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# Sorption of drugs by plastic infusion bags

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## Summary

The sorption of warfarin sodium, various benzodiazepines and a number of other drugs from aqueous solutions by polyvinyl chloride infusion bags was investigated. The sorption kinetics for warfarin and diazepam could be accounted for by a diffusional model in which the loss of drug is determined primarily by the diffusivity of the compound in the plastic matrix. The rate and extent of sorption of warfarin showed a dependence on pH which could be interpreted in terms of ionization of the drug, i.e. only the unionized form was sorbed. A rank order relationship was shown between the initial rate of uptake by the plastic bag and the hexane–water partition coefficients of the compounds. It is suggested that the latter parameter may be useful for the prediction of interactions between a drug substance and polyvinyl chloride infusion bags.

Sorption of the compounds by infusion bags made from polypropylene was insignificant except for the highly lipophilic medazepam and accordingly, such bags may be more safe to use than polyvinyl chloride bags in respect to drug sorption.

## Introduction

The use of plastic intravenous infusion bags in conjunction with plastic giving sets and in-line filters has become increasingly widespread in hospital practice. This may result, however, in a potential hazard because of loss of drug by sorption to the plastic material. Thus, recent studies have reported significant loss of nitroglycerin (Crouthamel et al., 1978; Sturek et al., 1978; Yuen et al., 1979; Baaske et al., 1980; Roberts et al., 1980; Christiansen et al., 1980; Mathot et al., 1980), diazepam (MacKichan et al., 1979; Parker et al., 1979; Parker and MacCara, 1980; Cloyd et al., 1980), insulin (Weisenfeld et al., 1968; Petty and Cunningham, 1974; Weber et

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al., 1977; Okamoto et al., 1979), chlormethiazole (Lingam et al., 1980; Tsuei et al., 1980), digitoxin (Butler et al., 1980) and vitamin A (Moorhatch and Chiou, 1974) from aqueous solutions stored in polyvinyl chloride infusion bags for various times or following infusion through intravenous giving sets. Detailed kinetic and mechanistic studies have been reported on the interaction of nitroglycerin with polyvinyl chloride bags. The kinetics of sorption of the drug could be described in terms of a diffusionally controlled absorption process, adsorption playing only a minor role in the overall loss of drug (Yuen et al., 1979; Roberts et al., 1980). Recently, a model describing the loss of nitroglycerin from the solution in the plastic bags as a rapid adsorption onto the plastic surface followed by partitioning into the plastic was proposed (Malick et al., 1981).

The purposes of this study were to define the kinetics and mechanism of the interaction between various drugs and plastic infusion bags and of developing criteria that may be used in the prediction of such interactions. To this end the sorption behaviour of warfarin sodium, various benzodiazepines and other drugs (including a number not being administered by intravenous infusion) with polyvinyl chloride infusion bags was examined from a kinetic approach. The sorption of some compounds by polypropylene infusion bags was also investigated.

## Materials and methods

*Materials and apparatus*

The drug substances studied were commerical products suitable for clinical use. Nitroglycerin was used in the form of a stock solution (10%) in ethanol. Buffer substances and all other chemicals or solvents used were of reagent grade. Plastic infusion bags (Viaflex®) of polyvinyl chloride (100 and 500 ml) were kindly provided by Travenol Laboratories and infusion bags of polypropylene (300 ml) were obtained from Haustrups Fabrikker, Denmark. The bags were filled with 0.9% sodium chloride in water. To study the influence of solvent on the sorption of the drugs the normal saline solution was removed from the bags and replaced by the appropriate solution.

A Spectronic 710 spectrophotometer and 1-cm quartz cells were used for the spectral measurements.

