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The effect of each of three physicochemical variables on solute uptake by polyvinylchloride infusion bags

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Summary

The effect of each of three physicochemical variables, solute concentration, electrolyte concentration and temperature on the uptake of six model solutes by polyvinylchloride (PVC) infusion containers has been investigated. It has been shown that the solute uptake is independent of the initial concentration of the solute and that both temperature and electrolyte concentration have significant effects on the extent of solute loss. The Arrhenius equation has been used to described the temperature effect on solute uptake into PVC bags. The extent of solute uptake from solution in the presence of electrolytes without large ions is a function of increasing ionic strength. It is suggested that the sorption number which can be used to predict solute uptake needs to be adjusted by the use of correction factors for temperature and for vehicle ionic strength, as appropriate.

Introduction

The mechanism and kinetics of solute disappearance from solutions stored in PVC containers have been considered by several authors and a number of models have been proposed to describe the interaction mathematically (for example, Sturek et al., 1978; Yuen et al., 1979; Roberts et al., 1980; Malick et al., 1981; Illum et al., 1983; Kowaluk et al., 1985). We have recently presented a predictive model (Roberts et al., 1991) based on a diffusion controlled uptake mechanism which we had proposed previously (Kowaluk et al., 1985). The model presented by Roberts et al. (1991) was based on several assumptions and we suggested that further work was required to establish a more refined equation.

One of the assumptions was that the rate of solute loss is independent of each of solute concentration and vehicle ionic strength. While the effect of temperature is important in establishing the mechanism of the uptake process, it has generally been disregarded because work in this area is often directed to the elucidation of a specific (room temperature) problem. While our model was intended for application only at room temperature it is nevertheless desirable, in develop-

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ing a reliable model, that the effect of temperature be considered. The present work addresses the effect of each of these three physicochemical factors on the rate of sorption of selected solutes by PVC infusion bags.

Materials and Methods

Materials

The substances used were acetophenone (May and Baker, lot 29399), chlorocresol (Sigma, lot J 716082), chloroxylenol (Central Medical Store, Hobart, Tasmania, lot 154/1), *p*-chlorophenol (BDH Chemicals, lot 2572870), nitrobenzene (BDH Chemicals, lot 2594000), phenol (Central Medical Store, Hobart, Tasmania, lot 3247), *o*-xylenol (Ega-chemie, lot 1606689), sodium bicarbonate (Merck, lot 6340665), dextrose (Supply and Tender Department, Hobart, Tasmania, lot 081174), potassium chloride (May and Baker, lot 56329), calcium chloride (Ajax Chemicals, lot 81995), sodium benzoate (BDH Chemicals, lot 56793) and sodium chloride (BDH Chemicals, lot 3971 and 10241). All of the substances used except sodium chloride and sodium bicarbonate, which were analytical grade, were laboratory grade. All chemicals were used as received without further purification. PVC infusion bags containing 500 ml of 0.9% sodium chloride (Travenol, Baxter Healthcare International, batch A46F4, A52P4, A62S4, A61F1, A62X9, A66N5, A67H1, A67S5, A69S5, A70R3, and A73R8) were emptied and rinsed with distilled water before use.

Sample preparation

Aqueous solutions of each compound were prepared and quadruplicate lots of 500 ml of the required solutions transferred to the infusion bag and stored, as described below, for periods of up to 8 h. The bags were suspended in an upright position from a metal frame by wire hooks and were not disturbed at any time during the required period except to remove samples for analysis. The experiments were run in the open at room temperature or in a closed oven at the other temperatures. Solute concentrations were selected such that solution absorbances could be read without dilution. At selected times, up to 480 min, a sample of approx. 4 ml was removed from the bag, following gentle agitation, by drawing this volume into a glass syringe through an elongated 16 gauge metal needle and transferring this volume directly into a quartz UV cell. The concentration was read without dilution using a Pye Unicam SP8-100 spectrophotometer at the wavelength of maximum absorbance for each substance as determined prior to commencement of the sorption experiments, i.e., 245, 225, 280, 279, 276, 267, and 269 nm. for acetophenone, chlorocresol, *p*-chlorophenol, chloroxylenol, *o*-xylenol, nitrobenzene, and phenol, respectively, and the sample was immediately returned to the PVC bag. All compounds used obeyed Beer's law. A full (scanning) UV absorbance spectrum was run for each solution prior to the commencement of the experiment and subsequently at the conclusion. In no case was any change in the spectrum determined and it can therefore be concluded that no interference occurred under the conditions used in this study.

