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THE STORAGE OF SELECTED SUBSTANCES IN AQUEOUS SOLUTION IN POLYETHYLENE CONTAINERS: THE EFFECT OF SOME PHYSICOCHEMICAL FACTORS ON THE DISAPPEARANCE KINETICS OF THE SUBSTANCES

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SUMMARY

The disappearance kinetics of certain solutes in aqueous solution during storage in polyethylene containers is described. For solutes with low affinity for polyethylene, loss is characterized by mono-exponential kinetics. If the solute has a strong affinity for the polyethylene, bi-exponential kinetics exist due to significant uptake of solute into the polyethylene in addition to loss by permeation. A 'compartmental' model is used to examine the observed kinetics and is based on sorption of the solute by the container wall followed by permeation of the solute into the atmosphere. The disappearance kinetics of the solutes examined in this study is dependent on the formulation of the solution to be stored in the container, presoaking of the container in solutions of the solute, and the nature of the external environment in which the containers are stored.

INTRODUCTION

Numerous publications on various aspects of drug–plastic interaction have appeared in the literature. In two recent papers (Richardson et al., 1977; Blackburn et al., 1978) the authors have shown that there may be a considerable difference between the actual concentration of a preservative in an aqueous solution in a plastic container and that stated on the label. These findings indicate that the problems consequent upon drug–plastic interaction continue to be matter for concern.

Despite the accumulated knowledge in this area very little attention has been directed specifically to the mechanisms by which solutes are lost from aqueous solution in polyethylene containers or to methods by which such loss can be minimized. Polack et al. (1970) suggested that several factors may affect the loss of solutes from plastic containers during autoclaving. They related to loss of solute from the container to the hexane–water partition coefficient of the solute and a parameter reflecting the diffusivity of the solute in polyethylene. Subsequent work by Serota et al. (1972) and Jordan and Polack (1972b) has also shown that the rate of permeation of a solute through polyethylene film may be correlated with the hexane–water partition coefficient of the solute.

The present study is concerned with the disappearance kinetics of solutes from aqueous solution in polyethylene containers and with some of the methods by which the loss due to sorption and/or permeation could be minimized.

MATERIALS AND METHODS

Reagent grade chemicals and solvents have been used in this study. The concentrations of these chemicals in solution were determined by measurement of absorbance on a Beckman DB-G spectrophotometer at the wavelength of maximum absorption and by reference to Beer's law plots. Aniline and 2-nitrophenol were analyzed at their iosbestic wavelengths. These methods, and the methods used to determine the hexane–water partition coefficients of some of the solutes in the present work, have been described in greater detail in previous publications (Polack et al., 1970; Jordan and Polack, 1972a). In this work two types of containers have been used and are designated A and B. Containers A (Duranol A64, 10 ml capacity) and B (Duranol A50, 15 ml capacity) are polyethylene dropper bottles (Duranol Plastics, Mt. Waverley, Victoria) with the same average wall thickness of 0.71 mm. These containers are described by their manufacturers as 'autoclavable'. They consist of three parts — the actual container, a dropper nozzle which was inserted after the contents had been placed in the container, and a screw cap. Both these brands of container are constructed of 'high density' polyethylene.

Storage experiments

Storage experiments were carried out for solutions of each solute as follows: An aliquot (10 ml unless stated otherwise) of a specified concentration of solute was placed in a polyethylene container and stored either in a constant temperature room or an oven at the specified temperature. For each solute a number of concentrations were used. These were generally below half the saturation solubility of the solute. For most solutes, the main concentration used to derive the kinetic data for a particular solute was 0.05% (chloroxylenol, 0.015%). An aliquot of the solution was also stored in a sealed glass ampoule at the same temperature and for the same time period as the container. At various times the container was removed from the room and the solution assayed for the content of solute remaining (the glass ampoule serving as a control). The containers were not shaken during the period of the study, except for gentle swirling of the contents immediately prior to removal of the aliquot for assay. Each determination reported is the mean of three containers, the coefficient of variation for such a determination being less than 5%. The data obtained is plotted as a fraction of solute remaining in (or lost from) solution against time. In some instances, to ascertain the effect of the boundary layer at the container wall–atmosphere interface, containers were immersed in various solvents at 37 ± 1°C and the disappearance kinetics monitored.

