Dynamics of Clomethiazole Edisylate Interaction with Plastic Infusion Systems

ELIZABETH A. KOWALUK ˣ, MICHAEL S. ROBERTS and ALAN E. POLACK

Received March 29, 1982, from the *School of Pharmacy, University of Tasmania, G.P.O. Box 252C, Hobart, Tasmania, 7001 Australia.* Accepted for publication November 22, 1982.

Abstract □ The dynamics of the interaction of clomethiazole edisylate (I) with polyvinyl chloride and cellulose propionate, the main plastics used in the manufacture of infusion bags and sets, was examined. An experimental system in which the plastic was either open or closed to the environment was used to determine the relative contribution of the sorption and permeation processes to loss from solutions of clomethiazole edisylate (I) in contact with the plastic infusion systems. Sorption by the plastic infusion materials accounted for most of the drug loss, while permeation into the external environment accounted for the remainder. The sorption and permeation into and through polyvinyl chloride was temperature dependent. The diffusion coefficient and permeation rate constant both increased with temperature, while the polyvinyl chloride–water partition coefficients were independent of temperature. The activation energy for the diffusion in polyvinyl chloride was 13.5 kcal/mol. The permeability of the infusion bag plastic and the evaporation across an unstirred air boundary layer adjacent to the external surface of the plastic both appeared to contribute to the overall diffusional resistance encountered in the permeation process. The plastic–water partition coefficients are independent of initial concentration, suggesting that the concentration-dependent loss of the drug from solutions stored in plastic infusion bags and burets is a result of the greater diffusivity of the drug in the plastic at the higher initial concentrations. Plasticization of the polymers by the drug is indicated by the increase in the diffusivity of the drug in polyvinyl chloride and cellulose propionate, the increase in the rate and extent of sorption of a radiolabeled marker (diazepam) by the plastic, and the decreased stiffness of polyvinyl chloride exposed to higher concentrations of the drug.

Keyphrases □ Clomethiazole edisylate—dynamics of interaction with plastic infusion systems, polyvinyl chloride, cellulose propionate □ Infusion systems, plastic—dynamics of clomethiazole edisylate interaction, polyvinyl chloride, cellulose propionate □ Polyvinyl chloride—dynamics of clomethiazole edisylate interaction with plastic infusion systems, cellulose propionate □ Cellulose propionate—dynamics of clomethiazole edisylate interaction with plastic infusion systems, polyvinyl chloride

Clomethiazole edisylate (I), a sedative and hypnotic with anticonvulsant properties (1), has been administered by intravenous infusion in the treatment of delirium tremors (1), pre-eclampsia, and eclampsia (2, 3) and to control status epilepticus (4, 5). Infusions of I have also been used for sedation of patients having surgery under epidural anesthesia (6) or receiving artificial ventilation of the lungs during intensive care (7).

During the course of recent investigations it was observed that the drug was lost from solutions stored in plastic infusion bags and during infusion through plastic administration sets. The loss was attributed to sorption and possibly permeation of the drug through the plastic components of the intravenous delivery systems (8, 9). Tsuei and coworkers (10) have also reported sorption of I by plastic infusion sets and have suggested that I is lost from the infusion set to the atmosphere. The present work reports on the relative contribution of sorption and permeation to the loss of I from solutions stored in polyvinyl chloride infusion bags and cellulose propionate buret chambers. The kinetics and thermodynamics of the sorption process are also examined, as are the kinetics of the permeation process.

Lingham *et al.* (11) have noted that "intravenous clomethiazole reacts with the plastic giving sets and may soften the burette." Softening of polyvinyl chloride infusion bags after contact with solutions has also been observed (8). It was suggested that this may be due to the ability of the drug to plasticize or swell the polyvinyl chloride resin. This hypothesis was investigated in the present work by monitoring the rate and extent of sorption of a radiolabeled marker substance (diazepam) by infusion bags and burets in the presence of varying concentrations of I. In addition, the softening of polyvinyl chloride on exposure to solutions of clomethiazole edisylate (I) was measured using tensile creep tests.