Control studies were performed using glass volumetric flasks and essentially the same procedure as for the PVC bags; i.e., the flasks were stored in an upright position throughout the study to prevent contact of the drug solution with any material except glass. In all instances, unless otherwise noted, quadruplicate samples were run. The sorption number (Sn) of each compound was calculated by the method described by Roberts et al. (1991).

Effect of temperature, concentration and vehicle ionic strength on solute uptake by PVC bags

Temperature, concentration of the drug and the presence of electrolytes such as sodium chloride in the system are factors which may affect the rate of drug uptake. To determine their propensity to affect the sorption process, a three-factor, two-level factorial design experiment was used in the study. The factors and levels selected were as follows:

Factor A: concentration of the solute. The concentrations used, as shown in Table 1, were chosen to provide an absorbance between 0.2 and 0.7.

TABLE 1

Concentration of the solute used in the investigation of the effects of vehicle ionic strength, concentration and temperature on solute uptake by PVC bags

Solute	Concentration ($\times 10^5$ M)	
	High	Low
Acetophenone	4.99	3.83
Chlorocresol	8.48	5.62
Nitrobenzene	11.06	5.53
p-Chlorophenol	45.89	27.22
Phenol	54.09	24.00

Factor B: temperature; 20 ± 2 and 40 ± 2°C.
Factor C: absence or presence of an electrolyte (0.9% sodium chloride).

The experiments were set up as shown in Table 2 in which low levels of a factor are represented by − and high levels by +. Thus, for example, experiment ab was carried out at high drug concentration, in the absence of sodium chloride, at a storage temperature of 40 ± 2°C. In this design possible interactions can be defined. There are three two-way interactions (A with B, A with C, and B with C) and one three-way interaction (A with B and C) possible. In this study, the experiments were run in duplicate.

Effect of concentration on sorption

Acetophenone, chlorocresol, *p*-chlorophenol and chloroxylenol were used in the study. Aqueous solutions of each compound were prepared at four separate concentrations. The concentration ranges used, as shown in Table 3, were chosen to provide an absorbance value, at the wavelength of maximum absorbance, between 0.2 and 0.7. The experimental procedure used was as described above.

TABLE 2

Factorial design to show sorption of the solute by PVC bags

Experiment	Factor A (concentration)	Factor B (temperature)	Factor C (electrolyte)
(1)	−	−	−
a	+	−	−
b	−	+	−
ab	+	+	−
c	−	−	+
ac	+	−	+
bc	−	+	+
abc	+	+	+

TABLE 3

Solute concentrations used in the effect of concentration on sorption study

Solute	Concentration ($\times 10^5$ M)			
	conc1	conc2	conc3	conc4
Acetophenone	3.83	4.49	4.99 [a]	5.49
Chlorocresol	5.62	7.00	8.48 [a]	9.86
Chloroxylenol	12.67	38.22	51.10 [a]	63.56
p-Chlorophenol	27.50	33.60	39.70	45.80 [a]

[a] Concentration used in the effect of vehicle ionic strength on sorption study.

Effect of vehicle ionic strength

A single concentration of solute was used at five different sodium chloride concentrations (Tables 3 and 4) and controls containing all the ingredients of the solutions except sodium chloride were used to represent zero ionic strength solutions. The experimental procedure and the compounds used were as described above. The effect of vehicle ionic strength of other common infusion solutions such as Ringer's solution, D5W, and 1.4% $NaHCO_3$ solution on the rate of sorption were also studied on *p*-chlorophenol and/or *o*-xylenol solution. Additionally, the effect of vehicle ionic strength of electrolyte solutions with a large anion was investigated using five different

TABLE 4

Sodium chloride concentrations used in the effect of vehicle ionic strength on sorption study

Sample	Sodium chloride concentration (% w/v)	Ionic strength
ionic0	0.000	0.0000
ionic1	0.225	0.0385
ionic2	0.450	0.0770
ionic3	0.675	0.1155
ionic4	0.900	0.1540
ionic5	1.125	0.1925