*Sorption studies*

Aliquots of stock solutions of the compounds in water or ethanol were added to the infusion bags. A number of different concentrations were used, all of them being below the saturation solubility of the solute. When ethanolic stock solutions were employed, the maximum concentration of ethanol in the final solution was 1%. The bags were stored at ambient temperature (20–24°C) and were kept upright to expose the maximum surface area of the bag to the solution and were not shaken during the period of study, except for gentle swirling of the contents immediately prior to removal of an aliquot for assay. The solute concentration in the samples withdrawn (0.5–2 ml) at regular intervals was determined spectrophotometrically at a suitable

wavelength; for nitroglycerin the kinetic assay of Yap et al. (1975) was used. Each sorption experiment was performed in duplicate and was found to be highly reproducible. To check the chemical stability of the drugs under the experimental conditions used control experiments were performed with glass infusion bottles containing similar solvents and solute concentrations as those used in the sorption study. In no cases was degradation observed.

*Determination of partition coefficients*

The apparent partition coefficients of the various compounds were determined in a hexane–water system. The aqueous phase was either pure water or an aqueous buffer solution. The solute concentration in the aqueous phase was measured spectrophotometrically as described above before and after partitioning with an appropriate volume of hexane. The two phases were previously saturated mutually with each other and each determination was performed in triplicate.

## Results and discussion

*Kinetics of sorption*

The disappearance of various drugs from aqueous solutions stored in 100 ml infusion bags of polyvinyl chloride (Viaflex) at 20–24°C was followed for 150–200 h or until an equilibrium was reached. Fig. 1 shows plots of the percentage amount of various benzodiazepines remaining in the plastic bag as a function of time. Similar

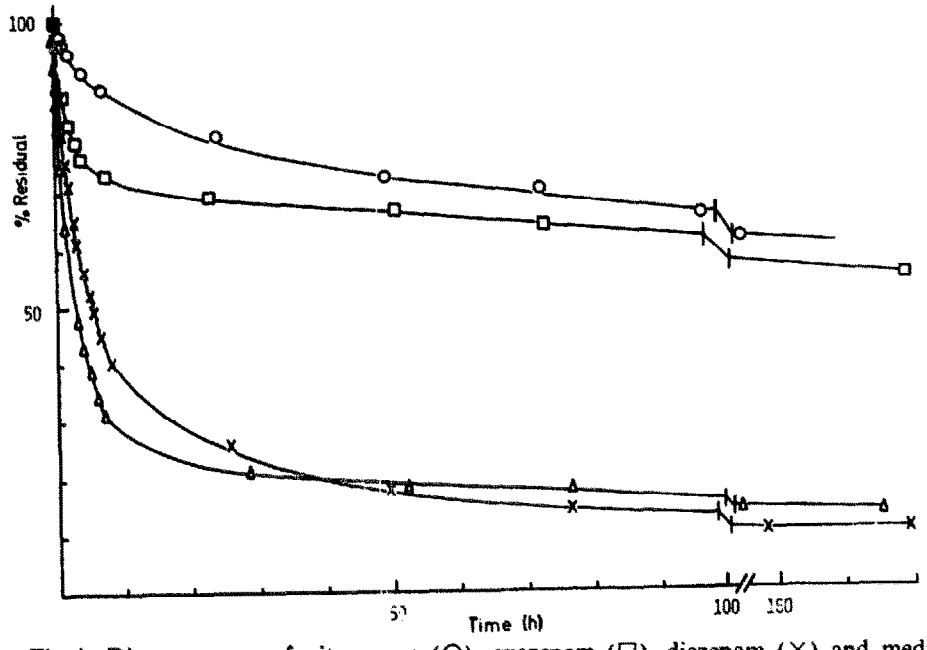


Fig. 1. Disappearance of nitrazepam (○), oxazepam (□), diazepam (×) and medazepam (△) from normal saline solutions (40 μg ml$^{-1}$ of benzodiazepine) stored in polyvinyl chloride infusion bags (100 ml) for various times at room temperature.

