PREDICTION OF THE TIME COURSE OF THE SORPTION OF THERAPEUTIC DRUGS AND OTHER SOLUTES BY POLYVINYLCHLORIDE IN STATIC AND DYNAMIC PHARMACEUTICAL SYSTEMS

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This thesis contains no material which has been accepted for the award of any other degree in any University or College and to the best of my knowledge and belief the thesis contains no material previously published or written by another person except when due reference is made in the text of the thesis.

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ABSTRACT

Polyvinylchloride (PVC) has several uses and one of these is as the principal constituent of containers used in the storage of pharmaceutical solutions. It has been shown previously that the use of PVC containers for some liquid pharmaceutical systems has not been satisfactory in that the solute may lose potency with time. Similarly, the use of PVC as a tubing is not always desirable.

In this work, the effect of each of three physicochemical variables, solute concentration, electrolyte concentration and temperature on the uptake of a number of model solutes by PVC infusion bags has been investigated. Additionally, a study on the kinetics of the sorption of the model solutes by PVC tubing has been carried out and the influence of factors such as solute concentration, flow rate, tubing diameter and tubing length on the extent of solute uptake by PVC tubing has also been investigated.

It has been shown that the extent of solute uptake by PVC infusion bags is independent of the inital concentration of the solute and that both temperature and electrolyte concentration have significant effects on the extent of solute loss. The Arrhenius equation is used to describe 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. A prediction model based on the diffusion model is used to describe the sorption profile of the model solutes. It is suggested that the sorption number which has been used to

predict solute uptake by PVC bags needs to be adjusted by the use of correction factors for temperature and for vehicle ionic strength.

A well-stirred compartment model and a well-stirred diffusion model are examined for their ability to describe the uptake of the model solutes from aqueous solutions infused through PVC tubings. It is shown that a biexponential model which is a simplified form of both the well-stirred-compartment model and the well-stirred-diffusion model can be used to adequately describe the sorption profiles of the model solutes during a 24-hour infusion period. Furthermore, it is found that, at a certain time after the beginning of an infusion, the first exponential term of the biexponential model will approach zero and the biexponential formula will be reduced resulting in the monoexponential form which is a general form of the equation used to describe the uptake of all solutes regardless of their affinity for PVC tubings.

The solute uptake by PVC tubings has been found to be independent of the initial concentration of the infusion solution while it is shown to be a function of flow rate, tubing diameter, and tubing length. In order to describe the difference in the extent of sorption between two separate kinetic runs conducted with differing flow rate, tubing diameter, and/or tubing length, a model based on chemical similarity theory was developed. This allows for an approximation of the rate and extent of solute uptake in one system from a knowledge of the uptake in a separate system operating under different conditions. Results reported previously by other investigators for a number of drugs and those predicted using the proposed model are presented.

An attempt was made to correlate the extent of sorption of the model solutes by PVC infusion bags, or by PVC tubing, with selected physicochemical properties of the solutes such as octanol-water partition coefficient, dipole moment, intrinsic molecular volume and solvatochromic parameters.

The plasticizers used in the formulations of PVC bags and tubings being studied were identified. The infrared spectra and ultraviolet absorption spectra of the methanolic extracts of the PVC sheets cut from an unprinted area of PVC bag and tubing reveal that the phthalate-type plasticizer, DEHP, was used in both formulations. Therefore, the DEHP-water partition coefficients were determined for the model solutes and the utility of this value in predicting the uptake of the model solutes by PVC materials was evaluated. Some attempts to relate chemical structure and chemical interaction to solute sorption by PVC infusion bags are described.

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LIST OF ABBREVIATIONS

ATBC	acetyl tri-n-butyl citrate
cm	centimetre
CuF_t	cumulative fraction of the original concentration of solute in the effluent solution collected to the specified time.
DEHP	di-2-ethylhexyl phthalate
DF	degrees of freedom
D5W	5% dextrose in water
Ea	activation energy
F	F-value
f_t	fraction of the original concentration of solute in the effluent solution collected from the distal end of a PVC tubing at time t_{sink}.
F_t	fraction of the original concentration of solute remaining in a solution stored in a PVC bag or fraction of the original concentration of solute in the effluent solution collected from the distal end of a PVC tubing at time t.
ESR	electron spin resonance spectrometry
g	gram
G	gauge
HBA	hydrogen bond acceptor
HBD	hydrogen bond donor
HPLC	high pressure liquid chromatography
I	ionic strength
i.d.	internal diameter

IR	infrared
i.v.	intravenous
kcal	kilocalorie
kg	kilogram
ln	natural logarithm
log	logarithm
log A	frequency factor
log P_{DEHP}	logarithm of DEHP-water partition coefficient
log $P_{polymer}$	logarithm of polymer-water partition coefficient
log $P_{octanol}$	logarithm of octanol-water partition coefficient
L	litre
LD_{50}	dosage for 50% lethality
LSER	linear solvation energy relationship
M	molar
mg	milligram
min	minute
mL	millilitre
mm	millimetre
mol	mole
n	sample size
nm	nanometre
NMR	nuclear magnetic resonance spectrometry
o/w	oil-in-water
PAH(s)	polycyclic aromatic hydrocarbon(s)
PVC	polyvinylchloride
QSAR	quantitative structure-activity relationship
r	correlation coefficient

R	gas constant
rpm	revolutions per minute
RSD	relative standard deviation
SE	standard error of regression
SD	standard deviation
Sn	Sorption number (hour $^{-1}$)
Sn_i	Sorption number for cases where vehicle ionic strength is greater than zero (hour $^{-1}$)
t	time
T	temperature
t_{min}	the time required for the elution of that volume of solution which is present in the tubing at the beginning of the infusion (eqn.3.6)
TPN	total parenteral nutrition
t_{sink}	the time required for the initial rapid uptake of solute from the infusion solution into the surface of the PVC tubing to reach completion (eqn.3.16)
U_t	fractional solute loss at t_{sink}
UV	ultraviolet
V_{sink}	total volume of the effluent collected from the distal end of a PVC tubing from t=0 to t=t_{sink}
µg	microgram
µL	microlitre
µm	micrometre

CHAPTER 1. INTRODUCTION

1.1. The use of PVC in pharmaceutical systems

1.1.1. General

The term "plastic" is generally regarded as applying to a wide range of solid composite materials which are largely organic, usually based upon synthetic resins or upon modified polymers of natural origin and which possess mechanical strength. Plastic materials are prepared from monomers by polymerization in a number of ways (Billmeyer, 1962; Autian, 1963a, 1963b). In terms of processing technology, plastics can be divided into two classes, thermoplastics and thermosets (Yahya et al., 1988). Thermoplastics are plastics that melt, without degrading, when heated and thermosets are plastics that do not melt, but degrade when heated (Ziter, 1987).

In the medical/pharmaceutical field, medication containers, intravenous tubing and unit-dose packages are normally thermoplastics which are found to have wider application than thermosets (Wang and Chien, 1984). Examples of thermoplastic materials are polyethylene, polystyrene, polypropylene, PVC and cellulose acetate (Yahya et al., 1988).

The composition of plastics is quite complex. Specific additives such as lubricants, stabilizers, plasticizers, antioxidants, antistatic agents, slip agents and dyes and pigments are frequently used to modify the properties of the plastics. These additives may vary in concentration

from a few parts per million to as much as 60% of the total weight of the finished plastic material (Wang and Chien, 1984).

Lubricants are used to facilitate removal from moulds used during production. Stabilizers are used to retard or to prevent the deterioration of plastic materials which may result from exposure to light, heat and pressure and to improve aging characteristics. Plasticizers are materials of low volatility that are added to plastics to enhance flexibility, resilience and melt flow. Antioxidants are added to prevent discoloration from reaction with oxygen in the air. Antistatic agents are used to prevent the build-up of static charges, that causes plastics to cling, on the surface of plastics. Slip agents are added to reduce the coefficient of friction of the plastics. Dye and pigments impart colour to plastic materials (Wang and Chien, 1984; Ziter, 1987).

1.1.2. PVC

PVC, one of the more versatile plastics, is produced from the monomer, vinyl chloride, in a number of ways. The simplest structure representing PVC may be shown with alternating atoms of chlorine throughout the polymer chain (Autian, 1963a, 1963b). The structural formula of PVC is shown in Figure 1.1 (Florence and Attwood, 1988).

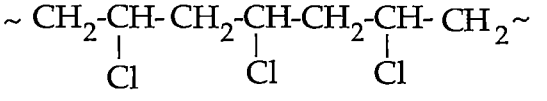


Figure 1.1. The structural formula of PVC.

Unmodified PVC is hard and transparent. In general, 60% of the material is in an amorphous state. PVC has unique properties which permit it to be modified in numerous ways giving a spectrum of end uses. For instance, a properly formulated flexible PVC which is PVC modified with the addition of large amounts of low molecular weight additives, primarily plasticizer, has found use as medication containers and tubings due to its softness and its flexibility (Autian, 1963a, 1963b). Diethylhexyl phthalate (DEHP) is the most widely used plasticizer in PVC formulations (Rudin, 1982). The precise formulation of flexible PVC is, in general, not revealed by manufacturers. An example of a flexible PVC formulation which, as near as possible, mimics commercial formulations intended for use in medical applications is as follows (Bray, 1983):

Ingredient	Parts by Weight
PVC resin (medium molecular weight, suspension polymerised)	100.0
Epoxydised soya bean oil	6.0
Calcium stearate	0.2
Liquid paraffin	0.5
Plasticizer (DEHP or ATBC)	q.s.

Despite the fact that there are approximately 50 other types of plastics (Ziter, 1987), flexible or plasticized PVC is sometimes refered to as soft plastic or plastic (Petrick et al., 1977). Some physical properties of rigid and of plasticized PVC are given in Table 1.1.

Table 1.1. Some physical properties of the rigid and the plasticized PVC

Properties	Rigid PVC	Plasticized PVC	Reference
Degree of crystallinity (%)	0	0	Schott (1982)
Solubility parameter $(cal.cm^{-3})^{1/2}$	9.8	9.2	Schott (1982)
O_2 transmission rate $(mL.m^{-2}\text{-}24hr\text{-}1atm)$	120	190-3100	Autian (1963a)
N_2 transmission rate $(mL.m^{-2}\text{-}24hr\text{-}1atm)$	20	58-810	Autian (1963a)
CO_2 transmission rate $(mL.m^{-2}\text{-}24hr\text{-}1atm)$	320	430-19,000	Autian (1963a)
EO uptake (ppm)	15648	20760	Schott (1982)
Water vapour transport rate $(g.s^{-1}.cm^{-2})$	-	$8.61x10^{-9}$	Wood and Mulski (1989)

Since the introduction of PVC into the pharmaceutical field in the form of a unique intravenous fluid bag in 1971, the use of PVC, particularly in medication containers and intravenous tubings, has become increasingly widespread in the pharmaceutical industry.

PVC, like other plastics, offers obvious advantages over glass. Plastic medical products are not as fragile as glass, are relatively lightweight, are not space-consuming and the walls of plastic containers need not be as thick as glass. These factors decrease shipping and handling costs. The application of single use plastic devices is not only convenient but also helps reduce cleaning and sterilizing costs and assures individual use. Through the use of a variety of formulation ingredients, plastics are

adaptable to many packaging forms such as bottles, tubes and syringes. It is easier to remove the pooling effect of drugs in a hanging infusion bag than in a hanging glass bottle. In addition, plastic intravenous containers reduce the chances of airborne contamination and particulate matter contamination of sterile products and may reduce the risk of touch contamination (Ziter, 1987).

The widespread use of PVC intravenous infusion bags and PVC admininistration sets has not, however, been without problems. For instance, the problem of drug sorption to the PVC material and consequent reduction in the potency of the solution has become recognised and studies on different types of plastics have shown that the degree of sorption to PVC infusion bags is generally higher than that to polyethylene or polypropylene bags (Amann et al., 1980; Lee and Fenton-May, 1981; Illum and Bungaard, 1982). A review of sorption and other problems arising from the use of plastics is presented in Section 1.1.3.

1.1.3. Problems arising from the use of PVC and other plastics

The problems which occur when drugs are in contact with plastics have been reviewed by numerous authors (for example: D'Arcy, 1983; Wang and Chien, 1984; Stella, 1986; Ziter, 1987; Yahya et al, 1988). These problems, the severity of which depends primarily upon the particular plastic and the drug, can be divided into five broad categories: chemical reaction, alteration in the properties of the plastic, permeation, leaching and sorption (Autian, 1971; Ziter, 1987). Each of these categories is considered below.

Chemical reaction. Drug ingredients may react with the polymer or one of the additives in the plastic. This may result in a change in the physical or chemical properties of the drug product and/or the plastic. For drugs which are sensitive to light radiation energy, photodegradation of the drug product is likely to occur unless ultraviolet absorbers are added to the polymer compositions or in coatings.

Alteration in the properties of the plastic. Environmental factors such as heat, humidity and prolonged exposure to ultraviolet light accelerate the ageing characteristics of plastic. The properties of plastics may also change as a consequence of permeation or leaching or sorption problems. Furthermore, the change in plastic properties may then, in turn, result in one or more additional problems.

Permeation. With plastic materials there is a problem of permeation in two directions: (a) the permeation of water vapour and/or volatile components in the drug product through the plastic into the ambient environment or (b) the permeation of oxygen, water vapour and/or other gases from the ambient environment through the plastic into the product. Excessive loss or gain of water, gases or volatile organic compounds can cause deterioration of the product either chemically or physically. PVC, for example, is a very poor barrier to water vapour and extensive water loss may result unless the bags are overwrapped.

Leaching. Leaching or desorption of the components of the plastic device into the content of the container occurs mainly in liquid and semi-solid dosage forms. The plasticizer, DEHP, is the most common

additive leached from plastic material into drug solutions or blood stored in flexible PVC bags.

Sorption. This term describes the loss of drug to the plastic materials and includes adsorption of the drug onto the plastic surface and its absorption into the body of the plastic. Sorption differs from permeation in that a limiting value or loss occurs with sorption after which time no further uptake will occur. It is suggested that the extent of loss of drugs by the sorption process is greater with PVC than with polyolefin, polyethylene or polypropylene (Kowaluk et al., 1983).

1.2. Mechanisms of the sorption of therapeutic drugs and other solutes by PVC

1.2.1. General

In general, when a solution is in contact with a solid phase, both the solvent and solute molecules will be continually striking the solid surface. If the conditions are optimum, both types of molecules may be adsorbed to the surface of the solid. Normally, with non-reactive materials, the quantity of molecules adsorbed, either solvent or solute, will be negligible and for all practical purposes it may be assumed that no adsorption has taken place. On the other hand, if the chemical structures of the components making up the solid phase are of such a nature that they can electrically attract a molecule in the solution with comparative ease, a situation may exist (depending on the total surface area of the solid phase exposed to the solution) where a significant quantity of the solute might be removed from the solution. With plastic

materials there is usually not only surface attachment, but actual penetration of the solid phase by the solute molecules which in turn come into contact with receptor sites in the polymer. The greatest extent of uptake of the solute from a solution would be a consequence of the solute penetrating and diffusing into the plastic material (Autian, 1963a, 1963b; Illum and Bundgaard, 1982).

The linear sorption isotherms, which belong to the so-called C-type partition isotherms, observed for the sorption of various benzodiazepines into a PVC matrix confirm this suggested mechanism since it indicates that the interaction sites remain available and the amount which can be sorbed is independent of the amount previously sorbed (Illum and Bundgaard, 1982). The term "sorption" is usually used to describe total uptake of solute into plastic matrix and it does not identify the precise mechanism.

A number of mathematical models have been proposed to describe the mechanism of the sorption of therapeutic drugs and other solutes by PVC and some of these are discussed in the following section.

1.2.2. Mechanisms of the sorption of therapeutic drugs and other solutes by PVC in static conditions

A variety of equations have been developed for analyzing the kinetic data of drug binding to PVC in static condition as described below. In the first two models, only equilibrium concentrations have been considered whereas other models have been used to analyse data obtained at a given time.

1.2.2.1. Constant partition model

Sorption phenomena can be described by a simple distribution law (Wang and Chien, 1984):

$$q = K_{app} C_{eq} \quad (1.1)$$

or

$$q = K_{app} [1+K_{app}(\text{solution volume/plastic weight})]^{-1} C_i \quad (1.2)$$

where q is the amount of solute taken up by a plastic material (in $mg.g^{-1}$ or $mole.kg^{-1}$), K_{app} is the apparent partition coefficient, C_i and C_{eq} are initial solute concentration and concentration at equilibrium ($mg.mL^{-1}$ or $mole.litre^{-1}$) respectively.

These equations were used to follow the sorption of benzodiazepines and a number of other drugs by PVC infusion bags, where the sorption process can be considered to be approximating the constant partition model and in which the PVC container corresponds to an organic phase (Illum and Bundgaard, 1982; Illum et al., 1983). Eqn.1.1 is of the same form as the Freundlich equation (eqn.1.3) when n = 1.

$$q = K_f C_{eq}^{1/n} \quad (1.3)$$

where q and C_{eq} have the same meanings as described previously and K_f is the Freundlich binding constant and n is an empirical constant. The Freundlich equation is used in surface adsorption to relate the amount of adsorbate taken up by the adsorbent to the concentration of adsorbate in the solution at equilibrium (Wang and Chien, 1984).

Recently, Jenke (1993) has suggested that the distribution of a solute at equilibrium can be expressed by the equilibrium interaction constant (E_b) as follows:

$$E_b = (m_c/W_c)(m_p/V_p) \tag{1.4}$$

where m is the mass of the solute in either phase at equilibrium, W is the container weight, V is the product volume and c and p refer to the container and product respectively. In fact, E_b is analogous to a partition coefficent, with the density of the container as the conversion factor.

1.2.2.2. The Langmuir equation

Langmuir proposed an equation based on the theory that molecules or atoms of gas are adsorbed on the active site of a solid to form a layer one molecule thick (monolayer) (Wang and Chien, 1984). The equation developed is also applicable to the adsorption of solute molecules from solution.

$$\frac{1}{q} = \frac{1}{S_l} + \frac{1}{k_l S_l} x \frac{1}{C_{eq}} \tag{1.5}$$

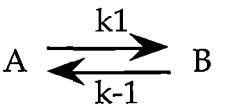
where terms used previously have the same meaning and where k_l is the ratio of adsorption rate to desorption rate (litre/mole) and S_l is a theoretical saturation value that represents the saturation concentration when all binding sites are occupied by a monolayer of molecules. The amount of uptake and the equilibrium concentration are represented by q (mole/kg) and C_{eq} (mole/litre), respectively. A plot of $1/q$ against $1/C_{eq}$ will produce a straight line from which S_l and k_l can be determined

from the intercept and the slope (Wang and Chien, 1984). Hirsch and co-workers (1977) showed that, for the sorption of insulin to a PVC intravenous delivery system, a Langmuir relationship is followed.

1.2.2.3. Compartment models

a. Closed two-compartment model

It has been shown that nitroglycerin sorption by rubber or PVC (Viaflex container) follows a reversible first order process (Sturek et al., 1978).



A semilog plot of the amount remaining in solution at time t minus the amount in solution at equilibrium is a linear function of time following the relationship:

$$\ln(A_t - A_{eq}) = \ln(A_o - A_{eq}) - (k_1 + k_{-1})t \qquad (1.6)$$

where A_o, A_{eq} and A_t are concentrations at zero, equilibrium, and any time t, respectively, and k_1 and k_{-1} are rate constants.

b. Open two-compartment model

Malick and co-workers (1981) suggested that the loss of nitroglycerin from its solution in plastic bags can be described as a two step processes: rapid adsorption of nitroglycerin by the surface of the bag at a rate of k_1, followed by dissolution of the nitroglycerin into the plastic. The

adsorbed molecule either diffuses into the plastic matrix at a rate of k_3, or partitions back to the solution at a rate of k_2. Through a steady-state approximation, the amount of nitroglycerin in the solution, A, can then be expressed as:

$$A = ße^{-k_3t} + (A_o - ß)e^{-k_1t} \tag{1.7}$$

where

$$ß = \frac{A_o}{\frac{k_3^2}{k_1k_2} + \frac{k_1^2}{k_2} - \frac{2k_3}{k_2}} \tag{1.8}$$

and A_o is the initial amount of nitroglycerin in the solution. Eqn.1.7 indicates that the amount of nitroglycerin in solution decreases in a biexponential manner.

1.2.2.4. Diffusion model

Diffusion is the process by which matter is transported from one part of a system to another as a result of random molecular motions under a concentration gradient. It can be defined by the following expression derived from Fick's first law of diffusion:

$$q = DA \int_0^t -(dc/dx)\, dt \tag{1.9}$$

where q is the amount of diffusing drug substance penetrating through a plastic piece with a surface area of A, in a finite time dt; dc/dx is the concentration gradient along the distance x from the origin and D is the

diffusion coefficient, which is assumed to be constant irrespective of the change in concentration (Wang and Chien, 1984).

Yuen and co-workers (1979) suggested that nitroglycerin uptake by a plastic strip cut from a plastic intravenous container is a sorption process which can be quantified using a diffusion model in which the concentration in the aqueous solution phase falls with time. The equation relating F, the fractional uptake and time is:

$$F = \frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2 q_n^2} \exp(-Dq_n^2 t/l^2) \qquad (1.10)$$

where M_t is the total amount of solute in the plastic at time t and M_∞ is the corresponding amount after infinite time. The half thickness of the plane sheet is used for l, if sorption occurs on both sides of the plastic strip. The value of α is the ratio of the final concentration, C_∞, to the total concentration drop in the aqueous solution (initial concentration, C_o, minus the final (equilibrium) concentration). The values of q_n are the non-zero positive roots of

$$\tan q_n = -\alpha q_n \qquad (1.11)$$

and can be obtained from literature data (Yuen et al., 1979). This group of investigators also suggested that the adsorption of drug on the surface of the plastic is possible. However, the quantity of the drug adsorbed may be insignificant when compared with the amount absorbed and the rate of adsorption may be much faster than the rate of absorption. As a result, the adsorption process is obscured (Yuen et al., 1979).

A diffusion model of the same form as eqn.1.10 was found by Roberts and co-workers (1980) to describe the disappearance kinetics of nitroglycerin from solutions stored in plastic tubing, burette and infusion bag more accurately than the closed two-compartment kinetic model suggested by Sturek and co-workers (1978). It was later suggested by Roberts and co-workers (1983) that the rate and extent of uptake of nitroglycerin, isosorbide dinitrate and ethylene glycol dinitrate from aqueous solutions to plastic intravenous delivery systems depends on the partitioning of the substance between the plastic and aqueous phases, its diffusion in the plastic matrix and its subsequent escape from the external surface of the plastic to the atmosphere.

When compared with an open two-compartment model (Malick et al., 1981), the diffusion model (Yuen et al., 1979; Roberts et al., 1980) appears to be more satisfactory in respect of both its description and its capacity to accurately predict the rate and extent of uptake of drugs such as nitroglycerin by PVC under a variety of storage conditions (Illum and Bundgaard, 1982; Kowaluk et al., 1985). Illum and Bundgaard (1982) have reported that minute amounts of nitroglycerin were actually adsorbed to the PVC container in comparison with the amounts absorbed. A migration of drug into the PVC matrix may, therefore, be the dominant process in sorption.

Bundgaard and Illum (1983) showed that the kinetics of disappearance of warfarin sodium, diazepam and other benzodiazepines from aqueous solutions stored in PVC infusion bags (Viaflex) could be described by a diffusion model; the loss of nitroglycerin to PVC bags has been described similarly (Yuen et al., 1979; Roberts et al. 1980). Nevertheless, the

sorption kinetics of warfarin and diazepam was also found to be equally well described by an open two-compartment model (Illum and Bundgaard, 1982; Lin and Kawashima, 1987).

According to Kowaluk and co-workers (1985), the compartment model appears to be useful only for describing drug uptake at early times. It is suggested by Kowaluk and co-workers (1985) that this is a consequence of its biexponential kinetics, which is similar to that of the approximation of the diffusion model used to predict the sorption profile of the drug for most times prior to its reaching equilibrium.

Although the diffusion model is able to describe the loss as equilibrium is approached and accurately predict the disapearance profiles of solutes with alterations in solution volume, infusion bag size or solution pH (Kowaluk et al., 1985, 1986), it is limited by its mathematically complexity and the requirement of data collection at both early times and at very long times when uptake into the plastic is approaching equilibrium.

A simplified diffusion model was subsequently proposed by Roberts and co-workers (1991). This model appears to be suitable for the estimation of the extent of sorption in the storage times likely to be encountered in clinical usage and enables the magnitude of the uptake in a specific time to be described by a single parameter, referred to as the sorption number (Sn):

$$Sn = \left[\frac{K^1A}{V}\right]^2 D = \left[\frac{KA}{V}\right]^2 f_u^2 D \qquad (1.12)$$

where K is the plastic-water partition coefficient for an unionized solute, K^1 is an apparent partition coefficient of solute between the plastic and the solution, A is the surface area of the infusion bag, V is the volume of the infusion solution, D is the diffusion coefficient of the solute in the plastic and f_u is the fraction of solute unionized in solution. This simple parameter, the sorption number, is sufficiently versatile to permit the prediction of the extent of solute loss during early times in a variety of situations; that is, it is not restricted by change in time, plastic surface area, solution volume or solution pH (Roberts et al., 1991).

An approximation of the model allows a ready estimation of the sorption number from the fraction remaining in solution at a given time (F_t) or vice versa (eqn.1.13).

$$Sn \cdot t = 0.75\left[\ln F_t + \frac{1}{2F_t^2} - \frac{1}{2}\right] \qquad (1.13)$$

1.2.3. Mechanisms of the sorption of therapeutic drugs and other solutes by PVC in dynamic conditions

As indicated above, a number of models have been proposed to describe the uptake of solutes by plastic infusion bags whereas the loss of solute from aqueous solution during flow through plastic tubing has not been as extensively investigated.

The compartment model assumes that the solute is first adsorbed onto the surface of the plastic and then dissolved instantaneously throughout the plastic (Amann and Baaske, 1982; De Muynck et al., 1988). This

model assumes that the solution within the tube can be described as being in a well-stirred compartment and does not take into account the observed decrease in the concentration along the tube. Kowaluk and co-workers (1982, 1983) presented the convection model which takes into account the decline in concentration along the tubing length but its use is limited to a simple first-order irreversible loss of solute.

It was shown that a convective diffusion model can be applied to the problem of Vitamin A loss to plastic tubing under clinical perfusion conditions (Amidon et al., 1981). Yliruusi and co-workers (1986a, 1986b) suggested a model for estimating adsorption of diazepam to PVC tubing during the first four hours during which the flow of liquid through tubing can be described as Poiseuille flow and a radial concentration gradient is always present in a tube if a sorptive drug is flowing through it. However, this model is applicable for some specific conditions only.

Roberts (1992) has described the initial loss of solute from solution flowing through tubing, in a convection-diffusion model, as a consequence of the plastic acting as an infinite sink. More recently, Donaldson and co-workers (1992) have proposed four models to describe the uptake of solutes by plastic tubing. These models are based on the two models used to describe convection down a tube, the well-stirred model (Amann and Baaske, 1982) and a plug flow of fluid down the tube with no longitudinal diffusion (Kowaluk et al., 1982, 1983; Roberts, 1992) and are combined with two models to describe uptake into the plastic - a compartment model and a diffusion model. Each of the models is represented schematically in Figure 1.2.

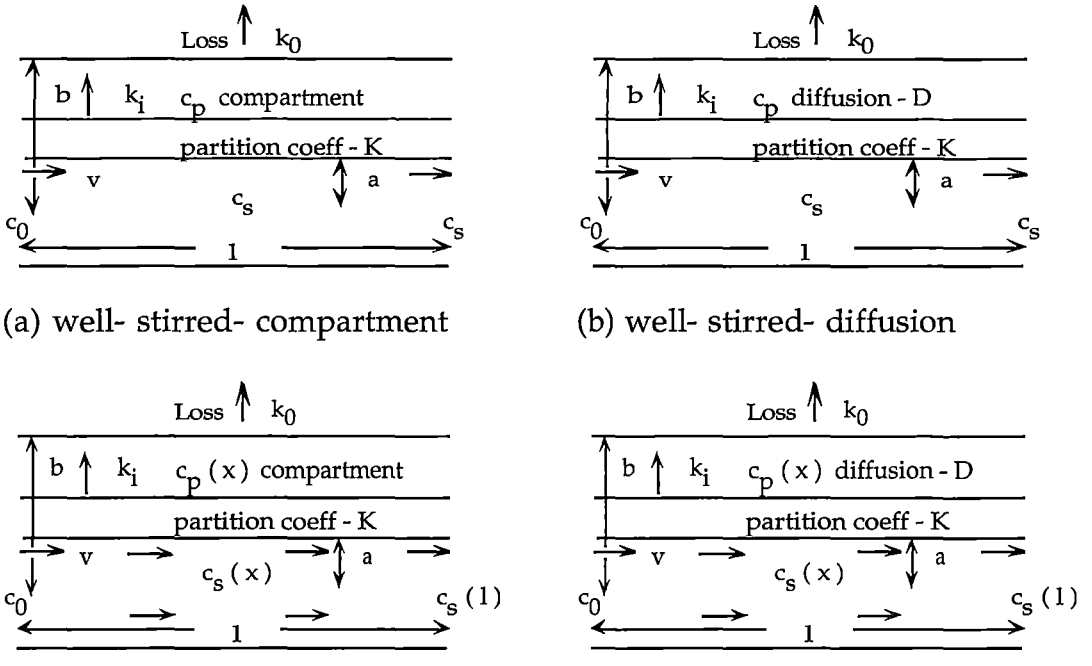


Figure 1.2. Schematic diagram of the four models considered: (a) well-stirred- compartment, (b) well- stirred- diffusion, (c) convection-compartment, (d) convection- diffusion.

The general mathematical expression for the well-stirred-compartment model and the well-stirred-diffusion model are of the same form and can be described as follows:

$$C_s = C_o (A + (B_1 + B_2) \exp [\rho_1 t] + (C_1 + C_2) \exp [\rho_2 t]) \qquad (1.14)$$

and the general mathematical expression for the convection-compartment model and the convection-diffusion model are of the same form and can be described as follows:

$$\frac{C_s}{C_o} = B_1' \exp(\rho_1' t) + C_1' \exp(\rho_2' t) + \exp\left(\alpha_1' \frac{x}{v}\right)\left(H\left(t - \frac{x}{v}\right)\left(1 - B_1' \exp\left(\rho_1'\left(t - \frac{x}{v}\right)\right)\right.\right.$$
$$- C_1' \exp\left(\rho_2'\left(t - \frac{x}{v}\right)\right) + \exp\left(\alpha_1' \frac{x}{v}\right)\int_0^t \left(H\left(u - \frac{x}{v}\right)\left(1 - B_1' \exp\left(\rho_1'\left(u - \frac{x}{v}\right)\right) -\right.\right.$$
$$C_1' \exp\left(\rho_2'\left(u - \frac{x}{v}\right)\right)\exp(\beta 2(t-u)) \times \left(\frac{\beta_1 \alpha_2 x}{v(t-u)}\right)^{1/2}$$
$$I_1\left(2\left(\frac{\beta_1 \alpha_2 x(t-u)}{v}\right)^{1/2}\right)du \qquad (1.15)$$

where C_s is the concentration of the solute in solution at time t and C_o is the initial solute concentration in each equation. The details and definition of other terms of eqns 1.14 and 1.15 are given by Donaldson and co-workers (1992).

1.3. Factors influencing the sorption of drugs into PVC

The uptake of a drug from a solution onto and into plastic is directly related to the chemical structure of both the drug and polymer. All other factors, such as pH, solvent systems, concentration of solute, presence of other ingredients in both the solution and the plastic and temperature only diminish or increase the magnitude of sorption (Autian, 1963a, 1963b). The effect of each of these factors is considered briefly below:

1.3.1. Infusion system

1.3.1.1. Type and concentration of plasticizer

It is well recognised that the extent of sorption of a number of drugs is most pronounced when PVC is used as a polymer material (Krieglstein

et al., 1972; Baaske et al., 1980; Illum and Bundgaard, 1982; Kowaluk et al., 1983; Hancock and Black, 1985; Lee, 1986; Yliruusi et al., 1986a, 1986b; Upton et al., 1987; Paborji et al., 1988; De Muynck et al., 1988, 1991). Illum and Bundgaard (1982) and Smith and Bird (1982) have attributed the higher uptake of lipophilic drugs by PVC to the presence of plasticizers or other additives which are not present in polyethylene or polyolefin. This result is supported by Weir and co-workers (1985) who suggested that the decrease in amiodarone concentrations after storage in flexible PVC bags or passage through i.v. administration sets of the same material might be attributable to an effect of the DEHP plasticizer.

Differences noted in the sorption pattern of various PVC infusion sets were found to be attributable to the formulation differences of the tubing (Baaske et al., 1980). Both the plasticizer type and concentration were found to have an influence on benzocaine sorption into PVC (Bray and Meakin, 1975, 1977; Bray, 1983). However, De Muynck and co-workers (1991) have shown that the Shore hardness of the tubing, which is proportional to the plasticizer content of the plastic, rather than the type of plasticizer used, was the determining factor for isosorbide dinitrate sorption.

1.3.1.2. Properties of the infusion system

The rate and extent of solute loss appears to be a function of the ratio of surface area of plastic in contact with the infusion solution (A) to the volume of the solution (V). Therefore sorption can be reduced by storing the largest possible volume in a given infusion bag or by using short lengths of small-diameter tubing during infusion (Roberts et al.,

1980; Baaske et al., 1980; Kowaluk et al., 1983; Yliruusi et al., 1986a). The effects of tubing length and radius on sorption have been reported for a number of drugs (Baaske et al., 1980; Amidon et al., 1981; Mason et al., 1981; Kowaluk et al., 1982, 1983; Yliruusi et al., 1986a).

Sorption of diazepam from large-volume i.v. admixtures to administration-set components was found to be directly proportional to the tubing length (Mason et al., 1981). This finding contrasts with those of Kowaluk (1982, 1983) and Yliruusi (1986a). According to Kowaluk and co-workers (1982, 1983), the steady-state effluent drug concentration decreases logarithmically with increasing tubing length. This result is consistent with that presented previously by Yliruusi and co-workers (1986a) who found an exponential dependence of diazepam concentration in the effluent on the tubing length. Theoretically, it seems impossible that the percentage adsorption of diazepam can be linearly related to the tubing length; if tubing length was increased to infinity, the percentage of diazepam adsorbed to the tubing would increase without limits, which clearly has no physical meaning (Yliruusi, 1986a).

The extent of drug sorption is dependent upon the design and make of the infusion set (Ingram and Miller, 1979; Baaske et al., 1980; Lingham et al., 1980; Tseui et al., 1980). For example, a perfusion apparatus with a roller pump sorbed considerably more chlorpromazine than a system with a piston pump. It is suggested that the use of a roller pump means more plastic material is in close contact with the perfusion medium (Krieglstein et al., 1972). An increase in the quantity of plastic in contact

with the perfusion medium leads to an increase in the amount of drug loss into the plastic (Krieglstein et al., 1972).

1.3.2. Infusion condition

1.3.2.1. Agitation and flow of an infusion solution

Static conditions. It has been reported that shaking the containers increases the rate and extent of diazepam sorption by eliminating the long distance transitions of the molecules, thus decreasing the average diffusion distance from the solution to the container wall (Yliruusi et al., 1986b). Similarly, it has been shown that stirring increased the rate and extent of trifluoperazine hydrochloride and warfarin sodium uptake from solution into PVC bags (Kowaluk et al., 1986). However, the rate and extent of loss of *p*-nitrophenol and *p*-toluidine was unaffected by the increased agiatiton of the solution (Kowaluk et al., 1986).

Dynamic conditions. Several investigators have reported that the availability of a number of drugs administered through flexible PVC tubing is greater with faster flow rates (Cossum et al., 1978; Roberts et al., 1980; Dasta et al., 1980; Baaske et al., 1980; Kowaluk et al., 1982, 1983; Lee, 1986). Predictive dosing charts for calculation of the actual diazepam doses delivered at various flow rates have been published (Mason et al., 1981; Yliruusi et al., 1986b). Parker and MacCara (1980) have found, however, that flow rate does not have an influence on diazepam availability and it has been suggested that insulin uptake into administration sets, which can be explained by an electrostatic

mechanism, was not substantially affected by flow rate (Furberg et al., 1986).

1.3.2.2. Infusion time

The extent of sorption of drugs from solutions in contact with PVC increases with time (Moorhatch and Chiou, 1974a; Kowaluk et al., 1981, 1983). The amount of diazepam sorbed into an i.v. administration system was found to be more dependent on flow rate and infusion time than on the type of container used (Dasta, 1980; Winses et al., 1981; Yliruusi et al., 1986b). The shorter the infusion time, the greater the percentage of drug sorbed (Parker and MacCara, 1980; Yliruusi et al., 1986b).

1.3.2.3. Pre-treatment of the infusion system before use

Pre-treating or priming the tube with 0.9% sodium chloride injection before adding diazepam to the burette did not effect final drug delivery (Lee, 1986). However, a 0.9% sodium chloride injection has a conditioning effect on PVC administration sets for drugs such as insulin which undergo an electrostatic sorption mechanism (Furberg et al., 1986). It was shown that imbibed water did not affect sorption of nitroglycerin by PVC strips cut from an infusion container (Yuen et al., 1979).

Although the loss of nitroglycerin can be reduced or avoided by rinsing the infusion system with the infusion solution before administration to the patient (Ingram and Miller, 1979; Christiansen et al., 1980; Roberts et

al., 1980), presaturation of i.v. administration sets with concentrated solution of nitroglycerin may complicate the titration of nitroglycerin infusions (Nix et al., 1984).

1.3.2.4. Temperature

An increase in the sorption of vitamin A and nitroglycerin by PVC strips cut from infusion bags was found to occur with an increase in temperature (Moorhatch and Chiou, 1974a; Yuen et al., 1979). The effect of temperature on sorption is the result of an increase in the rate of diffusion of the solute through the plastic matrix with a resultant increase in drug uptake (Moorhatch and Chiou, 1974a). The effect of temperature on the diffusion coefficient is found to follow an Arrhenius relationship whereas the effect of temperature on the partition coefficient is negligible (Yuen et al., 1979).

Temperature-dependence studies of sorption using the whole infusion bags have shown that a reduction in temperature causes a marked fall of the rate and extent of drug sorption (Baaske et al., 1980; Smith and Bird, 1982; Kowaluk et al., 1983). The diffusion coefficient and permeation rate constant both increase with temperature, while the PVC-water partition coefficient is independent of temperature (Roberts et al., 1983; Kowaluk et al., 1984). In addition, at higher temperatures, evaporation of drugs like nitroglycerin and ethylene glycol dinitrate from the plastic to the atmosphere also contributes to the total loss of these compounds (Roberts et al., 1983).

The enhanced sorption, at higher temperature, of chlorpromazine by

PVC pieces cut from PVC tubing indicates hydrophobic interactions. This could be observed in aqueous solution as well as in protein solution (Krieglstein et al., 1972).

1.3.3. Infusion solution

1.3.3.1. Drug properties

The hydrophobic/lipophilic character of a drug appears to be a premise for an interaction with synthetic materials such as PVC (Krieglstein et al., 1972; Kowaluk et al., 1981, 1983, 1986; Illum and Bundgaard, 1982; Bundgaard and Illum, 1983; Hancock and Black, 1985; Lee, 1986; Upton et al., 1987; Paborji et al., 1988). For example, Paborji and co-workers (1988) have shown that the substantial difference in the extent of drug uptake by PVC i.v. administration sets between two structurally similar cytotoxic agents, perilla ketone and ipomeanol, is due to the difference in lipophilicity. A considerable amount of perilla ketone, a highly lipophilic cytotoxic drug, was lost during infusion through plastic i.v. administration sets while ipomeanol, a structurally similar cytotoxic agent with reduced lipophilicity (a methyl group was replaced by a hydroxyl group) was not subject to uptake.

Besides lipophilicity, other physicochemical properties such as molecular size and shape may also affect drug uptake into the PVC matrix (Varsano and Gilbert, 1973; Moorhatch and Chiou, 1974a; Roberts et al., 1983, 1991).

1.3.3.2. Drug concentration

There are basically three types of concentration dependencies for a drug which interacts with plastic material (Wang and Chien, 1984):

a. For drugs such as chloroquine (Yahya et al., 1986) which undergo a Langmuir sorption mechanism, the extent of sorption of these drugs by PVC decreases at high drug concentration.

b. For drugs which undergo a partitioning or diffusion-controlled sorption mechanism, an increase in initial drug concentration results in an increase in the amount of drug uptake in fixed time. When the amount of drug uptake is plotted against the initial or equilibrium concentration of the drug in the solution, a linear relationship is obtained. However, the loss expressed as a fraction or percentage of the initial concentration of the drug is independent of the initial concentration of the drug.

   Examples are the sorption of nitroglycerin (Yuen et al., 1979; Roberts et al., 1980), vitamin A acetate and sodium methohexital (Moorhatch and Chiou, 1974a), chlorpromazine hydrochloride, diazepam, promazine hydrochloride, promethazine hydrochloride, thiopental sodium, thioridazine hydrochloride and trifluoperazine dihydrochloride (Kowaluk et al., 1982, 1983) and flunitrazepam (Nakajima et al., 1989).

   For diazepam, the result obtained by Kowaluk and co-workers (1983) contrasts with those reported by Parker and MacCara (1980)

and by Smith and Bird (1982) who both showed that diazepam sorption is dependent upon the initial concentration of the infusion solution. Kowaluk and co-workers (1983) have suggested that this might, in the case of the Parker and MacCara study, be due to the difference in the solution volumes used in that study.

c. For drugs which can enhance their own sorption by plasticizing or swelling the plastic at higher concentrations, the fractional amount of these drugs sorbed into a plastic infusion system is found to increase with concentration. It has been suggested that this results from the greater diffusivity of the drug in the plastic obtained at the higher initial concentration of an infusion solution and is essentially a consequence of an increase in free volume in the plastic matrix (Kowaluk et al., 1986). Examples are the sorption of clomethiazole edisylate (Kowaluk et al., 1981, 1982) and ranitidine HCl (Galante et al., 1990).

1.3.3.3. pH of the infusion solution

The rate and extent of sorption of ionizable drugs into a PVC matrix shows a dependence on pH. This could be interpreted in terms of ionization of the drug (Kowaluk et al., 1981, 1986; Yahya et al., 1986; Upton et al., 1987) and the unionized form of the drug is shown to be the partitioning species (Illum and Bundgaard, 1981, 1982; Monnot et al., 1990; Roberts et al., 1991). Thus, changes in the fraction of the unionized drug species induced by varying drug concentrations in unbuffered

aqueous solutions may have a pronounced influence on drug sorption (Bundgaard and Illum, 1983).

Adjustment of pH may, therefore, be required for systems in which drugs are weak acids or weak bases since sorption of these drugs is strongly dependent on the pH of the solution and is greatest when the drug is in its neutral, unionized form (Monnot et al., 1990). For example, without pH adjustment, spirogermanium, a cytotoxic agent, has shown substantial loss to a PVC container and to PVC tubing (Monnot et al., 1990).

1.3.3.4. Diluents and additives

The extent of the sorption of a number of drugs has been shown to be dependent on the diluent used in the preparation of the drug solution (Moorhatch and Chiou, 1974a; Illum and Bundgaard, 1982; Ray et al., 1983; Galante et al., 1990; Stewart et al., 1990). There is a trend toward a greater loss of diazepam to PVC-based tubing from a 0.9% sodium chloride injection than from a 5% dextrose injection (Hancock and Black, 1985). This result may be related to the pH differences of the solutions, since the pH of 5% dextrose injection (5.0) is closer to the pKa of diazepam (3.4) than is the pH of 0.9% sodium chloride injection (5.7). More diazepam is in the unionized form in 0.9% sodium chloride injection than in the 5% dextrose injection and this favours sorption by the PVC-based tubing. According to Hancock and Black (1985), the absorption is not, however, significantly different from the two vehicles because the difference in the unionized fraction of diazepam present in the two vehicles is very small. Similarly, there is no obvious difference

in the extent and time course of clonazepam loss into PVC infusion bags and PVC administration sets between 0.9% sodium chloride and 5% dextrose injections (Nation et al., 1983).

Despite a pH difference of less than 0.5 units, a solution of pentamidine isethionate in 5% dextrose infused through a PVC administration set showed a loss, relative to its initial concentration, of about 2%, while the same drug in a 0.9% sodium chloride admixture infused through the same set lost about 10%, relative to its initial concentration, after infusion (De et al., 1986). A possible explanation for the increase in the extent of sorption when the electrolyte is used is that ions may salt out the drug in the same way that electrolytes decrease the aqueous solubility of non-polar solutes. This mechanism was used to explain the difference in the amount of isosorbide dinitrate sorbed into PVC tubing from a 0.9% sodium chloride and from a 10% glucose solution (De Muynck et al., 1988). Greater adsorption of insulin onto the surface of PVC infusion bags was also found to occur from normal saline than from 5% dextrose solution (Hirsch et al., 1977).

The progressive decrease in nitroglycerin availability from a solution infused through PVC administration sets is also suggestive of a salting-out type of interaction in which nitroglycerin molecules removed from the admixture are deposited on the set. The availability of nitroglycerin was found to be an inverse function of increasing ionic strength irrespective of the type of electrolyte solution used (Loucas et al., 1990). In contrast, the result reported previously by Baaske and co-workers (1980) showed that the rate and extent of nitroglycerin loss from sodium chloride injection into PVC infusion bags appears to be less than that

from dextrose injection. These investigators suggested that the difference in drug sorption may be attributable to the change in ionic strength of the infusion solution.

The availability of lipophilic drugs such as chlorpromazine is increased when bovine serum albumin is added to the infusion solution. As the concentration of albumin in the chlorpromazine buffer solution is increased the sorption of the drug into PVC tubing is decreased. The interaction of the drug with albumin counteracts its sorption to PVC materials (Krieglstein et al., 1972). The addition of albumin or electrolytes and vitamins also decreases insulin loss from solution stored in PVC infusion bags (Weber et al., 1977). It has been shown that the presence of Pluronics F-68 surfactant can effectively prevent potency loss of diazepam solution stored in PVC bags by increasing the solubility of the drug in water. The Pluronics F-68 surfactant aqueous solution can, therefore, be used as a vehicle for a diazepam injection stored in PVC bags (Lin and Kawashima, 1987).

The uptake of perilla ketone by PVC based i.v. administration sets was completely prevented when a parenteral o/w emulsion was used as a vehicle for the formulation. In such a case, the drug, which is highly lipophilic, would reside mainly in the internal oil phase of the emulsion, thereby significantly reducing its affinity for the plastic during infusion (Paborji et al., 1988). Similarly, the material of the container (glass or PVC) was found to have little effect on the stability of vitamin A, a drug with a high affinity for PVC, in a paediatric TPN lipid emulsion and in an aqueous glucose/ amino acid solution (Bluhm et al., 1991). Examples of the use of parenteral emulsion dosage forms for

delivery through the plastic infusion system of novel cytotoxic agents which have low water solubility, lack stability to hydrolysis, are irritant or have substantial affinity for the plastic infusion system are given by Prankerd and Stella (1990).

1.4. Relationships between the sorption of drugs into PVC and their physicochemical properties

The principal physicochemical parameter used by several authors in prediction of drug/solute-PVC interaction is the partition coefficient of the drug/solute between an organic solvent and water (Kowaluk et al., 1981; Illum and Bundgaard, 1981; Bundgaard and Illum 1983). Since, it appears that the mechanism of the drug/solute-PVC interaction is similar in principle to that of a drug-receptor interaction, other physicochemical parameters which are used in QSAR studies, such as chemical structure contribution, intrinsic molecular volume, solvatochromic parameters and dipole moment, are also considered in the present study.

1.4.1. Partition coefficient

Since the lipid solubility or lipophilicity of a drug, which is one of the main physicochemical determinants controlling drug sorption into a PVC matrix, can be expressed in terms of the partition coefficient of the drug between an organic solvent and water (Kowaluk et al., 1981; Illum and Bundgaard, 1981; Bundgaard and Illum 1983), various organic solvent systems have been utilized to mimic the interaction between

PVC and drug solutions. These solvent systems have included heptane-water (Upton et al., 1987), hexane-water (Illum and Bundgard, 1981, 1982; Bundgaard and Illum 1983; Illum et al., 1983; De Muynck et al., 1988), dichloromethane-water (Illum et al., 1983), carbon tetrachloride-water (Illum et al., 1983), chloroform-water (Roberts et al., 1983, 1991) and octanol-water (Kowaluk et al., 1981; Illum and Bundgard, 1982; Illum et al., 1983; Pitt et al., 1988; Hayward et al., 1990; Atkinson and Duffull, 1991; Roberts et al., 1991).

Octanol-water appears to be the preferred reference solvent system and it is suggested by several authors that octanol-water partition data can be used to predict sorption into PVC (Illum et al., 1983; Atkinson and Duffull, 1991; Roberts et al., 1991). An advantage of using the octanol-water system as the reference base is that there is a large literature database of experimental octanol-water partition coefficient values (Leo et al., 1971; Hansch and Leo, 1979; Hansch et al., 1990b) and it is possible to calculate octanol-water partition coefficients (Hansch and Leo, 1979).

The several forms of a relationship between the sorption behaviour of solutes in PVC-water systems and octanol-water partition data (Illum et al., 1983; Atkinson and Duffull, 1991; Roberts et al., 1991) is of the same form as that between the polymer-water partition coefficient ($\log P_{polymer}$) and the octanol-water partition coefficient ($\log P_{octanol}$) of a number of solutes, in six other polymer-water systems, as follows:

$$\log P_{polymer} = a \log P_{octanol} + b \qquad (1.16)$$

where a and b are constants (Pitt et al., 1988).

When, for example, the rate and extent of sorption of a solute into PVC is expressed in terms of the logarithm of the sorption number (log Sn) (Roberts et al., 1991), eqn.1.16 can be written as

$$\log Sn = 0.78 \log P_{octanol} - 4.18 \qquad (1.17)$$
$$(n = 12, r = 0.825, p < 0.01)$$

It is suggested, however, that the ability of a single solvent to model the material-solute interaction (in static conditions) is limited because of the multiple mechanisms by which the PVC and the solute can interact (Jenke, 1993). Consequently, bimodal expressions with two dissimilar solvent systems (octanol-water and hexane-water) have been developed to model the interactions that occur between a PVC container and its contained solution (Hayward et al., 1990; Hayward and Jenke, 1990; Jenke, 1993). In addition to the octanol and hexane system, other bimodal solvent systems, including DEHP and PVC resin, and octanol and heptane can also mimic the behaviour of polymers studied with a high degree of accuracy (Jenke, 1993).

Furthermore, the octanol-water partition coefficient has been shown to be an inadequate model for predicting drug loss during infusion through plastic infusion sets (Kowaluk et al., 1982). This lack of correlation between the extent of loss and partition coefficient value arises from the inability of this simple relationship to account for the dynamic nature of the sorption process (Kowaluk et al., 1981).

1.4.2. Intrinsic molecular volume and solvatochromic parameters

Solubility has been shown to be well correlated with solvent dependent properties by equations that include linear combinations of free energy or enthalpy contributions by three types of terms:

$$XYZ = XYZ_0 + \text{cavity term} + \text{dipolar term} + \text{hydrogen bonding term(s)} \quad (1.18)$$

where XYZ_0 is a constant. The cavity term is given by $\bar{V}$, the molar liquid volume of the solute and the solvatochromic parameters, π^*, α, and ß, are the solute polarity and hydrogen bond donor and acceptor abilities, respectively (Kamlet et al., 1983, 1986). Thus, for solubility properties of multiple solutes in single solvents, or distribution between pairs of solvents, the general equation is of the form:

$$XYZ = XYZ_0 + (m\bar{V}/100) + s\pi^* + a\alpha + bß \quad (1.19)$$

where m, s, a, and b are system-dependent constants (Kamlet et al., 1983; Kamlet and Taft, 1985).

The cavity term is a measure of the free energy necessary to separate the solvent molecules (or to overcome solvent-solvent interactions) to provide a suitably sized cavity for the solute. This term is given by $\bar{V}$, the molar liquid volume, which is obtained by dividing the molecular weight by the liquid density at 25 °C (Kamlet et al., 1986). A new, calculated value of the van der Waals or intrinsic molecular volume, V_I has been shown to be as effective as the molar volume, $\bar{V}$, as a measure of the cavity term in linear solvation energy relationships for octanol-

water partition coefficients and aqueous solubilities (Leahy, 1986). Additionally, as V_I is computed by using a molecular modelling system, equations which contain this term can be extended to compounds that are solids or gases (Leahy, 1986).

The dipolar term is a measure of exoergic effects of solute-solvent, dipole-dipole, dipole-induced dipole and dispersion interactions; π^* is the solvatochromic parameter that influences this term (Kamlet et al., 1977).

The use of the solvatochromic comparison method has been used to formulate a π^* scale of solvent polarity-polarizabilities, so named because it was derived from and was best fitted to correlate solvent effects on p -> π^* and π -> π^* electronic spectral transitions of uncharged molecules (Kamlet et al., 1977, 1979, 1983; Chawla et al., 1981). The hydrogen bonding terms describe the exoergic effects of complexation between HBD and HBA and α and ß are the solvatochromic parameters that characterize HBD acidity and HBA basicity, i.e., they express the abilities to donate and accept a proton to form a hydrogen bond respectively (Kamlet et al., 1986).

The original set of solvatochromic parameters was mainly for liquid compounds and was constructed by using a solvatochromic comparison method, as first described by Kamlet and Taft (1976). This method was based on the solvent effect on UV, IR, ESR, or NMR spectra of indicator molecules (Abboud et al., 1977; Kamlet et al., 1977, 1983; Chawla et al., 1981; Kamlet and Taft, 1976, 1985; Taft et al., 1985). Since it was found that these parameters and this methodology could be used to correlate

solubilities and other properties of solutes, parameter estimation rules have been proposed and a database of parameters for solid solutes has been assembled. This allows the accurate prediction of octanol-water partition coefficients of a wide range of organic nonelectrolyte solutes, such as non-hydrogen bonding, hydrogen bond acceptor and weak and strong hydrogen bond donor aliphatic and aromatic solutes, whose solvatochromic parameters have not yet been measured. However compounds with intramolecular hydrogen bonding cannot be adequately described by these rules (Kamlet et al., 1988). In addition, for most monofunctional aliphatic compounds, these parameters can be estimated from corresponding values of closely related compounds (Kamlet et al., 1986). A comprehensive collection of the solvatochromic parameters, π^*, α, and ß, and some methods for simplifying the generalized solvatochromic equation are also available (Kamlet et al., 1983, 1988). Determination of the intrinsic molecular volumes and solvatochromic parameter values (mainly for aromatic solutes) are described in Appendix I.

In order to correlate all aromatic and aliphatic solutes together and to extend the methodology to solutes of more complex functionality, it was found necessary to modify some of the solvatochromic parameters by a set of ground rules (Leahy, 1986). The general LSER (linear solvation energy relationship) is shown as follows: (Kamlet et al., 1988)

$$XYZ = XYZ_o + (m\bar{V}/100) + (s(\pi^*+d\partial)) + a\alpha_m + b\beta_m \quad (1.20)$$

where ∂ is a polarizabilty correction parameter. The subscript m indicates that, for compounds that are capable of self-association (i.e.,

amphi-hydrogen bonding compounds), the parameter applies to the non-self-associated "monomer" solute rather than the self-associated "oligomer" solvent. In practice, most of the linear solvation energies that have been reported are simpler than indicated by the general equation proposed because one or more of the terms is not appropriate (Kamlet et al., 1986). It is also suggested that the solvatochromic parameters and linear solvation energy relationships may serve as powerful tools toward the solution of important problems in biomedical QSAR studies (Taft et al., 1985).

1.4.3. Dipole moment

All forces between atoms or drug molecules and receptors or biomacromolecules are electrostatic in origin (Lien et al., 1982). Several types of noncovalent interactions between drugs and receptors can be described as interactions between charges (long-range force), between charge and a dipole and between dipoles (short-range forces) (Lien et al., 1982) and these electronic effects can be considered to be represented by the electric dipole moment, μ (Hansch et al., 1990a).

Most of the dipole moment values are determined from measurement of the dielectric constant. There are approximately 20 equations for converting dielectric constant data to dipole moment, but most workers use the Debye or Onsager equations (McClellan, 1963). A table of the experimental dipole moments of a large number of compounds has been compiled by McClellan (1963).

Dipole-charge and dipole-dipole interactions are dependent both on the orientation of the dipoles and the distances between charges and/or partial charges, that is, the energy of interaction between two dipoles, μ_1 and μ_2, can be approximated as shown in eqn.1.21, where D is the dielectric constant, r is the distance between the dipoles and θ and ϕ are the angles between the lines joining the middles of the dipoles and the lines between the ends of the dipoles (Hansch et al., 1990a). In simple studies of drug-receptor interactions it can be assumed that the receptor remains unchanged and only the relevant property of the drug is considered (Hansch et al., 1990a).

$$E = (2\mu_1\mu_2 \cos\theta \cos\phi)/Dr^3 \qquad (1.21)$$

There are two uses of dipole moments in correlation studies (Hansch et al., 1990a). The first is the use of substituent group dipole moments to characterize the substitution, which, in QSAR study, is shown to be less common than that of polar substituents such as Hammett σ constants and the Taft polar constant σ^* (Hansch and Leo, 1979; Lien et al., 1982). The second is the use of molecular dipole moments which are a function of all component dipole moments in a molecule and can be very complicated in their structural definition (Hansch et al., 1990a). The examples of the latter application are the successful correlations obtained between octanol-water partition coefficients and molecular dipole moments and the antishock activity of miscellaneous anticonvulsants (eqn.1.22) and the acute lethal toxicity of a series of lactams, thiolactams, ureas and thioureas having convulsant activity (eqn.1.23) (Lien et al., 1973), as follows:

$$\log (1/C) = -0.222 (\log P)^2 + 1.153 \log P - 0.368\mu + 2.994 \quad (1.22)$$

$$(n = 18, r = 0.99, s = 0.24)$$

$$\log (1/C) = -0.364 (\log P)^2 + 1.055 \log P + 0.247\mu + 1.298 \quad (1.23)$$

$$(n = 20, r = 0.89, s = 0.24)$$

where log (1/C) denotes the drug activity, logP and μ denote logarithm of octanol-water partition coefficients and molecular dipole moments, respectively.

1.4.4. Chemical structure contribution

The use of the additive mathematical model was proposed by Free and Wilson (1964) as a means of describing the structure-activity relationships of a series of chemical analogs. The model is based on the assumption that each substituent in the structure makes a constant contribution to biological activity. This contribution can be calculated by multiple linear regression analysis. It should be additive and independent of contributions from other substituents. The data requirements include specific side chain arrangements and performance characteristics of all analogs tested. The results rank the structural changes per position by estimating the amount of activity attributed to each change. The estimates are both positive and negative.

Successful solutions can provide reasonable estimates of inherent variation within the testing system. The suggested models do not compensate for the three dimensionality of compounds, pH, pKa, or other similar physical properties. The use of this model, in which the

performance characteristics are measures of biological activity, is described as follows:

Example 1. The simplest problem is the structure-activity of four analogs developed through two different changes at a single carbon in the molecule (Figure 1.3). The biological response of interest of these analgesic compounds is the LD_{50} as shown in Table 1.2.

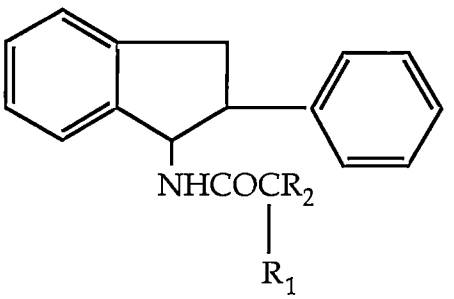


Figure 1.3. General structure of four analogs studied

Table 1.2. LD_{50} values for four analgesic compounds

R_2	R_1			
	H	CH_3	Total	Mean
$N(CH_3)_2$	2.13	1.64	3.77	1.885
$N(C_2H_5)_2$	1.28	0.85	2.13	1.065
Total	3.41	2.49		2.950
Mean	1.705	1.245	2.950	1.475

The mathematical models described are based upon the assumption that there is some such additivity in a series of analogs, i.e.,

Response = average + effect of R_1 substituent + effect of R_2 substituent

There are therefore four equations with five unknowns as follows:

$$2.13 = \mu + a(H) + b(N(CH_3)_2) \quad (1.24)$$

$$1.28 = \mu + a(H) + b(N(C_2H_5)_2) \quad (1.25)$$

$$1.64 = \mu + a(CH_3) + b(N(CH_3)_2) \quad (1.26)$$

$$0.85 = \mu + a(CH_3) + b(N(C_2H_5)_2) \quad (1.27)$$

The contributions at each position sum to zero, that is,

$$a(H) + a(CH_3) = 0$$

and $$b(N(CH_3)_2) + b(N(C_2H_5)_2) = 0$$

By imposing this restriction one needs solve for only μ, a(H), and $b(N(CH_3)_2)$. The overall average (1.475) is substituted for μ, and the mean value for each substituent minus μ for the other terms in eqns.1.24 to 1.27. Thus, for the four analgesic compounds studied, the constant contribution to LD_{50} value of each substituent can be obtained as follows:

$$a(H) = 1.705 - 1.475 = +0.23$$

$$a(CH_3) = 1.245 - 1.475 = -0.23$$

$$b(N(CH_3)_2) = 1.885 - 1.475 = +0.41$$

$$b(N(C_2H_5)_2) = 1.065 - 1.475 = -0.41$$

1.5. Objectives of the present work

This work has been undertaken to test the general applicability of a number of mathematical models for the quantitative prediction of drug

plastic interaction, which have been proposed by workers from this laboratory in recent years.

More specifically, the "sorption number" model for the prediction of the rate and extent of drug/solute uptake from aqueous solutions by PVC infusion bags (Roberts et al., 1991) was developed largely through a retrospective review of previously published work and its potential applicability in a more general way has been limited to results presented by other authors. The final paragraph in the report of Roberts and co-workers (1991) specifically cautions others in this field against using the "sorption number" model until it has been subjected to a longer period of scrutiny - and refinement.

Similarly, mathematical models directed to the quantitative prediction of drug/solute loss to a PVC tubing system during the flow of an aqueous solution through such a system have been presented recently (Donaldson et al., 1992). The development of these model has, similarly, been based on limited experimental data and more extensive testing, and possible refinement, is appropriate.

A secondary objective of this work is to consider the possibility that one or more other (new) models may be more appropriate to meet a specific purpose - the quantitative prediction of drug plastic interaction in infusion bags and in flow-through applications in polymeric tubing.

CHAPTER 2. SOLUTE-PVC INTERACTION IN STATIC CONDITIONS

2.1. 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 (Chapter 1). Workers from this laboratory have presented a predictive model (Roberts et al., 1991) based on a diffusion controlled uptake mechanism which had been proposed previously (Kowaluk et al., 1985). This model (Roberts et al., 1991) is based on several assumptions and it has been suggested that further work is required to establish a more refined equation.

One of the assumptions in the 'Roberts' model is 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 the model proposed by Roberts and co-workers (1991) was intended for application only at room temperature it is nevertheless desirable, in developing 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. The correlation between the rate and extent of solute uptake by PVC infusion bags as expressed by the single term, sorption

number (Roberts et al., 1991) and selected physicochemical properties of solutes such as octanol-water partition coefficient, dipole moment, intrinsic molecular volume and solvatochromic parameters, are examined. The influence of chemical structure and chemical interaction on solute sorption by PVC infusion bags is also studied.

2.2. 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), *p*-bromophenol (BDH Chemicals, lot 1818810), *p*-methylacetophenone (Aldrich, lot 2805CJ), thymol (Naarden, Sydney, Australia, lot P692/1), 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.