TABLE 5

F values of analysis of variance table of logarithm of sorption number following Yates' treatment

Experiment	Acetophenone	Chlorocresol	Nitrobenzene	*p*-Chlorophenol	Phenol
a	4.00	1.00	3.48×10^3	49.00	2.25
b	2.25×10^4	6.55×10^6	8.76×10^6	3.36×10^3	2.52×10^2
c	4.41×10^2	4.11×10^5	4.88×10^4	1.00	5.06
ab	9.00	1.68×10^3	3.61×10^2	64.00	2.25
ac	4.00	6.56×10^3	1.00	25.00	1.89
bc	16.00	3.96×10^4	9.80×10^3	49.00	1.00
abc	1.00	1.00	1.00	36.00	1.89

sodium benzoate concentrations in aqueous solutions of nitrobenzene or *p*-chlorophenol.

Effect of storage temperature on sorption

For acetophenone and chlorocresol, aqueous solutions of each compound were used at four separate concentrations. The sorption studies were conducted at four different temperatures, i.e., 20 ± 2, 30 ± 2, 40 ± 2, and 50 ± 2°C.

Evaluation of data

An objective assessment of the relative importance of the various factors and interactions is obtained by applying an analysis of variance, as first described by Yates (Armstrong and James, 1990), to the sorption numbers and the fractions remaining in solution at 8 h. For the evaluation of the effect of each single factor, data were subjected to a single-factor factorial analysis of variance of the fractions remaining in the solution at 8 h by using a suitable computer software package (StatView on a Macintosh computer).

Results and Discussion

Effects of vehicle ionic strength, concentration, and temperature on solute uptake by PVC bags

Table 5 is the complete analysis of variance table for the logarithm of sorption number and Table 6 is that of the fraction remaining in solution at 8 h. The significance of the values of F is assessed by comparing them with tabulated values. Thus, for all substances used, the storage temperature is clearly the most important factor at a 99% level of significance. The effect of the vehicle ionic strength is obvious for chlorocresol and nitrobenzene which have substantial losses. The concentration of solute and the interactions between factors have a negligible effect on solute uptake by PVC infusion bags.

TABLE 6

F values of analysis of variance table of fraction remaining at 8 h following Yates' treatment

Experiment	Acetophenone	Chlorocresol	Nitrobenzene	*p*-Chlorophenol	Phenol
a	1.00	81.00	4.00	2.66	36.00
b	2.09×10^3	1.49×10^5	5.02×10^4	5.58×10^2	9.92×10^2
c	45.76	8.84×10^3	2.25×10^2	1.00	42.25
ab	1.83	1.00	1.00	7.20	56.25
ac	1.25	25.00	1.00	3.39	30.25
bc	5.82	1.60×10^3	49.00	9.00	1.00
abc	1.53	25.00	1.00	3.39	16.00

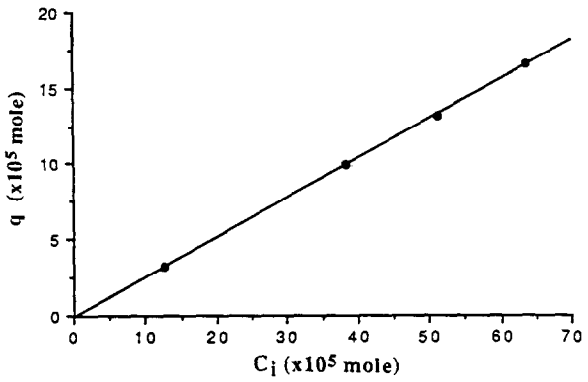

Fig. 1. Sorption pattern of chloroxylenol as a function of drug concentration.

Although the method described above is the favoured approach, further studies on each factor were carried out to confirm these results and to determine what degree of influence these factors had on the process.

