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A constant partition model for examining the sorption of drugs by plastic infusion bags

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Summary

The sorption of two weak acids (warfarin and thiopentone) and two weak bases (chlorpromazine and diltiazem) into PVC containers, can be described by a constant partition model. PVC–water partition coefficients can be obtained using 3 different methods; equilibrium values for sorption into PVC bags; the sorption versus pH relationship; and partition into PVC strips. These data have been compared with similar values derived using a liquid–liquid partition system and different organic solvents (octanol, dichloromethane, carbon tetrachloride and hexane). Octanol is the preferred reference solvent and it is suggested that octanol–water partition data can be used to predict sorption behaviour.

Introduction

The uptake of drugs into plastic bags used as infusion containers is recognized as a potential loss of active principle that may have clinical consequences. Drug loss may occur through adsorption to the surface of the plastic (e.g. insulin), absorption into the plastic (e.g. the unionized forms of various drugs) or penetration through (permeation) the plastic (e.g. nitroglycerin) (Roberts et al., 1979, 1980; Kowaluk et al., 1982; Illum and Bundgaard, 1982; Moorhatch and Chiou, 1974; Okamoto et al., 1979). Detailed kinetic and mechanistic studies have been reported for various drugs and plastics (Roberts et al., 1980).

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The kinetics of sorption can be described in terms of a diffusionally controlled absorption process, adsorption playing only a minor role in the overall loss of drug (Yeun et al., 1979; Roberts et al., 1980; Illum and Bundgaard, 1982). In previous publications, Illum and Bundgaard (1982) and Bundgaard and Illum (1982) showed that the kinetics of sorption for warfarin and various benzodiazepines by polyvinyl chloride (PVC) infusion bags could be accounted for by a diffusional model in which the loss of a 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 ionisation of the drug, i.e. only the unionized form was sorbed.

In the present work the sorption of various weak acids and bases by PVC bags has been studied in detail using a constant partition model.

Materials and Methods

Materials and apparatus

The drug substances studied were commercial products suitable for clinical use. They were selected so as to provide examples of weak acids and bases with a range of lipophilicity.

Thiopentone sodium ($pK_a = 7.6$) (Leo Laboratories), warfarin ($pK_a = 5.1$) (Nycomed), chlorpromazine hydrochloride ($pK_a = 9.3$) (DAK), Diltiazem ($pK_a = 7.7$) (LERS/Synthelabo), buffer substances and all other chemicals or solvents used were of reagent grade. Plastic infusion bags (Viaflex) of polyvinylchloride (nominal volume of 100 ml) were kindly provided by Travenol Laboratories. The density of the plastic as determined by the density bottle method was 1.19.

The bags were filled with 0.9% sodium chloride solution. To study the influence of pH on sorption of the drug, the saline solution was removed from the bags and replaced by 100 ml of an appropriate buffer solution.

A Spectronic 70 spectrophotometer and 1-cm quartz cells were used for the spectral measurements

Sorption studies

Aliquots of stock solutions of the compounds in water were added to the infusion bags. A number of different concentrations (typically 5–100 μg/ml) were used, each was below the saturation solubility of the solute. The bags were stored at ambient temperature (20–24°C) in the dark as previously described (Illum and Bundgaard, 1982).

The solute concentrations in 2 ml samples were determined spectrophotometrically at suitable intervals from zero time until equilibrium was reached. Each sorption experiment was performed in duplicate and was found to be highly reproducible. The chemical stability of the drug and the possibility of permeation of the solute through the plastic was checked using control experiments with glass infusion bottles, some containing PVC and buffer solutions and solutes similar to those used in the sorption study. Stability indicating assays (e.g. HPLC) were used as appropriate.

Determination of PVC–buffer partition coefficients

The partition of the solutes into strips of PVC (approximately 6 × 2 cm of about 1 g weight) was studied at different pH values, by placing the strips into 100 ml of buffer solution contained in glass infusion bottles (100 ml). 1 ml samples of the solutions were assayed at suitable intervals until equilibrium was obtained as described above.

PVC–buffer solution partition coefficients (apparent partition coefficient) were calculated knowing the weight of the plastic and its density. These values for the PVC strips could be compared with similar values determined from the sorption studies using intact bags. The equivalent "oil" volume of a 100 ml PVC bag was found by weighing a dry empty bag and converting to the volume using the density value above.

