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STUDIES ON EFFECT OF MOLECULAB STRUCTURE OF SOME AROMATIC COMPOUNDS ON THEIR UPTAKE RATES BY A LIQUID MEMBRANE SYSTEM

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STUDIES ON EFFECT OF MOLECULAR STRUCTURE OF SOME AROMATIC COMPOUNDS ON THEIR UPTAKE RATES BY A LIQUID MEMBRANE SYSTEM

BY

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ABSTRACT

The uptake of each of eleven structurally related solutes from pH 1 donor solution by an invariant liquid membrane formulation was investigated. The presence of polyamino surfactants in liquid membrane formulation significantly altered the partition of solutes between aqueous phase and oil phase. Benzoic acid and salicylic acid followed monoexponential kinetics while the uptake of other solutes followed biexponential processes, except p-aminobenzoic acid which was not transported at all. Both benzoic acid and salicylic acid were removed with a much faster rate compared to other sclutes. Approximately, 90% of these solutes were removed in two and half minutes from the donor solution. It is proposed that the presence of a phenolic group allowed salicylic acid to be transported with a significantly high rate as it can form intramolecular hydrogen bonding which increases its solubility in non-polar solvents. This is supported by the fact that meta and para-hydroxybenzoic acids were removed at a much slower rate. As expected, p-amino benzoic acid was not transported through liquid membrane from an acidic donor solution probably because of the ionized amino group.

In presence of methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, acetaminophen and salicylamide rupture of the liquid membrane was apparent. This is possibly due to the formation cf alcohols in the internal aqueous phase when

these esters react with the encapsulated buffer. From the data obtained, it appears that the apparent leakage follows zero order kinetics.

A new and more sophisticated kinetic model is proposed in an attempt to rationalize the basic mechanisms behind the solute uptake by the liquid membranes. The data for benzoic acid, salicylic acid and acetylsalicylic acid were analysed by this model. Benzoic acid was not fit by this model. The lack of success to fit the data for benzoic acid is probably due to the dimerization of benzoic acid in the liquid membrane. For salicylic acid, which followed monoexponential kinetics, micro-rate constant k1 is significantly higher than k2 and k3 while k1 is significantly smaller than k2 and k3 for acetylsalicylic acid which followed biexponential kinetics. Hence, it is possible that depending on the magnitude of these micro-rate constants, the uptake process may follow either mono or biexponential kinetics.

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I. INTRODUCTION

A. Some Aspects of Surface Chemistry

1. Definition of emulsions

An emulsion can be defined as a dispersed system containing at least two immicible liquid phases (1). Emulsions are thermodynamically unstable due to excess free energy associated with the surface of the droplets. Present day emulsion technology allows us to prepare stable emulsions, even though emulsions are thermodynamically unstable.

Generally, emulsions contain an aqueous phase and an oil phase. Depending on which liquid is dispersed in another, emulsions can be classified into oil-in-water (o/w) and water-in-oil (w/o) types. The particle diameter of the dispersed phase may range from 0.1 to 100 microns depending on the method of preparation.

2. Emulsification

To obtain a stable emulsion, an emulsifying agent is added to the two immiscible liquids. The emulsifing agent plays an important role in emulsification. It reduces interfacial tension and allows the formation of a greatly enlarged interfacial area with a reduced energy input. The type of emulsion formed, oil-in-water or water-in-oil primarily depends upon 'Hydrophile-Lipophile Balance' (HLB) value of the emulsifying agent. The HLB value is the

percentage weight of the hydrophilic group divided by five in order to reduce the range of values (2). If the emulsifier is more hydrophilic, it helps to form an o/w emulsion. Conversly, with more lipophilic emulsifiers w/o emulsions are formed. The HLB value also determines whether a surfactant is an emulsifier, wetting agent, detergent, or solubilizing agent. Generally, w/o emulsions are formed when the HLB value of emulsifier ranges between 4-6 and o/w emulsions are formed when the range is 8-18. In most emulsions, a combination of emulsifying agents are used rather than a single emulsifying agent. Not only, the HLB value of the emulsifying agent determines the type of emulsion formed, other factors like phase volume ratio and densities alsc influence the type of emulsion formed.

Stability is one of the most important considerations when dealing with emulsions. Physical instability of an emulsion can result from creaming and sedimentation; aggregation and possible coalescence of the internal phase; and phase inversion. Upward movement of dispersed particles is termed as Creaming while downward movement is refered as Sedimentation. Creaming and Sedimentation may facilitate Coalescence of internal phase. Separation of two immicible phases is termed as Coalescence. Phase inversion may result from addition of an electrolyte or a change in phase volume ratio. An emulsion of o/w type may be converted to w/o type or vice versa. Constant vigil was given to the stability of Liquid Membrane formulatien with which we were dealing,

considering the above factors of instability.

3. Multiple Emulsions

A multiple emulsion is one in which both types of emulsions exist simultaneously (3). Multiple emulsions are some times refered as Complex Emulsions. A water-in-oil emulsion can be dispersed in water forming a water-in-oil-in-water (w/o/w) emulsion. Similarly, an oil-in-water-in-oil (o/w/o) emulsion can be formed by dispersing an oil-in-water emulsion in an oil phase. Multiple emulsions may contain any number of simple emulsions one dispersed in another.

B. Liquid Membranes

1. General description of liquid membrane systems

Liquid membranes were invented at Exxon Corporation by Li in 1968 (4). They have been developed to solve a variety of separation problems. Liquid membranes consist of a liquid film stabilized on both inner and outer surfaces by appropriate surfactants. In general, liquid membranes are formed by first making an emulsion with an oil phase and a water phase and then dispersing the emulsion in a third phase, which constitutes continuous phase. The phase which is in between the continuous phase and the internal phase of the emulsion is termed as Liquid Membrane.

There are two types of liquid membranes. One is oil type and the other water type. If a water-in-oil emulsion is dispersed in an oil phase (continuous phase), an oil type liquid membrane will result. Conversly, a water type liquid

membrane can be obtained by dispersing an oil-in-water emulsion in an oil phase. Both types of liquid membranes have many applications in separation science, which will be discussed in a latter part. In this investigation, oil type liquid membranes, which have wide range of applications were used. Liquid membranes may also contain other additives in addition to surfactants. The surfactants and additives are used to control permeability, selectivity and stability of the membrane.

2. Characteristics of Liquid Membranes

The internal aqueous phase of w/o/w liquid membranes can be formulated into a sink or a reservoir. For example, in treatment of drug overdose and in artificial kidney replacement, the internal aqueous phase can serve as a sink. For oral prolonged released products, intramuscular products and for oxygenation of blood, it can act as a reservoir. In conventional encapsulating membranes, transport occurs through pores in the membranes. But, in liquid membranes transport is accomplished by dissolution of the material in the membrane. Due to this different mechanism of mass transfer in liquid membranes, selective mass transfer can be achieved. Molecules can be transported through membranes into the central aqueous phase and can be trapped by selective reaction with an encapsulated reagent. The central aqueous phase can be formulated into a high capacity sink by

1) Plasma proteins

2) pH control

3) Activated charcoal

4) Specific antibodies

For drugs strongly protein bound such as barbiturates, plasma proteins may serve as a sink. For acidic solutes a central aqueous phase with a pH of more than 7 and for basic solutes a pH of less than 7 will act as a sink. A schematic diagram of solute uptake by pH control using sodium hydroxide as a trapping agent is shown in Figure 1. Solutes having significant oil solubility diffuse from external aqueous phase into central aqueous phase due to concentration gradient. A membrane made from hydrocarbon oil has no solubility for icns due to the low dielectric constant of hydrocarbons. Therefore, only uncharged species in the donor phase can be dissolved in the membrane and transported into central aqueous phase where an appropriate trapping agent present. A good example of a material which can be transported by this method is the molecular species ammonia (NH_3). The ammonia molecules, dissolved in oil are transported through liquid membrane into the internal aqueous phase where it reacts with hydrogen ions from an encapsulated acid to form (NH^+_4) ions which can not get back out through membrane since it is an ion species. Liquid membranes can encapsulate reagents which may not be encapsulated by conventional encapsulation techniques. In addition, these liquid membranes have the ability to encapsulate very ccncentrated reagents. Liquid membranes

also can be tailored to transport ions. Here high molecular weight organic molecules having ion exchange capacity are incorporated into the liquid membranes. These organic molecules are firmly bound in the membrane. Once the ions are transfered through membrane, they can be trapped by chemical precipitation with an encapsulated reagent. Anions like sulfide, nitrate, cyanide and phosphate were efficiently transfered (5). Using the molecules with cationic exchange capacity, cupric, mercuric and silver ions were efficiently transported.