EXPERIMENTAL

Materials—Solutions of clomethiazole edisylate (I) were prepared by diluting I infusion solution[1] (0.8%) with 4% dextrose solution. The pH of each solution was measured[2] and found to be the same as that of the undiluted infusion solution (pH 5.8 ± 0.1). The storage studies were conducted using polyvinyl chloride infusion bags[3] and the cellulose

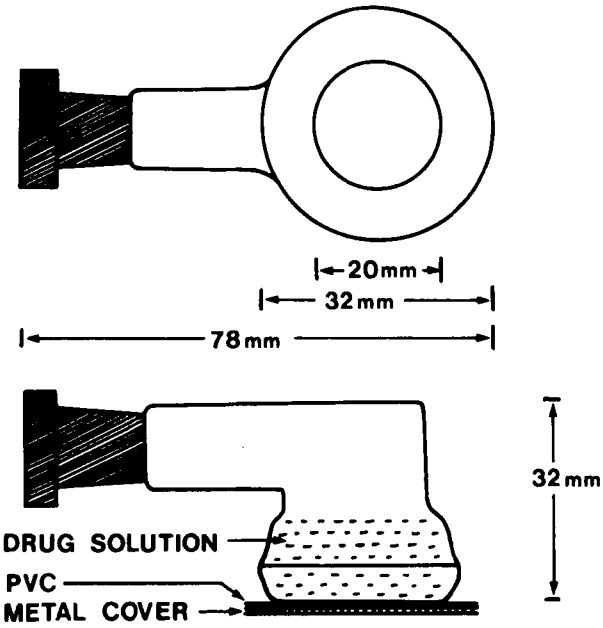

Figure 1—*Diagrammatic representation of the diffusion cell used in permeation studies. The plastic sheet (PVC) is held between the drug solution and the annular (open diffusion cell) or solid square (closed diffusion cell) metal cover by a metal clamp. The cells were stored resting on a wire gauze in the position shown in the lower diagram.*

[1] Heminevrin, batch FL1911 lot D106; Astra Pharmaceuticals, Sodertalje, Sweden.
[2] Metrohm Hensau E520 pH meter.
[3] Viaflex (polyvinyl chloride), code AHB8098 empty container, 500 mL, batch R39NO; Travenol Laboratories, Old Toongabbie, NSW, Australia, 2146.

0022-3549/84/0100-0043$01.00/0
© 1984, American Pharmaceutical Association

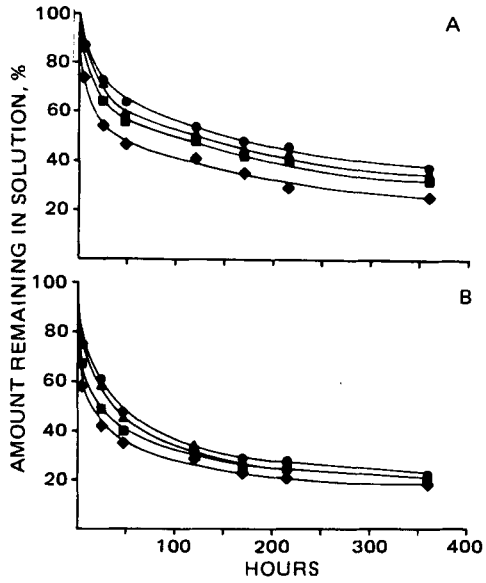

Figure 2—*Percentage of I remaining in solutions stored in polyvinyl chloride infusion bags (A) and cellulose propionate buret chambers (B). Initial I concentration: (●) 0.2%; (▲) 0.4%; (■) 0.6%; (◆) 0.8%.*

propionate buret chambers of the infusion sets[4]. The buret chambers were separated from the infusion tubing, and the outlet of each chamber was closed using a metal screw clamp. Where strips or sheets of polyvinyl chloride or cellulose propionate were required, these were cut from the unprinted areas of the infusion bags and buret chambers. The polyvinyl chloride tubing used for permeation studies was cut from an infusion set[4]. All experiments in the present study were performed in duplicate.

Storage Studies—Loss of clomethiazole edisylate (I) and the effect of this drug on the loss of the radiolabeled marker (diazepam) from solution during storage in plastic infusion bags and buret chambers were examined in the following manner. Each infusion bag and isolated buret chamber was filled with 500, and 150 mL, respectively, of I solution prepared at concentrations of 0.2, 0.4, 0.6, or 0.8%, or with diluent. In addition, each solution contained [methyl-^{3}H]diazepam[5] at a concentration of 1.8×10^{-8} mg/mL, 8.2×10^3 dpm/mL; 100 mL of each solution was stored in a glass container to act as a control. The infusion bags, buret chambers, and glass controls were stored in a controlled-temperature room at 20 ± 1°C. Aliquots of drug solution were removed from each container immediately after introduction of the solution and at regular intervals during storage, and assayed for I and diazepam content.