Liquid–liquid partition with organic solvents

The apparent partition coefficients of the selected compounds were determined in various organic solvent/aqueous buffer systems at 25°C for different pH values. The organic solvents were 1-octanol, *n*-hexane and dichloromethane. The two phases were mutually saturated. The shake flask and filter probe methods (Tomlinson, 1982) were used as appropriate. Solute concentrations in the aqueous phase were measured spectrophotometrically. The partition coefficients for the unionized solutes were calculated from the apparent partition coefficient in the usual way (Florence and Attwood, 1981).

Results and Discussion

Sorption studies

The disappearance of the various drugs from aqueous solutions stored in 100 ml infusion bags of polyvinyl chloride was followed until equilibrium was reached (about 8 days).

At a given constant pH value the amount of drug taken up into the plastic was linearly related to the initial concentration in the aqueous phase (linear isotherm). The changes in percentage of drug sorbed found for different concentrations of drug in normal saline were due to the corresponding change in pH and thereby the percentage of drug ionized. This confirms earlier experiments performed with warfarin (Illum and Bundgaard, 1982). Consequently the sorption process can be considered to be one approximating to constant partition where the PVC container corresponds to an organic solvent phase. The control experiments conducted using glass containers indicated that permeation of drug through the plastic was not a significant source of drug loss and that all compounds were stable in solution except for diltiazem at pH values above 8.0. The simultaneous degradation and partitioning of diltiazem at pH values above 8.0 will affect both the apparent sorption kinetics and the amount taken up by the plastic at equilibrium. A separate publication will deal with these aspects and the application of the model proposed by Byron et al.

(1980). The partitioning data for diltiazem derived in the present work have been calculated at pH values where drug instability was not significant during the time of the experiment.

The percentage loss of drug to the plastic at equilibrium for different pH conditions is shown in Fig. 1 for the two weak acids and the two weak bases. It will be seen that the sorption–pH curves conform to an S-shape and thus are similar to a dissociation–pH profile, indicating clearly that the unionized form of the drug is critical in the sorption process.

A PVC–aqueous buffer apparent partition coefficient (P_{app}(bag)) can be obtained at each pH value (Figs. 2 and 3) and the partition coefficient of the unionized form of the drug (P_u) can be calculated (Table 1).

The inflexion points for all 4 drugs shown in Fig. 1 occur at pH values different from the respective pK_a value. This so-called "pH-shift" phenomenon is related to the partition coefficient of the unionized form of the drug (Bundgaard and Illum, 1982). If the sorption of drugs into the plastic container is considered as a simple partition process where only the unionized form is absorbed, then for a given pH value the concentration in the aqueous phase (C_a) compared to the total concentra-