3. Applications of Liquid Membranes

Liquid membrane systems have many potential applications in separation science. For example they may be used in purificatien cf waste water (5), separation of hydrocarbon types (6), for the treatment of chronic uremia (7), and in treatment of drug overdose (8,9,10). Liquid membranes are capable of reducing levels of NH_4^+, Cr^{6+}, Cu^{2+}, Hg^{2+} and Cd^{2+} from several hundred ppm to less than 1 ppm in waste water treatment (11). Separation of phenol and other weakly ionized acids and bases from waste water is also described in litrature (12).

A number of potential applications of liquid membranes have been proposed in biomedical sciences. Among them are the use of liquid membranes for emergency treatment of drug over dose, oxygenation of blood, treatment of chronic uremia, oral prolonged release products, intramuscular dosage forms, and enzyme processes

encapsulated by liquid membranes. Most of the work dealing with treatment of drug overdose has been carried out at the College of Pharmacy, University of Rhode Island.

Human poisoning by drug overdose is common in the United States (13). Suicidal attempts by barbiturate ingestion accounts for 75% of all suicides by drugs or 50% by chemicals (14). Child poisoning by aspirin is also common. One of the most obvious methods of treatment for cases of drug overdose is the use of techniques designed to remove drug from body. Current methods of treatment involving both invasive and non-invasive include peritoneal dialysis, ingestion of adsorbents, such as charcoal, or administration of emetics. All of these methods have some disadvantages. Peritonial dialysis, as it is invasive technique, requires skilled man power and is not always effective. Activated charcoal is of very limited utility for some drugs, can be inactivated by food such as ice cream and cannot be administered to comatose patients. The use of emetics is extremely unpleasent. Rhodes et al suggested the use of liquid membranes for this purpose (8,9,10). Liquid membrane devices have considerable advantages over the current methods of treatment. They are easily administered since they have a consistancy, similar to a milkshake and can probably be supplied by a stomach tube directly to the small intestines. A mixture of drug sinks in different liquid membranes may provide an almost "universal" binding source.

Preliminary *in vitro* studies indicated that phenobarbital and aspirin can be efficiently trapped by liquid membranes from either pH 2 or 7 buffered solutions (9). Aspirin is extracted somewhat faster than phenobarbital. It was also shown that the membrane viscosity has considerable effect on uptake rate; the lower the viscosity, the more rapid removal of the drug (9). The stability of the membrane to the leakage varies in the other direction, that is, the stability of the membrane decreases with decrease in membrane viscosity. Rhodes *et al* investigated the *in vitro* removal of six barbiturates from pH 2 donor solutions by liquid membranes (10). More than 90% of amobarbital, phencbarbital and secobarbital were removed within 10 minutes by liquid membranes. The relative order of extraction efficiency did not follow either base strength or apparent partition coefficients. The liquid membranes showed some instability in presence of bile salts. The kinetics of unassisted drug transfer of various drugs through liquid membranes were discussed by Frankenfeld, Fuller and Rhodes (9,10). For removal of some of the toxins in chronic uremia, Asher and his associates are developing a liquid membrane system. The mechanism for removal of urea from gastrointestinal tract by liquid membranes is its hydrolysis by the enzyme urease to carbon dioxide and ammonia. The ammonia would be removed by liquid membranes specially formulated for this purpose while the carbon dioxide is readily eliminated by lungs. In order to achieve

faster rate of hydrolysis of urea, it may be necessary to supply urease encapsulated in liquid membrane in addition to naturally available urease in the gut. Thus, a dual membrane system, one containing a formulation with a trap to remove ammonia and the other containing encapsulated urease should be formulated. However, under certain physiological conditions these two formulations should work in an opposite way. The former must be stable enough to maintain its integrity in order to trap ammonia efficiently and the latter must be somewhat unstable so that the urease is released at the proper rate. Citric acid has been successfully encapsulated for trapping ammonia. Work on treatment of chronic uremia with liquid membranes is continuing.

Asher et al suggested that liquid membrane systems for oxygenation of blood (15,16). Conventional blood oxygenators, although are efficient oxygenators, may damage blood protiens and red cells. Flurocarbons are well suited as membranes for this purpose because of the high solubility of oxygen and carbon dioxide. Flurocarbons have good compatibility with blood. The encapsulated oxygen permeats through the membrane and oxygenates the blood while carbon dioxide in the blood can diffuse into the membrane. Work is progressing in this area mainly on development of a commercial type oxygenator. Liquid membrane devices show considerable potential for enzyme encapsulation in order to enhance rates, to gain additional control over enzyme

reactions or to understand biochemical enzyme mechanisms. Phenolase and urease were successfully encapsulated in liquid membrane devices (17,18).

C. Justification for and Significance of the study

It is evident that liquid membrane systems have high potential for many biomedical uses. However, more basic and applied research is needed in order to exploit pharmaceutical applications of these fasinating systems. Since these liquid membranes were invented only a few years ago, little work has been done on the kinetics of solute uptake. Because the structure-transport rate relationship is very important in predicting potential of liquid membranes in separation science, the major goal of this study is to investigate the effect of molecular structure of some aromatic solutes on their uptake rates by liquid membranes. Since the transport rate may depend on partition coefficient of the solute, it is of considerable interest to correlate the partition coefficient and the transport rate with the molecular structure.

Rhodes and his coworkers investigated the uptake of six barbiturates (10). They proposed a simple model for solute uptake by the membranes. However, by using a number of structurally related species, it may be possible to understand the complex process behind the solute transfer across the liquid membranes. Interestingly, the relative order of extraction efficiency for barbiturates did not follow either base strength or the apparent partition

coefficients. By using different solute species with different rates of uptake, it may be possible to understand the process of solute transfer more clearly. Some amphoteric solutes like p-amino salicylic acid may provide more information on solute transfer. Hence considerable attention was given not only to correlate uptake rate of solutes with their molecular structure, but also to understand the basic mechanism behind the uptake process.

THEORETICAL

A. Henderson-Hasselbalch Equation

Organic acids dissociate into ions in aqueous solutions. The extent of dissociation depends up on hydrogen ion concentration of the solution and dissociation constant of the solute and can be readly predicted by Henderson-Hasselbalch equation. According to this equation (19),

$$pH = pKa + \log(salt)/(acid) \qquad \text{Eq. 1}$$

where,

pH = hydrogen ion concentration

pKa = dissociation constant

(salt)/(acid) = ratio cf molar concentrations of ionized and unionized species

From the above equation, the pH at which minimum or maximum ionization of an organic acid exists in a solution can be easily calculated. The central aqueous phase of liquid membrane was formulated to form a high capacity sink by pH control. The Henderson-Hasselbalch equation was used in calculating the pH of the central aqueous phase. The pH of donor phase was also calculated from the same equation. An aqueous solution of pH 1 was used as donor solution to minimize the ionization cf solutes, so that, maximum number of unionized molecules can be transported across the membrane. The central aqueous phase was formulated with a

pH 10 buffer, which can induce ionization of molecules transfered into central aqueous phase and thereby traps the solute in the central aqueous phase.

B. Diffusion and Fick's law

Diffusion is the spontaneous penetration of one substance into another in the direction of a concentration gradient (20). Fick's law states that the rate of diffusion across a semipermeable membrane is directly proportional to the concentration gradient between the two surfaces of the membrane and to the area of the membrane but inversely proportional to the membrane thickness (20). Rhodes et al suggested that the solute transfer from the donor solution to the central aqueous phase is accomplished by solution of the solute in the membrane and diffusion in the direction of the concentration gradient (10). According to Fick's law, the transport of the unionized solute across the membrane is,

$$dCo/dt = -DA/\Delta X\ (Co-Ci) \qquad \text{Eq. 2}$$

dCo/dt = rate of diffusion

D = diffusion coefficient of solute in the membrane

A = area of contact between the donor solution and liquid membrane (this is a function of the volume of the liquid membrane used when the stirring speed is kept constant)

ΔX = membrane thickness

Co = concentration cf solute in external phase

Ci = concentration cf solute in internal phase

Rhodes and his coworkers also suggested that if transport process is governed by simple fickian diffusion, first order kinetics may be followed. First order rate equations were derived mathematically from Fick's law. It has also been suggested that the first order rate constant is a function of diffusion coefficient of the solute, the area of contact between the donor phase and liquid membrane, and the membrane thickness.

