [b]	177		Monoexponential
Benzaldehyde	9.5 [c]	372 [e]		Monoexponential
Acetophenone	14.0 [b]		270	Biexponential
Nitrobenzene	24.1 [c]		632	Biexponential
Methylacetophenone	40.7 [a]		463	Biexponential

[a] Determined in present work.
[b] From Nasim et al. (1972).
[c] From Jordan and Polack (1972).
[d] From plot of mean of fraction remaining against time.
[e] Not corrected for decomposition.

solute (Nasim et al., 1972; Serota et al., 1972; Jordan and Polack, 1973). The applicability of this relationship in the case of polyethylene containers (rather than films) has, so far as we are aware, not been reported. We have therefore undertaken rate studies on some additional compounds. We have compared the computer determined exponential constant, k (for monoexponential fits) and the exponential constant, β (for biexponential fits) with the appropriate hexane–water partition coefficients. A simple correlation coefficient, *r*, of 0.76 is obtained which is significant at the 95% confidence level. These results are summarized in Table 6. The value of k shown for benzaldehyde has not been corrected for decomposition. We have found that about 6% of the initial amount of benzaldehyde present in an aqueous solution in a glass container is lost in 240 h at 71°C. This effect has been disregarded in determining the value of k at 54.5°C. The correlation between the exponential constants and the hexane–water partition coefficients of the compounds is independent of the nature of the plot of fraction of solute remaining against time, some of these being monoexponential and others biexponential.

This work has confirmed the complex nature of the interaction between polyethylene containers and their aqueous solutions. The implications for the use of the containers of this type in pharmaceutical systems are obvious. It is to be hoped that further studies in this field will provide the means for the prediction, and thereby the prevention, of interactions which are potentially hazardous to man.

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