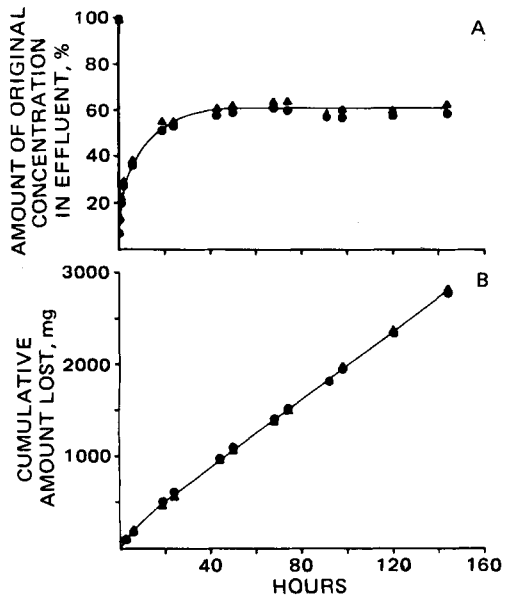

Figure 3—*Percentage of original I concentration in the effluent (A) and cumulative amount of I lost from solution (B) at various times during infusion through polyvinyl chloride tubing at a flow rate of 0.095 mL/min. Key: (●) infusion tubing only (open); (▲) infusion tubing encased by glass tubing (closed).*

[4] Code ACH0317 solution administration set, batch no. R39F8; Travenol Laboratories, Old Toongabbie, NSW, Australia.

[5] New England Nuclear, Boston, MA 02118.

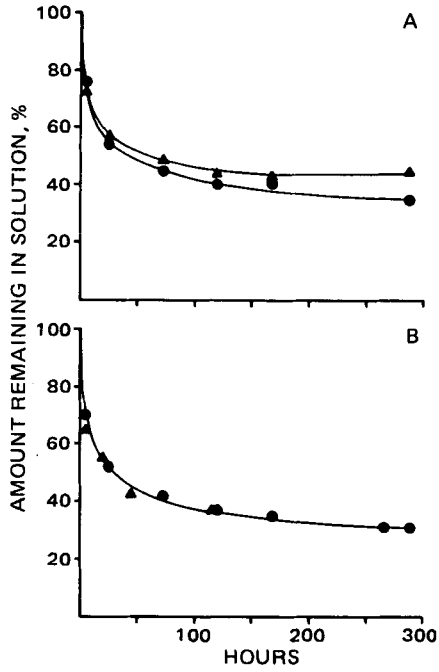

Figure 4—*Percentage of I remaining in solutions stored in open (●) and closed (▲) diffusion cells in contact with polyvinyl chloride (A) or cellulose propionate (B) sheets at 20°C.*

Permeation Studies—The permeation of clomethiazole edisylate (I) through polyvinyl chloride and cellulose propionate sheets was examined using the diffusion cell shown in Fig. 1. A sheet of polyvinyl chloride or cellulose propionate was held firmly in place across the cell opening by either an annular or solid square stainless steel sheet. In this way the plastic sheet was either open to the ambient environment, permitting transfer of molecules of I to the atmosphere, or closed, preventing such transfer. A volume of I infusion solution (4.4 mL) sufficient to result in the same surface area of plastic–volume ratio as in the infusion bags was stored in each diffusion cell at 4 ± 1°C, 10 ± 1°C, 20 ± 1°C, and 36 ± 1°C. Aliquots of solution were removed from the cells periodically during storage and assayed for clomethiazole edisylate content. Solutions were also stored in glass containers to act as controls.

Plastic–water partition coefficients were calculated as the ratio of the equilibrium concentration of the drug in the plastic and aqueous phases in the closed system. The concentrations were calculated as weight of drug per weight of water or plastic in contact with the solution.

Permeation of clomethiazole edisylate (I) through polyvinyl chloride tubing was examined using two 150-cm lengths of tubing—one encased tightly by glass tubing (closed), the other left exposed to the atmosphere (open). Infusion solution (0.8% of I) was infused[6] through the tubings at an average flow rate of 0.095 mL min for a period of 144 h. The effluent was collected over 10-min intervals at specified times for analysis.

Evaporation—The evaporation of I was examined at various temperatures by storing 9.8 mL of the 0.8% infusion solution in an open 25-mL glass beaker to give the same surface area of solution–volume ratio as in the infusion bags. The percentage of I remaining at various times was calculated by determining the drug concentration of the solution and correcting for water loss. Evaporation of water was monitored by weighing each beaker of solution at the time of assay. Evaporation rate constants were evaluated from the slopes of log percentage remaining *versus* time plots.

Tensile Properties—An experiment was designed to examine the stiffness of polyvinyl chloride strips exposed to solutions of clomethiazole edisylate (I). The stiffness of a plastic film can be assessed by examining its stress–strain curve. Because of the viscoelastic nature of plastics, stress–strain relationships are measured indirectly by tensile creep tests,

[6] Waters Associates M45 solvent delivery system.

