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# Factors affecting the availability of organic nitrates from plastic infusion systems: structure of organic nitrate, nature of plastic and effect of temperature

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## Summary

The organic nitrate most recently introduced for clinical use (isosorbide-5-mononitrate) is not lost by sorption into the plastics of infusion systems. Other organic nitrates with 2 or 3 nitrate groups are lost by sorption into the plastic matrix of infusion systems at ambient temperature. At higher temperatures, evaporation of nitroglycerin and ethylene glycol dinitrate from the plastic to the atmosphere also contributes to the total loss of these compounds. The temperature-dependent sorption of all 3 organic nitrates by the plastic infusion bags is accounted for by changes in the diffusion coefficients of the organic nitrates in the plastic matrix, the plastic–water partition coefficients being independent of temperature. The extent of loss of the 3 organic nitrates corresponds to the rank order of their plastic (and organic solvent)–water partition coefficients i.e. nitroglycerin > isosorbide dinitrate > ethylene glycol dinitrate. It is suggested that the chloroform–water partition coefficient may be a useful parameter for the prediction of the interaction of a drug with polyvinyl chloride infusion systems.

## Introduction

It has recently been reported that isosorbide-5-mononitrate may be useful in the treatment of angina pectoris (Taylor et al., 1981). In two recent pharmacokinetic studies (Taylor et al., 1981; Abshagen et al., 1981) this compound has been

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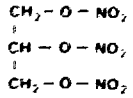
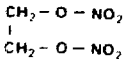
administered by intravenous infusion. The nature of the infusion systems used in these studies is not clear, nor is any indication of the stability of isosorbide-5-mononitrate in the infusion system presented. Other organic nitrates (nitroglycerin, isosorbide dinitrate), commonly infused for the same indication, have shown extensive interaction with polyvinyl chloride infusion systems (Cossum et al., 1978; Yuen et al., 1979; Roberts et al., 1980; Cossum and Roberts, 1981). It is possible to overcome this interaction by using an inert (polyolefin) infusion system (Cossum et al., 1978; Cossum and Roberts, 1981).

In the present study the dynamics of the interaction of isosorbide-5-mononitrate, nitroglycerin, isosorbide dinitrate, isosorbide-2-mononitrate and ethylene glycol dinitrate (Fig. 1) with the plastics of infusion systems have been compared. The relative contributions of the sorption of the drug by the plastic and escape of the sorbed drug from the external surface of the plastic to the environment to the overall loss of the organic nitrates from solutions stored in contact with polyvinyl chloride infusion bags has been examined. In addition, the partition coefficients of these organic nitrates between water and a number of organic solvents were determined in an attempt to find a useful solvent system for the prediction of the sorption of drugs by polyvinyl chloride infusion systems.

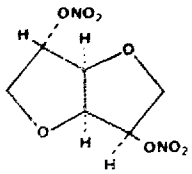
NITROGLYCERIN



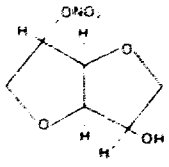
ETHYLENE GLYCOL DINITRATE



ISOSORBIDE DINITRATE



ISOSORBIDE 2-MONONITRATE



ISOSORBIDE 5-MONONITRATE

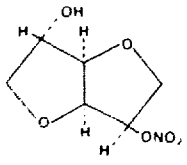


Fig. 1. Chemical structures of the organic nitrates.

## Materials and Methods

*Materials*

Stock solutions of nitroglycerin (5%) in ethanol were obtained from the Department of Manufacturing Industry, Melbourne. Isosorbide dinitrate (40%) on lactose (Schweiz, Sprengstoff-Fabrik) was purified by ether extraction of the powder and recrystallization from an ethanol/water mixture. Stock solutions of the pure isosorbide dinitrate were made up in absolute alcohol. Ethylene glycol dinitrate, as a 5% w/w solution in ethanol, was donated by I.C.I. Operations, Australia. Samples of isosorbide-2-mononitrate and isosorbide-5-mononitrate were donated by Ayerst Laboratories, Australia. Polyvinyl chloride infusion bags (Viaflex, containing 500 ml normal saline) and plastic infusion sets (Buretrol, Code AHC0132) were donated by Travenol Laboratories, Australia. All experiments in the present study were performed in duplicate.