Effect of concentration on sorption

The effect of concentration on solute loss is typically as shown in Fig. 1. For each substance, control solutions showed no loss of solute over the period of 8 h and a linear relationship between the uptake and the initial concentration was observed over the concentration range studied. It can be seen that equilibrium was not achieved within the 8 h course of the experiments. However, it appears that the sorption process can be described by a simple distribution law, as described by Eqn 1 (Wang and Chien, 1984):

$$q = K_{app}\left(1 + K_{app} \times (\text{solution volume}/\text{plastic weight})\right)^{-1} C_i \quad (1)$$

where q is the amount of solute sorbed by the plastic, K_{app} denotes the apparent partition coefficient and C_i is the initial concentration of the solution. If the fractions remaining in solution are considered for all substances used, the means of the fractions remaining in solutions of four different concentration over the period of 8 h are not different ($p > 0.01$). This indicates that the solute uptake by PVC infusion bags in the period being used is independent of the initial concentration of the infusion solution. This type of relationship has been described previously for a number of other drugs (Roberts et al., 1980; Cossum and Roberts, 1981; Kowaluk et al., 1981, 1983; Smith and Bird, 1982; Illum and Bundgaard, 1982) and is consistent with an equilibrium sorption or partitioning process controlled by the diffusion of drug into the plastic matrix (Kowaluk et al., 1981, 1982).

Effect of vehicle ionic strength

For the four substances used, it has been found that varying the concentration of sodium chloride had a statistically significant effect on the extent of solute loss in 8 h ($p < 0.05$). Loucas et al. (1990) have found that nitroglycerin availability from PVC administration sets was an inverse function of increasing ionic strength. The mechanism can be explained by a salting-out type of interaction, the extent of which is controlled by the ionic strength of the vehicle. This phenomenon is supported by the results of Sturek et al. (1978), Baaske et al. (1980) and Muynck et al. (1988). To study the effect of vehicle ionic strength on solute uptake, the logarithm of sorption number (h^{-1}) is plotted against vehicle ionic strength calculated from the valencies and molality of each ion (Florence and Attwood, 1988). Linear relationships are obtained as shown in Fig. 2

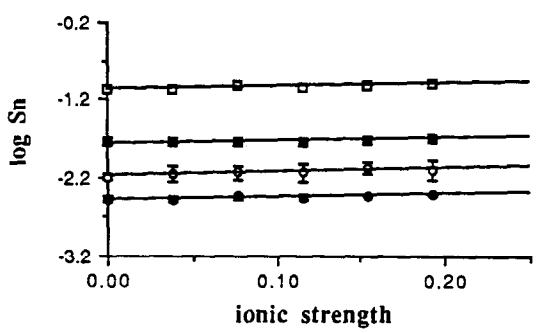

Fig. 2. Relationship between logarithm of sorption number and vehicle ionic strength. (●) *p*-Chlorophenol, (□) chloroxylenol, (○) acetophenone, (■) chlorocresol.

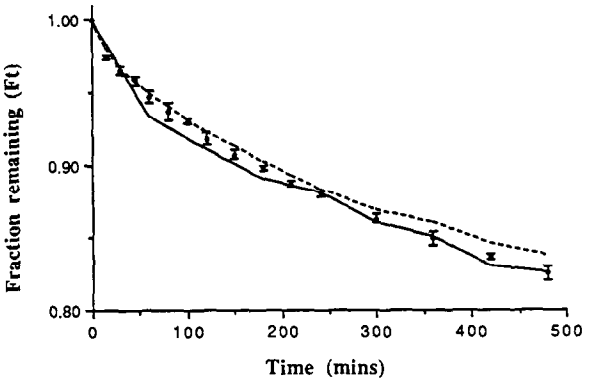

Fig. 3. Sorption profile of 4.54×10^{4} M *p*-chlorophenol in Ringer's solution. (●) Ft in Ringer's solution; (- - - - - -) Ft in water; (———) Ft predicted from log Sn_i calculated from Eqn 2.

($r = 0.959$, 0.949, 0.915, and 0.923 for *p*-chlorophenol, chloroxylenol, acetophenone, and chlorocresol, respectively, $p < 0.05$). It follows that modification of the prediction equation of Roberts et al. (1991) by an adjustment of the log Sn value, by the addition of an ionic strength correction factor, is appropriate.