2.2.1. Leaching (desorption) from the bag

500 mL of distilled water was transferred into the infusion bag and stored, as described below, for periods of up to 8 hours. The bag was suspended in an upright position from a metal frame by wire hooks and was not disturbed at any time during the required period except to remove samples for analysis. The experiments were run in quadruplicate in the open at room temperature. At selected times, up to 480 minutes, a sample of approximately 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. An ultraviolet-light absorbance of the sample was then measured between 200 and 300nm using a Pye Unicam SP8-100 spectrophotometer and the sample was immediately returned to the PVC bag. Solution from time zero was used as a blank.

2.2.2. Sorption profiles of model solutes

The solutes used in this study were acetophenone, chlorocresol, chloroxylenol, *p*-chlorophenol, nitrobenzene, phenol, *o*-xylenol, *p*-bromophenol, *p*-methylacetophenone and thymol. An aqueous solution of each compound was prepared using glass distilled water and was transferred to the infusion bag and stored for periods of up to 8 hours. Solute concentrations used are shown in Table 2.1. At selected times, a sample was removed from the bag and the solute concentration was determined without dilution, using UV spectrophotometry and the procedure described in Section 2.2.1, at the wavelength of maximum

absorbance for each solute as determined prior to commencement of the sorption experiments, i.e., 245, 225, 280, 279, 276, 267, 269, 279, 256 and 273nm for acetophenone, chlorocresol, *p*-chlorophenol, chloroxylenol, *o*-xylenol, nitrobenzene, phenol, *p*-bromophenol, methylacetophenone and thymol, respectively. The sample was then immediately returned to the PVC bag. All compounds used obeyed Beer's law. In all instances, quadruplicate samples were run and the equivalent solution without solute was used as a blank.

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; that is, the flasks were stored in an upright position throughout the study to prevent contact of the drug solution with any material except glass.

Table 2.1. Solute concentrations used in sorption profiles study

Solute	Concentration ($x10^5$M)	Solute	Concentration ($x10^5$M)
Acetophenone	4.99	Nitrobenzene	5.52
Phenol	54.10	*o*-Xylenol	38.90
Methylacetophenone	3.92	*p*-Chlorophenol	45.80
p-Bromophenol	47.40	Chlorocresol	8.48
Thymol	32.10	Chloroxylenol	51.10

2.2.3. Investigation of chemical interaction(s) between PVC and selected solutes

PVC samples cut from an unprinted area of PVC infusion bag were rinsed with water and allowed to dry before use. The PVC strip was soaked in pure acetophenone or nitrobenzene liquid overnight. The PVC strip soaked overnight in pure liquid was then removed and drained before study by infrared spectroscopy. Infrared spectra were determined using a Digilab FT5-20E Fourier transform infrared spectrometer. All samples were run using ATR accessory and 512 scans. The resolution used was 4 cm^{-1}.

2.2.4. Factors affecting solute sorption into PVC bag

In this study, all sample solutions were prepared, transferred to the infusion bags and analysed using the methods similar to those described above in Section 2.2.2. The experiments were run in the open at room temperature or in a closed oven at the other temperatures. In all instances unless otherwise noted, quadruplicate samples were run.

2.2.4.1. Solute concentration, electrolyte concentration/vehicle ionic strength and temperature studied simultaneously

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 the propensity of each of these factors to affect a sorption process, a three-factor, two-level factorial design

experiment (Armstrong and James, 1990) 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 2.2, were chosen to provide an absorbance between 0.2 and 0.7.

Factor B: temperature; 20±2 and 40±2°C.

Factor C: absence or presence of an electrolyte (0.9% sodium chloride).

Table 2.2. Concentration of the solutes used in the investigation of the effects of solute concentration, electrolyte concentration/vehicle ionic strength and temperature on solute uptake by PVC bags

Solute	Concentration ($x10^5M$)	
	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

The experiments were set up as shown in Table 2.3 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 part of the work, the experiments were run in duplicate.

Table 2.3. Factorial design to show sorption of the drug by PVC bags

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

2.2.4.2. Effect of solute concentration

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 2.4, were chosen to provide an absorbance value, at the wavelength of maximum absorbance, between 0.2 and 0.7.

Table 2.4. Solute concentrations used in the effect of concentration on sorption study

Solute	Concentration ($x10^5$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.

2.2.4.3. Effect of electrolyte concentration/vehicle ionic strength

A single concentration of solute was used at five different sodium chloride concentrations (Tables 2.4 and 2.5) and controls containing all the ingredients of the solutions except sodium chloride were used to represent zero ionic strength solutions.

Table 2.5. Sodium chloride concentrations used in the effect of vehicle ionic strength on sorption study

Experiment	Sodium chloride concentration (%w/v)	Ionic strength
1	0.000	0.0000
2	0.225	0.0385
3	0.450	0.0770
4	0.675	0.1155
5	0.900	0.1540
6	1.125	0.1925

The experimental procedure used was as described above in Section 2.2.2. 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 and extent of sorption were also studied on 4.54×10^{-4}M *p*-chlorophenol and/or 3.89×10^{-4}M *o*-xylenol aqueous solutions. Additionally, the effect of vehicle ionic strength of electrolyte solutions with a large anion was investigated by using five different sodium benzoate concentrations in nitrobenzene or *p*-chlorophenol aqueous solutions. For 5.53×10^{-5}M nitrobenzene aqueous solution, sodium benzoate concentrations used were 0.00, 1.11×10^{-4}, 2.22×10^{-4}, 5.55×10^{-4} and 1.11×10^{-3}M. For 2.74×10^{-4}M

p-chlorophenol aqueous solution, sodium benzoate concentrations used were 0.00, 2.74×10^{-4}, 4.58×10^{-4}, 1.11×10^{-3} and 2.78×10^{-3}M.

2.2.4.4. Effect of storage temperature

For acetophenone and chlorocresol, aqueous solutions of each compound were used at four separate concentrations (Table 2.4). The sorption studies were conducted at four different temperatures, i.e., 20±2, 30±2, 40±2 and 50±2°C.

2.3. Data Analysis

For comparative purposes, the data obtained from Section 2.2.2 and 2.2.4 was expressed as the fraction of the original concentration of solute remaining in solution at time t (F_t). The sorption number (hour $^{-1}$) of each compound was calculated from the slope of a plot between a function of the fraction of the original concentration of solute remaining in the solution ($\ln F_t + 1/2F_t^2 - 1/2$) and t using the method described by Roberts and co-workers (1991) (see eqn.1.13) and in this work is the value determined for the period up to 8 hours.

The relationships between the sorption numbers of the solutes and physicochemical parameters of each solute were investigated using regression analysis and the StatView SE+ Graphics software (Abacus Concepts Inc.) on a Macintosh computer.

The contribution of the substituents in the structure to the sorption behaviour (as expressed by the logarithm of the sorption number) of

selected solutes which have the same basic structure; phenol, acetophenone, methylacetophenone, *o*-xylenol, chlorocresol and *p*-chlorophenol was calculated by multiple linear regression analysis using Free-Wilson analysis in the QSAR-PC:PAR software on an IBM compatible computer. Three substituents of interest are at positions a, b and c in the structure shown in Figure 2.1 and the details for each solute used is shown in Table 2.6.

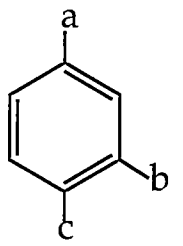


Figure 2.1. The general chemical structure of six solutes used in Free-Wilson analysis

Table 2.6. Solutes used in Free-Wilson analysis

Solute	$aCOCH_3$	aOH	bH	bCH_3	cH	cCH_3	cCl
Phenol	0	1	1	0	1	0	0
Acetophenone	1	0	1	0	1	0	0
Methylacetophenone	1	0	1	0	0	1	0
o-Xylenol	0	1	0	1	0	1	0
Chlorocresol	0	1	0	1	0	0	1
p-Chlorophenol	0	1	1	0	0	0	1

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 eight hours. 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 eight hours by using the StatView SE+ Graphics software (Abacus Concepts Inc.) on a Macintosh computer.

2.4. Results and Discussion

2.4.1. Leaching (desorption) from the bag

It was found that the UV spectrum, from 200 to 300nm, of the distilled water sample stored in PVC infusion bags for a period of 8 hours has no absorbance peak. This indicates that an insignificant amount of UV-absorbing materials had leached from the PVC infusion bag into the aqueous solution during the storage period of 8 hours under static condition.

2.4.2. Sorption profiles of model solutes

The sorption profiles of the solutes used in this study are shown in Figures 2.2 and 2.3. The sorption number (Sn) of each compound was then calculated from the slope of a plot between the function of the fraction of the original concentration of solute remaining in the solution (Ft), ($\ln F_t + 1/2\ F_t^2 - 1/2$), and time as suggested by Roberts and co-workers (1991). The correlation coefficient for each of these plots was greater than 0.98 ($p<0.05$).

The logarithm of the sorption number of solutes used are presented in Table 2.7 together with the solute octanol-water partition coefficient

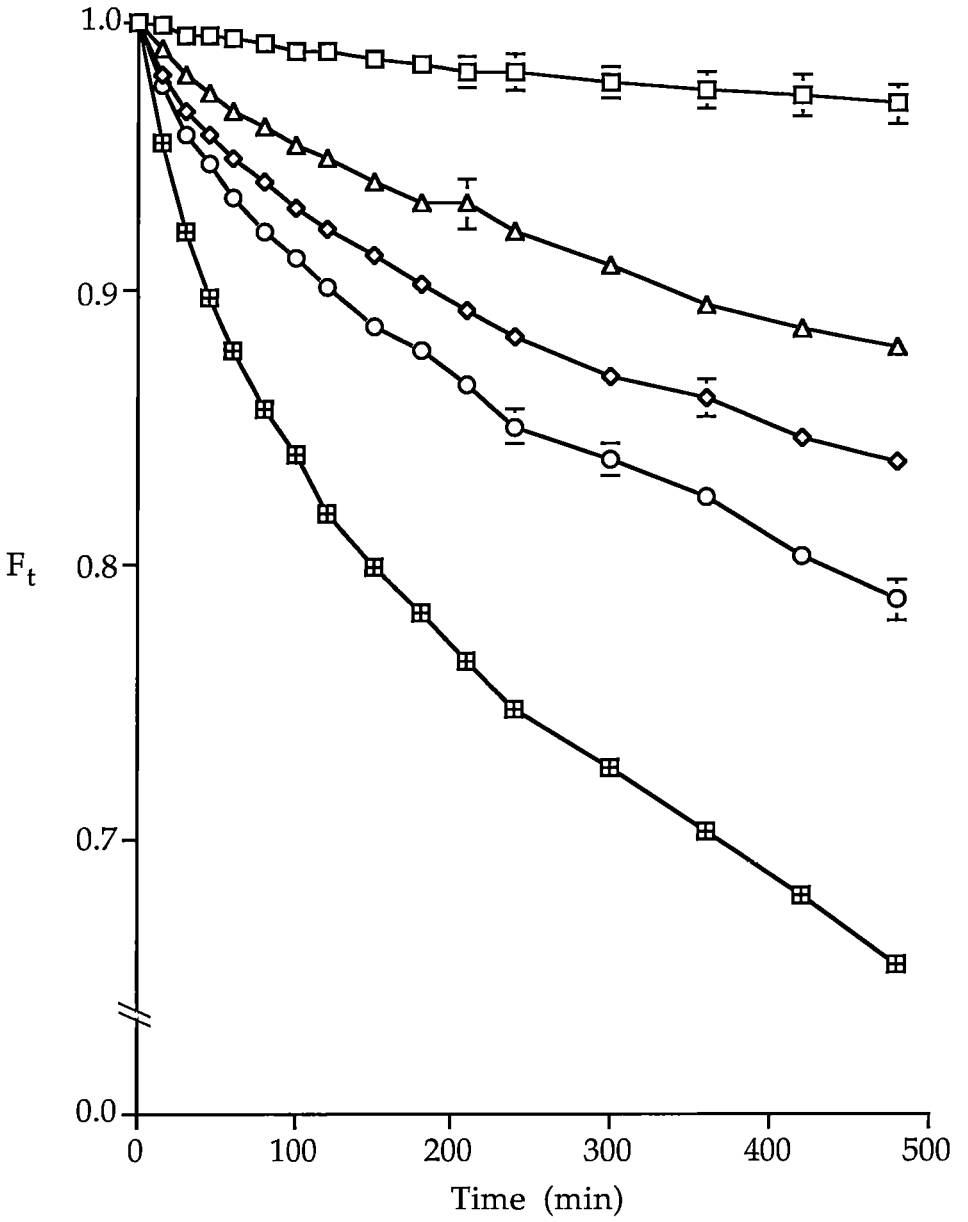


Figure 2.2. Fraction of the original concentration of solute remaining in a solution stored in a PVC infusion bag for 8 hours; —○— = *p*-bromophenol, —◇— = *p*-chlorophenol, —△— = *o*-xylenol, —□— = phenol, —⊞— = chlorocresol.

Note: Error bars indicate SD values. Error bars are shown only for points for which SD's are "visible" at the scale used on the y-axis. Points without error bars have SD's smaller than is "visible" on the scale used on the y-axis.

This convention applies in all subsequent graphs.

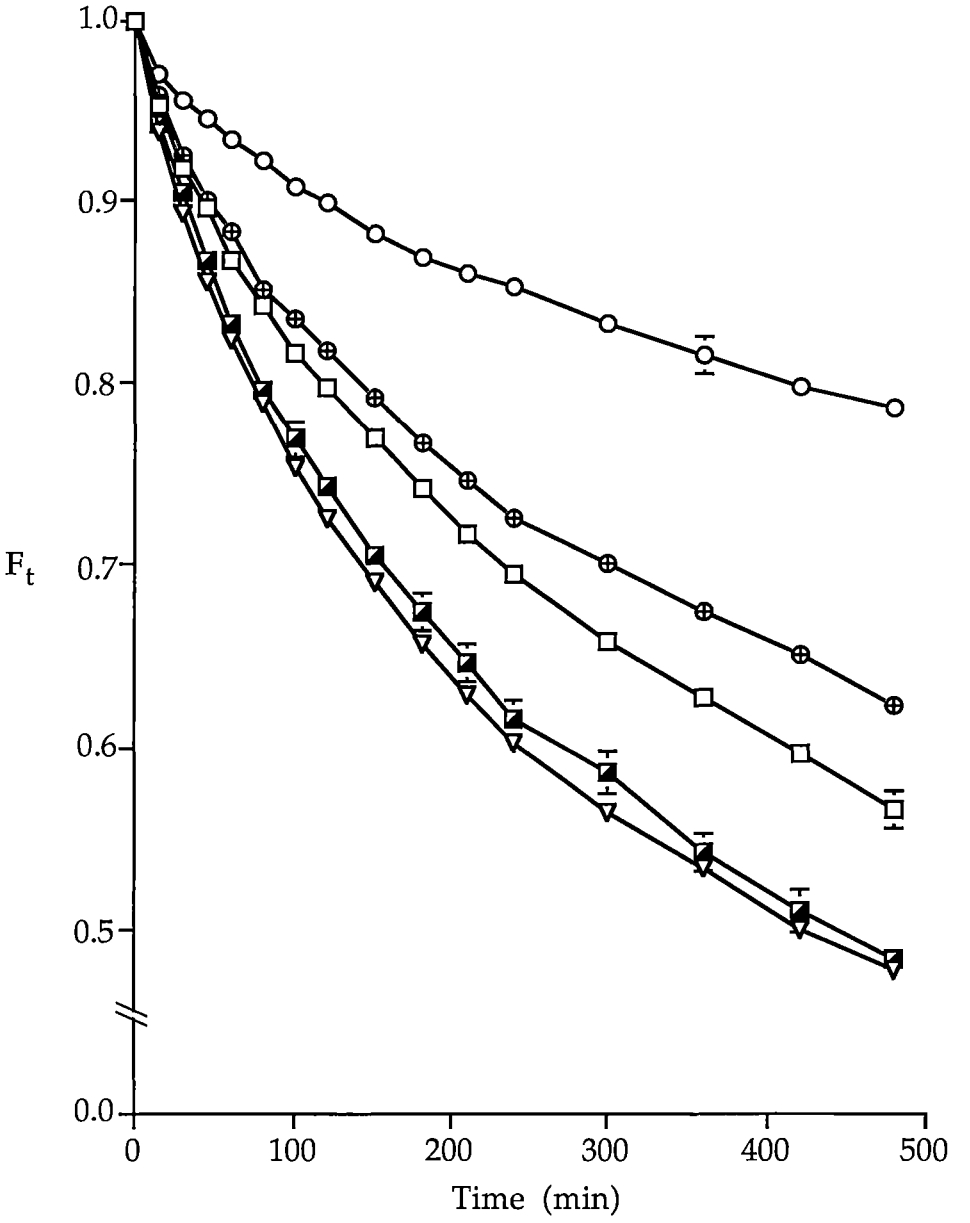


Figure 2.3. Fraction of the original concentration of solute remaining in a solution stored in a PVC infusion bag for 8 hours; —⊕— = methylacetophenone, —◪— = thymol, —□— = nitrobenzene, —○— = acetophenone, —▽— = chloroxylenol.

(logP), dipole moment (μ), intrinsic molecular volume (V_I) and solvatochromic parameters (π*, ß and α).

Table 2.7. Logarithm of the sorption number and physicochemical parameters[a] of solutes investigated in this study

Solute	log Sn±SD	logP[b]	μ[c]	$(V_I/100)$[d]	π*[d]	ß[d]	α[d]
Acetophenone	-2.20±0.00	1.66	2.90	0.690	0.90	0.49	0.04
Nitrobenzene	-1.35±0.03	1.84	4.00	0.631	1.01	0.30	0.00
Phenol	-4.00±0.23	1.28	1.52	0.536	0.72	0.33	0.61
o-Xylenol	-2.76±0.03	2.23	1.75	0.732	0.64	0.35	0.60
Methylacetophenone	-1.54±0.00	2.28	3.22	0.788	0.86	0.50	0.00
p-Chlorophenol	-2.48±0.01	2.42	2.28	0.626	0.72	0.23	0.67
p-Bromophenol	-2.21±0.03	2.60	2.37	0.699	0.79	0.30	0.67
Chlorocresol	-1.76±0.02	3.10	(2.28)	(0.724)	(0.72)	(0.23)	(0.67)
Thymol	-1.07±0.03	3.30	(1.55)	(0.928)	(0.60)	(0.35)	(0.60)
Chloroxylenol	-1.07±0.00	3.48	(2.92)	(0.822)	(0.64)	(0.25)	(0.64)

[a] Values in parentheses are estimated from corresponding values for closely related compounds (see Appendix I) and are not included in the regression.

[b] obtained from Hansch and Leo, 1979. An average value is used where there is more than one value reported.

[c] obtained from McClellan, 1963.

[d] obtained from Kamlet et al., 1988; Tayar et al., 1991. The intrinsic molecular volume and solvatochromic parameters of 3, 5 dimethylphenol are used for *o*-xylenol (3, 4 dimethylphenol).

It was found that the correlation between the logarithm of the sorption number and the logarithm of octanol-water partition coefficient is not significant ($p > 0.05$). This result contrasts with that reported previously by Roberts and co-workers (1991) who suggested that a reasonable correlation exists between log Sn and log $P_{octanol}$ as expressed by eqn.1.17

$$\log Sn = 0.78 \log P_{octanol} - 4.18 \qquad (1.17)$$

The actual log Sn values and those predicted using eqn.1.17 are shown in Figure 2.4. A fair correlation between the logarithm of the sorption number and the dipole moment term (μ) for all seven solutes has been obtained as follows:

$$\log Sn = 0.91\,\mu - 4.71 \qquad (2.1)$$

$$(n = 7;\ r = 0.899;\ SE = 0.419;\ F = 21.163)$$

An addition of the logarithm of the octanol-water partition coefficient term to eqn.2.1 improves the correlation significantly, as judged by the correlation coefficients (r) and standard error of regressions (SE). The two-parameter equation is given by:

$$\log Sn = 0.76 \log P_{octanol} + 0.88\,\mu - 6.20 \qquad (2.2)$$

$$(n = 7;\ r = 0.987;\ SE = 0.175;\ F = 72.796)$$

It can be seen that the calculated coefficients of variable log $P_{octanol}$ obtained in eqns.2.2 and 1.17 (Roberts et al., 1991) are almost identical. This probably indicates that the plastic infusion bags used for the two studies were of similar composition (Roberts et al., 1991). Furthermore, it is noted that substituting the dipole moment term, μ, in eqn.2.2 by the arbitrary value of 2.3 results in an equation of similar form to eqn.1.17. Thus, there is a possibility that eqn.2.2 and eqn.1.17 may be the same equation and the arbitrary value of 2.3 may be the average dipole moment value of the drugs used in deriving eqn.1.17.

When log Sn is correlated with the intrinsic molecular volume and solvatochromic parameters, the four-parameter equation is given by

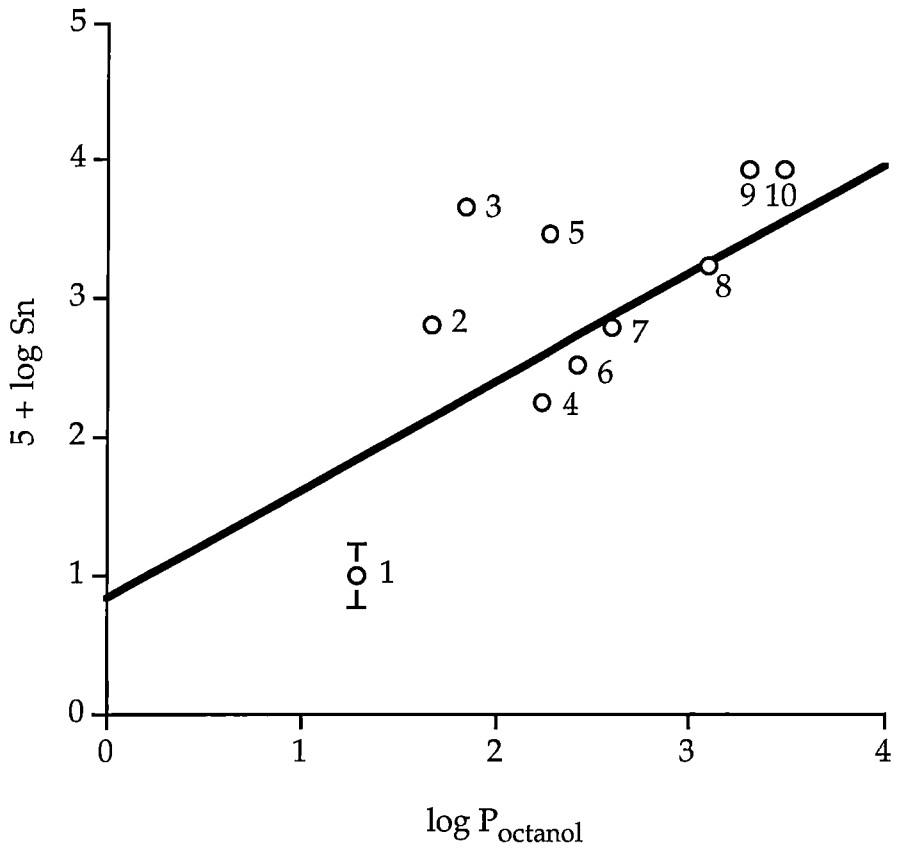


Figure 2.4. A correlation between logarithm of sorption number and logarithm of octanol-water partition coefficient of ten solutes used; data points represent the actual values (see Table 2.7) and a solid line represents the predicted values using eqn.1.17 (Roberts et al., 1991); 1=phenol, 2=acetophenone, 3=nitrobenzene, 4=*o*-xylenol, 5=methylacetophenone, 6=*p*-chlorophenol, 7=*p*-bromophenol, 8=chlorocresol, 9=thymol, 10=chloroxylenol.

$$\log Sn = -7.766 + 2.637\pi^* - 6.279\beta - 1.394\alpha + 9.034(V_I/100) \quad (2.3)$$

$$(n = 7; r = 0.997; SE = 0.125; F = 73.683)$$

It is to be expected that equations 2.2 and 2.3 will provide reasonable estimates of the loss of other solutes/drugs from solutions stored in PVC infusion bags for times up to eight hours.

The usefulness of eqn1.17 proposed previously by Roberts and co-workers (1991) should not, however, be overlooked especially for cases where the physicochemical parameters, such as dipole moment, intrinsic molecular volume and solvatochromic parameters, are not readily available making eqn.2.2 or 2.3 inapplicable.

According to the additive mathematical model proposed by Free and Wilson (1964), the model for the calculation of the logarithm of the sorption number of six selected solutes; phenol, acetophenone, methylacetophenone, *o*-xylenol, chlorocresol and *p*-chlorophenol, will be based upon the assumption that

$$\log Sn = \text{average} + \text{effect of substituent a} + \text{effect of substituent b} + \text{effect of substituent c} \quad (2.4)$$

The calculated coefficients for the data given in Tables 2.6 and 2.7 are shown in Table 2.8.

This result shows that the equation is a true relationship between the variables ($p < 0.05$) and the regression accounts for up to 99.9% of the total variation. Therefore, it may be concluded that each substituent in the structure of solutes in this series makes a constant contribution to the sorption behaviour of the solute and this contribution is additive

and independent of contributions from other substituents. In addition, it has been found that the substituents -Cl and -$COCH_3$ account for high solute uptake into the PVC infusion container.

Table 2.8. Calculated coefficients obtained from Free-Wilson analysis

Variable	Calculated coefficients	Standard error
intercept	-2.4567	0.0230
a$COCH_3$	+1.2310	0.0220
aOH	-0.6156	0.0220
bH	-0.2240	0.0110
bCH_3	+0.4489	0.0440
cH	-0.7270	0.0250
cCH_3	-0.1133	0.0380
cCl	+0.8400	0.0380

Number of compounds (n) = 6
Standard error of regression (s) = 0.0572
Calculated F-ratio = 295.61; Table F(4, 1, 0.05) = 225
Multiple correlation coefficient (r) = 1.000
Variance in Y explained by the regression = 99.9%

2.4.3. Investigation of chemical interaction(s) between PVC and selected solutes

From the results reported in Section 2.4.2, it is found that the octanol-water partition coefficient values alone cannot adequately describe the diffusion-controlled sorption behaviour of all the solutes used and it is suggested that the molecular dipole moment together with the octanol-water partition coefficient values of the solutes should be used to describe diffusion-controlled sorption behaviour of solutes into the PVC matrix.

There is a possibility, however, that solutes with relatively low octanol-water partition coefficient values ($\log P_{octanol}<2$) used in Section 2.3.2, such as acetophenone and nitrobenzene, may undergo a different sorption mechanism because the uptake of these solutes is larger than expected (Figure 2.4). This larger than expected uptake may be due to a chemical reaction between the solute and PVC rather than a simple diffusion of solute into the PVC matrix as proposed previously (Kowaluk et al., 1985; Roberts et al., 1991).

An examination of the PVC samples which have sorbed acetophenone or nitrobenzene to a considerable level was carried out using infrared spectroscopy in order to establish whether chemical reaction had occured during the sorption process of these solutes. Figures 2.5 to 2.9 show that, for both acetophenone and nitrobenzene, the spectrum of the PVC strip soaked in pure solute in the liquid state is the simple sum of the spectra of PVC and the pure solute. This indicates that no chemical reaction has taken place between the PVC surface and acetophenone or nitrobenzene. It may therefore be concluded that acetophenone and nitrobenzene undergo the diffusion-controlled sorption mechanism proposed previously (Kowaluk et al., 1985; Roberts et al., 1991).

2.4.4. Factors affecting solute sorption into the PVC bag

2.4.4.1. Solute concentration, electrolyte concentration/vehicle ionic strength and temperature studied simultaneously

The fraction of the original concentration of solute remaining in solution at 8 hours and the logarithm of sorption number of each solute

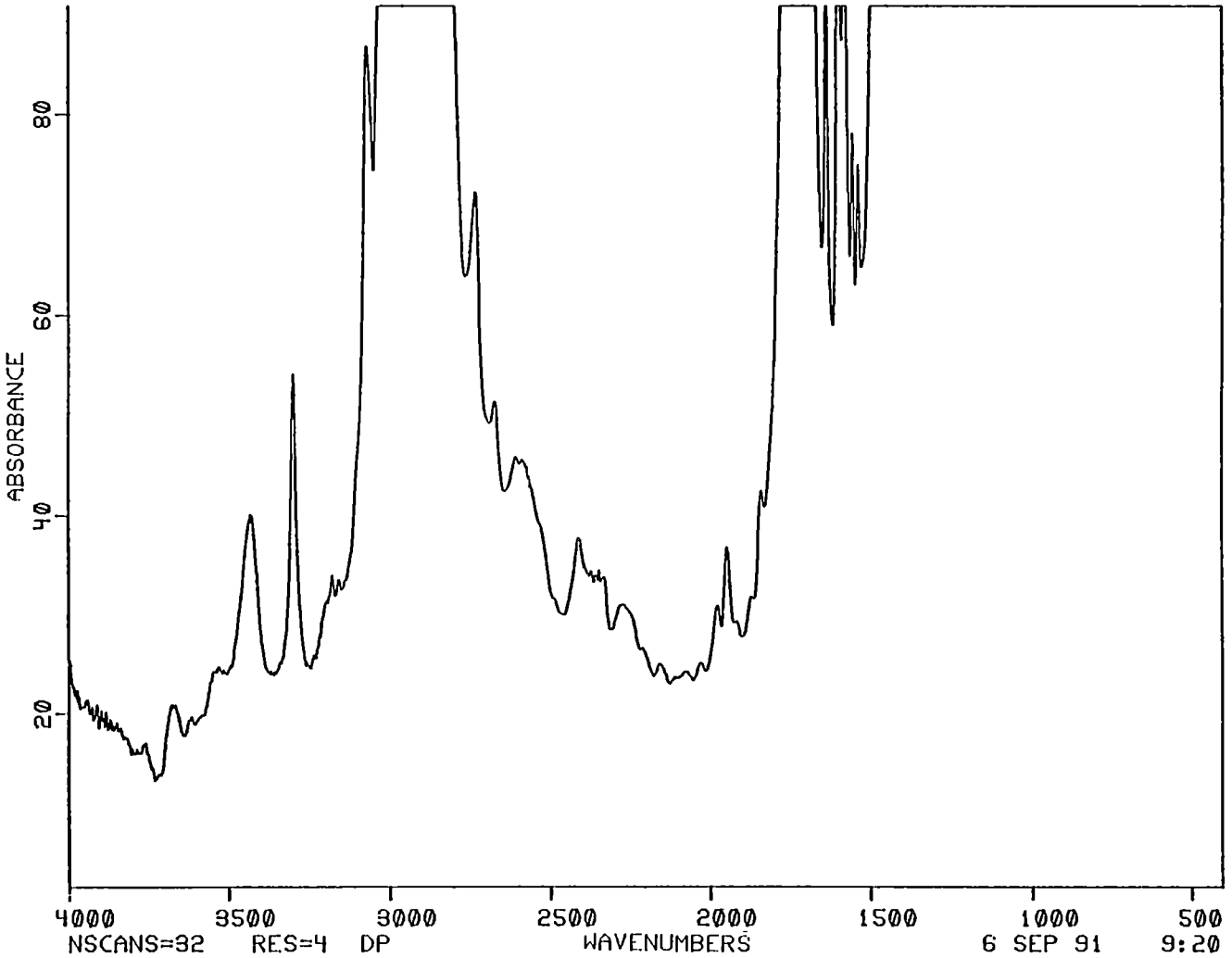


Figure 2.5. IR spectrum of a PVC strip cut from an infusion bag

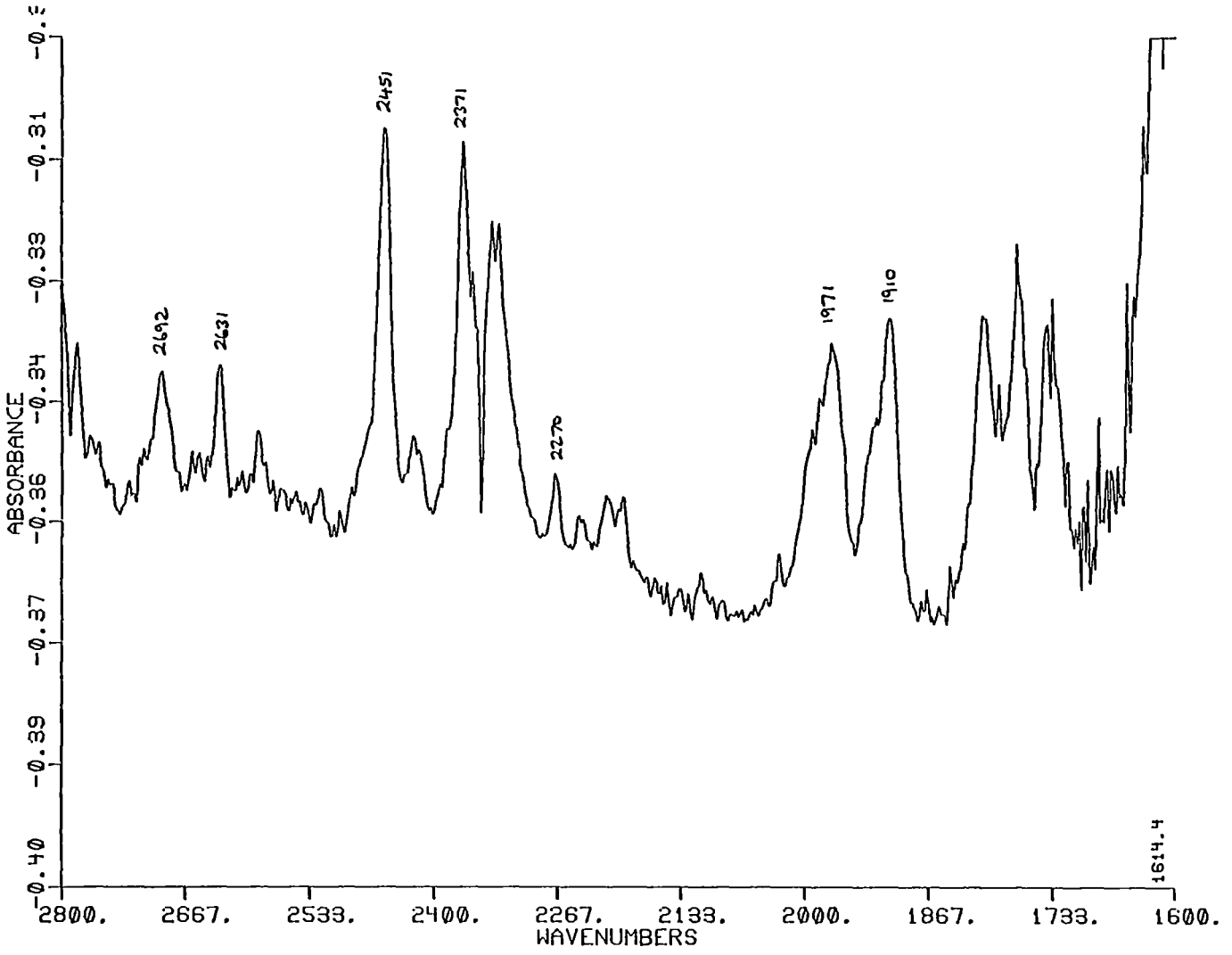


Figure 2.6. IR spectrum of pure nitrobenzene

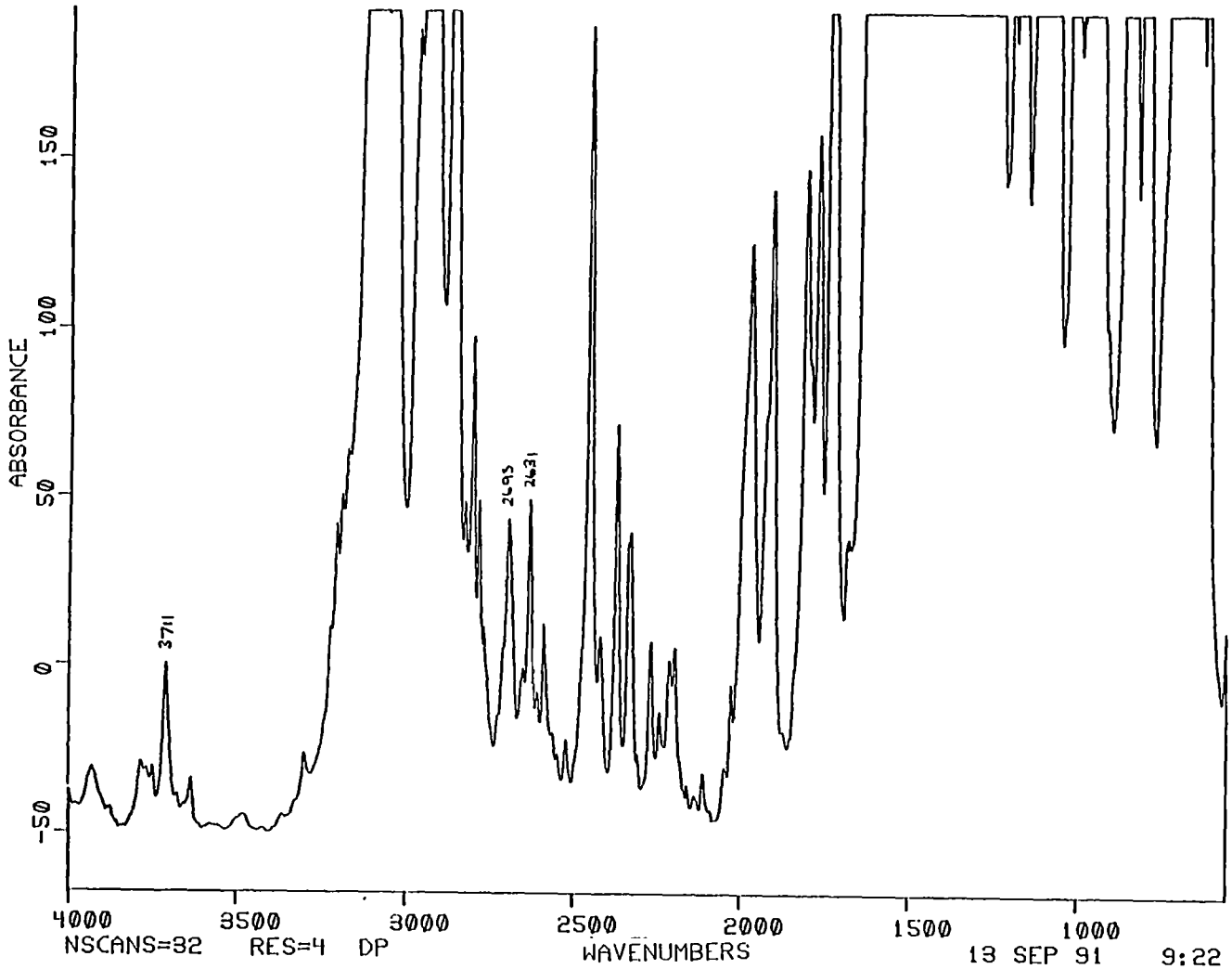


Figure 2.7. IR spectrum of a PVC strip soaked in pure nitrobenzene overnight

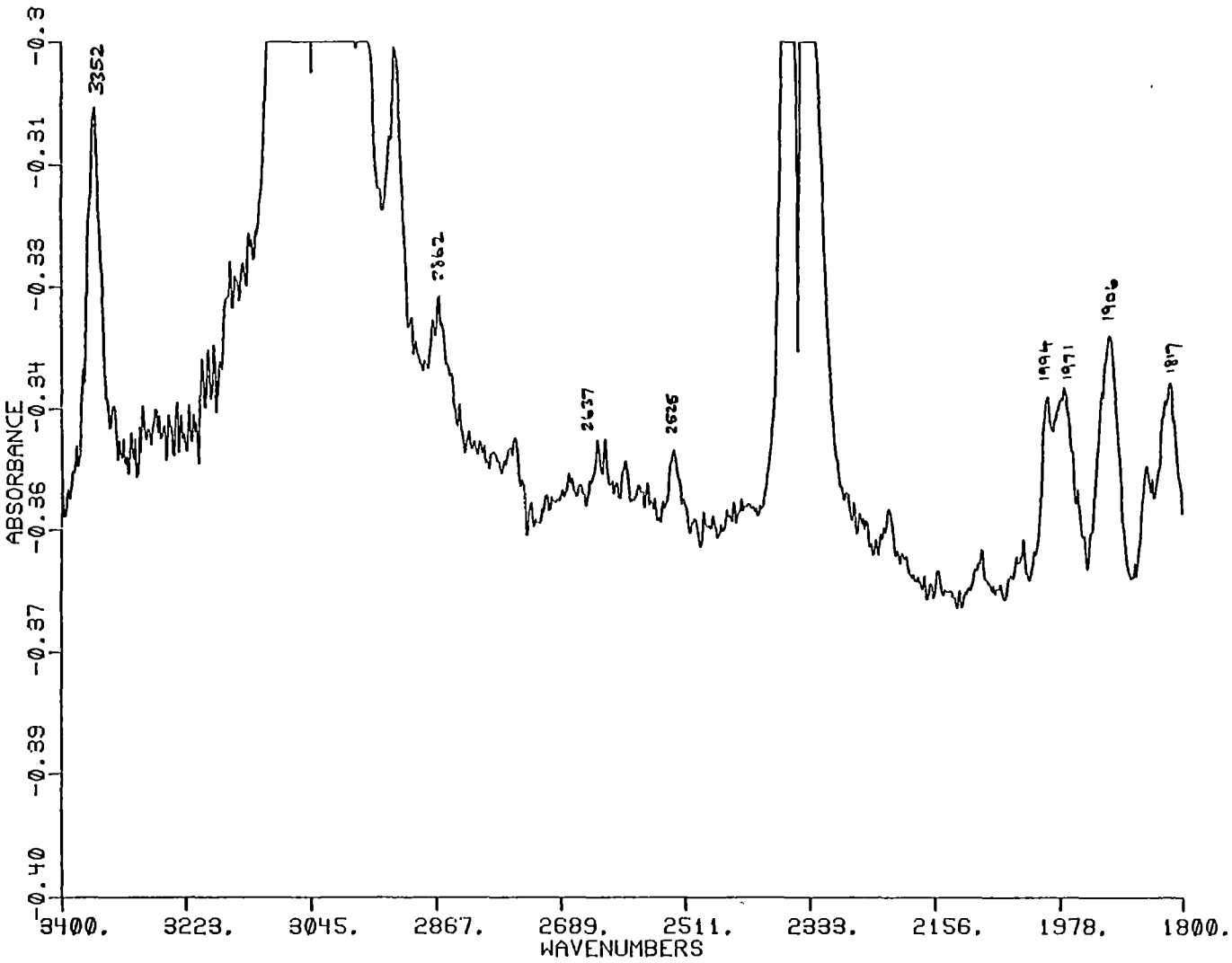


Figure 2.8. IR spectrum of pure acetophenone

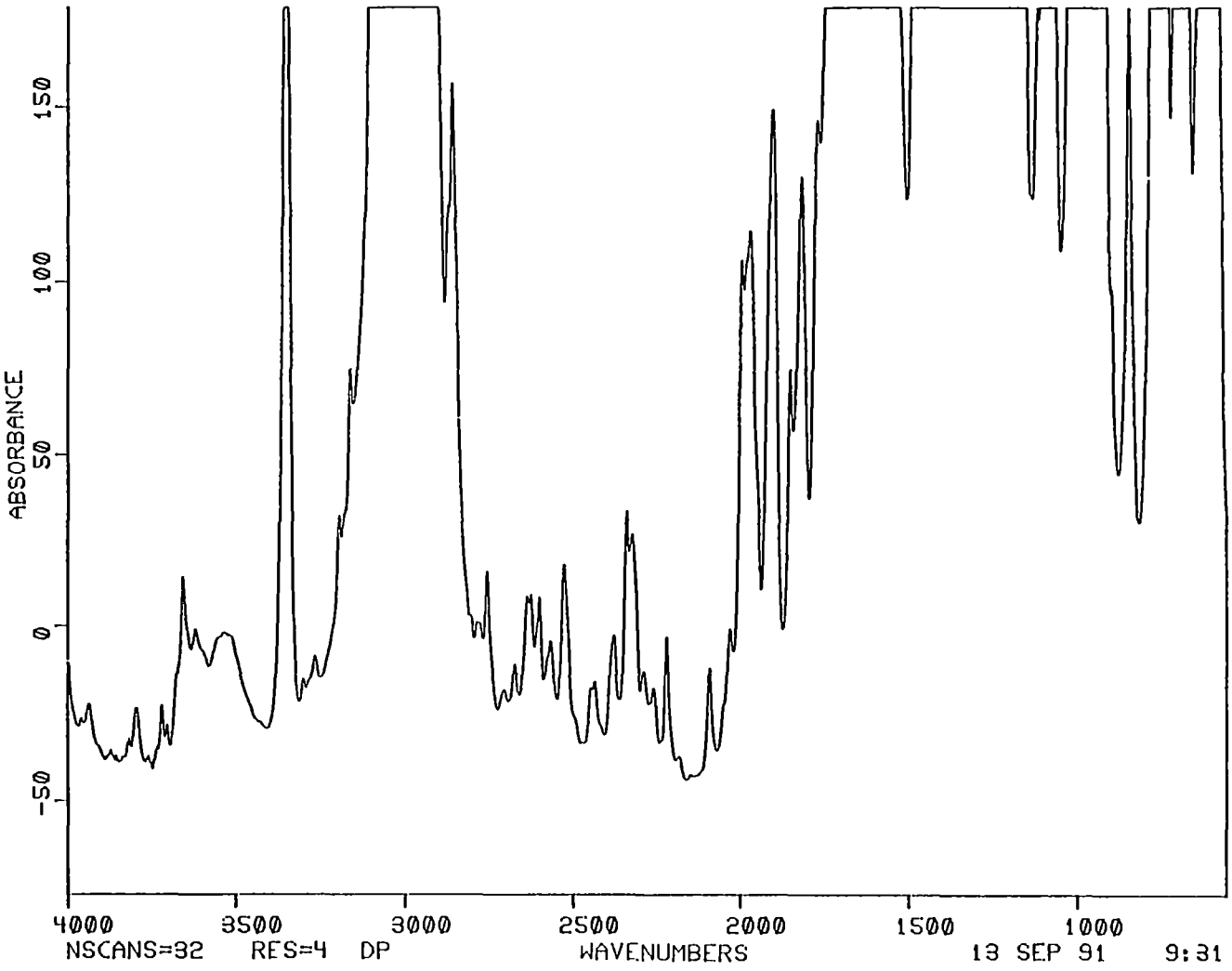


Figure 2.9. IR spectrum of a PVC strip soaked in pure acetophenone overnight

is presented in Tables 2.9 and 2.10. Table 2.11 is the Analysis of Variance table of the fraction remaining in solution at 8 hours and Table 2.12 is that for the logarithm of sorption number. The significance of the values of F is assessed by comparison with published 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. The concentration of solute and the interactions between factors have a negligible effect on solute uptake by the PVC infusion bags.

Table 2.9. Fraction of the original concentration of solute remaining in solution stored in a PVC bag for 8 hours[a]

Experiment[b]	Acetophenone	Chlorocresol	Nitrobenzene	*p*-Chlorophenol	Phenol
(1)	0.79(0.00)	0.69(0.01)	0.56(0.01)	0.84(0.00)	0.97(0.01)
a	0.79(0.00)	0.68(0.00)	0.56(0.01)	0.84(0.01)	0.97(0.01)
b	0.61(0.01)	0.52(0.00)	0.35(0.01)	0.74(0.00)	0.94(0.02)
c	0.77(0.01)	0.66(0.00)	0.56(0.01)	0.87(0.01)	0.96(0.01)
ab	0.59(0.01)	0.51(0.00)	0.35(0.01)	0.75(0.01)	0.94(0.01)
ac	0.77(0.01)	0.66(0.01)	0.56(0.01)	0.83(0.00)	0.96(0.00)
bc	0.56(0.01)	0.44(0.01)	0.32(0.01)	0.72(0.00)	0.92(0.01)
abc	0.56(0.01)	0.44(0.01)	0.33(0.01)	0.73(0.00)	0.94(0.01)

[a] Values in parentheses are SD values.
[b] For details of the experimental design see Table 2.3.

Table 2.10. Logarithm of the sorption number of five solutes used in this portion of the study[a]

Experiment[b]	Acetophenone	Chlorocresol	Nitrobenzene	*p*-Chlorophenol	Phenol
(1)	-2.19(0.01)	-1.76(0.00)	-1.32(0.00)	-2.52(0.00)	-3.99(0.03)
a	-2.19(0.01)	-1.75(0.01)	-1.34(0.00)	-2.48(0.01)	-3.99(0.22)
b	-1.48(0.00)	-1.18(0.01)	-0.61(0.00)	-1.99(0.00)	-3.39(0.28)
c	-2.10(0.00)	-1.63(0.00)	-1.29(0.00)	-2.69(0.01)	-3.94(0.24)
ab	-1.44(0.00)	-1.15(0.01)	-0.62(0.00)	-1.99(0.01)	-3.40(0.18)
ac	-2.11(0.00)	-1.66(0.01)	-1.31(0.00)	-2.43(0.01)	-3.94(0.01)
bc	-1.34(0.00)	-0.95(0.00)	-0.53(0.00)	-1.90(0.00)	-3.15(0.07)
abc	-1.33(0.00)	-0.96(0.01)	-0.54(0.00)	-1.92(0.02)	-3.38(0.06)

[a] Values in parentheses are SD values.
[b] For details of the experimental design see Table 2.3.

Table 2.11. F values of analysis of variance table of fraction of the original concentration of solute remaining at 8 hours following Yates' treatment

Experiment[a]	Acetophenone	Chlorocresol	Nitrobenzene	*p*-Chlorophenol	Phenol
(1)	-	-	-	-	-
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

[a] For details of the experimental design see Table 2.3.

Table 2.12. F values of analysis of variance table of logarithm of sorption number following Yates' treatment

Experiment[a]	Acetophenone	Chlorocresol	Nitrobenzene	*p*-Chlorophenol	Phenol
(1)	-	-	-	-	-
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

[a] For details of the experimental design see Table 2.3.

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 those factors had on the process.

2.4.4.2. Effect of solute concentration

The effect of concentration on solute loss is shown in Figures 2.10 - 2.13. For each substance, control solutions showed no loss of solute over the period of 8 hours and a linear relationship between the amount of solute loss (q) and the initial concentration (C_i) was observed over the concentration range studied. It can be seen that equilibrium was not achieved within the 8 hour course of the experiments. It is, however, apparent that the sorption process can be described by a simple distribution law, as described by eqn.1.2 (Wang and Chien, 1984).

$$q = K_{app} (1 + K_{app} (\text{solution volume} / \text{plastic weight}))^{-1} C_i \qquad (1.2)$$

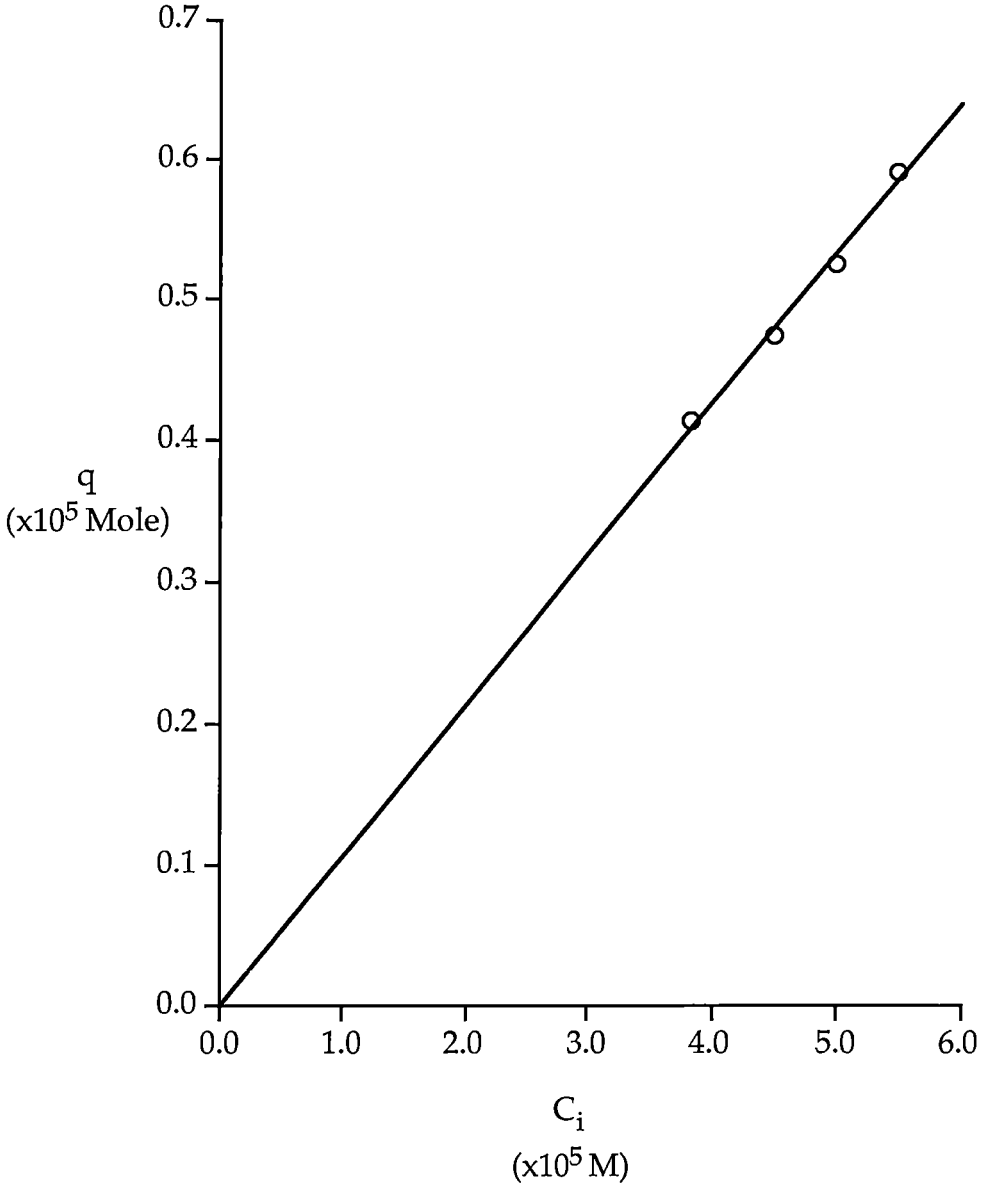


Figure 2.10. Sorption pattern of acetophenone from a solution stored in a PVC infusion bag for 8 hours as a function of solute concentration. The solid line is a linear fit to the data.

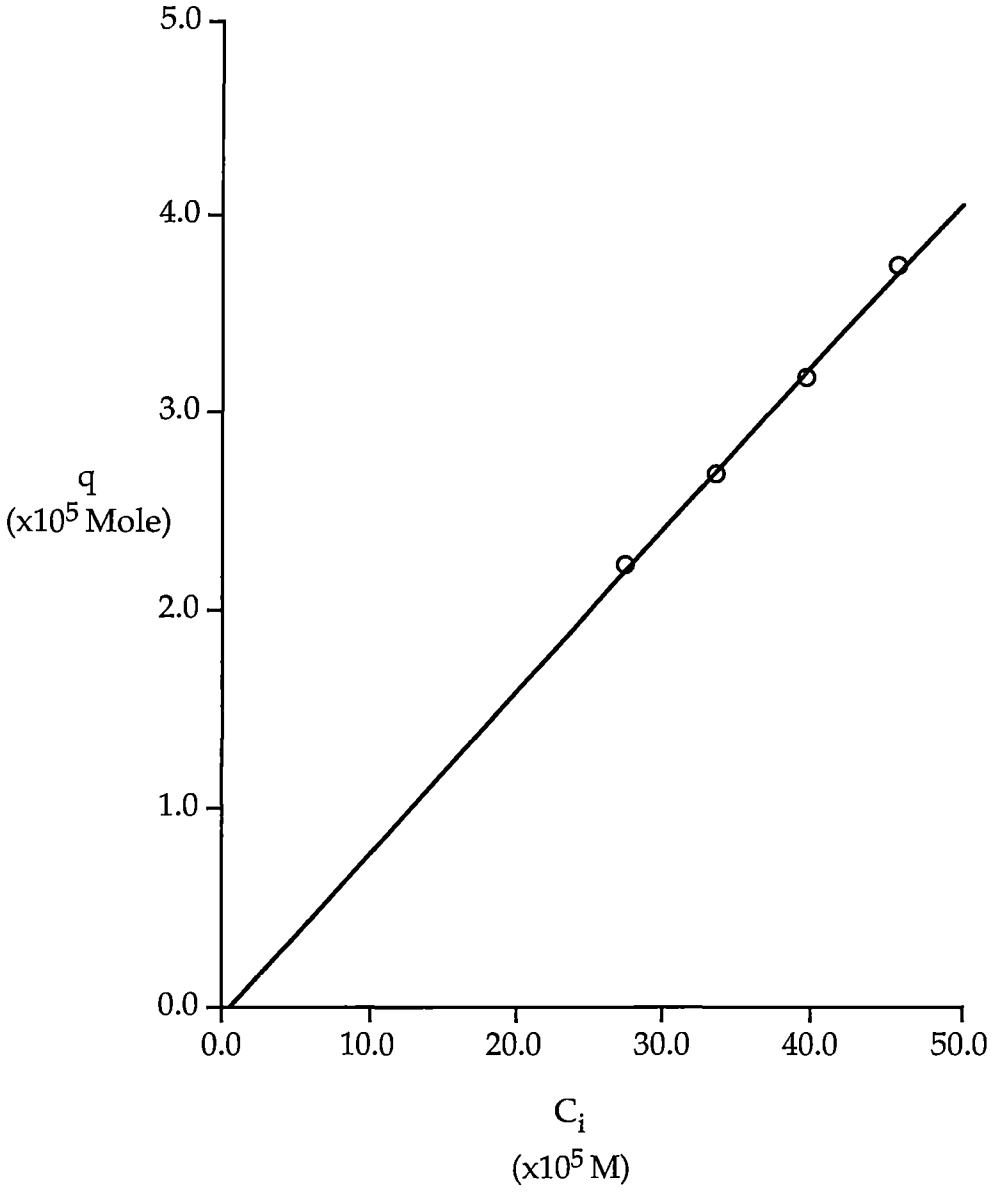


Figure 2.11. Sorption pattern of *p*-chlorophenol from a solution stored in a PVC infusion bag for 8 hours as a function of solute concentration. The solid line is a linear fit to the data.

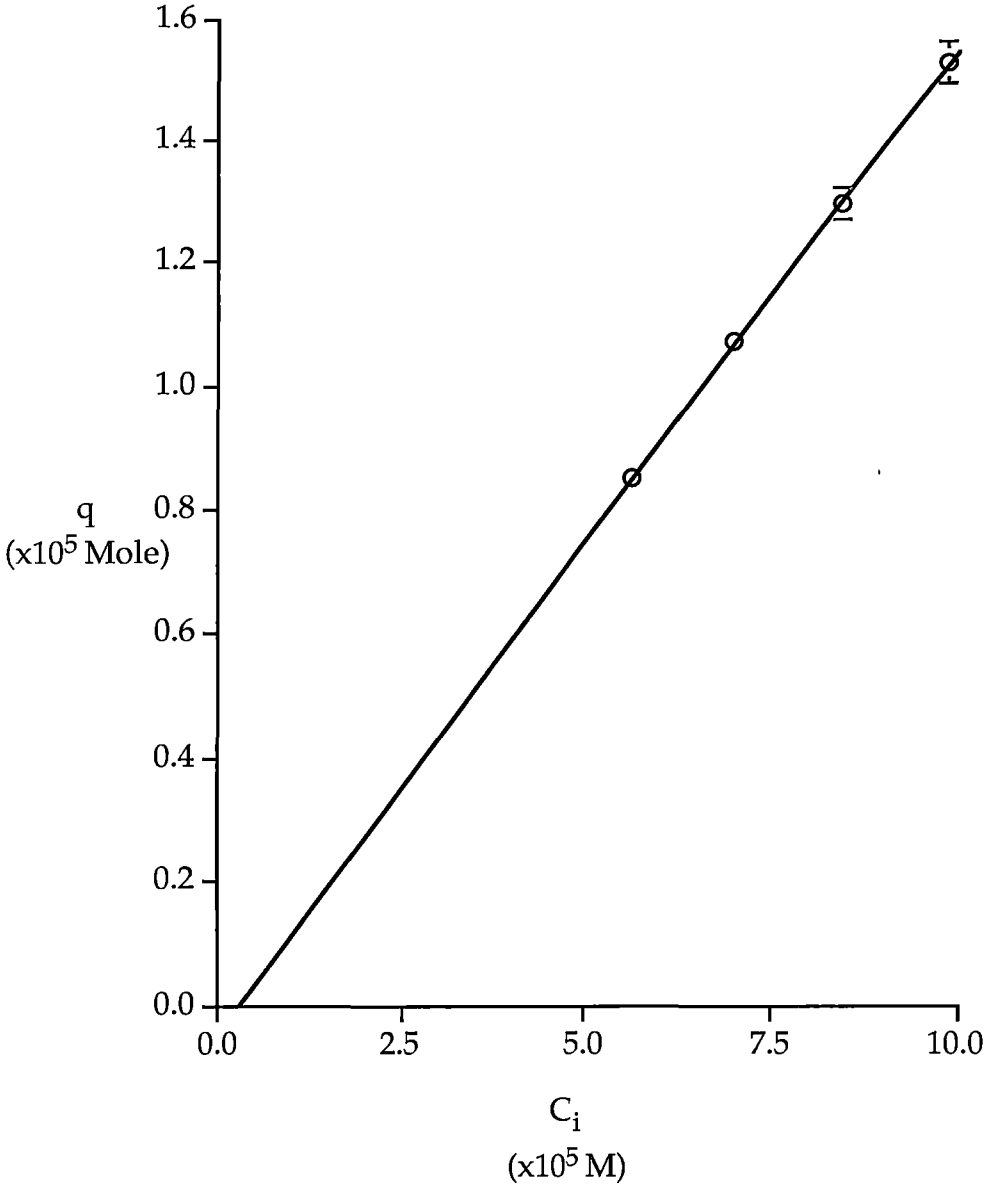


Figure 2.12. Sorption pattern of chlorocresol from a solution stored in a PVC infusion bag for 8 hours as a function of solute concentration. The solid line is a linear fit to the data.