Presoaking

Presoaking of the container was carried out by the total immersion of the containers in a solution of the solute in the concentration to be used in the subsequent storage experiment. Solutions were changed daily during the period of the presoaking study and all air was excluded.

Formulation variables

All pH values were determined on a Radiometer 28 pH-meter. All solutions for the pH study were buffered solutions of 0.1 M and adjusted to an ionic strength of 0.5 (Jordan and Polack, 1972b). Solutions of varying viscosity were prepared using aqueous glycerol solutions and aqueous methylcellulose solutions. The viscosity of these solutions was determined using a Brookfield RVT viscometer.

Data analysis

Disappearance kinetics data has been analyzed by non-linear regression analysis using the program NONLIN (Metzler, 1969).

RESULTS AND DISCUSSION

Water vapour transmission from both containers (A and B) is less than 3% for solutions stored at 71 ± 1°C for 10 weeks. Water is lost from container B at a constant rate, 0.38% of a volume of 10 ml being lost following storage at 37 ± 1°C for 10 weeks. This loss is negligible in comparison to the observed losses of solutes and has therefore been disregarded in an examination of the experimental data. The change in concentration for each of the solutes in aqueous solutions stored in glass ampoules to monitor for solute decomposition (same storage conditions as used for polyethylene containers), was negligible and has been disregarded.

Disappearance kinetics

Representative plots for the fraction of solute remaining in aqueous solution against time following storage in polyethylene containers are shown in Fig. 1. The plots show that for some solutes, the disappearance follows first-order mono-exponential kinetics. For solutes with greater rates of loss, the disappearance is bi-exponential. The disappearance kinetics of the solutes used in this study were studied for a number of concentrations and found to be superimposable, i.e. consistent with first-order kinetics. Polack et al. (1970) also observed that the loss of solutes from polyethylene containers during autoclaving was independent of the initial concentration. The concentrations of solutes used in this study were generally below half their aqueous saturation solubility because it has been reported that high concentrations of solute may lead to increased permeation rates through polyethylene films (Jordan and Polack, 1972b).

Mono- or bi-exponential kinetics has also been observed for the disappearance of solutes from the lumen of the in situ intestinal segment (Doluisio et al., 1970) and from solutions in contact with subcutaneous tissue (Levy and Rowland, 1974).

Since the polyethylene–water partition coefficient of a solute may be directly related to its hexane–water partition coefficient (Jordan and Polack, 1972b), the relative value of the polyethylene–water partition coefficients for each of the solutes examined is provided by its reported hexane–water partition coefficient. Mono-exponential disap-

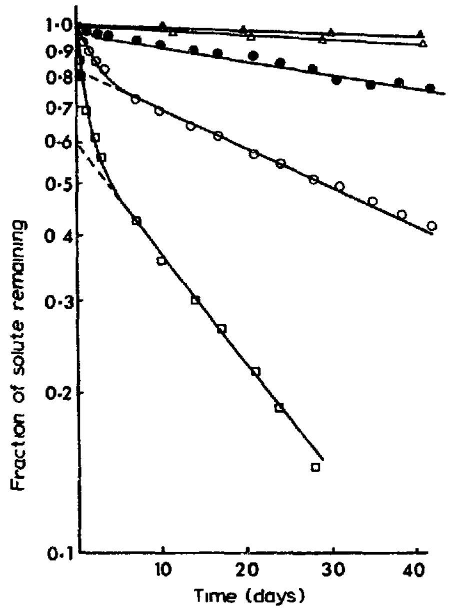


Fig. 1. Representative plots of fraction of solute remaining in aqueous solution in polyethylene containers (brand A) at 37 ± 1°C. ▲, benzyl alcohol; △, phenyl ethanol; ●, chlorocresol; ○, acetophenone; □, nitrobenzene.

pearance kinetics is observed for benzyl alcohol and phenyl ethanol (Fig. 1) and these solutes have reported hexane–water partition coefficients of less than one (Table 1). For solutes with hexane–water partition coefficients greater than one, bi-exponential kinetics is apparent (Fig. 1, Table 1).