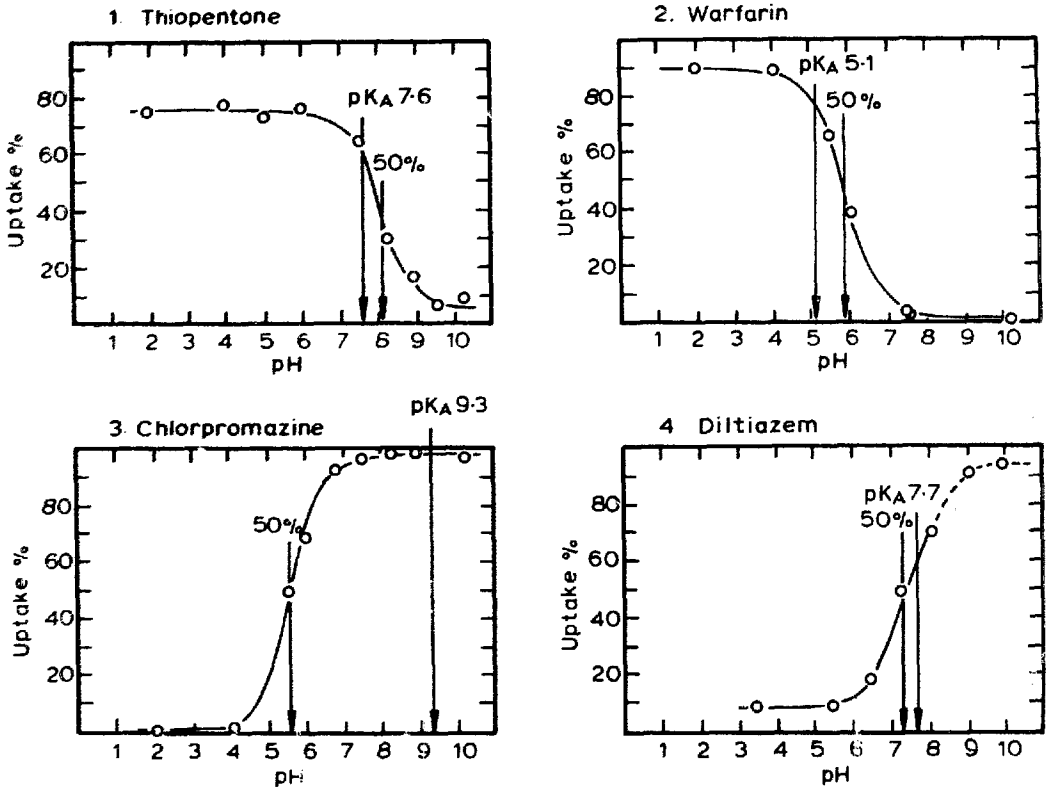

Fig. 1. Sorption of drugs into PVC containers. Equilibrium data. (1) Thiopentone; (2) warfarin; (3) chlorpromazine; (4) diltiazem.

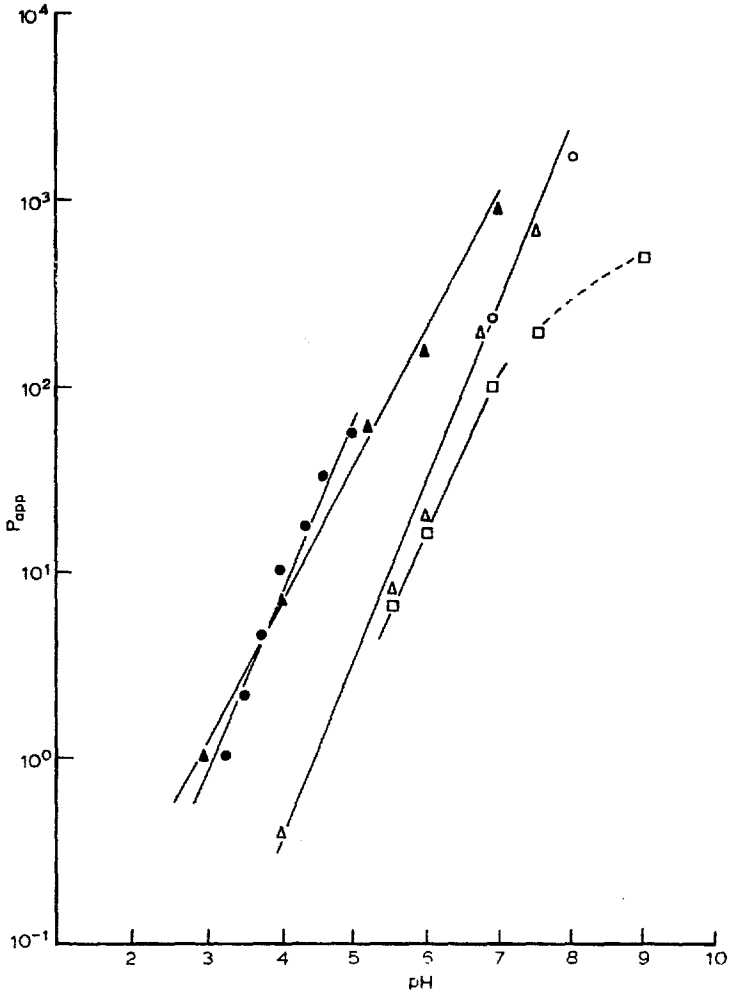

Fig. 2. pH–partition profile for c' 'orpromazine. PVC–aqueous buffer partition: ○, PVC strips; □, PVC bags. Organic solvent–aqueous buffer partition: ▲, octanol; △, hexane; ●, dichlormethane.

tion of the drug in the system (C_T) is

$$\frac{C_a}{C_T} = \frac{1}{\left(1 + P_{app} \cdot \frac{V_p}{V_a}\right)} \tag{1}$$

where V_p and V_a are the volumes of the plastic and aqueous phases respectively, and P_{app} is the apparent (pH-dependent) partition coefficient of the drug. P_{app} is related to the partition coefficient of the unionized form P_u by