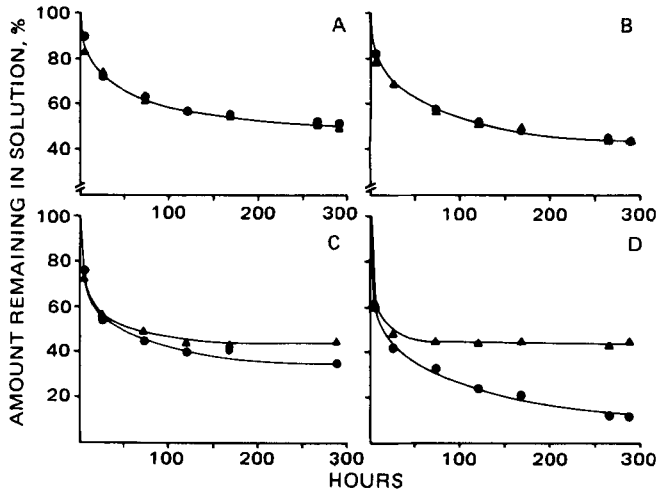

Figure 5—*Percentage of I remaining in solutions stored in open (●) and closed (▲) diffusion cells in contact with polyvinyl chloride sheets at 4°C (A), 10°C (B), 20°C (C), and 36°C (D).*

the results of which may be expressed in the form of strain–time curves at constant stress. Isochronous stress–strain curves can be plotted from the strain–time curves (12, 13). Strips of polyvinyl chloride (12.5 cm × 1 cm) were stored in I solution (0.2, 0.4, 0.6, and 0.8%) or in diluent in glass containers; after 9 d they were removed, rinsed lightly with distilled water, and allowed to dry. Each strip was suspended from a fixed clamp and loads of 517, 770, or 1020 g were applied to the end of the strip. The length of the strip was measured before and at regular intervals for at least 48 h after application of the load. Experiments were performed at room temperature (15–20°C).

Equilibrium Sorption Studies—Strips of polyvinyl chloride and cellulose propionate (1 × 1 cm) were stored in 5 mL of the drug solution (0.2, 0.4, 0.6, or 0.8%) in a glass container until equilibrium was reached (≤168 h). Plastic–water partition coefficients were calculated as the ratio of equilibrium concentrations of clomethiazole edisylate (I) in the plastic and the aqueous phases. The concentrations were calculated as weight of drug per weight of plastic or water.

Assay of Drug Solutions—Solutions of clomethiazole edisylate (I) were assayed spectrophotometrically[7]. Solutions were diluted 1:200 with distilled water, and the absorbance was measured at 257 nm. The absorbance of the infusion solutions was proportional to concentration of I over the concentration range studied. Solutions were analyzed for diazepam content by placing a 200-μL aqueous sample in a counting vial[8] together with 5 mL of scintillation cocktail[9] and determining the radioactivity by liquid scintillation counting[10].

RESULTS AND DISCUSSION

The loss of clomethiazole edisylate from aqueous solutions stored in polyvinyl chloride infusion bags and cellulose propionate buret chambers at 20°C is shown in Fig. 2. Extensive concentration-dependent losses are observed in both cases, confirming and extending previous reports (8, 9). It can be concluded, by comparing the losses found in this study with those previously observed (8, 9), that the loss of I was unaffected by the presence of trace amounts of radiolabeled diazepam. Significant I losses were also observed from solutions infused through polyvinyl chloride tubing (Fig. 3). Since the loss of I from solutions stored in glass for 400 h was negligible, it is reasonable to suggest that the loss of this drug during storage in plastic infusion bags and burets and during infusion through plastic tubing is the result of sorption of the drug by the plastic (and possibly its subsequent permeation into the atmosphere) (8–10). Sorption appears to be the predominant mechanism of the loss in all three cases (Figs. 3 and 4). Figure 4A shows that the loss is decreased, and eventually reaches equilibrium, when the polyvinyl chloride sheet is covered by metal. However, loss from solution in the open diffusion cell continued, suggesting that permeation also contributes to the loss from polyvinyl chloride infusion bags. No difference was observed in losses from solution

[7] Beckman DB-G grating spectrophotometer.
[8] Packard Minivial.
[9] Packard Insta-Gel Liquid scintillation cocktail.
[10] LKB Wallac RackBeta II Liquid scintillation counter.