Analysis of variance of the slopes shows that the effect of vehicle ionic strength is consistent for the four substances used in the study ($p > 0.01$) with the mean value of 0.41. Thus, for cases where vehicle ionic strength is greater than zero, the logarithm of the sorption number (log Sn_i) is

$$\log Sn_i = \log Sn + 0.41\mu \qquad (2)$$

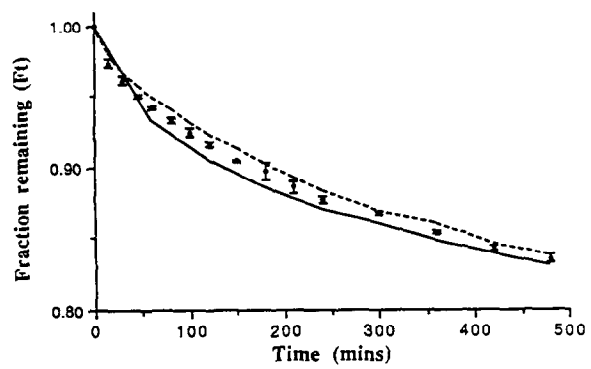

Fig. 4. Sorption profile of 4.54×10^{4} M *p*-chlorophenol in 1.4% sodium bicarbonate solution. (●) Ft in 1.4% sodium bicarbonate solution; (- - - - - -) Ft in water; (———) Ft predicted from log Sn_i calculated from Eqn 2.

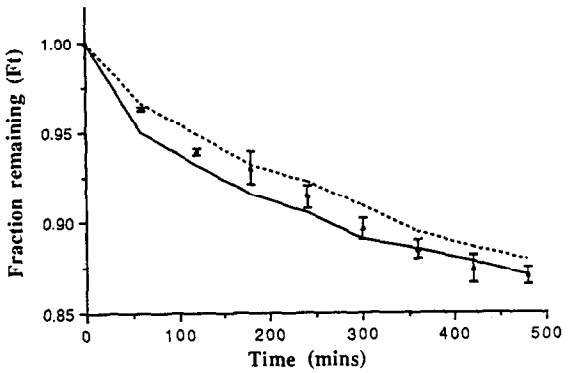

Fig. 5. Sorption profile of 3.89×10^{4} M *o*-xylenol in Ringer's solution. (●) Ft in Ringer's solution; (- - - - - -) Ft in water; (———) Ft predicted from log Sn_i calculated from Eqn 2.

where μ is the vehicle ionic strength of the solution.

Good agreement has been obtained between Eqns 2 and 3 described previously for the effect of ionic strength on the reaction rate of uncharged reacting molecules (Martin et al., 1983)

$$\log k = \log k_o + b\mu \qquad (3)$$

where b is a constant, and log k and log k_o denote the reaction rate in the presence and absence of electrolyte, respectively.

Figs 3–6 show the sorption profiles of *p*-chlorophenol and *o*-xylenol in other common infusion solutions. The sorption profiles predicted by Eqn 2 are also shown in Figs 3–6. It can be seen that

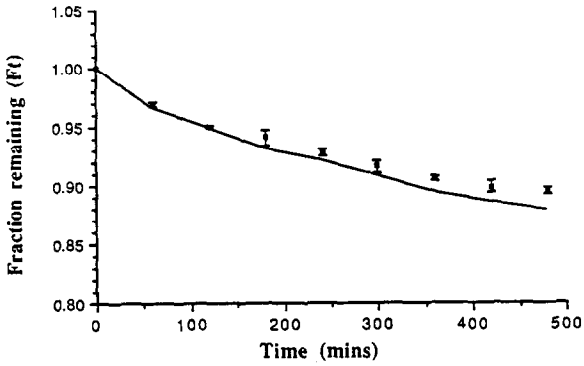

Fig. 6. Sorption profile of 3.89×10^{4} M *o*-xylenol in D5W; (■) Ft in D5W; (———) Ft in water and Ft predicted from log Sn value of -2.76 calculated from Eqn 2.

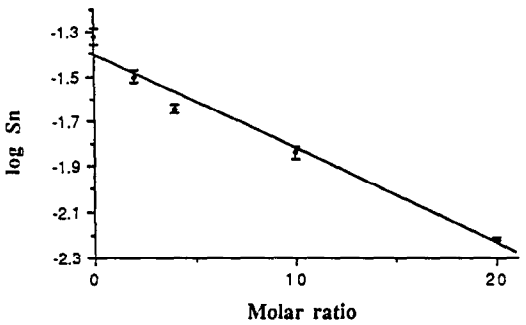

Fig. 7. Effect of sodium benzoate on sorption of 5.53×10^{5} M nitrobenzene with log Sn value of -1.35 by PVC infusion bags.

the modified equation using the ionic strength correction factor closely approximates the exact result and provides better accuracy than the original equation (Roberts et al., 1991). The progressive reduction in solute availability in the presence of electrolytes appears to be controlled by the ionic strength of the vehicle which depends on the total number of charges and not on the properties of the salts in solution.