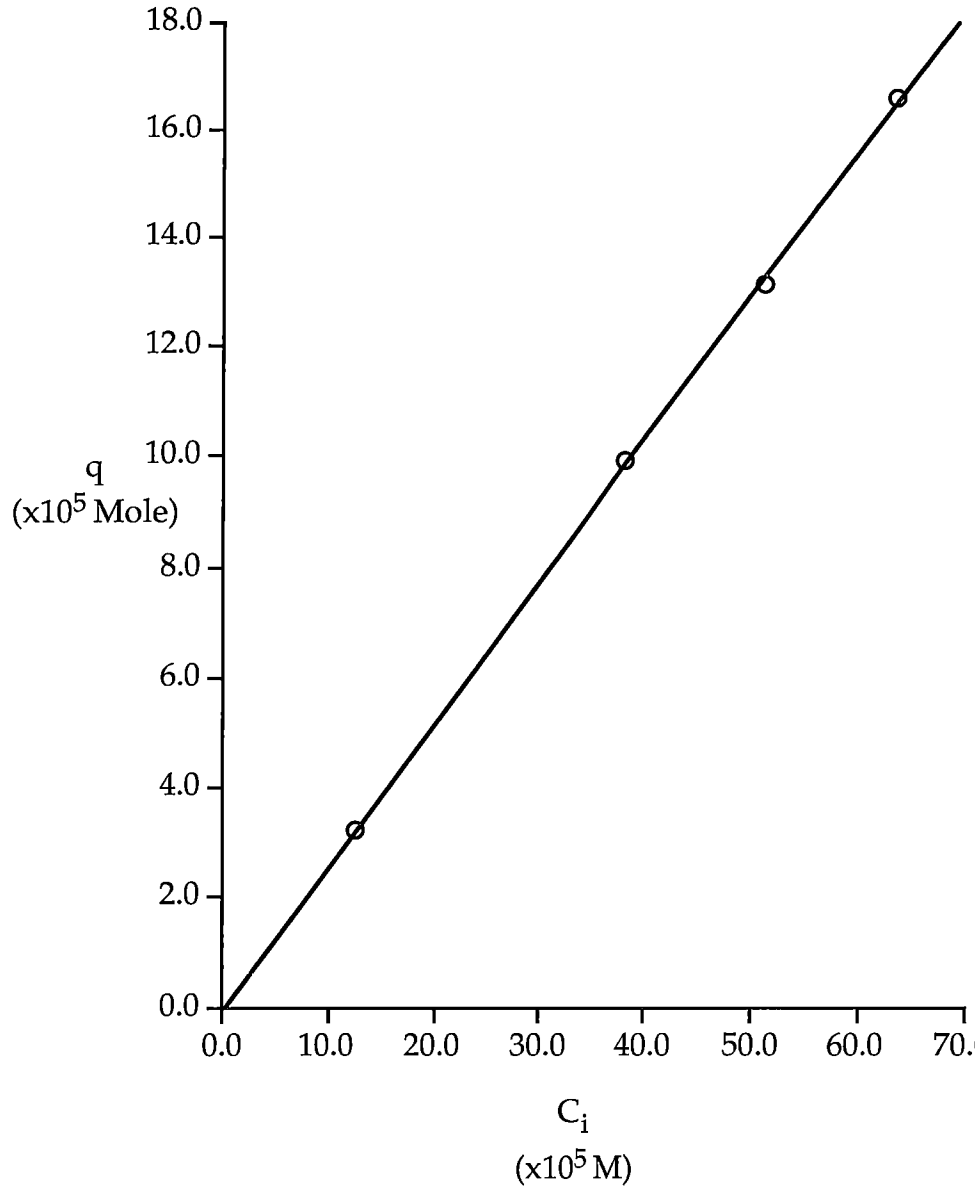


Figure 2.13. Sorption pattern of chloroxylenol from a solution stored in a PVC infusion bag for 8 hours as a function of solute concentration. The solid line is a linear fit to the data.

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 of the original concentration of solute remaining in solution are considered for all substances used, as shown in Tables 2.13-2.16, the means of the fractions remaining of four different concentration solutions over the period of 8 hours 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 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).

Table 2.13. Effect of solute concentration on the fraction of the original concentration of acetophenone remaining (F_t) in solution stored in a PVC bag for 8 hours[a,b]

Time (mins)	F_t			
	conc1	conc2	conc3	conc4
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.97(0.00)	0.97(0.00)	0.98(0.00)	0.97(0.00)
30	0.96(0.01)	0.96(0.00)	0.96(0.00)	0.96(0.00)
45	0.95(0.01)	0.95(0.00)	0.95(0.00)	0.95(0.01)
60	0.95(0.02)	0.94(0.01)	0.94(0.00)	0.93(0.00)
80	0.92(0.00)	0.92(0.00)	0.92(0.01)	0.92(0.01)
100	0.91(0.01)	0.91(0.01)	0.91(0.00)	0.91(0.01)
120	0.90(0.00)	0.90(0.01)	0.90(0.01)	0.90(0.00)
150	0.88(0.01)	0.89(0.00)	0.89(0.01)	0.88(0.00)
180	0.87(0.01)	0.88(0.01)	0.87(0.01)	0.87(0.00)
210	0.86(0.00)	0.86(0.01)	0.86(0.00)	0.86(0.00)
240	0.85(0.01)	0.85(0.01)	0.85(0.01)	0.85(0.01)
300	0.83(0.01)	0.83(0.01)	0.84(0.01)	0.83(0.01)
360	0.82(0.00)	0.82(0.02)	0.82(0.01)	0.81(0.01)
420	0.80(0.01)	0.80(0.01)	0.80(0.01)	0.80(0.01)
480	0.79(0.01)	0.79(0.01)	0.79(0.01)	0.79(0.01)

[a] For details of each condition see Table 2.4.

[b] Values in parentheses are SD values.

Table 2.14. Effect of solute concentration on the fraction of the original concentration of *p*-chlorophenol remaining (F_t) in solution stored in a PVC bag for 8 hours[a,b]

Time (mins)	F_t			
	conc1	conc2	conc3	conc4
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.98(0.01)	0.98(0.00)	0.98(0.00)	0.98(0.00)
30	0.97(0.00)	0.97(0.00)	0.97(0.00)	0.97(0.00)
45	0.96(0.00)	0.96(0.00)	0.96(0.00)	0.96(0.00)
60	0.95(0.00)	0.95(0.01)	0.95(0.00)	0.95(0.00)
80	0.94(0.00)	0.94(0.00)	0.94(0.00)	0.94(0.00)
100	0.93(0.00)	0.93(0.00)	0.93(0.00)	0.93(0.00)
120	0.92(0.00)	0.93(0.01)	0.93(0.00)	0.92(0.00)
150	0.91(0.00)	0.91(0.00)	0.91(0.00)	0.91(0.00)
180	0.90(0.00)	0.91(0.00)	0.90(0.00)	0.90(0.00)
210	0.90(0.00)	0.90(0.00)	0.89(0.00)	0.89(0.00)
240	0.89(0.01)	0.89(0.00)	0.89(0.00)	0.88(0.00)
300	0.87(0.00)	0.87(0.00)	0.87(0.00)	0.87(0.00)
360	0.86(0.01)	0.87(0.00)	0.86(0.01)	0.86(0.01)
420	0.85(0.01)	0.86(0.01)	0.85(0.00)	0.85(0.01)
480	0.84(0.01)	0.84(0.00)	0.84(0.00)	0.84(0.00)

[a] For details of each condition see Table 2.4.
[b] Values in parentheses are SD values.

Table 2.15. Effect of solute concentration on the fraction of the original concentration of chlorocresol remaining (F_t) in solution stored in a PVC bag for 8 hours[a,b]

Time (mins)	F_t			
	conc1	conc2	conc3	conc4
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.95(0.00)	0.96(0.01)	0.96(0.00)	0.97(0.01)
30	0.95(0.01)	0.95(0.03)	0.94(0.01)	0.94(0.01)
45	0.92(0.02)	0.92(0.01)	0.91(0.00)	0.92(0.01)
60	0.89(0.00)	0.90(0.01)	0.90(0.00)	0.90(0.00)
80	0.89(0.01)	0.89(0.02)	0.88(0.01)	0.88(0.01)
100	0.86(0.01)	0.87(0.02)	0.86(0.01)	0.87(0.01)
120	0.85(0.01)	0.85(0.01)	0.85(0.01)	0.85(0.01)
150	0.84(0.02)	0.84(0.02)	0.84(0.02)	0.84(0.02)
180	0.82(0.02)	0.82(0.01)	0.82(0.01)	0.82(0.02)
210	0.81(0.02)	0.81(0.02)	0.80(0.01)	0.80(0.01)
240	0.78(0.02)	0.79(0.02)	0.78(0.01)	0.79(0.02)
300	0.76(0.01)	0.77(0.02)	0.76(0.02)	0.76(0.01)
360	0.74(0.02)	0.74(0.02)	0.74(0.02)	0.74(0.01)
420	0.72(0.01)	0.72(0.01)	0.71(0.01)	0.71(0.01)
480	0.70(0.01)	0.70(0.00)	0.69(0.00)	0.69(0.00)

[a] For details of each condition see Table 2.4.
[b] Values in parentheses are SD values.

Table 2.16. Effect of solute concentration on the fraction of the original concentration of chloroxylenol remaining (F_t) in solution stored in a PVC bag for 8 hours[a,b]

Time (mins)	F_t			
	conc1	conc2	conc3	conc4
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.94(0.01)	0.94(0.01)	0.94(0.01)	0.94(0.00)
30	0.90(0.00)	0.90(0.00)	0.90(0.00)	0.89(0.01)
45	0.86(0.00)	0.86(0.01)	0.86(0.00)	0.86(0.01)
60	0.83(0.01)	0.83(0.01)	0.83(0.00)	0.82(0.00)
80	0.80(0.01)	0.79(0.01)	0.79(0.01)	0.79(0.00)
100	0.76(0.01)	0.76(0.00)	0.76(0.00)	0.75(0.00)
120	0.73(0.01)	0.73(0.00)	0.73(0.00)	0.70(0.00)
150	0.70(0.01)	0.70(0.00)	0.70(0.00)	0.69(0.00)
180	0.67(0.01)	0.66(0.01)	0.66(0.00)	0.66(0.00)
210	0.64(0.00)	0.64(0.01)	0.63(0.00)	0.63(0.00)
240	0.61(0.00)	0.61(0.00)	0.61(0.00)	0.60(0.00)
300	0.57(0.00)	0.57(0.00)	0.57(0.00)	0.56(0.01)
360	0.54(0.01)	0.54(0.01)	0.54(0.01)	0.53(0.01)
420	0.51(0.01)	0.51(0.01)	0.51(0.00)	0.50(0.01)
480	0.49(0.01)	0.48(0.00)	0.49(0.01)	0.48(0.01)

[a] For details of each condition see Table 2.4.

[b] Values in parentheses are SD values.

2.4.4.3. Effect of electrolyte concentration/vehicle ionic strength

Fractions of the original concentration of solute remaining in solutions stored in PVC bags for 8 hours in the presence of varying electrolyte concentrations are presented in Tables 2.17-2.20.

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 eight hours ($p<0.05$). Loucas and co-workers (1990) have found that nitroglycerin availability from PVC administration sets was an inverse function of increasing ionic strength.

Table 2.17. Effect of electrolyte concentration on the fraction of the original concentration of acetophenone remaining (F_t) in solution stored in a PVC bag for 8 hours[a,b]

Time (mins)	F_t					
	Experiment1	Experiment2	Experiment3	Experiment4	Experiment5	Experiment6
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.98(0.00)	0.97(0.01)	0.97(0.00)	0.97(0.00)	0.97(0.01)	0.96(0.01)
30	0.96(0.00)	0.95(0.01)	0.95(0.01)	0.95(0.01)	0.95(0.00)	0.94(0.01)
45	0.95(0.00)	0.93(0.01)	0.93(0.01)	0.93(0.01)	0.94(0.01)	0.93(0.01)
60	0.94(0.00)	0.92(0.01)	0.92(0.01)	0.92(0.01)	0.92(0.00)	0.91(0.01)
80	0.92(0.01)	0.91(0.01)	0.90(0.01)	0.90(0.01)	0.91(0.01)	0.90(0.02)
100	0.91(0.00)	0.90(0.02)	0.89(0.02)	0.89(0.02)	0.89(0.01)	0.89(0.02)
120	0.90(0.01)	0.88(0.02)	0.88(0.02)	0.88(0.02)	0.89(0.01)	0.88(0.02)
150	0.89(0.01)	0.87(0.02)	0.87(0.02)	0.87(0.02)	0.87(0.01)	0.87(0.02)
180	0.87(0.01)	0.86(0.02)	0.86(0.02)	0.85(0.02)	0.86(0.01)	0.85(0.02)
210	0.86(0.00)	0.85(0.02)	0.85(0.02)	0.84(0.02)	0.85(0.01)	0.84(0.02)
240	0.85(0.01)	0.84(0.02)	0.84(0.02)	0.84(0.03)	0.84(0.02)	0.83(0.03)
300	0.84(0.01)	0.82(0.02)	0.82(0.02)	0.82(0.02)	0.81(0.02)	0.81(0.02)
360	0.82(0.01)	0.81(0.02)	0.81(0.02)	0.80(0.02)	0.80(0.02)	0.80(0.02)
420	0.80(0.01)	0.79(0.02)	0.79(0.02)	0.79(0.03)	0.78(0.02)	0.78(0.03)
480	0.79(0.01)	0.78(0.02)	0.78(0.02)	0.77(0.02)	0.76(0.02)	0.77(0.02)

[a] For details of each experiment see Tables 2.4 and 2.5.

[b] Values in parentheses are SD values.

Table 2.18. Effect of electrolyte concentration on the fraction of the original concentration of *p*-chlorophenol remaining (F_t) in solution stored in a PVC bag for 8 hours[a,b]

Time (mins)	F_t					
	Experiment1	Experiment2	Experiment3	Experiment4	Experiment5	Experiment6
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.98(0.00)	0.98(0.00)	0.97(0.01)	0.98(0.00)	0.98(0.00)	0.98(0.00)
30	0.97(0.00)	0.96(0.00)	0.96(0.00)	0.97(0.00)	0.96(0.00)	0.96(0.00)
45	0.95(0.00)	0.96(0.00)	0.95(0.01)	0.96(0.01)	0.96(0.01)	0.95(0.00)
60	0.95(0.00)	0.95(0.01)	0.95(0.01)	0.95(0.00)	0.94(0.00)	0.94(0.00)
80	0.94(0.01)	0.94(0.00)	0.94(0.01)	0.94(0.00)	0.93(0.00)	0.93(0.00)
100	0.93(0.00)	0.93(0.00)	0.92(0.01)	0.93(0.00)	0.92(0.00)	0.92(0.00)
120	0.92(0.00)	0.92(0.01)	0.92(0.01)	0.92(0.00)	0.92(0.00)	0.92(0.00)
150	0.91(0.00)	0.91(0.00)	0.91(0.00)	0.91(0.01)	0.91(0.01)	0.91(0.00)
180	0.90(0.00)	0.90(0.01)	0.90(0.01)	0.90(0.01)	0.90(0.00)	0.90(0.00)
210	0.89(0.00)	0.89(0.00)	0.89(0.01)	0.89(0.01)	0.89(0.00)	0.89(0.00)
240	0.89(0.01)	0.88(0.01)	0.88(0.01)	0.88(0.01)	0.88(0.00)	0.88(0.00)
300	0.87(0.00)	0.87(0.01)	0.87(0.01)	0.87(0.01)	0.87(0.01)	0.87(0.01)
360	0.86(0.01)	0.86(0.00)	0.86(0.01)	0.86(0.01)	0.85(0.00)	0.85(0.00)
420	0.85(0.00)	0.85(0.00)	0.84(0.01)	0.84(0.01)	0.84(0.00)	0.84(0.00)
480	0.84(0.01)	0.84(0.01)	0.83(0.01)	0.83(0.01)	0.83(0.00)	0.83(0.00)

[a] For details of each experiment see Tables 2.4 and 2.5.

[b] Values in parentheses are SD values.

Table 2.19. Effect of electrolyte concentration on the fraction of the original concentration of chlorocresol remaining (F_t) in solution stored in a PVC bag for 8 hours[a,b]

Time (mins)	F_t					
	Experiment1	Experiment2	Experiment3	Experiment4	Experiment5	Experiment6
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.95(0.00)	0.96(0.01)	0.97(0.01)	0.97(0.02)	0.97(0.01)	0.97(0.02)
30	0.93(0.00)	0.94(0.01)	0.94(0.01)	0.94(0.01)	0.94(0.01)	0.93(0.01)
45	0.90(0.01)	0.92(0.01)	0.92(0.01)	0.92(0.01)	0.92(0.01)	0.91(0.01)
60	0.90(0.01)	0.90(0.01)	0.90(0.01)	0.90(0.02)	0.90(0.01)	0.89(0.01)
80	0.89(0.01)	0.88(0.01)	0.88(0.00)	0.88(0.01)	0.88(0.00)	0.87(0.01)
100	0.86(0.00)	0.85(0.00)	0.86(0.01)	0.86(0.00)	0.86(0.01)	0.85(0.00)
120	0.85(0.01)	0.84(0.01)	0.85(0.01)	0.85(0.01)	0.84(0.01)	0.83(0.01)
150	0.82(0.00)	0.82(0.00)	0.83(0.01)	0.82(0.01)	0.82(0.01)	0.82(0.01)
180	0.80(0.00)	0.80(0.00)	0.80(0.01)	0.80(0.01)	0.80(0.01)	0.79(0.00)
210	0.80(0.01)	0.78(0.00)	0.79(0.01)	0.79(0.01)	0.78(0.00)	0.78(0.00)
240	0.78(0.00)	0.77(0.01)	0.77(0.01)	0.77(0.01)	0.77(0.02)	0.76(0.01)
300	0.76(0.01)	0.74(0.01)	0.75(0.01)	0.74(0.01)	0.74(0.01)	0.74(0.01)
360	0.72(0.00)	0.73(0.00)	0.72(0.00)	0.72(0.01)	0.72(0.01)	0.71(0.00)
420	0.70(0.00)	0.71(0.00)	0.70(0.00)	0.70(0.00)	0.70(0.00)	0.69(0.01)
480	0.69(0.01)	0.69(0.00)	0.69(0.00)	0.69(0.00)	0.68(0.01)	0.67(0.00)

[a] For details of each experiment see Tables 2.4 and 2.5.

[b] Values in parentheses are SD values.

Table 2.20. Effect of electrolyte concentration on the fraction of the original concentration of chloroxylenol remaining (F_t) in solution stored in a PVC bag for 8 hours[a,b]

Time (mins)	F_t					
	Experiment1	Experiment2	Experiment3	Experiment4	Experiment5	Experiment6
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.94(0.00)	0.94(0.00)	0.94(0.01)	0.94(0.01)	0.94(0.02)	0.93(0.02)
30	0.89(0.00)	0.90(0.01)	0.89(0.01)	0.90(0.01)	0.89(0.01)	0.88(0.00)
45	0.86(0.00)	0.86(0.00)	0.85(0.00)	0.86(0.00)	0.85(0.00)	0.85(0.00)
60	0.82(0.00)	0.83(0.00)	0.82(0.01)	0.83(0.00)	0.82(0.00)	0.81(0.00)
80	0.79(0.00)	0.80(0.00)	0.77(0.01)	0.79(0.01)	0.78(0.00)	0.78(0.01)
100	0.76(0.00)	0.77(0.00)	0.75(0.00)	0.76(0.00)	0.75(0.01)	0.74(0.01)
120	0.73(0.00)	0.74(0.00)	0.72(0.01)	0.74(0.01)	0.72(0.01)	0.71(0.01)
150	0.69(0.00)	0.70(0.01)	0.69(0.00)	0.70(0.01)	0.68(0.01)	0.68(0.00)
180	0.66(0.00)	0.67(0.00)	0.65(0.01)	0.66(0.00)	0.65(0.01)	0.64(0.01)
210	0.63(0.01)	0.64(0.01)	0.62(0.00)	0.64(0.01)	0.62(0.01)	0.61(0.01)
240	0.61(0.00)	0.61(0.01)	0.60(0.00)	0.61(0.00)	0.59(0.00)	0.59(0.01)
300	0.57(0.01)	0.58(0.00)	0.56(0.01)	0.57(0.01)	0.55(0.01)	0.55(0.01)
360	0.54(0.01)	0.54(0.00)	0.53(0.01)	0.54(0.00)	0.52(0.01)	0.51(0.01)
420	0.51(0.01)	0.51(0.00)	0.50(0.01)	0.50(0.01)	0.49(0.01)	0.48(0.01)
480	0.48(0.01)	0.48(0.01)	0.47(0.01)	0.47(0.00)	0.46(0.01)	0.46(0.01)

[a] For details of each experiment see Tables 2.4 and 2.5.

[b] Values in parentheses are SD values.

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 and co-workers (1978), Baaske and co-workers (1980) and De Muynck and co-workers (1988). To study the effect of vehicle ionic strength on solute uptake, the logarithm of sorption number ($hour^{-1}$), calculated from the data presented in Tables 2.17-2.20 using the method described in Section 2.3, 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 Figure 2.14 ($r = 0.959$, 0.949, 0.915, and 0.923 for *p*-chlorophenol, chloroxylenol, acetophenone, and chlorocresol respectively, $p<0.05$) and the y-intercept value of each plot represents the logarithm of the sorption number of each solute in water. It follows that modification of the prediction equation of Roberts and co-workers (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 of the lines shown in Figure 2.14 (Table 2.21) shows that the effect of vehicle ionic strength is consistent for the four substances used in this study ($p>0.01$) with the mean value of 0.41. Thus, for cases where vehicle ionic strength is greater than zero, logarithm of the sorption number ($\log Sn_i$) is

$$\log Sn_i = \log Sn + 0.41I \qquad (2.5)$$

where I is the vehicle ionic strength of the solution and log Sn is the logarithm of the sorption number of the solute in water.

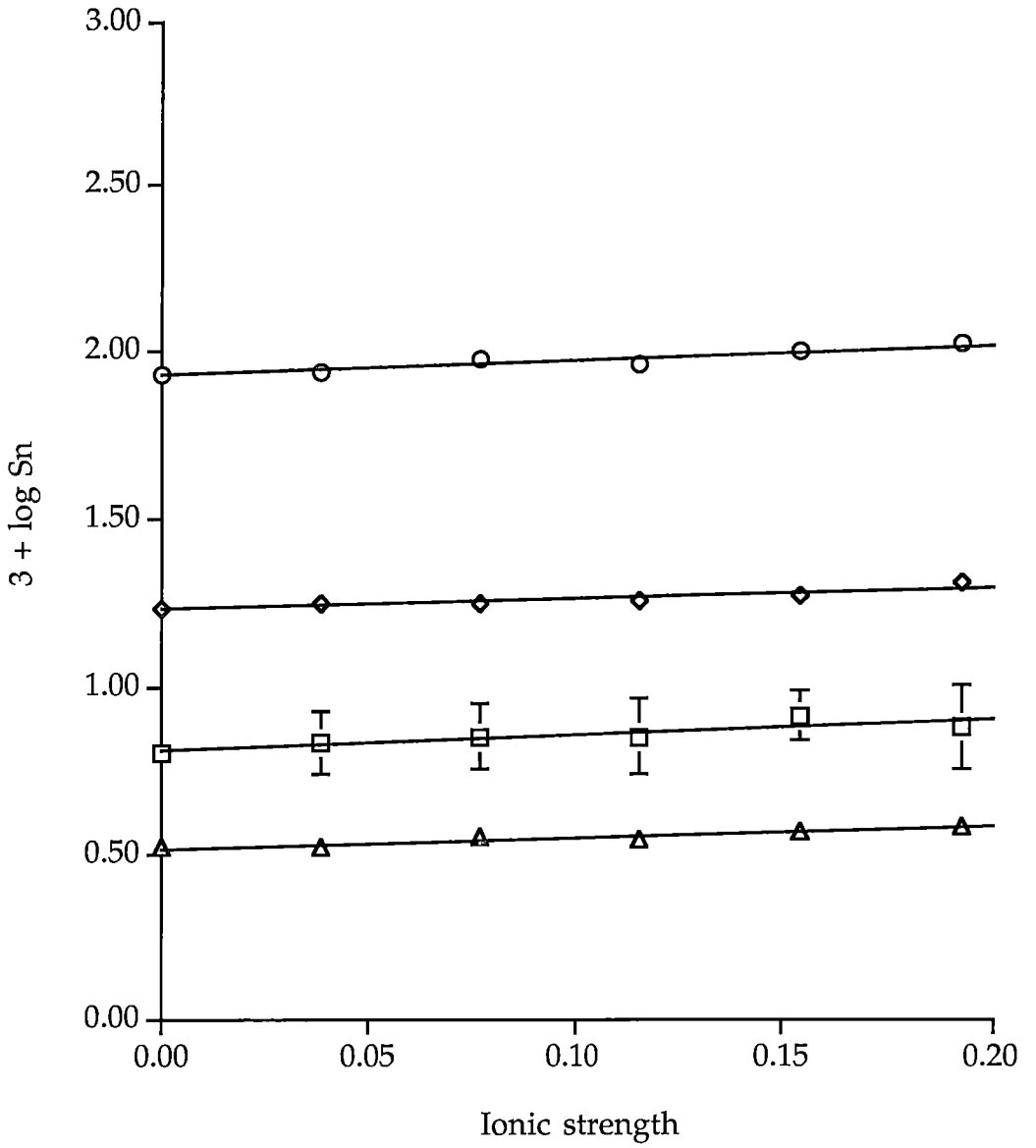


Figure 2.14. Relationship between logarithm of sorption number and vehicle ionic strength;

□ = acetophenone, ○ = chloroxylenol,

◇ = chlorocresol, △ = *p*-chlorophenol.

The solid line is a linear fit to the data of each solute.

Table 2.21. Slope of a plot of the logarithm of the sorption number versus vehicle ionic strength (Figure 2.14) obtained for each solute[a]

Solute	Slope
Acetophenone	0.48(0.15)
p-Chlorophenol	0.34(0.10)
Chlorocresol	0.34(0.14)
Chloroxylenol	0.46(0.15)

[a] Values in parentheses are SD values.

The relationship presented in eqn.2.5 is consistent with that described previously for the effect of ionic strength on the reaction rate of uncharged reacting molecules (Martin et al., 1983) as follows:

$$\log k = \log k_0 + bI \qquad (2.6)$$

where b is a constant and log k and log k_0 denote the reaction rate in the presence and absence of electrolyte, respectively.

Figures 2.15 - 2.18 show the sorption profiles of *p*-chlorophenol and *o*-xylenol in other common infusion solutions. The sorption profiles predicted by eqn.2.5 are also shown in these figures. It can be seen that the modified equation using the ionic strength correction factor closely approximates the exact result and appears to provide better accuracy than the original prediction equation (eqn.1.17, Roberts et al., 1991) which does not account for the effect of the vehicle ionic strength, that is, the

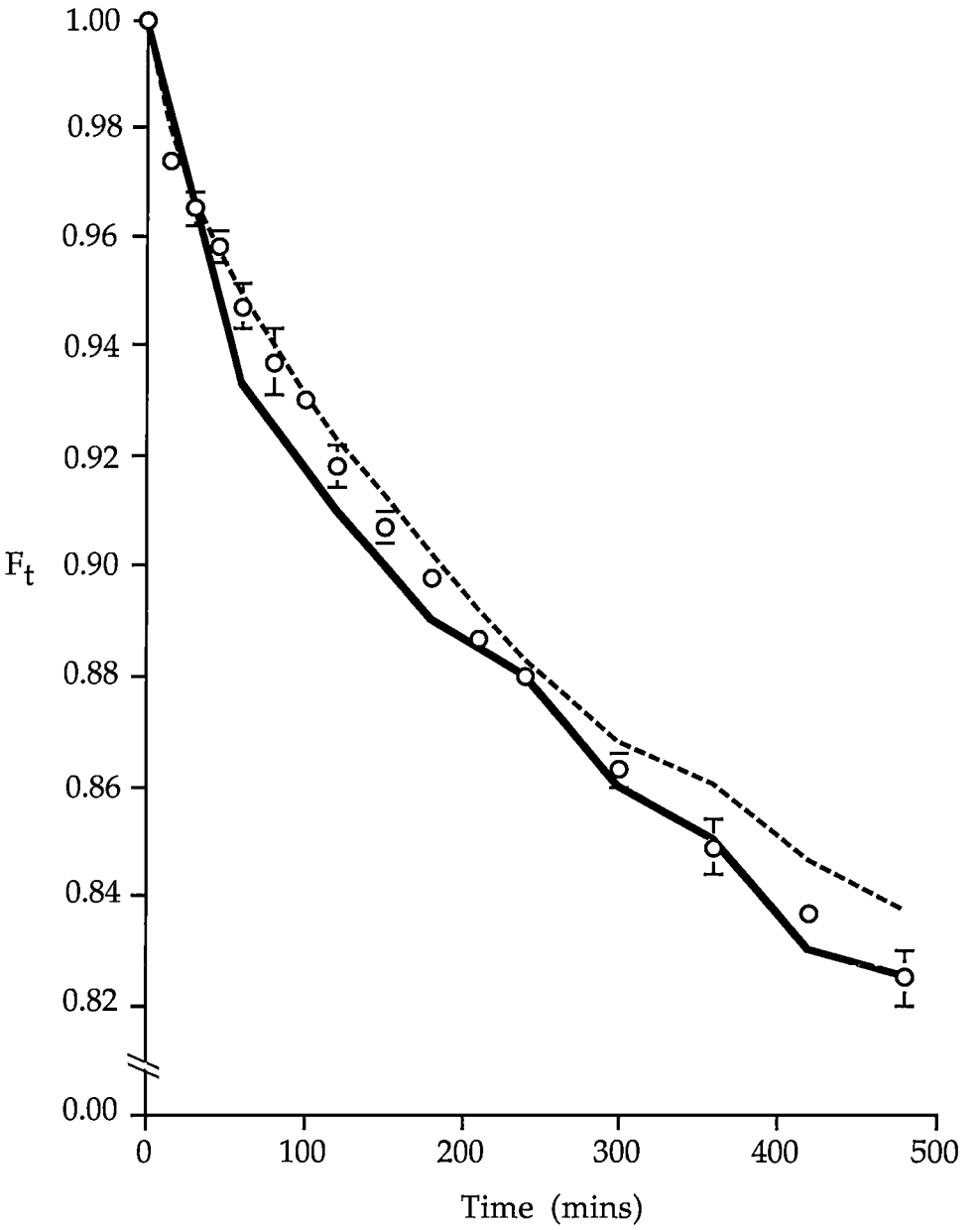


Figure 2.15. Sorption profile of *p*-chlorophenol in Ringer's solution stored in a PVC infusion bag;
o = F_t in Ringer's solution, ------- = F_t in water,
——— = F_t predicted from log Sn_1 calculated from eqn.2.5.

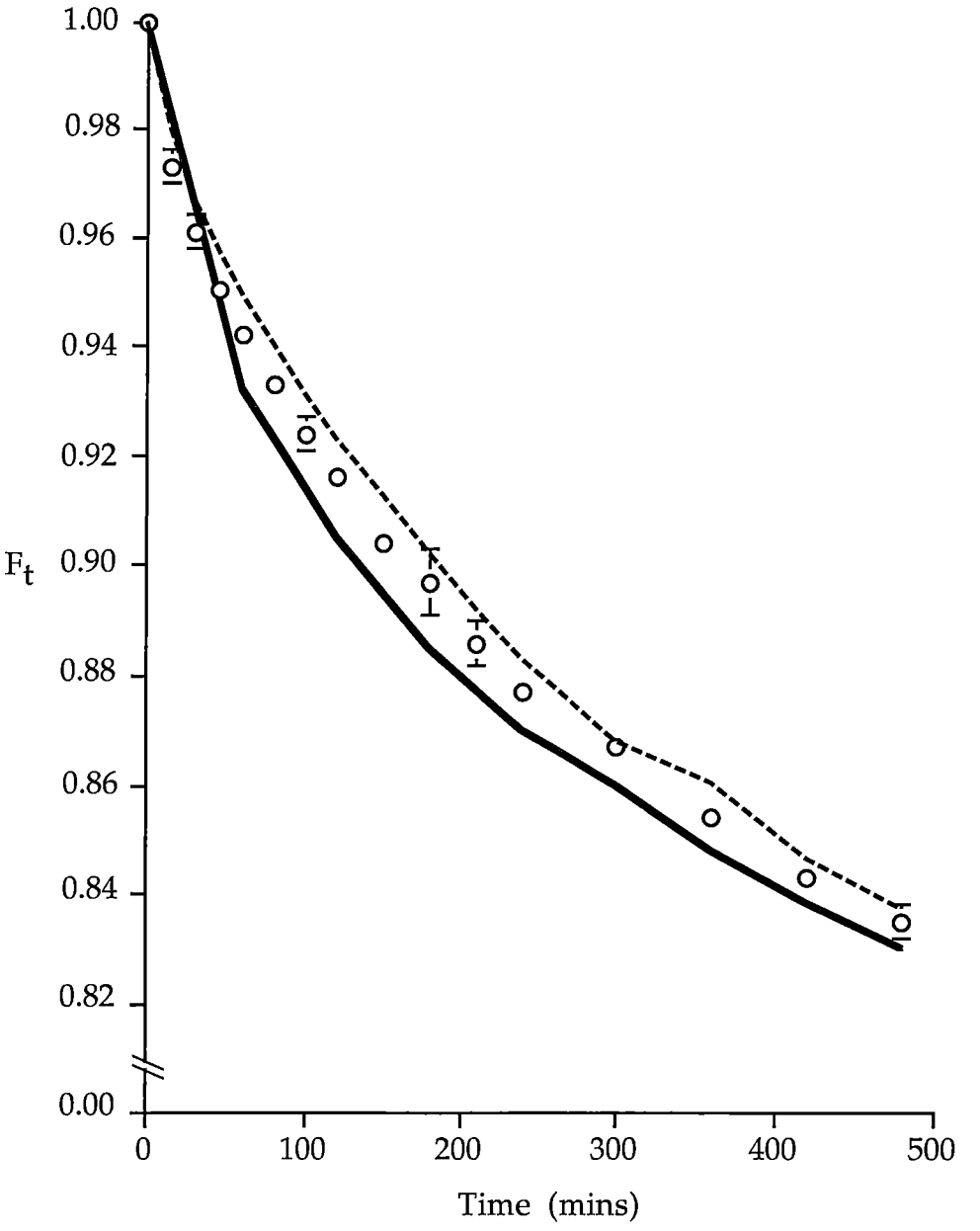


Figure 2.16. Sorption profile of *p*-chlorophenol in 1.4% sodium bicarbonate solution stored in a PVC infusion bag; o = F_t in 1.4% sodium bicarbonate solution, ——— = F_t predicted from logSn_i calculated from eqn.2.5, ------- = F_t in water.

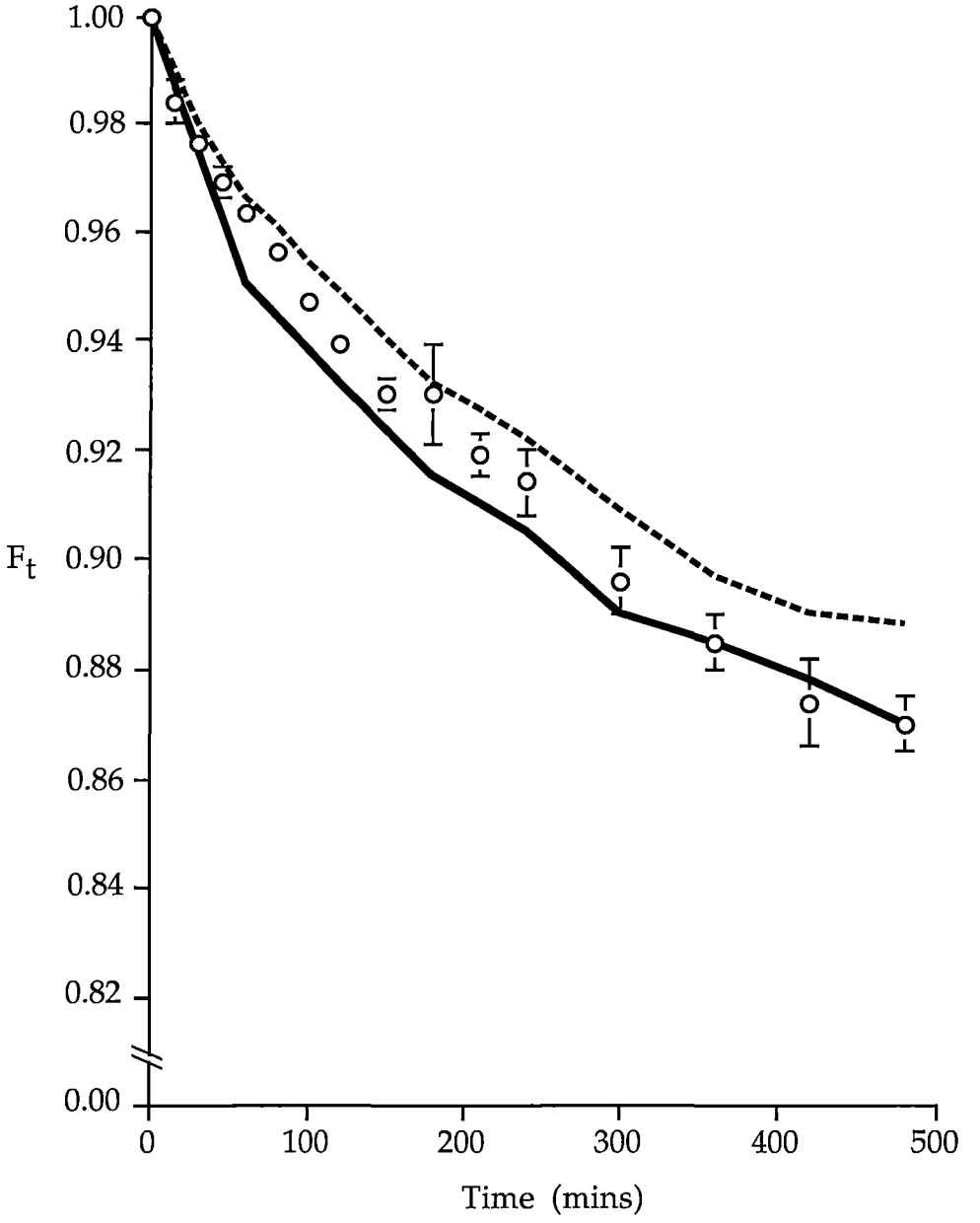


Figure 2.17. Sorption profile of *o*-xylenol in Ringer's solution stored in a PVC infusion bag;

o = F_t in Ringer's solution, ------- = F_t in water,

——— = F_t predicted from log Sn_i calculated from eqn.2.5.

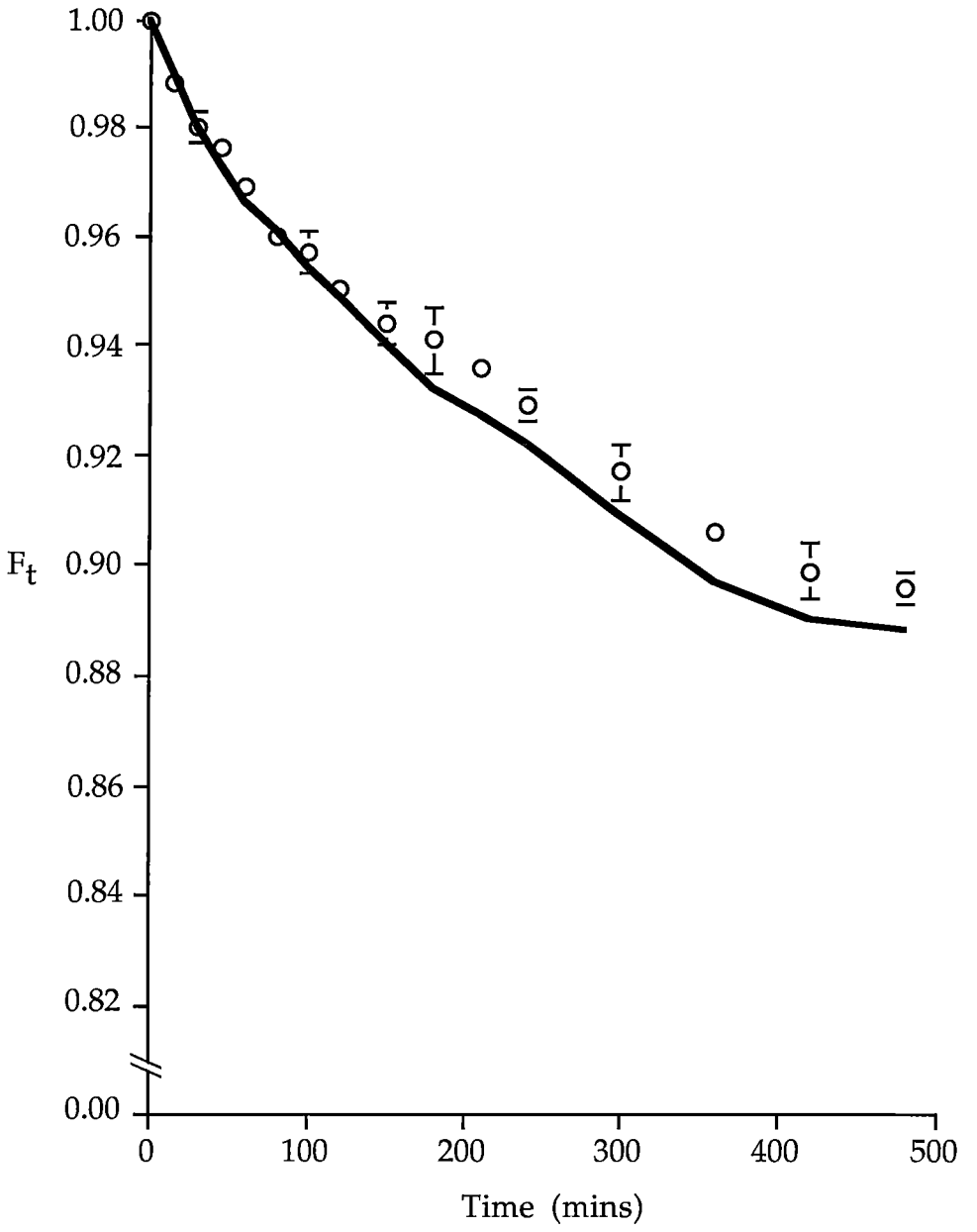


Figure 2.18. Sorption profile of *o*-xylenol in D5W solution stored in a PVC infusion bag; o = F_t in D5W, ——— = F_t in water and F_t predicted from log Sn_i calculated from eqn.2.5.

predicted values of the fraction of the original concentration of solute in any electrolyte solution at any time t (using eqn.1.17) would be the same as that in water. The increased loss of the solute in the presence of electrolytes appears to be controlled by the ionic strength of the vehicle and this 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 results in a decrease in the extent of solute uptake by PVC bags. The linear relationship between log Sn and molar ratio of sodium benzoate to solute (mole/mole) has been obtained for both nitrobenzene and *p*-chlorophenol as shown in Figures 2.19 and 2.20. This phenomenon, known as hydrotropy, can be explained by a salting-in of the solute following the addition of very soluble salts 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 bags.

2.4.4.4. Effect of storage temperature

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

$$\log k = \log A - \left(\frac{Ea}{2.303RT}\right) \qquad (2.7)$$

where A is the frequency factor, R represents the gas constant, k is the reaction rate constant, T denotes an absolute temperature and Ea is the

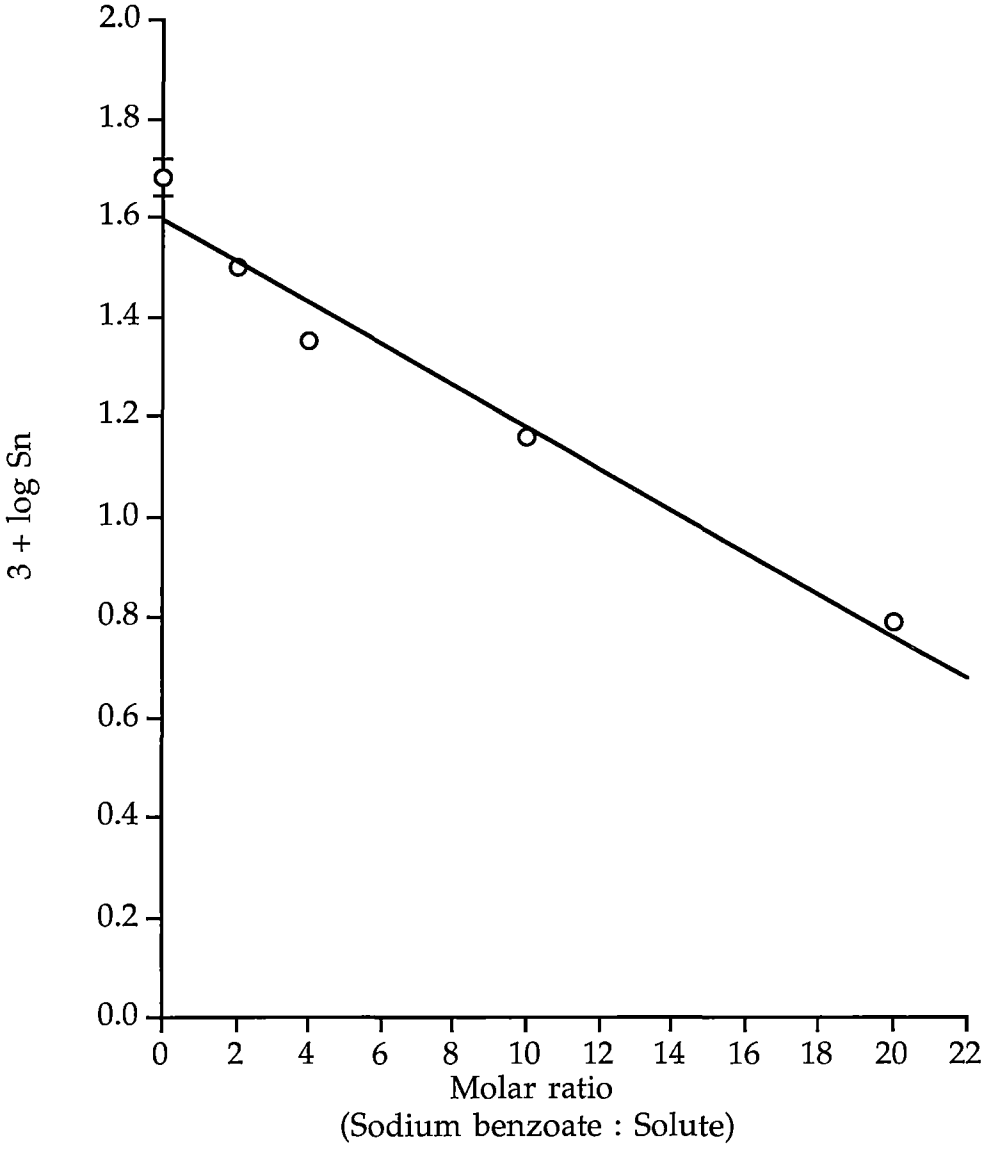


Figure 2.19. Effect of sodium benzoate on sorption of nitrobenzene from a solution stored in a PVC infusion bag for 8 hours. The solid line is a linear fit to the data.

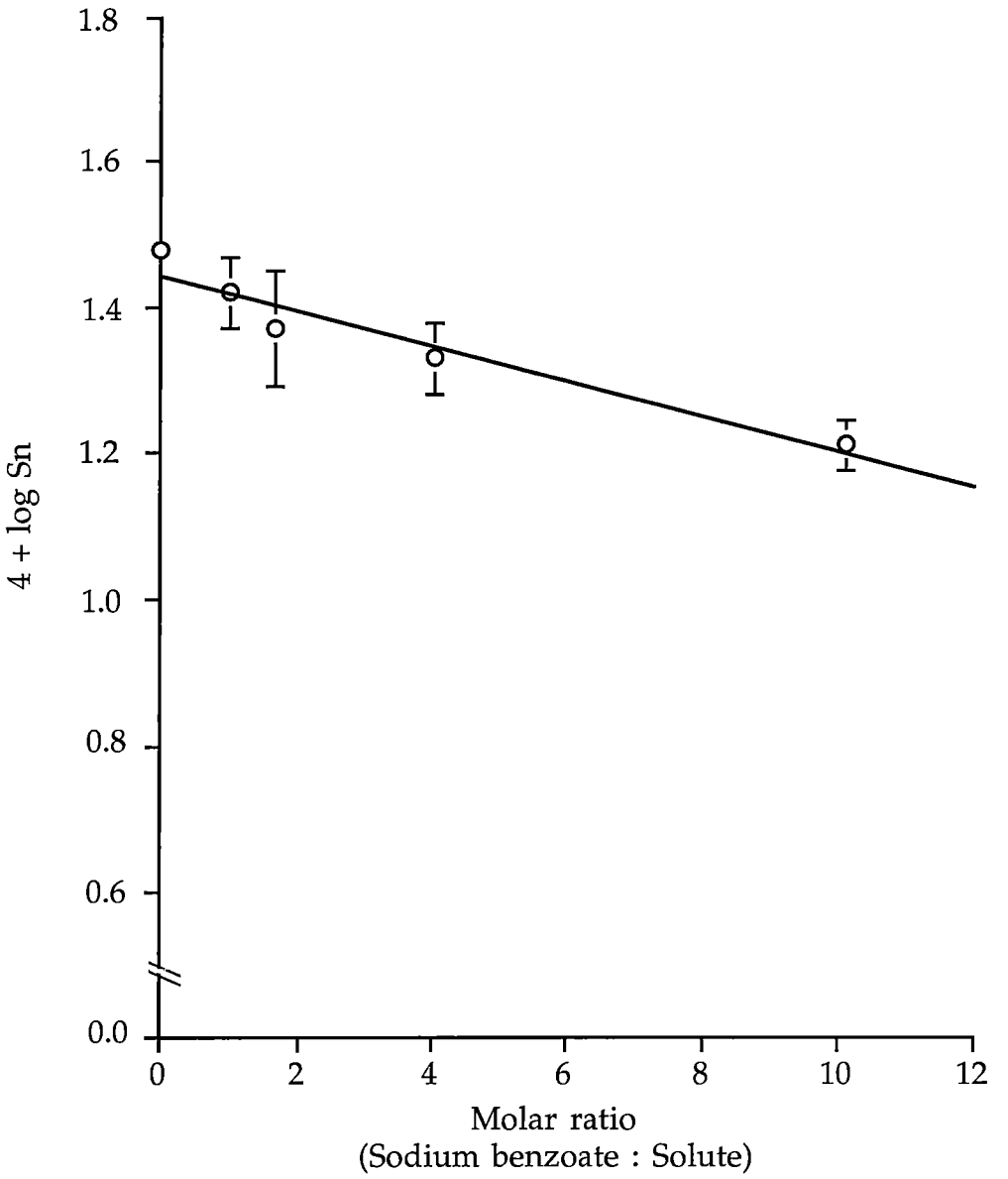


Figure 2.20. Effect of sodium benzoate on sorption of *p*-chlorophenol from a solution stored in a PVC infusion bag for 8 hours. The solid line is a linear fit to the data.

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.2.8 (Florence and Attwood, 1988):

$$\log k_2 - \log k_1 = \frac{Ea}{2.303R} \frac{(T_2 - T_1)}{T_2T_1} \qquad (2.8)$$

Thus Ea can be calculated from log k, which is expressed in terms of log Sn in this work, obtained under two different storage conditions in the first portion of this study (Experiments (1), a, b and ab in Table 2.10) by using eqn.2.8. The results are shown in Table 2.22.

Table 2.22. The activation energy Ea (kcal.mol^{-1}) for the sorption of a solute from its aqueous solution into a PVC bag[a]

Solute	Ea (kcal.mol^{-1})	
	High Concentration	Low Concentration
Phenol	13.85(0.91)	14.34(0.69)
Nitrobenzene	14.63(0.13)	16.44(1.63)
Acetophenone	16.77(0.51)	15.77(0.36)
Chlorocresol	14.08(0.30)	13.61(0.30)
p-Chlorophenol	11.40(0.69)	12.24(0.56)

[a] Values in parentheses are SD values.

Analysis of variance of Ea in Table 2.22 shows that Ea 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 $kcal.mol^{-1}$ 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 Ea / 2.303R in eqn.2.8 with the value of 3.13×10^3 obtained from five substances in this work yields:

$$\log k_2 - \log k_1 = 3.13 \times 10^3 \frac{(T_2 - T_1)}{T_2 T_1} \qquad (2.9)$$

or

$$\log Sn_2 - \log Sn_1 = 3.13 \times 10^3 \frac{(T_2 - T_1)}{T_2 T_1} \qquad (2.10)$$

Rearranging eqn.2.10 gives:

$$\log Sn_2 = \log Sn_1 + 3.13 \times 10^3 \frac{(T_2 - T_1)}{T_2 T_1} \qquad (2.11)$$

It is expected that eqn.2.11 may be useful for estimation of the sorption number at a second temperature from a knowledge of its value at another temperature.

Further study on the effect of temperature on the fraction of the original concentration of chlorocresol and acetophenone remaining in solutions stored in PVC bags was then carried out using solutions of four different original concentrations and four different storage temperatures. The

results are shown in Tables 2.23-2.30. Sorption numbers (Sn) were calculated from the data presented in Tables 2.23-2.30 using the method described earlier in Section 2.3 and a plot of log Sn versus 1/T is shown in Figures 2.21 and 2.22.

Table 2.23. Fraction of the original concentration of chlorocresol remaining (F_t) in solution stored in a PVC bag for 8 hours at 20±2°C[a,b]

Time (mins)	F_t			
	conc1	conc2	conc3	conc4
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.95(0.00)	0.96(0.01)	0.96(0.00)	0.97(0.01)
30	0.95(0.03)	0.95(0.01)	0.94(0.01)	0.94(0.01)
45	0.92(0.02)	0.92(0.01)	0.91(0.00)	0.92(0.01)
60	0.89(0.00)	0.90(0.01)	0.90(0.00)	0.90(0.00)
80	0.89(0.01)	0.89(0.02)	0.88(0.01)	0.88(0.01)
100	0.86(0.01)	0.87(0.02)	0.86(0.01)	0.87(0.01)
120	0.85(0.01)	0.85(0.01)	0.85(0.01)	0.85(0.01)
150	0.84(0.02)	0.84(0.02)	0.84(0.02)	0.84(0.02)
180	0.82(0.02)	0.82(0.01)	0.82(0.01)	0.82(0.02)
210	0.81(0.02)	0.81(0.02)	0.80(0.01)	0.80(0.01)
240	0.78(0.02)	0.79(0.02)	0.78(0.01)	0.79(0.02)
300	0.76(0.01)	0.77(0.02)	0.76(0.02)	0.76(0.01)
360	0.74(0.02)	0.74(0.02)	0.74(0.02)	0.74(0.01)
420	0.72(0.01)	0.72(0.01)	0.71(0.01)	0.71(0.01)
480	0.70(0.01)	0.70(0.02)	0.69(0.01)	0.69(0.02)

[a] For details of each condition see Table 2.4.

[b] Values in parentheses are SD values.

Table 2.24. Fraction of the original concentration of chlorocresol remaining (F_t) in solution stored in a PVC bag for 8 hours at 30±2°C[a,b]

Time (mins)	F_t			
	conc1	conc2	conc3	conc4
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.93(0.01)	0.93(0.00)	0.93(0.00)	0.93(0.00)
30	0.90(0.01)	0.89(0.01)	0.89(0.00)	0.89(0.01)
45	0.86(0.01)	0.86(0.00)	0.85(0.00)	0.86(0.01)
60	0.84(0.01)	0.84(0.01)	0.83(0.01)	0.83(0.00)
80	0.81(0.02)	0.81(0.01)	0.81(0.02)	0.80(0.00)
100	0.78(0.01)	0.78(0.01)	0.78(0.01)	0.77(0.01)
120	0.77(0.01)	0.77(0.01)	0.76(0.01)	0.76(0.00)
150	0.75(0.01)	0.75(0.01)	0.74(0.01)	0.74(0.01)
180	0.72(0.01)	0.72(0.01)	0.72(0.00)	0.71(0.00)
210	0.71(0.01)	0.70(0.01)	0.70(0.01)	0.69(0.01)
240	0.69(0.01)	0.69(0.01)	0.68(0.01)	0.67(0.01)
300	0.66(0.01)	0.66(0.01)	0.65(0.01)	0.65(0.02)
360	0.63(0.01)	0.63(0.01)	0.62(0.01)	0.62(0.01)
420	0.61(0.01)	0.61(0.01)	0.59(0.01)	0.59(0.02)
480	0.58(0.00)	0.59(0.01)	0.58(0.01)	0.57(0.01)

[a] For details of each condition see Table 2.4.
[b] Values in parentheses are SD values.

Table 2.25. Fraction of the original concentration of chlorocresol remaining (F_t) in solution stored in a PVC bag for 8 hours at 40±2°C[a,b]

Time (mins)	F_t			
	conc1	conc2	conc3	conc4
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.91(0.01)	0.90(0.00)	0.91(0.01)	0.91(0.01)
30	0.87(0.01)	0.87(0.00)	0.87(0.01)	0.87(0.01)
45	0.83(0.01)	0.82(0.01)	0.82(0.01)	0.82(0.01)
60	0.80(0.01)	0.79(0.01)	0.79(0.00)	0.79(0.01)
80	0.77(0.01)	0.77(0.01)	0.76(0.00)	0.76(0.01)
100	0.75(0.00)	0.74(0.01)	0.74(0.00)	0.73(0.01)
120	0.72(0.01)	0.71(0.01)	0.71(0.01)	0.71(0.01)
150	0.70(0.01)	0.69(0.01)	0.68(0.00)	0.68(0.01)
180	0.67(0.01)	0.67(0.01)	0.67(0.01)	0.66(0.01)
210	0.65(0.01)	0.65(0.00)	0.64(0.01)	0.64(0.01)
240	0.63(0.00)	0.63(0.02)	0.62(0.01)	0.61(0.01)
300	0.59(0.00)	0.59(0.01)	0.58(0.01)	0.59(0.02)
360	0.57(0.01)	0.57(0.01)	0.56(0.01)	0.56(0.02)
420	0.54(0.00)	0.54(0.00)	0.53(0.01)	0.53(0.01)
480	0.52(0.01)	0.52(0.00)	0.51(0.01)	0.50(0.01)

[a] For details of each condition see Table 2.4.
[b] Values in parentheses are SD values.

Table 2.26. Fraction of the original concentration of chlorocresol remaining (F_t) in solution stored in a PVC bag for 8 hours at 50±2°C[a,b]

Time (mins)	F_t			
	conc1	conc2	conc3	conc4
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.89(0.02)	0.88(0.01)	0.88(0.01)	0.88(0.01)
30	0.84(0.01)	0.84(0.02)	0.83(0.01)	0.83(0.01)
45	0.80(0.01)	0.79(0.00)	0.79(0.01)	0.78(0.01)
60	0.77(0.01)	0.76(0.01)	0.76(0.01)	0.75(0.01)
80	0.74(0.01)	0.73(0.00)	0.73(0.00)	0.72(0.01)
100	0.71(0.01)	0.70(0.01)	0.69(0.00)	0.69(0.01)
120	0.69(0.00)	0.68(0.01)	0.67(0.01)	0.66(0.00)
150	0.66(0.01)	0.65(0.01)	0.64(0.01)	0.64(0.01)
180	0.63(0.01)	0.62(0.00)	0.60(0.00)	0.61(0.01)
210	0.61(0.01)	0.60(0.01)	0.58(0.01)	0.58(0.00)
240	0.59(0.01)	0.58(0.01)	0.56(0.01)	0.56(0.00)
300	0.56(0.01)	0.55(0.02)	0.53(0.01)	0.53(0.01)
360	0.52(0.02)	0.51(0.02)	0.50(0.02)	0.49(0.02)
420	0.50(0.01)	0.49(0.01)	0.47(0.01)	0.48(0.01)
480	0.48(0.01)	0.47(0.01)	0.45(0.00)	0.44(0.01)

a For details of each condition see Table 2.4.

b Values in parentheses are SD values.

Table 2.27. Fraction of the original concentration of acetophenone remaining (F_t) in solution stored in a PVC bag for 8 hours at 20±2°C[a,b]

Time (mins)	F_t			
	conc1	conc2	conc3	conc4
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.97(0.00)	0.97(0.00)	0.98(0.00)	0.97(0.00)
30	0.96(0.01)	0.96(0.00)	0.96(0.00)	0.96(0.00)
45	0.95(0.01)	0.95(0.00)	0.95(0.00)	0.95(0.01)
60	0.95(0.02)	0.94(0.00)	0.94(0.00)	0.93(0.00)
80	0.92(0.00)	0.92(0.00)	0.92(0.01)	0.92(0.01)
100	0.91(0.01)	0.91(0.01)	0.91(0.00)	0.91(0.01)
120	0.90(0.00)	0.90(0.00)	0.90(0.01)	0.90(0.00)
150	0.88(0.01)	0.89(0.00)	0.89(0.01)	0.88(0.00)
180	0.87(0.01)	0.88(0.01)	0.87(0.01)	0.87(0.00)
210	0.86(0.00)	0.86(0.01)	0.86(0.00)	0.86(0.00)
240	0.85(0.00)	0.85(0.01)	0.85(0.01)	0.85(0.01)
300	0.83(0.01)	0.83(0.01)	0.84(0.01)	0.83(0.01)
360	0.82(0.00)	0.82(0.02)	0.82(0.01)	0.81(0.01)
420	0.80(0.01)	0.80(0.01)	0.80(0.01)	0.80(0.01)
480	0.79(0.01)	0.79(0.01)	0.79(0.01)	0.79(0.01)

a For details of each condition see Table 2.4.

b Values in parentheses are SD values.

Table 2.28. Fraction of the original concentration of acetophenone remaining (F_t) in solution stored in a PVC bag for 8 hours at 30±2°C[a,b]

Time (mins)	F_t			
	conc1	conc2	conc3	conc4
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.94(0.00)	0.95(0.01)	0.94(0.01)	0.94(0.01)
30	0.91(0.01)	0.92(0.00)	0.92(0.01)	0.91(0.01)
45	0.89(0.00)	0.89(0.01)	0.89(0.01)	0.88(0.00)
60	0.87(0.01)	0.87(0.01)	0.87(0.00)	0.87(0.01)
80	0.85(0.00)	0.85(0.01)	0.85(0.01)	0.85(0.00)
100	0.83(0.01)	0.84(0.01)	0.83(0.00)	0.83(0.00)
120	0.81(0.01)	0.82(0.00)	0.82(0.00)	0.81(0.01)
150	0.80(0.01)	0.80(0.01)	0.80(0.01)	0.79(0.00)
180	0.78(0.01)	0.79(0.01)	0.78(0.01)	0.78(0.01)
210	0.76(0.01)	0.77(0.01)	0.76(0.02)	0.76(0.01)
240	0.75(0.02)	0.75(0.01)	0.75(0.01)	0.75(0.01)
300	0.73(0.01)	0.73(0.01)	0.72(0.01)	0.72(0.01)
360	0.70(0.01)	0.71(0.01)	0.70(0.01)	0.69(0.01)
420	0.68(0.00)	0.69(0.00)	0.68(0.00)	0.68(0.00)
480	0.67(0.01)	0.67(0.01)	0.66(0.01)	0.66(0.01)

[a] For details of each condition see Table 2.4.
[b] Values in parentheses are SD values.

Table 2.29. Fraction of the original concentration of acetophenone remaining (F_t) in solution stored in a PVC bag for 8 hours at 40±2°C[a,b]

Time (mins)	F_t			
	conc1	conc2	conc3	conc4
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.92(0.00)	0.92(0.01)	0.92(0.00)	0.92(0.01)
30	0.89(0.01)	0.89(0.01)	0.89(0.01)	0.89(0.01)
45	0.86(0.01)	0.86(0.01)	0.86(0.01)	0.85(0.01)
60	0.84(0.01)	0.84(0.01)	0.84(0.01)	0.84(0.01)
80	0.81(0.01)	0.81(0.01)	0.81(0.01)	0.81(0.01)
100	0.79(0.01)	0.79(0.01)	0.79(0.01)	0.78(0.01)
120	0.78(0.01)	0.78(0.01)	0.78(0.01)	0.77(0.02)
150	0.75(0.01)	0.75(0.01)	0.75(0.01)	0.74(0.01)
180	0.73(0.01)	0.73(0.01)	0.72(0.01)	0.72(0.00)
210	0.71(0.01)	0.71(0.01)	0.71(0.01)	0.70(0.01)
240	0.70(0.01)	0.70(0.01)	0.69(0.01)	0.69(0.01)
300	0.67(0.01)	0.67(0.01)	0.66(0.01)	0.66(0.01)
360	0.65(0.01)	0.65(0.01)	0.64(0.01)	0.63(0.01)
420	0.62(0.01)	0.62(0.01)	0.62(0.02)	0.61(0.01)
480	0.60(0.01)	0.60(0.01)	0.59(0.01)	0.58(0.01)

[a] For details of each condition see Table 2.4.
[b] Values in parentheses are SD values.