The disappearance profiles of the solutes which have high affinity for the polyethylene examined in this study are consistent with a rapid and significant uptake of solute from the solution by the container wall followed by a slower and essentially irreversible loss of the solute to the atmosphere (Polack et al., 1979). If the solute has a low affinity for the container wall, an insignificant amount of solute is sorbed by the wall giving rise to mono-exponential kinetics. Mathematically, the fraction of solute in the solution, F_s, is related to time in the case of bi-exponential kinetics by the following equation:

$$F_s = Ae^{-\alpha t} + Be^{-\beta t} \qquad (1)$$

where A and B are the fractional zero intercepts (A + B = 1) and α and β are the fast and slow rate constants. The best estimates for these parameters are given in Table 1. Disappearance by mono-exponential kinetics is described mathematically by the expression:

$$F_s = e^{-\partial t} \qquad (2)$$

where ∂ is the disappearance rate constant. The difference in the constants (A, B, α and β) for containers A and B (Table 1) probably reflect differences in the properties of the containers with respect to density, composition and thickness of the wall.

TABLE 1

KINETIC DATA FOR THE DISAPPEARANCE OF SOLUTES FROM AQUEOUS SOLUTIONS STORED IN POLYETHYLENE CONTAINERS AT 37 ± 1°C AND THE HEXANE–WATER PARTITION COEFFICIENTS (K) FOR EACH OF THE SOLUTES (25°C)

Solute	Container Brand	A	B	α (days^{-1})	β	∂	k_{12}	k_{21} (days^{-1})	k_{23}	Cl (ml/day)	P	R	K
Benzyl alcohol	A					0.001				0.01			0.17 [a]
	B					0.002				0.02			
Phenylethanol	A					0.002				0.02			0.41 [a]
	B					0.003				0.03			
Chlorocresol	A	0.023	0.977	0.622	0.0065		0.021	0.414	0.193	0.0665	0.21	0.0024	2.2
Acetophenone	A	0.146	0.854	1.05	0.018		0.169	0.786	0.113	0.213	1.69	0.17	10 [a]
Chloroxylenol	B	0.147	0.853	2.07	0.011		0.314	1.69	0.075	0.133	3.14	0.17	12
Nitrobenzene	A	0.338	0.662	1.54	0.056		0.557	0.885	0.154	0.831	5.57	0.51	24 [a]
	B	0.434	0.566	2.70	0.075		1.214	1.39	0.166	1.30	12.1	0.77	

[a] From Polack et al. (1970) and Jordan and Polack (1972b).

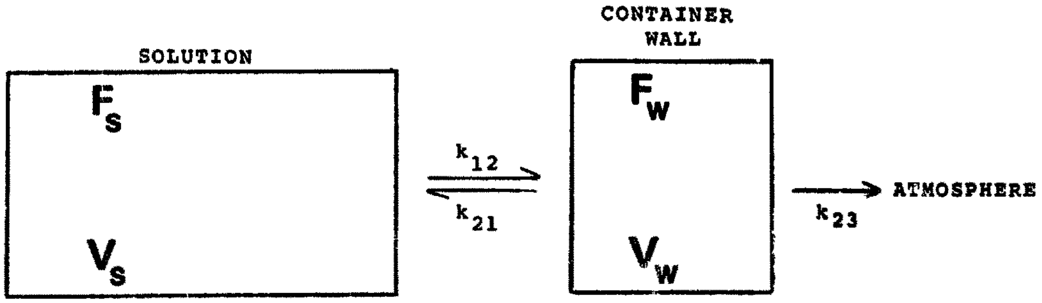


Fig. 2. Model used to examine disappearance kinetics of solutes from aqueous solutions stored in polyethylene containers. Symbols F and V refer to the fraction of solute remaining in, and the volume of, each of the 'compartments', solution (S), container wall (W) and atmosphere (A).

The values for the individual kinetic constants in the compartmental model (Fig. 2) were computed from the values of A, B, α and β using the following equations (Doluisio et al., 1970; Levy and Rowland, 1974):

$$k_{12} = A\alpha + B\beta \tag{3}$$

$$k_{23} = \alpha\beta/k_{12} \tag{4}$$

$$k_{21} = \alpha + \beta - k_{12} - k_{23} \tag{5}$$

$$Cl_s = V_s/[(A/\alpha) + (B/\beta)] \tag{6}$$

$$P = k_{12}V_s \tag{7}$$

where Cl_s is the clearance of the solute from the solution and P is the permeability coefficient of the solute in the container wall. It may also be shown that the distribution coefficient (R) of a solute between the wall of the container and the solution is related to the fractional zero-time intercepts A and B by