*Storage of infusion bags and burette chambers*

A sufficient volume of the appropriate stock solution was added to each infusion bag of normal saline to obtain the following initial concentrations: nitroglycerin, 400 $\mu$g/ml; isosorbide dinitrate, 275 $\mu$g/ml; isosorbide-2-mononitrate, 150 $\mu$g/ml; isosorbide-5-mononitrate, 150 $\mu$g/ml; and ethylene glycol dinitrate, 500 $\mu$g/ml. The infusion bags were stored at various temperatures. Drug solutions were also stored in the cellulose propionate burette chambers of the plastic infusion sets at room temperature. Samples were taken from all solutions at various times during storage and assayed for drug content. Drug solutions were also stored in glass containers to act as controls.

*Sorption studies*

Strips of polyvinyl chloride ($1 \times 1$ cm) were cut from the unprinted side of an infusion bag and strips of cellulose proprionate ($1 \times 1$ cm) were cut from the unprinted areas of a burette chamber. Each strip was weighed before being immersed in 5 ml of aqueous drug solution. These solutions were stored in glass-stoppered 10 ml glass tubes at various temperatures. The tubes were shaken vigorously at regular intervals throughout the course of the experiments. Aliquots of solution were removed from the glass tubes and assayed for drug content at the beginning of an experiment and again at known intervals thereafter until equilibrium was reached.

*Permeation studies*

Nitroglycerin, isosorbide dinitrate and ethylene glycol dinitrate solutions were stored in a glass diffusion cell in contact with a sheet of polyvinyl chloride ($3.5 \times 3.5 \times 0.039$ cm) cut from the unprinted side of an infusion bag (Kowaluk et al., 1983). The sheet of polyvinyl chloride was held firmly across the cell opening using a metal clamp and either an annular or solid square sheet of stainless steel. The solid metal sheets were intended to prevent sorbed drug molecules leaving the plastic at the external surface while the annular rings were intended to permit the

passage of sorbed drug molecules to the external environment. Studies were carried out at 45 ± 1°C unless otherwise specified. Aliquots of the solution were removed at various times during storage and assayed for drug content.

*Partition coefficients*

A known volume of water was saturated with hexane, *n*-octanol or chloroform before adding a known concentration of organic nitrate. An aliquot of the organic nitrate solution was then added to an aliquot of the organic solvent, which had been saturated with water before use, in a stoppered glass container. The containers were stored at room temperature (20–24°C) and were shaken vigorously at regular intervals. Aliquots were removed from the aqueous phase periodically for analysis until equilibrium was reached. Octanol–water, hexane–water and chloroform–water partition coefficients were calculated as the ratio of the equilibrium concentration of each drug in the organic phase and in the aqueous phase. Polyvinyl chloride–water and cellulose propionate–water partition coefficients were determined using the results of the sorption studies. The partition coefficients were calculated as the ratio of equilibrium drug concentrations in the plastic and in the aqueous phase. The concentrations were calculated as weight of drug per weight of plastic or water (Yuen et al., 1979; Roberts et al., 1980; Cossum, 1981). Polyethylene–water partition coefficients were determined similarly, using finely cut-up 2-cm lengths of high density polyethylene tubing (Intramedic PE50, Clay Adams, NJ) (Cossum, 1981).

*Analysis*

A modified version of two previously reported high-performance liquid chromatographic methods for the analysis of nitroglycerin in aqueous solutions (Crouthamel and Dorsch, 1979; Baaske et al., 1979) was used for the analysis of nitroglycerin, isosorbide dinitrate, the isosorbide mononitrates and ethylene glycol dinitrate. In the present method, aliquots (20 μl) of the sample solutions were injected into a Waters Associates high-performance liquid chromatograph equipped with a Micro Bondapak C18 column (Waters). A mobile phase of water and methanol (60 : 40) was pumped at a flow rate of 2 ml/min. A Waters Model 450 variable wavelength detector set at 218 nm was used for quantitation. The retention times for ethylene glycol dinitrate, isosorbide dinitrate and nitroglycerin were 5.8, 7.0 and 9.5 min, respectively. Isosorbide-2-mononitrate and isosorbide-5-mononitrate both had retention times of 3.5 min. Standard curves were constructed with and without the use of an internal standard. For any given organic nitrate, one of the other di- or trinitrates was used as the reference compound. Two-hundred microlitres of the reference solution (500 μg/ml) was added to 1 ml of solution containing a known concentration of the organic nitrate and vortexed for 10 s before injecting a 20 μl aliquot onto the chromatograph. Plots of the ratio of peak heights of test and reference compounds against concentration of test drug were constructed. When a reference compound was not used the peak height of the test drug was plotted against test drug concentration. Standard curves constructed both with and without a reference compound were linear in the range 0–400 μg/ml and passed through the origin, and the coefficients of variation for the analysis of a given concentration ranged from

0.5% to 1.7% (n = 10) (Cossum, 1981). Because reproducibility studies showed that the assays were both accurate and precise, an internal standard was not routinely used.