Table 2.30. Fraction of the original concentration of acetophenone remaining (F_t) in solution stored in a PVC bag for 8 hours at 50±2°C[a,b]

Time (mins)	F_t			
	conc1	conc2	conc3	conc4
0	1.00(0.00)	1.00(0.00)	1.00(0.00)	1.00(0.00)
15	0.90(0.01)	0.90(0.01)	0.90(0.01)	0.90(0.01)
30	0.85(0.01)	0.86(0.01)	0.85(0.01)	0.85(0.01)
45	0.82(0.01)	0.83(0.01)	0.82(0.01)	0.82(0.01)
60	0.80(0.01)	0.80(0.01)	0.79(0.01)	0.79(0.01)
80	0.77(0.01)	0.77(0.01)	0.76(0.01)	0.76(0.01)
100	0.75(0.00)	0.75(0.01)	0.74(0.01)	0.74(0.01)
120	0.73(0.01)	0.73(0.01)	0.72(0.01)	0.72(0.01)
150	0.70(0.01)	0.70(0.01)	0.68(0.00)	0.69(0.01)
180	0.67(0.01)	0.68(0.01)	0.66(0.01)	0.66(0.01)
210	0,65(0.00)	0.65(0.01)	0.64(0.01)	0.64(0.01)
240	0.64(0.01)	0.64(0.01)	0.63(0.01)	0.63(0.00)
300	0.60(0.00)	0.61(0.00)	0.59(0.00)	0.59(0.00)
360	0.57(0.01)	0.58(0.01)	0.56(0.00)	0.56(0.00)
420	0.55(0.01)	0.55(0.01)	0.53(0.01)	0.54(0.01)
480	0.53(0.01)	0.53(0.01)	0.51(0.01)	0.51(0.01)

[a] For details of each condition see Table 2.4.

[b] Values in parentheses are SD values.

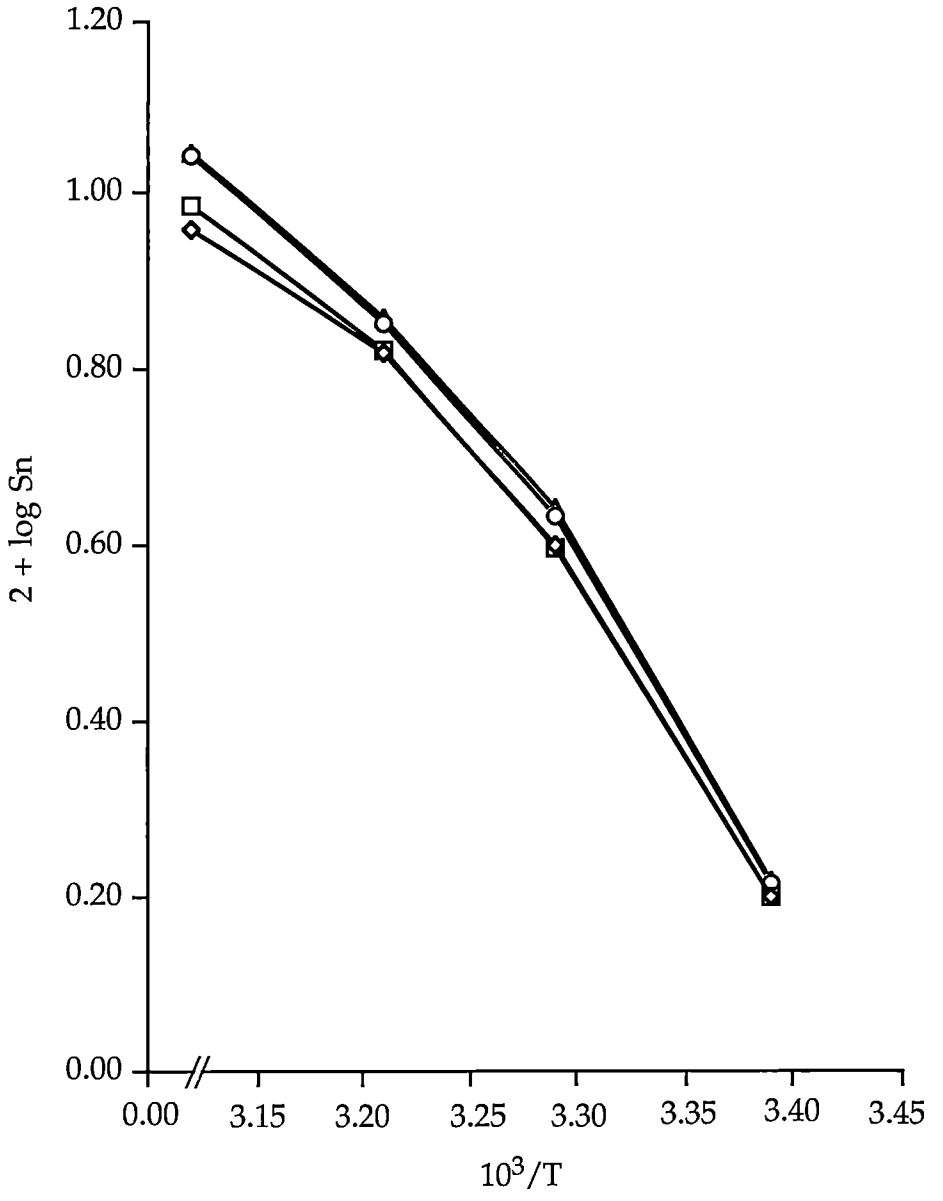


Figure 2.21. Effect of temperature on sorption rate of chlorocresol from a solution stored in a PVC bag for 8 hours;

—◇— = conc 1 —□— = conc 2

—○— = conc 3 —△— = conc 4

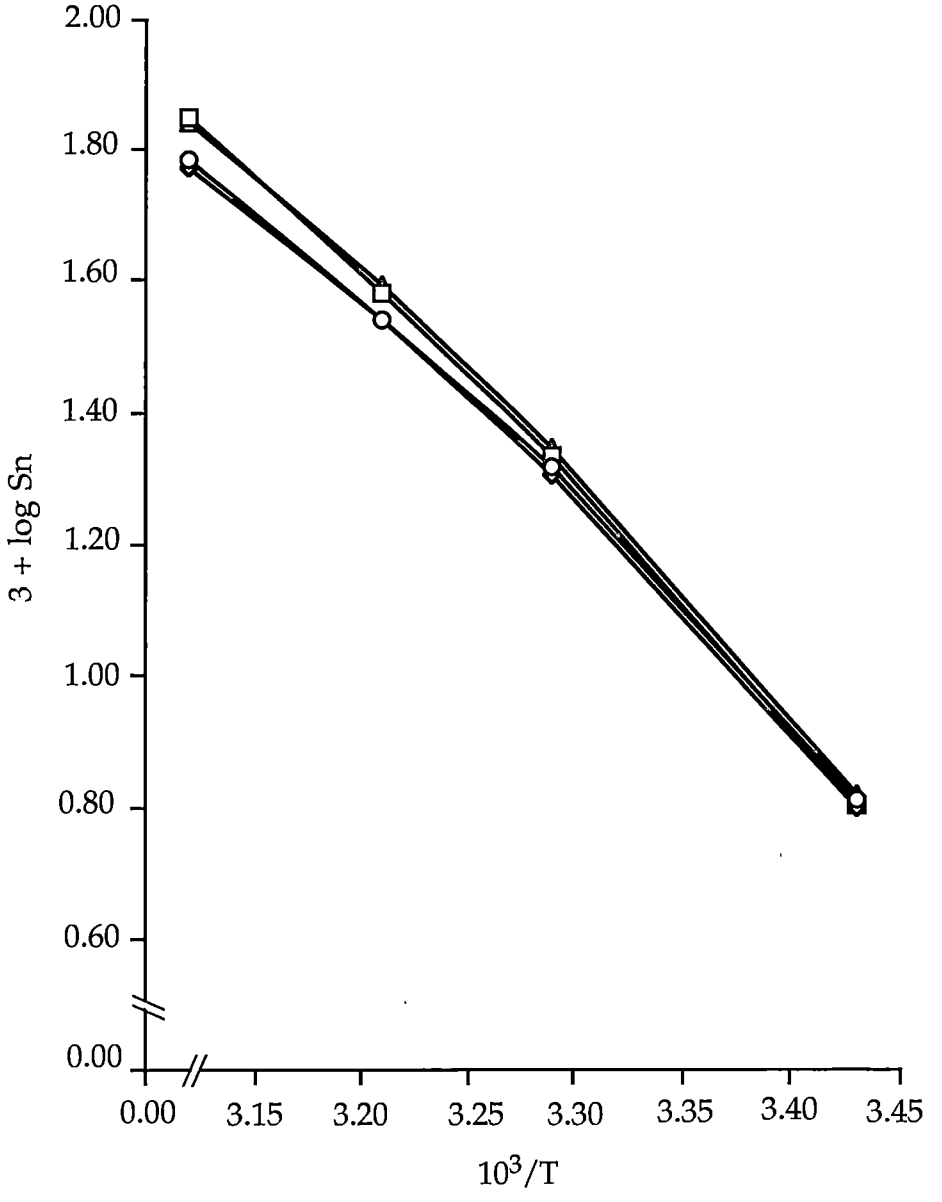


Figure 2.22. Effect of temperature on sorption rate of acetophenone from a solution stored in a PVC bag for 8 hours;

—○— = conc 1 —◇— = conc 2

—□— = conc 3 —△— = conc 4

The activation energy, Ea, and the logarithm of the frequency factor (log A) for the sorption of these solutes were then calculated from the slope and intercept values obtained from the linear curve fit of these lines using eqn.2.7 and are shown in Tables 2.31 and 2.32. The activation energy, Ea, and the logarithm of the frequency factor, log A, for the sorption of acetophenone calculated from the slope and intercept values of a plot of log Sn versus 1/T, where T values used are 20, 30 and 40°C, using eqn.2.7 are also shown in Table 2.32.

Table 2.31. The activation energy, Ea, and the logarithm of the frequency factor, log A, for the sorption of chlorocresol from solutions of four different concentrations[a]

Concentration ($x10^5$M)	Activation energy[b] (kcal.mol^{-1})	log A[c] (hour^{-1})
5.62	12.85(1.47)	7.78(1.04)
7.00	13.30(1.45)	8.11(1.02)
8.48	13.93(1.18)	8.59(0.83)
9.86	13.90(1.21)	8.57(0.86)

[a] Values in parentheses are SD values.

[b] Calculated from the slope obtained from a plot of log Sn against 1/T where T values used are 20, 30, 40 and 50°C.

[c] Obtained from the intercept values of a plot of log Sn against 1/T where T values used are 20, 30, 40 and 50°C.

Table 2.32. The activation energy, Ea, and the logarithm of the frequency factor, log A, for the sorption of acetophenone from solutions of four different concentrations[a]

Concentration ($x10^5$M)	For T up to 50°C		For T up to 40°C	
	Activation energy[b] (kcal.mol^{-1})	log A[c] (hour^{-1})	Activation energy[d] (kcal.mol^{-1})	log A[e] (hour^{-1})
3.83	14.66(0.32)	8.82(0.23)	16.02(0.53)	9.81(0.38)
4.49	14.72(0.42)	8.85(0.28)	16.29(0.65)	10.00(0.45)
4.99	15.78(0.48)	9.64(0.33)	17.09(0.75)	10.60(0.53)
5.49	15.47(0.27)	9.43(0.19)	17.00(0.35)	10.55(0.24)

[a] Values in parentheses are SD values.
[b] Calculated from the slope obtained from a plot of log Sn against 1/T where T values used are 20, 30, 40 and 50°C.
[c] Obtained from the intercept values of a plot of log Sn against 1/T where T values used are 20, 30, 40 and 50°C.
[d] Calculated from the slope obtained from a plot of log Sn against 1/T where T values used are 20, 30 and 40°C.
[e] Obtained from the intercept values of a plot of log Sn against 1/T where T values used are 20, 30 and 40°C.

For chlorocresol, both log A and Ea 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 was found 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 interactions with 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. It follows that eqn.2.11 may be applicable only for temperatures up to 40°C.

Eqn.2.11, which is derived from the data obtained at temperatures 20°C and 40°C, was used to estimate log Sn at 30°C, of acetophenone and chlorocresol in solutions of four different concentrations, from the values at 20°C or 40°C obtained from 5.49×10^{-5}M acetophenone and 9.86×10^{-5}M chlorocresol aqueous solutions. It should be noted that all of the conditions used in this prediction are different from those used in deriving eqn.2.11. The predicted values of log Sn at 30°C are presented in Tables 2.33 and 2.34.

A comparison of F_t obtained experimentally and that calculated from the predicted log Sn (Tables 2.33 and 2.34) by means of eqn.1.13, for times up to 480 minutes, is shown in Figures 2.23 and 2.24. It can be seen that a reasonable prediction of acetophenone and chlorocresol uptake into PVC infusion bags at a second temperature can be achieved from the data obtained from one particular set of conditions.

Table 2.33. The actual and predicted log Sn of acetophenone at 30°C.

Concentration[a]	logSn at 30°C		
	Actual	Predicted from data obtained at	
		20°C	40°C
conc1	-1.69±0.04	-1.84	-1.79
conc2	-1.70±0.03	-1.85	-1.79
conc3	-1.67±0.03	-1.85	-1.75
conc4	-1.65±0.02	-1.83	-1.74

[a] For details of each condition see Table 2.4.

Table 2.34. The actual and predicted log Sn of chlorocresol at 30°C.

Concentration[a]	logSn at 30°C		
	Actual	Predicted from data obtained at	
		20°C	40°C
conc1	-1.40±0.02	-1.46	-1.51
conc2	-1.40±0.03	-1.45	-1.51
conc3	-1.37±0.01	-1.44	-1.48
conc4	-1.36±0.04	-1.44	-1.47

[a] For details of each condition see Table 2.4.

Thus, it may be concluded that eqn.2.11 appears to be useful for estimation of the sorption number at a second temperature from a knowledge of its value at the first temperature. It is suggested that eqn.2.11 may be applicable only for temperatures up to 40°C.

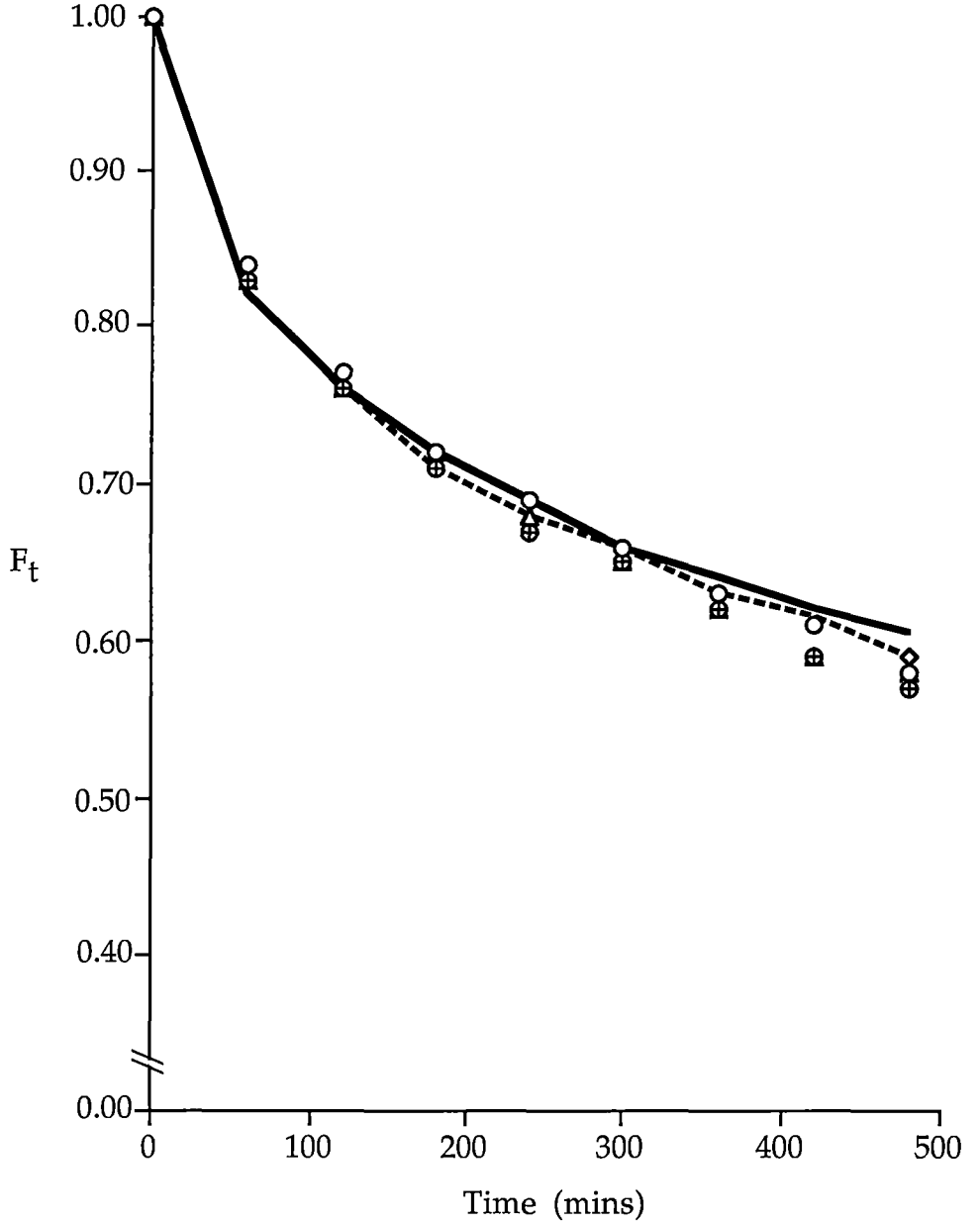


Figure 2.23. Sorption profile of chlorocresol from solutions stored in PVC infusion bags at 30 °C;

○ = F_t conc1, ◇ = F_t conc2,

△ = F_t conc3, ⊕ = F_t conc4,

- - - - - - = F_t predicted from data at 20°C,

——— = F_t predicted from data at 40°C.

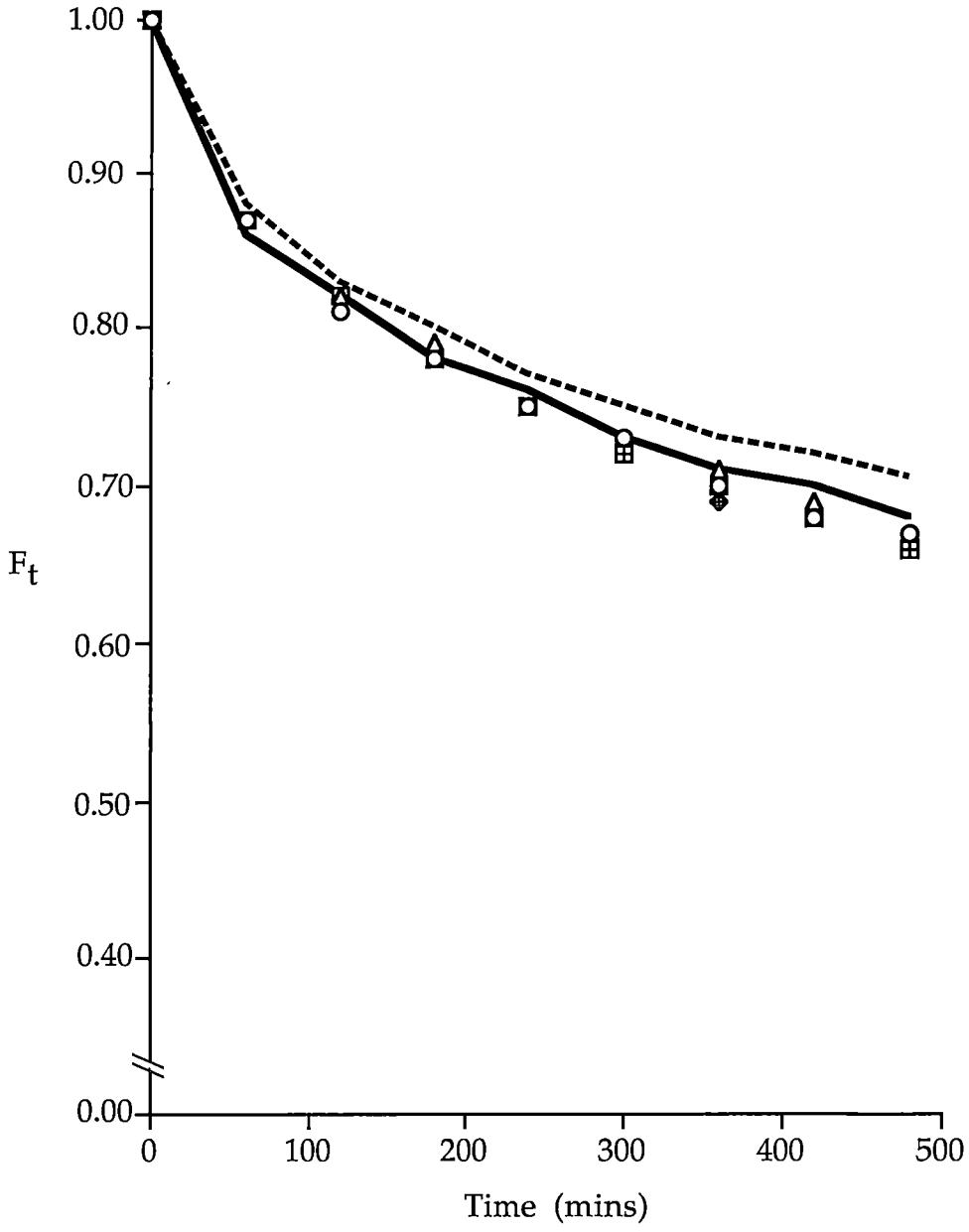


Figure 2.24. Sorption profile of acetophenone from solutions stored in PVC infusion bags at 30 °C;

○ = F_t conc1, △ = F_t conc2,

⊞ = F_t conc3, ◈ = F_t conc4,

▪▪▪▪▪▪▪ = F_t predicted from data at 20°C,

——— = F_t predicted from data at 40°C.

CHAPTER 3. SOLUTE-PVC INTERACTION IN DYNAMIC CONDITIONS

3.1. Introduction

The time course of the sorption of solutes by PVC infusion bags under varying conditions of clinical interest can be adequately described by using the original predictive model (Roberts et al., 1991) which has been shown to be able to account for the effect of important factors such as time, plastic surface area, solution volume and solution pH on fractional solute loss. Refined predictive equations, based on a diffusion model (Kowaluk et al., 1985; Roberts et al., 1991), which account for the additional effect of vehicle ionic strength and storage temperature on solute uptake by PVC infusion bags have been presented in Chapter 2.

The loss of drug during infusion through PVC tubing is also a potential problem. Although a number of complex mathematical models have been proposed to describe the sorption of solute during flow through tubing (Donaldson et al., 1992), a practical model for routine application is still unavailable.

A major objective of the present study is to investigate the kinetics of the sorption of model solutes by PVC tubing in order to develop a simplified model which is suitable for routine, practical use and the effect of solute concentration, flow rate, tubing diameter and tubing length on the extent of solute uptake by PVC tubing has been investigated in the present study. In addition, an attempt has been made to correlate the

extent of sorption of the model solutes by PVC tubing during flow, with selected physicochemical properties of the solutes.

3.2. Materials and Methods

Infusion solutions. The following solutes were used in preparing infusion solutions: acetophenone (May and Baker, lot 29399), nitrobenzene (BDH Chemicals, lot 2594000), phenol (Central Medical Store, Hobart, Tasmania, lot 3247), *p*-chlorophenol (BDH Chemicals, lot 2572870), *p*-bromophenol (BDH Chemicals, lot 1818810), *o*-xylenol (Ega-chemie, lot 1606689), *p*-methylacetophenone (Aldrich, lot 2805CJ), chloroxylenol (Central Medical Store, Hobart, Tasmania, lot 154/1) and thymol (Naarden, Sydney, Australia, lot P692/1). All chemicals were laboratory grade and were used as received without further purification. All solutions were prepared in glass distilled water.

Plastic tubings. A series of tubings (Food Contact-Clear Vinyl, Nylex Corporation Limited, Australia) composed of flexible polyvinylchloride was used. In this series, tubing internal diameter (i.d.) was varied (0.5 cm (lot 0134), 0.6 cm (lot 0099), 0.8 cm (lot 0270, and 0030)) while tubing wall thickness was constant at 0.15 cm. All tubings were of food contact grade and were used as received without any pretreatment.

Flow system. The infusion system used in this study consisted of three principal parts. The first of these was a 2-L glass percolator (Pyrex®, U.S.A.) with a glass outlet at the bottom as shown in Figure 3.1. The percolator was held vertically by means of a ring clamp and stand. A constant level of fluid was maintained in the percolator, which acted as a

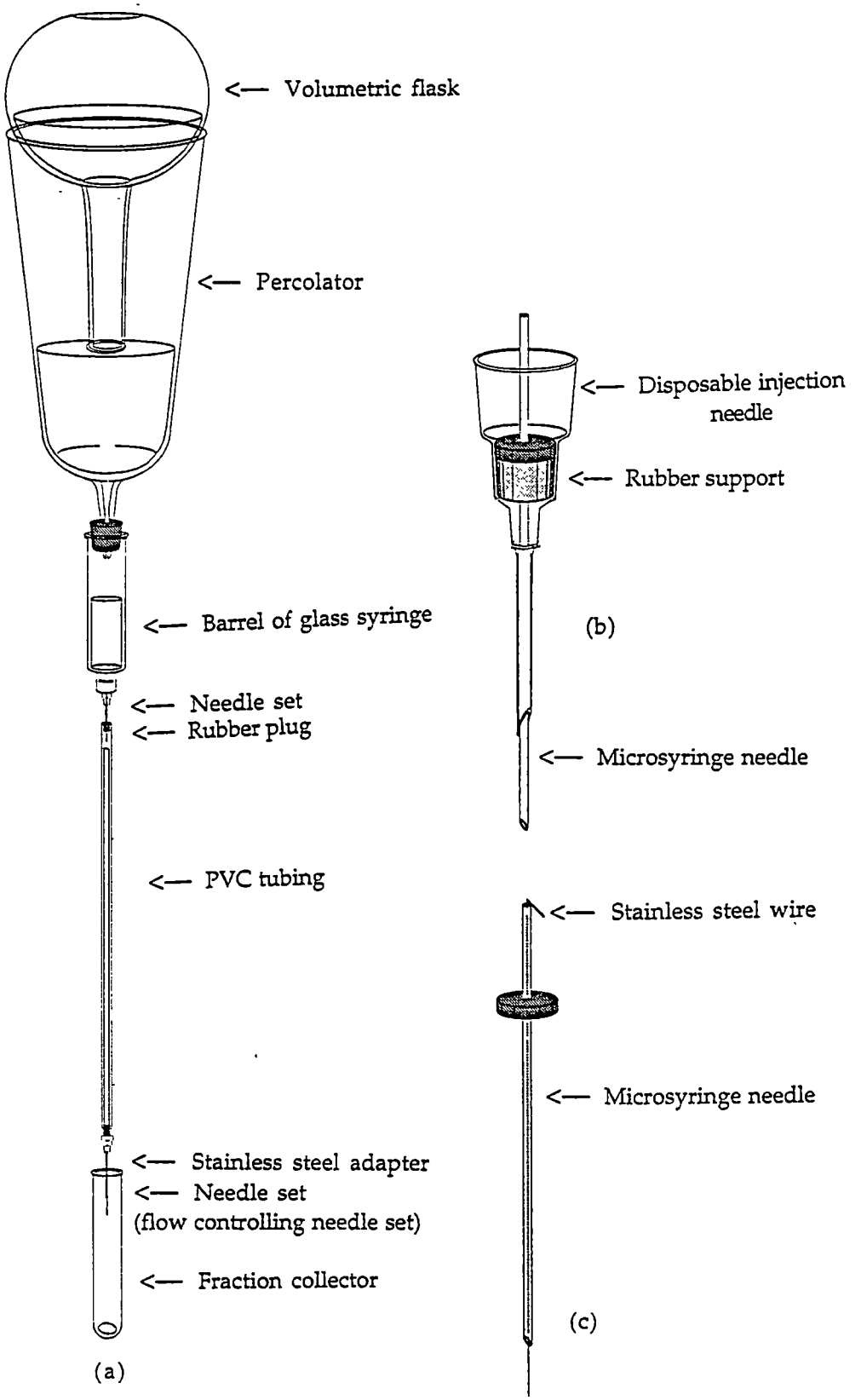


Figure 3.1. Flow system (a), needle set (b) and flow controlling needle(c).

reservoir, by the use of an inverted flask (Figure 3.1a). Solution was allowed to drip from the glass outlet, which passed through a hole drilled in a rubber stopper, into the barrel of a 20-mL glass syringe. The syringe was held vertically (plunger end up) by means of the rubber stopper and a stand and clamp. At the distal end of the syringe barrel, a microsyringe needle (0.32 diameter, 50 mm length with a bevel tip, SGE, Australia) was placed within a Terumo® 19G x 38 mm disposable injection needle (Figure 3.1b) which was attached to the outlet (metal fitting) on the syringe. The needles passed, in turn, through a rubber stopper which acted as a support for the tubing which was under investigation.

The fluid level in the syringe barrel was held constant by gravity replacement from the constant level reservoir in the percolator. Solution was allowed to drip from the syringe barrel into the tubing under investigation. The tubing was held vertically throughout its length by means of a stand and loose clamp arrangement.

The infusion rate was controlled by the use of a needle arrangement at the end of the tube (Figure 3.1b) which was identical to that described above for the proximal end of the tube. The needles were held in place at the end of the tube by means of a stainless steel adaptor. The dimensions of the microsyringe needle and disposable needle, which were used at the end of the tube, varied from experiment to experiment according to the flow rate which was required.

Before connecting the reservoir to the remainder of the infusion setup, the tubing was filled with the solution being studied by using the 20-mL

glass syringe, the barrel of which subsequently became part of the system. An air space of approximately 1 cm long was left between the surface of the solution in the tubing and the rubber plug fitted at the top end of the tubing in order to eliminate the influences of the stopper and/or the rubber material as well as to allow for observation of the fluid moving in the tubing. In addition, as this air space was constant throughout the infusion, it was assumed that the flow rate of the solution moving into the tubing was the same as that moving out.

After the tubing was filled, the syringe was detached from the tubing. The syringe, without plunger (that is, the barrel), was then attached to the needle set (which was passed through the rubber stopper fitted at the top end of the tubing) and filled to the 15mL mark with the solution being studied. This level would be sufficient to protect against entrainment of air in the fluid stream and the associated possibility of air bubbles in the tubing. The inlet end of the barrel was then attached to the rubber stopper at the outlet of the empty percolator (Figure 3.1). An air space was also kept between the solution surface in the barrel and the rubber stopper, into which the percolator outlet was inserted, for the same purpose as described earlier. After connecting the remainder of the infusion setup to the empty percolator, the volumetric flask containing the remaining infusion solution was immediately placed, in an inverted position, in the percolator. The level of fluid in the percolator is thus held constant and the solution in the flask acts as a reservoir. In every condition, the setting up time was less than 5 minutes.

Simulated infusion. The same procedure was used in all of the flow studies. The experiments were conducted at a constant temperature of

21±2 °C. An aqueous solution of the selected solute was prepared in a volumetric flask. An aliquot (15 mL) was used to "fill" the syringe barrel as described above and a further aliquot (10 mL) was withdrawn and stored in a glass bottle as a control. The remaining solution was infused through the tubing by gravity flow at a constant flow rate. Samples were collected individually from the distal end of the tubing into glass tubes in an automatic fraction collector at specified times. Each time indicated in this work is the mid-point of a collection period of 10 minutes. The effluent delivered, during the setting up time, was collected and was part of the first sample. The effluent concentrations were analysed using the methods described below for each solute. The initial concentration of the solution in the reservoir was determined before beginning the infusion. New tubing was used and duplicate runs were performed for each experiment.

3.2.1. Validation of the flow system

To verify the validity and the accuracy of the flow system, an in-process check was performed at specified time intervals during infusions of distilled water at a constant temperature of 21±2 °C. The main specifications of the flow system used are shown in Table 3.1.

The method used was as described above. Since increased accuracy may be obtained with fill checks done using weight rather than volume (Trappler, 1993), fill weight was used as a measurement in this study. By collecting 10-minute effluents individually in glass tubes of known weight, fill weights were then determined at specified times. The experiments were run in duplicate.

Table 3.1. Specifications of the flow system.

Experiment	Tubing		Flow controlling needle		Target flow rate ($mL.min^{-1}$)
	length (cm)	i.d.[a] (cm)	length (mm)	i.d.[a] (mm)	
1	40	0.5	50	0.25	0.6
2	100	0.5	50	0.20	0.6
3	100	0.5	50	0.32[b]	1.2
4	40	0.5	50	0.32	1.2
5	100	0.8	50	0.20	0.6
6	40	0.8	50	0.25	0.6
7	40	0.8	50	0.32	1.2
8	100	0.8	50	0.32[b]	1.2

[a] i.d. = internal diameter.

[b] contains a stainless steel wire (0.14 mm diameter, 73 mm length) through and beyond the entire length of the needle, see Figure 3.1c.

3.2.2. Leaching (desorption) from the tubing

Distilled water was allowed to flow through a tubing of 0.8 cm internal diameter and 40 cm length at a flow rate of 0.6 $mL.min^{-1}$ using the method described under "Flow system" in Section 3.2 above. The effluent from the distal end of the tubing was collected at specified times. The ultraviolet-light absorbance of the sample was then measured between 200 and 300nm using a Cary double-beam scanning ultraviolet spectrophotometer. Solution from time zero was used as a blank. The experiments were run in duplicate.

3.2.3. Sorption profiles of model solutes

Solutes used in this study were acetophenone, nitrobenzene, phenol, *p*-chlorophenol, *p*-bromophenol, *o*-xylenol, thymol, chloroxylenol and *p*-methylacetophenone. The sorption profile of each solute was obtained

by running the aqueous solution through tubing using the conditions and methods described above (Section 3.2.2). Solute concentrations used are as shown in Table 3.2. In all instances, duplicate samples were run. Effluent concentrations of each solute were determined using ultraviolet spectrophotometry at the previously determined wavelength of maximum absorbance (see Section 2.2.2).

Table 3.2. Solute concentrations used in sorption profile study.

Experiment	Solute	Concentration ($x10^5$ M)
1	Acetophenone	4.99
2	Nitrobenzene	12.50
3	Phenol	55.60
4	*o*-Xylenol	40.00
5	*p*-Chlorophenol	51.30
6	4-Bromophenol	48.70
7	*p*-Methylacetophenone	1.96
8	Chloroxylenol	25.50
9	Thymol	33.30

3.2.4. Factors affecting solute sorption into PVC tubing

3.2.4.1. Simultaneous investigation of the effect of solute concentration, flow rate, tubing diameter and tubing length on solute uptake by PVC tubing

The physicochemical factors most likely to affect drug sorption into PVC tubing are solute concentration, flow rate, tubing diameter and tubing length. To assess the influence of each of these factors and their interactions on the sorption process, a four-factor, two-level factorial fractional design experiment (Armstrong and James, 1990) was used in

the sorption studies on acetophenone, nitrobenzene and *p*-chlorophenol. The factors and levels selected were as follows:

Factor C: solute concentration. The concentration ranges used, as shown in Table 3.3, were chosen to provide an absorbance between 0.2 and 0.7.

Table 3.3. Concentration of solute used in the investigation of the effect of solute concentration, flow rate, tubing diameter and tubing length on solute uptake by PVC tubing

Solute	Concentration ($x10^5M$)	
	High	Low
Acetophenone	4.99	3.83
Nitrobenzene	12.50	5.63
p-Chlorophenol	51.30	25.70

Factor V: flow rate; 0.6 and 1.2 $mL.min^{-1}$.

Factor D: tubing diameter; 0.5 and 0.8 cm.

Factor L: tubing length; 40 and 100 cm.

The experiments were set up as shown in Table 3.4 in which low levels of a factor are represented by - and high levels by +. The procedure used was essentially the same as that described earlier in Section 3.2.3. All experiments were run in duplicate.

Table 3.4. Four-factor, two-level factorial fractional design to show sorption of the solute by PVC tubings

Experiment	Factor C (concentration)	Factor V (flow rate)	FactorD (tubing diameter)	Factor L (tubing length)
(1)	-	-	-	-
cl	+	-	-	+
vl	-	+	-	+
cv	+	+	-	-
dl	-	-	+	+
cd	+	-	+	-
vd	-	+	+	-
cvdl	+	+	+	+

3.2.4.2. Effect of a single factor: solute concentration, flow rate, tubing diameter and tubing length studied separately

Sorption studies on acetophenone aqueous solutions of two differing concentrations ($3.83x10^{-5}$ M and $4.99x10^{-5}$ M) using tubing of 0.8 cm internal diameter and 40 cm length and a flow rate of 0.6 $mL.min^{-1}$ were performed to determine the effect of solute concentration on sorption. The experiments were run in duplicate.

To determine the influence of flow rate on solute uptake, sorption studies using tubing of 0.8 cm internal diameter and 40 cm length and a flow rate of 0.6 and 1.6 $mL.min^{-1}$ were performed on $4.00x10^{-4}$ M *o*-xylenol aqueous solutions. In this study, duplicate samples were run.

To determine the influence of tubing diameter on solute uptake by PVC tubing, duplicate samples of $4.99x10^{-5}$ M acetophenone solution were

allowed to flow through 40 cm long tubing of three different internal diameters (0.5, 0.6 and 0.8 cm) at a constant flow rate of 0.6 mL.min^{-1}.

To determine the influence of tubing length on solute uptake by PVC tubing, duplicate samples of 4.87x10^{-4} M *p*-bromophenol solution were allowed to flow through 0.8 cm diameter tubing of two different lengths (40 and 100 cm) at a constant flow rate of 0.6 mL.min^{-1}.

3.2.4.3. Evaluation of the combined effect of flow rate and/or tubing diameter and/or tubing length

Aqueous solutions of *o*-xylenol and *p*-bromophenol were used at a concentration of 4.00x10^{-4} M and 4.87x10^{-4} M respectively. The experiments were run in duplicate and the conditions used were as shown in Table 3.5.

Table 3.5. Conditions used in the evaluation of the effect of flow rate, tubing diameter and tubing length study

Experiment	Solute	Tubing Length (cm)	Tubing i.d.	Flow controlling needle[a] i.d. (cm)	Flow rate (mL.min^{-1})
A	*o*-Xylenol	80	0.8	0.25	1.0
B	*p*-Bromophenol	80	0.8	0.25	1.0
C	*p*-Bromophenol	100	0.5	0.20	0.6
D	*p*-Bromophenol	100	0.5	0.32[b]	1.2
E	*o*-Xylenol[c]	40	0.8	0.25	0.6
F	*p*-Bromophenol[c]	40	0.8	0.25	0.6

[a] 50-cm needle was used.
[b] contains a stainless steel wire (0.14 mm diameter, 73 mm length) through and beyond the entire length of the needle, see Figure 3.1c.
[c] Data obtained from sorption studies described in Section 3.2.3.

3.3. Data Analysis

For comparative purposes, the data obtained is, unless otherwise indicated, expressed as the fraction of the original concentration of the solute which is present in the effluent solution (F_t) at the specified times. The area under the F_t - time curve is determined using the trapezoidal method (Swinbourne, 1971) and the cumulative fraction, of the original concentration of the solute, in the effluent solution collected to the specified time (CuF_t) is calculated from the area under the F_t - time curve.

In determining if significant differences existed among conditions, a one-way analysis of variance (ANOVA) or an unpaired *t*-test was applied, using a suitable computer software package, StatView SE+Graphics (Abacus Concepts Inc.) on a Macintosh computer, as appropriate.

Curve fitting of the data obtained from the sorption profile study of nine selected solutes was performed using the Mathematica (Wolfram Research) and SigmaPlot (Jandel Corp.) software packages on a Macintosh computer.

The relationships between the coefficient values obtained from the curve fitting and the physicochemical parameters of each solute were investigated using regression analysis (StatView SE+Graphics).

An objective assessment of the relative importance of the various factors and interactions was obtained by applying an analysis of variance, as first described by Yates (Armstrong and James, 1990), to the fraction and the

cumulative fraction of the original concentration of solute in the effluent solution (F_t and CuF_t respectively) obtained at 1, 3, 6, 12 and 24 hours.

In evaluating the effect of flow rate, tubing diameter and tubing length, effluent concentrations obtained during operation at one set of conditions were compared with those predicted from parameters obtained during another set of conditions, using regression analysis (StatView SE+Graphics). The precision and bias, as well as the 95% confidence intervals associated with this method, were calculated and compared to those associated with a naive standard using the method of Sheiner and Beal (1981).

3.4. Results and Discussion

3.4.1. Validation of the flow system

Figures 3.2 and 3.3 show flow system validation charts for a target flow rate of 0.6 ± 0.1 and 1.2 ± 0.2 $g.min^{-1}$ respectively. Average values of flow rate and flow RSDs are shown in Table 3.6.

In all experimental runs, flow rates obtained at each sampling time were within the specification limits, that is, 0.6 ± 0.1 $g.min^{-1}$ (or $mL.min^{-1}$) for the low flow rate group and 1.2 ± 0.2 $g.min^{-1}$ (or $mL.min^{-1}$) for the high flow rate group, throughout a 24-hour infusion period. Analysis of variance indicated that there was no statistically significant difference among the average flow rate of each individual run in both the low and

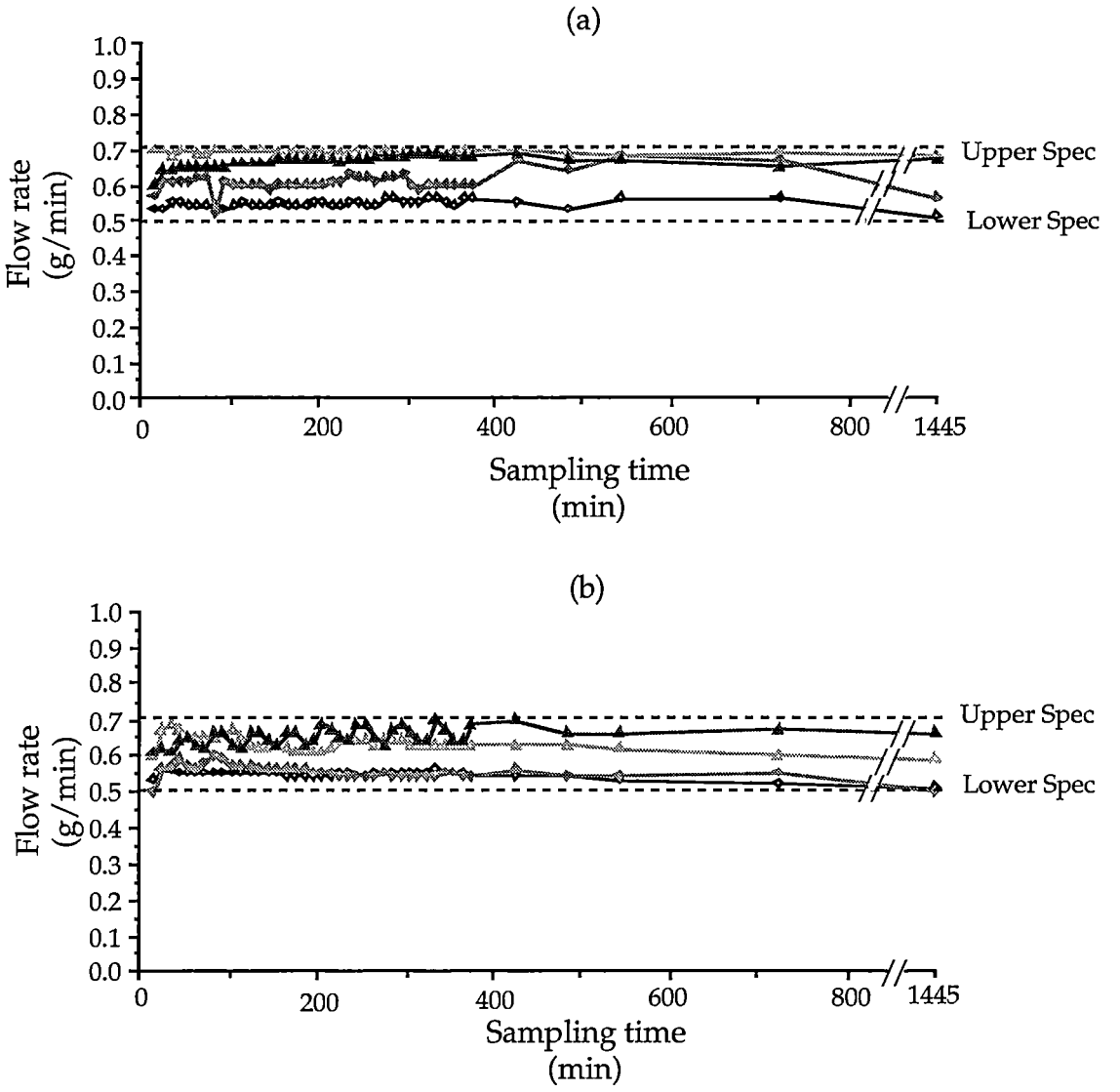


Figure 3.2. Low-flow rate system validation chart. (a) 0.8 cm i.d. tubing , (b) 0.5 cm i.d. tubing, —◇— 40 cm tubing run1, —◇— 40 cm tubing run2, —△— 100 cm tubing run1, —▲— 100 cm tubing run2.

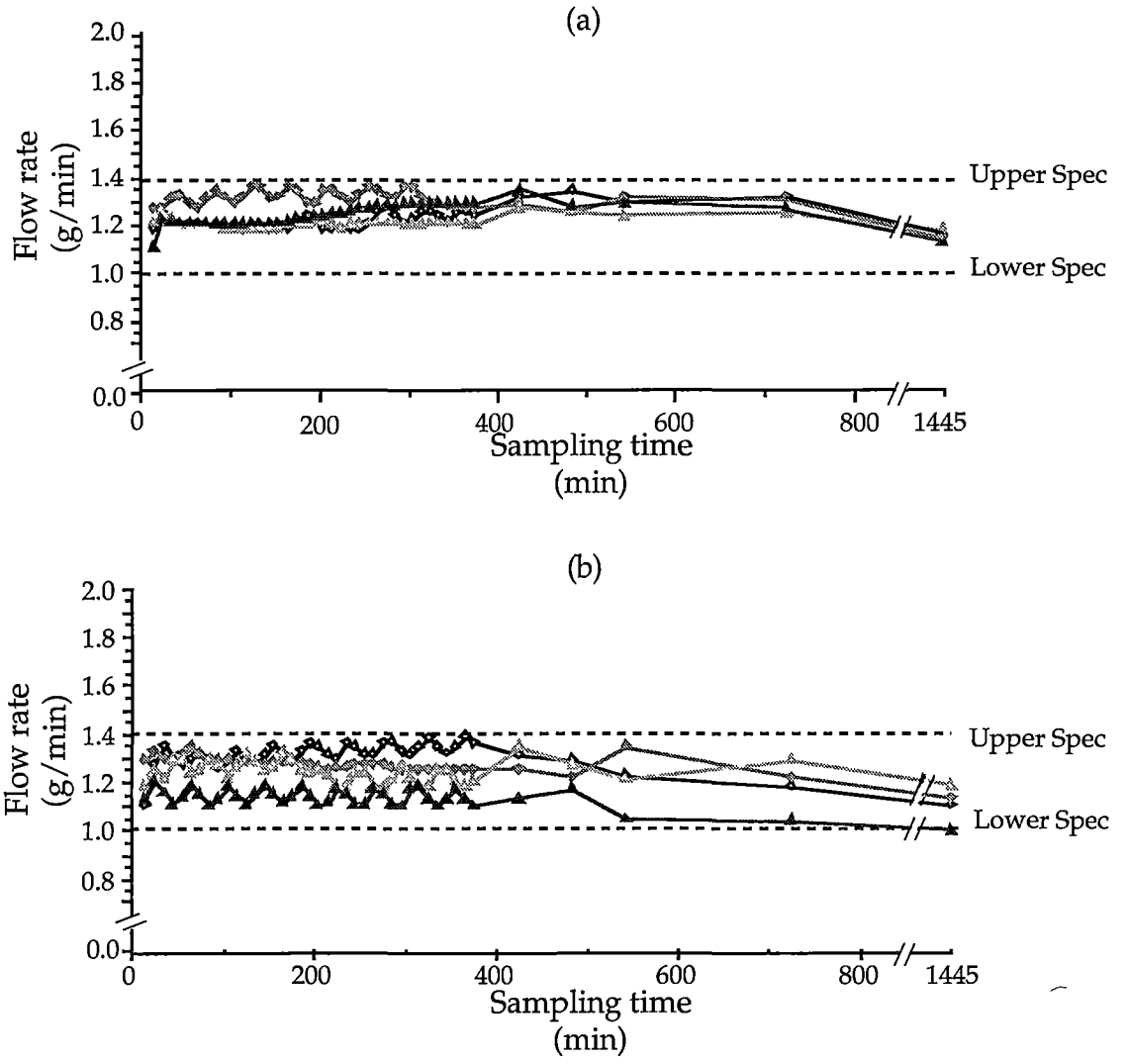


Figure 3.3. High-flow rate system validation chart. (a) 0.8 cm i.d. tubing , (b) 0.5 cm i.d. tubing, —◇— 40 cm tubing run1, —◇— 40 cm tubing run2, —◇— 100 cm tubing run1, —▲— 100 cm tubing run2.

the high flow rate groups ($p > 0.01$) and overall averages of the low and the high flow rate groups were 0.6 and 1.2 $g.min^{-1}$ respectively.

Filling RSD obtained from each run was less than 5% which is within the acceptable range used in validation of filling equipment for sterile products. In such a system, filling RSDs of 1 to 5 % can be achieved, depending on the nature of the product and the fill quantity (Hofmann, 1993). Therefore this flow system is considered appropriate to be used in the study of solute loss from a solution infused through a PVC tubing system.

Table 3.6. Average flow rate ($g.min^{-1}$) and RSD values of the 8 different experimental conditions identified in Table 3.1.

Experimental conditions[a]	Average flow rate		%RSD	
	run1	run2	run1	run2
1	0.5	0.6	1.8	3.5
2	0.6	0.7	3.2	3.6
3	1.2	1.1	3.6	3.6
4	1.3	1.3	4.7	2.8
5	0.7	0.7	0.9	2.6
6	0.5	0.6	1.9	4.3
7	1.2	1.3	3.4	2.9
8	1.2	1.2	1.7	3.8

[a] see Table 3.1.

3.4.2. Leaching (desorption) from the tubing

The ultraviolet absorbance spectrum of the distilled water sample over the range 200 to 300nm is shown in Figure 3.4. Between 200 and 240nm,

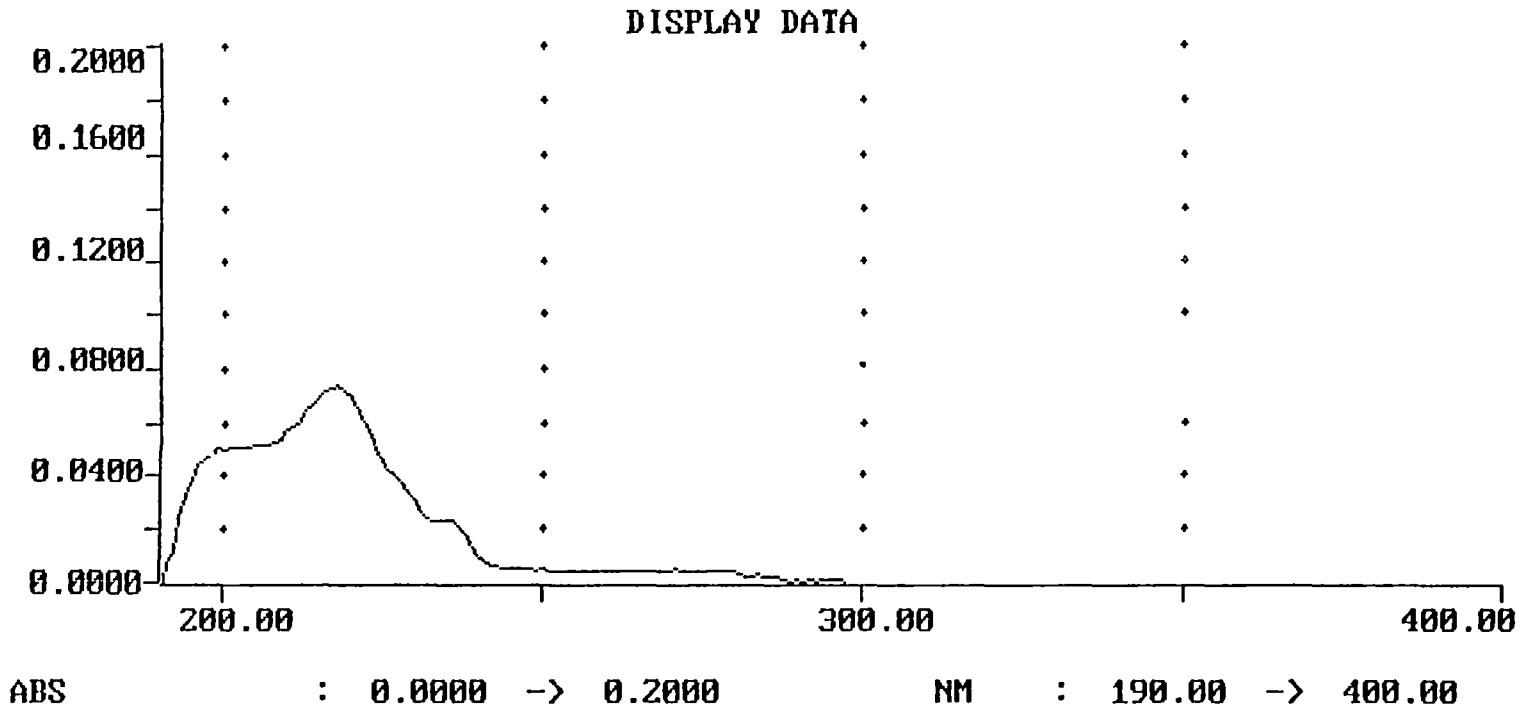


Figure 3.4: An ultraviolet absorbance spectrum of the distilled water effluent collected from the distal end of a PVC tubing at t = 15 min

the presence of an ultraviolet - light absorbing substance was detected in the effluent. The spectrum had an absorbance peak at around 218nm. It appears that the leaching process occured almost immediately after beginning the infusion. The absorbance at 218nm is plotted as a function of time in Figure 3.5. The maximum absorbance at 218nm was obtained at 45 minutes. Subsequently, the extent of leaching was found to decrease rapidly with the time of infusion until the plateau was reached at about 105 minutes. The effluent absorbances at 218nm obtained between 245 minutes and 24 hours were close to zero indicating the leaching of insignificant amounts of UV-absorbing materials after a 4-hour infusion period.

An ultraviolet-light absorbance of the sample was measured between 200 and 300nm because this wavelength range has been shown to be a reasonable scanning range for the detection of plasticizers (Moorhatch and Chiou, 1974a, 1974b). The presence of an ultraviolet-light absorbing substance in the effluent suggests that leaching of one or more phthalate-type plasticizers, such as DEHP, has occured. The low UV absorbance of the substance(s) may indicate that very little UV absorbing material is leached from the tube into the water and no attempt has been made to quantitate the results. As the absorbance of the leached material(s) was not significant at wavelengths greater than 240nm, the absorbance values of the solutes being used in this study, all of which have maximum absorbance wavelengths at or greater than 245nm, would not be compromised by the presence of the leached materials in solution.

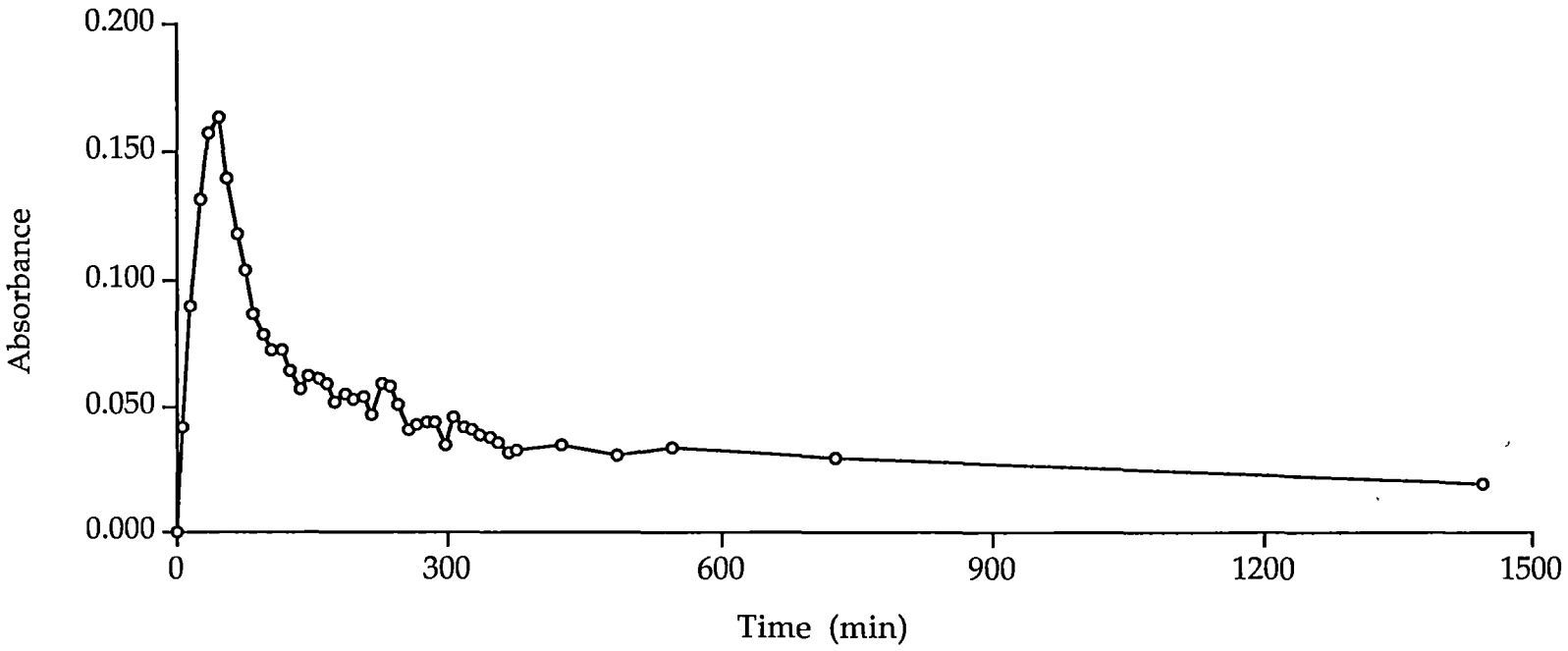


Figure 3.5. Absorbance at 218 nm of the materials leached from PVC tubing as a function of time.

3.4.3. Sorption profiles of model solutes

In all cases, the infusion solutions remained clear throughout the experimental run. The ultraviolet spectra of all the solutions used remained unchanged and solute concentrations in the reservoir were within the range of 100 ± 1 % over a period of 24 hours, indicating that no degradation had occured during the time of the infusion. All data presented in this Section (3.4.3) relates to infusion through a 40 cm tube of 0.8 cm internal diameter at a flow rate of 0.6 $mL.min^{-1}$.

The recovery rate of each of the solutes following infusion through a PVC tubing for 24 hours is shown in Figures 3.6 and 3.7. in which the fraction of the original concentration of solute (F_t) in the effluent solution is plotted on the y-axis.

It can be seen that the sorption profiles of all solutes, over a period of 24 hours, are similar while the differences in the extent of loss are apparent. The profile can be divided into two phases, as described previously for a number of other solutes (Cossum et al, 1978; Roberts et al, 1980; Cossum and Roberts, 1981; Kowaluk et al, 1982; Yliruusi et al, 1986a, 1986b, Paborji et al, 1988; De Muynck et al, 1991). The effluent solute concentration decreases rapidly, in all cases, to a minimum within 35 minutes and then appears to increase gradually with time until the end of the 6-hour infusion period. For all solutes, it appears that a steady state, which is defined as that situation in which the effluent concentration and, therefore, the rate of loss are relatively constant, was reached after a 6-hour infusion period; the fraction of the original concentration of solute

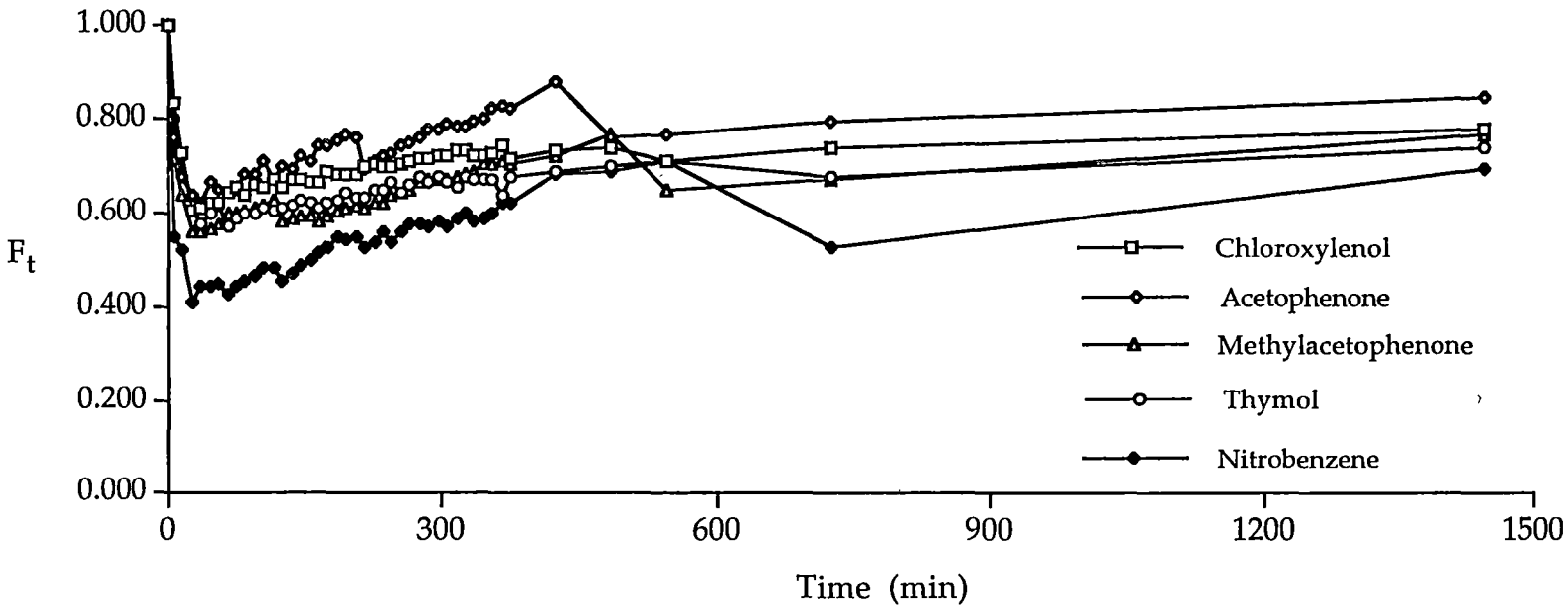


Figure 3.6. Fraction of the original concentration of solute in the effluent (F_t) as a function of time. Each point represents the mean of two separate experiments.