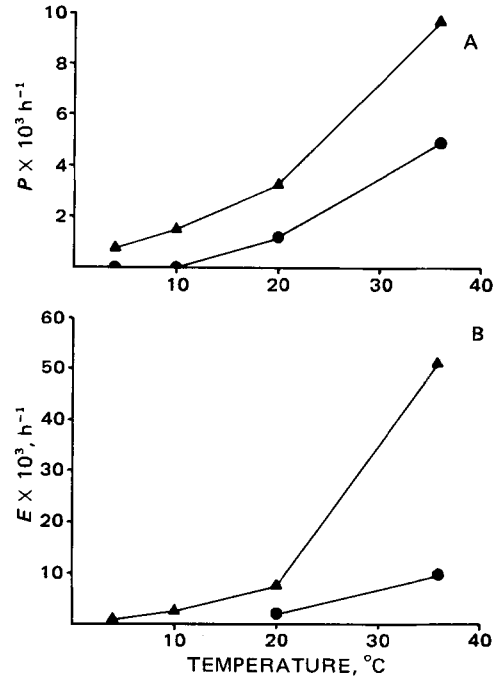

Figure 6—*(A) Rate constants for the permeation of I through polyvinyl chloride (P_{exp}) determined from open cell data (●) and membrane permeability rate constants (P_m) calculated by substituting D and K from closed cell data into Eq. 2 (▲). (B) Rate constants for the evaporation of I across the unstirred air boundary layer adjacent to the external surface of the polyvinyl chloride sheet in the open diffusion cell (●) and for the evaporation of I from aqueous solution (▲).*

in the open and closed infusion tubing (Fig. 3). However, the odor of I could be detected in the vicinity of the open tubing after the third day of infusion, suggesting that some permeation of I to the environment occurs. Permeation of I through cellulose propionate was not detected (Fig. 4B).

Kinetics of Sorption and Permeation—The sorption of clomethiazole edisylate (I) by polyvinyl chloride and cellulose propionate has been described previously as a diffusion-controlled process (8, 9). According to the diffusion model, the rate and extent of sorption is determined by the plastic–water partition coefficient of the solute and its diffusion

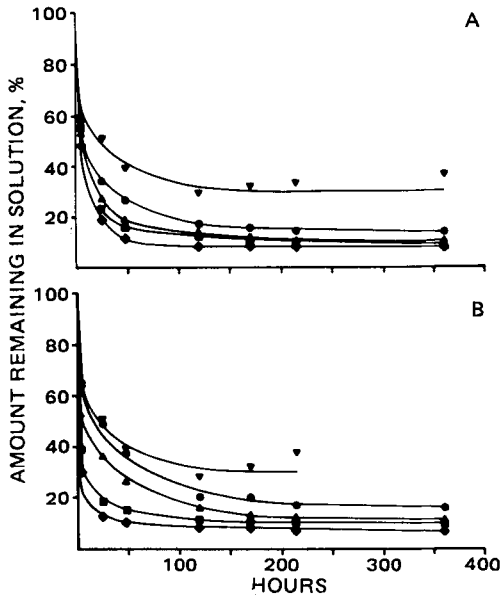

Figure 7—*Percentage of diazepam remaining in solutions containing different initial concentrations of I at various times during storage in polyvinyl chloride infusion bags (A) and cellulose propionate buret chambers (B). Key: (▼) diluent only; (●) 0.2%; (▲) 0.4%; (■) 0.6%; (◆) 0.8%.*

Table I—Diffusion Coefficients, Half-Times for Sorption, and Plastic–Water Partition Coefficients of I [a]

Temperature, °C	Apparent Diffusion Coefficient × 10^5, cm^2/h	$t_{1/2}$, h	Plastic–Water Partition Coefficient [b]
	Polyvinyl Chloride		
4	0.241	28	41
10	0.491	19	41
20	1.1	6.5	41
36	3.1	2	41
	Cellulose Propionate		
20	1.4	6.5	42

[a] Initial I concentration: 0.8%. [b] Determined from closed diffusion cell studies.

coefficient in the plastic. The fraction of the drug remaining in solution (F_t) at various times (t) is (14, 15):

$$\frac{F_t - F_\infty}{1 - F_\infty} = \sum_{n=1}^{\infty} \frac{2\alpha(1+\alpha)}{1 + \alpha + \alpha^2 q_n^2} \exp\left(-q_n^2 \frac{D_t}{l^2}\right) \qquad \text{(Eq. 1)}$$

where F_∞ is the fraction of I remaining in solution at equilibrium, $\alpha = F_\infty/(1 - F_\infty)$, q_n values are the nonzero positive roots of $\tan q = -\alpha q$, and D is the diffusion coefficient of solute in the plastic of thickness l. In the present work the diffusion coefficients of I in polyvinyl chloride and cellulose propionate were determined from plots of log $(F_t - F_\infty)$ *versus* time for the closed diffusion cell, using Eq. 1. In addition half-times for sorption were determined by inspection of disappearance profiles for the closed diffusion cell. These values and the plastic–water partition coefficients are shown in Table I.