## Results and Discussion

Fig. 2 shows that, in addition to the previously reported losses of nitroglycerin and isosorbide dinitrate (Yuen et al., 1979; McNiff et al., 1979; Roberts et al., 1980; Cossum and Roberts, 1981), ethylene glycol dinitrate is also lost from solutions stored in polyvinyl chloride infusion bags stored at various temperatures. These 3 organic nitrates are also lost from solutions stored in cellulose propionate burette chambers (Fig. 3). No loss of isosorbide-2-mononitrate or isosorbide-5-mononitrate from solutions stored in polyvinyl chloride infusion bags and cellulose propionate burette chambers at room temperature was observed in the present study.

The results of sorption studies were consistent with those of the storage studies.

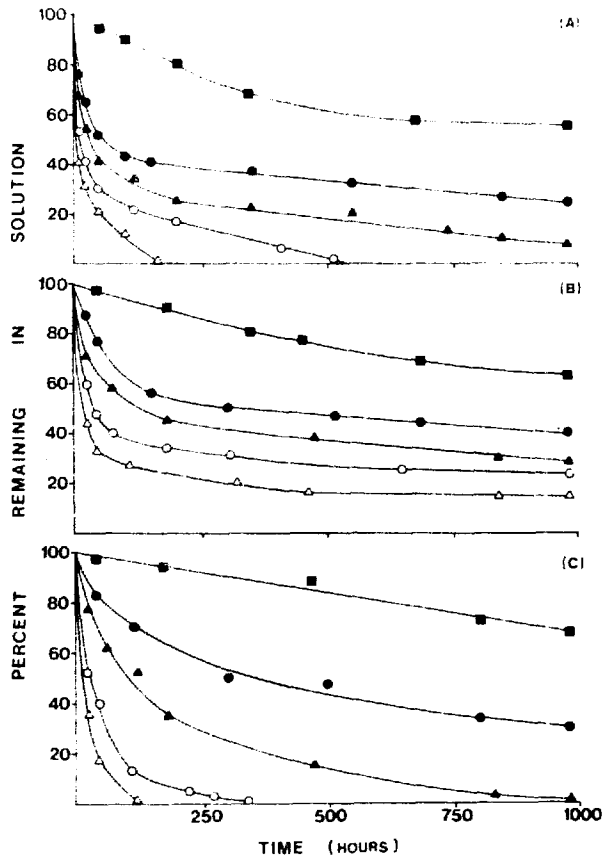



Fig. 2. Effect of temperature on the percentage of nitroglycerin (A), isosorbide dinitrate (B) and ethylene glycol dinitrate (C) remaining in solutions stored in polyvinyl chloride infusion bags. ■, 4°C; ●, room temperature (20–24°C); ▲, 37°C; ○, 45°C; △, 60°C.

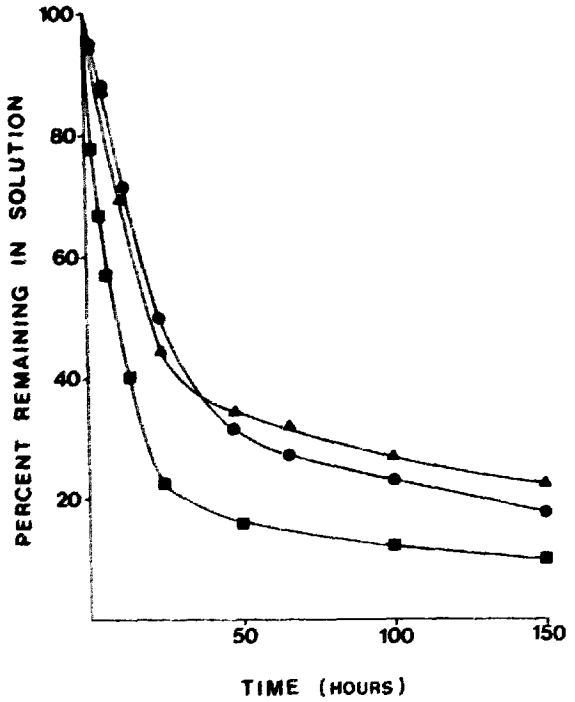



Fig. 3. Percentage of nitroglycerin (■), isosorbide dinitrate (●) and ethylene glycol dinitrate (▲) remaining in solutions stored in cellulose propionate burettes at room temperature (20–24°C).