C. Partition Coefficient

If a substance is added to two immiscible solvents, it will then become distributed between the two solvents in a definite concentration ratio. This ratio is termed as distribution ratic or partition coefficient of the substance. Partition coefficient can be expressed mathematically as (21),

$$C1/C2 = K \qquad \text{Eq. 3}$$

where C1 and C2 are equilibrium concentrations of substance in solvent 1 and solvent 2 and K is the partition coefficient. The distribution law applies only when the substance distributes between the two solvents in a common species, that is, as an unionized species and/or a monomer. For example, considering the distribution of our model solute benzoic acid between an oil phase and an aqueous

phase, a true partition coefficient will be obtained only when the benzoic acid exits in both solvents as unionized and as a monomer. The partition coefficient plays an important role in the solute transfer across the liquid membrane. Before a solute can be transported across liquid membrane, it should first dissolve in the membrane and this dissolution will definitely depend upon partition coefficient. Liquid membrane contains surfactants which may combine with solute and alter the partition coefficient. Rhodes et el reported that no linear relationship was obtained between the apparent partition coefficient (ie, partitioning between aqueous phase and oil phase containing surfactants) and liquid membrane transport rate constant (10). Hence, it is of considerable interest to investigate the effect of surfactants on the partition coefficient of the solute.

D. Biexponential Model

Frankenfeld, Fuller and Rhodes have discussed the kinetics of unassisted transfer of various drugs through liquid membranes (9,10). They suggested that the uptake process obeys Fick's law of diffusion and first order kinetics are followed, the rate equation for which can be written as

$$dCe/dt = - k\ Ce \qquad \text{Eq. 4}$$

where,

Ce = concentration of solute in the donor phase

t = time

k = first order rate constant

The model developed in this work proposes that solute uptake is described by biexponential process, (ie, a two compartment model). Considering the transfer of solute from donor solution to liquid membrane as one phase, and from liquid membrane to central aqueous sink as another phase, a biexponential curve will follow the equation

$$C = A\, e^{-\alpha t} + B\, e^{-\beta t} \qquad \text{Eq. 5}$$

where,

C = concentration of solute in the donor phase at time, t

A and B = preexponential terms containing micro-rate constants, initial concentration of donor solution and volume of the system.

α and β = macro-rate constants

The rate equations for the above model are as follows

$$d(Ce)/dt = -ka(Ce) \qquad \text{Eq. 6}$$

$$d(Co)/dt = ka(Ce) - kb(Co) \qquad \text{Eq. 7}$$

$$d(Ci)/dt = kb(Co) \qquad \text{Eq. 8}$$

where,

Ce = concentration of solute in the donor phase

Co = concentration of solute in the oil phase

Ci = concentration of solute in the central aqueous phase

Ka and Kb = first order rate constants

A combination of computer programs, 'AUTOAN' and 'NONLIN' were used to estimate the parameters of the transport process. From these parameters, the macro-rate constants α and β were calculated. The above model has a limitation; it gives us the macro-rate constants. It is difficult to understand the 'basic mechanism' of solute transfer from the macro-rate constants. However, for the purpose of comparing the different solute uptakes, the use of macro-rate constants is quite justified.

A more sophisticated model including micro-rate constants will enable us to understand the basic mechanism behind the solute uptake by the liquid membranes. A schematic representation of this model is presented in Figure 2. Here k1 represents the transfer of solute from external aqueous phase to the liquid membrane, k2 represents the transfer of solute back to external aqueous phase from liquid membrane, k3 transfer from liquid membrane to the internal aqueous phase and k4 transfer back from internal aqueous phase to the liquid membrane. The rate equations for this model are

$$dA/dt = k2B - k1A \qquad \text{Eq. 9}$$

$$dB/dt = k1A + k4C - (k3+k2)B \qquad \text{Eq. 10}$$

$$dC/dt = -k4C + k3B \qquad \text{Eq. 11}$$

where,

A = concentration of solute in external phase

B = concentration of solute in liquid membrane

C = concentration of solute in in internal phase

k1,k2,k3, and k4 = micro-rate constants

The ratio between k2 and k1 is the partition coefficient of the solute between the external aqueous phase and liquid membrane. Hence, these twc rate constants may depend upon the partition coefficient. When the solute enters the internal aqueous phase, most of it will be disssociated into ions and ions have no solubility in the liquid membrane. Hence, k4 would be very small and can be considered negligible. However, k4 might depend upon the dissociation constant of the solute. The data was simulated by the computer program 'NONLIN' and a FORTRAN subroutine. A further discussion of this simulation can be found in results and discussion section.

III. EXPERIMENTAL

A. Materials

Equipment: The following items were used.

Perkin-Elmer Hitachi 200 Spectrophotometer with recorder, Perkin Elmer Corporation, Norwalk, Conn.

Constant speed and torque control unit, Cole-Parmer Instrument Company, Chicago, Ill.

Photoreflectance Tachometer, Photo Tech model 1030, Pioneer Electric and Research Corporation, Forest Park, Ill.

Motor generator Motamatic, Electro Craft Corporation, Hopkins, Minn.

Water heater, Porta-temp with stir pump, Precision Scientific Company, Chicago, Ill.

Mettler balance, Type H5, Mettler Instrument Corporation, Hightstown, N. J

Hewlett-Packard Calculator Model 10, Hewlett Packard Calculators Division, Loveland, Colorado

Computer, Itel AS/5, running IBM os/MVT with HASP II Version 3, URI Academic Computer Center, Tyler Hall, URI, Kingston, RI

B. Chemicals

Salicylamide, lot A8A, Eastman Kodak Company, Rochester,
N. Y

Hydrochloric acid, lot E612430, Allied Chemical, Specialty Chemicals Division, Morristown, N. J

The following chemicals were obtained from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin.

benzoic acid, lot DC 111477

salicylic acid, lot DC 041987

m-hydroxy benzoic acid, lot JC 072487

p-hydroxy benzoic acid, lot EB 050277

acetylsalicylic acid, lot KC 040577

4-amino salicylic acid, lot PB 110875

p-amino benzoic acid, lot JC 032787

4-acetamidophenol, lot JC 062887

methyl p-hydroxy benzoate, lot JC 071387

ethyl p-hydroxy benzoate, lot KC 030287

The following Liquid Membrane formulations and oil were supplied by Exxon Research and Engineering Company, Linden, N. J

Liquid membrane formulation A, lot 6159-156

Liquid membrane formulation B, lot 6854-9

Hydrocarbon oil, lot 6159-156 - MS

C. Method

The uptake of eleven structurally related compounds by an invariant liquid membrane formulation was monitored as a function of time. This liquid membrane formulation contained pH 10 buffer as a trapping agent in the internal aqueous phase. For certain solutes, equilibrium concentrations after mixing with another liquid membrane formulation with pH 1 buffer as internal aqueous phase were determined in order to determine the micro-rate constants governing the transport process. Partition coefficients of the solutes between the hydrocarbon oil (which was used in the preparation of above two liquid membrane formulations) and water were determined.

1. Spectrophotometric Determination

The spectrophotometer was calibrated for each solute at its wavelength of maximum absorbance in 0.1 normal hydrochloric acid. Wavelengths of maximum absorbance for each solute species in 0.1 normal hydrochloric acid were determined previously using the Perkin Elmer recorder attached to the spectrophotometer. According to Beer's law, absorbance is the product of absorptivity, optical path length and analytical concentration (22), that is,

$$A = ab\,C \qquad \text{Eq. 12}$$

where

A = absorbance

a = absorptivity

b = sample path length, cm

C = concentration, grams/liter

A plot of absorbance as a function of concentration gives a slope equivalent to the term 'ab' which is the product of absorptivity and sample path length. Therefore, the concentration of an unknown sample of solute can be determined using above equation in the form of

Conc.(gm/l) = absorbance/slope of plot, abs. vs conc. By using a Hewlett Packard model 10 calculator and recorder, plots of absorbance versus concentration were plotted for each solute. Slopes and correlation coefficients were also determined. Wavelengths of maximum absorbance, molar absorptivities and correlation coefficients for Beer's plots were shown in Table I. (page 32)