$$R = \frac{V_s}{V_W} \cdot \frac{A}{B} \tag{8}$$

providing $A/\alpha \ll B/\beta$ (Levy and Rowland, 1974). For solutes in which mono-exponential kinetics is apparent, the values of Cl_s and P have been determined from the following equation:

$$Cl_s = P = V_s\partial \tag{9}$$

Each of these individual kinetic constants is given in Table 1. There was greater error involved in the estimation of α than in the estimation of A, B and β due to the rapid uptake of the solute by the container wall. The values for clearance (Cl_s) and distribution coefficient (R) are therefore more reliable estimates than the individual rate constants (k_{12}, k_{21}, k_{23}) and the permeability coefficient (P).

It is apparent from the Table that the clearance of the solute from the solution in the container and the permeability coefficient of the wall are related in rank order to the distribution coefficient of the solute between the wall and the solution. Greater loss, as reflected by increased clearance and permeability coefficient, occurs for solutes with greater distribution coefficients. Values for the distribution coefficients R are similarly related to the reported hexane–water partition coefficients for these solutes (Table 1) which further confirms the observation of Jordan and Polack (1972b) that the polyethylene–water partition coefficient of a solute may be directly related to its hexane–water partition coefficient. Loss of solute from the wall of the container to the atmosphere is not related to the hexane–water partition coefficient of the solute as indicated by the fairly constant values of k_{23} in Table 1.

Volume and temperature

Fig. 3 shows the effect of volume of solution in the container on the loss of nitrobenzene, acetophenone and chlorocresol following storage for 5 days at 37 ± 1°C. The greater loss observed for the lower volumes is probably due to an increase in the ratio, surface area of the container in contact with solution/volume of solution at the lower volumes. Polack et al. (1970) showed that, on autoclaving, the greater losses observed for lower volumes of solution could be directly related to the surface area/volume ratio.

The loss of solutes from aqueous solutions during storage in polyethylene containers is markedly temperature dependent, as illustrated by the disappearance kinetics of nitrobenzene at various temperatures (Fig. 4). The extent of loss due to sorption (as indicated by the intercept) and permeation (as indicated by the terminal phase slope) increases with temperature. Similar configurations were observed for other solutes. The

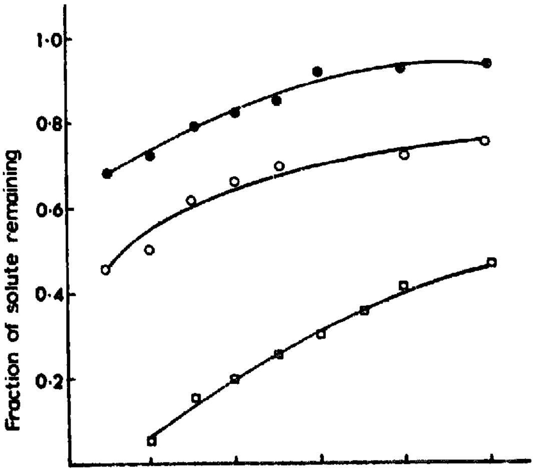
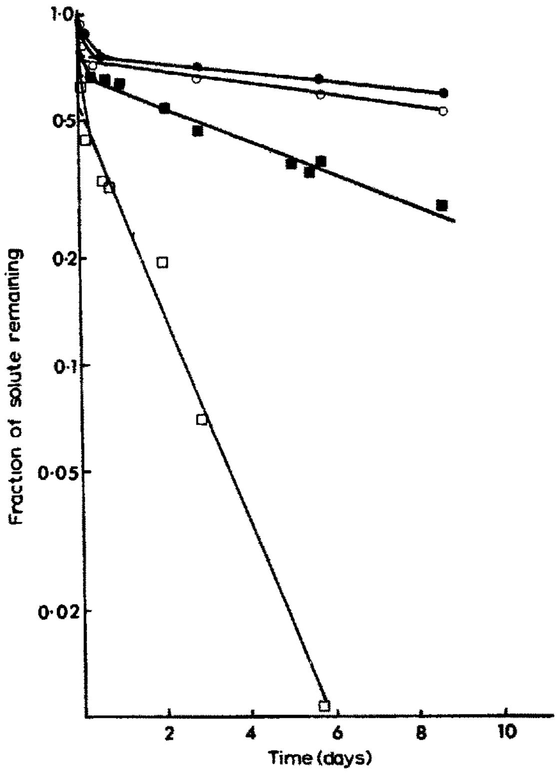


Fig. 3. Effect of volume on the fraction of solute remaining in aqueous solution following storage in polyethylene containers (brand A) for 5 days at 37 ± 1°C. ●, chlorocresol; ○, acetophenone; □, nitrobenzene.