$$P_{app} = \frac{P_u}{1 + 10^{pH - pK_a}} \tag{2}$$

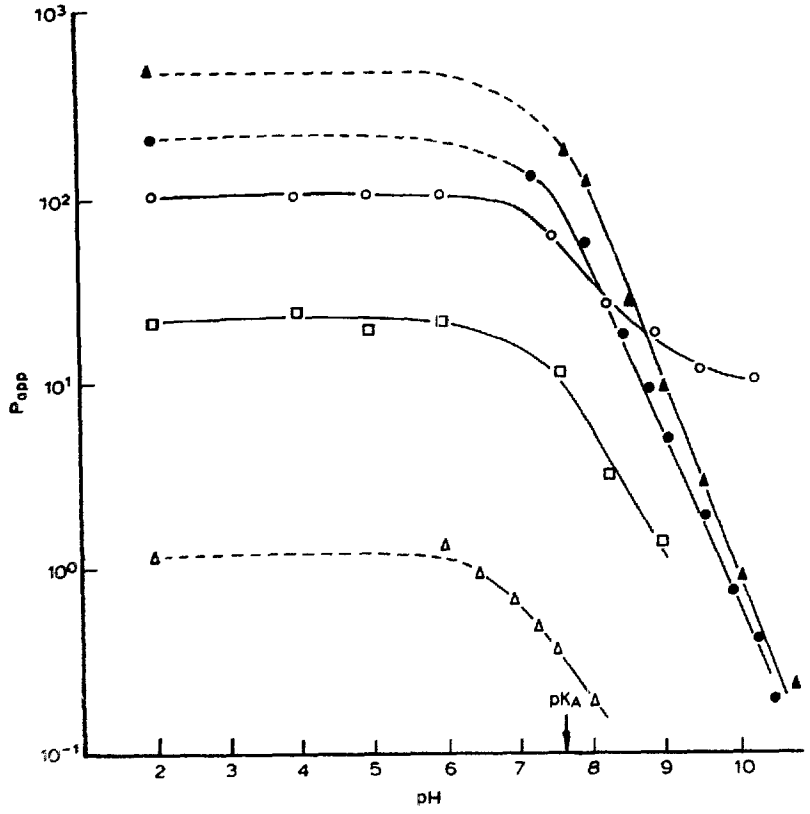

Fig. 3. pH–partition profile for thiopentone. PVC–aqueous buffer partition: ○, PVC strips; □, PVC bags. Organic solvent–aqueous buffer partition: ▲, octanol; △, hexane; ●, dichlormethane.

Thus

$$\frac{C_a}{C_T} = \frac{1}{1 + \frac{V_p}{V_a} \cdot \frac{P_u}{1 + 10^{pH - pK_a}}} \tag{3}$$

For $C_a/C_T = 0.5$ (i.e. 50% change in the initial concentration in the aqueous phase). Eqn. 3 leads to

$$\frac{P_u V_p}{V_a} = 1 + 10^{pH - pK_a} \tag{4}$$

Eqn. 4 predicts that the greater the PVC–aqueous buffer partition coefficient of the drug the greater will be the uptake into the plastic and consequently the greater the shift of the inflexion point from the pK_a value. The pK_a and the inflexion point will coincide only when $(P_u V_p)/V_a = 2$ (which for the 100 ml Viaflex bag would correspond to $P_u = 14$). The equation also allows the direct calculation of the partition coefficient of the unionized form of the drug for the PVC buffer system from the

pH-shift (P_u(shift)) provided V_p can be measured. The values shown in Table 1 have been calculated on the basis that V_p for a 100 ml Viaflex bag is 14.0 ml.

Partition studies

Apparent partition coefficient values for the uptake of chlorpromazine and thiopentone into plastic bags and strips and for the distribution into organic solvents are shown in Figs. 2 and 3 for different pH values. Calculated partition coefficients for the unionized species of four compounds studied are given in Table 1.

Comparison of partition values

The log P_{app} versus pH curves shown in Figs. 2 and 3 conform well to the theory that only the unionized species is able to partition between water and oil phases. The agreement between the experimental results and the theoretical curve is generally good. Deviations from theory at low values of P_{app} for liquid–liquid partition can be attributed to the problems of measuring small apparent partition coefficients; whereas the deviations in the data derived using PVC strips ("the tail") (and to certain extent the PVC bags) may be attributed to adsorption of the drug to the available surface of the plastic.

Three different methods have been used to determine the partition coefficients of the unionized forms of the drugs for the PVC container/aqueous buffer system: (i) intact bag at equilibrium; (ii) pH-shift; and (iii) PVC strips in buffer solution.

The agreement between methods (i) and (ii) is good (Table 1), although the values obtained using the strip method (iii) are generally higher. This may be attributed to an overestimate of the *available* volume of PVC container (14 ml) and to a state of pseudo-equilibrium where the drug diffuses quite rapidly into the parts of the bag in direct contact with the solution but much more slowly into the sealed ends of the bag and the attached tubing.