2. Uptake of solutes by liquid membrane formulation

Figure 3 illustrates the apparatus set up for uptake of solute by liquid membrane formulation. A ten gallon aquarium with Precision porta-temp unit and stir pump was set up to maintain the required temperature. A round bottomed beaker with baffles (2000ml capacity) was set up in the water bath using a firm stand and a ring clamp. The beaker was tied with a chain clamp so that it was in a fixed position throughout the experiment. Then a constant speed stirrer with one and a half inch propeller was mounted to the stand so that the stirring rod passed through central axis of the beaker. Two hundred ml of donor solution was poured into beaker and the propeller was adjusted so that it was just below the surface of the donor solution. Then the

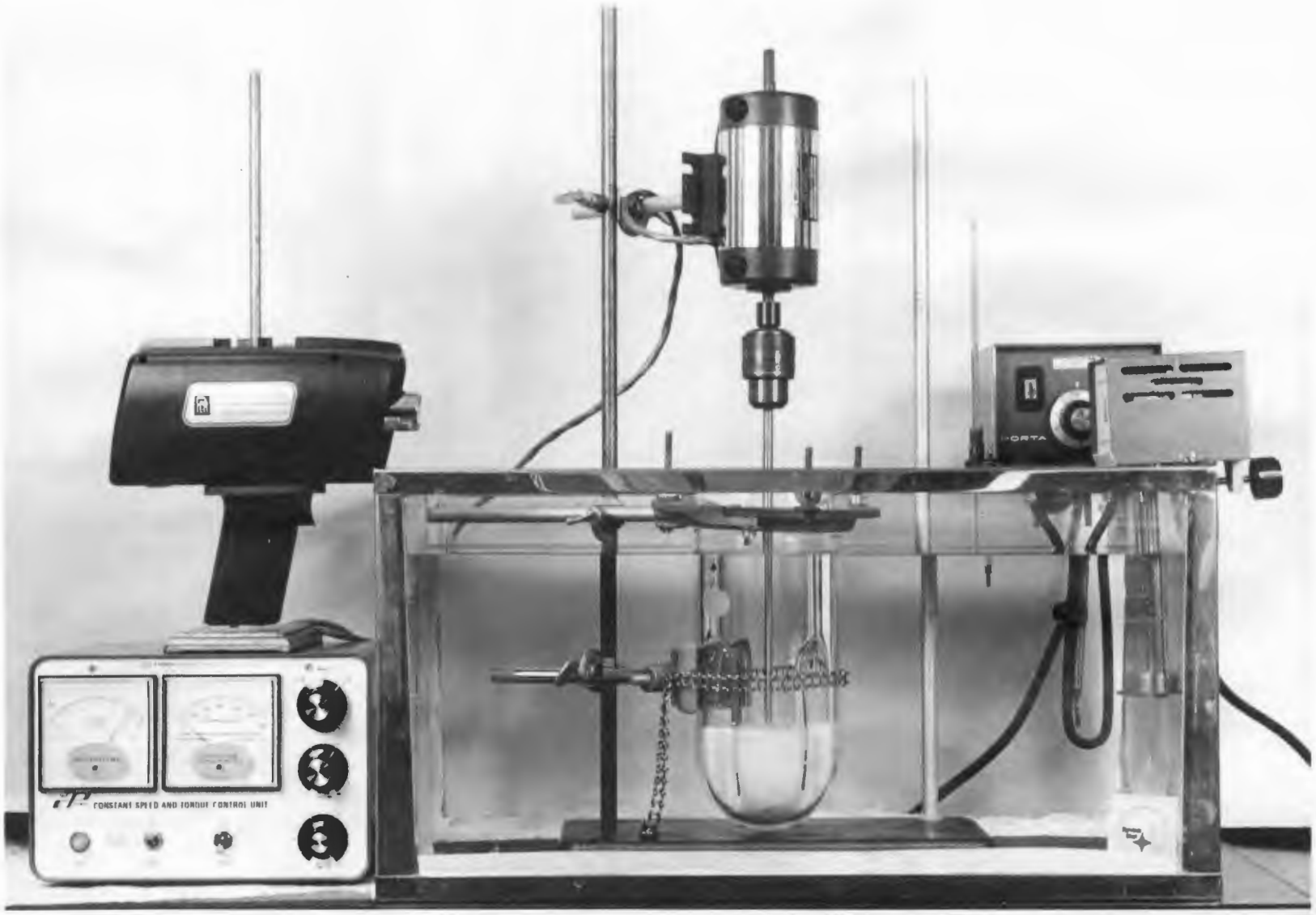

Figure 3. Apparatus for determination of uptake rates of solutes across liquid membrane systems

stirrer was set at 250 r.p.m and the stirring speed was checked with photoreflectance tachometer.

Two hundred ml of liquid membrane was poured into donor solution. Mixing of donor solution and liquid membrane formulation is shown in Figure 4. During the extraction experiments, samples were taken at appropriate intervals using a glass tube (25 ml 'buret for pinch cock'). Separate burets were used for each individual sample. The samples were filtered immediately using Whatman No:42 filter paper by suction. The sampling procedure was started 10 seconds before the theoretical sampling time and filtration was stopped 5 seconds after the theoretical sampling time. Of these 15 seconds, the first 5 seconds were utilized for taking the sample and the latter 10 seconds for filtration, so that the middle of the 10 seconds of filtration will represent the theoretical sampling time. The filtrate was then diluted suitably with 0.1 normal hydrochloric acid and the concentration of solute in each sample was determined by ultraviolet spectroscopy. A solution with an initial concentration of 1 gram/liter of solute was used as donor solution in each experiment except for the uptake of p-hydroxybenzoic acid and ethyl p-hydroxybenzoate. An initial concentration of 0.5 gram/liter was used for these solutes.

3. Determination of Partition Coefficients

Solutions of solutes in 0.1 normal hydrochloric acid with a concentration of 0.5 gm/l were prepared. A volume