Neither of the isosorbide mononitrates was lost from its solution when stored in contact with strips of polyvinyl chloride or cellulose propionate at room temperature (Table 1), nor at any of the other temperatures examined. However, the sorption studies revealed significant losses of nitroglycerin, isosorbide dinitrate and ethylene glycol dinitrate to strips of polyvinyl chloride and cellulose propionate at different temperatures (Figs. 4 and 5).

All of the organic nitrates studied showed negligible loss when stored as aqueous solutions in glass containers at the temperatures used. In addition, high-performance liquid chromatographs did not reveal the presence of any decomposition product in these aqueous solutions. The apparent stability of the organic nitrates in aqueous solutions under the conditions used (temperature to 60°C, storage times of 1000 h) is consistent with the data of Urbanski (1965). The loss of nitroglycerin, isosorbide dinitrate and ethylene glycol dinitrate during storage in polyvinyl chloride infusion bags and cellulose propionate burette chambers (Figs. 2 and 3) is therefore the result of sorption of these substances by the plastic. The complete disappearance of nitroglycerin and ethylene glycol dinitrate during storage in infusion bags at higher temperatures (Fig. 2) suggests that sorbed drug molecules may subsequently be leaving the plastic film at the external surface, that is, that permeation may also be contributing to drug loss. The increased loss of nitroglycerin at higher temperatures (Fig. 2A) is consistent with the results of McNiff et al. (1979) and Yuen et al. (1979).

TABLE 1

PLASTIC AND ORGANIC SOLVENT–WATER PARTITION COEFFICIENTS OF THE ORGANIC NITRATES AT AMBIENT TEMPERATURE (20–24°C)

| Organic nitrate | Partition coefficients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | polyvinyl [a] chloride–water | cellulose [c] propionate–water | polyethylene [e]–water | octanol–water | hexane–water | chloroform–water | cottonseed oil–water | corn oil–water |
| Nitroglycerin | 115.2 | 1118 | 0.3 | 41.8 | 2.1 | 93, 109 [f] | 115 [g] | 77 [h] |
| Isosorbide dinitrate | 38.7 | – [d] | < 0.3 | 20.6 | 1.4 | 50 | 41 [g] | 28 [h] |
| Isosorbide-2-mononitrate | N [b] | N | – | 0.4 | – | 1.1 | – | – |
| Isosorbide-5-mononitrate | N | N | – | 0.7 | – | 0.3 | – | – |
| Ethylene glycol dinitrate | 31.2 | 130 | < 0.3 | 14.6 | 1.3 | 28 | – | – |

[a] Cut from Travenol Viaflex 500 ml infusion bags.

[b] Negligible loss from aqueous solution was observed.

[c] Cut from the burette chamber of a Travenol Code AHC0132 Buretrol infusion set.

[d] Equilibrium not reached by 600 h.

[e] Intramedic PE50 polyethylene tubing.

[f] Florence and Atwood (1981).

[g] Needleman and Johnson (1975).

[h] Levy (1970).

TABLE 2

HALF-TIMES FOR SORPTION OF ORGANIC NITRATES BY PLASTIC STRIPS AT DIFFERENT TEMPERATURES

| | Half-time (h) | | | | | | | Activation energy (kcal/mol) |
|---|---|---|---|---|---|---|---|---|
| | 4°C | 10°C | 22°C | 30°C | 37°C | 45°C | 60°C | |
| *Polyvinyl chloride* | | | | | | | | |
| nitroglycerin | 61 | – | 13 | 3.2 [a] | 2 | 1.2 | 1 | 13.9 |
| isosorbide dinitrate | 100 | – | 14 | – | 6.5 | 4 | 2 | 12.1 |
| ethylene glycol dinitrate | 130 | – | 16 | – | 8.5 | 4.5 | 2.5 | 12.3 |
| *Cellulose propionate* | | | | | | | | |
| nitroglycerin | – | 48 | 24 | – | 11.5 | 7 | – | 10.1 |
| isosorbide dinitrate [b] | – | – | – | – | – | – | – | – |
| ethylene glycol dinitrate | – | 35 | 23 | – | 6 | 6 | – | 9.2 |

[a] Yuen et al. (1979).