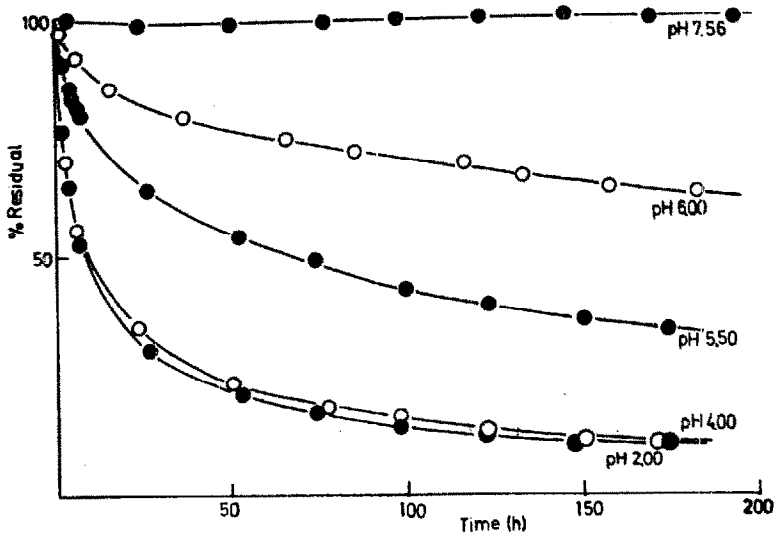


Fig. 2. Disappearance of warfarin sodium from various aqueous buffer solutions stored in polyvinyl chloride infusion bags (100 ml) for various times at room temperature.

plots are shown in Fig. 2 for warfarin sodium solutions of varying pH. The losses observed for these drugs as well as for a number of other drugs after storage for 8 h are listed in Table I. As is evident from the results the various compounds exhibited different sorption behaviour. Diazepam, medazepam and unionized warfarin showed the most rapid and extensive sorption while pentobarbital sodium and hydrocortisone acetate showed no significant uptake by the infusion bag. The loss found for

TABLE I

LOSSES OF DRUGS FROM NORMAL SALINE SOLUTIONS IN POLYVINYL CHLORIDE (PVC) BAGS STORED AT 22°C FOR 8 h

| Drug | Initial solute conc. (μg/ml) | % loss | |
|---|---|---|---|
| | | PVC (100 ml) | PVC (500 ml) |
| Diazepam | 40 | 60 | 31 |
| | 120 | 58 | 31 |
| Medazepam | 40 | 76 | – |
| Oxazepam | 40 | 22 | 12 |
| Nitrazepam | 40 | 15 | 10 |
| Warfarin sodium [a] | 20 | 49 | – |
| Warfarin sodium | 20 | 29 | – |
| Nitroglycerin | 200 | 54 | – |
| Thiopental sodium [b] | 30 | 25 | – |
| Pentobarbital sodium | 30 | 0 | 0 |
| Hydrocortisone acetate | 20 | 0 | 0 |

[a] At pH 2 and 4.
[b] At pH 4.0 and 7.2.

nitroglycerin (Table 1) is in accordance with previous findings at similar experimental conditions (Roberts et al., 1980).

The kinetics of disappearance of nitroglycerin from solutions stored in Viaflex bags has recently been described by a diffusion model (Roberts et al., 1980) as also having the kinetics of nitroglycerin loss from aqueous solutions to immersed strips of Viaflex bags (Yuen et al., 1979). To test the general application of this model the data derived for diazepam and warfarin (pH 2 and 4) were analyzed by the model. According to this, the fraction of drug remaining in solution ($F_t$) at various times (t) is given by Eqn. 1 (Crank, 1975):

$$\frac{F_t - F_\infty}{1 - F_\infty} = \sum_{n=1}^{\infty} \frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2 q_n^2} \exp\left(-q_n^2 Dt/\ell^2\right) \tag{1}$$

where D is the diffusion coefficient of solute in plastic of thickness $\ell$, $F_\infty$ is the equilibrium fraction of drug remaining in solution and $\alpha$ is the ratio of the final concentration to the total concentration drop in the aqueous solutions:

$$\alpha = \frac{F_\infty}{1 - F_\infty} \tag{2}$$

The values of $q_n$ are the non-zero positive roots of $\tan q_n = -\alpha q_n$ and can be obtained from published tables (Crank, 1975) for various $\alpha$ values.