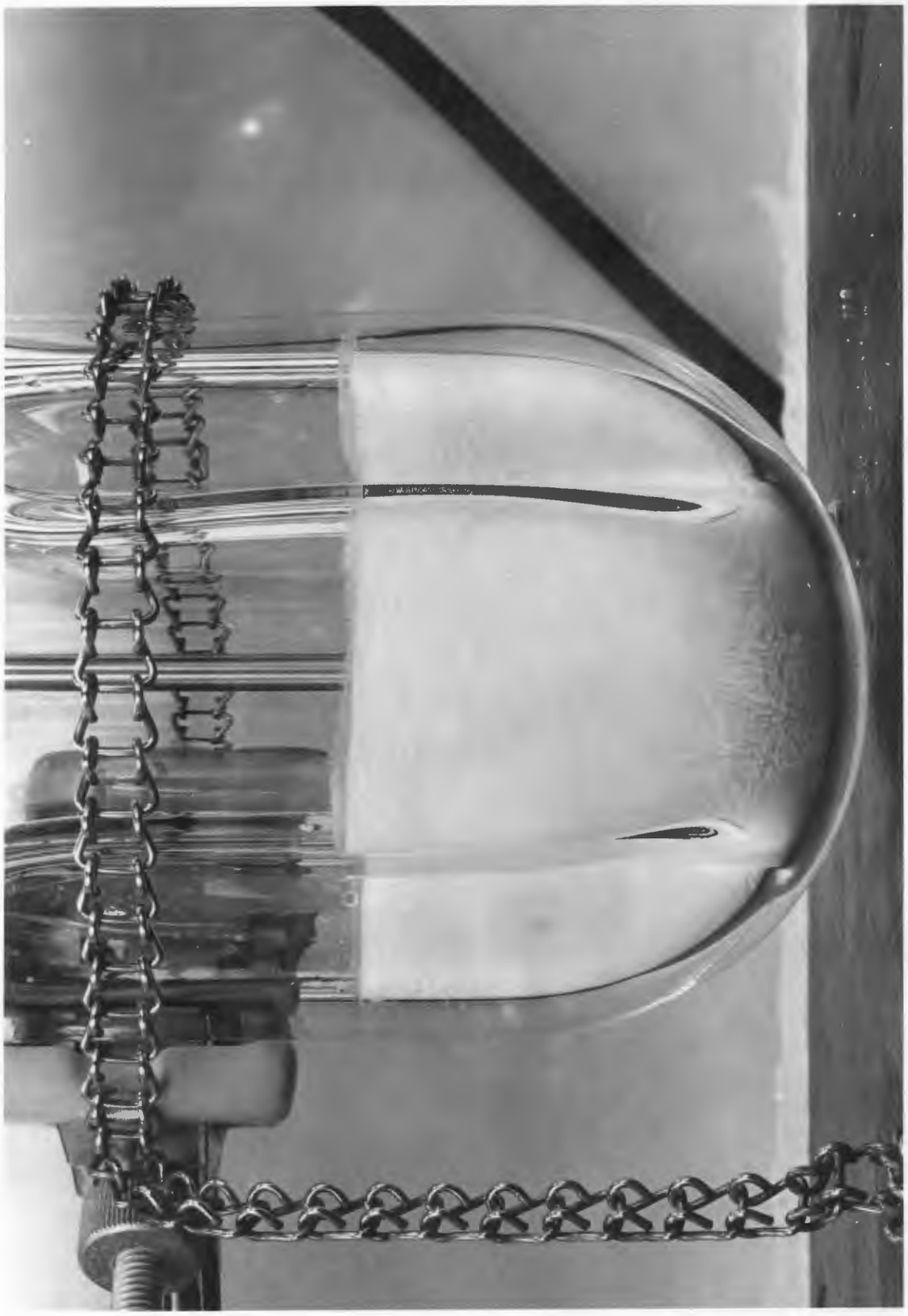

Figure 4. Mixing of liquid membrane formulation and donor solution

of 50ml of each solution was shaken with 50ml of hydrocarbon oil in a 125ml separating funnel. The systems were kept at 22-25° C and were shaken frequently until equilibium distribution of solute between the aqueous phase and the oil phase was reached. Samples of aqueous phase were taken at appropriate intervals to determine the concentration of solute in the sclution. The samples were then analysed by ultraviolet spectroscopy. For certain solutes partition coefficients between 0.1 normal hydrochloric acid and the liquid membrane containg surfactants were also calculated from the data obtained from the uptake of solutes by liquid membrane formulation which contained pH 1 buffer as internal aqueous phase. The calculations involved are,

Amount of solute in external aqueous phase at equilibrium = concentration (grams/liter) of external aqueous phase / 5
(since 200ml of donor sclution was used as external aqueous phase)

Amount of solute in internal aqueous phase at equilibrium = amount of solute in external phase / 2
(since the liquid membrane contained oil and aqueous phases in 1:1 ratio and 200ml of liquid membrane was used in each experiment)

Amount of solute in membrane at equilibrium = amount of solute in the external aqueous phase before mixing with liquid membrane - (amount in external phase + amount in internal phase)

Partition coefficient of solute = concentration in oil (moles/liter) / concentation in aqueous phase (moles/liter)

4. Computerized Data Analysis

Computer programs AUTOAN and NONLIN were used to fit the data (23,24). The program AUTOAN was used to estimate the macro-rate constants. This program first determines the best number of exponentials and then automatically links with NONLIN to estimate the parameters. The micro-rate constants were estimated by the program NONLIN. The uptake data was fit by the equations 9,10,11 (page 18). A copy of the subroutine used to fit these equations by NONLIN can be found in the appendix.

IV. RESULTS AND DISCUSSION

The effect of molecular structure of eleven structurally related solutes on their uptake rates by a liquid membrane system was investigated. A new and more sophisticated kinetic model which can yield more information on the transport process of solutes across liquid membranes is proposed. The chemical structures of solutes used in this investigation are shown in Figure 5.

Wavelengths of maximum absorbance, λ_{max}, were determined for each solute in 0.1 normal hydrochloric acid. Molar absorptivities (product of absorptivity and the molecular weight) of solutes were calculated from the Beer's plots. Table I shows the wavelengths of maximum absorbance, molar absorptivities and correlation coefficients obtained for the Beer's plot for each solute. For all the plots, a correlation coefficient of more than 0.999 was obtained.

A. Partition Coefficients Studies

Table II lists the partition coefficients for all the solutes, obtained between a) oil and 0.1 normal hydrochloric acid and b) liquid membrane and 0.1 normal hydrochloric acid. The hydroxybenzoic acids showed decrease in partition coefficient values between aqueous phase and oil as the position of hydroxyl group is changed from ortho to meta to para positions. A partition coefficient of 0.139 was obtained for o-hydroxybenzoic acid. m-Hydroxybenzoic acid

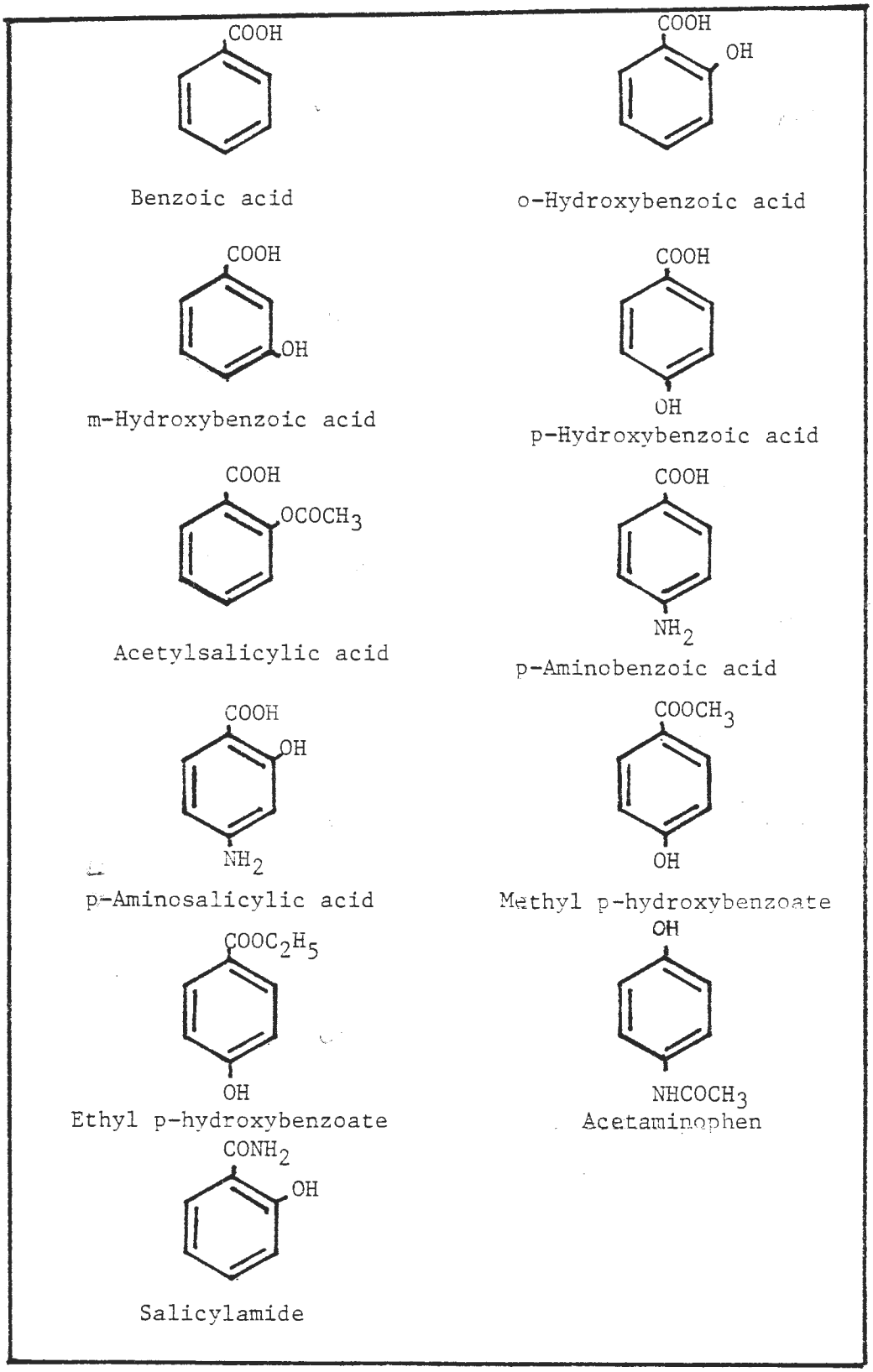

Figure 5. Chemical structures of solutes for which uptake rates by liquid membrane were investigated.