[b] Equilibrium not reached by 600 h.

*Sorption at ambient temperature*

The dynamics of sorption of nitroglycerin by polyvinyl chloride infusion bag strips has been described by a diffusion model (Yuen et al., 1979; Roberts et al., 1980). According to this model the sorption of nitroglycerin is determined by its plastic–water partition coefficient and its diffusion coefficient in the plastic matrix. Table 1 shows the polyvinyl chloride–water partition coefficients of the organic nitrates at ambient temperature. The half-times for sorption, which are inversely related to the diffusion coefficients, are given in Table 2. At room temperature, both the polyvinyl chloride–water partition coefficients of the organic nitrates and their diffusion coefficients in the infusion bag plastic are in the rank order: nitroglycerin > isosorbide dinitrate > ethylene glycol dinitrate. Accordingly, at room temperature nitroglycerin shows the most extensive loss from solutions stored in plastic infusion bags (Fig. 2). Of the organic nitrates examined, nitroglycerin also has the greatest affinity for other types of plastics used in infusion systems (Tables 1 and 2; Fig. 3).

It is interesting to note that the nitroglycerin molecule has 3 nitrate groups, while isosorbide dinitrate and ethylene glycol dinitrate, which appear to have a lesser affinity for the plastics than nitroglycerin, have only two nitrate groups (Fig. 1). When one of the nitrate groups of isosorbide dinitrate is replaced by a hydroxyl

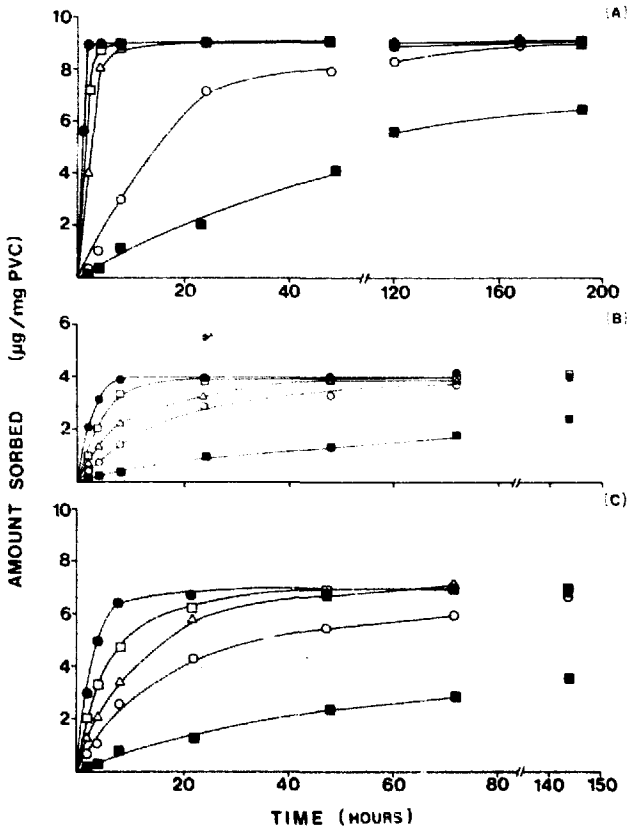



Fig. 4. Effect of temperature on sorption of nitroglycerin (A), isosorbide dinitrate (B) and ethylene glycol dinitrate (C) from aqueous solutions by polyvinyl chloride infusion bag strips at: ■, 4°C; ○, room temperature (20–24°C); △, 37°C; □, 45°C; ●, 60°C.

group to give isosorbide-5-mononitrate or isosorbide-2-mononitrate (Fig. 1), the molecule does not appear to be sorbed by the plastics at all. Diamond and Wright (1969) have suggested that selectivity in non-electrolyte partitioning and permeation is dominated by differences in solute–water forces, since the differences in these strong forces largely swamp the differences in the weaker solute–lipid (plastic) forces. Thus it is suggested by those authors that explanations for differences in the affinity of solutes for membranes may be found by considering the interaction of the solute with the aqueous phase, and particularly its ability to form hydrogen bonds. For the organic nitrates, substitution of the $-NO_2$ group by the $-OH$ group may increase the ability of the molecule to form hydrogen bonds in the aqueous phase, thereby increasing its affinity for the water and reducing its sorption by the plastic (Diamond and Wright, 1969).