Contrary to the results described above, the addition of sodium benzoate to the system resulted in a decrease in the extent of solute uptake by PVC bags. The linear relationship between log Sn and the molar ratio of sodium benzoate to solute (mol/mol) has been obtained for both nitrobenzene and *p*-chlorophenol as shown in Figs 7 and 8. This phenomenon, known as hydrotropy, can be explained by a salting in of the solute following the addition of very soluble salts

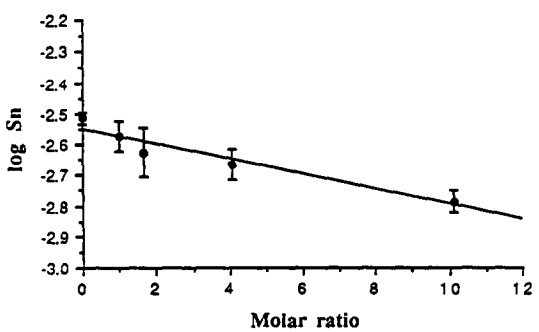

Fig. 8. Effect of sodium benzoate on sorption of 2.74×10^{4} M *p*-chlorophenol by PVC infusion bags.

with large anions or cations (Florence and Attwood, 1988). The increase in aqueous solubility of the solute leads to a reduction in the extent of the partitioning of solute from the infusion solution into the PVC bag.

Effect of the storage temperature

The effect of temperature on the reaction rate is generally described by the equation proposed by Arrhenius:

$$\log k = \log A - \left(\frac{E_a}{2.303RT} \right) \tag{4}$$

where A is the frequency factor, R represents the gas constant, k is the reaction rate constant, T denotes the absolute temperature and E_a is the activation energy which, in the diffusion process, may be considered as corresponding to the energy needed to move polymer chains sufficiently apart to create a hole and the energy needed to move the diffusing molecule into the hole (Autian, 1971).

The reaction rate constant k_2 at a second temperature T_2 can be calculated from a knowledge of its value at any temperature by using Eqn 5 (Florence and Attwood, 1988):

$$\log k_2 - \log k_1 = \frac{E_a}{2.303R} \frac{(T_2 - T_1)}{T_2 T_1} \tag{5}$$

Therefore, E_a for other substances can be calculated from log Sn data obtained in the first portion of this study. The results are shown in Table 6.

Analysis of variance of E_a in Table 7 shows that E_a is independent of concentration and the properties of the solute in solution ($p > 0.01$). These values are of the same order as 13.9, 12.1, 12.3 and 13.5 kcal/mol reported previously for nitroglycerin, isosorbide dinitrate, ethylene glycol dinitrate (Roberts et al., 1983), and clomethiazole edisylate (Kowaluk et al., 1984), respectively. Thus, it would seem reasonable to assume that there is a negligible change in an activation energy from one diffusing species to another. Therefore, substituting $E_a/2.303R$ in Eqn. 5 with

TABLE 7

The activation energy E_a (kcal/mol) for sorption of a solute from its aqueous solution into PVC bags

Solute	E_a (kcal/mol)	
	High concentration	Low concentration
Phenol	13.85	14.34
Nitrobenzene	14.63	16.44
Acetophenone	16.77	15.77
Chlorocresol	14.08	13.61
p-Chlorophenol	11.40	12.24

the value of 3.13×10^3 obtained from five substances in this work yields:

$$\log k_2 - \log k_1 = 3.13 \times 10^3 \frac{(T_2 - T_1)}{T_2 T_1} \quad (6)$$

or

$$\log \mathrm{Sn}_2 - \log \mathrm{Sn}_1 = 3.13 \times 10^3 \frac{(T_2 - T_1)}{T_2 T_1} \quad (7)$$

Rearranging Eqn 7 gives:

$$\log \mathrm{Sn}_2 = \log \mathrm{Sn}_1 + 3.13 \times 10^3 \frac{(T_2 - T_1)}{T_2 T_1} \quad (8)$$