TABLE I

MOLAR ABSORPTIVITIES AND WAVELENGTHS OF MAXIMUM ABSORBANCE

SOLUTE	REPORTED IN LITERATURE*			OBSERVED**		
	λ Max (nm)	Molar Absorptivity x 10^{-3}	Solvent	λ Max (nm)	Molar Absorptivity x 10^{-3}	Correlation Coefficient
Benzoic acid	229	11.1(1)	0.5N HCL	230	11.1(6)	1.0000
o-Hydroxybenzoic acid	233	1.2(6)	H_2O	237	8.3(8)	0.9998
m-Hydroxybenzoic acid	234	6.2(3)	Methanol	237	7.1(0)	1.0000
p-Hydroxybenzoic acid	254	15.1(0)	Methanol	256	14.4(9)	1.0000
Acetylsalicylic acid	229	8.7(2)	0.1N H_2SO_4	228	8.4(2)	0.9997
p-Aminobenzoic acid	228	4.6(6)	Ethanol	226	11.6(8)	0.9996
p-Aminosalicylic acid	234	6.3(8)	0.1N HCL	234	7.1(2)	0.9999
Methyl p-hydroxybenzoate	259	9.1(2)	Methanol	256	15.2(0)	1.0000
Ethyl p-hydroxybenzoate	256	16.4(0)	Methanol	256	15.2(7)	1.0000
Acetaminophen	249	13.6(1)	Methanol	243	9.7(2)	1.0000
Salicylamide	235	7.4(4)	Ethanol	236	7.7(5)	0.9998

*, **Ref. 28,29

in 0.1 normal hydrochloric acid

for the plot, absorbance versus conc., with seven data points.

TABLE II

COMPARISON OF PARTITION COEFFICIENTS

SOLUTE	PARTITION COEFFICIENT	
	OIL	LIQUID MEMBRANE
Benzoic acid	0.37(3)	1.13(9)
o-Hydroxybenzoic acid	0.13(9)	1.58(8)
m-Hydroxybenzoic acid	0.07(3)	0.60(4)
p-Hydroxybenzoic acid	0.00(0)	0.37(9)
Acetylsalicylic acid	0.18(3)	0.38(1)
p-Aminobenzoic acid	0.000	--
p-Aminosalicylic acid	0.000	0.47(7)
Methyl p-hydroxybenzoate	0.02(2)	--
Ethyl p-hydroxybenzoate	0.07(7)	--
Acetaminophen	0.000	--
Salicylamide	0.000	--

yielded a partition coefficient of 0.073 which is approximately one half of the value of o-hydroxybenzoic acid and p-hydroxybenzoic acid did not show any partitioning into oil from aqueous solution. For benzoic acid a partition coefficient of 0.373 was obtained which is almost two and half times higher than o-hydroxybenzoic acid. Hence, the position of hydroxyl group is a very important factor in partitioning of hydroxybenzoic acids between water and oil. Acetylsalicylic acid yielded a partition coefficient slightly higher than o-hydroxybenzoic acid (salicylic acid) indicating that the acetylation of o-hydroxybenzoic acid has an effect on the partitioning or the solubility of the solute in the oil. Para-aminobenzoic acid, p-aminosalicylic acid, acetaminophen and salicylamide showed no partitioning into oil from aqueous phase. Ethyl p-hydroxybenzoate showed a partition coefficient slightly higher than methyl p-hydroxybenzoate. This may be because of increase in chain length from $-CH_3$ to $-C_2H_5$.

Those solutes, for which partition coefficients were determined between aqueous phase and liquid membrane, showed a significant increase in their values of partition coefficients when compared with the partitioning between aqueous phase and oil indicating that the surfactants play an important role in partitioning between an aqueous phase and an oil phase. Hydroxybenzoic acids showed a tremendous increase in their partition coefficients with liquid membrane. Para-hydroxybenzoic acid which did not show any

partitioning with oil yielded a partition coefficient of 0.379 between aqueous phase and liquid membrane. An increase of eight times in partition coefficient was observed for m-hydroxybenzoic acid and eleven times for o-hydroxybenzoic acid over the partition coefficients obtained between aqueous phase and oil. Hence, the phenolic group is probably responsible for this tremendous increase in partition coefficient. This may be tenatively attributed to the combination of the polyamino surfactants with phenolic groups forming a chemical complex. This argument is further supported by acetylsalicylic acid partitioning. Only a two fold increase was observed for acetylsalicylic acid compared to eleven fold increase for salicylic acid. Another possible explanation for this tremendous increase in partition coefficient of o-hydroxybenzoic acid (salicylic acid) is its ability to form intramolecular hydrogen bonding which increases its solubility in non-polar sovents. Para-aminosalicylic acid which did not show any partitioning with oil, gave a partition coefficient of 0.477 with liquid membrane. The above two factors mentioned for salicylic acid are also resposible for this increase of partition coefficient. Para-aminobenzoic acid showed no uptake by liquid membrane (which contained pH 10 buffer as sink) supporting the above explanation. The effect of partition coefficient on the transport of solutes across liquid membrane is dissussed in the following section.

B. Solute Uptake Across Liquid Membrane

The uptake of benzoic acid and salicylic acid followed monoexponential process. The transport of the other solutes obeyed biexponential kinetics. A plot of benzoic acid uptake as a function of time is shown in Figure 6. Ninety percent of benzoic acid was removed in two and half minutes and more than 99% in eight minutes. Figure 7 illustrates the salicylic acid uptake by liquid membrane formulation. A comparision of percent of solutes remaining in the donor phase after treatment with liquid membrane formulation can be found in Table III. Like benzoic acid, 90% of salicylic acid was removed in two and half minutes, but it took only five minutes to remove more than 99% of salicylic acid. First order rate constants (obtained by fitting the data into the computer program AUTOAN) for benzoic acid, salicylic acid and acetylsalicylic acid along with the partition coefficients and dissociation constants are presented in Table IV. Salicylic acid yielded a rate constant and an apparent partition coefficient higher than benzoic acid. However, the partition coefficient of salicylic acid with oil was less than one half of the value obtained for benzoic acid. As discussed before, complexation of polyamino surfactants with the phenolic group and the ability of salicylic acid to form intramolecular hydrogen bonding are attributed to this increase in partition coefficient. Benzoic acid and salicylic acid are only the solutes that showed an apparent

partition coefficient (equilibrium concentration in liquid membrane / equilibrium concentration in aqueous solution) of more than 1.0. These solutes are also the only solutes to follow moncexponential uptake process. It is speculated that the reason for observing moncexponential process rather than biexponential process is that the rate of transer in one phase is dominated by the other, possibly the rate of transfer from membrane to internal aqueous phase is dominated by the rate of transfer from external aqueous phase into the membrane. Apparent partition coefficients of more than 1.0 for these solutes supports this theory. This phenomena is further explained by analysing the data of these solutes by a more sophisticated kinetic model which is discussed in a latter part of this section. It is unlikely that the rate constants depend on the dissociation constants (pKa) , since more than 99% of both benzoic acid and salicylic acid will be ionized in the internal aquous phase (pH 10) and the rate of solute transfer from donor solution to liquid membrane is much higher than rate of transfer from liquid membrane to internal aqueous phase.

The uptake of acetylsalicylic acid followed biexponential process and is shown in Figure 8. Ninety percent of acetylsalicylic acid was removed in 16 minutes and in about 80 minutes a steady state was reached with more than 98% of solute extracted. From Table IV it can be found that the apparent partition coefficient for acetylsalicylic acid is significantly smaller than that of salicylic acid