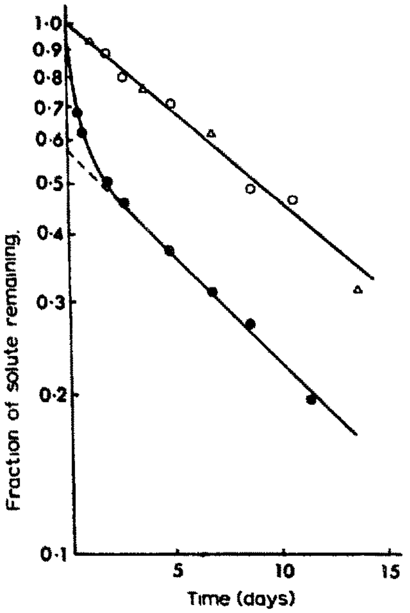


Fig. 4. Effect of temperature on the disappearance kinetics of nitrobenzene from aqueous solutions stored in polyethylene containers (brand B). ●, 18 ± 1°C; ○, 25 ± 1°C; ■, 37 ± 1°C; □, 60 ± 1°C.

Fig. 5. Effect of presoaking the container in an aqueous solution of nitrobenzene (0.05% w/v) on the loss of nitrobenzene (0.05% w/v) from aqueous solutions in polyethylene containers (brand B) at 37 ± 1°C. ○, presoaked one week; △, presoaked one month; ●, no presoaking.

thermodynamic parameters which can be derived from temperature studies will be reported in other work.

Presoaking

The extent to which a solute is taken up by the container wall rather than lost to the atmosphere is of particular interest if the loss of solute is to be reduced by pretreatment of the container wall. Fig. 5 shows the effect of presoaking the container on the disappearance kinetics of nitrobenzene from aqueous solutions. A similar profile was observed for chloroxylenol loss on storage in treated and untreated containers. It is apparent that presoaking abolishes the initial rapid phase of the disappearance versus time profile leading to a significant reduction in loss.

In theory, the fraction of solute in the wall F_w at any time t can be calculated by use of Eqn. 10 derived by the method of Benet (1972) for the present compartmental model, i.e.

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

where k_{12}, α and β are the previously estimated values. It has however been shown by Polack et al. (1979) that this equation may not be applicable for solutes which have a high affinity for the plastic other than to estimate the maximum fraction in the wall. According to Eqn. 10 about 30% of the nitrobenzene is in the container wall after 2 days at 37 ± 1°C. The extent of the initial loss of nitrobenzene abolished by presoaking (Fig. 5) is also of this order. It is therefore suggested that the initial rapid phase results from sorption of the solute from the solution into the container. For solutes with a high affinity for the container, the extent of sorption can be significant. The profile of a plot of disappearance against time following presoaking is similar to that observed for a solute with a low hexane–water partition coefficient and for which accumulation of solute in the wall is negligible. The terminal phase of the disappearance kinetics profile for an untreated container has a slope not significantly different to that of the presoaked container (Fig. 5). Presoaking therefore appears to significantly influence the extent of loss resulting from sorption but to have a minimal influence on the loss of solute to the atmosphere by a permeation process. Furthermore, the time required to presoak the container to abolish significant sorption is relatively short (less than a week under the conditions used in this work).

The importance of presoaking containers to diminish the extent of loss of ingredients on storage or during autoclaving is well recognized. The Australian Pharmaceutical Formulary (1974) recommends that for eye drops containing bacteriocides or preservatives and stored in plastic containers, the plastic containers should be impregnated with the bacteriocide prior to use. It is important to recognize that such treatment may reduce the loss due to sorption but not necessarily that due to permeation.