The effect of temperature on the sorption rates of acetophenone and chlorocresol is shown in Figs 9 and 10 as a plot of log Sn vs $1/T$. The activation energy, E_a, and the frequency factor, A, for the sorption of these solutes were calculated according to Eqn 4. For chlorocresol, both

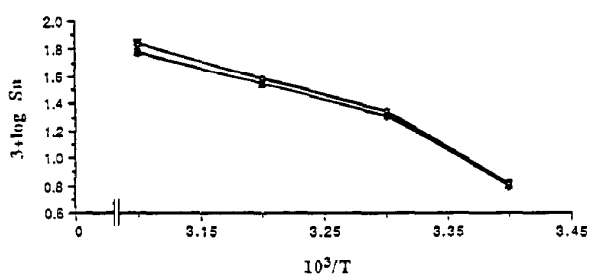

Fig. 9. Effect of temperature on sorption rate of acetophenone: (□) conc1; (●) conc2; (■) conc3; (○) conc4.

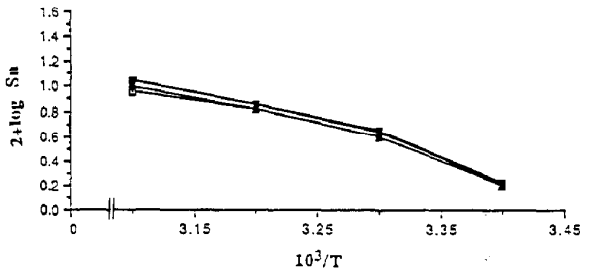

Fig. 10. Effect of temperature on sorption rate of chlorocresol: (□) conc1; (●) conc2; (■) conc3; (○) conc4.

log A and E_a at four different solute concentrations are not different ($p > 0.01$). This result is consistent with the results described earlier; i.e., the sorption process obeys a simple distribution law.

For acetophenone, a similar result was obtained only over the temperature range up to 40°C. It indicated that, at higher temperature (50°C), other processes such as the evaporation of the drug across an unstirred air boundary layer and the changes in the characteristics of the plastic and/or the solute must be taken into account, together with the diffusion process, in determining the extent of drug interaction with the plastic intravenous delivery system. Another possible explanation is that there is a change in the mechanism involved due to the added kinetic energy introduced at the higher temperature. This leads to an increasing of the diffusion of solute into plastic material. Therefore, the interaction might no longer be a diffusion process only and it might in any case already have reached an equilibrium state before the end of the study period.

However, Eqn 8 appears to be useful for estimation of the sorption number at a second temperature from a knowledge of its value at another temperature. It is suggested that Eqn. 8 may be applicable only for temperatures up to 40°C.

Conclusions

The results described here demonstrate that the solute uptake by PVC infusion containers is

independent of the initial concentration of the infusion solution. Hence the uptake mechanism can be explained by a partitioning process controlled by the diffusion of drug into the plastic matrix. The data also indicate that the extent of solute uptake is highly dependent on temperature and on vehicle ionic strength. The effect of temperature on sorption can be described by the Arrhenius equation. By assuming that there is a negligible change in an activation energy from one diffusing species to another, an equation which can be used for estimation of the sorption number at second temperature from a knowledge of its value at another temperature is proposed. It is suggested that this equation may be applicable only up to 40°C. The expression of the sorption number for cases where vehicle ionic strength is greater than zero was derived from data obtained from four substances in terms of the sorption number in water and the ionic strength value of the admixture. It is expected that a reasonable prediction of solute uptake from solutions in the presence of electrolytes without large ions can be made by using this equation. The addition of sodium benzoate which contains large anions was found to reduce the extent of solute loss.

While the equations proposed here provide a means for predicting solute uptake into PVC infusion bags under varying conditions of temperature or vehicle ionic strength, these equations are based on limited laboratory work and their general applicability has yet to be proven through an evaluation of their usefulness in studies involving a much wider range of solutes.

References

Armstrong, N.A. and James, K.C., *Understanding Experimental Design and Interpretation in Pharmaceutics*, Ellis Horwood, London, 1990, pp. 34–39.