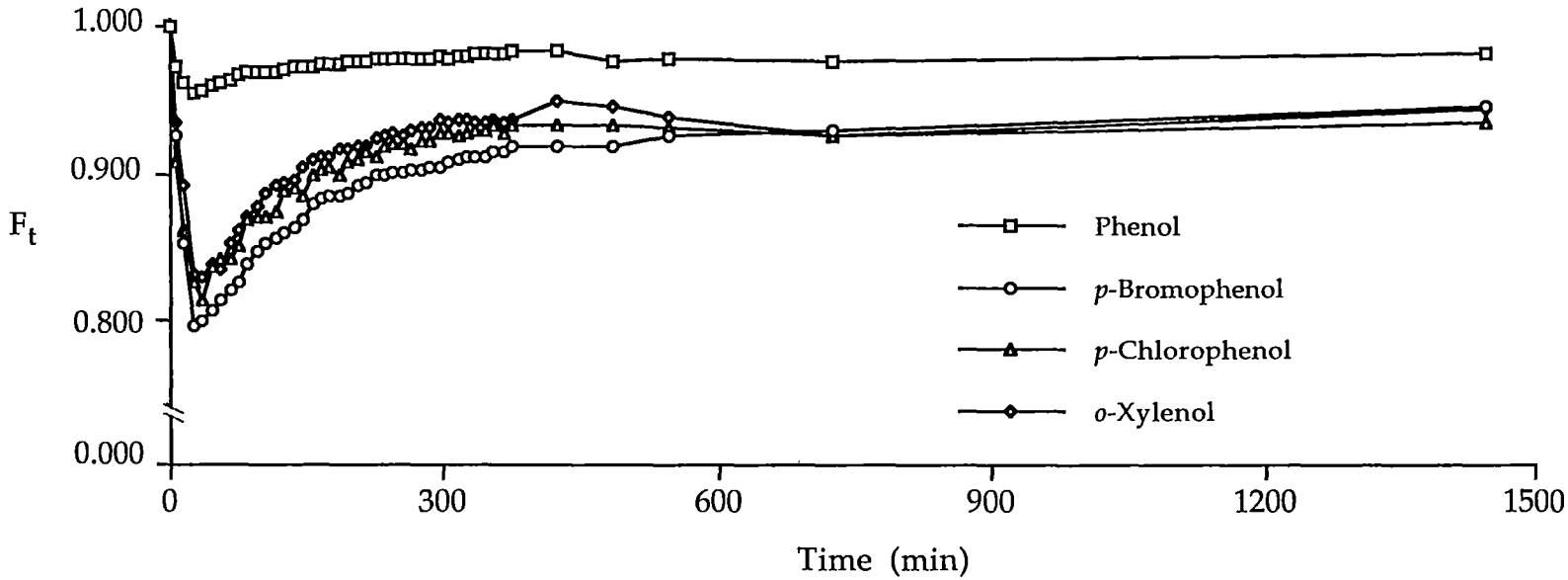


Figure 3.7. Fraction of the original concentration of solute in the effluent (F_t) as a function of time. Each point represents the mean of two separate experiments.

in the effluent solution (F_t) collected at six hours and at twenty four hours, as shown in Table 3.7, were not significantly different ($p > 0.01$).

Table 3.7. Fraction of the original concentration (F_t) of solute, in the effluent of the solution infused through a PVC tubing, collected at six and twenty four hours[a,b]

Solute	F_t in the effluent collected at	
	6 hours	24 hours
Acetophenone	0.82	0.85
	(0.01)	(0.00)
Nitrobenzene	0.60	0.69
	(0.03)	(0.10)
Phenol	0.98	0.98
	(0.00)	(0.00)
o-Xylenol	0.94	0.95
	(0.00)	(0.01)
p-Chlorophenol	0.93	0.94
	(0.01)	(0.00)
p-Bromophenol	0.92	0.95
	(0.01)	(0.01)
p-Methylacetophenone	0.71	0.77
	(0.02)	(0.06)
Chloroxylenol	0.73	0.78
	(0.01)	(0.02)
Thymol	0.67	0.74
	(0.02)	(0.03)

[a] For details of the conditions used see Section 3.2.3.
[b] Values in parentheses are SD values.

It is suggested that the rapid uptake of solute into the PVC tubing at the early times is due to sorption of the solute by the surface layer of the tubing, in immediate contact with the infusion solution. The subsequent solute uptake is slow and continuous, indicating that the process is diffusion-controlled. This is consistent with the results reported previously for the uptake of a number of drugs into PVC

infusion systems (Moorhatch and Chiou, 1974a; Cossum et al, 1978; Roberts et al, 1980; Cossum and Roberts, 1981; Kowaluk et al, 1981, 1982; Yliruusi et al 1986a, 1986b; Paborji et al, 1988; De Muynck et al, 1988, 1991).

Sorption profiles of acetophenone, nitrobenzene, methylacetophenone, thymol and chloroxylenol during the time before steady state was achieved are shown in Figures 3.8 and 3.9. To describe the data mathematically, the SigmaPlot curve fitter was used to fit the data, obtained during the six-hour infusion period, to models proposed previously (Donaldson et al, 1992). This software is based on the Marquardt-Lavenberg algorithm which uses an iterative least squares procedure to minimize the sum of the squares of the differences between the model values and the data values.

The models proposed by Donaldson and co-workers (1992) are based on the two models used to describe convection down a tube, the well-stirred model and a plug flow of fluid down the tube with no longitudinal diffusion. The main qualitative difference between the models is that the shape of the minimum in the well-stirred compartment model is smooth, whereas that of the convection model is cusp-like. Since the sorption profiles obtained in this work are smooth without a sharp turning point at the time when the minimum concentration is obtained, the well-stirred compartment model and the well-stirred diffusion model are applicable.

These models may generally be expressed by eqn. 3.1 or 3.2 as follows

$$C_s = C_o (A + (B_1+B_2)\, e^{\rho_1 t} + (C_1+C_2)\, e^{\rho_2 t}) \qquad (3.1)$$

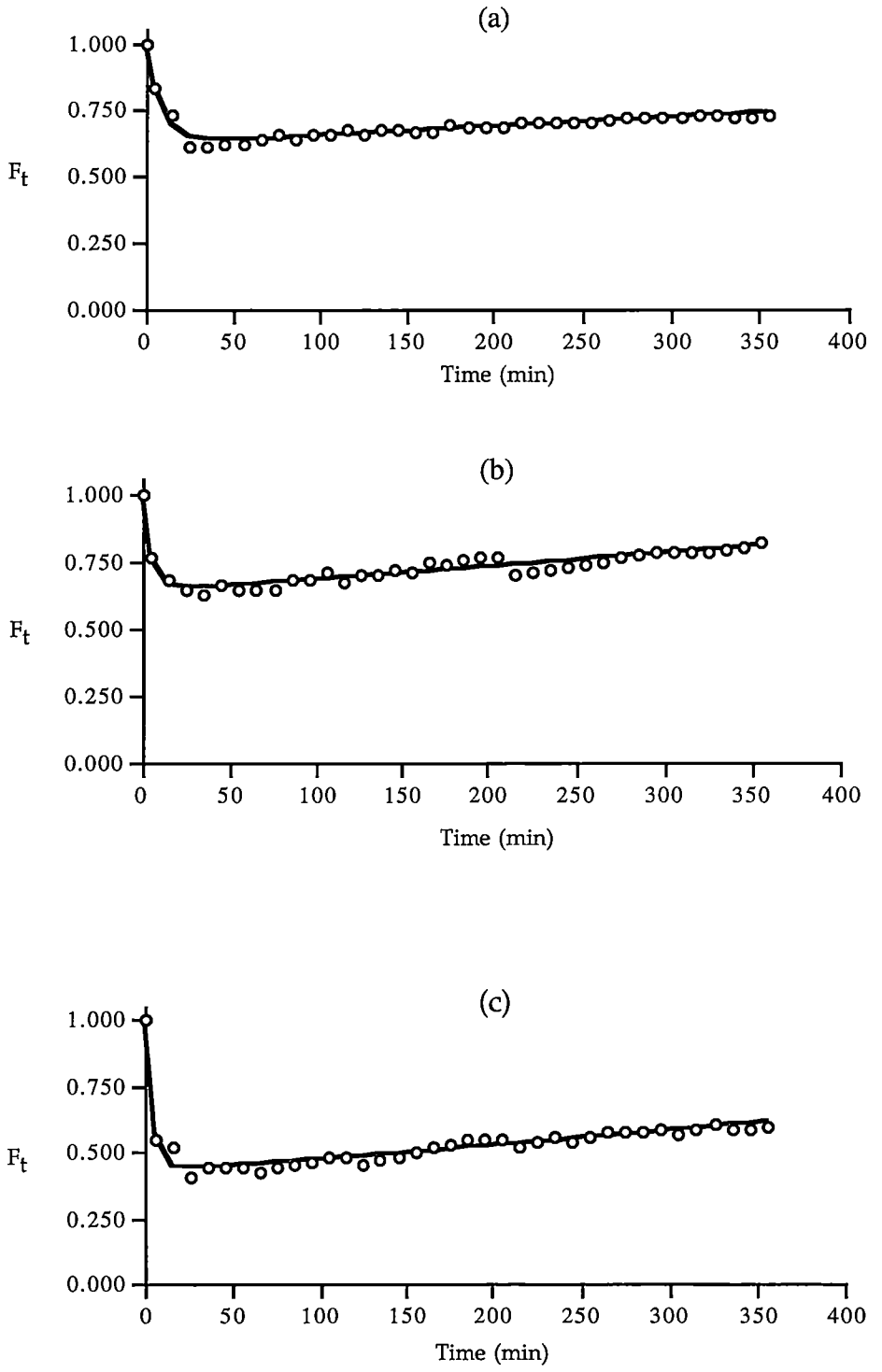


Figure 3.8. Fraction of the original concentration of solute in the effluent during 6-hour infusion of chloroxylenol (a), acetophenone (b), and nitrobenzene (c). The solid lines are calculated curve fittings having coefficient values listed in Table 3.9.

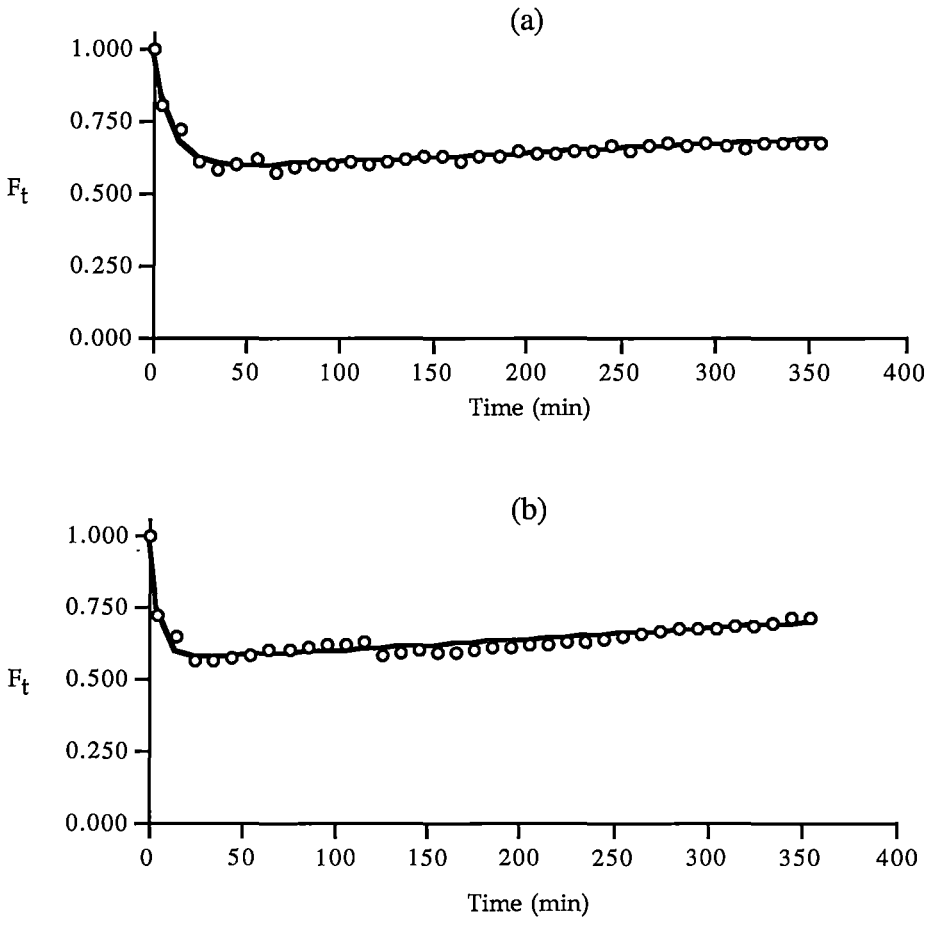


Figure 3.9. Fraction of the original concentration of solute in the effluent during 6-hour infusion of thymol (a), and methylacetophenone (b). The solid lines are calculated curve fittings having coefficient values listed in Table 3.9.

$$F_t = \frac{C_s}{C_o} = A + (B_1+B_2)\, e^{\rho 1 t} + (C_1+C_2)\, e^{\rho 2 t} \qquad (3.2)$$

in which F_t denotes the fraction of the original concentration of solute in the effluent solution at time t (min), C_s is the concentration of solution in the tube, C_o is the initial solute concentration and A, B_1, B_2, C_1, C_2, ρ_1 and ρ_2 are all functions of flow rate, tubing dimension, rates of solute transfer across the inner and outer surfaces of the tube and an apparent partition coefficient of solute between solution and plastic considered collectively (Donaldson et al, 1992).

It was found that dependencies, which can be defined by eqn.3.3 (SigmaPlot manual, 1992), obtained from fitting the experimental data to eqn.3.2 were very near 1.0 (>0.99).

$$\text{dependency} = 1 - \frac{\text{(variance of the parameter, other parameters constant)}}{\text{(variance of the parameter, other parameters changing)}} \qquad (3.3)$$

This indicates that the data has been over-parameterized and a less complex model is required. The parameters A, B_1, B_2, C_1, C_2, ρ_1 and ρ_2 (in eqn.3.2) were, however, also computed from the experimental data (Figures 3.8 and 3.9) using the Mathematica software and are shown in Table 3.8.

Eqn.3.2 was then simplified by eliminating parameter A and combining parameters B_1 and B_2, and C_1 and C_2 to give a simple biexponential equation. It can be shown that the data in Figures 3.8 and 3.9 is well described by the biexponential equation 3.4 below.

$$F_t = a_1 e^{-b_1 t} + a_2 e^{-b_2 t} \qquad (3.4)$$

Table 3.8. Parameters[a] A, B_1, B_2, C_1, C_2, ρ_1 and ρ_2 calculated from the experimental data of five solutes (Figures 3.8 and 3.9) using the Mathematica software package.

Solute	A	B_1	B_2	ρ_1	C_1	C_2	ρ_2 (x10 ^{4})
Acetophenone	-0.0252	0.1807	0.1807	0.2063	0.3311	0.3311	-6.41
Nitrobenzene	-0.4383	0.2854	0.2854	0.2868	0.4327	0.4327	-5.42
Methylacetophenone	0.5686	0.2083	0.2083	0.2077	0.0059	0.0059	-70.98
Thymol	-0.0707	0.2061	0.2061	0.0946	0.3229	0.3229	-4.41
Chloroxylenol	-0.6348	0.1923	0.1923	0.1118	0.6256	0.6256	-2.66

[a] Parameters given are for the equation $F_t = A + (B_1+B_2)\, e^{\rho 1 t} + (C_1+C_2)\, e^{\rho 2 t}$

where F_t denotes the fraction of the original concentration of solute in the effluent solution at time t (min), a_1 and a_2 are the fractional zero intercepts ($a_1 + a_2 = 1$), and b_1 and b_2 are the fast and slow rate constants, respectively. The solid lines in Figures 3.8 and 3.9 are the calculated fits of the data points and have the coefficient values and dependencies listed in Tables 3.9 and 3.10.

Although sorption profiles of the solutes which have a low affinity for PVC, such as phenol, *o*-xylenol, *p*-chlorophenol and *p*-bromophenol, as shown in Figures 3.10 and 3.11, are slightly curved during early time, the "break" associated with the two distinct exponentials is not obvious. The dependency of the biexponential fit, to the experimental data shown in Figures 3.10 and 3.11 is very near to 1. Consequently, mono-exponential disappearance kinetics, as described by

$$F_t = a_2 e^{-b_2 t} \qquad (3.5)$$

has been applied to the data obtained for these solutes.

Table 3.9. Coefficient values[a, b] obtained from biexponential curve fitting of the data in Figures 3.8 and 3.9.

Solute	a_1	b_1	a_2	b_2 ($\times 10^4$)
Acetophenone	0.3613	0.2064	0.6372	-6.6920
	(0.0214)	(0.0330)	(0.0070)	(0.4908)
Nitrobenzene	0.5678	0.2915	0.4303	-10.0000
	(0.0223)	(0.0339)	(0.0069)	(0.6968)
Methylacetophenone	0.4367	0.1776	0.5570	-6.0380
	(0.0195)	(0.0210)	(0.0066)	(0.5261)
Thymol	0.4120	0.0948	0.5754	-4.9300
	(0.0147)	(0.0084)	(0.0059)	(0.4507)
Chloroxylenol	0.3831	0.1127	0.6179	-5.1500
	(0.0132)	(0.0098)	(0.0050)	(0.3564)

[a] Coefficient values given are for the equation $F_t = a_1e^{-b_1t} + a_2e^{-b_2t}$.
[b] Values in parentheses are the standard error of the coefficients.

Table 3.10. Dependencies of the coefficient values[a] obtained from biexponential curve fitting of the data in Figures 3.8 and 3.9.

Solute	Dependency of			
	a_1	b_1	a_2	b_2
Acetophenone	0.1900	0.1945	0.8195	0.8082
Nitrobenzene	0.1371	0.1236	0.8213	0.8133
Methylacetophenone	0.2132	0.2316	0.8232	0.8106
Thymol	0.2923	0.3854	0.8551	0.8365
Chloroxylenol	0.2720	0.3432	0.8442	0.8273

[a] Coefficient values for the equation $F_t = a_1e^{-b_1t} + a_2e^{-b_2t}$ are given in Table 3.9.

The solid lines in Figures 3.10 and 3.11 are calculated curve fittings with coefficient values and dependencies given in Tables 3.11 and 3.12, respectively.

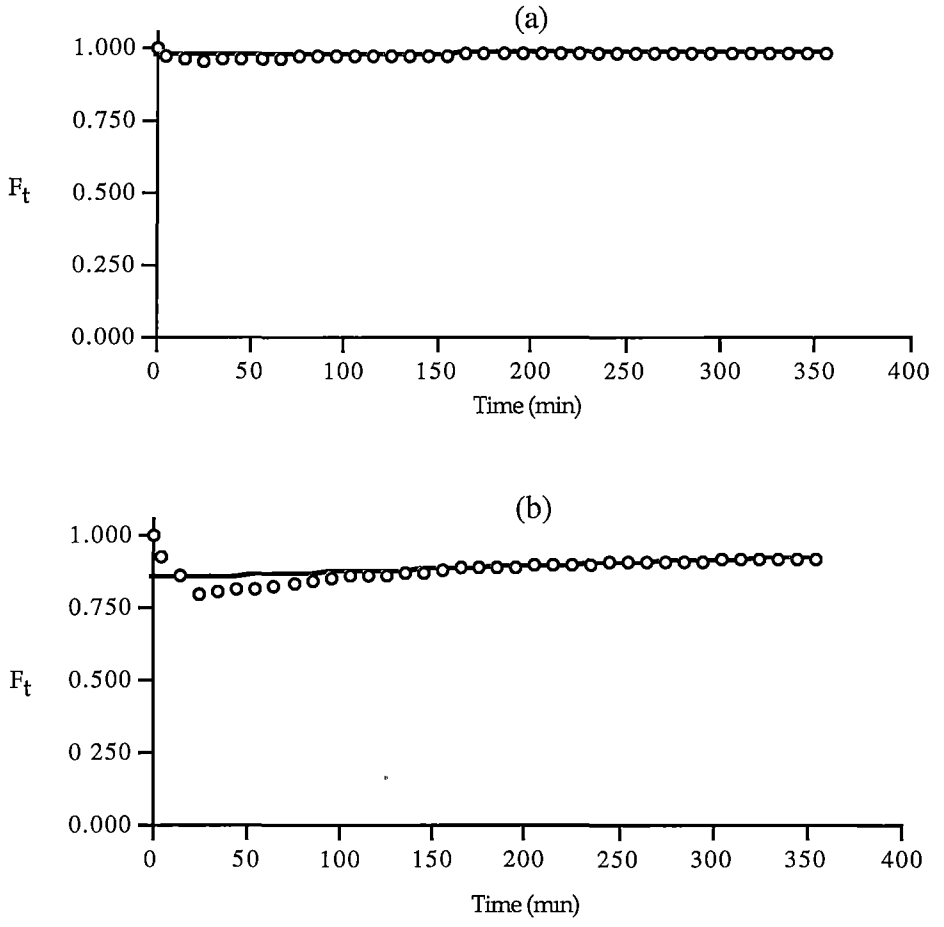


Figure 3.10. Fraction of the original concentration of solute in the effluent during 6-hour infusion of phenol (a), bromophenol (b). The solid lines are calculated curve fittings having coefficient values listed in Table 3.11.

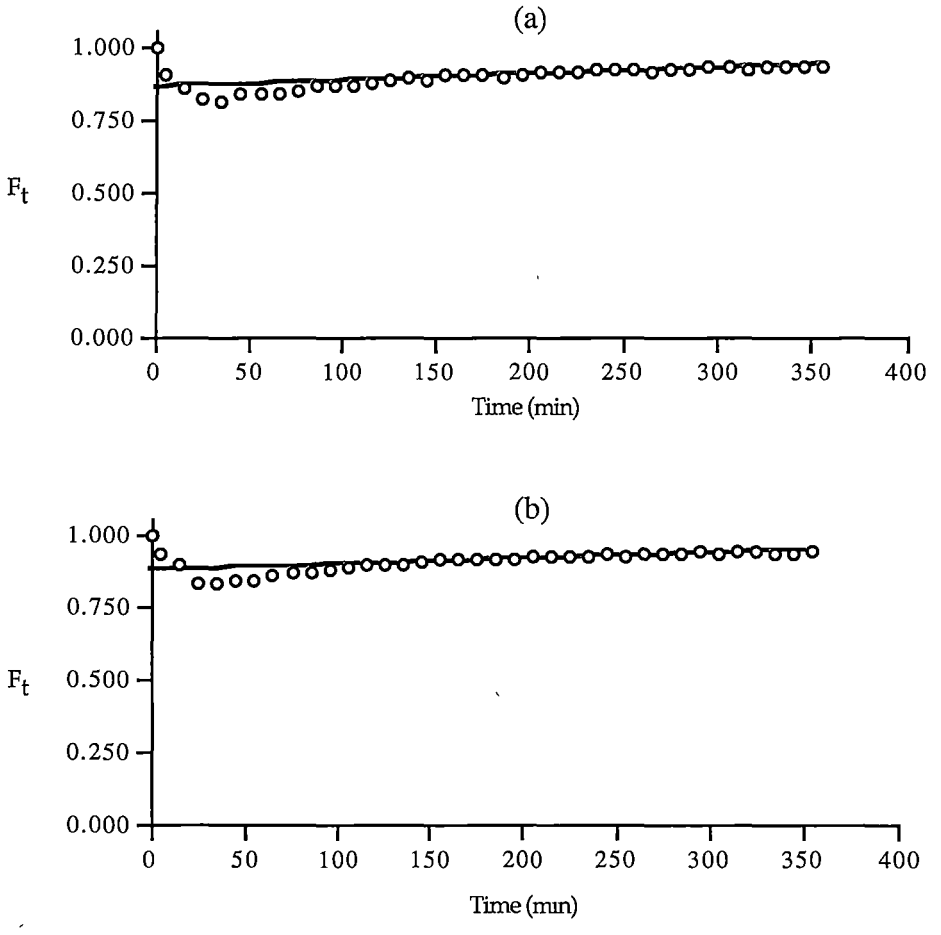


Figure 3.11. Fraction of the original concentration of solute in the effluent during 6-hour infusion of chlorophenol (a), *o*-xylenol (b). The solid lines are calculated curve fittings having coefficient values listed in Table 3.11.

Table 3.11. Coefficient values[a, b] obtained from monoexponential curve fitting of the data in Figures 3.10 and 3.11.

Solute	a_2	b_2 (x10 ^{4})
Phenol	0.9662(0.0022)	-0.4538(0.1082)
o-Xylenol	0.8724(0.0093)	-2.2250(0.5103)
p-Chlorophenol	0.8607(0.0092)	-2.4000(0.5103)
p-Bromophenol	0.8439(0.0110)	-2.3400(0.6203)

[a] Coefficient values given are for the equation $F_t = a_2e^{-b_2t}$.
[b] Values in parentheses are standard error of the coefficients.

Table 3.12. Dependencies of the coefficient values[a] obtained from monoexponential curve fitting of the data in Figures 3.10 and 3.11.

Solute	Dependency of	
	a_2	b_2
Phenol	0.7322	0.7322
o-Xylenol	0.7412	0.7412
p-Chlorophenol	0.7420	0.7420
p-Bromophenol	0.7417	0.7417

[a] Coefficient values for the equation $F_t = a_2e^{-b_2t}$ are given in Table 3.11.

The parameters A, B_1, B_2, C_1, C_2, ρ_1 and ρ_2 were also computed from the experimental data for phenol, *o*-xylenol, *p*-chlorophenol and *p*-

bromophenol using the Mathematica software and are shown in Table 3.13.

Table 3.13. Parameters[a] A, B_1, B_2, C_1, C_2, ρ_1 and ρ_2 calculated from the experimental data of four solutes (Figures 3.10 and 3.11) using the Mathematica software.

Solute	A	B_1	B_2	ρ_1	C_1	C_2	ρ_2 ($\times 10^5$)
Phenol	0.0538	0.0195	0.0195	0.2485	0.4537	0.4537	-7.10
o-Xylenol	-1.4850	0.0786	0.0786	0.1237	1.1650	1.1650	-13.00
p-Chlorophenol	-2.9630	-0.1317	0.2963	0.1680	1.9000	1.9000	-8.19
p-Bromophenol	-1.2990	-0.1181	0.3119	0.1266	1.0550	1.0550	-15.69

[a] Parameters given are for the equation $F_t = A + (B_1+B_2)\, e^{\rho 1 t} + (C_1+C_2)\, e^{\rho 2 t}$.

It can be seen that the simple biexponential equation describes the sorption data, for solutes which have a high affinity for PVC such as acetophenone, nitrobenzene, methylacetophenone, thymol and chloroxylenol quite well, while sorption data for the solutes which have low affinity for PVC such as phenol, *o*-xylenol, *p*-chlorophenol and *p*-bromophenol can be described by a monoexponential relationship. However it does not imply that the solutes with a low affinity for PVC are sorbed in a manner that is any different from that of the solutes with a high affinity for PVC. This is explained as follows:

Consider eqn.3.4

$$F_t = a_1 e^{-b_1 t} + a_2 e^{-b_2 t} \qquad (3.4)$$

It is apparent that the first term, $a_1e^{-b_1t}$, in eqn.3.4 describes the initial sorption of the solute to the surface of the plastic tubing in immediate contact with the infusion solution. If a negligible amount of solute is sorbed by the tubing surface during the period when initial rapid uptake is expected, this term will become insignificant. As a result, eqn.3.4 will approach the limit

$$F_t = a_2e^{-b_2t} \tag{3.5}$$

which is a monoexponential expression. Alternatively, if the initial sorption is not negligible and is very rapid relative to the rate of sorption in the terminal phase (i.e., if a_1 and a_2 (in eqn.3.4) have the same order of magnitude and $b_1 >> b_2$), then $a_1e^{-b_1t} << a_2e^{-b_2t}$, and the reduced form of the rate equation (eqn.3.4), as shown in eqn.3.5, may also apply.

Additionally, it may be concluded from the data presented in Table 3.9, that, at some later time, the term $a_1e^{-b_1t}$ in eqn.3.4 will approach zero while the term $a_2e^{-b_2t}$ will still have a value. At this time, eqn.3.4 will be reduced resulting in a monoexponential equation of the same form as eqn.3.5.

The cumulative fraction of the original concentration of solute in the effluent solution (CuF_t) was plotted against time for all solutes studied and is presented in Figures 3.12 and 3.13. The graphs show that substantial sorption occurs immediately after the beginning of the infusion and that a plateau is reached at about 85 minutes. Subsequently, CuF_t increases slightly with time until the end of the twenty four-hour infusion period.

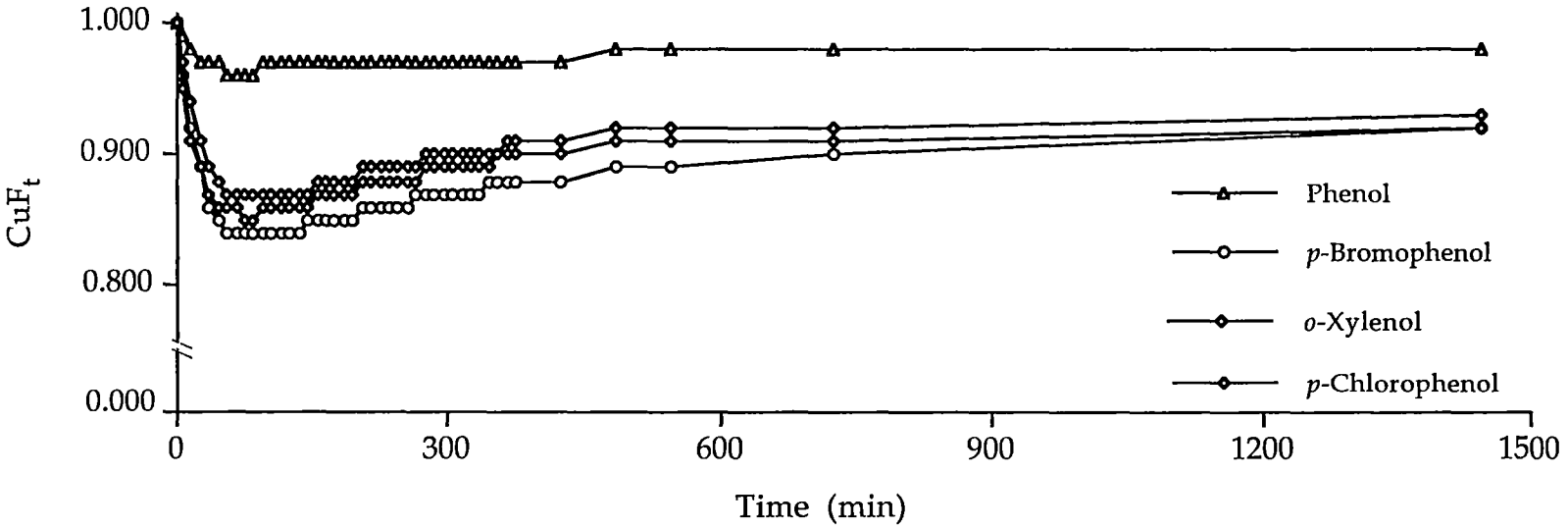


Figure 3.12. Cumulative fraction of the original concentration of solute in the effluent (CuF_t) as a function of time. Each point represents the mean of two separate experiments.

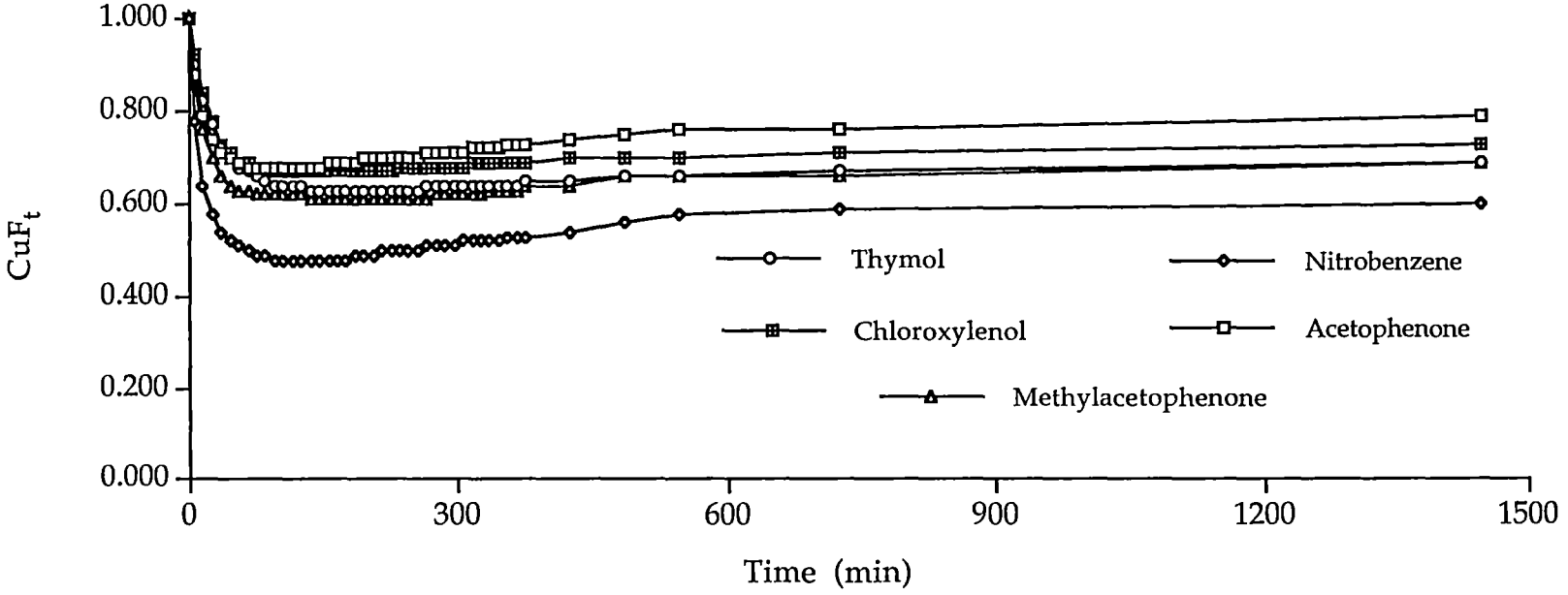


Figure 3.13. Cumulative fraction of the original concentration of solute in the effluent (CuF_t) as a function of time. Each point represents the mean of two separate experiments.

It is postulated that the period of time required for the rate of the initial rapid uptake of solute into the surface of the PVC tubing to decrease to zero (t_{sink}) can be estimated from the plot of the cumulative fraction of the original concentration of solute in the effluent solution (CuF_t) against time as shown in Figures 3.12 and 3.13.

The data presented in Figures 3.12 and 3.13 shows that, for all solutes being studied, the initial uptake commences immediately after the beginning of the infusion and the rate of uptake decreases continuously until the plateau is reached at about 85 minutes. This period of time is practically about 2.5 times t_{min}, the time required for the elution of that volume of solution (V) which is present in the tubing at the beginning of the infusion. Kowaluk and co-workers (1983) have described t_{min} as shown in eqn.3.6:

$$t_{min} = \frac{V}{v} \tag{3.6}$$

where v denotes a rate of infusion ($mL.min^{-1}$).

By assuming that the time required for the rate of the initial rapid uptake of solute into the surface of the PVC tubing to decrease to zero (t_{sink}) is a constant and is equal to 2.5 times t_{min}, eqn.3.7 is obtained:

$$t_{sink} = \frac{2.5V}{v} \tag{3.7}$$

Furthermore, it is found that the fraction of the original concentration of solute in the effluent at t_{sink} and the cumulative fraction of the original concentration of solute, in the effluent obtained during the period t=0 to

$t=t_{sink}$ for each individual solute, as shown in Table 3.14, are not significantly different ($p > 0.01$).

Table 3.14. Fraction of the original concentration of solute (F_t) in the effluent at t_{sink} and the cumulative fraction of the original concentration of solute (CuF_t), in the effluent obtained during the period $t=0$ to $t=t_{sink}$ of the model solutes[a,b].

Solute	F_t obtained at t_{sink}	CuF_t obtained at t_{sink}
Acetophenone	0.68	0.68
	(0.01)	(0.00)
Nitrobenzene	0.55	0.51
	(0.03)	(0.03)
Phenol	0.97	0.97
	(0.00)	(0.01)
o-Xylenol	0.87	0.87
	(0.01)	(0.00)
p-Chlorophenol	0.87	0.86
	(0.01)	(0.01)
p-Bromophenol	0.84	0.84
	(0.00)	(0.00)
p-Methylacetophenone	0.60	0.62
	(0.03)	(0.02)
Chloroxylenol	0.64	0.68
	(0.00)	(0.00)
Thymol	0.60	0.65
	(0.02)	(0.02)

[a] For conditions used in this study see Section 3.2.3; t_{sink}, estimated by means of eqn.3.7, is 83.8 minutes.
[b] Values in parentheses are SD values.

Thus, it may be possible to estimate the overall rate of decrease in solute concentration in the effluent during the initial phase by replacing t in eqn.3.5 with the value of t_{sink} calculated by means of eqn.3.7.

It appears that eqn.3.4 is a general form of the equation which can be used to describe solute uptake from solution during flow through PVC

tubing. This equation is of the same form as that of the well-stirred models, (eqn.3.2) proposed previously by Donaldson and co-workers (1992) where only the first term of the series, A, in the models is omitted. The derivation of eqn.3.4 is given in Appendix II. However, the approximation of eqn.3.4, as expressed by eqn.3.5, seems to be applicable for all solutes regardless of their affinity for PVC tubing and it may be used to estimate the actual solute concentration in the diffusate during prolonged infusion at any time t between t_{sink} and that at which achievement of a true steady-state occurs. Although eqn.3.5 is unable to be used to estimate the solute concentration in the effluent at any individual time point during the rapid initial uptake period, the overall loss of solute during the initial period (t=0 to $t=t_{sink}$) can be estimated by using this equation.

As the concentration of solutes in solutions infused through PVC tubing can be described at any time beyond t_{sink} by eqn.3.5, an attempt was made to correlate the extent of sorption of these solutes by the tubing with the physicochemical properties, such as octanol-water partition coefficient, dipole moment, intrinsic molecular volume and solvatochromic parameters, of the solutes.

The constants a_2 and b_2 obtained from a curve fitting of the plot of fraction of the original concentration of solute in the effluent and time for each solute are presented in Table 3.15 together with the solute octanol-water partition coefficient (log P), dipole moment (μ), intrinsic molecular volumes (V_I) and solvatochromic parameter values (π^*, ß and α).

Table 3.15. Sorption constants (a_2 and b_2 of eqn.3.5) and physicochemical parameters[a] of the solutes used

Solute	a_2	b_2 ($x10^4$)	logP[b]	μ[c]	$(V_I/100)$[d]	π^*[d]	β[d]	α[d]
Acetophenone	0.6372	-6.69	1.66	2.90	0.690	0.90	0.49	0.04
Nitrobenzene	0.4303	-10.00	1.84	4.00	0.631	1.01	0.30	0.00
Phenol	0.9662	-0.45	1.28	1.52	0.536	0.72	0.33	0.61
o-Xylenol	0.8724	-2.23	2.23	1.75	0.732	0.64	0.35	0.60
Methylacetophenone	0.5570	-6.04	2.28	3.22	0.788	0.86	0.50	0.00
p-Chlorophenol	0.8607	-2.40	2.42	2.28	0.626	0.72	0.23	0.67
p-Bromophenol	0.8439	-2.34	2.60	2.37	0.699	0.79	0.30	0.67
Thymol	0.5754	-4.93	3.30	(1.55)	(0.928)	(0.60)	(0.35)	(0.60)
Chloroxylenol	0.6179	-5.15	3.48	(2.92)	(0.822)	(0.64)	(0.25)	(0.64)

[a] Values in parentheses are estimated from corresponding values for closely related compounds (see Appendix I) and are not included in the regression.

[b] obtained from Hansch, and Leo, 1979. An average value is used where there is more than one value reported.

[c] obtained from McClellan, 1963.

[d] obtained from Kamlet et al., 1988; Tayar et al., 1991. The intrinsic molecular volume and solvatochromic parameters of 3, 5 dimethylphenol are used for *o*-xylenol (3, 4 dimethylphenol).

It is found that the correlations between a_2 or b_2 and octanol-water partition coefficients are not significant ($p>0.05$). The lack of correlation between the rate and extent of solute uptake from infusion solution into PVC tubing and the octanol-water partition coefficient has been reported previously for a number of other solutes (Kowaluk et al, 1981).

Surprisingly, dipole moment values show excellent correlation with both a_2 and b_2 values. The linear regression equations are given by:

$$a_2 = 1.313 - 0.223\,\mu \qquad (3.8)$$

$$(n = 7;\ r = 0.975;\ SE = 0.048;\ F = 95.429)$$

and

$$b_2 = (5.34\times10^{-4}) - (3.74\times10^{-4})\,\mu \qquad (3.9)$$

$$(n = 7;\ r = 0.962;\ SE = 1.01\times10^{-4};\ F = 61.903)$$

When the constant a_2 is correlated with the intrinsic molecular volume (V_I) and the solvatochromic parameters (π^*, ß and α), the four-parameter multiple linear regression is given by

$$a_2 = 0.787 - 0.183\,\pi^* + 0.988\,ß + 0.619\,\alpha - 0.726\,(V_i/100) \qquad (3.10)$$

$$(n = 7;\ r = 0.998;\ SE = 0.019;\ F = 157.096)$$

This multiple regression model accounts for approximately 99 % of the variance associated with the constant a_2 and for a statistically significant portion of the variance, ($F = 157.096$; $DF = 4, 2$; $p<0.01$).

In contrast, it is found that the correlation obtained between b_2 and the intrinsic molecular volumes (V_I) and the solvatochromic parameters

(π^*, ß and α) is not significant ($p>0.05$). Nevertheless, when V_I, ß and α are excluded, a fair correlation between b_2 and π^* is obtained as follows:

$$b_2 = (1.54\text{x}10^{-3}) - (2.45\text{x}10^{-3}\ \pi^*) \qquad (3.11)$$

$$(n = 7;\ r = 0.922;\ SE = 1.43\text{x}10^{-4};\ F = 28.338)$$

It can be seen that the use of the intrinsic molecular volumes and the solvatochromic parameters for the prediction of a_2 values produced an improved regression over those derived using dipole moments. On the other hand, the intrinsic molecular volumes and the solvatochromic parameters were found to be inferior to dipole moments for the prediction of b_2 values. However both approaches may be useful in the prediction of solute uptake into PVC tubing for times between t_{sink} and the achievement of a steady state.

3.4.4. Factors affecting solute sorption into PVC tubing

3.4.4.1. Simultaneous investigation of the effect of solute concentration, flow rate, tubing diameter and tubing length on solute uptake by PVC tubing

The fraction and the cumulative fraction of the original concentration of solute in the effluent (F_t and CuF_t) under eight different conditions (see Table 3.4) for acetophenone, nitrobenzene and *p*-chlorophenol are shown in Tables 3.16 - 3.21. Analysis of variance as first described by Yates (Armstrong and James, 1990) was used to determine the specific causes of variation in the extent of sorption of the selected solute under different conditions. Tables 3.22 - 3.24 are the complete analysis of

variance tables for fractions of the original concentration of solute in the effluent and Tables 3.25 - 3.27 are those of the cumulative fraction of the original concentration of solute in the effluent. The significance of the value of F is assessed by comparing it in each case with tabulated values.

Table 3.16. Fractions of the original concentration of solute in the effluent (F_t) of acetophenone solution infused through PVC tubing under various conditions [a,b]

Experiment	Time (hour)				
	1	3	6	12	24
(1)	0.715	0.756	0.809	0.812	0.864
	(0.022)	(0.002)	(0.013)	(0.001)	(0.033)
cl	0.591	0.662	0.736	0.754	0.860
	(0.011)	(0.024)	(0.021)	(0.049)	(0.025)
vl	0.693	0.758	0.833	0.856	0.898
	(0.061)	(0.018)	(0.039)	(0.005)	(0.021)
cv	0.825	0.865	0.917	0.909	0.924
	(0.057)	(0.030)	(0.005)	(0.006)	(0.010)
dl	0.553	0.608	0.667	0.699	0.816
	(0.028)	(0.023)	(0.008)	(0.031)	(0.029)
cd	0.648	0.742	0.821	0.794	0.847
	(0.031)	(0.038)	(0.012)	(0.008)	(0.003)
vd	0.799	0.824	0.852	0.876	0.899
	(0.031)	(0.007)	(0.033)	(0.025)	(0.002)
cvdl	0.676	0.740	0.808	0.804	0.861
	(0.025)	(0.004)	(0.007)	(0.033)	(0.015)

[a] Values in parentheses are S.D. values.
[b] for definition of conditions see Table 3.4.

Table 3.17. Fractions of the original concentration of solute in the effluent (F_t) of nitrobenzene solution infused through PVC tubing under various conditions [a,b]

Experiment	Time (hour)				
	1	3	6	12	24
(1)	0.467	0.487	0.622	0.603	0.698
	(0.017)	(0.045)	(0.004)	(0.041)	(0.066)
cl	0.323	0.390	0.497	0.503	0.635
	(0.007)	(0.035)	(0.015)	(0.015)	(0.052)
vl	0.536	0.595	0.628	0.650	0.680
	(0.010)	(0.026)	(0.025)	(0.020)	(0.083)
cv	0.716	0.739	0.819	0.766	0.829
	(0.010)	(0.031)	(0.023)	(0.002)	(0.005)
dl	0.334	0.370	0.431	0.423	0.552
	(0.053)	(0.031)	(0.010)	(0.011)	(0.008)
cd	0.464	0.550	0.620	0.560	0.670
	(0.029)	(0.038)	(0.007)	(0.070)	(0.069)
vd	0.637	0.717	0.723	0.745	0.806
	(0.013)	(0.016)	(0.034)	(0.019)	(0.038)
cvdl	0.500	0.555	0.607	0.609	0.653
	(0.026)	(0.023)	(0.006)	(0.018)	(0.005)

[a] Values in parentheses are S.D. values.

[b] for definition of conditions see Table 3.4.

Table 3.18. Fractions of the original concentration of solute in the effluent (F_t) of *p*-chlorophenol solution infused through PVC tubing under various conditions [a, b]

Experiment	Time (hour)				
	1	3	6	12	24
(1)	0.891	0.934	0.957	0.953	0.964
	(0.004)	(0.007)	(0.004)	(0.002)	(0.004)
cl	0.754	0.833	0.886	0.907	0.936
	(0.007)	(0.016)	(0.000)	(0.011)	(0.005)
vl	0.872	0.917	0.947	0.935	0.944
	(0.031)	(0.007)	(0.004)	(0.037)	(0.036)
cv	0.942	0.964	0.970	0.970	0.977
	(0.009)	(0.011)	(0.005)	(0.006)	(0.007)
dl	0.745	0.796	0.847	0.889	0.923
	(0.013)	(0.015)	(0.019)	(0.015)	(0.031)
cd	0.842	0.905	0.933	0.926	0.935
	(0.005)	(0.003)	(0.008)	(0.002)	(0.002)
vd	0.918	0.940	0.954	0.954	0.959
	(0.020)	(0.020)	(0.019)	(0.022)	(0.019)
cvdl	0.791	0.859	0.908	0.921	0.940
	(0.006)	(0.009)	(0.001)	(0.005)	(0.002)

[a] Values in parentheses are S.D. values.

[b] for definition of conditions see Table 3.4.

Table 3.19. Cumulative fractions of the original concentration of solute in the effluent (CuF_t) of acetophenone solution infused through PVC tubing under various conditions [a, b]

Experiment	Time (hour)				
	1	3	6	12	24
(1)	0.720	0.740	0.760	0.800	0.820
	(0.030)	(0.020)	(0.010)	(0.020)	(0.000)
cl	0.620	0.630	0.670	0.720	0.760
	(0.040)	(0.010)	(0.020)	(0.030)	(0.030)
vl	0.710	0.730	0.770	0.810	0.840
	(0.050)	(0.060)	(0.050)	(0.020)	(0.000)
cv	0.820	0.830	0.860	0.890	0.900
	(0.030)	(0.030)	(0.020)	(0.010)	(0.010)
dl	0.640	0.600	0.620	0.670	0.710
	(0.030)	(0.010)	(0.010)	(0.000)	(0.020)
cd	0.690	0.690	0.730	0.760	0.790
	(0.020)	(0.010)	(0.010)	(0.000)	(0.000)
vd	0.810	0.820	0.830	0.850	0.870
	(0.020)	(0.020)	(0.020)	(0.030)	(0.020)
cvdl	0.720	0.720	0.750	0.780	0.810
	(0.010)	(0.010)	(0.010)	(0.010)	(0.020)

[a] Values in parentheses are S.D. values.

[b] for definition of conditions see Table 3.4.

Table 3.20. Cumulative fractions of the original concentration of solute in the effluent (CuF_t) of nitrobenzene solution infused through PVC tubing under various conditions [a, b]

Experiment	Time (hour)				
	1	3	6	12	24
(1)	0.510	0.510	0.530	0.610	0.630
	(0.020)	(0.010)	(0.010)	(0.050)	(0.050)
cl	0.400	0.380	0.410	0.460	0.510
	(0.001)	(0.000)	(0.010)	(0.000)	(0.020)
vl	0.510	0.550	0.570	0.620	0.640
	(0.020)	(0.010)	(0.000)	(0.010)	(0.030)
cv	0.690	0.710	0.730	0.760	0.780
	(0.000)	(0.010)	(0.020)	(0.000)	(0.000)
dl	0.440	0.380	0.380	0.420	0.460
	(0.050)	(0.040)	(0.030)	(0.000)	(0.000)
cd	0.520	0.505	0.545	0.595	0.605
	(0.042)	(0.021)	(0.007)	(0.007)	(0.035)
vd	0.680	0.680	0.680	0.720	0.750
	(0.000)	(0.000)	(0.010)	(0.000)	(0.010)
cvdl	0.550	0.530	0.550	0.600	0.610
	(0.000)	(0.020)	(0.020)	(0.000)	(0.000)

[a] Values in parentheses are S.D. values.

[b] for definition of conditions see Table 3.4.

Table 3.21. Cumulative fractions of the original concentration of solute in the effluent (CuF_t) of *p*-chlorophenol solution infused through PVC tubing under various conditions [a, b]

Experiment	Time (hour)				
	1	3	6	12	24
(1)	0.860	0.900	0.920	0.940	0.950
	(0.000)	(0.000)	(0.000)	(0.00)	(0.000)
cl	0.740	0.780	0.820	0.860	0.890
	(0.070)	(0.010)	(0.000)	(0.010)	(0.000)
vl	0.820	0.880	0.910	0.920	0.930
	(0.050)	(0.020)	(0.010)	(0.010)	(0.020)
cv	0.920	0.940	0.960	0.960	0.970
	(0.010)	(0.010)	(0.001)	(0.010)	(0.010)
dl	0.820	0.780	0.800	0.830	0.870
	(0.000)	(0.010)	(0.010)	(0.000)	(0.001)
cd	0.860	0.870	0.900	0.910	0.920
	(0.010)	(0.000)	(0.000)	(0.000)	(0.000)
vd	0.910	0.920	0.940	0.950	0.950
	(0.010)	(0.020)	(0.020)	(0.020)	(0.020)
cvdl	0.830	0.830	0.860	0.890	0.910
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)

[a] Values in parentheses are S.D. values.
[b] for definition of conditions see Table 3.4.

Table 3.22. Analysis of variance table for fractions of the original concentration of solute in the effluent (F_t) of acetophenone solution infused through PVC tubing under various conditions[a]

Experiment	Time (hour)				
	1	3	6	12	24
(1)	-	-	-	-	-
cl	1.00	49.00	9.00	2.00	2.25×10^2
vl	5.90×10^2	2.17×10^3	85.00	1.04×10^3	3.80×10^4
cv	4.00	4.00	1.00	22.00	1.52×10^3
dl	55.00	1.99×10^2	13.00	1.73×10^2	1.51×10^4
cd	3.00	17.00	6.00	5.00	8.41×10^2
vd	10.00	1.00	1.00	1.00	1.00
cvdl	5.62×10^2	2.17×10^3	75.00	5.37×10^2	9.80×10^3

[a] for definition of conditions see Table 3.4.

Table 3.23. Analysis of variance table for fractions of the original concentration of solute in the effluent (F_t) of nitrobenzene solution infused through PVC tubing under various conditions[a]

Experiment	Time (hour)				
	1	3	6	12	24
(1)	-	-	-	-	-
cl	1.00	12.00	3.94×10^2	1.00	1.00
vl	7.63×10^2	1.81×10^3	7.52×10^3	1.61×10^3	46.00
cv	4.00	28.00	2.00	11.00	1.00
dl	14.00	1.00	6.98×10^2	1.18×10^2	7.00
cd	2.00	2.00	1.00	1.00	4.00
vd	18.00	31.00	49.00	13.00	1.00
cvdl	4.15×10^2	9.42×10^2	7.87×10^3	8.27×10^2	63.00

[a] for definition of conditions see Table 3.4.

Table 3.24. Analysis of variance table for fractions of the original concentration of solute in the effluent (F_t) of *p*-chlorophenol solution infused through PVC tubing under various conditions[a]

Experiment	Time (hour)				
	1	3	6	12	24
(1)	-	-	-	-	-
cl	33.00	3.00	1.00	1.00	1.00
vl	2.93×10^2	1.76×10^2	3.80×10^2	2.25×10^2	9.61×10^2
cv	1.00	7.00	23.00	2.00	2.25×10^2
dl	92.00	86.00	2.18×10^2	1.15×10^2	1.02×10^3
cd	5.00	26.00	1.21×10^2	5.00	36.00
vd	8.00	1.00	1.00	5.00	1.00×10^2
cvdl	6.43×10^2	4.46×10^2	7.98×10^2	4.65×10^2	2.12×10^3

[a] for definition of conditions see Table 3.4.

Table 3.25. Analysis of variance table for cumulative fractions of the original concentration of solute in the effluent (CuF_t) of acetophenone solution infused through PVC tubing under various conditions[a]

Experiment	Time (hour)				
	1	3	6	12	24
(1)	-	-	-	-	-
cl	25.00	1.00	81.00	1.00	4.00
vl	6.24×10^3	7.57×10^3	7.57×10^3	6.93×10^2	1.16×10^3
cv	2.89×10^2	25.00	1.00	1.00	9.00
dl	1.00	5.29×10^2	8.41×10^2	1.21×10^2	2.56×10^2
cd	49.00	1.00	25.00	3.00	1.00
vd	1.00	81.00	49.00	3.00	1.00
cvdl	4.76×10^3	6.56×10^3	5.63×10^3	4.69×10^2	6.76×10^2

[a] for definition of conditions see Table 3.4.

Table 3.26. Analysis of variance table for cumulative fractions of the original concentration of solute in the effluent (CuF_t) of nitrobenzene solution infused through PVC tubing under various conditions[a]

Experiment	Time (hour)				
	1	3	6	12	24
(1)	-	-	-	-	-
cl	1.00	1.00	6.76	4.00	49.00
vl	3.14×10^3	2.04×10^4	7.29×10^2	9.30×10^2	1.37×10^4
cv	64.00	81.00	1.00	1.00	49.00
dl	36.00	2.89×10^2	9.00	30.25	6.25×10^2
cd	1.96×10^2	3.61×10^2	1.00	6.25	1.00
vd	1.00	9.00	6.76	1.00	25.00
cvdl	2.40×10^3	1.19×10^4	5.48×10^2	8.41×10^2	1.14×10^4

[a] for definition of conditions see Table 3.4.

Table 3.27. Analysis of variance table for cumulative fractions of the original concentration of solute in the effluent (CuF_t) of *p*-chlorophenol solution infused through PVC tubing under various conditions[a]

Experiment	Time (hour)				
	1	3	6	12	24
(1)	-	-	-	-	-
cl	9.00	2.03×10^{29}	5.00	2.03×10^{27}	9.00
vl	1.00×10^{2}	5.07×10^{30}	2.05×10^{2}	5.86×10^{29}	6.25×10^{2}
cv	25.00	1.00	1.00	1.00	1.00
dl	25.00	8.11×10^{29}	59.00	2.92×10^{29}	2.89×10^{2}
cd	1.00	2.03×10^{29}	25.00	7.30×10^{28}	25.00
vd	16.00	7.30×10^{28}	1.00	1.00	25.00
cvdl	2.89×10^{2}	1.17×10^{31}	4.69×10^{2}	1.37×10^{30}	1.37×10^{3}

[a] for definition of conditions see Table 3.4.

For all solutes used, analysis of variance indicates that significant losses are not associated with the initial concentration of the infusion solution at a 99% level of significance.

The effect of tubing length, when considered in conjunction with flow rate and/or tubing diameter, is clearly important while single factors such as flow rate and tubing diameter appear to have less effect on solute uptake from solution infused through PVC tubing during a 24-hour period.

The typical sorption - $(time)^{1/2}$ relationships as described by Rogers (Crank, 1975) of acetophenone solution infused through PVC tubing, under various conditions, are shown in Figures 3.14 and 3.15 where both fraction of the original concentration of solute in the effluent (F_t) and cumulative fraction of the original concentration of solute in the effluent (CuF_t) are plotted on the y-axis. From Figures 3.14 and 3.15, it

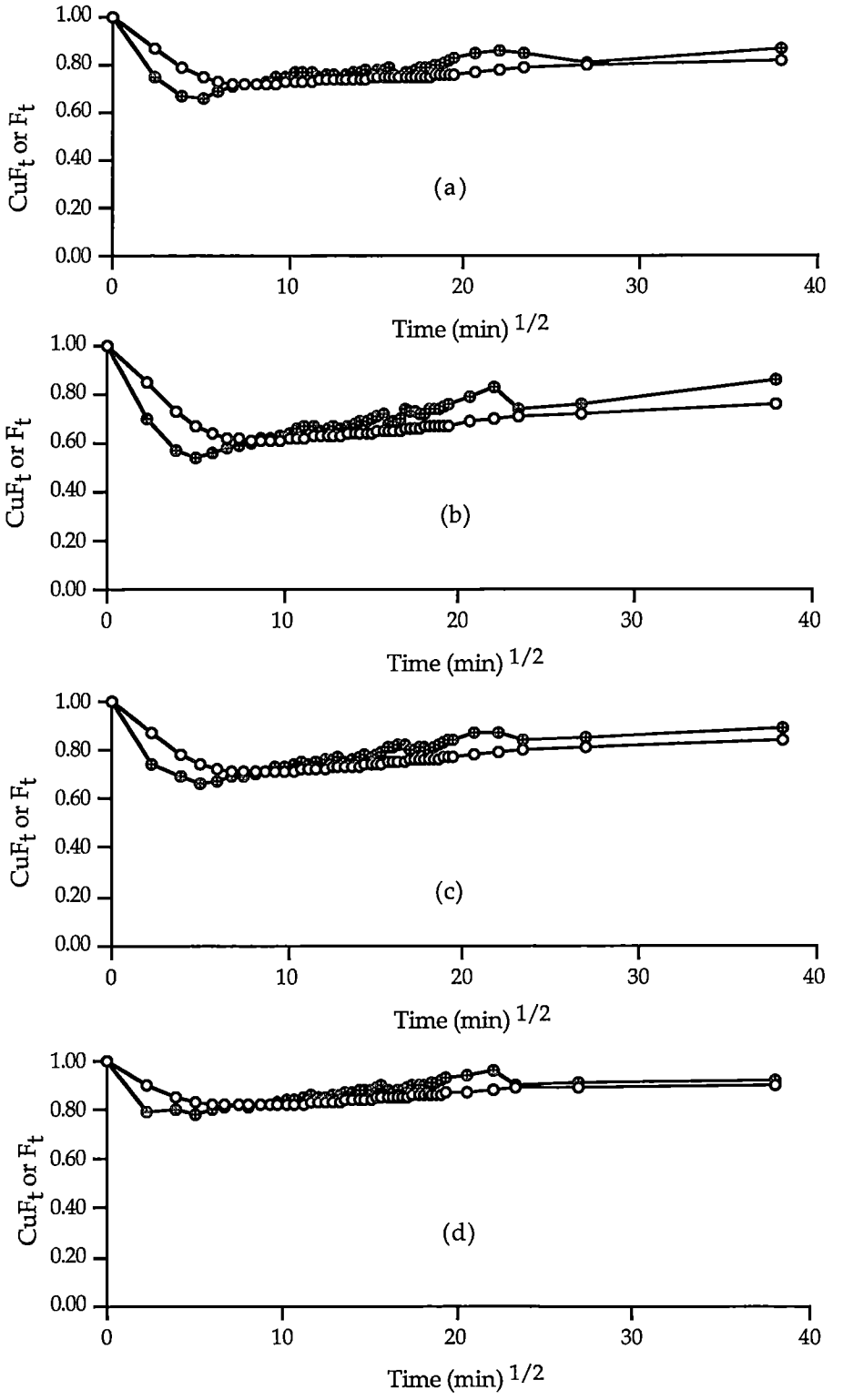


Figure 3.14. Cumulative fraction (open symbol) and fraction (closed symbol) of the original concentration of solute in the effluent as a function of time of acetophenone solution, (a) experiment (1), (b) experiment cl, (c) experiment vl, (d) experiment cv.

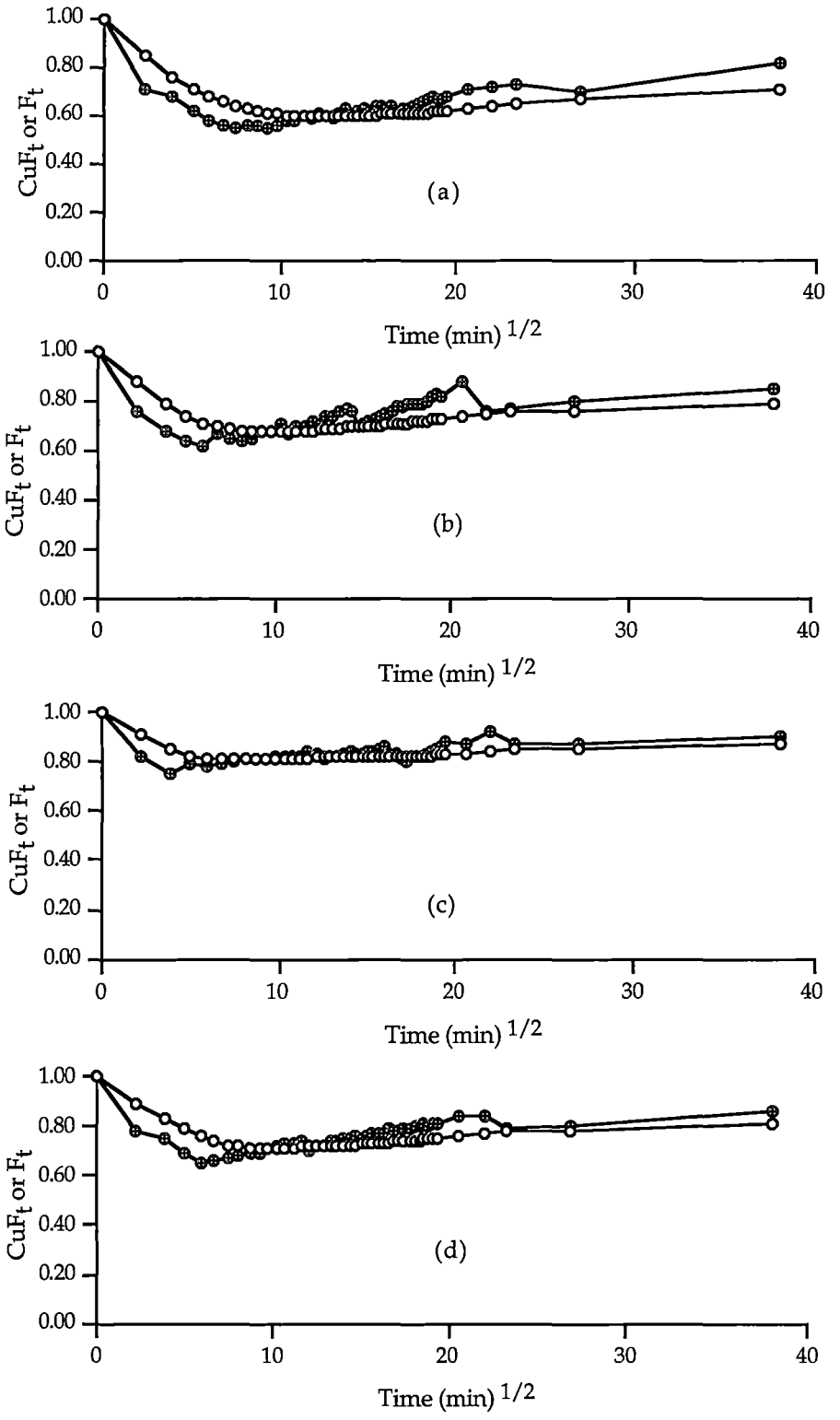


Figure 3.15. Cumulative fraction (open symbol) and fraction (closed symbol) of the original concentration of solute in the effluent as a function of time of acetophenone solution, (a) experiment dl, (b) experiment cd, (c) experiment vd, (d) experiment cvdl.

can be seen that the CuF_t - $(time)^{1/2}$ curves are all sigmoid in shape with a minimum value at which time (t) is about 2.5 and 4 times t_{min} for the tubings of internal diameter of 0.8 and 0.5 cm respectively. Similar results have been obtained for other solutes in solution infused through a tubing of 0.8 cm internal diameter (see eqn.3.7 in Section 3.4.3).