Fig. 3 shows semilogarithmic plots of fraction of diazepam and warfarin remaining to be sorbed by the plastic bag versus time. As can be seen the plots become linear as time progresses which is due to the fact that at those times only the first q-term under the summation in Eqn. 1 is important. Hence, at such values of t Eqn. 1 is reduced to

$$\log \frac{F_t - F_\infty}{1 - F_\infty} = \log \frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2 q_1^2} - 0.4343\, q_1^2 \left(D/\ell^2\right) t \tag{3}$$

Thus, values of $D/\ell^2$ were calculated from the slope of the linear portion of the plots. Using these values (given in the figure legend) the entire solid curves in Fig. 3 were constructed on the basis of Eqn. 1. The good agreement observed between the experimental data and the calculated curves show that the diffusional model adequately describes the kinetics of sorption of the two drugs by the PVC bags.

These results along with similar findings for nitroglycerin (Yuen et al., 1979; Roberts et al., 1980) appear to indicate that the loss of drug substances from solutions stored in polyvinyl chloride bags is determined primarily by the diffusivity of drug in the plastic. Absorption rather than adsorption is the major process being responsible for the drug loss. The quantity of solute adsorbed on the plastic surface is likely to be small compared with the amount migrating into the plastic matrix and also, the rate of adsorption may be much faster than the rate of absorption, as has been shown for nitroglycerin (Sokoloski et al., 1980). Recently, Malick et al. (1981) proposed a new model for the sorption of nitroglycerin by polyvinyl chloride bags

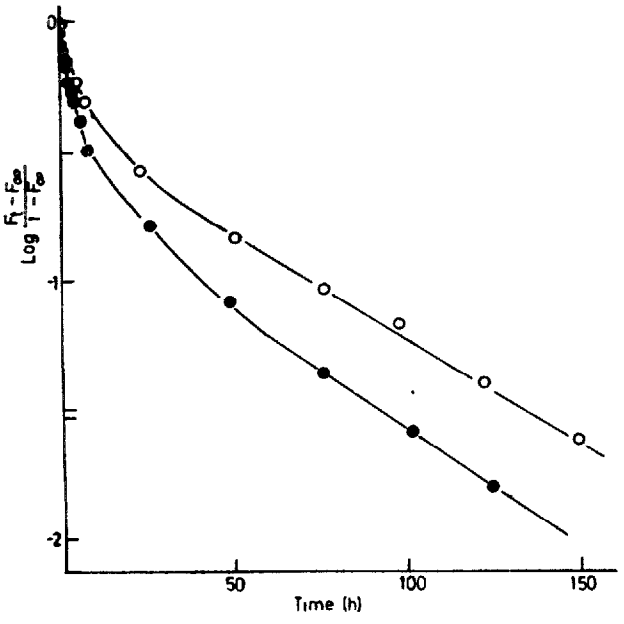


Fig. 3. Plots of the sorption data for diazepam (●) in normal saline solution and warfarin sodium (○) in acetate buffer solution of pH 4.0 according to Eqn. 3. The points are experimental data while the solid curves are constructed on basis of Eqn. 1 and values of $\alpha = 0.111$ and $D/\ell^2 = 0.0026\ h^{-1}$ for diazepam and $\alpha = 0.111$ and $D/\ell^2 = 0.0023\ h^{-1}$ for warfarin sodium.

consisting of both adsorption onto the surface of the plastic bag and a subsequent slower dissolution and migration of nitroglycerin into the plastic matrix. This model can be described in terms of a reaction scheme of the form $A \rightleftharpoons B \rightarrow C$ and it predicts a bi-exponential loss of drug with time. However, the diffusion model used above also requires a bi-exponential disappearance rate (cf. Fig. 3) and in fact, it appears that the kinetic data for the sorption are compatible with both models. Thus, it was found that the sorption kinetics of warfarin and diazepam could equally well be described by the adsorption-absorption model. In view of the minute amounts of nitroglycerin actually being adsorbed to polyvinyl chloride in comparison with the amounts absorbed (Yuen et al., 1979; Sokoloski et al., 1980) the diffusion model involving absorption as the dominant process appears to be the preferable model.