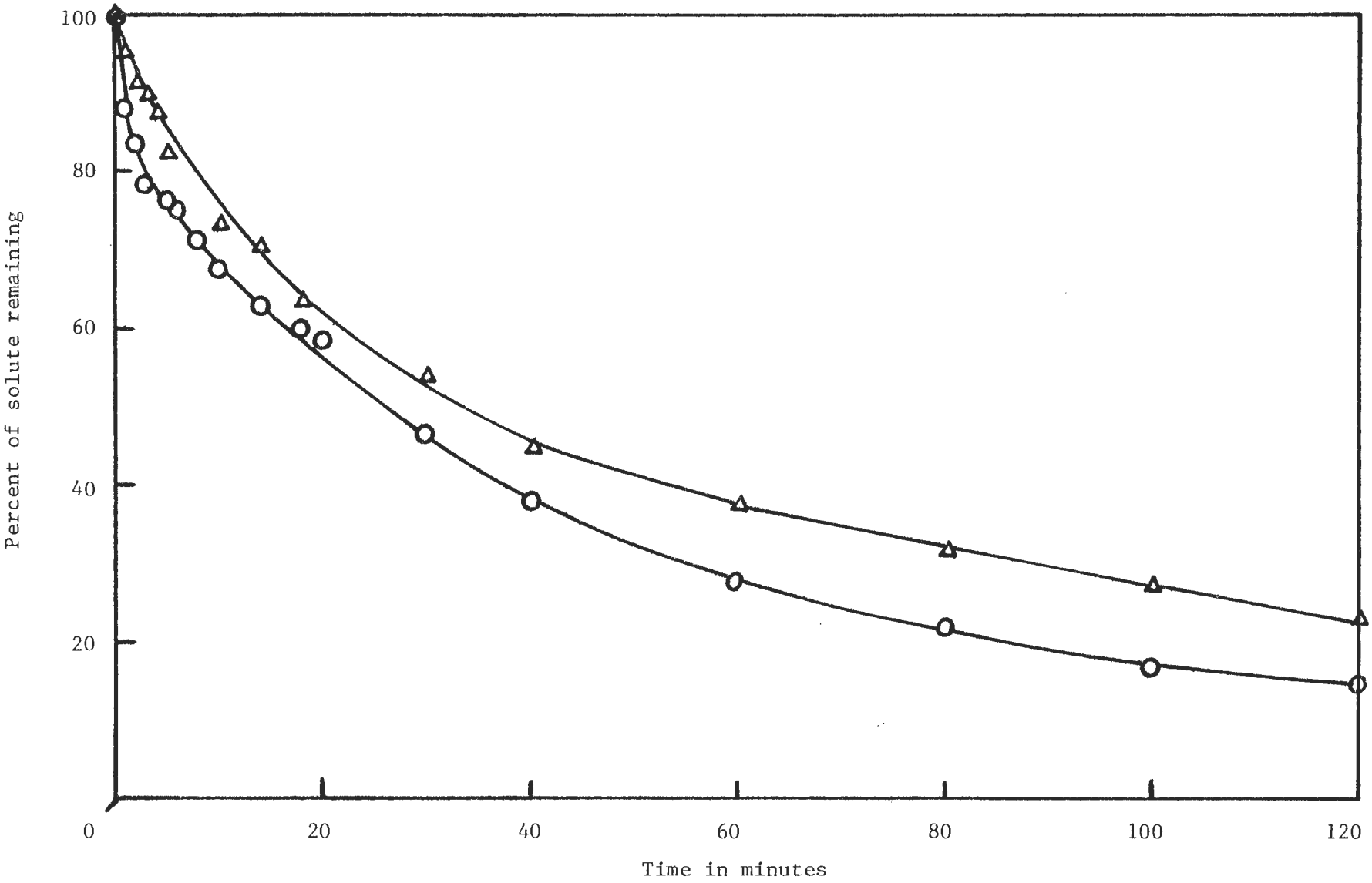

Figure 9. Uptake of m-hydroxybenzoic acid and p-hydroxybenzoic acid.

Key: O m-hydroxybenzoic acid and Δ p-hydroxybenzoic acid.

and no uptake was observed. However, p-aminosalicylic acid was transported across the liquid membrane. Seventy percent of the p-aminosalicylic acid was removed in two hours. Hence, it is possible that the presence of phenolic group is responsible for the uptake of p-aminosalicylic acid by the liquid membrane since the phenolic group may form intramolecular hydrogen bonding which increases the solubility of solute in the membrane. The uptake of p-aminosalicylic acid is shown in Figure 10. From the dissociation constants (Table V) for amino groups, it is evident that more ionization of p-aminosalicylic acid takes place than of p-aminobenzoic acid at pH 1. This indicates that the difference in extent of dissociation for these amino groups is dominated by another factor, possibly the hydroxyl group in p-aminosalicylic acid. When the uptake rate of p-aminosalicylic acid is compared with the uptake rate of salicylic acid, p-aminosalicylic acid was removed with a much slower rate. This decrease in rate is probably due to the presence of amino group in p-aminosalicylic acid.

A plot showing the uptake of methyl p-hydroxybenzoate and ethyl p-hydroxybenzoate is presented in Figure 11. The rate constants for these processes are listed in Table VI. Ethyl p-hydroxybenzoate was removed with a slightly higher rate than methyl p-hydroxybenzoate. This is probably due to the presence of an extra $-CH_2$ group in ethyl p-hydroxybenzoate (increase in chain length) or the difference in their initial concentrations. An initial

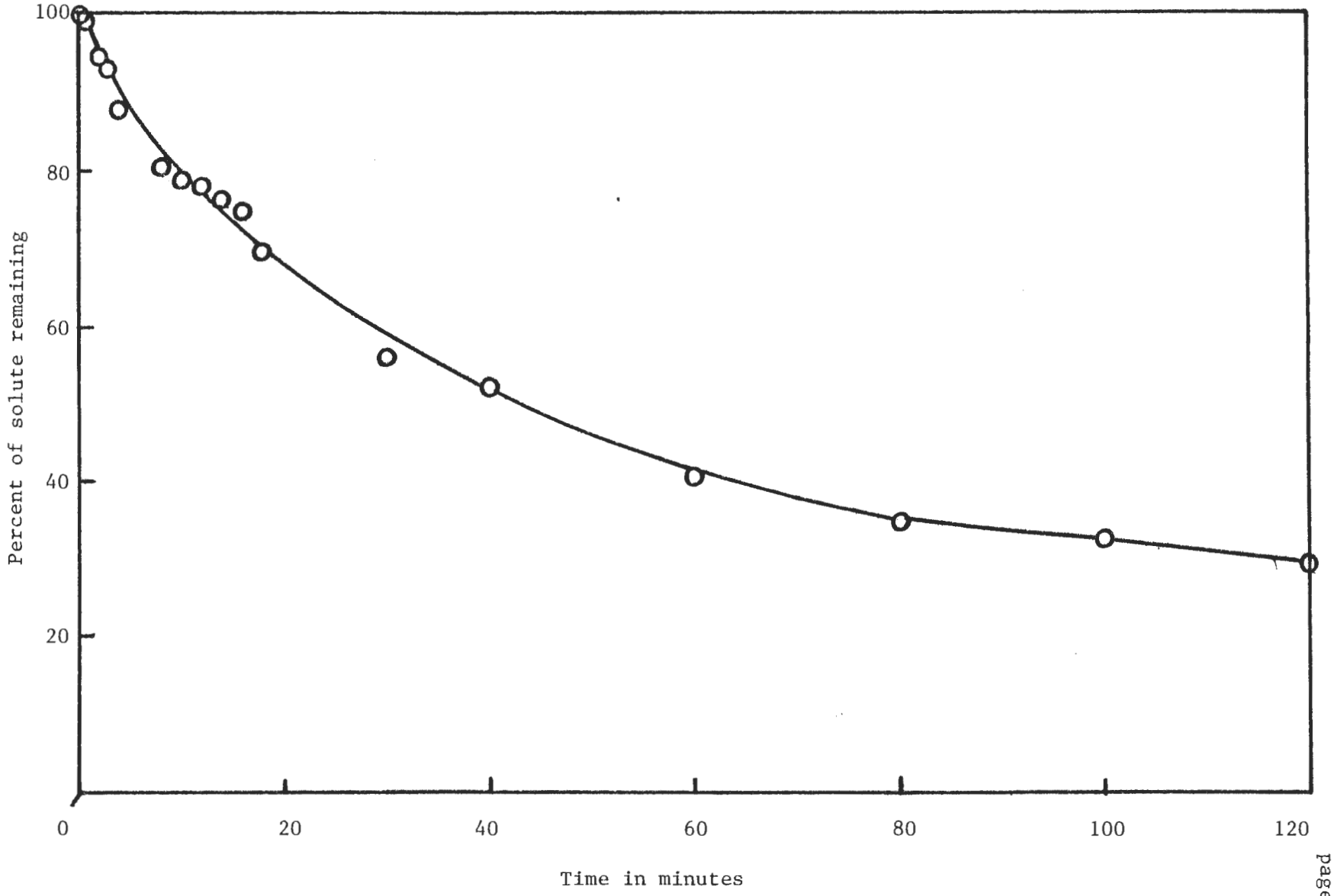

Figure 10. Uptake of p-aminosalicylic acid by liquid membrane.

concentration of 0.5 gram/liter was used for ethyl p-hydroxybenzoate, because of its low agueous solubility. The liquid membrane system showed a leakage after these two solutes were mixed for 20 minutes with donor solution. Eighty three percent of ethyl p-hydroxybenzoate and 70% of methyl p-hydroxybenzcate were removed by liquid membrane before leakage became evident. One of the explanations for leakage of solutes is the possible formation of methanol or ethanol when these solutes reach the internal aqueous phase. These alcohols may cause membrane rupture resulting in leakage. The phenolic group in these solutes may be partially responsible for the membrane rupture. However, no supporting data was obtained from this investigation. When the apparent percent of leak is plctted against the time, it appears that the leakage follows zero order kinetics. There is no evidence that the membrane is not rupturing before the leakage was observed, that is, the leakage might have started before the leak was observed in donor phase. Hence, the leakage occurs atleast with the rates represented by the rate constants observed. Methyl p-hydroxybenzoate yielded a rate constant of 0.186 moles lt^{-1} sec^{-1} and a rate constant of 0.119 moles lt^{-1} sec^{-1} was observed for ethyl p-hydroxybenzoate. The leakage plots are shown in Figure 12. From this figure, it is obvious that the apparent solute leakage is a linear function of time. However, there appears to be a lag time before rupture is initiated. Another possible explanation is that the

membrane rupture may have started at time zero, but the leakage was observed only after a certain amount of solute was extracted from the donor phase.