The rate of sorption is temperature dependent, appearing to progress more rapidly at higher temperatures (Fig. 5). The half-time for sorption decreases and its diffusion coefficient increases with increasing temperature. In contrast, the plastic–water partition coefficients appear to be independent of temperature over the temperature range examined (Table I). The temperature dependence of the sorption process is, therefore, a result of the increased diffusivity in the polymer matrix, the equilibrium fractional uptake being unaffected by changes in temperature.

The permeation is also a temperature-dependent process. Figure 5 shows that while at the lower temperature permeation through polyvinyl chloride appears to be negligible, at 36°C a large percentage of the initial amount of the drug contained in the solution is lost by permeation to the atmosphere. Rate constants for the permeation process (P_{exp}) were determined from the slope of the terminal phase of log percentage I remaining in solution *versus* time plots for the open diffusion cell (Fig. 6A). It is apparent that the permeation process is more rapid at higher temperatures.

The membrane permeability rate constant (P_m) for I in polyvinyl chloride may be evaluated by substituting the values of the apparent diffusion coefficient (D) and the polyvinyl chloride–water partition coefficient (K) determined for the closed system (Table I) into the following (16):

$$P_m = \frac{DKA}{2.303Vl} \qquad \text{(Eq. 2)}$$

Table II—Plastic–Water Partition Coefficients of I at Different Initial Concentrations [a]

Concentration of I, %	Plastic–Water Partition Coefficient
Polyvinyl Chloride	
0.2	55
0.4	58
0.6	55
0.8	53
Cellulose Propionate	
0.2	80
0.4	71
0.6	77
0.8	77

[a] Determined using equilibrium sorption studies.

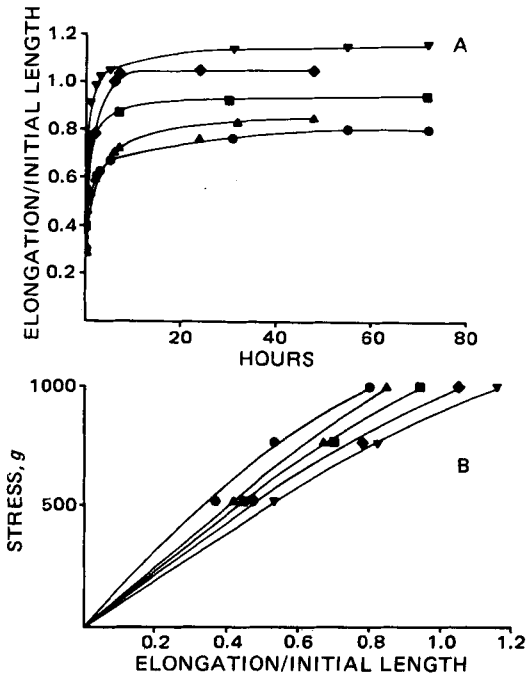

Figure 8—*Strain–time curves at a constant stress of 1020 g (A) and 48-h isochronous stress–strain curves (B) for polyvinyl chloride strips treated with I solutions of various initial concentrations. Key: (▲) 0.2%; (■) 0.4%; (◆) 0.6%; (▼) 0.8%; (●) diluent only.*

where V is the volume of I solution in contact with an area (A) of polyvinyl chloride of thickness l. The use of Eq. 2 in the present context assumes that the extent of plasticization in the open and closed systems is identical. P_m is related to the final observed permeation rate constant (P_{exp}) by (17, 18):

$$\frac{1}{P_{exp}} = \frac{1}{P_m} + \frac{1}{E} \qquad \text{(Eq. 3)}$$

where E represents the rate of evaporation of I across an unstirred air boundary layer adjacent to the external surface of the plastic in the open diffusion cell.

Figure 6A and B shows the individual rate constants at different temperatures. Values of E, calculated using Eq. 3, are of similar magnitude to the values of P_m, suggesting that the permeability of the infusion bag plastic and the evaporation of I across an unstirred air boundary layer contribute to a similar extent to the overall diffusional resistance encountered in the permeation process. Rate constants for the evaporation of I from aqueous solution at different temperatures are shown in Figure 6B. It is apparent that the evaporation of the drug from solution is faster than its evaporation from polyvinyl chloride, suggesting that I has a lower vapor pressure in the plastic than in water.