*Influence of concentration, pH and other variables*

The fractions of the benzodiazepines sorbed from normal saline solutions by Viaflex infusion bags (100 ml) were found to be independent of initial solute concentrations over the range 5–120 $\mu g\ ml^{-1}$. This is apparent from Fig. 4 showing sorption isotherms for the compounds. The amount of drug in the plastic bag was calculated from the difference between initial concentration and the concentration found at equilibrium in the aqueous phase. It was also shown that the rate of fractional uptake was independent of the initial drug concentration. Similar findings have been reported for nitroglycerin (Roberts et al., 1980), vitamin A and methohe-

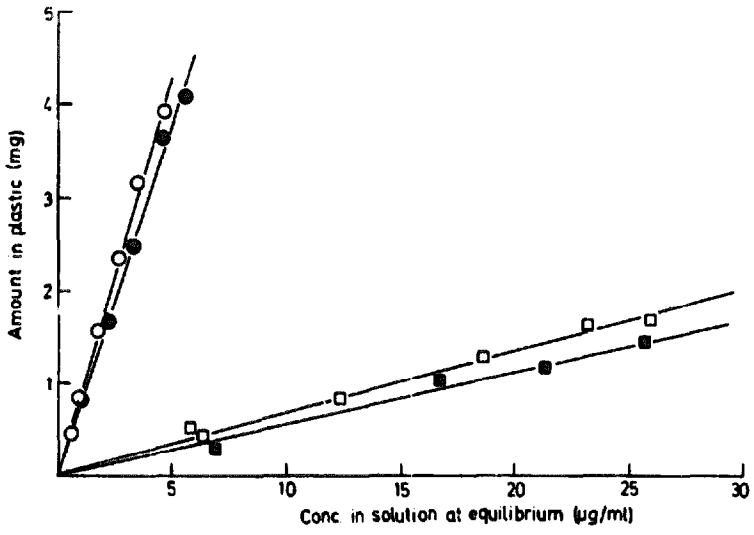


Fig. 4. Sorption isotherms for diazepam (○), medazepam (●), nitrazepam (□) and oxazepam (■) (normal saline solutions in 100-ml polyvinyl chloride infusion bags).

xital (Moorhatch and Chiou, 1974). Parker et al. (1979) have reported that the percentage loss of diazepam from Viaflex bags was a function of concentration, but their results are most likely a reflection of the different bag sizes used for the two concentrations studied (cf. Parker et al., 1980). Thus, it was found that a greater fractional uptake of diazepam occurred from 100-ml bags than from 500-ml bags (Table 1). The determining factor resulting in this difference is the surface area of plastic to volume of solution ratio and this ratio increases as the volume of solution in the bag is decreased. Other investigators (Roberts et al., 1979 and 1980) have reported similar results with other compounds.

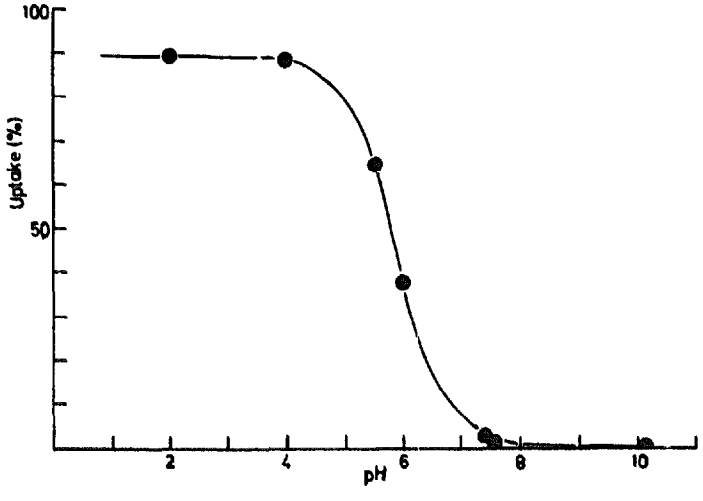


Fig. 5. The influence of pH on the percentage amount of warfarin absorbed by polyvinyl chloride infusion bags (100 ml) at equilibrium.