External environment

In order to ascertain the role of the boundary layer at the container wall–atmosphere interface on the disappearance kinetics of solutes from solutions stored in polyethylene containers, the containers were placed in various external solutions of different viscosity and solvent characteristics. The disappearance kinetics of nitrobenzene and phenylethanol from solutions stored in polyethylene containers at 37 ± 1°C was not significantly different for the environments of air, water, ethanol, glycerol and propylene glycol. Significant increases in the rate of disappearance were observed when hexane or carbon tetrachloride was used as the external environment. The minimal effects of varying the external environment about the container (except if hexane or carbon techrachloride is used) is consistent with the atmosphere boundary layer exerting a negligible contribution to the overall resistance of the container wall to the permeation of solutes.

Flück (1967) has shown that ethanol does not interact with polyethylene to any significant extent; chloroform, cyclohexane and other solvents, however, produce swelling of the polyethylene. The acceleration in the disappearance kinetics of nitrobenzene and phenylethanol from aqueous solutions stored in polyethylene containers with an external environment of hexane or carbon tetrachloride may therefore be attributed directly to their effects on the polyethylene which leads to a reduction in the barrier properties of the polyethylene.

Formulation variables

Since the polyethylene–water partition coefficient appears to be the predominant factor controlling the extent of loss due to sorption and permeation it follows that the extent of the loss may be reduced by appropriate formulation alterations. Fig. 6 shows the effect of adding the non-ionic surface active agent Tween 80 to aqueous solutions of nitrobenzene on the disappearance profile of that substance. In general, increased concentrations of the Tween reduce the extent of sorption (as reflected by the intercept) and permeation (as reflected by the slope) and therefore the overall extent of loss. The reduction in the loss can be directly attributed to the solubilization of the nitrobenzene by the Tween and the consequent decrease in the polyethylene–solution partition coefficient of the solute. Alteration of the solution polarity by the addition of a co-solvent can also diminish loss. In Fig. 7 it can be observed that the addition of glycerol will affect both the viscosity of the solution and the affinity of the solute for the polyethylene as indicated by its hexane–water partition coefficient. The reduction in the extent of the loss may be attributed to the alteration in the polarity of the solution rather than to any viscosity effects because equivalent viscosities produced by solutions of methyl cellulose have no effect on the extent of loss. The minimal effect of variation in the viscosity of the solution on the extent of the loss confirms the earlier suggestion that the rate-limiting barrier for loss of solutes of aqueous solutions on storage in polyethylene containers is the polyethylene wall alone and that the boundary layer exerts a negligible effect on the rates of sorption and permeation.

It could be anticipated that the extent of loss will also be dependent on the degree of

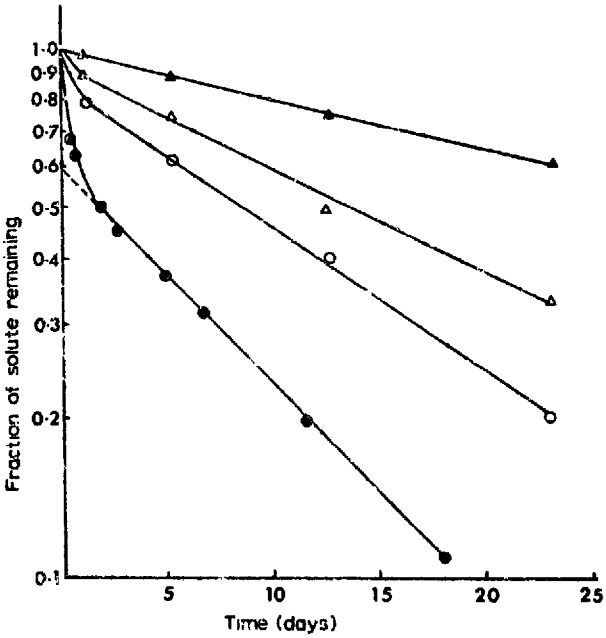


Fig. 6. Disappearance kinetics of nitrobenzene from aqueous solutions of Tween 80 in polyethylene containers (brand B) at 37 ± 1°C. Percentage (v/v) Tween 80 in aqueous solution: ●, 0; ○, 2; △, 4; ▲, 10.