The organic nitrate partition coefficients between water and all plastics/organic solvents used were in the same rank order: nitroglycerin > isosorbide dinitrate > ethylene glycol dinitrate > isosorbide mononitrates (Table 1). The organic solvents showing organic nitrate partition coefficients in closest agreement with polyvinyl chloride were cottonseed oil and chloroform. As chloroform and polyvinyl chloride are both halogenated hydrocarbons, the chloroform–water partition coefficient may be a useful parameter for the prediction of interactions with polyvinyl chloride infusion bags. None of the organic solvent–water partition coefficients determined showed agreement with the cellulose propionate–water partition coefficient. The polyethylene–water partition coefficients of the organic nitrates appear to be closely paralleled by the hexane–water partition coefficient, consistent with earlier studies (Jordan and Polack, 1972; Serota et al., 1972; Roberts et al., 1979; Polack et al., 1979).

*Effect of temperature on sorption*

For all the organic nitrates, the polyvinyl chloride–water and cellulose propionate–water partition coefficients appear to be independent of temperature (Figs. 4 and 5). The half-time for sorption of the organic nitrates by the polyvinyl chloride and by the cellulose propionate decreased with increasing temperature (Table 2). Since the diffusion coefficient is inversely related to the half-time for sorption (Crank, 1975), it is apparent that the variation in the rate of sorption of each of the organic nitrates with temperature (Figs. 4 and 5) is a result of the temperature dependence of the diffusion coefficients of the organic nitrates in the plastic.

Table 2 gives the activation energies for diffusion of the organic nitrates in the polyvinyl chloride and the cellulose propionate, determined using the Arrhenius relationship (Autian, 1971; Yuen et al., 1979). The Student's *t*-test was used to test whether the slopes of the lines describing the relationship between log D and (1/T) for the organic nitrates, where D is the diffusion coefficient and T is the absolute temperature, differed significantly. The slopes and hence the activation energies for diffusion were found not to be statistically significantly different. Autian (1971) suggested that the activation energy for diffusion of solutes in plastic corresponds to the energy required to move the polymer chains apart sufficiently to create a "hole" and the energy required to move the diffusing molecule into the "hole". The