TABLE 2

OBSERVED AND PREDICTED EXTENT OF SORPTION AT EQUILIBRIUM OF WARFARIN SODIUM FROM NORMAL SALINE SOLUTIONS AS A FUNCTION OF INITIAL DRUG CONCENTRATION (100-ml PVC BAGS)

| Initial conc. of warfarin sodium (mg $ml^{-1}$) | pH of the solutions | Observed extent of sorption (%) | Predicted extent of sorption [a] (%) |
|---|---|---|---|
| 0.009 | 5.65 | 66 | 58 |
| 0.024 | 5.78 | 45 | 50 |
| 0.048 | 5.90 | 30 | 40 |
| 0.093 | 6.04 | 24 | 31 |
| 0.190 | 6.27 | 18 | 20 |
| 0.433 | 6.55 | 6 | 10 |
| 1.31 | 6.95 | 4 | 5 |

[a] Calculated from the measured pH and the sorption data in Fig. 5.

The linear sorption isotherms observed (Fig. 4) which belong to the so-called C-type partition isotherms (Giles et al., 1974) confirm the suggested mechanism involving absorptive loss of the drugs. The linearity of the isotherms indicate that the drugs penetrate into the plastic matrix since the availability of the interaction sites appears to remain constant and independent of the amount previously sorbed.

It has been reported (Moorhatch and Chiou, 1974) that the percentage loss of warfarin sodium to strips of Viaflex bags immersed in aqueous solutions increased with a decrease in initial concentration from 24 to 6 $\mu g\ ml^{-1}$. Using the whole infusion bag (100 ml) the present study similarly revealed a decreased percentage uptake with increased initial warfarin sodium concentration over the range 5 $\mu g\ ml^{-1}$–1.3 mg $ml^{-1}$ (Table 2). As discussed below this is due to a pH effect.

A major factor anticipating to influence the sorption of acidic or basic drugs is pH of the solution. The unionized drug species is of the form which will be most lipophilic and thus most favorably sorbed by the plastic and the relative amount of the unionized form is controlled by the solution pH and $pK_a$ of the drug. Thus, the sorption of aniline and 2-nitrophenol by polyethylene containers has been shown to be directly related to the relative concentration of unionized species (Roberts et al., 1979) and sorption of sorbic acid by plastic cellulose acetates (Saski, 1963) and of benzocaine by nylon 6 powder (Richardson and Meakin, 1974) have shown a similar dependency.

The effect of pH on sorption behaviour was investigated for warfarin which is a weak acid with a $pK_a$ of 5.1 (Hiskey et al., 1962). Fig. 2 shows that both the rate and extent of drug loss increase with decreasing pH, i.e. with diminishing extent of ionization of the drug. In Fig. 5 the fractional loss of warfarin at equilibrium is plotted against pH. The pH–sorption profile clearly indicates that it is the unionized form of the drug which is sorbed. The sorption of warfarin to strips of Viaflex bags has been reported to be greater from 5% dextrose solutions (pH 4.5) than from normal saline (Moorhatch and Chiou, 1974) and this difference may accordingly be

ascribed to the greater relative concentration of unionized drug species in the more acidic dextrose solution.