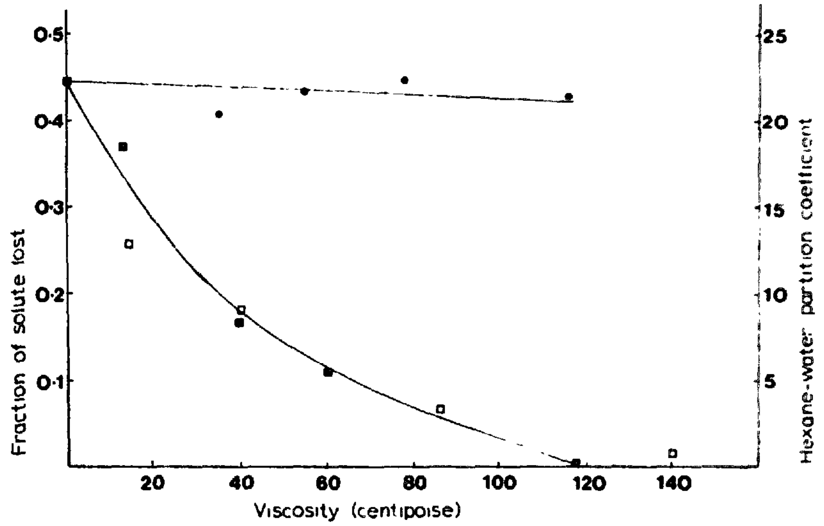


Fig. 7. Effect of the viscosity on the loss of nitrobenzene (0.05% w/v) from polyethylene containers (brand B) in 4 days at 37 ± 1°C. Open symbols, fraction of solute lost; closed symbols, hexane–water partition coefficient ▫ and ▪, glycerol; ○ and ●, methylcellulose.

ionization of the solute in solution. Fig. 8 shows that the extent of loss is greatest when the solute is present as the unionized moiety. For the acid 2-nitrophenol, loss is greatest below the pKa of 7.23 whereas for aniline which is a base, loss is greatest above the pKa of 4.58. Diminished ionization results in an increased affinity of the solute for the polyethylene and an increased loss.

McCarthy (1970) has reported losses from aqueous solutions in polyethylene containers which indicate an initial rapid sorption process followed by a slower permeation process. These data also indicate that solutes having a high affinity for the polyethylene (as reflected by high literature hexane–water partition coefficients) show the most extensive loss. Although this study, a previous report (Polack et al., 1970) and other

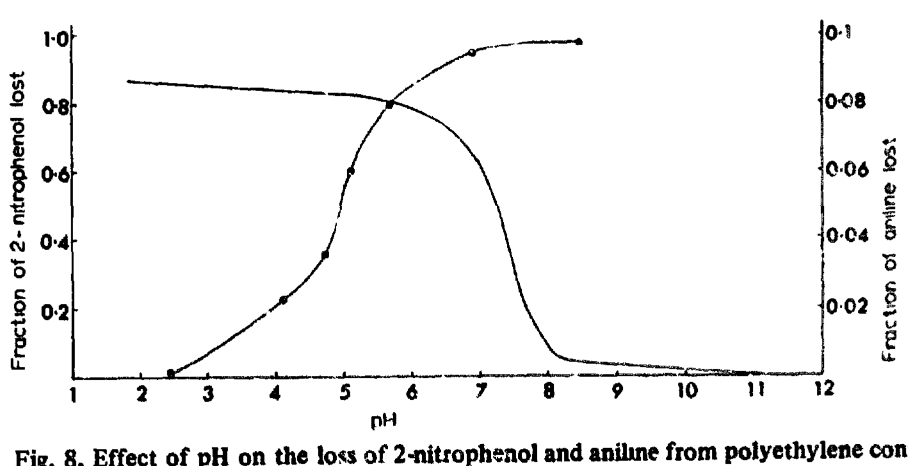


Fig. 8. Effect of pH on the loss of 2-nitrophenol and aniline from polyethylene contrainers (brand B) at 60 ± 1°C for 2 days and 25 ± 1°C for 19 days, respectively. ●, aniline; ○, 2-nitrophenol.

publications suggest that some solutes may be lost to a significant extent from polyethylene containers during either storage or autoclaving, polyethylene does have certain advantages as a container for packaging pharmaceuticals. It may in some instances prove to be the container of choice but in such cases it is important that the active ingredient(s) and the adjuncts should have little affinity for polyethylene. The characteristics which separate solutes having significant permeation rates through polyethylene with loss to the atmosphere from solutes with significant sorption into polyethylene but little loss to the atmosphere have yet to be ascertained. Current research in this laboratory is directed to this end.

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