Autian, J., In Martin, E.W. (Ed.), *Dispensing of Medication*, Mack, Easton, 1971, p. 692.

Baaske, D.M., Amann, A.H., Wagenknecht, D.M., Mooers, M., Carter, J.E., Hoyt, H.J. and Stoll, R.G., Nitroglycerin compatibility with intravenous fluid filters, containers and administration sets. *Am. J. Hosp. Pharm.*, 37 (1980) 201–205.

De Muynck, C., Remon, J.P. and Colardyn, F., The sorption of isosorbide dinitrate to intravenous delivery systems. *J. Pharm. Pharmacol.*, 40 (1988) 601–604.

Florence, A.T. and Attwood, D., *Physicochemical Principles of Pharmacy*, Macmillan, London, 1988, pp. 112–141.

Illum, L. and Bundgaard, H., Sorption of drugs by plastic infusion bags. *Int. J. Pharm.*, 10 (1982) 339–351.

Illum, L., Bundgaard, H. and Davis, S.S., A constant partition model for examining the sorption of drugs by plastic infusion bags. *Int. J. Pharm.*, 17 (1983) 183–192.

Kowaluk, E.A., Roberts, M.S. and Polack, A.E., Comparison of models describing the sorption of nitroglycerin and diazepam by plastic infusion systems: Diffusion and compartment models. *J. Pharm. Sci.*, 74 (1985) 625–633.

Kowaluk, E.A., Roberts, M.S. and Polack, A.E., Dynamics of clomethiazole edisylate interaction with plastic infusion systems. *J. Pharm. Sci.*, 73 (1984) 43–47.

Kowaluk, E.A., Roberts, M.S. and Polack, A.E., Factors affecting the availability of diazepam stored in plastic bags and administered through intravenous sets. *Am. J. Hosp. Pharm.*, 40 (1983) 417–423.

Kowaluk, E.A., Roberts, M.S. and Polack, A.E., Interactions between drugs and intravenous delivery systems. *Am. J. Hosp. Pharm.*, 39 (1982) 460–467.

Kowaluk, E.A., Roberts, M.S., Blackburn, H.D. and Polack, A.E. Interactions between drugs and polyvinyl chloride infusion bags. *Am. J. Hosp. Pharm.*, 38 (1981) 1308–1314.

Loucas, S.P., Maager, P., Mehl, B. and Loucas, E.R., Effect of vehicle ionic strength on sorption of nitroglycerin to a polyvinyl chloride administration set. *Am. J. Hosp. Pharm.*, 47 (1990) 1559–1562.

Malick, A.W., Amann, A.H., Baaske, D.M. and Stoll, R.G., Loss of nitroglycerin from solutions to intravenous plastic containers: A theoretical treatment. *J. Pharm. Sci.*, 70 (1981) 798–800.

Martin, A., Swarbrick, J. and Cammarata, A., *Physical Pharmacy*, Lea and Febiger, Philadelphia, 1983, p. 376.

Roberts, M.S., Cossum, P.A., Galbraith, A.J. and Boyd, G.W., The availability of nitroglycerin from parenteral solutions. *J. Pharm. Pharmacol.*, 32 (1980) 237–244.

Roberts, M.S., Cossum, P.A., Kowaluk, E.A. and Polack, A.E., Factors affecting the availability of organic nitrates from plastic infusion systems: structure of organic nitrate, nature of plastic and effect of temperature. *Int. J. Pharm.*, 17 (1983) 145–159.

Roberts, M.S., Kowaluk, E.A. and Polack, A.E., Prediction of solute sorption by polyvinyl chloride plastic infusion bags. *J. Pharm. Sci.*, 80 (1991) 449–455.

Smith, A. and Bird, G., The compatibility of diazepam with infusion fluids and their containers. *J. Clin. Hosp. Pharm.*, 7 (1982) 181–186.

Sturek, J.K., Sokoloski, T.D., Winsley, W.T. and Stach, P.E. Stability of nitroglycerin injection determined by gas chromatography. *Am. J. Hosp. Pharm.*, 35 (1978) 537–541.

Yuen, P.-H., Denman, S.L., Sokoloski, T.D. and Burkman, A.M. Loss of nitroglycerin from aqueous solution into plastic intravenous delivery systems. *J. Pharm Sci.*, 68 (1979) 1163–1166.