As previously noted the percentage loss of warfarin from solutions of the sodium salt in normal saline stored in 100-ml PVC bags decreased with increasing drug concentration (Table 2). This result can be fully explained on basis of the effect of pH on the sorption of warfarin. Normal saline possesses very weak buffer capacity and addition of warfarin sodium results in an increase in pH (Table 2) and hence in a decrease of the fraction of the sorbable unionized warfarin species. As seen from Table 2, the percentage loss observed from warfarin sodium solutions of different concentrations corresponds well with that predicted on basis of the pH–sorption relationship shown in Fig. 5.

Finally, the influence of a co-solvent such as propylene glycol on the sorption behaviour of diazepam was examined. It can be seen from Fig. 6 that both the rate and extent of sorption decreases from a solution containing 10% of propylene glycol as compared with normal saline solution. After 8 h the loss of diazepam was 60% from the latter solution and 40% from the solution with propylene glycol. The effect of the co-solvent may simply be interpreted by increased solubility of diazepam in the aqueous phase and hence a decreased affinity for the plastic bag, cf. Richardson and Meakin (1975). This was confirmed by the values of the partition coefficients for diazepam in hexane–water (log P 0.9) and hexane–water with 10% propylene glycol (log P 0.75).

*Sorption by polypropylene bags*

Nitroglycerin, diazepam, oxazepam, nitrazepam, warfarin (pH 2–7) and thiopental sodium all showed insignificant (< 3%) sorption from aqueous solutions stored for several days in 300-ml polypropylene infusion bags. Only the highly lipophilic

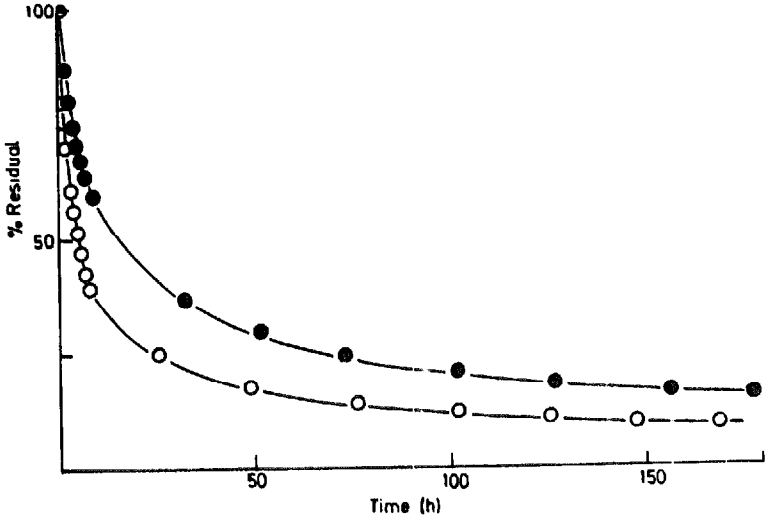


Fig. 6. Disappearance of diazepam from normal saline solutions with (●) and without (○) addition of 10% propylene glycol stored in polyvinyl chloride infusion bags (100 ml) for various times at room temperature.

medazepam was found to be sorbed, the loss being 42% after 8 h. These results show that the affinity of the drugs for polypropylene is much less than for polyvinyl chloride and that polypropylene infusion bags are more safe to use than the polyvinyl chloride bags in respect to drug sorption. It was previously reported that nitroglycerin also showed a greatly reduced sorption by polyolefin bags (Amann et al., 1980) and by polyethylene and polypropylene plastics (Pikal et al., 1977; Mathot et al., 1980). Similarly, insulin has shown a reduced sorption by polyolefin bags as compared with polyvinyl chloride bags (Hirsch et al., 1981).

Both polypropylene, polyethylene and polyolefin plastics are without plasticizers and it seems likely that the plasticizer present in polyvinyl chloride, di-2-ethylhexyl phthalate, is of main importance for the sorption of chemicals to polyvinyl chloride materials.