Additionally it is seen, not unexpectedly, that the F_t - $(time)^{1/2}$ curve appears to pass through/close to the minimum value of the CuF_t - $(time)^{1/2}$ curve obtained under the same conditions irrespective of the values of solute concentration, flow rate, tubing diameter and tubing length. Similar common points of intersection are also found for the other two solutes (nitrobenzene and *p*-chlorophenol) as shown in Figures 3.16 - 3.19. The values of F_t and CuF_t obtained at this common point for each of the three solutes under eight different conditions are shown in Table 3.28.

By applying the unpaired *t* - test, it is confirmed that the F_t and CuF_t values obtained at the point of intersection under the same conditions are not significantly different ($p>0.01$). The time at this point of intersection is, therefore, equal to t_{sink} which can be expressed by eqns.3.7 and 3.12 for tubing of internal radius of 0.40 and 0.25 cm, respectively:

$$t_{sink} = \frac{2.5\,V}{v} \qquad (3.7)$$

$$t_{sink} = \frac{4.0\,V}{v} \qquad (3.12)$$

where V is the volume of solution in mL that is present in the tubing at the beginning of the infusion and v is the infusion rate in $mL.min^{-1}$.

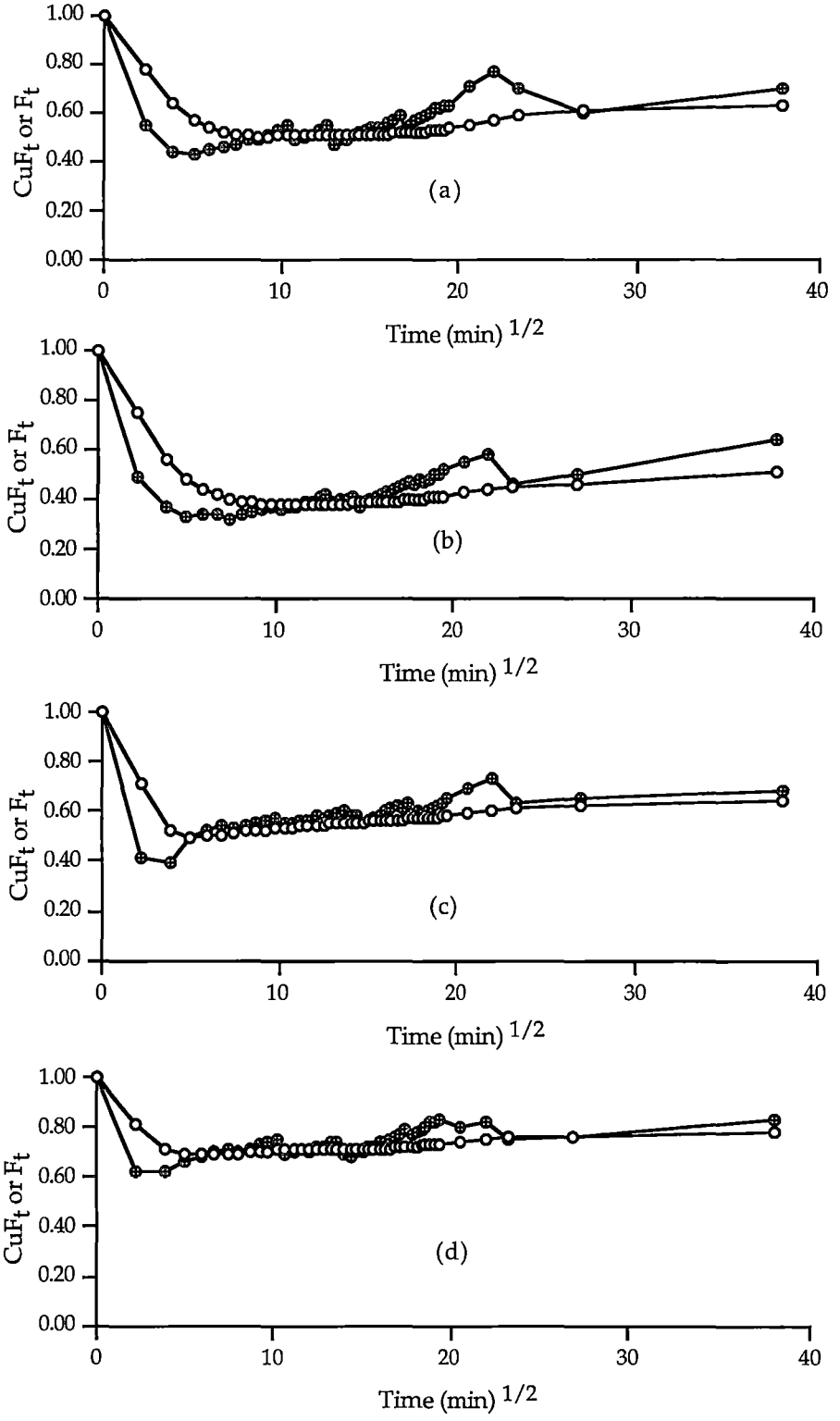


Figure 3.16. Cumulative fraction (open symbol) and fraction (closed symbol) of the original concentration of solute in the effluent as a function of time of nitrobenzene solution, (a) experiment (1), (b) experiment cl, (c) experiment vl, (d) experiment cv.

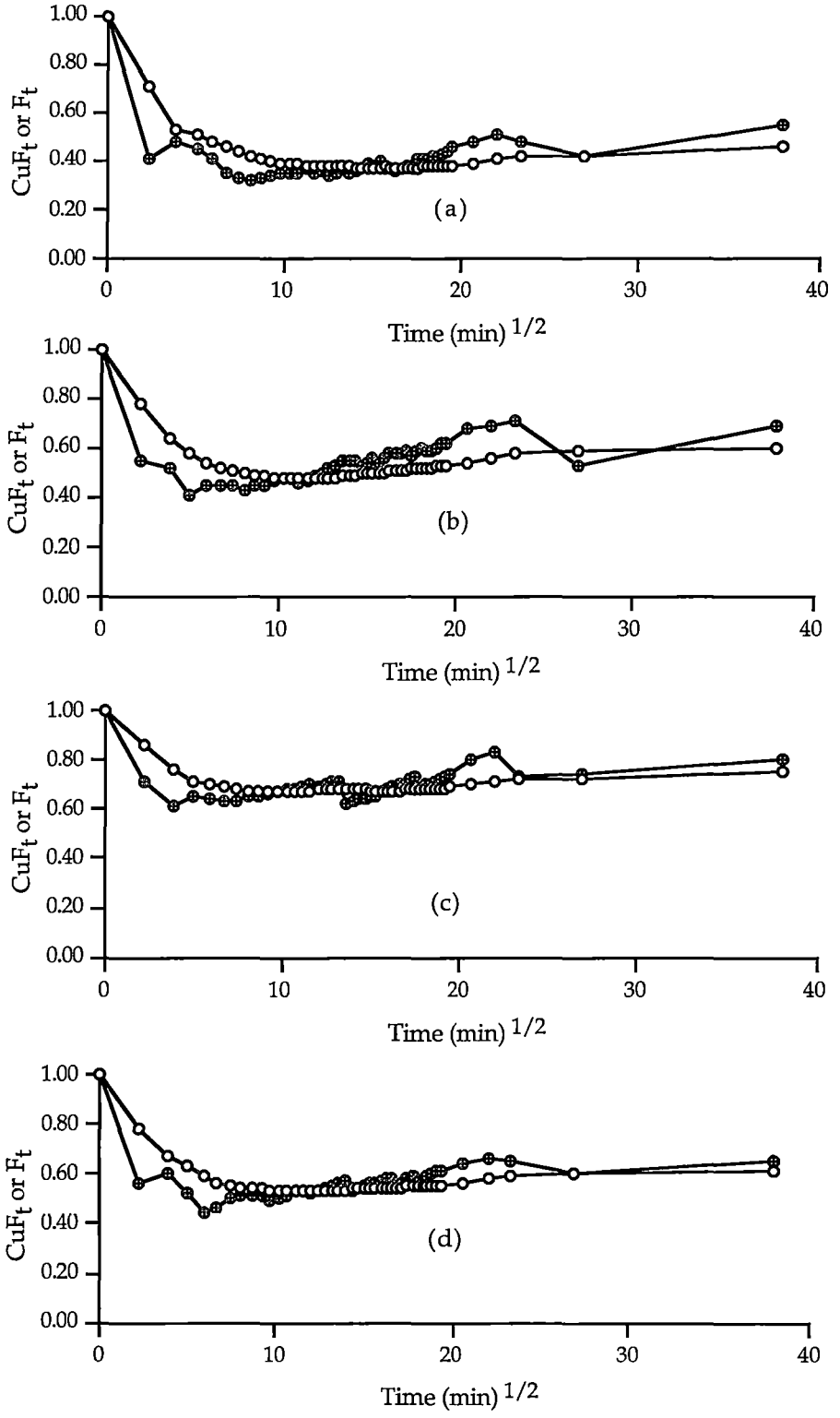


Figure 3.17. Cumulative fraction (open symbol) and fraction (closed symbol) of the original concentration of solute in the effluent as a function of time of nitrobenzene solution, (a) experiment dl, (b) experiment cd, (c) experiment vd, (d) experiment cvdl.

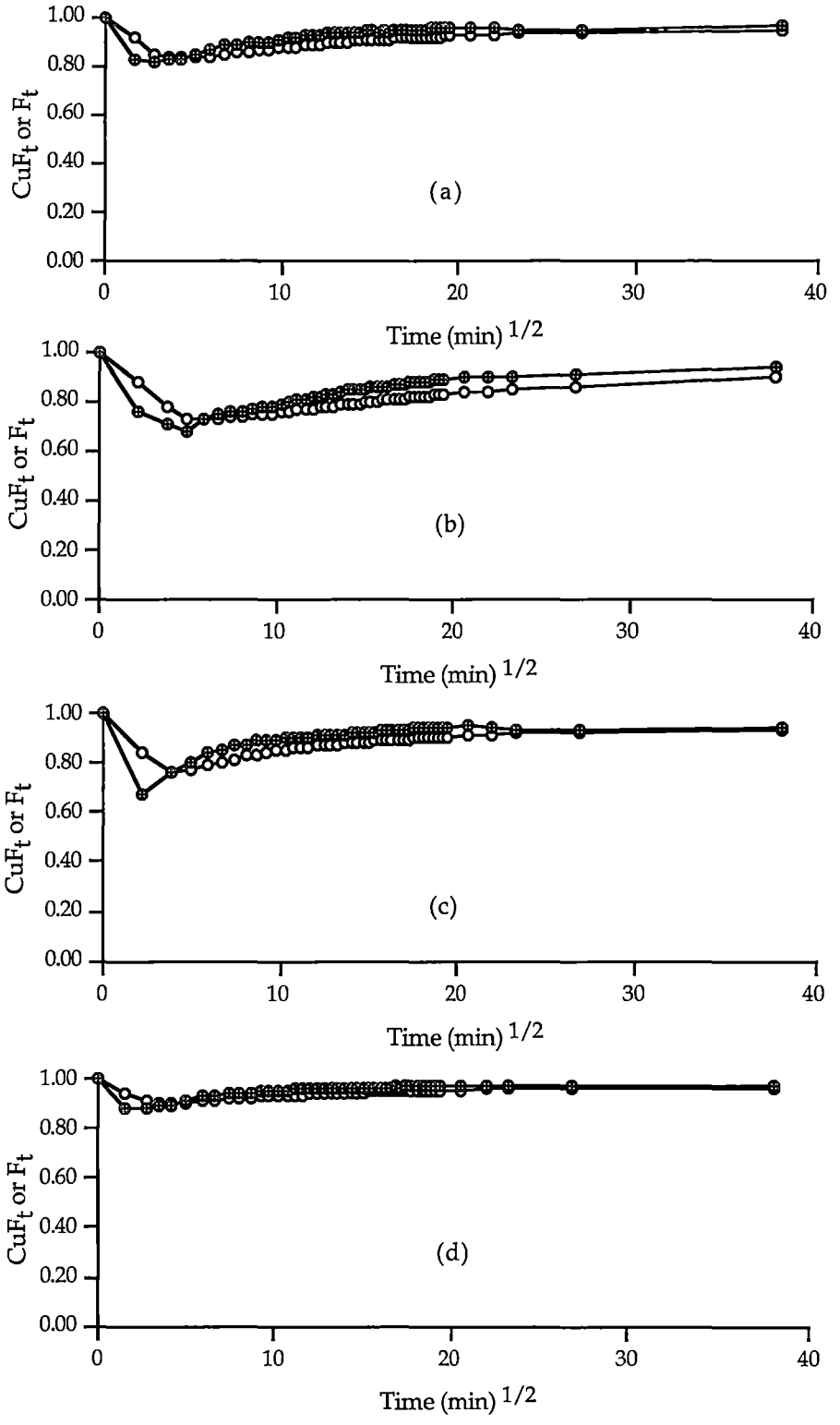


Figure 3.18. Cumulative fraction (open symbol) and fraction (closed symbol) of the original concentration of solute in the effluent as a function of time of *p*-chlorophenol solution, (a) experiment (1), (b) experiment cl, (c) experiment vl, (d) experiment cv.

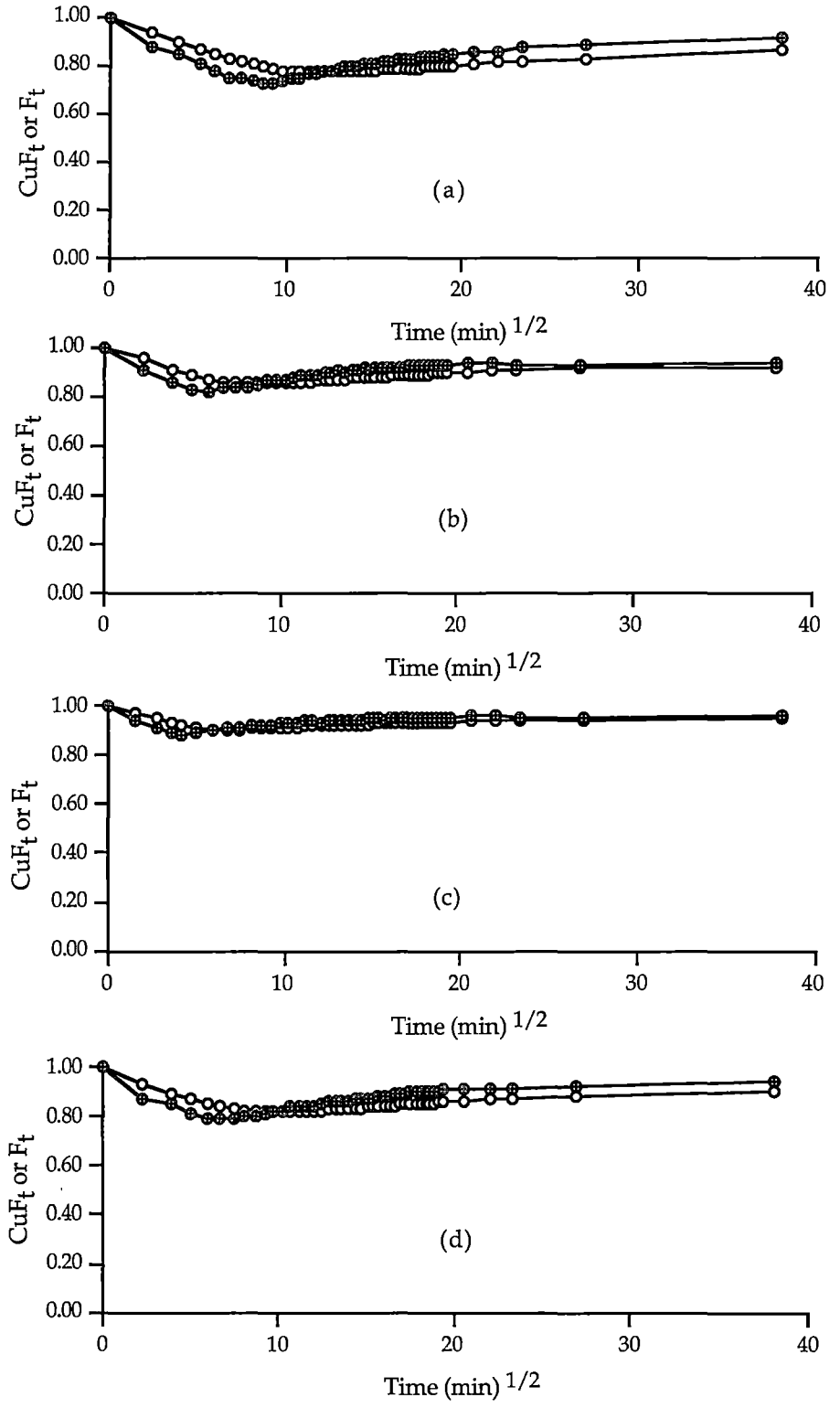


Figure 3.19. Cumulative fraction (open symbol) and fraction (closed symbol) of the original concentration of solute in the effluent as a function of time of *p*-chlorophenol solution, (a) experiment dl, (b) experiment cd, (c) experiment vd, (d) experiment cvdl.

Table 3.28. The values of fraction (F_t) and cumulative fraction (CuF_t) of the original concentration of solute in the effluent obtained at the theoretically common point of intersection[a]

Experiment	Time[b] (min)	Acetophenone		Nitrobenzene		*p*-Chlorophenol	
		F_t	CuF_t	F_t	CuF_t	F_t	CuF_t
(1)	52.4	0.72	0.72	0.47	0.51	0.88	0.86
		(0.02)	(0.03)	(0.01)	(0.01)	(0.00)	(0.01)
cl	131.0	0.67	0.62	0.37	0.38	0.82	0.77
		(0.00)	(0.01)	(0.00)	(0.00)	(0.02)	(0.01)
vl	65.5	0.72	0.71	0.55	0.52	0.87	0.84
		(0.06)	(0.06)	(0.01)	(0.01)	(0.03)	(0.04)
cv	26.2	0.79	0.83	0.67	0.69	0.91	0.91
		(0.05)	(0.00)	(0.02)	(0.02)	(0.01)	(0.01)
dl	209.5	0.62	0.60	0.36	0.38	0.80	0.78
		(0.01)	(0.01)	(0.01)	(0.04)	(0.01)	(0.01)
cd	83.8	0.68	0.68	0.49	0.51	0.88	0.86
		(0.01)	(0.00)	(0.04)	(0.03)	(0.01)	(0.01)
vd	41.9	0.80	0.81	0.65	0.69	0.90	0.91
		(0.04)	(0.01)	(0.03)	(0.01)	(0.01)	(0.01)
cvdl	104.8	0.74	0.72	0.51	0.53	0.85	0.82
		(0.01)	(0.02)	(0.04)	(0.01)	(0.01)	(0.00)

[a] Values in parentheses are S.D. values.
[b] The theoretical time point of intersection.

Rearranging eqn.3.7 gives

$$t_{sink} = \frac{V}{0.40v} \tag{3.13}$$

Since 0.40 is the internal radius, r, of the tubing used, replacing 0.40 in eqn.3.13 with r yields

$$t_{sink} = \frac{V}{vr} \tag{3.14}$$

Similarly, eqn.3.12 can also be rewritten to give an equation of the same form as eqn.3.14.

Substituting V in eqn.3.14 with $\pi r^2 l$, where l is the length of the tube, yields

$$t_{sink} = \frac{\pi r^2 l}{v r} \tag{3.15}$$

or

$$t_{sink} = \frac{\pi r l}{v} \tag{3.16}$$

Eqn.3.16 is, hence, the general formula for t_{sink}, the time required for the initial rapid uptake of solute from the infusion solution into the surface of the PVC tubing used in this study to reach completion. The applicability of eqn.3.16 to this PVC tubing of other dimensions, or to other PVC tubing has not been tested experimentally in this work.

It may be concluded that, for all of the separate kinetic runs conducted with differing solute species and different concentration, flow rate, tubing length and tubing diameter, the shortest time required for the sorption process to proceed to the same degree of completion is t_{sink}. Given this, conditions of chemical similarity (Bosworth, 1956) may be established between systems which differ only in their order of magnitude. In such a case the conditions are determined by the equality of certain dimensionless quantities describing the state of the system. For the process of solute sorption from infusion solution into PVC tubing, the dimensionless groups in terms of which the state of similarity is recognized is

$$U_t' \frac{(v'^{1/2})}{(l'^{1/3})} = U_t \frac{(v^{1/2})}{(l^{1/3})} \qquad (3.17)$$

where U_t' and U_t are the fractional solute losses at t_{sink} , v and v' are infusion rates in $mL.min^{-1}$ and l and l' are tubing lengths in centimetres. The prime symbol is used to distinguish between two different systems. The derivation of eqn.3.17 is given in Appendix III

As the solute loss is given by the equation $U_t = 1 - ft$, where ft denotes the fraction of the original concentration of solute in the effluent at t_{sink}, eqn.3.17 can be expressed as

$$(1 - ft)\frac{(v^{1/2})}{(l^{1/3})} = (1 - ft')\frac{(v'^{1/2})}{(l'^{1/3})} \qquad (3.18)$$

The usefulness of eqn.3.18 is obvious, as it allows for an approximation of the fraction of the original concentration of solute in the effluent at t_{sink} in one system from a knowledge of the performance of another system operating under a differènt set of conditions. This model allows for the infusion rate, the tubing radius and the tubing length as variables.

Since factors such as tubing length and its interaction with infusion rate and/or tubing diameter were found to have a significant effect on solute uptake from a solution infused through PVC tubing, it is assumed that the rate constant (b_2 in eqn.3.5) which can be used to estimate the fraction of the original concentration of solute in the effluent (F_t) at any time equal to or greater than t_{sink} is a function of infusion rate (v), tubing radius (r) and tubing length (l), as shown in equation 3.19:

$$b_2 = \frac{(v^{1/2})}{(l^{1/3})r} k_b \qquad (3.19)$$

where k_b is a function of the permeability constant of the drug in the plastic. Therefore the rate constant of sorption at one condition may be approximated from the value obtained from another condition by using the following equation:

$$b_2 = b_2' \frac{(l'^{1/3})r'}{(v'^{1/2})} \frac{(v^{1/2})}{(l^{1/3})r} \qquad (3.20)$$

Given this, the rate constant, b_2, obtained from experiment cd (Table 3.4) may be used in the estimation of the rate constant, b_2', for the other seven conditions for each solute by means of eqn.3.20. The value of a_2' used in the prediction equation (eqn.3.5) for the other seven conditions can be determined by using the values of F_t, b_2 and t obtained from eqns.3.18, 3.20 and 3.16, respectively, in eqn.3.5.

From the result obtained in the sorption profiles of model solutes study (Section 3.4.3), it appears that eqn.3.5 may be used to estimate the actual solute concentration in the effluent during prolonged infusion, at any time t between t_{sink} and that at which achievement of a true steady-state occurs, and that the steady state was reached at a time greater than 6 hours which is approximately 4 times t_{sink} of the condition used in that experiment (experiment cd in Table 3.4).

To examine the ability of eqn.3.20 to predict the rate constant of sorption, b_2', at one condition from the value, b_2, obtained at another condition, the predicted rate constant was used to estimate the fraction of the

original concentration of solute which would be expected in the effluent (F_t) obtained at time t, which is approximately 4 times t_{sink}, for 7 different conditions of each of the three solutes used in this study by means of equation 3.5. The value of a_2' used in the calculation was determined from the actual fraction of the original concentration of solute in the effluent at t_{sink} by using eqn.3.5.

It is suggested that the fraction of the original concentration of solute in the effluent at t_{sink}, which can be predicted by means of eqn.3.18, may be used to determine the value of a_2'. The actual fraction of the original concentration of solute in the effluent at t_{sink} was, however, used to estimate the constant a_2' in this portion of the study. This was done so as to ensure that the calculation of F_t, in this specific part of the work, which is testing the capacity of eqn.3.20 to predict the rate constant b_2', is not compromised. The results are shown in Tables 3.29 - 3.31 where it can be seen that the predictions are consistent with the average F_t values determined experimentally. Thus, the prediction model (eqn.3.20) for the rate constant of sorption (b_2) appears to be qualitatively correct.

The influence of single factors such as infusion rate, tubing radius and tubing length on the extent of solute uptake by PVC infusion tubing in any time has been reported for a number of drugs. However, to quantitatively predict the rate and extent of the uptake of a drug into PVC tubing under various conditions, the model which accounts for the interaction of infusion rate, tubing radius and tubing length must be used.

Table 3.29. Fractions of the original concentration of solute in the effluent (F_t) of acetophenone solution obtained at a time t which is about 4 times t_{sink} [a]

Experiment	Time (min)	a_2	b_2 ($x10^3$)	F_t actual	F_t calculated
(1)	223	0.673	1.09	0.775(0.021)	0.859
cl	486	0.633	0.47	0.830(0.028)	0.796
vl	294	0.684	0.61	0.800(0.057)	0.817
cv	95	0.754	1.68	0.835(0.049)	0.885
dl	725	0.580	0.29	0.700(0.028)	0.716
cd	368	0.639	0.67	0.820(0.014)	-
vd	145	0.763	1.02	0.840(0.042)	0.885
cvdl	473	0.703	0.38	0.845(0.007)	0.840

[a] Values in parentheses are S.D. values.

Table 3.30. Fractions of the original concentration of solute in the effluent (F_t) of nitrobenzene solution obtained at a time t which is about 4 times t_{sink} [a]

Experiment	Time (min)	a_2	b_2 ($x10^3$)	F_t actual	F_t calculated
(1)	234	0.429	1.56	0.540(0.057)	0.619
cl	545	0.338	0.68	0.455(0.007)	0.491
vl	270	0.517	0.93	0.615(0.007)	0.663
cv	99	0.626	2.41	0.740(0.014)	0.796
dl	725	0.327	0.44	0.420(0.014)	0.450
cd	359	0.443	1.00	0.625(0.007)	-
vd	162	0.612	1.48	0.715(0.021)	0.779
cvdl	413	0.475	0.59	0.645(0.007)	0.607

[a] Values in parentheses are S.D. values.

Table 3.31. Fractions of the original concentration of solute in the effluent (F_t) of *p*-chlorophenol solution obtained at a time t which is about 4 times t_{sink} [a]

Experiment	Time (min)	a_2	b_2 ($x10^3$)	F_t actual	F_t calculated
(1)	226	0.860	0.40	0.945(0.007)	0.942
cl	575	0.797	0.16	0.895(0.007)	0.873
vl	274	0.856	0.23	0.935(0.007)	0.912
cv	100	0.896	0.60	0.955(0.007)	0.952
dl	725	0.783	0.11	0.890(0.014)	0.846
cd	387	0.855	0.24	0.930(0.000)	-
vd	153	0.887	0.38	0.940(0.014)	0.940
cvdl	466	0.831	0.14	0.915(0.007)	0.887

[a] Values in parentheses are S.D. values.

From the result obtained in the sorption profile of model solutes study (Section 3.4.3), it appears that the model based on a first-order absorption process, as shown in eqn.3.5, can be used to adequately describe the sorption of solute into PVC tubing, at any time t equal to or greater than t_{sink} until the steady state is achieved.

$$F_t = a_2 e^{-b_2 t} \tag{3.5}$$

The result obtained in this portion of the study shows that the rate constant, b_2, at any infusion rate, tubing radius and tubing length may be estimated from the value obtained from another condition by using the equation

$$b_2 = b_2' \frac{(l'^{1/3})r'}{(v'^{1/2})} \frac{(v^{1/2})}{(l^{1/3})r} \tag{3.20}$$

To describe the effluent drug concentration - time profile, the constant a_2 in eqn.3.5 must also be known. By using the values of F_t, b_2 and t obtained from eqns.3.18, 3.20 and 3.16, respectively, in eqn.3.5, the constant a_2 can be determined.

It follows that the extent of sorption of a drug into plastic tubing during infusion can be minimized by using a short length of small-diameter tubing with the fastest possible flow rate. This result is consistent with others, reported previously (Amidon et al., 1981; Kowaluk et al., 1982). According to Amidon and co-workers (1981), the exit concentration of Vitamin A infused through PVC intravenous infusion tubing is given by:

$$\frac{C_m}{C_o} = \sum_{n=1}^{\infty} M_n \exp\left[-B_n^2 G_z\right] \tag{3.21}$$

where M_n and B_n are functions of only P_w^*, the wall permeability, C_m is the outlet concentration of the drug, C_o is an inlet concentration and G_z can be expressed by

$$G_z = \pi DL/2Q \tag{3.22}$$

where D is diffusion coefficient, L is tubing length, and Q is flow rate. The effluent concentration of Vitamin A solution infused through PVC tubing is, therefore, a function of the ratio of L/Q. This model is based on a first-order sorption process.

The first-order sorption process has also been the basis for a model used to describe the sorption of a number of other drugs into silastic tubing.

In the steady state, effluent drug concentration (C_o) from infusion tubing is expressed as a function of infusion rate, tubing radius and tubing length as follows (Kowaluk et al., 1982):

$$\log C_o/C_i = (-2k_p\pi rl)/(2.303f) \qquad (3.23)$$

where C_i is the drug concentration in the solution about to be infused through the delivery system, k_p is the permeability constant of the drug in the plastic, f is the flow rate, r is the internal radius and l is the length of the tube.

It would seem possible, therefore, to describe the effluent drug concentration - time profile of solute in a solution infused through PVC tubing, at time beyond t_{sink}, at differing infusion rates and tubing dimensions from the data obtained from another condition by using the model described above. If such a model works satisfactorily, then the extent of drug loss to tubing at any time beyond t_{sink} can be estimated under a variety of conditions likely to be encountered in clinical practice.

3.4.4.2. Effect of a single factor: solute concentration, flow rate, tubing diameter and tubing length studied separately

Unlike solute sorption by PVC infusion bags which is largely influenced by individual factors, such as the surface area to volume ratio, the extent of sorption by PVC tubing is highly influenced by the interaction between the flow rate and the tubing dimensions, as described earlier in Section 3.4.4.1. Any change in the flow rate and/or tubing diameter and/or tubing length will result in a change in the extent of solute sorption by PVC tubing. Thus, it is more appropriate to study the

combined effect of flow rate, tubing diameter and tubing length on solute sorption by PVC tubing rather than to study the effect of each individual factor. However, before evaluating the degree of influence the interaction between these factors has on the process (Section 3.4.4.3), studies on each single factor such as solute concentration, flow rate, tubing diameter and tubing length were carried out to show the effect of each individual factor on solute uptake from solution infused through PVC tubing.

Table 3.32 shows the effect of initial drug concentration on the fraction (F_t) and cumulative fraction (CuF_t) of the original concentration of acetophenone in the effluent of solutions infused through PVC tubing. It is seen that the fractions of acetophenone remaining in the effluents collected at each of 1, 3, 6, 12 and 24 hours are not significantly different for two initial drug concentration ($p>0.05$). The cumulative fraction of the original concentration of solute in the effluent (CuF_t) of acetophenone in the effluent collected at each of 1, 3, 6, 12 and 24 hours is also compared. No significant difference was observed between the two solutions of different initial drug concentration ($p>0.05$).

A similar result is obtained for sorption by a PVC bag (Chapter 2). It may be concluded, therefore, that the initial concentration of solute has no effect on the extent of solute uptake into the PVC matrix in either static or dynamic conditions, that is, the fraction of solute remaining in a solution stored in a PVC infusion container for a given period or the fraction of the original concentration of solute in the effluent collected at the distal end of a PVC tubing at a specific time would be the same in each of the two cases for different initial drug concentrations.

Table 3.32. The effect of initial drug concentration on acetophenone sorption into PVC tubing[a].

Time	Low conc		High conc	
(hours)	F_t	CuF_t	F_t	CuF_t
1	0.72	0.72	0.72	0.71
	(0.02)	(0.03)	(0.02)	(0.03)
3	0.76	0.74	0.75	0.74
	(0.00)	(0.02)	(0.07)	(0.03)
6	0.81	0.76	0.80	0.75
	(0.01)	(0.01)	(0.00)	(0.01)
12	0.81	0.80	0.88	0.81
	(0.00)	(0.02)	(0.06)	(0.00)
24	0.86	0.82	0.87	0.84
	(0.03)	(0.00)	(0.01)	(0.01)

[a] Values in parentheses are S.D. values.

The effect of flow rate on the fraction, and cumulative fraction of the original concentration of solute in the effluent (F_t and CuF_t), of *o*-xylenol solutions infused through PVC tubing is shown in Table 3.33.

Table 3.33. The effect of flow rate on *o*-xylenol sorption into PVC tubing[a].

Time	Low rate		High rate	
(hours)	F_t	CuF_t	F_t	CuF_t
1	0.84	0.87	0.94	0.93
	(0.01)	(0.00)	(0.00)	(0.01)
3	0.91	0.88	0.96	0.95
	(0.00)	(0.00)	(0.00)	(0.00)
6	0.94	0.90	0.97	0.96
	(0.00)	(0.00)	(0.00)	(0.00)
12	0.93	0.92	0.98	0.97
	(0.01)	(0.00)	(0.01)	(0.00)
24	0.95	0.93	0.98	0.97
	(0.01)	(0.00)	(0.00)	(0.00)

[a] Values in parentheses are S.D. values.

Flow rate was found to have a significant effect on the fraction and cumulative fraction of the original concentration of *o*-xylenol in the effluent collected at each of 1, 3, 6, and 12 hours ($p<0.05$).

An increase in flow rate results in an increase in the fraction and cumulative fraction of the original concentration of *o*-xylenol in the effluent of solutions infused through PVC tubing. This result is consistent with previous reports (Cossum et al., 1978; Roberts et al., 1980; Dasta et al., 1980; Baaske et al., 1980; Kowaluk et al., 1982, 1983; Lee, 1986).

Tables 3.34 and 3.35 show the effect of tubing diameter on the fraction and cumulative fraction of the original concentration of acetophenone in the effluent of solutions infused through PVC tubings.

Table 3.34. The effect of tubing diameter on the fraction of the original concentration of acetophenone in the effluent of solutions infused through PVC tubing[a]

Time	F_t		
	Tubing diameter (cm)		
(hours)	0.5	0.6	0.8
1	0.72	0.66	0.65
	(0.02)	(0.04)	(0.03)
3	0.75	0.73	0.74
	(0.07)	(0.02)	(0.04)
6	0.80	0.82	0.82
	(0.00)	(0.02)	(0.01)
12	0.88	0.75	0.79
	(0.06)	(0.08)	(0.01)
24	0.87	0.87	0.85
	(0.01)	(0.06)	(0.00)

[a] Values in parentheses are S.D. values.

Table 3.35. The effect of tubing diameter on the cumulative fraction of the original concentration of acetophenone in the effluent of solutions infused through PVC tubing[a].

Time	CuF_t		
	Tubing diameter (cm)		
(hours)	0.5	0.6	0.8
1	0.71	0.71	0.69
	(0.03)	(0.01)	(0.02)
3	0.74	0.70	0.69
	(0.03)	(0.01)	(0.01)
6	0.75	0.74	0.73
	(0.01)	(0.01)	(0.01)
12	0.81	0.79	0.76
	(0.00)	(0.01)	(0.00)
24	0.84	0.80	0.79
	(0.01)	(0.03)	(0.00)

[a] Values in parentheses are S.D. values.

No significant difference was found in the fractions or cumulative fractions of the original concentration of acetophenone in the effluent collected at each of 1, 3, 6, 12 and 24 hours when tubing of three different diameters was used ($p>0.05$) even though there was a trend toward greater loss of acetophenone to the PVC tubing of larger diameter. This might be due to the short tubing length (40 cm) and the relatively small differences in the tubing diameter between the three tubings used in the study; a significant difference in the extent of uptake for different diameter tubing has been noted earlier (Section 3.4.4.1). It is suggested that the effect of tubing diameter should not be overlooked especially when an infusion at relatively low flow rate is carried out with tubing of long length.

Table 3.36 shows the effect of tubing length on the fraction and cumulative fraction of the original concentration of *p*-bromophenol in the effluents collected at each of 1, 3, 6, 12 and 24 hours. A significant difference is observed between the effluent concentration of solutions infused through different tubing lengths ($p<0.05$).

Table 3.36. The effect of tubing length on *p*-bromophenol sorption into PVC tubing[a].

Time	Short length		Long length	
(hours)	F_t	CuF_t	F_t	CuF_t
1	0.82	0.84	0.66	0.77
	(0.01)	(0.00)	(0.02)	(0.02)
3	0.89	0.85	0.73	0.71
	(0.01)	(0.00)	(0.01)	(0.01)
6	0.92	0.88	0.80	0.74
	(0.01)	(0.01)	(0.01)	(0.00)
12	0.93	0.90	0.84	0.79
	(0.01)	(0.01)	(0.00)	(0.00)
24	0.95	0.92	0.87	0.82
	(0.01)	(0.01)	(0.00)	(0.00)

[a] Values in parentheses are S.D. values.

It is seen that the availability of *p*-bromophenol administered through flexible PVC tubing is greater with a shorter tubing length ($p<0.05$). This result is in good agreement with the results reported previously which suggest that sorption, of a number of drugs, can be reduced by using short lengths of small-diameter tubing during infusion (Baaske et al., 1980; Amidon et al., 1981; Mason et al., 1981; Kowaluk et al., 1982, 1983; Yliruusi et al., 1986a).

3.4.4.3. Evaluation of the combined effect of flow rate and/or tubing diameter and/or tubing length

Fractions of the original concentration of *o*-xylenol and *p*-bromophenol in the effluent of solutions infused through PVC tubing under various conditions are shown in Figures 3.20 to 3.23. In the same figures, a prediction of the fraction of the original concentration of the solute in the effluent at time equal to and greater than t_{sink} is also presented. The prediction of the fraction of the original concentration of the solute at times after t_{sink} is based on the general equation:

$$F_t = a_2 e^{-b_2 t} \qquad (3.5)$$

where F_t is the fraction of the original concentration of solute in the effluent at time t, where $t_{sink} \leq t \leq 4t_{sink}$, a_2 is a constant and b_2 is a rate constant. The solute concentration in the effluent at any time t greater than $4t_{sink}$ after the start of an infusion will remain constant until the end of the 24-hour infusion period. The results obtained from infusing the same solute through PVC tubing of 0.8 cm internal diameter and 40 cm length at a flow rate of 0.6 $mL.min^{-1}$ (which are presented in section 3.4.4.1.) have been used as a reference in the prediction. The actual calculation procedure is shown in Appendix IV.

The performance of a prediction method is often evaluated by computing the correlation coefficient of predictions on true (reference) values. However, it has been suggested that the mean squared prediction error (precision) and the mean prediction error (bias) provide

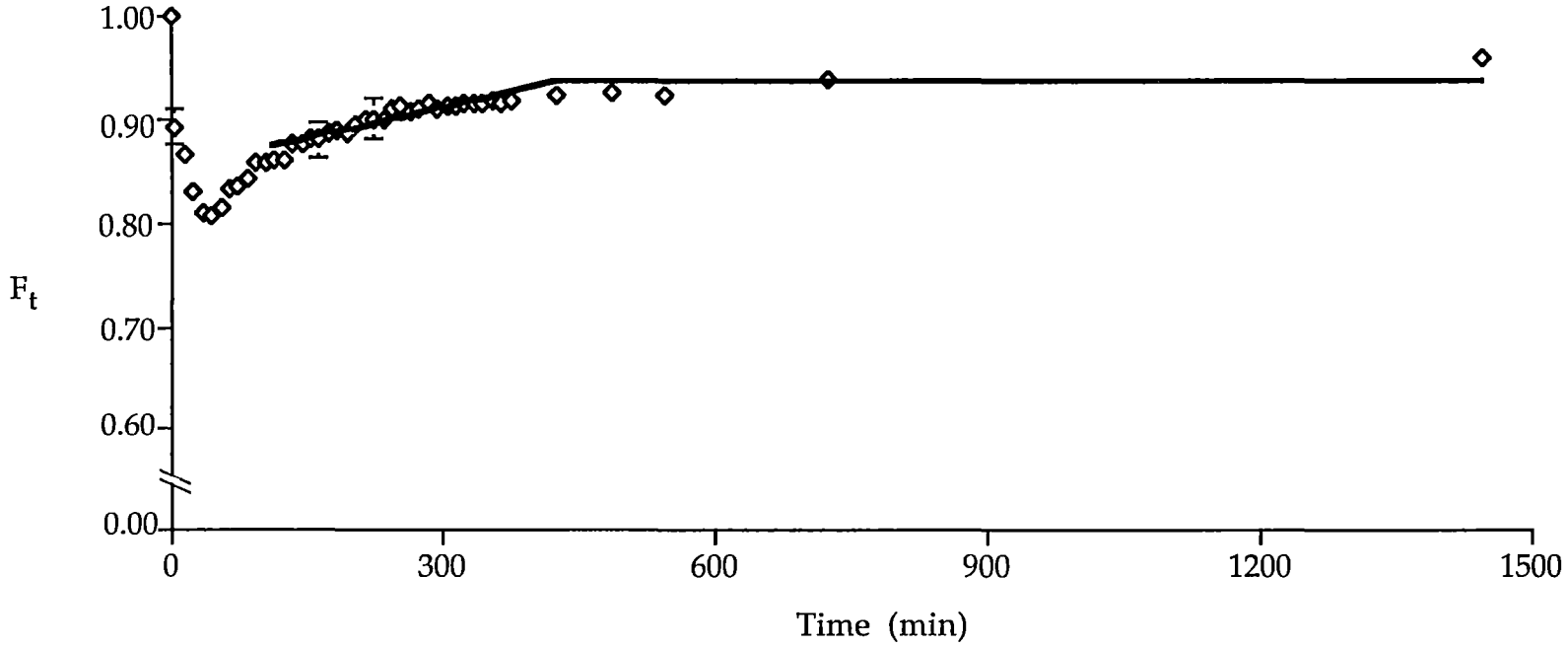


Figure 3.20. Effect of flow rate and tubing length on the fraction of the original concentration of *o*-xylenol in the effluent. Data points represent the actual values and the solid line represents the predicted values using the proposed model.

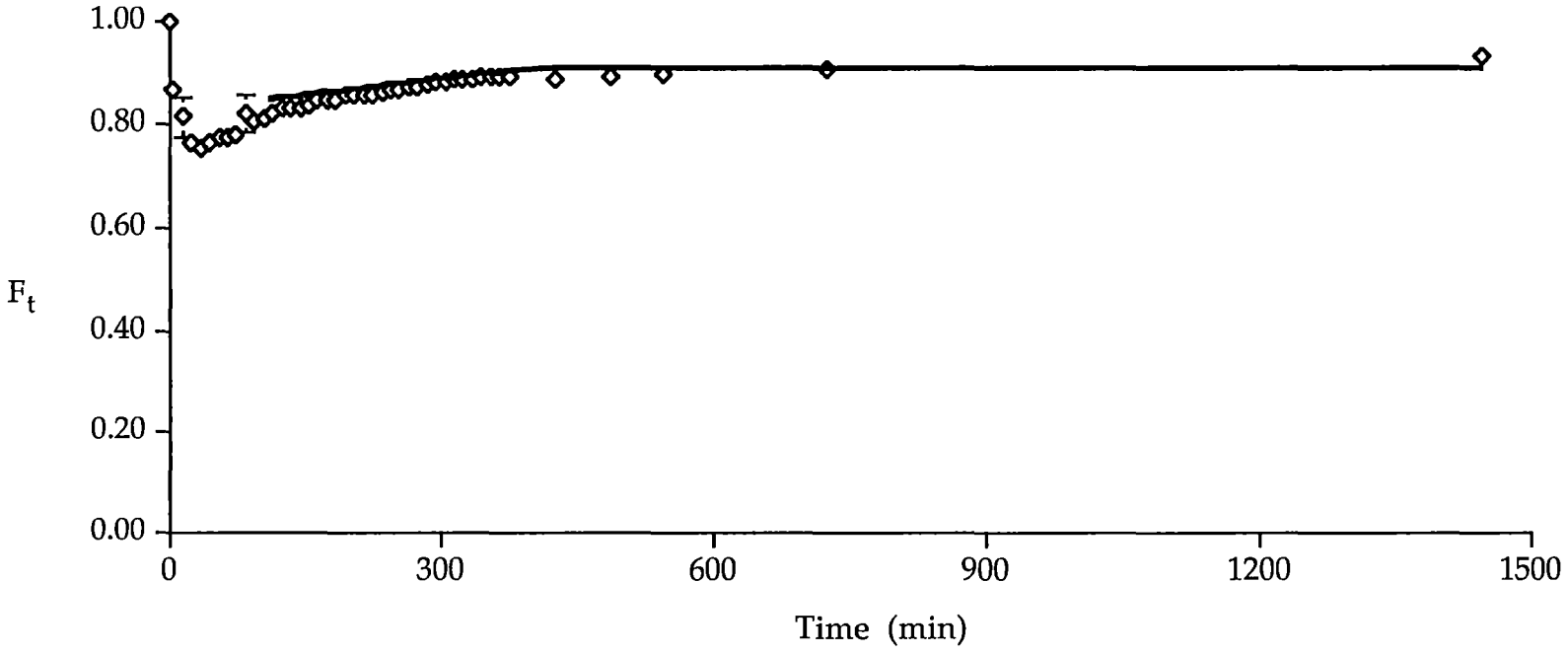


Figure 3.21. Effect of flow rate and tubing length on the fraction of the original concentration of *p*-bromophenol in the effluent. Data points represent the actual values and the solid line represents the predicted values using the proposed model.

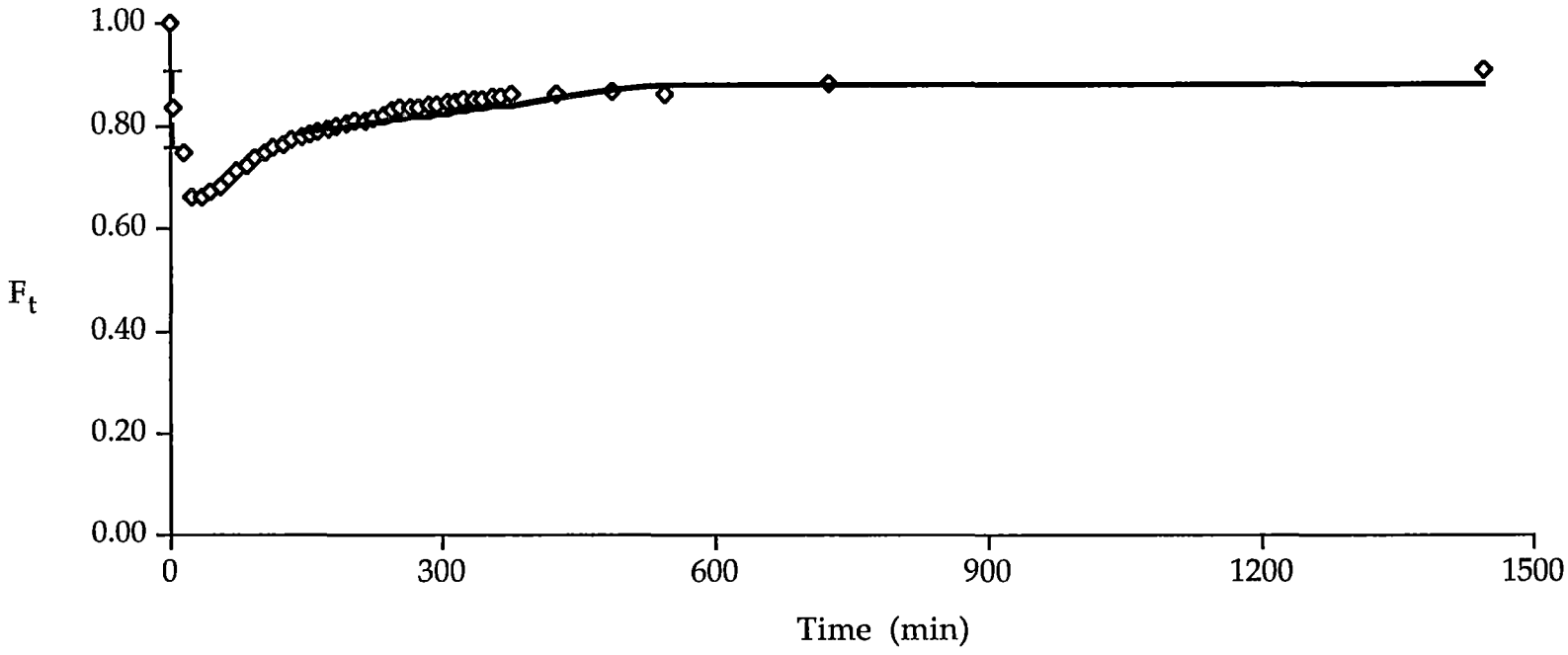


Figure 3.22. Effect of tubing diameter and tubing length on the fraction of the original concentration of *p*-bromophenol in the effluent. Data points represent the actual values and the solid line represents the predicted values using the proposed model.

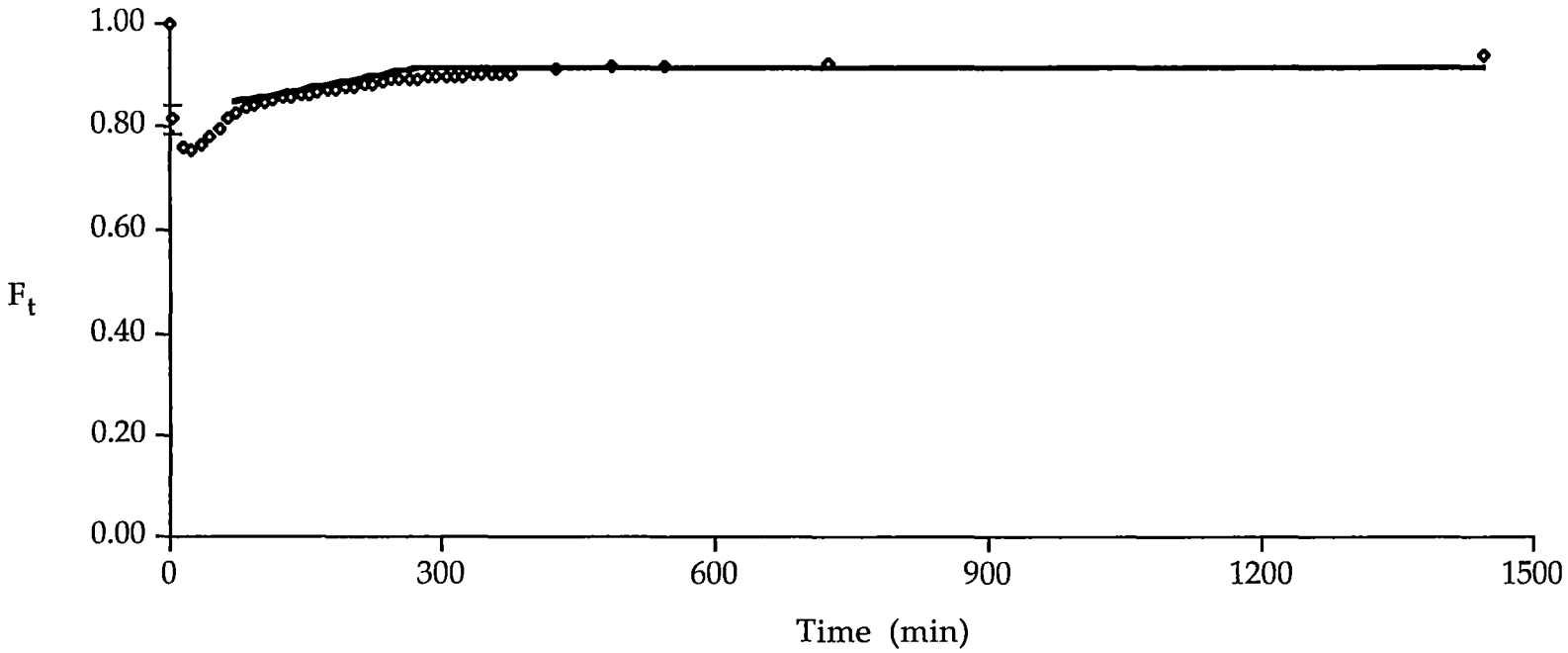


Figure 3.23. Effect of flow rate, tubing diameter and tubing length on the fraction of the original concentration of *p*-bromophenol in the effluent. Data points represent the actual values and the solid line represents the predicted values using the proposed model.

better descriptions of the predictive performance (Sheiner and Beal, 1981). Therefore, the correlation coefficient of predictions on true (reference) values as well as the mean squared prediction error (precision) and the mean prediction error (bias) were used to evaluate the performance of the proposed prediction model in this work. Table 3.37 is a summary of the precision and bias values of this prediction method.

Table 3.37. Performance evaluation of the predictor.

	Performance Evaluation[a]	
	Precision	Bias[b]
Experiment[c] A		
Standard	4.20×10^{-4} (1.91×10^{-4}, 6.49×10^{-4})	0.00
Predictor	5.32×10^{-5} (1.84×10^{-5}, 8.80×10^{-5})	1.04×10^{-4} (-2.56×10^{-3}, 2.77×10^{-3})
Experiment[c] B		
Standard	6.53×10^{-4} (3.40×10^{-4}, 9.66×10^{-4})	0.00
Predictor	1.85×10^{-4} (1.10×10^{-4}, 2.60×10^{-4})	1.03×10^{-2} (7.04×10^{-3}, 1.35×10^{-2})
Experiment[c] C		
Standard	8.67×10^{-4} (4.03×10^{-4}, 1.29×10^{-3})	0.00
Predictor	3.06×10^{-4} (2.11×10^{-4}, 4.00×10^{-4})	-1.36×10^{-2}(-1.78×10^{-2},-9.32×10^{-3})
Experiment[c] D		
Standard	6.72×10^{-4} (3.80×10^{-4}, 9.65×10^{-4})	0.00
Predictor	1.53×10^{-4} (1.09×10^{-4}, 1.97×10^{-4})	8.90×10^{-3} (5.96×10^{-3}, 1.18×10^{-2})

[a] Values in parentheses are 95% confidence interval.
[b] the standard (naive predictor) has zero bias (Sheiner and Beal, 1981).
[c] see Table 3.5.

Overall, the effluent concentrations predicted using the proposed model are in good agreement with those determined experimentally. In all cases, the predicted and the true values are in a good linear relationship (Figure 3.24) as the correlation coefficient, r, between all true value-prediction pairs is higher than 0.9 (r = 0.931, 0.956, 0.929 and 0.946 for experiment A, B, C and D, respectively) and a decrease of over 60% in the

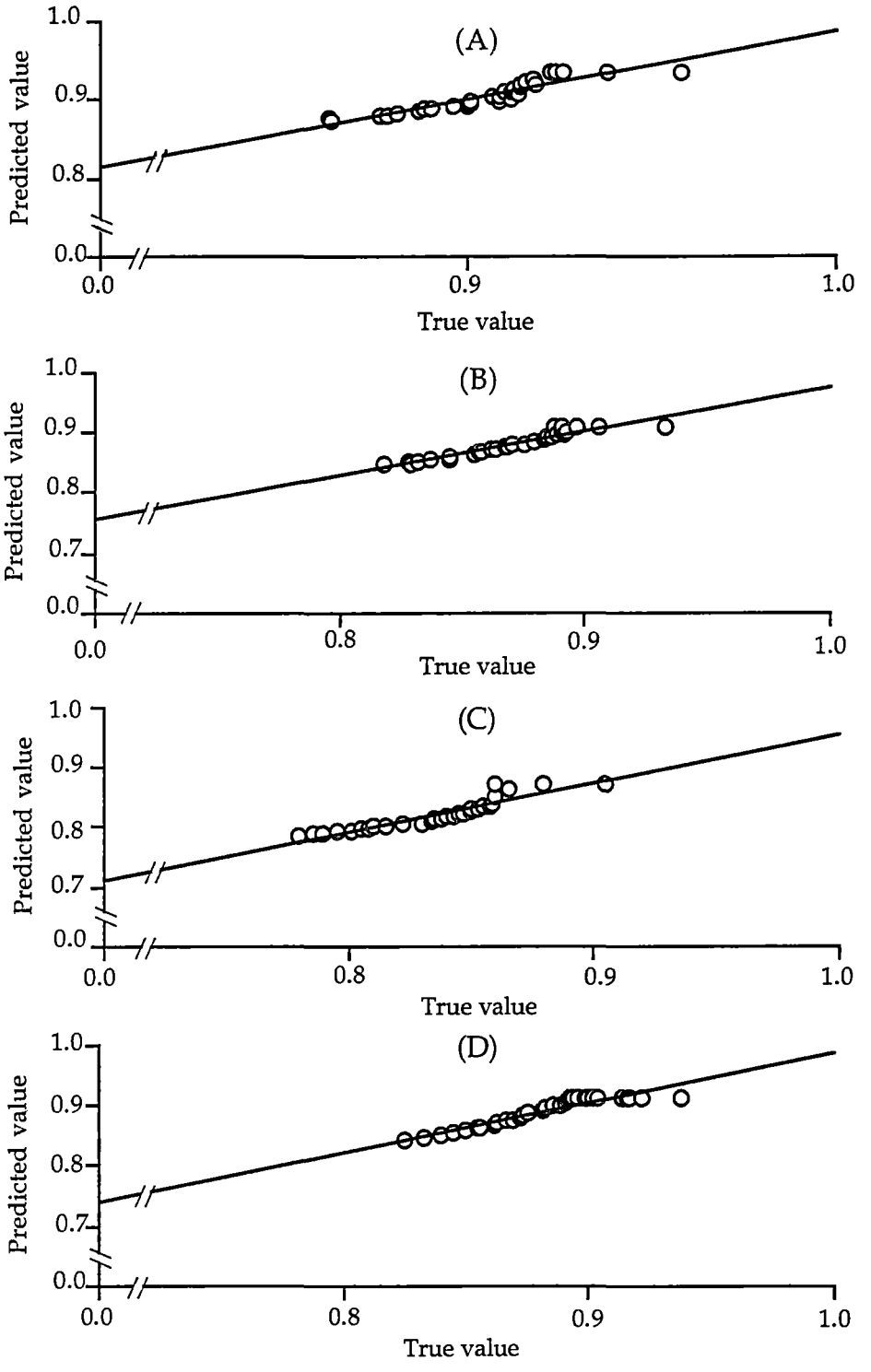


Figure 3.24. Relationship between the predicted and the actual values of the fraction of the original concentration of solute in the effluent (F_t) obtained under various experimental conditions (see Table 3.5 for details of each condition). The solid line presented in each figure is a linear fit to the data.

mean square error (precision) associated with the naive standard was obtained.

For each case, the prediction method, which does not appear markedly biased, has better precision than the naive predictor since a smaller value of precision means a smaller error magnitude. This indicates that the prediction method accounts reasonably well for the solution flow rate, tubing diameter and tubing length.

Consequently, it may be concluded that the proposed prediction method based upon a simple exponential model appears to have significant utility in predicting the fraction of the original concentration of solute in the effluent from solution infused through PVC tubing under various conditions of flow rate, tubing diameter and tubing length. It should be noted that this model can be used to estimate the actual solute concentration in the effluent at any individual time point t, where $t_{sink} \leq t \leq 4t_{sink}$. Since it is assumed that a steady state is reached when the infusion time is equal to $4t_{sink}$, the solute concentration in the effluent at any time t greater than $4t_{sink}$ after the start of an infusion will remain constant until the end of the 24-hour infusion period. In addition, an estimation of an overall loss during the initial rapid uptake which occurs immediately after the beginning of the infusion until a saturation is obtained, i.e., during $t = 0$ to $t = t_{sink}$, is also possible.

However, the major limitations of this technique are:

1) This model is applicable only in cases where the initial solute concentration is kept constant throughout the infusion period.

2) To predict the extent of solute uptake under a particular condition, the constants a_2 and b_2 used in the prediction equation must be determined from the values obtained experimentally for the same solute under another set of conditions using the model based on chemical similarity theory (see Appendix III). If there is no such experimental data available, the constants a_2 and b_2 may be estimated from other readily available data such as the dipole moment or intrinsic molecular volume and the solvatochromic parameters of the solute using the correlations described earlier for tubing of 0.4-cm diameter, 40-cm length and a flow rate of 0.6 $mL.min^{-1}$.

However, it should be noted that the correlations between the constants a_2 or b_2 and the dipole moments or the intrinsic molecular volumes and the solvatochromic parameters of various solutes were established using a particular PVC tubing and a particular set of solutes, which are benzene derivatives, containing only one hydrogen bonding substituent, with reported log $P_{octanol}$ values lower than 4.0 (Hansch and Leo, 1979) and molecular weights lower than 200. Hence, if there is any difference between the properties of the plastic and/or the solute used in this work and those under investigation, this model might not accurately estimate the amount lost into the tubing wall at any specific time.

CHAPTER 4. PREDICTION OF DRUG-PVC INTERACTION

4.1. Introduction

In the previous chapters, a number of reasonable correlations were established between the extent of sorption of solutes, by PVC infusion bags and PVC tubing, and their selected physicochemical properties. These correlations allow the fraction of the original concentration of solute remaining in a plastic infusion bag at a given storage time, and the fraction of the original concentration of a solute in the effluent collected at the distal end of the PVC tubing at a selected time, to be estimated from the octanol-water partition coefficient of the solute and other readily available data. To examine the ability of these relationships to predict solute uptake by plastics, the sorption profiles of 4-aethylphenol and benzocaine, neither of which has not been used before in this work, in both PVC infusion bags and PVC tubing systems are investigated.

Comparisons of the results reported previously by other investigators for the extent of sorption of a number of drugs by plastic infusion bags from the same manufacturer, as those used in this study, and values predicted from solute physicochemical parameters, using the relationships proposed in earlier chapters, are also presented.

Additionally, the fraction of solute remaining in 0.9% sodium chloride solution stored in PVC bags, determined experimentally, is compared with the value predicted using vehicle ionic strength and sorption number in water (Chapter 2). The method proposed for routine,

practical use which allows the fraction of the original concentration of solute in the effluent of a solution being infused through PVC tubing to be estimated under differing condition of infusion rate, tubing diameter, and/or tubing length is also presented. The data obtained using this model (and the same pair of solutes and PVC tubing material) under another set of conditions is also examined, using both the data obtained experimentally and the results reported previously by other investigators (in cases where the complete descriptions of the PVC samples used is provided).

4.2. Materials and Methods

Infusion solutions. Aqueous solutions of 4-aethylphenol (Ega-Chemie, lot 11531485), and benzocaine (Sigma Chemical, lot 91F-0071) were used at a concentration of 1.89×10^{-4} M, and 3.87×10^{-5} M, respectively. Both chemicals were laboratory grade and were used as received without further purification. Sodium chloride and other solutes used in this study have been described previously (Chapters 2 and 3). These solutes have included nitrobenzene, phenol, *p*-bromophenol, *p*-methylacetophenone and thymol. The chemical structures of all solutes used in this study are presented in Appendix V. All solutions were prepared in glass distilled water.

Plastic bags and tubings. PVC infusion bags containing 500 mL of 0.9% sodium chloride (Travenol, Baxter Healthcare International, batch A73R8, A67S5, A69S5) were emptied and rinsed with distilled water before use.