The 3 organic solvents used for the liquid–liquid partition studies were selected so as to provide organic reference phases of different polarities. 1-Octanol has been

TABLE 1

COMPARISON OF PARTITION DATA (log P_u) OBTAINED USING PVC BAGS AND LIQUID–LIQUID PARTITIONING

Drug	pK_a	Liquid–liquid partitioning (log P_u)				PVC–aqueous partitioning (log P_u)		
		n-Hexane	Dichlor-methane	Carbon-tetrachloride	Octanol	pH shift	PVC strips	PVC bags
Thiopentone	7.6	0.1	2.35	1.10	2.54	1.5	2 0	1.4
Warfarin	5.1	0.20	2.82	1.20	2.70	1.7	2.4	1.8
Chlorpromazine	9.3	4.8	6.26	6.11	5.00	4.7	4.8	4.5
Diltiazem	7.7	1.0	4.63	3.52	2.70	1.3	1.5	1.4

used widely in the pharmaceutical sciences as a solvent for estimation of the lipophilicity of solutes for subsequent use in structure–activity predictions, preformulation studies and pharmacokinetic evaluations (Leo et al., 1971). Hydrocarbon solvents such as cyclohexane, iso-octane and *n*-hexane have been preferred by others (Rytting et al., 1972; Davis et al., 1974) on theoretical grounds and such solvents would appear to be a sensible model for plastic containers based on polyethylene (Roberts et al., 1979). Illum and Bundgaard (1982) reported that the initial rate of sorption of benzodiazepines, thiopentone, nitroglycerin and warfarin by PVC containers could be correlated in a rank order manner with the corresponding *n*-hexane–water partition coefficient.

The data in Figs. 2 and 3 and in Table 1 show that the nature of the organic phase can have an important effect on the value of log P_u and in general

$$\log P_{u(\text{dichloromethane})} \equiv \log P_{u(\text{octanol})} > \log P_{u(\text{carbon tetrachloride})} > \log P_{u(\text{hexane})} \quad (5)$$

Such differences are to be expected and can be related to solute–solute and solute–solvent interactions as well as to the water content of the organic phase (Davis, 1975; Kojima and Davis, unpublished). Chlorpromazine with very high log P_u values demonstrates a much smaller sensitivity to the nature of the organic solvent.

Comparison of the liquid–liquid partition data with the PVC–aqueous buffer system partition data indicates that none of the chosen solvents mirrors the behaviour of PVC. Octanol is to be preferred for use in predicting sorption into PVC

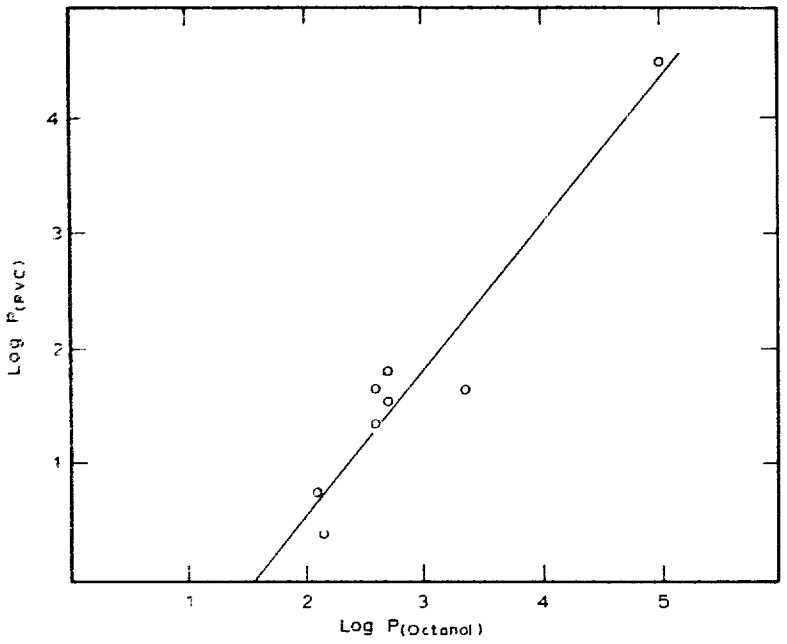

Fig. 4. Correlation between PVC and octanol partition data.

containers since a large data bank exists for partition data obtained with this solvent and partition values may also be estimated using group contributions and fragmental constants (Hansch and Leo, 1979).