*Correlation of sorption behaviour with partition coefficients*

The compounds included in this study show vastly different sorption behaviours, ranging from highly sorbed substances like diazepam and medazepam to non-sorbed compounds such as hydrocortisone acetate. The main physicochemical determinant controlling sorption by the PVC infusion bag should be anticipated to be the PVC–water partition coefficient of the solute since this is a measure of the relative affinity of solute for the plastic. It has previously been reported that the rate of permeation of various chemicals from aqueous solutions through polyethylene membranes is directly related to the polyethylene–water partition coefficients (Serota et al., 1972; Nasim et al., 1972; Jordan and Polack, 1972) and that this also applies to rate of sorption by polyethylene of a number of various chemicals (Roberts et al., 1979; Polack et al., 1979). These studies further showed that the polyethylene–water partition coefficient of a solute may be directly related to its hexane–water partition coefficient.

Similar correlations appear to be valid for sorption of solutes to polyvinyl chloride bags. The apparent partition coefficients (K) of the compounds between the plastic bag and solution can be estimated by the following equation:

$$K = \frac{\rho V}{W_p \alpha} \tag{4}$$

where V is the volume of solution of density $\rho$ in contact with a given weight ($W_p$) of plastic (= 11 g for a 100-ml bag) and $\alpha$ is defined by Eqn. 2 and experimentally determined. Values of K for various drugs as calculated from Eqn. 4 are given in Table 3. Table 3 also contains experimentally determined hexane–water partition coefficients and octanol–water partition coefficients derived from the literature along with initial rates of drug sorption. The latter were calculated on basis of Eqn. 5:

$$\text{initial rate} = -\frac{d[A]}{dt} / [A]_0 \tag{5}$$

TABLE 3

SORPTION AND PARTITION DATA FOR VARIOUS COMPOUNDS [a]

| Compound | Initial rate of sorption ($h^{-1}$) | Extent of sorption at equilibrium (%) | log K | log P | |
|---|---|---|---|---|---|
| | | | | hexane/water | octanol/water |
| Medazepam | $51 \times 10^{-2}$ | 85 | 1.7 | 2.9 | 4.1 [b] |
| Diazepam | $27 \times 10^{-2}$ | 90 | 1.9 | 0.9 | 2.7 [b] |
| Warfarin (at pH 2–4) | $22 \times 10^{-2}$ | 90 | 1.9 | 0.2 | – |
| Nitroglycerin | $20 \times 10^{-2}$ | 83 | 1.6 | 0.2 | 2.2 [c] |
| Thiopental (at pH 4) | $6.0 \times 10^{-2}$ | 73 | 1.4 | 0.1 | 3.0 [d] |
| Oxazepam | $4.6 \times 10^{-2}$ | 46 | 0.9 | −0.1 | 2.2 [b] |
| Nitrazepam | $4.1 \times 10^{-2}$ | 47 | 0.9 | −0.1 | 2.1 [b] |
| Hydrocortisone acetate | 0 | 0 | – | −1.2 | 2.4 [e] |
| Pentobarbital (at pH 4) | 0 | 0 | – | −1.3 | 2.0 [d] |

[a] Sorption data refer to studies with 100-ml polyvinyl chloride bags.
[b] From Biagi et al. (1980).
[c] From Leo et al. (1971).
[d] From Hansch et al. (1968).
[e] This study.

where $[A]_0$ is the initial drug concentration in the aqueous solution and $-d[A]/dt$ is the initial decrease in solute concentration as determined from the initial slopes of drug loss vs time curves.

It is apparent from Table 3 that the rate of sorption of the compounds from aqueous solution by the PVC bags is related in rank order to their hexane–water partition coefficients. In contrast, the octanol–water partition system is less useful to predict the sorption behaviour; hexane being more lipophilic than octanol seems to be a better 'model' of the polyvinyl chloride matrix. The extent of uptake of solutes into the plastic bags which per definition is related to the plastic–water partition coefficient of the solute shows a rougher correlation with the hexane–water partition coefficient.

Although only a limited number of substances have been investigated, the results obtained indicate that the hexane–water partitioning behaviour of a drug may be a useful parameter for the prediction of interactions with polyvinyl chloride infusion bags.

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