Flexible PVC tubing of 0.15 cm wall thickness, 0.5 and 0.8 cm internal diameter (Food Contact-Clear Vinyl, Nylex Corporation Limited, Australia, lot 0134 and 0030, respectively) was used.

Loss from solutions stored in PVC infusion bags. Quadruplicate lots of 500 mL of the required solutions were transferred to the infusion bag and stored, using the methods described earlier in Chapter 2, for periods of 8 h. Since it was found that an HPLC assay method modified from that proposed by Gigante and co-workers (1991) was not specific enough to determine benzocaine concentration in the effluent obtained from the distal end of the tubing due to the interference from material(s) leached from the tubing into the effluent (Appendix VI), UV spectrophotometry was used for quantification of benzocaine as well as the other solutes used in this study.

The solute concentration was read without dilution using a Cary double-beam scanning ultraviolet spectrophotometer at the wavelength of maximum absorbance for each substance determined prior to commencement of the sorption experiments, i.e., 275 and 285 nm for 4-aethylphenol and benzocaine, respectively. The wavelengths of maximum absorbance of other solutes have been given earlier in Chapter 2. For each sample, an equivalent solution without the drug was used as a blank. Control studies were performed using glass volumetric flasks and essentially the same procedure as for the PVC bags.

Simulated infusion. The sorption profile of each solute was obtained by running the aqueous solution through tubing using the methods

described earlier in Chapter 3. All experiments were run in duplicate and the conditions used are as described in Table 4.1. Drug analyses were carried out as described above.

Table 4.1. Conditions used in sorption studies of 4-aethylphenol and benzocaine into PVC tubings

Experiment	Solute	Tubing		Target flow rate ($mL.min^{-1}$)
		length (cm)	i.d. (cm)	
1	4-aethylphenol	40	0.8	0.6[a]
2	4-aethylphenol	80	0.8	1.0[a]
3	benzocaine	40	0.8	0.6[a]
4	benzocaine	100	0.5	1.2[b]

[a] Flow controlling needle (50 cm length, 0.25 mm i.d.) was used.
[b] Flow controlling needle (50cm length, 0.32 mm i.d.) contains a stainless steel wire (0.14 mm diameter, 73 mm length) through and beyond its entire length was used (see Figure 3.1c).

Data analysis. In all experiments, the data obtained is expressed as the fraction of the original concentration of solute remaining in solution (F_t) or as the fraction of the original concentration of solute in the effluent (F_t) at a specified time and is compared to the sorption value predicted from the physicochemical properties of the solute using the equations proposed in Chapter 2 (eqns.2.2, 2.3 and 2.5) and Chapter 3 (eqns.3.5, 3.8 to 3.11, 3.18 and 3.20) and that proposed previously by Roberts and co-workers (1991) (eqns.1.13 and 1.17). The calculating procedure used to compute the predicted values in dynamic conditions is similar to that described in Appendix IV. All graphs were constructed using Cricket Graph III (Computer Associates) on a Macintosh computer.

4.3. Results

4.3.1. Static conditions

Table 4.2 shows a comparison of the experimentally determined sorption number of selected solutes in 0.9% sodium chloride solution and values predicted from the sorption number of the same solute in water using eqn.2.5 proposed in Chapter 2.

Table 4.2. Observed and predicted logarithm of sorption number of solutes, from solutions stored in PVC bags for 8 hours[a]

Solute	log Sn		
	in water	in normal saline	
	observed	observed	predicted[b]
Phenol	-4.05 (0.23)	-4.00 (0.07)	-3.99
p-Bromophenol	-2.21 (0.03)	-2.17 (0.02)	-2.15
Methylacetophenone	-1.54 (0.00)	-1.49 (0.01)	-1.48
Nitrobenzene	-1.34 (0.03)	-1.31 (0.06)	-1.28
Thymol	-1.08 (0.03)	-1.02 (0.03)	-1.02

[a] Values in parentheses are the SD values.
[b] Using eqn.2.5.

Figure 4.1 shows the extent of sorption of each solute in 8 hours, obtained experimentally, and predicted from the calculated sorption

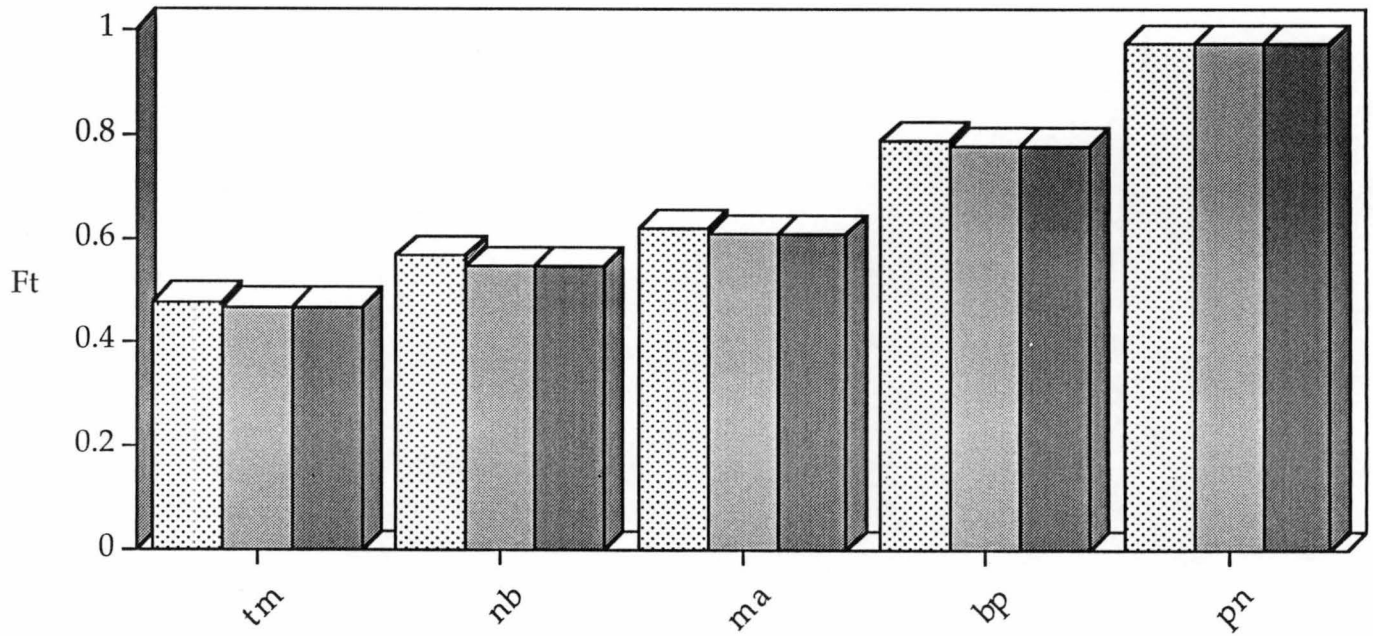


Figure 4.1 Fraction of solute remaining in solution stored in PVC bags for a period of 8 hours; tm=thymol, nb=nitrobenzene, ma=methylacetophenone, bp=*p*-bromophenol, pn=phenol. ⬚ in water (actual), ▒ and ▓ in 0.9% sodium chloride solution (actual and predicted, respectively).

numbers, given in Table 4.2, by means of eqn.1.13 proposed by Roberts and co-workers (1991).

Fractions remaining in solutions stored in PVC infusion bags for 8 hours, obtained experimentally for the model solutes and those reported previously for drug solutions stored in PVC infusion bags, from the same manufacturer, as those used in this study (Christiansen et al., 1980; Illum and Bundgaard, 1982) are compared, with the values predicted using eqn.1.13 (Roberts et al., 1991) and each of eqn.1.17 (Roberts et al., 1991), eqn.2.2 and eqn.2.3 (together with eqn.2.5 for cases where vehicle ionic strength is greater than zero) as proposed in Chapter 2, in Table 4.3.

4.3.2. Dynamic conditions

The fraction of the original concentration of 4-aethylphenol and benzocaine in the effluent from solution infused through PVC tubing of 0.4 cm internal diameter and 40 cm length at a flow rate of 0.6 $mL.min^{-1}$ are plotted as a function of time in Figures 4.2 and 4.3. The sorption profiles predicted using two sets of equations, i.e., equations 3.5, 3.8 and 3.9, and equations 3.5, 3.10 and 3.11, respectively, are also presented.

Figure 4.4 shows a comparison of the sorption profile of 4-aethylphenol from a solution infused through PVC tubing of 0.4 cm internal diameter and 80 cm length at a flow rate of 1.0 $mL.min^{-1}$ and that predicted using the results obtained from infusing the same solution through PVC tubing of 0.4 cm internal diameter and 40 cm length at a flow rate of 0.6 $mL.min^{-1}$ and equations 3.5, 3.18 and 3.20.

Table 4.3. Observed and predicted fraction of solutes/drugs remaining in solutions stored in 500-mL PVC bags for 8 hours[a]

Solute/drug	log P[b]	μ[c]	F_t			
			observed	predicted using eqn.1.13&		
				eqn.2.3	eqn.2.2	eqn.1.17
4-Aethylphenol	2.4	1.8	0.85[d]	0.81[e]	0.88	0.81
Benzocaine	1.9	3.6	0.89[d]	0.70[f]	0.63	0.87
Methylparaben	2.0	2.9	0.96[g]	-	0.86[h]	0.91[h]
Medazepam	4.1	2.3	(0.24)[g]	-	(0.27)	(0.25)
Diazepam	2.8	2.6	0.69[g]	-	0.66	0.74
			(0.41)[g]	-	(0.48)	(0.56)
Nitroglycerin	2.2	3.4	0.63[i]	-	0.62	0.84
			(0.46)[g]	-	(0.42)	(0.69)

[a] Values in parentheses are those obtained using 100-mL PVC bags.

[b] Obtained from Hansch and Leo, 1979 and Hansch, 1990b. An average value is used where there is more than one value reported.

[c] Obtained from McClellan, 1963 and Lien et al., 1979. The value of *p*-cresol is used for 4-aethylphenol.

[d] Determined experimentally in aqueous solution.

[e] Values used in calculation, $(V_I/100)=0.73$, $\pi^*=0.68$, $\beta=0.34$, $\alpha=0.60$, are estimated from those of *p*-cresol (Tayar et al., 1991) using the estimation rules (see Appendix I).

[f] Values used in calculation, $(V_I/100)=0.81$, $\pi^*=1.00$, $\beta=0.58$, $\alpha=0.30$, are estimated from those of methyl-4-aminobenzoate (Kamlet et al., 1988) using the estimation rules (see Appendix I).

[g] Obtained from the results reported previously for drugs in normal saline solution (Illum and Bundgaard, 1982).

[h] pH 7.8, pKa 8.4.

[i] Extrapolated from the results reported previously for nitroglycerin in dextrose 50 $mg.mL^{-1}$ solution (Christiansen et al., 1980).

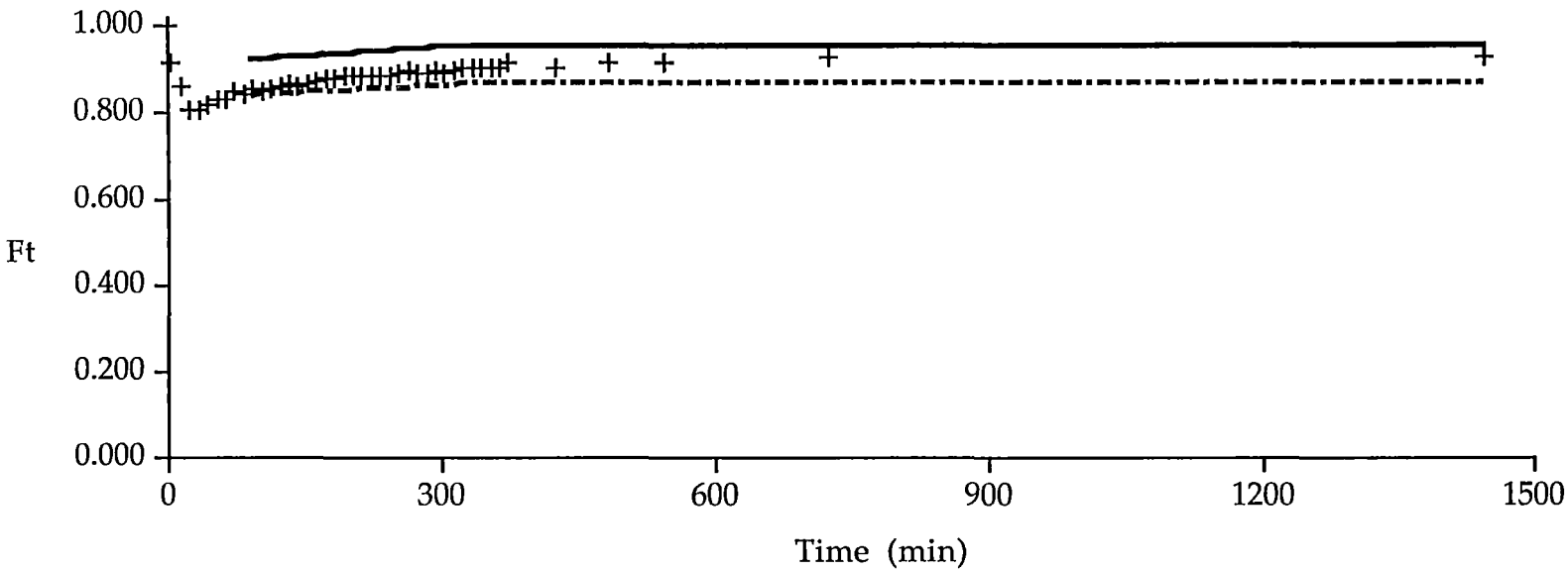


Figure 4.2. Prediction of the fraction of 4-aethylphenol remaining in the solution infused through PVC tubing of 0.4 cm diameter and 40 cm length with flow rate of 0.6 $mL.min^{-1}$. Data points represent the actual values and the solid and broken lines represents the predicted values using eqns.3.5, 3.8, 3.9 and 3.5, 3.10, 3.11, respectively.

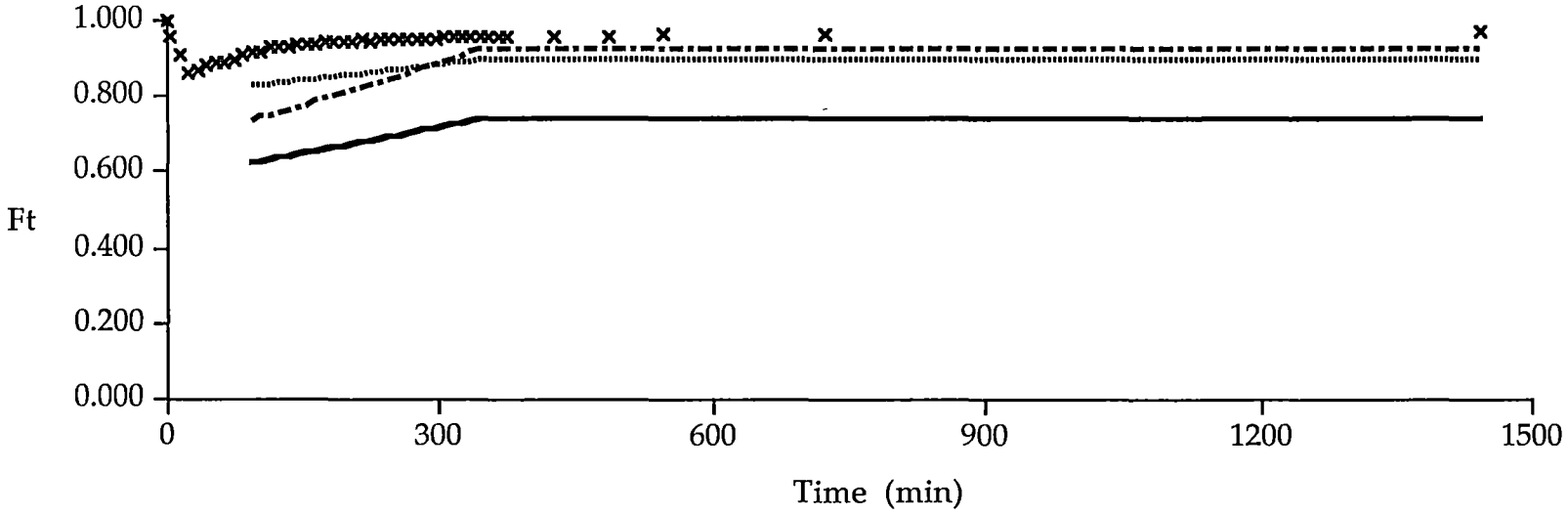


Figure 4.3. Prediction of the fraction of benzocaine remaining in the solution infused through PVC tubing of 0.4 cm diameter and 40 cm length with flow rate of 0.6 $mL.min^{-1}$. Data points represent the actual values and the broken line represents the predicted values using eqns.3.5, 3.10 and 3.11. The solid and the dotted lines represent the predicted values using eqns.3.5, 3.8 and 3.9 with μ=3.3 and 2.3, respectively.

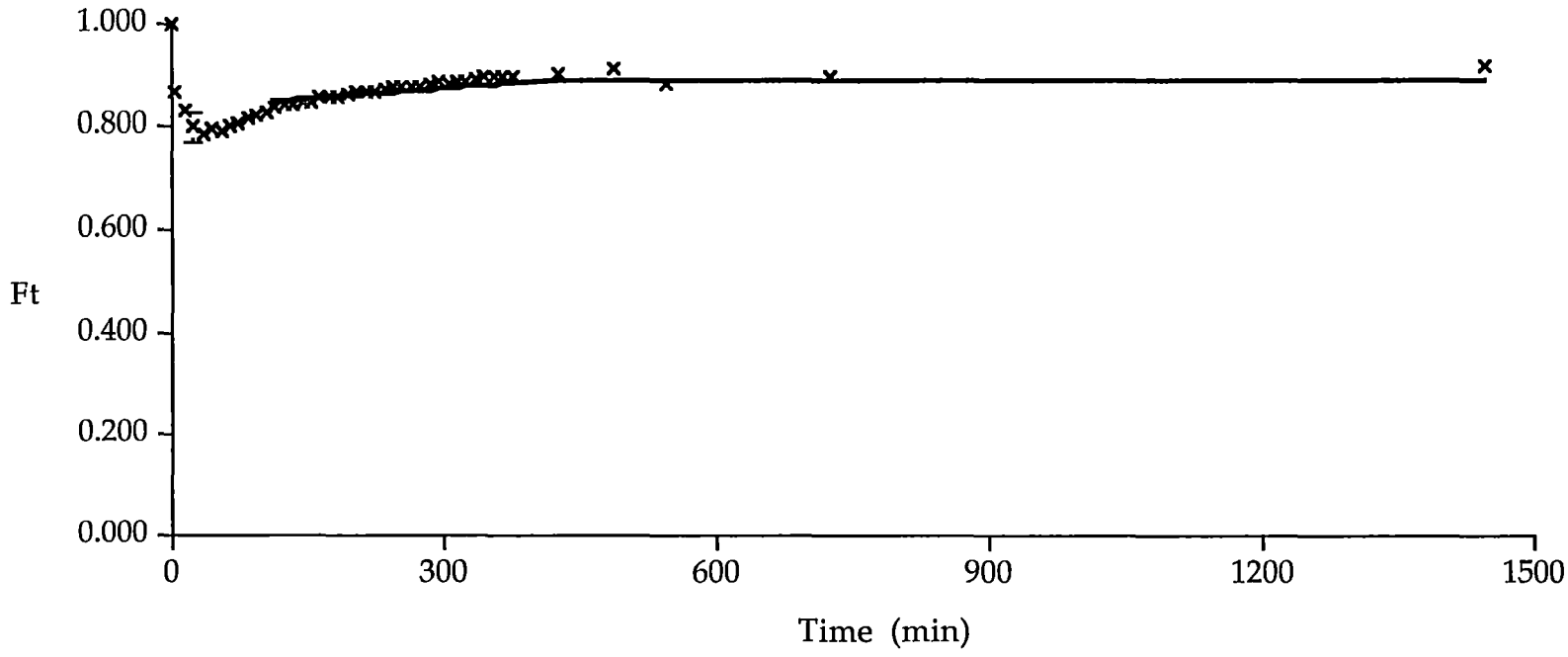


Figure 4.4. Prediction of the fraction of 4-aethylphenol remaining in the solution infused through PVC tubing of 0.4 cm diameter and 80 cm length with flow rate of 1.0 $mL.min^{-1}$. Data points represent the actual values and the solid line represents the predicted values using data obtained after infusing the same solution through tubing of 0.4 cm diameter and 40 cm length with flow rate of 0.6 $mL.min^{-1}$.

A comparison of the sorption profile of benzocaine in the solution infused through PVC tubing of 0.5 cm internal diameter and 100 cm length at a flow rate of 1.2 $mL.min^{-1}$ and that predicted using the results obtained from infusing the same solution through PVC tubing of 0.4 cm internal diameter and 40 cm length at a flow rate of 0.6 $mL.min^{-1}$ and equations 3.5, 3.18 and 3.20 is presented in Figure 4.5.

The availability of nitroglycerin from solutions infused from glass infusion bottles through plastic giving sets reported previously (Roberts et al., 1980) is compared with that predicted from the results obtained under another set of conditions (of differing flow rate) in the same study, using equations 3.5, 3.18 and 3.20, in Table 4.4. Similarly, a comparison of diazepam availability from solutions infused from glass bottles through PVC tubings reported previously (Mason et al., 1981) and that predicted from the results obtained under another set of conditions (of differing flow rate and tubing length) in the same study is presented in Table 4.5.

4.4. Discussion

From the results presented in Table 4.2 and Figures 4.1, it appears that eqn.2.5 can be used to predict the extent of sorption of solute from solution in the presence of electrolytes such as sodium chloride into PVC bags reasonably well provided that the extent of sorption of solute from aqueous solution into PVC bags, as expressed in terms of sorption number, is known. Furthermore it is shown that, for cases like phenol where the extent of sorption is small, the effect of the ionic strength of

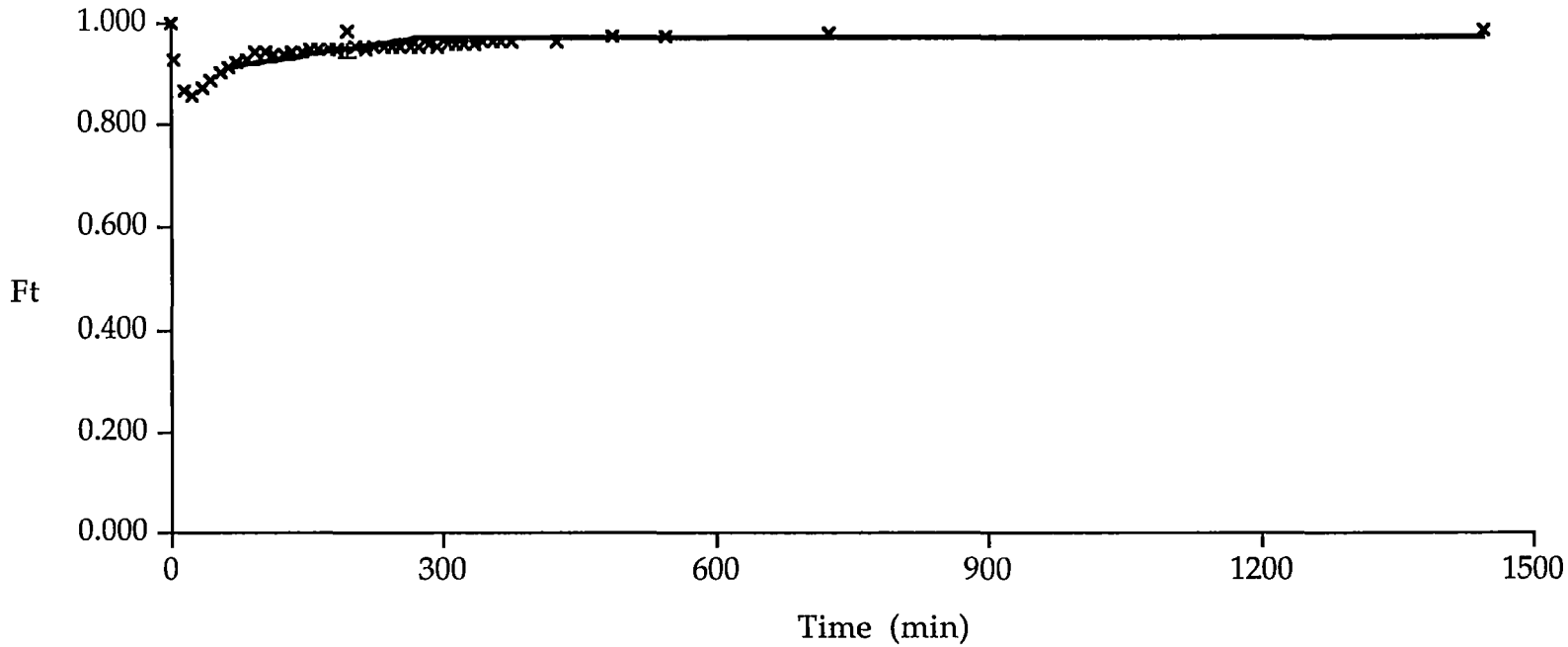


Figure 4.5. Prediction of the fraction of benzocaine remaining in the solution infused through PVC tubing of 0.5 cm diameter and 100 cm length with flow rate of 1.2 $mL.min^{-1}$. Data points represent the actual values and the solid line represents the predicted values using data obtained after infusing the same solution through tubing of 0.4 cm diameter and 40 cm length with flow rate of 0.6 $mL.min^{-1}$.

Table 4.4 Prediction of the availability of nitroglycerin from solutions infused from glass infusion bottles through plastic giving sets under various conditions using data read from graphical results reported previously by Roberts and co-workers (1980).

Time	Fraction of nitroglycerin in the effluent solution after infusing through tubing[a] at the indicated flow rate			
	0.75 mL.min^{-1}		0.23 mL.min^{-1}	
$(t_{sink} \times z)$[b]	Actual	Predicted[c]	Actual	Predicted[c]
z				
1	0.70	0.73	0.63	0.52
2	0.82	0.82	0.77	0.63
3	0.91	0.92	0.89	0.78
4	0.96	1.00	0.96	0.95
5	0.99	1.00	-	0.95
6	0.99	1.00	-	0.95

[a] tubing (Buretrol) of 7.9 cm^3 volume and 148 cm^2 surface area was used (Roberts et al., 1980).

[b] the values of t_{sink}, calculated by means of eqn.3.16, are 98.7 and 321.7 minutes for conditions using flow rate of 0.75 and 0.23 mL.min^{-1}, respectively; that is at z=1 time is either 98.7 or 321.7 minutes and at z=2 time is either 197.4 or 643.4 minutes, etc.

[c] using data obtained from infusing the same solution through the same type of tubing with flow rate of 0.52 mL.min^{-1}. The calculating procedure used is similar to that described in Appendix IV.

Table 4.5 Prediction of the fraction (Ft) of diazepam in the effluent of solution infused from glass infusion bottle through plastic tubing[a] under various conditions using data read from graphical results reported previously by Mason and co-workers (1981).

Condition used			Ft	
Tubing length (cm)	Flow rate ($mL.min^{-1}$)	Collecting time (min)	Actual	Predicted[b]
100	2.02	19.8	0.76	0.74
		39.5	0.80	0.78
		59.3	0.86	0.83
		79.0	0.86	0.88
		98.8	0.86	0.88
198	0.23	343.6	0.16	0.03
		687.2	0.34	0.04
198	0.53	149.1	0.36	0.38
		298.2	0.50	0.43
198	0.95	83.2	0.52	0.51
		166.4	0.60	0.60
198	1.97	40.1	0.67	0.58
		80.2	0.62	0.73
198	4.40	18.0	0.78	0.73
		36.0	0.80	0.83

[a] Abbott tubing (Venoset 78) of 2.54 mm inside diameter.

[b] using data obtained from infusing the same solution through the same type of tubing of 150 cm length using flow rate of 2.02 $mL.min^{-1}$. The calculating procedure used is similar to that described in Appendix IV.

normal saline on the extent of sorption of solute into PVC bags is negligible.

Although a reasonable correlation has been shown to exist between the logarithm of the sorption numbers of a series of benzene derivatives, with one hydrogen bonding group, and the octanol-water partition coefficients considered together with the dipole moment values, as shown by eqn.2.2 in Chapter 2, it was found that the ability of this equation to predict the sorption number of other structurally different solutes is limited. The results presented in Table 4.3 show that eqn.2.2 can be used to predict the fractions of each of diazepam and nitroglycerin remaining in a solution stored in a PVC bag of either of two different sizes for a period of 8 hours with much better accuracy than the equation using only octanol-water partition coefficients proposed previously (eqn.1.17) (Roberts et al., 1991). For each of 4-aethylphenol and medazepam, which have a dipole moment in the range of 1.8 to 2.3, both eqn.2.2 and eqn.1.17 appear to have an ability to accurately predict the extent of sorption of solute from a solution stored in a PVC bag for 8 hours.

Furthermore, eqn.1.17 seems to be the more satisfactory model, when compared with eqn.2.2, in prediction of the fractions of benzocaine and methylparaben remaining in solutions stored in PVC bags for a period of 8 hours. As benzocaine and methylparaben are structurally similar in that both solutes are disubstituted benzene derivatives with an electron-donor substituent para to a mesomeric electron-acceptor substituent, it may be concluded that the use of eqn.2.2 appears somewhat promising for estimation of the extent of sorption into PVC bags of aliphatic and

aromatic solutes which are not disubstituted benzene derivatives with an electron-donor substituent para to a mesomeric electron-acceptor substituent. The limitation of eqn.2.2 might be due to the vector nature of the dipole moment parameter used in this equation. The prediction equation derived from the data obtained from one particular congeneric series is, therefore, not always applicable to all solutes of such diverse structures unless subgroups are considered.

Although it has been found that the use of the prediction equation of sorption number using the octanol-water partition coefficients together with the dipole moment values of the solute (eqn.2.2) is not entirely satisfactory, the influence of the noncharged electronic effect of the solute, which can be represented by its electric dipole moment, on its sorption behaviour has been illustrated.

It is suggested, from the results presented in Chapter 2, that eqn.1.17 (Roberts et al., 1991), which is shown to satisfactorily describe the sorption behaviour of benzocaine and methylparaben into PVC bags, may be the simplified form of eqn.2.2 where the dipole moment term in eqn.2.2 is replaced by the value of 2.3. If this is the case, it would seem possible that eqn.2.2 may be the general form of an equation suitable for practical use in the prediction of the sorption behaviour of all solutes from solutions into PVC bags where the molecular dipole moment term used in this equation should be replaced by an arbitrary value of 2.3, when applied to certain groups of solutes such as disubstituted benzene derivatives with an electron-donor substituent para to a mesomeric electron-acceptor substituent.

Similarly, the prediction equation using intrinsic molecular volume and solvatochromic parameters describes the extent of sorption of 4-aethylphenol from solution stored in PVC bags quite well yet it fails to describe the extent of sorption of benzocaine adequately. This also indicates that, in order to predict the extent of sorption of any solute accurately, the prediction equation derived from the data obtained from other structually similar solutes is required.

The hypothesis that a particular prediction equation is required for each congeneric series of solutes has to be tested using wider ranges of structurally different solutes; it appears, nevertheless, that no one model can adequately describe all of the sorption behaviour into PVC bags for all the varieties of solute chemical structures and properties.

It is seen in Figures 4.2 and 4.3, that both of the prediction equations using dipole moments (eqns.3.8 and 3.9) and that using intrinsic molecular volume and solvatochromic parameters (eqns. 3.10 and 3.11) can be used to estimate the extent of sorption of 4-aethylphenol from solution infused through PVC tubing of 0.4 cm internal diameter and 40 cm length at a flow rate of 0.6 $mL.min^{-1}$ reasonably well yet it fails to describe the extent of sorption of benzocaine under the same conditions adequately. As this result is similar to that obtained from the same solutes in static conditions, similar conclusions as that described above for sorption of solutes into PVC bags may be made for the sorption of solutes from solution infused through PVC tubings. Surprisingly, when the arbitrary value of 2.3 obtained from the sorption study in static condition is used instead of the actual molecular dipole moment of

benzocaine in the prediction equations (eqns.3.8 and 3.9) much better prediction is obtained as shown in Figure 4.3.

When the results obtained from infusing 4-aethylphenol or benzocaine solution through PVC tubing of 0.4 cm internal diameter and 40 cm length with flow rate of 0.6 $mL.min^{-1}$ are used to predict the availability of the same solution, infused through tubing made of the same PVC material, under differing conditions of tubing diameter, tubing length, and/or flow rate, as shown in Figures 4.4 and 4.5, it is found that a satisfactory prediction is obtained in both cases.

To examine if this prediction approach, which is based on the chemical similarity theory (Bosworth, 1956), is applicable to other types of solutes and PVC tubing, published results in which the complete description of the tubing used is provided are used in this study. It is seen in Tables 4.4 and 4.5, that the availability of both nitroglycerin and diazepam from solutions infused from glass bottles through PVC tubing under one particular condition of tubing length and infusion rate can be adequately predicted using the results obtained from another condition.

It is hoped that the present approach (eqns.3.5, 3.18, 3.20) may be useful in predicting the drug loss, from a solution infused from a glass container through a PVC administration set under various clinical conditions. This approach can be applied in conditions in which one or more of tubing diameter, tubing length and infusion rate may be varied, provided that the reference values of fraction of solute in the effluent solution collected from the distal end of the tubing at two time points, i.e., at time t equal to t_{sink} and at another time t at which $t_{sink} < t \leq 4t_{sink}$,

obtained from the same drug and PVC material under a specific set of conditions is known. It is suggested that caution should be taken when this prediction approach is applied to conditions where a flow rate lower than 0.5 $mL.min^{-1}$ is to be used.

CHAPTER 5. EVALUATION OF A PLASTICIZER-WATER SYSTEM FOR MODELLING SOLUTE SORPTION INTO PVC MATERIALS

5.1. Introduction

It has been shown previously that the plasticizer can be extracted from a PVC sheet by using an organic solvent such as methanol (Kim et al., 1976). Ultraviolet absorption spectra and infrared spectra can then be obtained from the methanolic extracts to characterize the nature of the plasticizer. A time-release profile of the plasticizer from the surface of the plastic sheet into methanol can also be made.

As the sorption capacity of the PVC material has been shown to be greatly increased by the addition of a plasticizer to the plastic formulation (Bray, 1983; Weir et al., 1985), the plasticizer-water partition coefficients were determined for the model solutes used in this study and the utility of these values in predicting the sorption behaviour of the model solutes by PVC materials was evaluated.

5.2. Materials and Methods

5.2.1. Characterization of plasticizer(s)

Materials. PVC samples cut from an unprinted area of a PVC infusion bag containing 500 mL of 0.9% sodium chloride (Travenol, Baxter Healthcare International, batch A73R8) were used. Samples of 0.2 g weight cut cross-sectionally from PVC tubings of 0.5, 0.6 and 0.8 cm internal diameter (Food Contact-Clear Vinyl, Nylex Corporation

Limited, Australia, lot 0134, lot 0099 and lot 0030, respectively) were also studied. A reference sample of DEHP was obtained from Aldrich, U.S.A. (lot 0403 DL).

Extraction and Characterization of the plasticizer. The plastic sample obtained from the PVC infusion bag or the PVC tubing of 3 different sizes was cut into small pieces and 0.2 g pieces of the plastic were then transfered to a glass jar, fitted with a screw cap, containing 20 mL of methanol. The glass jar was shaken continuously using a flask shaker. At the end of a 24-hour period, the ultraviolet absorption spectra of aliquots of the solvent were determined using a Pye Unicam SP8-100 spectrophotometer. All experiments were performed in duplicate.

The methanolic extracts were evaporated to dryness under nitrogen gas. Infrared spectra were determined using a Digilab FT5-20E Fourier transform infrared spectrometer. All samples were run as thin film on ZnSe plates with 32 scans. The resolution used was 4 cm^{-1}. Ultraviolet absorption and infrared spectra were also obtained for the $2.4x10^{-2}$ $mg.mL^{-1}$ DEHP in methanol and for pure DEHP, respectively.

Release of the plasticizer from PVC surface. PVC samples of approximately 0.2 g weight were obtained from a PVC bag cut into rectangular shapes (2x2.5 cm) or from the PVC tubings (of 3 different sizes) cut cross-sectionally into a cylindrical shape. Each plastic sample was stored in 20 mL of methanol for varying periods. The quantity of DEHP released was determined using a Pye Unicam SP8-100 spectrophotometer at the maximum absorbance determined previously from a full (scanning) ultraviolet absorbance spectrum and reference to a

linear Beer's law plot prepared previously. DEHP in methanol was found to exhibit its maximum absorbance at a wavelength of 225nm. This compound obeys Beer's law over a concentration range of $1.0x10^{-2}$ to $3.6x10^{-2}$ $mg.mL^{-1}$. All experiments were run in duplicate.

5.2.2. Determination of DEHP-water partition coefficients

Materials. The solutes used in this study, acetophenone, nitrobenzene, phenol, *p*-chlorophenol, *p*-bromophenol, *o*-xylenol, *p*-methyl-acetophenone, chloroxylenol and thymol, have been described previously (Chapters 2 and 3). DEHP was obtained from Aldrich, U.S.A. (lot 0403 DL).

Chlorocresol was excluded from the model solute set used in this study because it shows a maximum absorbance in the same wavelength range as that of DEHP. All chemicals were laboratory grade and were used as received without further purification. The solutions were prepared in glass distilled water.

Methods. A known volume of distilled water was saturated with DEHP before a known amount of solute was added. An aliquot of this solution was then added to a known volume of DEHP, which had been saturated with water before use, in a glass container fitted with a glass stopper. The solute concentrations and initial volume ratios of aqueous to organic phase used are shown in Table 5.1. The glass containers were shaken continuously using a mechanical shaker, as shown diagrammatically in Appendix VII, at a controlled room temperature (20 ± 2°C) until equilibrium was reached. For each solute, the approximate

time required for equilibrium to be achieved was determined prior to the commencement of this study by using the same procedure as that used in the actual experiment and the aqueous phase was analyzed periodically until equilibrium was achieved.

Table 5.1. Determination of DEHP-water partition coefficient; solute concentrations and initial volume ratios of aqueous and organic phases.

Solute	Initial solute concentration in aqueous phase, M ($x10^5$)	Ratio of aqueous phase to organic phase
Acetophenone	5.23	124 : 3
Nitrobenzene	12.45	125 : 2
Phenol	73.39	40 : 1
o-Xylenol	49.93	60 : 1
Methylacetophenone	4.19	40 : 1
p-Chlorophenol	54.49	83 : 2
p-Bromophenol	50.41	45 : 1
Thymol	42.50	100 : 1
Chloroxylenol	71.00	100 : 1

When equilibrium had been reached, the phases were separated. To achieve as complete a separation of aqueous and organic phases as possible, the aqueous phase was centrifuged at 3000 rpm for 15 min prior to assay. The aqueous phase was then analysed using a UV spectrophotometer as described in Chapter 2. Each DEHP-water partition coefficient was determined in duplicate.

5.3. Results and Discussion

5.3.1. Characterization of plasticizer(s)

The ultraviolet absorption and infrared spectra of the extracts and of pure DEHP are shown in Figures 5.1 to 5.6. It can be seen that the plasticizer used in both PVC bags and tubings is DEHP since the ultraviolet absorption spectra as well as the infrared spectra of the extracts are identical to those of pure DEHP.

When the amount of DEHP released from the PVC infusion bags is plotted against time (Figure 5.7), the release of DEHP from the infusion bag surface appears to consist of two steps. The curve is parabolic for a short time. After about 24 hours, the amount of DEHP released increases linearly.

The release profiles of DEHP from the surface of the tubings of 0.5, 0.6, and 0.8 cm internal diameter are also shown in Figure 5.7. It can be seen that the release profiles of DEHP from the surface of the tubings of three different sizes are similar to that obtained from the PVC infusion bags, i.e., they are parabolic at first and then become linear after about 24 hours.

From the results obtained in this study, it is seen that DEHP was used in both the PVC bag and the PVC tubing formulations. It is suggested that the mechanism of the two-stage release process of DEHP from the surface of the PVC bag and the PVC tubing can be described as follows. When the plastic sheet is immersed in methanol, the surface plasticizer

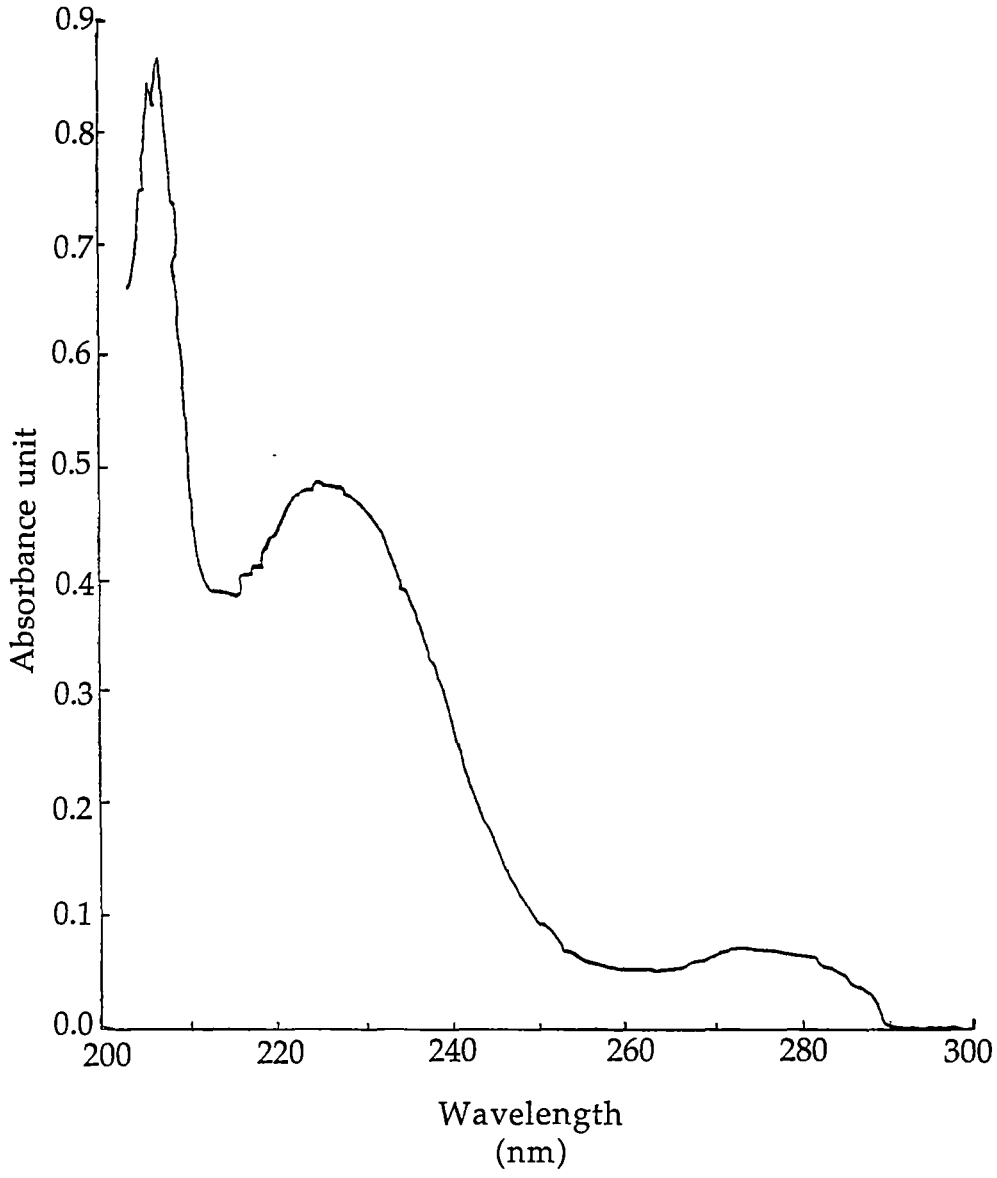


Figure 5.1. An ultraviolet spectrum of the methanolic extract from the surface of a PVC bag.

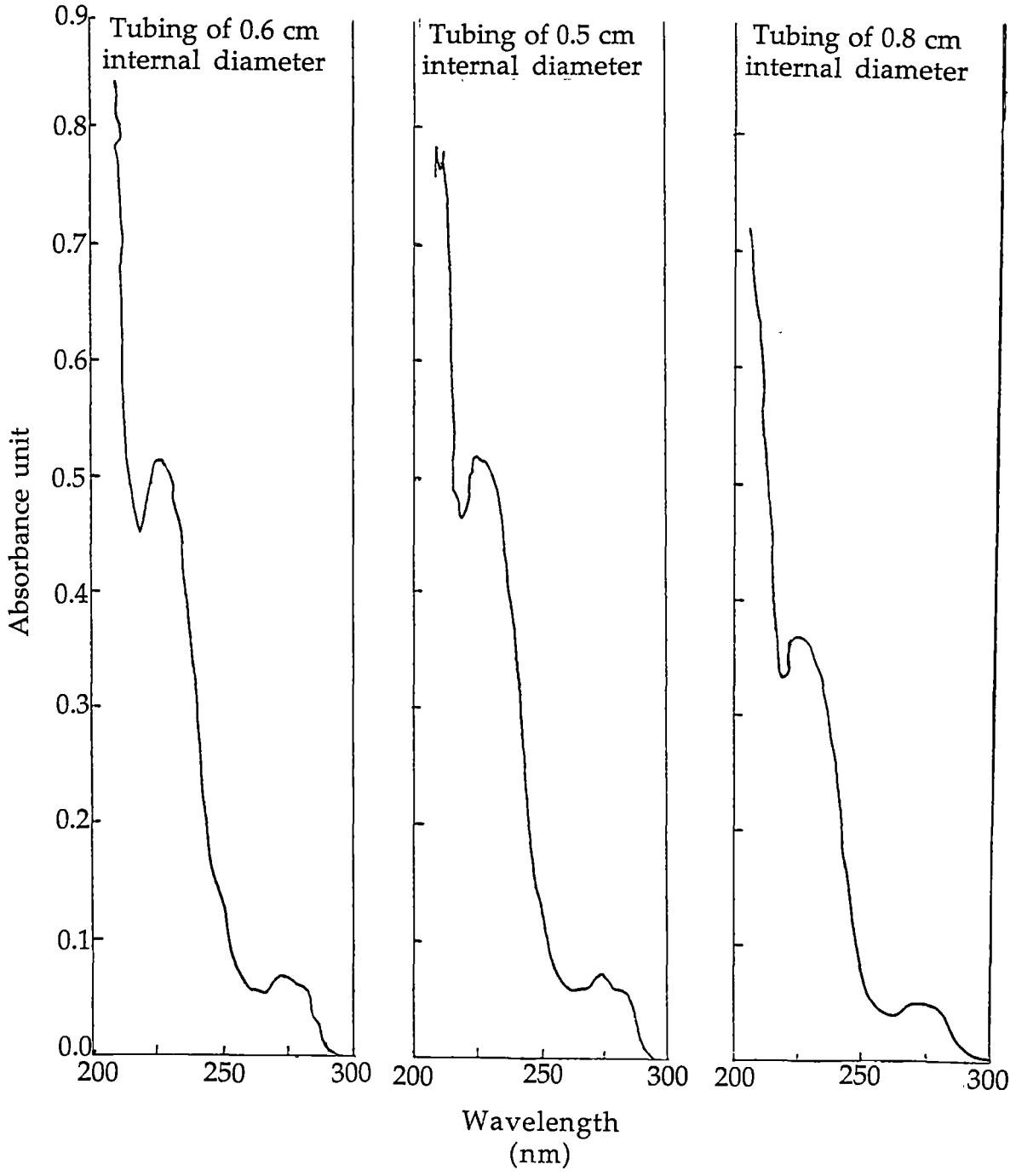


Figure 5.2. Ultraviolet spectra of the methanolic extract from the surface of the PVC tubings.

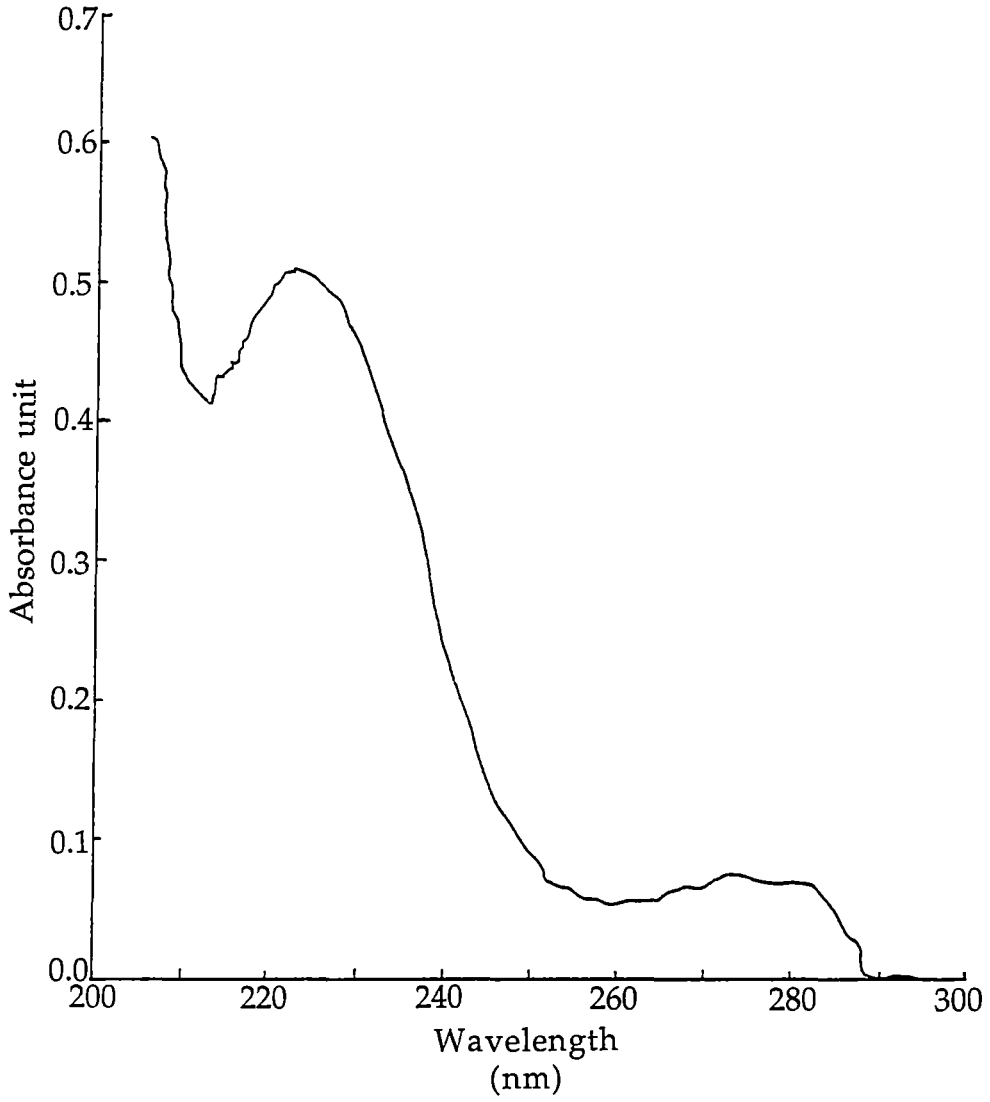


Figure 5.3. An ultraviolet spectrum of 2.4 mg.mL^{-1} DEHP in methanol.

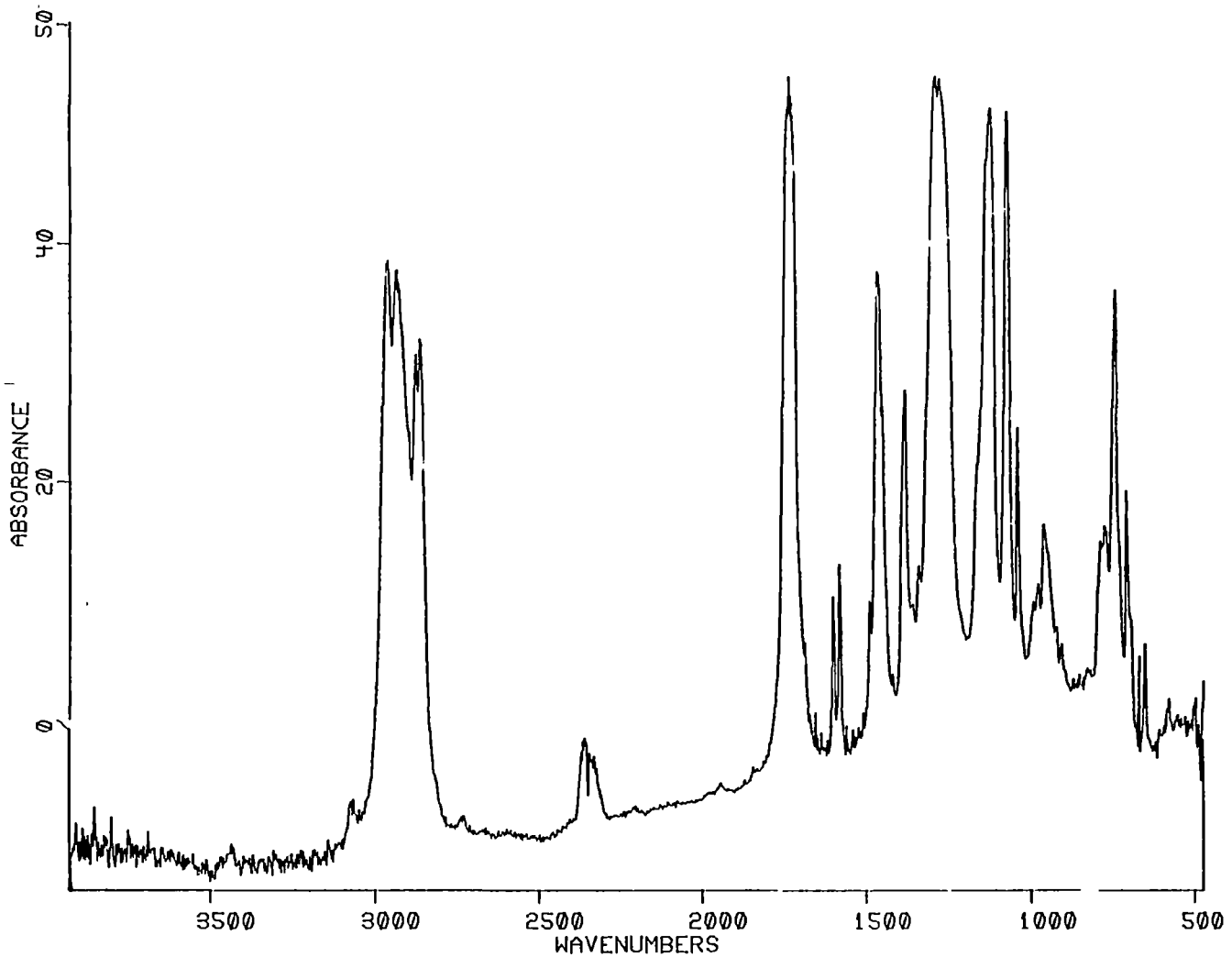


Figure 5.4. An infrared spectrum of the methanolic extract from the surface of a PVC bag.

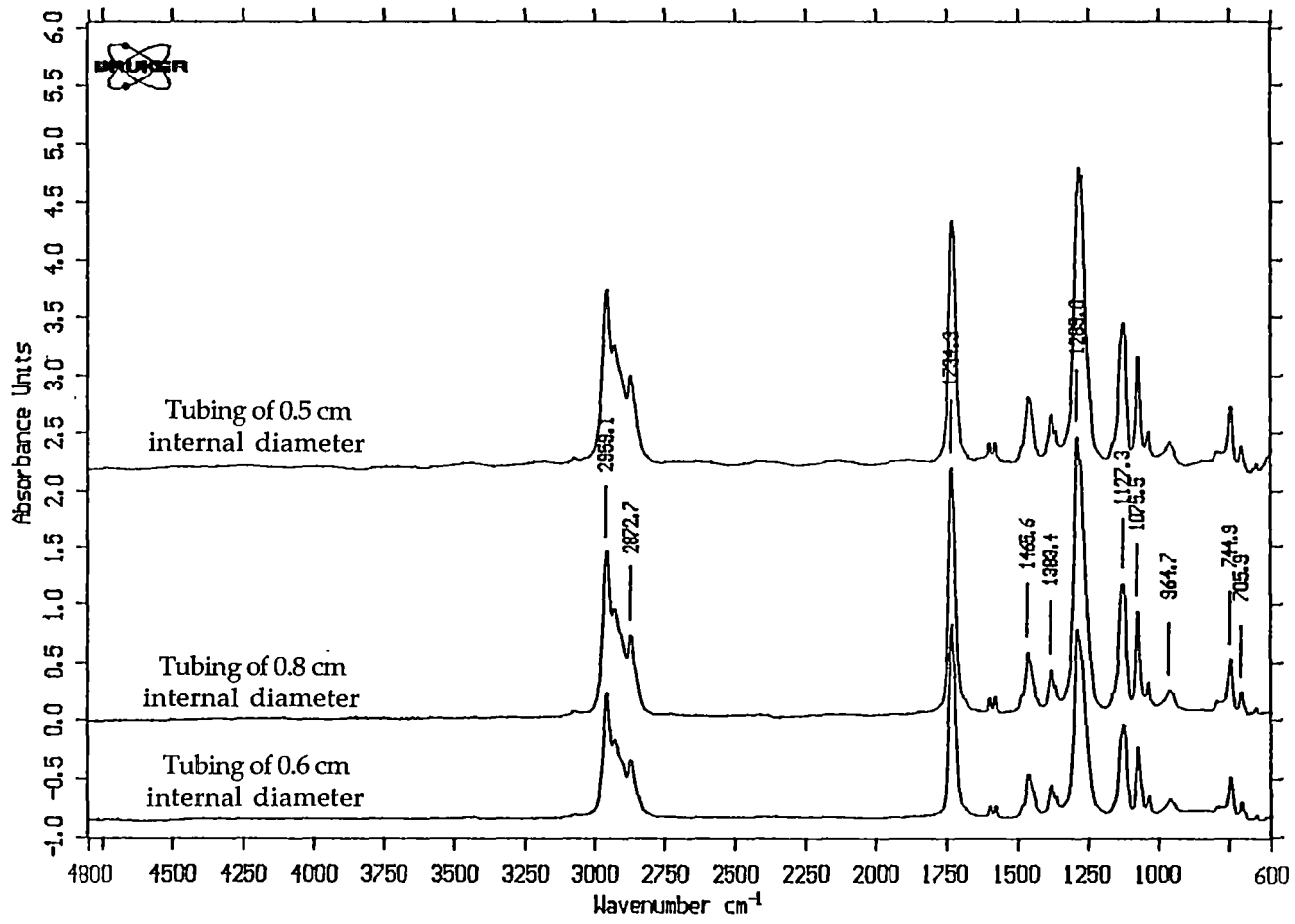


Figure 5.5. Infrared spectra of the methanolic extract from the surface of the PVC tubings.

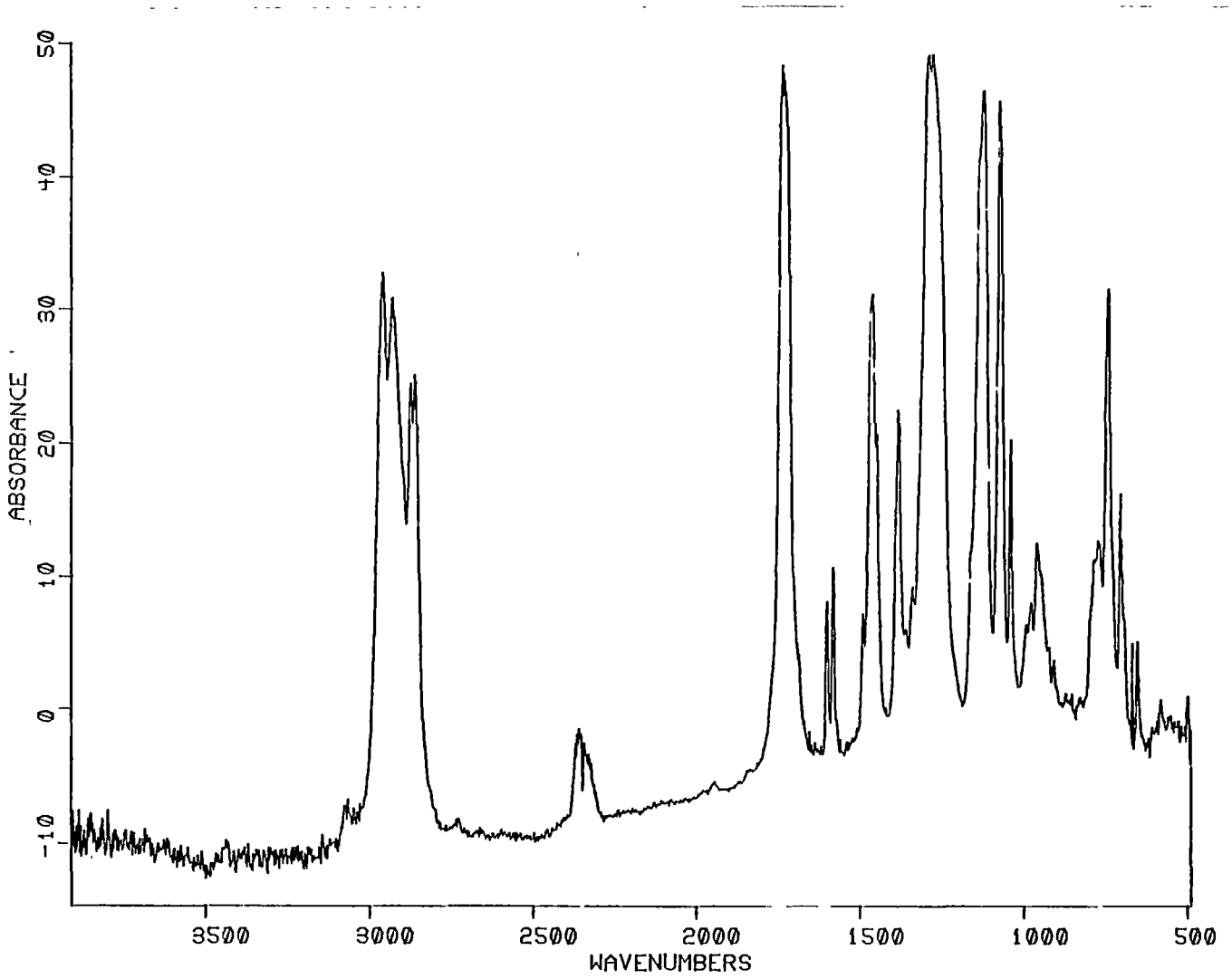


Figure 5.6. An infrared spectrum of pure DEHP.