An equation of the form

$$\log P_1 = a \log P_2 + b \tag{6}$$

has often been used to correlate partition data obtained with one solvent (P_1) and various solutes, with similar data obtained with a second solvent (P_2) (Leo et al., 1971). Fig. 4 shows the graphical representation of Eqn. 6 for PVC bags and octanol. The data points include those in Table 1 and also additional values on the benzodiazepines from the work of Illum and Bundgaard (1982). The regression equation is

$$\log P_{PVC}(\text{bag}) = 1.3 \log P_{\text{octanol}} - 1.9 \tag{7}$$

with a correlation coefficient of 0.963.

Eqn. 7 can be used to predict partition data for PVC bags and in turn sorption–pH isotherms and sorption kinetics for practical situations. These aspects will be discussed in a later publication.

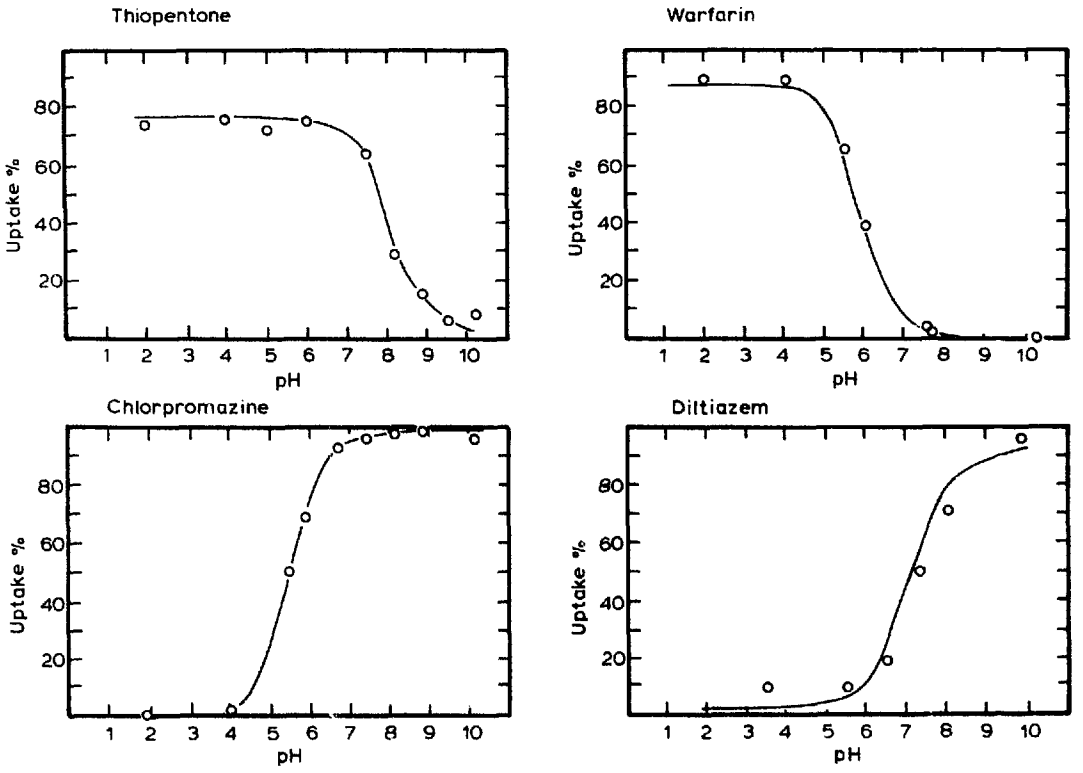

Fig. 5. Computer-generated pH–sorption profiles using $V_a = 100$ ml, $V_p = 14$ ml. ○, Experimental points, ———, theoretical curve.

Fig. 5 shows computer-generated theoretical pH–sorption profiles for the 4 solutes in Table 1 calculated using Eqn. 3, a V_p value of 14, a V_a value of 100 (or 110 as appropriate) and the log P_u (PVC) values calculated from Eqn. 7. The agreement between the theoretical curves and the experimental results is good.

Conclusions

The equilibrium uptake of drugs by PVC infusion bags can be described by a constant partition model. Partition coefficients for the unionized form of drugs can be obtained using PVC/aqueous buffer systems and compared with liquid–liquid partition data. The agreement between theoretical predictions using 1-octanol–water partition coefficients and a constant partition model and experimental equilibrium data for weak acids and bases stored in PVC bags is good.

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