At a storage temperature of 20°C permeation is evident after 24 h (Fig. 5C). This lag time probably reflects the time required for the drug molecules to travel through the polyvinyl chloride film to its external surface. It can be seen from Fig. 5D that the lag time is much shorter at 36°C. This is consistent with increased diffusivity of I in the polyvinyl chloride at the higher temperature. The lag time for I in polyvinyl chloride tubing is apparently longer than in the infusion bag plastic, since no difference was observed in loss from the open and closed tubing during the 6 d of infusion (Fig. 3). The longer lag time is consistent with the greater thickness and density of the infusion tubing plastic compared with infusion bag plastic.

The results of this study suggest that the constant rate of I loss from solutions infused through a plastic administration set does not reflect loss of the drug to the atmosphere as suggested by Tsuei *et al.* (10), but that it results mainly from sorption. The constant rate of I sorption into the infusion tubing over 1–6 d (Fig. 3) is consistent with the plastic acting as a semi-infinite sink over this time. Kowaluk *et al.* (9) have reported that the sorption of a number of other drugs by plastic infusion tubing also shows a constant rate over a limited period and have described an equation relating the steady-state effluent concentrations of those drugs sorbed by tubing (in the period in which the plastic acts as a semi-infinite sink) to the infusion conditions.

Thermodynamics of Sorption—The plastic–water partition coeffi-

cient (K) can be related to the thermodynamic parameters in the partition process by (19, 20):

$$\log K = \frac{-\Delta H^0}{2.303RT} + \frac{\Delta S^0}{2.303R} \qquad \text{(Eq. 4)}$$

where ΔH^0 and ΔS^0 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 partition coefficient is independent of temperature (Table I), the standard enthalpy of transfer is zero, implying an entropy-controlled partition process (20). The positive entropy change associated with this process probably reflects movement of I molecules from the relatively ordered aqueous environment to the more random environment of the polymer matrix.

The diffusion of solute molecules through a polymeric field has been described as a series of jumps from one hole to another, the holes being formed by movements of the polymer chains (21, 22). The energy required to move the polymer chains apart sufficiently to create a hole and to move the diffusing molecule into this hole corresponds to the activation energy of diffusion. This energy is supplied by the kinetic energy of the polymer chains and of the diffusing molecule (22). The activation energy of diffusion for I in polyvinyl chloride, determined from the Arrhenius equation, has a value of 13.5 kcal/mol. This value is of the same order as that for the organic nitrates (23) and would be consistent with the hypothesis (22) that the energy required for diffusion of solute 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 diffusivity of I in the polyvinyl chloride with temperature probably reflects an increase in the kinetic energy of the polymer chains at higher temperatures (22).

Plasticization—It has previously been suggested that the concentration-dependent loss of I from solutions stored in plastic infusion bags and burets (Fig. 2) is the result of the plasticization process (8, 9). Plasticizer molecules insert themselves between the polymer chains, reducing the intermolecular forces between the polymer chains and generating additional free volume (22–26). Consequently, plasticizers accelerate the diffusive process (21) and produce greater flexibility and softness of the material (22).

It is apparent that the increased drug loss at higher concentrations cannot be attributed to a greater affinity of I for the drug-impregnated plastic, since the I–plastic–water partition coefficients are independent of initial drug concentration (Table II). Increased loss is probably due to greater diffusivity of I in the polymer matrix at higher drug concentrations, consistent with plasticization. The rate and extent of sorption of the marker substance (diazepam) by plastic infusion bags and buret chambers [a diffusion-controlled process (8, 9)] is enhanced by the presence of I in the infusion solutions (Fig. 7), further suggesting plasticization of the plastic matrix of bags and burets by the drug (17). Bray and Meakin (27) have shown that the sorption and permeation of benzocaine through polyvinyl chloride increased with increasing concentration of the plasticizers di-2-ethylhexylphthalate and tri-*n*-butyl citrate.

Figure 8 shows strain–time curves at constant stress and isochronous stress–strain curves (12, 13) for I-treated polyvinyl chloride strips. These curves are concentration dependent; the stiffness of the polyvinyl chloride decreases with increasing drug concentrations. These data confirm the previously reported softening and greater pliability of plastic infusion bags in the presence of the solutions (8) and provides further evidence for plasticization of polyvinyl chloride by clomethiazole edisylate (I).