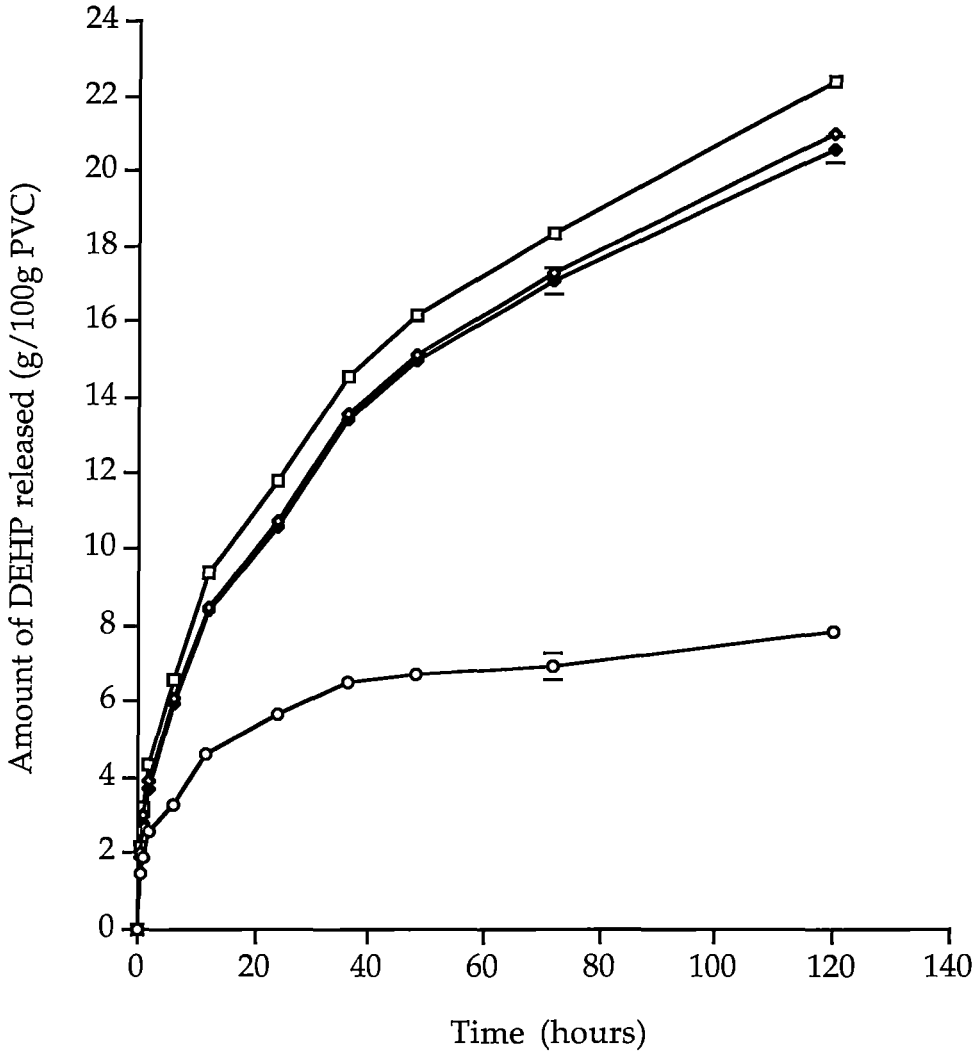


Figure 5.7. Release profile of DEHP from the surface of PVC samples; —o— PVC bags, —◇— Tubing of 0.5 cm i.d., —□— Tubing of 0.6 cm i.d., —◆— Tubing of 0.8 cm i.d.

is initially removed by a dissolution process. In the second stage, the surface plasticizer is renewed by replacement from the bulk plasticizer due to the concentration gradient. The diffusion of the bulk plasticizer to the plastic surface is found to obey Fick's law of diffusion since a linear relationship is obtained between the amount of DEHP released and time.

This suggested mechanism is consistent with results reported previously for the release of a plasticizer from a PVC sheet used in the fabrication of blood storage bags (Kim et al., 1976). A free surface plasticizer was also found on the inner walls of the PVC tubing used in dialysis (Fayz et al., 1977). It is probably reasonable to conclude that the DEHP plasticizer in the PVC bags and tubings used in the present work can initially be regarded as being either in the surface or in the bulk, according to its orientation in the PVC matrix. The bulk plasticizer can probably be regarded as a number of discrete particles of irregular size and shape randomly embedded in the PVC matrix while the surface plasticizer may exist in the form of a discontinuous film or small particles distributed on the PVC surface.

The surface plasticizer may be that which is used in surface coating, which helps enhance the flow and leveling properties of a material during application and helps reduce the brittleness of the dried plastic film (Rudin, 1982), or merely the bulk plasticizer which has migrated to the surface of a plastic sheet (Wang and Chien, 1984). This appears to be the case because, from the results obtained in Chapter 3, the configuration of a plot of the fraction of the initial concentration of the solute in the solution delivered at the distal end of the PVC tubing at

early times is well explained using the biexponential equation, eqn.3.4, which is based on the assumption that there are two groups of plasticizer, i.e., surface and bulk plasticizers, in the PVC tubing formulation (see Appendix II).

5.3.2. Determination of DEHP-water partition coefficients

The DEHP-water partition coefficients of the solutes are shown in Table 5.2.

Table 5.2. Logarithm of DEHP-water partition coefficients (log P_{DEHP}), logarithm of the sorption number (log Sn), constants a_2 and b_2 determined experimentally in this study (Chapter 5, 2 and 3, respectively) together with the literature logarithm of octanol-water partition coefficients (log $P_{octanol}$) of the solutes used in this study.

Solute	(log P_{DEHP})[a]	(log $P_{octanol}$)[b]	(log Sn)[a]	$(a_2)^c$	$(b_2)^c$ (x10^4)
Acetophenone	1.21	1.66	-2.20	0.6372	-6.6920
	(0.02)		(0.00)	(0.0070)	(0.4908)
Nitrobenzene	2.15	1.84	-1.35	0.4303	-10.0000
	(0.04)		(0.03)	(0.0069)	(0.6968)
Phenol	0.98	1.28	-4.00	0.9662	-0.4538
	(0.08)		(0.23)	(0.0022)	(0.1082)
o-Xylenol	1.89	2.23	-2.76	0.8724	-2.2250
	(0.01)		(0.03)	(0.0093)	(0.5103)
Methylacetophenone	2.04	2.28	-1.54	0.5570	-6.0380
	(0.16)		(0.00)	(0.0066)	(0.5261)
p-Chlorophenol	1.91	2.42	-2.48	0.8607	-2.4000
	(0.16)		(0.01)	(0.0092)	(0.5103)
p-Bromophenol	2.12	2.60	-2.21	0.8439	-2.3400
	(0.14)		(0.03)	(0.0110)	(0.6203)
Thymol	2.72	3.30	-1.07	0.5754	-4.9300
	(0.11)		(0.03)	(0.0059)	(0.4507)
Chloroxylenol	3.04	3.48	-1.07	0.6179	-5.1500
	(0.03)		(0.00)	(0.0050)	(0.3564)

[a] Values in parentheses are the SD values.
[b] obtained from Hansch and Leo, 1979. An average value is used where there is more than one value reported.
[c] Values in parentheses are the standard error of the coefficients.

Figure 5.8 shows the relationship between the literature octanol-water partition coefficients (Hansch and Leo, 1979) and the DEHP-water partition coefficients determined experimentally for the solutes used in this work. The relationship is described by the following regression equation:

$$\log P_{DEHP} = 0.06 + 0.83 \log P_{octanol} \quad (5.1)$$
$$(n = 9; r = 0.930; SE = 0.25; F = 45.11)$$

In order to evaluate the ability of the DEHP-water system to model the PVC-solute interaction, the correlations between the extent of sorption by the PVC infusion bag (i.e., the sorption numbers for solute uptake), or the constants a_2 and b_2 (see equation 3.5) for solute uptake by the PVC tubing, and the DEHP-water partition coefficients were examined.

Figure 5.9 shows the relationship between the DEHP-water partition coefficients and the logarithm of the sorption numbers of the model solutes. The regression equation is:

$$\log Sn = -4.52 + 1.22 \log P_{DEHP} \quad (5.2)$$
$$(n = 9; r = 0.829; SE = 0.57 ; F = 15.40)$$

For the PVC tubing system, it was found that the correlations between the constants a_2 or b_2 and DEHP-water partition coefficients were not significant ($p>0.05$).

It is seen in Figure 5.8 that the octanol-water partition coefficients and DEHP-water partition coefficients are linearly related.

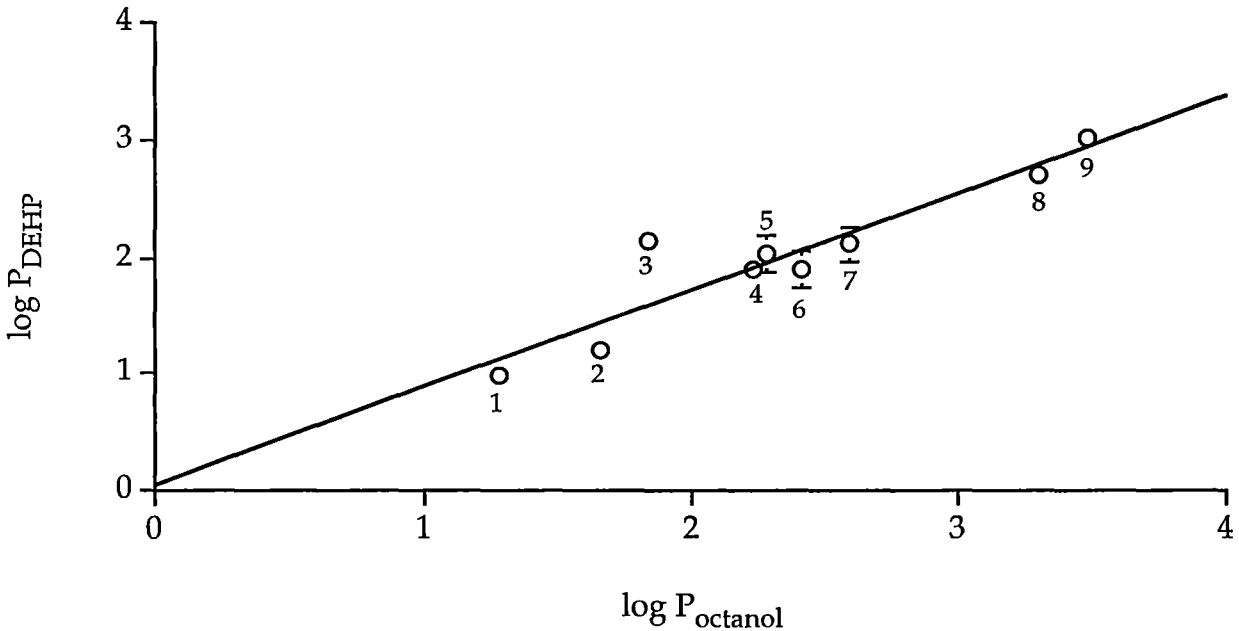


Figure 5.8. Relationship between the octanol-water partition coefficients and DEHP-water partition coefficients; 1=phenol, 2=acetophenone, 3=nitrobenzene, 4=*o*-xylenol, 5=methylacetophenone, 6=*p*-chlorophenol, 7=*p*-bromophenol, 8=thymol, 9=chloroxylenol. The solid line is a linear fit to the data.

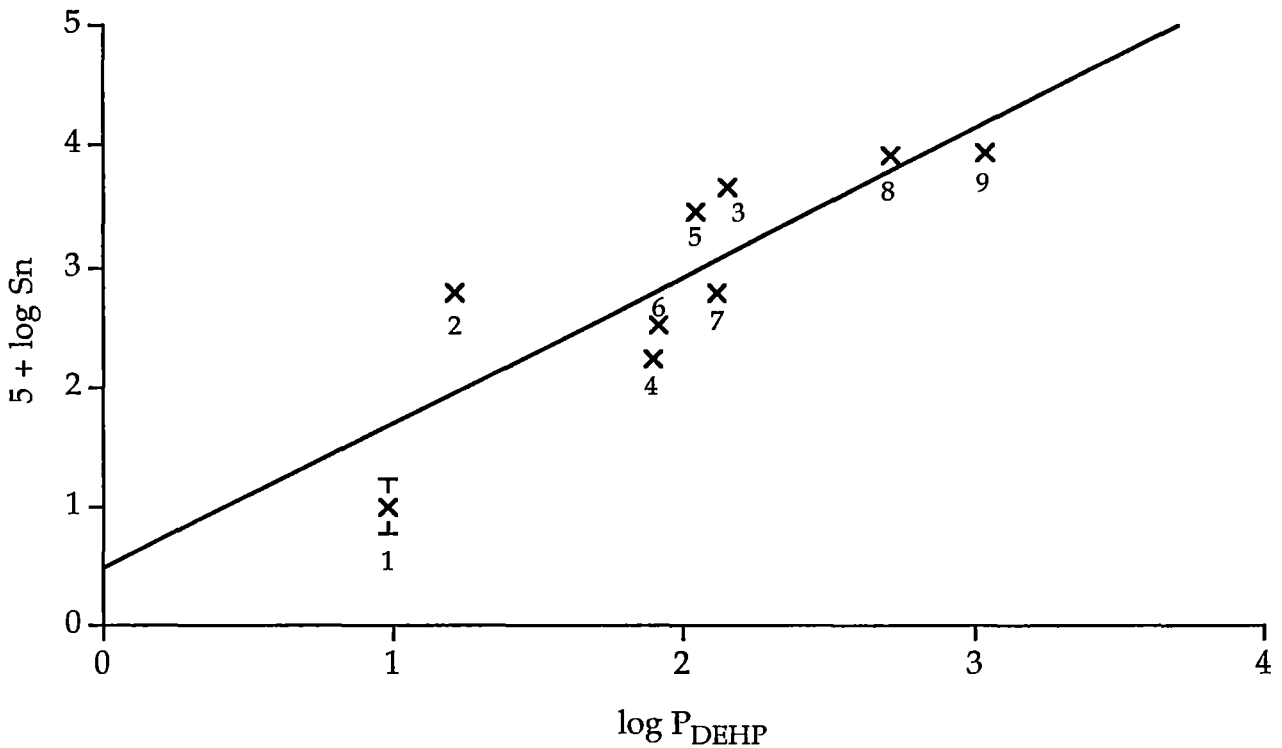


Figure 5.9. Relationship between the logarithm of sorption numbers and the DEHP-water partition coefficients; 1=phenol, 2=acetophenone, 3=nitrobenzene, 4=*o*-xylenol, 5=methylacetophenone, 6=*p*-chlorophenol, 7=*p*-bromophenol, 8=thymol, 9=chloroxylenol. The solid line is a linear fit to the data.

Such a relationship was apparently first expressed by Collander (1951) in precise terms as follows:

$$\log P_2 = a \log P_1 + b \qquad (5.3)$$

where the subscripts 1 and 2 refer to solvent systems 1 and 2, respectively. This suggests that both DEHP and octanol have similar physical properties and that the DEHP-water partition coefficient of any solute can be estimated if its octanol-water partition coefficient value is known. Eqn.5.1 is only valid, however, when the solute of interest and the solutes used in derivation of this equation have similar properties.

Although plasticizers such as DEHP have been reported to have a major influence on the sorption behaviour of plasticized PVC because of their highly lipophilic nature and considerable concentration in the PVC material (Bray, 1983; Jenke, 1993), it was found that a simple system based on the solute DEHP-water partition coefficient is not adequate for the accurate prediction of the sorption behaviour of the solutes into PVC (see eqn.5.2). This result is consistent with that reported by Jenke (1993) who suggested that the ability of a single system, such as DEHP or PVC resin, to model the PVC-solute interaction was limited because of the multiple interaction properties of PVC which should be expressed more appropriately as the mass weighted average of the properties of its individual (major) components, i.e., the polymer and the plasticizer. A similar type of multiple mechanism was also proposed by Bray (1983) to describe the sorption behaviour of benzocaine by PVC material. The use of unplasticized PVC dry blends (PVC resin) to represent PVC by these investigators might not, however, have been appropriate, because PVC

sheets are more likely to have a definitive structure than is a simple physical mixture of its individual components.

The considerable uptake of benzocaine by the unplasticized PVC dry blends reported by Bray (1983) might possibly be due mainly to the entanglement of the solute molecules in the irregular structure of the PVC resin. Furthermore, Weir and co-workers (1985) reported that the concentrations of amiodarone, a drug with a high affinity for plasticized PVC containers, did not decrease appreciably after storage in rigid (unplasticized) PVC bottles. Thus, it seems probable that the interaction between the solute and the plasticized PVC containers or i.v. administration sets, which can contain as much as 40 % of the DEHP plasticizer (Singh, et al., 1972), was attributable to the effect of DEHP alone.

Despite the fact that DEHP appears to have a large influence on the binding properties of the plasticized PVC materials, the results obtained in this work and those reported by Jenke (1993) show that the logarithm of the DEHP-water partition coefficient alone is not effective in terms of its ability to adequately mimic (or predict) the behaviour of the plasticized PVC materials. Furthermore, it was found that the use of the logarithm of the DEHP-water partition coefficient to predict the logarithm of sorption number (eqn.5.2) is no better than that of the logarithm of the octanol-water partition coefficient presented previously by Roberts and co-workers (1991) (eqn.1.17). This might be due to a modification of the characteristics of the plasticizer which may occur during the processing of the dryblend into the plastic film. As a result, the behaviour of DEHP molecules in a plasticized PVC formulation and

the behaviour of DEHP molecules in pure DEHP liquid may not be the same. This modification might be related to geometrical restrictions since the plasticizer molecules must be orientated between polymer segments in order to reduce the intensity of polymer-polymer interactions.

In addition, PVC plasticizers like DEHP are found to have specific interactions with the polymer as these plasticizers will reduce the effective number of polymer-polymer contacts by selectively solvating the polymer at the contact points (Rudin, 1982). The influence of the intermolecular forces between the plasticizer molecules and the polymer, and the arrangement of the plasticizer molecules in the composite structure, may provide an explanation of experimental observations of solute sorption by plasticized PVC system which can not be explained by the behaviour of the pure plasticizer alone.

CHAPTER 6. SUMMARY

In this work, the sorption of a number of model solutes from solutions stored in PVC infusion containers or infused through PVC tubings has been studied under various conditions. The results described here demonstrate that the fraction of solute remaining in solution stored in PVC infusion containers for a period up to 8 hours is independent of the initial concentration of the infusion solution and that both temperature and electrolyte concentration have significant effects on the extent of the solute loss. The effect of temperature on solute sorption into PVC bags can be described by the Arrhenius's equation.

An equation to predict the rate and extent of sorption at any temperature is proposed (eqn2.11). Its validity is based on the assumption that the energy of activation of solutes which are sorbed into PVC are not substantially different from one another. As changes in the sorption mechanism and the plastic and/or solute characteristics might take place at higher temperatures, it is suggested that the proposed equation may be applicable only for a temperature range up to 40°C.

The progressive reduction in solute availability in solution in the presence of an increase in electrolytes appears to be controlled by the ionic strength of the vehicle and this depends on the total number of charges, and not on the properties of the salts, in solution. An expression of the sorption number for cases in which vehicle ionic strength is greater than zero has been derived from data obtained from four substances in terms of the sorption number in water and the ionic strength of the admixture (eqn.2.5). It is expected that a reasonable

prediction of solute uptake from solution in the presence of electrolytes without large ions can be made by using equation 2.5 since the addition of sodium benzoate which contains a large anion was found to diminish the extent of solute loss by increasing the aqueous solubility of the solute.

It is shown that the approach using the sorption number, which is an approximation of a diffusion model, proposed by Roberts and co-workers (1991) can be used to adequately describe the time course of the sorption of the model solutes by PVC infusion bags used in this work. Hence it may be concluded that the uptake mechanism of these solutes can be explained by a partitioning process followed by the diffusion of drug into the plastic matrix as proposed previously (Kowaluk et al., 1985; Roberts et al., 1991). Although these investigators (Kowaluk et al., 1985; Roberts et al., 1991) also suggested that the sorption behaviour can be estimated from the octanol-water partition coefficient of the solute, it was found, in this study, that the relationship between the sorption numbers and the solute octanol-water partition coefficients is not significant ($p > 0.05$).

The molecular dipole moment was shown to be a useful indicator of the solute affinity for the PVC bag but the ability of this parameter alone to model the solute sorption into the PVC bag is limited. Nevertheless, the effectiveness of this model can be improved upon by the use of an additional parameter, the octanol-water partition coefficient (see eqn. 2.2). Additionally, it was found that the logarithm of the sorption number correlated well with the intrinsic molecular volume and solvatochromic parameters of the solute (see eqn.2.3).

Since it was found that the uptake of some model solutes such as acetophenone and nitrobenzene by the PVC infusion bag is considerable in spite of the low solute octanol-water partition coefficient, infrared spectroscopy was used to examine the chemical interaction between these solutes and the PVC surface. The results indicate that no chemical interaction has taken place between the PVC surface and acetophenone or nitrobenzene. It may therefore be concluded that the substantial uptake of acetophenone and nitrobenzene is due mainly to the high affinity of the PVC surface for these solutes.

In addition, it has been shown that the chemical structure of the solute also has an important role on its sorption behaviour. The contribution of the substituents in the solute structure to the sorption number of a selected series of solutes can be expressed by the additive mathematical model similar to that proposed by Free and Wilson (1964) to describe the contribution of the substituents in the structure, to the biological activity of four analgesic compounds from the same series of chemical analogs.

The kinetics of the sorption of the model solutes from their solutions infused through PVC tubings was investigated. A well-stirred compartment model and a well-stirred diffusion model were examined for their ability to describe the uptake of the model solutes from aqueous solutions infused through PVC tubings. It was shown that a biexponential model, which is probably a simplified form of both the well-stirred compartment model and the well-stirred diffusion model, can be used to adequately describe the sorption profiles of the model solutes during a 24-hour infusion period. According to the biexponential model proposed in this work, the time course of the

sorption of solutes from solutions infused through PVC tubing can be divided into two steps.

The sorption process commences immediately after the infusion is begun and continues until a steady state is reached at a time t which is approximately equal to four times t_{sink} (where t_{sink} is a function of an infusion rate, tubing internal radius and tubing length and can be calculated by the use of eqn.3.16). The solute concentration in the effluent collected at any time greater than $4t_{sink}$ will therefore remain constant until the end of a 24-hour infusion period. The sorption process itself can also be divided into two steps; the initial rapid sorption of the solute to the surface of the plastic tubing in immediate contact with the infusion solution and the subsequent diffusion of solute into/through the plastic matrix which is the terminal phase of the sorption.

It was found that at time t where $t_{sink} \leq t \leq 4t_{sink}$ after the beginning of an infusion, the sorption profile of all solutes can be described by a simple monoexponential equation (eqn.3.5) which is independent of the affinity of the solutes for the PVC tubings. Thus it appears that reasonable estimates of the solute concentration in the effluent collected at the distal end of the PVC tubing at any time t where $t_{sink} \leq t \leq 24$ hours can be made by using equation 3.5 together with the steady state assumption, provided that the constants a_2 and b_2 (see eqn.3.5) are known. Although it is not possible to estimate the solute concentration in the effluent at any individual time point during the initial period ($t = 0$ to $t = t_{sink}$) the overall loss during this period can be estimated because the cumulative fraction of the original solute concentration in the

effluent collected during the initial period is equal to the fraction of the original solute concentration in the effluent at time t_{sink}.

It has also been found that leaching of phthalate-type plasticizer(s) from the PVC tubing into the infusion solution occurs almost immediately after the infusion begins. This leaching process appears to be rapid, that is, the extent of leaching has become minimal by time t_{sink}. Although the toxic effects in humans of the material(s) leached from PVC into infusion solution are still unknown, this material has been shown to cause toxic effects in animals when used in extremely high doses (Ziter, 1987). It is therefore suggested that priming or pre-treating the tubing before an infusion is desirable.

Pre-treatment of the tubing may be carried out by flushing the tubing with the infusion solution from the attached glass bottle either at the specified infusion rate for a period of time equal to or greater than t_{sink} (the total volume discarded from $t = 0$ to $t = t_{sink}$, V_{sink}, can thus be calculated using the formula: $V_{sink} = \pi r l$ where r and l are the tubing internal radius and tubing length, respectively) or at a rapid rate until the total volume discarded is equal to or greater than V_{sink}. The latter method appears to be more practical in a clinical situation since the cumulative volume of the effluent is used as a measurement and the specific infusion rate is not required. This allows for the infusion rate to be varied in order to complete the pre-treatment process in the shortest possible time. For instance, by using common administration sets similar to those used by Mason and co-workers (1981) and Roberts and co-workers (1980) (see Tables 4.4 and 4.5) and a flow rate of 4 $mL.min^{-1}$, the pre-treating time required (t_{sink}) is approximately 20 minutes with a

total volume of approximately 80 mL (V_{sink}) being discarded. Furthermore an adjustment of the infusion rate to the specified value, which is an essential beginning step of an infusion, can also be carried out during the terminal stage of this pre-treatment process.

The effects of solute concentration, flow rate, tubing diameter, and tubing length on the rate and extent of solute uptake by PVC tubing were investigated. It was found that the rate and extent of solute uptake is a function of flow rate, tubing diameter and tubing length but that it is independent of the initial concentration of the infusion solution. In order to describe the differences in the extent of sorption between two separate kinetic runs conducted using differing flow rates, tubing diameters and/or tubing lengths, a model based on chemical similarity theory was developed (see eqns.3.18 and 3.20). This allows for an approximation of the rate and extent of solute uptake in one system from a knowledge of the rate and extent of the uptake in another system operating under different conditions.

An attempt was made to correlate the rate and extent of sorption of the model solutes by PVC tubing, as expressed by the constants a_2 and b_2 (see eqn.3.5), with the physicochemical properties (specifically the octanol-water partition coefficients, dipole moments, intrinsic molecular volumes and solvatochromic parameters) of the solutes. It was found that the correlations between the constants a_2 or b_2 and the octanol-water partition coefficients were not significant ($p > 0.05$) whereas the dipole moment considered alone was found to be well correlated with the constants a_2 and b_2 (see eqns.3.8 and 3.9). Intrinsic molecular volumes and solvatochromic parameters were also found to give an excellent

correlation with the constant a_2 (see eqn.3.10). Although the correlation between b_2 and intrinsic molecular volumes and solvatochromic parameters was found not to be significant ($p > 0.05$), a fair correlation between b_2 and π^*, one of the solvatochromic parameters, has been obtained (see eqn.3.11).

The ability of the models proposed in this work to describe and predict the sorption of other solutes by PVC infusion bags and PVC tubings was examined using data obtained experimentally and data reported previously by other investigators. It was found that the ability of the prediction equations, which use the physicochemical parameters of the solutes, to predict the rate and extent of sorption of solutes from solutions into PVC infusion bags or tubings is limited. It appears that prediction equations derived from data obtained from one particular congeneric series are not always applicable to all solutes/drugs of diverse structure unless subgroups are considered.

The model based on chemical similarity theory appears, nevertheless, to be promising in terms of its ability to make an approximation of solute loss from a solution infused from a glass container through a PVC tubing in one system, from a knowledge of uptake in another system operating under different conditions. Given that knowledge of the uptake in a system operating under a specific set of conditions, in which flow rate, tubing diameter and tubing length are known and that the conditions may be varied, it is expected that this model may be used to predict the extent of solute loss from solution infused through PVC tubing at any time t, where $t_{sink} \leq t \leq 24$ hours, under various clinical conditions. No attempt was made to develop a model which could be

used to predict the time course of the sorption of a solute by PVC tubing during the initial sorption period which takes place during t = 0 to t = t_{sink}, since compliance with the directive of pre-treating the tubing before an infusion, by discarding the effluent collected between t = 0 and t = t_{sink}, renders such a model unnecessary, particularly since the cumulative fraction of the original concentration lost in this time (up to t_{sink}) will be known.

The plasticizers used in the formulations of PVC bags and tubings used in this work were identified using infrared spectroscopy and scanning ultraviolet spectrometry. Both the infrared spectra and ultraviolet absorption spectra of the methanolic extracts of the PVC sheets cut from an unprinted area of PVC bag and tubing reveal that the phthalate-type plasticizer, di-2-ethylhexyl phthalate (DEHP) was used in both formulations. As the plasticizer used in the PVC formulation has been shown to be responsible for the sorption capacity of PVC (Bray, 1983; Weir et al., 1985), the DEHP-water partition coefficients of the model solutes were determined. It was found that the DEHP-water partition coefficient was not particularly useful in terms of its ability to adequately predict the sorption capacity of the DEHP in plasticized PVC materials. The difference in behaviour between pure DEHP and the DEHP in the plasticized PVC formulation is probably due to the modification of the characteristics of the plasticizer which might occur during the processing of the dry blend into the plastic film.

At present, it appears that the time course of the sorption of solutes by PVC infusion bags under varying storage conditions of clinical interest can be adequately described and predicted by using the simplified

diffusion model proposed by Roberts and co-workers (1991) together with the prediction equations proposed in this work. This approach accounts for the effect of all important factors such as time, plastic surface area, solution volume, solution pH, vehicle ionic strength and storage temperature on the extent of the solute loss.

In the dynamic situation, the effect of the infusion conditions, such as flow rate, tubing diameter and tubing length, on solute uptake from solution infused from a glass container through a PVC tubing has been investigated in this work. The effects which are related to the infusion solution, for example, the solute concentration, solution pH, diluent and additives used in the admixture, on solute uptake by PVC tubing have not been examined in this study.

It is also desirable to derive a combined model which could be used to predict the time course of the sorption of solutes from solution infused from a PVC container through a PVC tubing in a variety of clinical and other situations.

APPENDIX I

THE INTRINSIC MOLECULAR VOLUME AND SOLVATOCHROMIC PARAMETERS ESTIMATION RULES

The parameter estimation rules which follow are mainly for aromatic solutes and have been developed for the present purpose from Leahy (1986), Kamlet, et al. (1983, 1986, 1988) Abboud, et al. (1977, 1984), Bekarek (1981) and Tayar, et al. (1991).

Aromatic non-hydrogen bond donor solutes.

a. The intrinsic molecular volume, $V_I/100$, values for most of the monosubstituted benzene derivatives are computer-calculated results with simple additivity rules giving estimated $V_I/100$ for the polysubstituted benzenes. The most useful of these rules is to add 0.098 to $V_I/100$ for replacement of H by CH_3 or insertion of CH_2 into a side chain, 0.090 for replacement of H by Cl, 0.133 for Br and 0.140 for NO_2.

b. The solute π^* value for most of the monosubstituted benzene derivatives were compiled by Kamlet, et al. (1983). For two dipolar ortho substituents, add 0.10 to the higher π^* of monosubstituted derivatives; for two meta substituents, add 0.05 to π^*; for para substituents, add 0.00 to π^*; for example π^* of 4-chlorophenol is the same as that for phenol and 4-bromophenol is the same as that for bromobenzene. For replacement of H by CH_3 on a ring, subtract 0.04 from π^* ; for replacement on a side chain, subtract 0.02. For selected

solvents π^* values are approximately proportional to molecular dipole moments (μ); that is π^* values and dipole moment values are related for monofunctional aliphatic, monofunctional aromatic and polychloroaliphatic compounds as shown by eqn.A.I.1, A.I.2 and A.I.3, respectively.

$$\pi^* = 0.02 + 0.23\,\mu \qquad \text{(A.I.1)}$$

$$\pi^* = 0.56 + 0.11\,\mu \qquad \text{(A.I.2)}$$

$$\pi^* = 0.27 + 0.35\,\mu \qquad \text{(A.I.3)}$$

Tables of dipole moment values, normally obtained in dilute solution, are available (McClellan, 1963; Lien et al., 1982). Alternatively, by considering the dipole moment as a property of a bond, estimates can be made from closely related molecules. For certain multifunctional molecules such as dihalobenzenes, the crude assumption of additivity of dipole moments has been used. However it is suggested that the use of $\Sigma\mu$ is not appropriate for polyfunctional and nitro compounds. Additionally, for both aliphatic and aromatic solvents the π^* scale of solvent dipolarity/polarizability was also found to be related to refractive indexes and dielectric constants (Bekarek, 1981; Kamlet et al., 1983; Abboud et al., 1984).

c. For the first through the third CH_3 on a ring add 0.01 to ß; for the fourth through the sixth, add 0.02; add 0.01 to ß, for the first methyl -> ethyl, but nothing for further side chain enlargement. For substituents that are strong π-electron donors to the ring (NMe_2, NH_2,

OH, OCH_3), assume multiple hydrogen bonding effects at substituent and ring and add 0.10 to the solvent ß value for additional hydrogen bonding to the ring. For the addition of chlorine or bromine to halobenzene, alkylbenzene, or a benzene ring containing an electron-withdrawing substituent, subtract 0.04 from ß; for the addition of fluorine, subtract 0.02. For the addition of chlorine or bromine to a ring containing a strong electron-donor substituent or where the ring had been a second site of hydrogen bonding, subtract 0.10 from ß; for addition of fluorine, subtract 0.05.

Aromatic hydrogen bond donor solutes.

a. The π^* values of aromatic hydrogen bond donor solutes such as phenol and benzoic acid were estimated from the π^*/dipole moment relationship as described above.

b. The ß values of phenol and benzoic acid are similar to 0.33 for anisole and 0.40 for methyl benzoate respectively. The π^* and ß values of benzyl alcohol are summations of those for benzene and methanol; the values for phenylacetic acid are summations of those for benzene and acetic acid, and in both series 0.02 is subtracted from π^* for each side-chain methylene group. For substitution by chlorine or bromine, 0.10 is subtracted from ß of the phenols, phenylalkanols, and phenylacetic acids (since ß of the parent compounds had included increments of 0.10 for hydrogen bonding to the rings), and 0.04 is subtracted for the benzoic acid derivatives.

c. The α values can be estimated from equations relating solvent/water partition coefficients of hydrogen bond donor solutes to solvatochromic parameters of the solvents (i.e., the greater the response to solvent hydrogen bond acceptor basicity, the greater the hydrogen bond donor acidity of the solute) (Kamlet, et al., 1988; Tayar, et al., 1991). The values of α range from 0.58 to 0.69 and from 0.59 to 0.64 are used for phenols and benzoic acids with Cl, Br or CH_3 meta or para substituents respectively.

Compounds with aliphatic and aromatic moieties.

For compounds within which the main hydrogen bond acceptor site is on an aliphatic side chain and is separated from the ring by one or more methylene groups or oxygen, the rule is to estimate π^* and ß separately for the ring and the side chain (i.e., the ring where H replaces the side chain and the side chain where H replaces the ring) and use $\sum\pi^*$, ∂=1.00 and $\sum$ß in the correlation. If the ring is a third hydrogen bonding site, the increment of 0.10 to ß for hydrogen bonding to the ring is not required.

Polycyclic aromatic hydrocarbons.

For polycyclic aromatic hydrocarbons (PAHs), with reported log $P_{octanol}$ values lower than 6.0, parameter estimation rules are as follows:

a. For fused rings, add 0.0655 to $V_I/100$ for each ring-CH and 0.0815 for ring-CH_2. Hence 0.262 should be added for benzene -> naphthalene,

0.373 for naphthalene -> pyrene, and 0.163 for naphthalene -> acenaphthalene.

b. For naphthalene, $\pi^* = 0.70$, and $\partial = 0.15$. For each additional fused ring, add 0.10 to π^* and 0.05 to ß. Thus, for naphthalene -> dibenzanthracene, $\Delta\pi^* = 0.30$, and Δß = 0.15.

c. $\partial = 1.00$ is used for the entire PAH system but $\partial = 2.00$ is used for fluorene, which may be considered a biphenyl derivative.

d.For chloro and alkyl PAH derivatives, the same increments and decrements as for the corresponding benzene are used.

e. For hydrogen bond acceptor substituent on PAH, start with correspondingly substituted benzene; add 0.10 to π^*, nothing to ß for first additional fused ring, 0.10 to π^* and 0.05 to ß for further fused rings. Thus, for 1-nitroanthracene, $\pi^* = 1.21$, and ß = 0.35.

APPENDIX II

THE PROCESS OF SOLUTE SORPTION INTO PVC TUBING

The sorption process is represented schematically in Figure A.II.1.

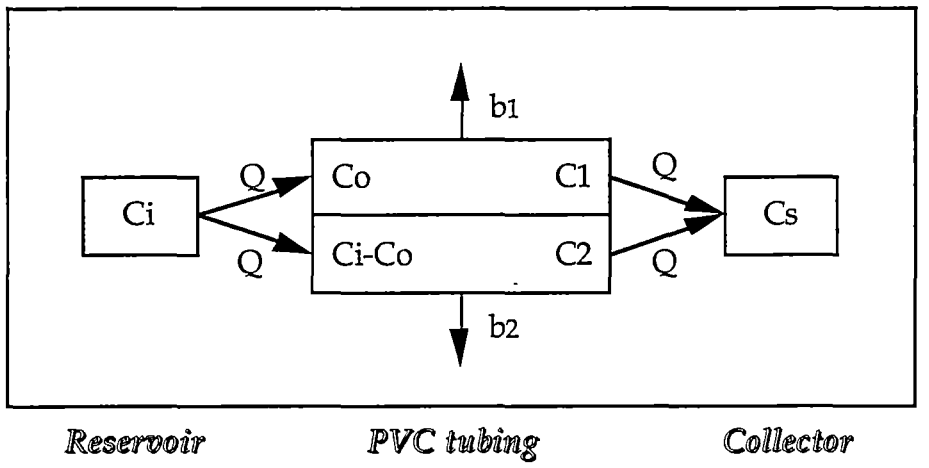


Figure A.II.1. A schematic representation of the sorption of solute into PVC tubing.

When a solution is infused through PVC tubing, it is assumed that the loss of solute from solution into the PVC tubing is due to two separate processes, i.e., adsorption of the solute onto the PVC surface and diffusion of the solute into and/or through the PVC matrix, and that these two processes do not interfere with each other. It is suggested that an interaction between the solute and an isolated surface plasticizer accounts for the adsorption of solute onto the PVC surface while the diffusion process involves a transferring of the solute into the bulk plasticizer and / or across the outer surface of the tube.

The overall concentration of solute in the solution about to be delivered at the distal end of the tubing, C_s, at time t after the start of infusion is equal to $C_1 + C_2$, due to the sum of the contributions of the solute remaining from the adsorption and diffusion processes:

$$C_s = C_1 + C_2 \qquad \text{(A.II.1)}$$

where C_1 denotes the contribution of the solute remaining from the adsorption process and C_2 denotes the contribution of the solute remaining from the diffusion process(es). The differential equations describing the rate of change of C_1 and C_2 are

$$\frac{dC_1}{dt} = QC_0 - b_1C_1 \qquad \text{(A.II.2)}$$

$$\frac{dC_2}{dt} = Q(C_i - C_0) - b_2C_2 \qquad \text{(A.II.3)}$$

where Q represents the infusion rate, C_i is the overall initial concentration of infusion solution, C_0 and $(C_i - C_0)$ are the initial concentrations of solution in the adsorption and diffusion processes respectively, b_1 is the first-order rate constant for the adsorption process and b_2 is the sum of the first-order rate constants for the diffusion processes:

$$b_2 = k_p + k_o \qquad \text{(A.II.4)}$$

where k_p is the rate constant for diffusion into the plastic matrix and k_o is the rate of transfer across the outer surface of the tube. Eq. A.II.2 may be integrated to yield

$$C_1 = \frac{QC_0}{b_1} + Ae^{-b_1 t} \qquad \text{(A.II.5)}$$

where A is a constant which can be obtained as follows:

At $t = 0$, $C_1 = C_0$. Eq. A.II.4 can then be expressed by

$$C_0 = \frac{QC_0}{b_1} + A \qquad \text{(A.II.6)}$$

Rearranging eq. A.II.6 gives

$$A = C_0 - \frac{QC_0}{b_1} \qquad \text{(A.II.7)}$$

Substituting eq. A.II.7 into eq. A.II.5 yields

$$C_1 = \frac{QC_0}{b_1} + \{ C_0 - \frac{QC_0}{b_1} \} e^{-b_1 t} \qquad \text{(A.II.8)}$$

Rearranging eq. A.II.8 gives

$$C_1 = C_0 e^{-b_1 t} + (1 - e^{-b_1 t}) \frac{QC_0}{b_1} \qquad \text{(A.II.9)}$$

At early time, it is assumed that the term $(b_1 t)$ is very small. Therefore, the term $(e^{-b_1 t})$ will approach 1 and eq. A.II.9 may be approximated to be

$$C_1 = C_0 e^{-b_1 t} \qquad \text{(A.II.10)}$$

Similarly, at early time, eq. A.II.3 may be expressed by eq. A.II.11

$$C_2 = (C_1 - C_0) e^{-b_2 t} \qquad \text{(A.II.11)}$$

Substituting eqs. A.II.10 and A.II.11 into eq. A.II.1 and solving for C_s:

$$C_s = C_0 e^{-b_1 t} + (C_1 - C_0) e^{-b_2 t} \qquad \text{(A.II.12)}$$

The fraction of the initial concentration of solute in solution at time t, F_t, after the start of the infusion can be obtained by dividing C_s by C_i:

$$F_t = a_1 e^{-b_1 t} + a_2 e^{-b_2 t} \qquad (3.4)$$

where $a_1 = C_0/C_i$, and $a_2 = (C_i - C_0)/C_i = (1 - a_1)$.

Equation 3.4 describes the fraction of the initial concentration of solute in the effluent solution at times prior to the steady state being achieved.

APPENDIX III

THE DERIVATION OF THE PREDICTION MODEL BASED ON CHEMICAL SIMILARITY THEORY

Eqn.A.III.1 shows the relationship for solute A, disappearing chemically according to the conventional rate law (Swinbourne, 1971).

$$\frac{-dC_A}{dt} = kC_A^n \qquad \text{(A.III.1)}$$

where C_A denotes solute concentration, k is a rate constant and n denotes a reaction order. The rate of a chemical change can also be assessed in terms of the concentration of product appearing, C_p, per unit time, as shown in eqn.A.III.2.

$$\frac{dC_p}{dt} = kC_A^n \qquad \text{(A.III.2)}$$

For the sorption process of solute from solution infused through PVC tubing, n = 1 is used since it has been found that the fractional loss of solute is independent of solute concentration. Substituting n in eqn.A.III.2 with 1 yields

$$\frac{dC_p}{dt} = kC_A \qquad \text{(A.III.3)}$$

Rearranging eqn.A.III.3 gives

$$\frac{1}{C_A} dC_p = kdt \qquad \text{(A.III.4)}$$

Eqn.A.III.4 may be integrated to yield

$$C_p/C_A = kt \qquad \text{(A.III.5)}$$

or

$$U_t = kt \qquad \text{(A.III.6)}$$

where C_p/C_A equals U_t, the fractional solute sorbed. Eqn.A.III.6 may be used to describe the fractional solute sorbed at any time (t) greater than or equal to t_{sink}, the time required for the initial rapid uptake of solute into the PVC tubing to decrease to zero, in situations in which the sorption process is governed by the diffusion process only. It has been suggested that the first-order rate constant for sorption, k, can be expressed in terms of the surface area of plastic (A) in contact with solution and the volume of solution (V) as follows (Kowaluk, et al, 1982):

$$k = k_p \frac{A}{V} \qquad \text{(A.III.7)}$$

or

$$k = k_p \frac{(2\pi rl)}{(\pi r^2 l)} \qquad \text{(A.III.8)}$$

where k_p is the permeability constant of the drug in the plastic, r is the internal radius of the tubing and l is the tubing length. Subtituting eqn.A.III.8 into eqn.A.III.6 gives

$$U_t = k_p \frac{(2\pi rl)}{(\pi r^2 l)} t \qquad \text{(A.III.9)}$$

According to the results presented in Chapter 3, t_{sink} may be described by eqn.3.15:

$$t_{sink} = \frac{(\pi r^2 l)}{v r} \tag{3.15}$$

where v is an infusion rate. Substituting eqn.3.15 into eqn.A.III.9 yields

$$U_t = k_p \frac{(2\pi r l)}{(\pi r^2 l)} \frac{(\pi r^2 l)}{v r} \tag{A.III.10}$$

Therefore

$$U_t = 2\pi k_p l v^{-1} \tag{A.III.11}$$

A similar type of relationship has been described previously for heterogenous reactions, in which a reacting fluid flows over a packed catalyst bed, as shown in eqn.A.III.12 (Bosworth, 1956).

$$O = \pi R^2 LS \tag{A.III.12}$$

where O, an output of a tubular flow - reactor, is a measure of the volume of resultant produced in unit time, S denotes flow velocity, R and L denote radius and length of the reactor respectively. In such a system, even when it is not possible to study the performance of the transport system in detail, it is still possible to lay down conditions under which the relevant transport processes will have the same influence on equipment of two different sizes. Two different conditions for which the ratio of pairs of linear dimensions is the same are said to be geometrically similar. Therefore, experiments performed on

equipment of one scale will give exact information on the performance of the reaction carried out using different sized equipment. These conditions are referred to as the conditions for chemical similarity (Bosworth, 1956).

Different types of similarity may be recognized depending on the nature of the dimensionless groups in terms of which the state of similarity is recognized. The dimensionless groups can be obtained when different physical properties are combined in such a way that all the dimensions cancel. It obviously has a measure which is independent of the values arbitrarily assigned as the fundamental units. For instance, the flow of fluids in two different sized vessels exhibits dynamical similarity with respect to inertial and viscous forces when the ratio:

$$\frac{\text{Velocity x Linear dimension x Density}}{\text{Viscosity}}$$

is the same in both vessels. This is a quantity of zero dimensions and is recognized as the Reynolds number (Bosworth, 1956).

When eqn.A.III.12 is combined with the conditions for chemical similarity in heterogeneous systems, the output O' in a chemically similar prototype reactor with radius n fold that of the model is

$$O' = n^z O \qquad \text{(A.III.13)}$$

where z is equal to 2/3 and 1 in heterogeneous systems with radiative transfer dominating and thermal conductivity dominating respectively (Bosworth, 1956).

Thus, if the conditions for chemical similarity are applied to eqn.A.III.11 in the same way as that described above, fractional solute loss in a chemically similar tubing, with tubing length and infusion rate n and m fold of those of the model respectively, may be given by

$$U_t' = n^x m^{-y} U_t \qquad \text{(A.III.14)}$$

or

$$U_t' \frac{(v')^y}{(l')^x} = U_t \frac{(v)^y}{(l)^x} \qquad \text{(A.III.15)}$$

where x and y are constants which, in this work, have been determined by using a method commonly used for determining reaction order for a single reactant species (Swinbourne, 1971). The method is one of trial and error, values of x and y being chosen until the data gives a satisfactory result, i.e., eqn.A.III.15 is found to be held. A one way analysis of variance (ANOVA) was applied to determine if significant differences existed among conditions in the values of $U_t \frac{(v)^y}{(l)^x}$ at significance level, α, of 0.01. For the PVC tubings being studied, it was found that x equals 1/3 and y equals 1/2. Therefore, at $t = t_{sink}$

$$U_t' \frac{(v')^{1/2}}{(l')^{1/3}} = U_t \frac{(v)^{1/2}}{(l)^{1/3}} \qquad (3.17)$$

APPENDIX IV

THE CALCULATION PROCEDURE USING THE PREDICTION MODEL BASED ON CHEMICAL SIMILARITY THEORY

The fraction of the original concentration of solute in the effluent of a solution (F_t) infused through PVC tubing under various conditions is predicted by using the results obtained from infusing the same solution through a PVC tubing of 0.8 cm internal diameter and 40 cm length at a flow rate of 0.6 $mL.min^{-1}$ and the model proposed in section 3.3.4.1. A comparison of the experimental and predicted F_t of *o*-xylenol and *p*-bromophenol are shown in Figures 3.20 to 3.23.

An example of the calculation is as follows:
The general equation to be used is

$$F_t = a_2 e^{-b_2 t} \qquad (3.5)$$

where F_t is the fraction of the original concentration of solute in the effluent collected at the distal end of a PVC tubing at time t, where $t_{sink} \leq t \leq 4t_{sink}$, a_2 is a constant and b_2 is a rate constant.

Step 1. Calculation of the reference values. The values a_2 and b_2, calculated by curve fitting the data obtained from infusing *p*-bromophenol solution through PVC tubing of 0.8 cm internal diameter (2r) and 40 cm length (l) at a flow rate (v) of 0.6 $mL.min^{-1}$, are 0.844 and -2.34×10^{-4} (min^{-1}), respectively. The fraction of solute in the effluent solution at time t_{sink} ($t_{sink} = \pi r l / v$), therefore, is

$$F_{t_{sink}} = 0.844e^{[-(-0.000234)((22/7)(0.4)(40)(1/0.6))]} = 0.861$$

and the fractional solute loss, U_t, at t_{sink} is given by

$$U_t = 1 - 0.861 = 0.139$$

Step 2. Calculation of the predicted fractional solute loss at time t_{sink} From the reference fractional solute loss value, U_t, obtained above, the predicted fractional solute loss, U_t', of the same drug infused through PVC tubing of 0.5 cm internal diameter (2r') and 100 cm length (l') at a flow rate (v') of 1.2 mL.min^{-1} can be calculated from

$$U_t' \frac{(v'^{1/2})}{(l'^{1/3})} = U_t \frac{(v^{1/2})}{(l^{1/3})} \qquad (3.17)$$

Thus,

$$U_t' = (0.146) \frac{(0.6)^{1/2}}{(40)^{1/3}} \frac{(100)^{1/3}}{(1.2)^{1/2}} = 0.134$$

and

$$(F_{t_{sink}})' = 1 - U_t' = 1 - 0.134 = 0.866$$

Step 3. Calculation of the predicted rate constant. The prediction of the rate constant can be done by means of the following equation:

$$b_2 = b_2' \frac{(l'^{1/3})r'}{(v'^{1/2})} \frac{(v^{1/2})}{(l^{1/3})r} \qquad (3.20)$$

or

$$b_2' = b_2 [(l/l')^{1/3} (v'/v)^{1/2} (r/r')]$$

Therefore,

$$b_2' = (-2.34\times10^{-4})\,[(40/100)^{1/3}\,(1.2/0.6)^{1/2}\,(0.4/0.25)] = -3.90\times10^{-4}\ \text{min}^{-1}$$

Step 4. Calculation of the constant a_2'. Rearranging the general equation (eqn.3.5), the constant a_2' is given by

$$a_2' = F_t e^{b'_2 t}$$

Thus,

$$a_2' = 0.866e^{(-0.00039)[(22/7)(0.25)(100)(1/1.2)]} = 0.838$$

It follows that, the equation which can be used to predict the sorption profile of *p*-bromophenol solution infused through PVC tubing of 0.5 cm internal diameter and 100 cm length at a flow rate of 1.2 mL.min^{-1} at any time t, where $t_{sink} \leq t \leq 4t_{sink}$, can be expressed as

$$F_t = 0.838e^{-(-0.00039t)}$$

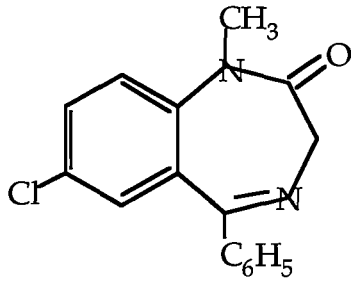
At time t, where $4t_{sink} \leq t \leq 24$ h, the steady-state assumption is applied and the steady-state fraction remaining in solution is given by

$$F_t = 0.838e^{-(-0.00039(4t_{sink}))} = 0.928$$

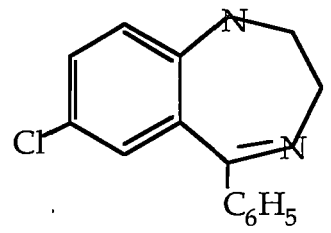
where t_{sink} is determined as shown in step 1 above. The calculation procedure required to obtain the prediction formula for any other condition is basically the same as that described above.

APPENDIX V

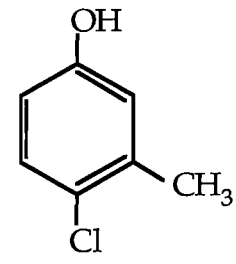
CHEMICAL STRUCTURE OF DRUGS AND SOLUTES USED IN THIS STUDY



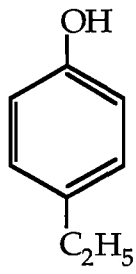
Diazepam



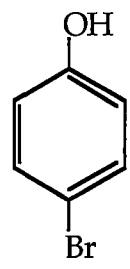
Medazepam



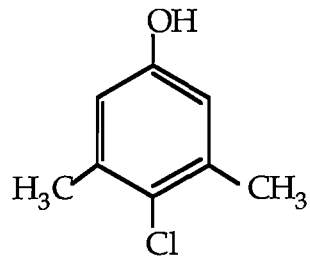
Chlorocresol



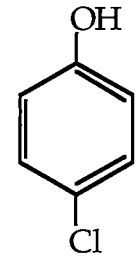
4-Aethylphenol



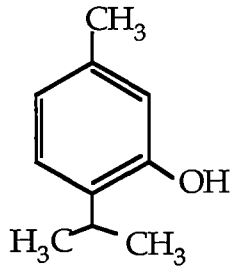
p-Bromophenol



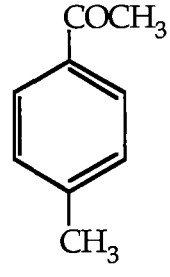
Chloroxylenol



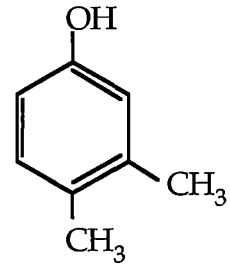
p-Chlorophenol



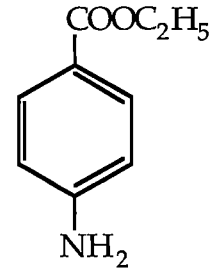
Thymol



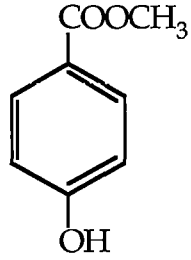
Methylacetophenone



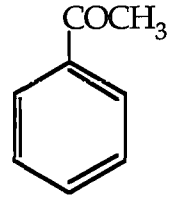
o-Xylenol



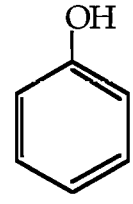
Benzocaine



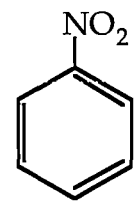
Methylparaben



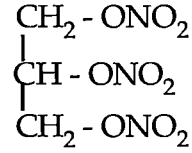
Acetophenone



Phenol



Nitrobenzene



Nitroglycerin

APPENDIX VI

QUANTIFICATION OF BENZOCAINE USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

EXPERIMENTAL

Chemicals. Benzocaine was obtained from Sigma, U.S.A. (lot 91F-0071), the internal standard, benzophenone, from a local supplier and acetonitrile (HPLC grade) from Waters, Division of MILLIPORE, Australia (lot 808432).

Apparatus. A method modified from that described by Gigante and co-workers (1991) was used to determine benzocaine concentration. A high-performance liquid chromatograph, consisting of a ETP KORTEC K 65 HPLC automated sample injector, a Waters Associates model M-45 solvent delivery system, and a Waters, model 441 UV Absorbance detector was used. The detector wavelength was set at 254 nm. The chromatographic peaks were recorded with a Milton Roy® Integrator model CI-4100. A 25 cm x 0.39 cm i.d. stainless-steel column containing C_{18} bonded phase silica, Analytical Sciences Inc., AS1C18, 10 μm, with a 2.5 cm guard column (Bondapak®, Waters, batch 113R) were used. The injection volume was 20 μL. A flow rate of 1 $mL.min^{-1}$ eluted benzocaine and benzophenone in 4.23 and 6.13 min, respectively. All analyses were performed at room temperature.

Mobile phase. The mobile phase consisted of acetonitrile-water (50:50,v/v), filtered through a 0.45-μm PTFE membrane and deaerated before use.

Standard solutions for calibration graphs. Stock solutions in distilled water of benzocaine (160 $\mu g.mL^{-1}$) and benzophenone (internal standard) (49 $\mu g.mL^{-1}$) were prepared.

Appropriate volumes of benzocaine stock solution and internal standard solution were measured and diluted to 25 mL with the mobile phase. The solution was mixed well and 20-μL aliquots of these standard preparations were used in the HPLC assay. The calibration was carried over a concentration range of 2.7 - 13.6 $\mu g.mL^{-1}$ for benzocaine and 24.5 $\mu g.mL^{-1}$ for the internal standard, benzophenone.

Sample preparation. A 1.0-mL volume of the effluent collected from the distal end of the tubing at a selected time was accurately pipetted into a test tube, followed by an addition of 1.0 mL of internal standard solution. It was mixed well using a Vortex mixer and 20-μL aliquots were used directly in the HPLC assay.

Assay procedure. Volumes of 20 μL each of the standard preparations and sample preparations were injected in duplicate at intervals of 9 minutes. The peak-area ratios of benzocaine with respect to the internal standard were calculated. By comparing the peak-area ratios for the standard and sample preparations the amount of drug in each solution could be calculated.

Linearity. The linearity of the method was determined from the calibration graph. A linear correlation was observed between the peak-area ratios of benzocaine to the internal standard and the concentrations of benzocaine. For benzocaine, the method was found to be linear over the concentration range of 2.7 - 13.6 $\mu g.mL^{-1}$ with a correlation coefficient of 0.995 ($p<0.05$) (n=5).

Recovery. To study the applicability of the method, a recovery experiment was carried out. A known amount of benzocaine was added to the effluent collected during the first hour of infusing distilled water through PVC tubing under the same condition as that described in the desorption study. A sample containing 8.0 $\mu g.mL^{-1}$ benzocaine was then processed according to the described method. Recovery was determined as a percentage relative to the results obtained for an aqueous reference standard of the same concentration.

RESULTS

Figure A.VI.1. is a chromatogram of 8.0 $\mu g.mL^{-1}$ benzocaine aqueous solution. The reproducibility of the assay is summarised in Table A.VI.1.

When the applicability of the method was tested by determining benzocaine in the effluent, a 116.97 % recovery (RSD = 4.75 %, n = 6) and a series of minor peaks found during 4.23 and 6.13 min after injection of the sample prepared from the effluent indicate an interference from material(s) leached from PVC tubing into the effluent. This complication was not detected when the sample prepared from distilled

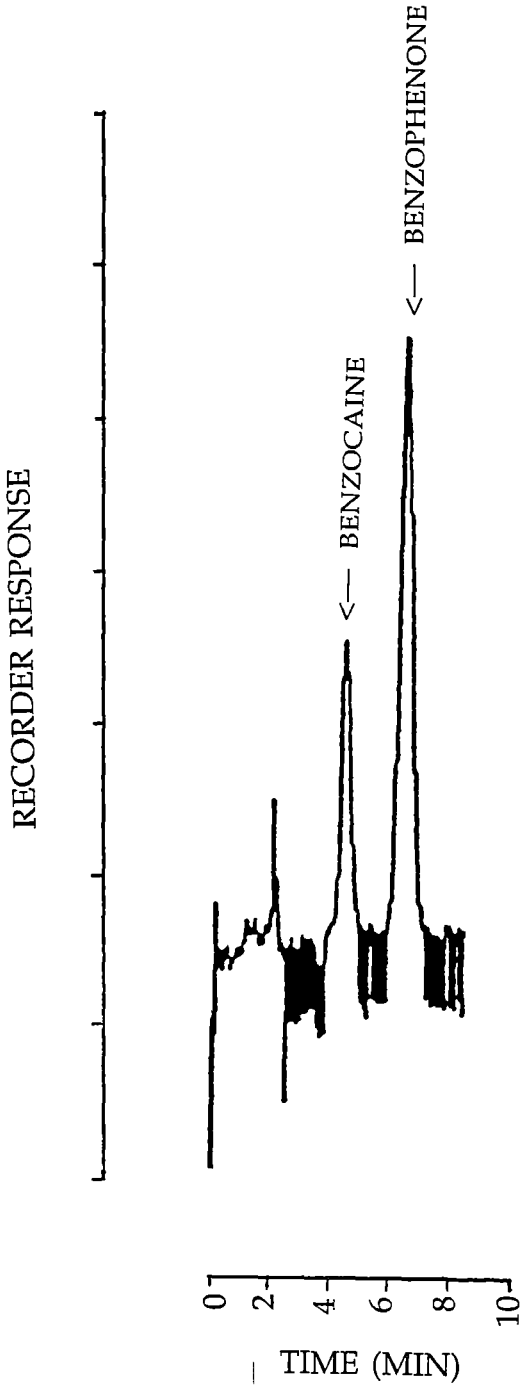


Figure A.VI.1. Chromatogram of a sample containing 8.0 $\mu g.mL^{-1}$ benzocaine and 24.5 $\mu g.mL^{-1}$ benzophenone (an internal standard) in an aqueous solution.

Table A.VI.1. Reproducibility of Assays

Benzocaine concentration ($\mu g.mL^{-1}$)	RSD (%) Interday (n = 5)	Intraday (n = 5)
13.6	2.24	3.44
5.4	2.96	2.66

water was analysed. It is, therefore, the interference from the material(s) leached from the PVC matrix into the effluent which have the same retention time as benzocaine and also show absorbance at 254nm. In addition, the RSD value obtained was higher than previously determined (4.75 %) indicating the limit of sample-to-sample resolution of the technique when applied to the sample prepared from the effluent.

DISCUSSION

Although HPLC methods have been described for the quantification of benzocaine (Gill et al., 1984; Jane et al., 1985; Gigante et al., 1991), none of these methods was designed to avoid the interference from the material(s) leached from PVC tubing into the effluent. The method, modified from that proposed by Gigante and co-workers (1991), used in this study is simple and precise enough to determine benzocaine concentration in aqueous solutions. However, it is not specific enough to avoid significant interference from unidentified peak(s) that sometimes co-eluted with benzocaine in samples obtained from solutions infused through PVC tubing. No attempt was made to

develop this method since the effluents collected from the distal end of the PVC tubing at different time points are likely to contain different types and proportions of the leached material(s), making the development of the analysis difficult. Furthermore, the exact formulation of the plastic is not known. The lack of a well characterized standard of the leached material(s) is also a problem for the development of this analytical method.

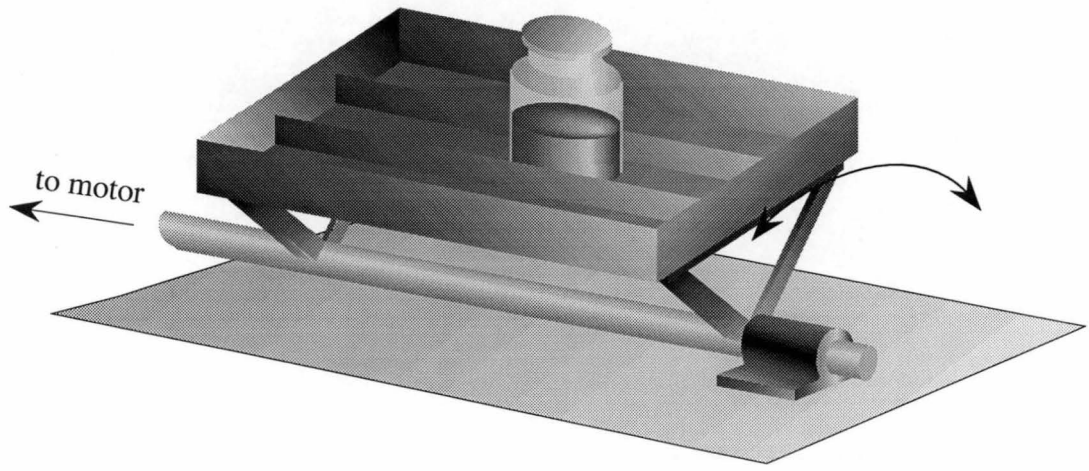
Similarly, UV spectrophotometry is also a nonspecific method since the presence of extraneous materials in a sample would interfere with the spectrum of the drug being determined. Nevertheless, certain techniques such as difference spectrophotometry can be used to correct for absorptive interferences. This technique involves the measurement of the absorbance difference, at a defined wavelength, between two samples or between the sample and an equivalent solution without the drug. It is suggested that the analytical wavelength value corresponding to a maximum in the difference spectrum be used to enhance the sensitivity and selectivity of the detection (Fell, 1986).

From the results obtained in the desorption from the tubing study, it was shown that the UV absorbance of the leached material(s) was very low (i.e., < 0.01 absorbance unit) at wavelengths higher than 240 nm. Hence, for compounds which show absorbance at wavelengths higher than 240 nm, the maximum in the difference spectrum can be obtained by using the wavelength of maximum absorption of each particular solute. It is suggested that, for the sorption into PVC tubing study of benzocaine or other drugs which lend themselves to spectrophotometric determination in aqueous solution at maximum absorbance

wavelengths higher than 240 nm, UV spectrophotometry appears to be an alternative analytical method.

APPENDIX VII

MECHANICAL SHAKER USED IN DETERMINATION OF DEHP-WATER PARTITION COEFFICIENT



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