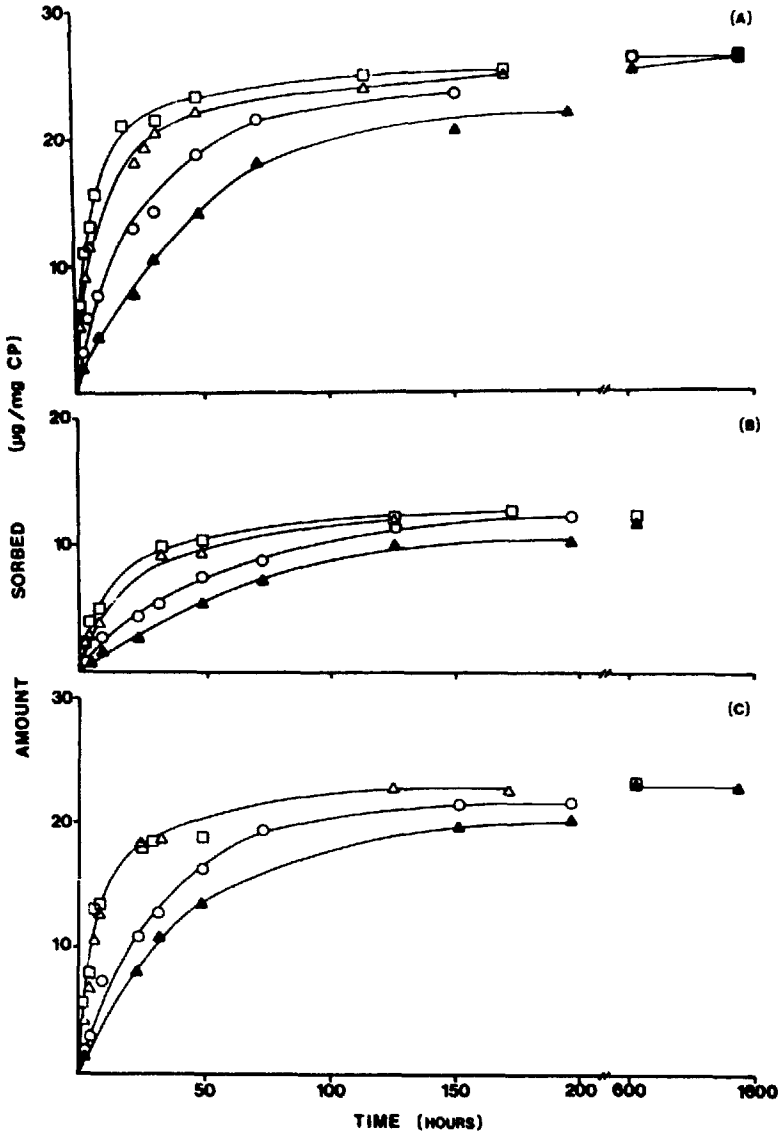



Fig. 5. Effect of temperature on sorption of nitroglycerin (A), isosorbide dinitrate (B) and ethylene glycol dinitrate (C) from aqueous solutions by cellulose propionate strips at: ▲, 10°C; ○, room temperature (20–24°C); △, 37°C; □, 45°C.

similarity of the activation energies of the 3 organic nitrates is consistent with the hypothesis (Autian, 1971) that the energy required for diffusion of the molecules in polyvinyl chloride is supplied mainly by the kinetic energy of the polymer chains and to a lesser degree by the kinetic energy of the diffusing molecule. The increase in the diffusion coefficients of the organic nitrates at higher temperatures probably reflects an increase in the kinetic energy of the basic polymer units of the polyvinyl chloride matrix and changes in the free volume of the plastic matrix with temperature.

The plastic–water partition coefficient (K) can be related to the thermodynamic

parameters in the partition process by (Diamond and Wright, 1969; Roberts et al., 1977);

$$\log K = \frac{-\Delta H^\circ}{2.303RT} + \frac{\Delta S^\circ}{2.303R} \quad (1)$$

where $\Delta H^\circ$ and $\Delta S^\circ$ are the standard enthalpy and entropy changes of partition respectively, R is the gas constant and T is the temperature. Since the polyvinyl chloride–water and cellulose propionate–water partition coefficients of the organic nitrates are independent of temperature (Figs. 4 and 5) the standard enthalpy of transfer is zero, implying an entropy-controlled partitioning process (Roberts et al., 1977). The positive entropy change probably reflects the movement of the organic nitrate molecules from the relatively ordered aqueous environment to the more random environment of the polymer matrix.

*Permeation*

It was noted earlier that some of the sorbed drug molecules may subsequently escape from the plastic film at the external surface, and that this permeation of the drug through the plastic may be responsible for the complete loss of nitroglycerin and ethylene glycol dinitrate from solutions stored in plastic infusion bags at higher temperatures (Fig. 2). The ability of the organic nitrates to permeate the plastic sheet was tested in the present study using an apparatus in which the internal surface of the plastic was exposed to drug solution and the external plastic surface was either covered or uncovered. In this way sorbed drug molecules were either prevented from, or permitted to escape from the external plastic surface to the atmosphere.

Fig. 6 shows that, at ambient temperature, the rate and extent of nitroglycerin loss from solutions stored in contact with the covered and uncovered plastic sheets was similar suggesting that none of the sorbed nitroglycerin is leaving the plastic at the external surface. This finding is consistent with the recovery experiments of McNiff et al. (1979). There is also no apparent difference in the rate and extent of isosorbide dinitrate loss from solutions stored in contact with covered and uncovered

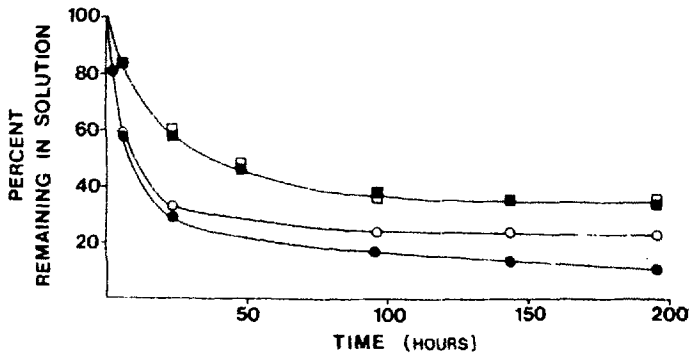



Fig. 6. Percentage of nitroglycerin remaining in solutions stored in diffusion cells in contact with sheets of polyvinyl chloride exposed to the atmosphere (closed symbols) and closed to the atmosphere (open symbols): □, room temperature (20–24°C); ○, 45°C.