The present study has shown that the loss of I from solutions stored in plastic infusion bags and buret chambers or infused through plastic tubing depends on (*a*) the partitioning of the drug between the plastic and aqueous phases, (*b*) the diffusion of I in the plastic matrix, (*c*) the evaporation of the drug across an unstirred air boundary layer, (*d*) the type of plastic, and (*e*) changes in the permeability characteristics of the plastic with drug concentration. Each of these processes must be taken into account in arriving at a predictive method for determining the extent of drug interactions with intravenous delivery systems.

As we know of no other drug which plasticizes polyvinyl chloride, it is not possible to define, using structure–activity relationships, the factors determining the ability of I to act as a plasticizer. However, the possibility that other drugs may plasticize polyvinyl chloride cannot be overlooked.

REFERENCES

(1) Astra Pharmaceuticals Pty. Ltd., Heminevrin package insert, Sodertalje, Sweden.

(2) J. Varma, *J. Obstet. Gynaecol. Br. Emp.*, **79,** 513 (1972).

(3) E. Tischler, *Aust. N.Z. J. Obstet. Gynaecol.*, **13,** 137 (1973).

(4) P. K. P. Harvey, T. W. Higenbottam, and L. Loh, *Br. Med. J.*, **2,** 603 (1975).

(5) G. Bentley and R. Mellick, *Med. J. Aust.*, **1,** 537 (1975).

(6) S. A. Schweitzer, *Anesth. Intens. Care (Berlin)*, **6,** 248 (1978).

(7) D. B. Scott, D. Beamish, I. N. Hudson, and G. G. Jostell, *Br. J. Anaesth.*, **52,** 541 (1980).

(8) E. A. Kowaluk, M. S. Roberts, H. D. Blackburn, and A. E. Polack, *Am. J. Hosp. Pharm.*, **38,** 1308 (1981).

(9) E. A. Kowaluk, M. S. Roberts, and A. E. Polack, *Am. J. Hosp. Pharm.*, **39,** 460 (1982).

(10) S. E. Tsuei, R. L. Nation, and J. Thomas, *Eur. J. Clin. Pharmacol.*, **18,** 333 (1980).

(11) S. Lingham, H. Bertwhistle, H. M. Elliston, and J. Wilson, *Br. Med. J.*, **280,** 155 (1980).

(12) S. Levy and J. H. DuBois, "Plastics Product Design Engineering Handbook," Van Nostrand Reinhold, New York, N.Y., 1977.

(13) R. H. Ogorkiewicz, "The Engineering Properties of Plastics," Oxford University Press, Oxford, England, 1977.

(14) J. Crank, "The Mathematics of Diffusion," 2nd ed., Clarendon Press, Oxford, England, 1975.

(15) M. S. Roberts, P. A. Cossum, A. J. Galbraith, and G. W. Boyd, *J. Pharm. Pharmacol.*, **32,** 237 (1980).

(16) H. Davson, "A Textbook of General Physiology," 4th ed. Vol. 1, Churchill, London, 1970, p. 395.

(17) G. L. Flynn and S. M. Yalkowsky, *J. Pharm. Sci.*, **61,** 838 (1972).

(18) E. M. Wright and R. J. Pietras, *J. Membr. Biol.*, **17,** 293 (1974).

(19) J. M. Diamond and E. M. Wright, *Annu. Rev. Phys.*, **31,** 581 (1969).

(20) M. S. Roberts, R. A. Anderson, D. E. Moore, and J. A. Swarbrick, *Aust. J. Pharm. Sci.*, **6,** 77 (1977).

(21) G. L. Flynn in "Advances in Experimental Medicine and Biology," Vol. 47, A. C. Tanquary and R. E. Lacey, Eds., Plenum, New York, N.Y., 1974, p. 73.

(22) J. Autian in "Dispensing of Medication," E. W. Martin, Ed., Mack Publishing Co., Easton, Pa., 1971, p. 652.

(23) P. A. Cossum, M.Pharm. thesis, University of Tasmania, 1981.

(24) J. Autian, *J. Pharm. Sci.*, **52,** 1 (1963).

(25) J. A. Brydson, "Plastics Materials," 3rd ed., Newnes-Butterworths, London, 1975.

(26) P. D. Ritchie, "A Chemistry of Plastics and High Polymers," Cleaver-Hume Press, London, England, 1979.

(27) C. S. Bray and B. J. Meakin, *J. Pharm. Pharmacol.*, **29,** 49P (1975).

ACKNOWLEDGMENTS

This research was supported in part by a grant from the National Health and Medical Research Council, Australia.

The donations of infusion bags and sets by Travenol Laboratories and Heminevrin infusion solution by Astra Pharmaceuticals, Australia are acknowledged.