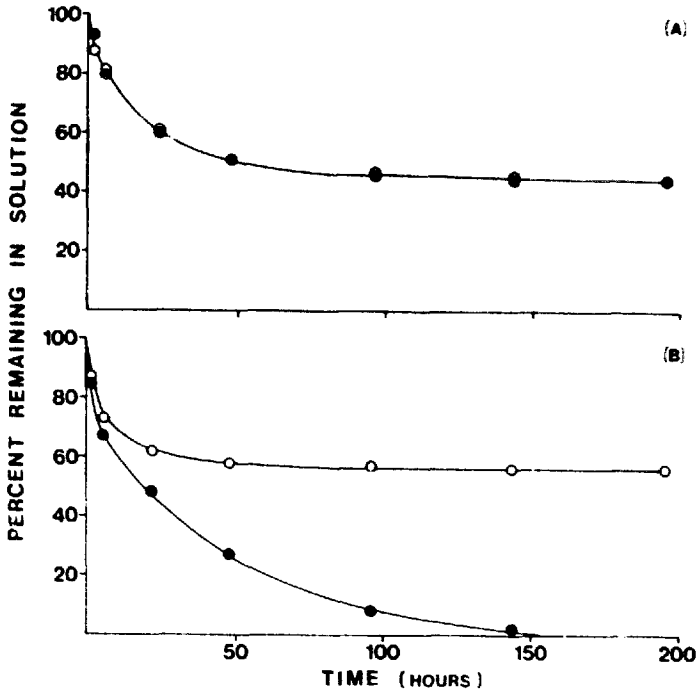



Fig. 7. Percentage of isosorbide dinitrate (A) and ethylene glycol dinitrate (B) remaining in solutions stored in diffusion cells in contact with sheets of polyvinyl chloride exposed to the atmosphere (closed symbols) and closed to the atmosphere (open symbols) at 45°C.

polyvinyl chloride sheets at 45°C (Fig. 7A). However, the rate and extent of loss of nitroglycerin and ethylene glycol dinitrate at 45°C varied according to the presence or absence of the metal barrier at the external plastic surface (Figs. 6 and 7B). When drug molecules were prevented from escaping to the external environment by the metal barrier an equilibrium concentration of drug in the solution was approached as might be expected when drug loss is due solely to sorption by the plastic matrix. However, in the absence of the metal barrier the nitroglycerin and ethylene glycol dinitrate loss from solution was greater and complete loss of ethylene glycol dinitrate from solution was observed (Fig. 7B). It is apparent that the accelerated loss of nitroglycerin and ethylene glycol dinitrate from their solutions stored in bags at the higher temps (Fig. 2) is not solely the result of an increase in the rate of diffusion of the drug in the plastic matrix, but also partially results from the fact that the sorbed drug molecules are escaping from the external plastic surface to the environment.

## Conclusion

The results of the present study indicate that, unlike nitroglycerin and isosorbide dinitrate, isosorbide-5-mononitrate can be safely administered using a polyvinyl chloride/cellulose propionate infusion system. Neither isosorbide-5-mononitrate nor isosorbide-2-mononitrate are lost from solutions stored in contact with the plastics of the infusion system.

The rate and extent of loss of nitroglycerin, isosorbide dinitrate and ethylene glycol dinitrate from aqueous solutions to the plastics of intravenous delivery systems depends on the partitioning of the substance between the plastic and aqueous phases, its diffusion in the plastic matrix and subsequent escape from the external surface of the plastic to the atmosphere. Although the partitioning process is unaffected by temperature, both the rate of diffusion and the escape of sorbed molecules to the external environment increase with increasing temperature. The greater rate and extent of loss of the organic nitrates at higher temperatures is due in part to the increased diffusivity of the organic nitrates in the polyvinyl chloride matrix. For nitroglycerin and ethylene glycol dinitrate, the escape of sorbed drug molecules from the external surface of the plastic also contributes to the increased and, in some cases, complete loss at higher temperatures.

Both the plastic–water (and organic solvent–water) partition coefficients and the diffusion coefficients of the organic nitrates examined are in the same rank order, and seem to be related to the molecular structures. It appears from the present work that the chloroform–water partition coefficients may be useful for the prediction of drug sorption by polyvinyl chloride infusion systems; however, the effect of the structural differences between molecules on their diffusion and partition coefficients must be examined before a reliable predictive procedure for loss can be developed.

## Acknowledgement

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