The uptake of acetaminophen and salicylamide is shown in Figure 13. Both the systems showed a leak towards the end of the experiments. Only 20% of acetaminophen was removed by liquid membrane in 100 minutes and thereafter a leak was observed. Salicylamide was removed at a faster rate than acetaminophen. A leak was observed at 40 minutes after 87% of salicylamide was removed from the donor solution. Partition ccefficients and rate constants along with the dissociation constants for these solutes can be found in Table VI. Neither of these two solutes showed any partitioning into oil. The uptake of salicylamide when compared to salicylic acid was significantly slower. The carboxyl group in salicylic acid was replaced by amido group in salicylamide and because of absence of carboxylic group in salicylamide there wcn't be any intramolecular hydrogen bonding.

The data was analysed by a more sophisticated kinetic model which is discussed in theoretical section. Extraction data for benzoic acid, salicylic acid and acetylsalicylic acid were fit by the computer program NONLIN. Best fits were obtained for salicylic acid and acetylsalicylic acid; benzoic acid showed much variability indicating that the uptake of this solute cannot be described by this model. The probable reason for the lack of success with the benzoic

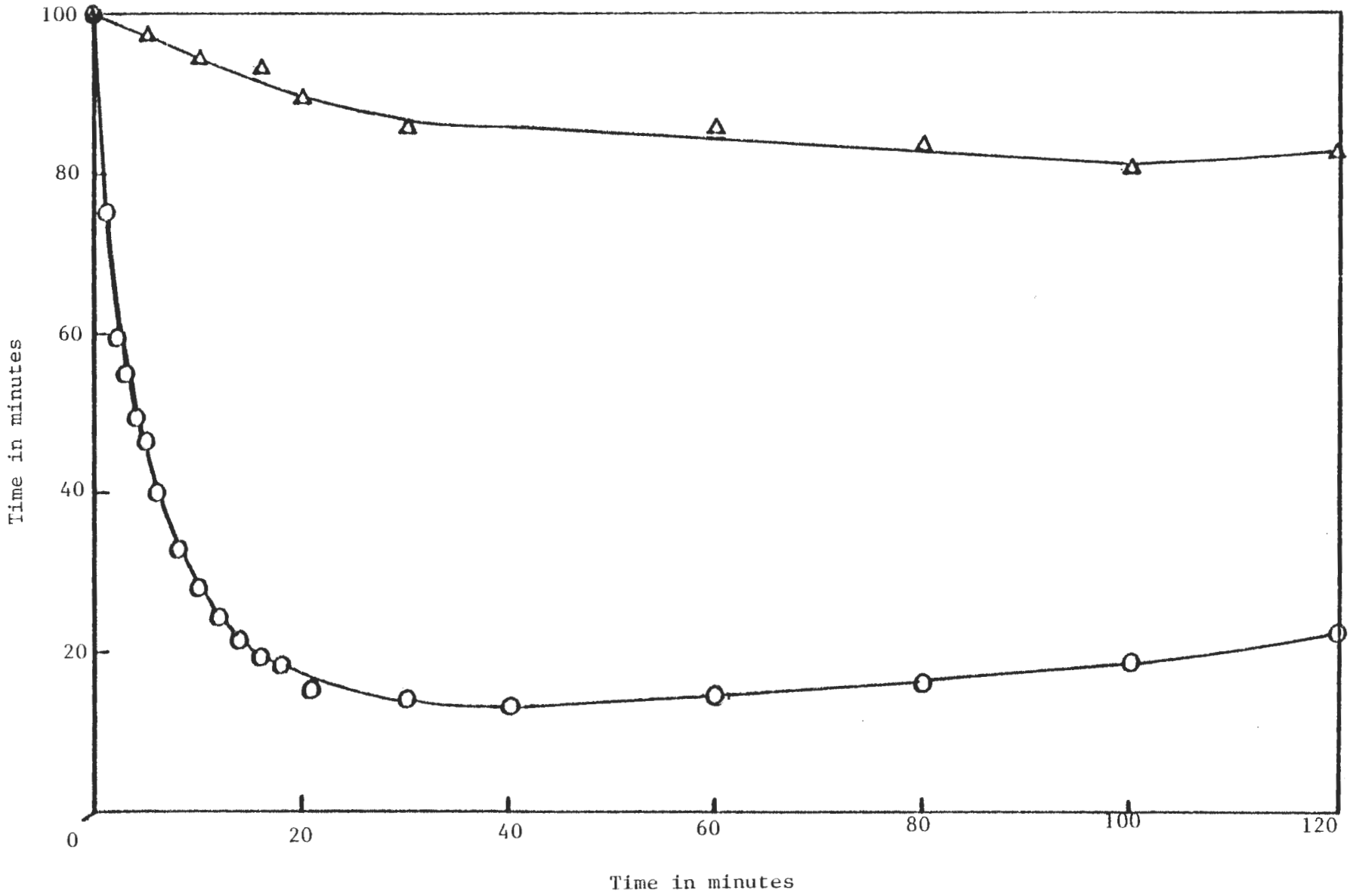

Figure 13. Uptake of acetaminophen and salicylamide by liquid membrane. Key: Δ acetaminophen and O salicylamide.

acid data, is the fact that the benzoic acid can exist as a dimer and/or a monomer in the mineral oil. It is known that the membrane oil is a non-hydrogen bonding solvent. The extent of dimerization depends upon the rate constant, kd, which governs the process of dimerization. Since the extent of dimerization is not known, the dimer partition coefficient cannot be calculated. It is known that if the partition coefficient is governed by simple dimerization, then a plot of concentration of solute in the liquid membrane against the square of concentration of solute in the aqueous phase should be linear. Since the data was not fit by the NONLIN program, perhaps, we can assume that benzoic acid may dimerize in the liquid membrane.

Table VII lists the best estimates and percent relative standard deviations for micro-rate constants obtained for salicylic acid and acetylsalicylic acid uptakes. Two procedures were followed in fitting the data. In first one, rate constant k4 was assumed to be zero and in the other procedure k4 was not assumed zero. When the data was analysed by procedure, which neglects k4, salicylic acid yielded a much variability in estimates for k4 and standard deviations were higher than the estimates (estimate, 4.22×10^{-5} ; standard deviation, 0.1116). Acetylsalicylic acid did not show much variation in k4 estimates (estimate, 6.188×10^{-3}; standard deviation, 7.627×10^{-4}). This indicates that k4 value for salicylic acid is very low and cannot be estimated by this method. When the data was analysed by

assuming k4 is equal to zero, best estimates were obtained for k1 and k3 for both salicylic acid and acetylsalicylic acid. From the values for k1, k2 values were calculated (k2=k1/partition coefficient). For salicylic acid k1 is more than k2 and k3. The value of k1 for acetylsalicylic acid is less than k2 and k3 values. Salicylic acid followed monoexponential process while acetylsalicylic acid followed biexponential process. Hence, it is possible that if k1 is greater than k2, and k3 is significantly smaller than k1, that is, if k1 dominates other rate constants, then the uptake process follows monoexponential kinetics. But, if k2 is greater than k1, and/or k1 is smaller than k3, a biexponential process will be followed. However, these conclusions are drawn from only two data sets and hence these conclusions are considered only provisional. Other solutes were not analysed by this data because a leakage was observed with their uptake or a steady state was not reached. For the data on solutes which causes membrane rupture, it is possible to analyse the data by including a leakage constant. However, then the model becomes more complicated. At this point, suffice to say that from the above proposed model, more information can be obtained on membrane rupture and membrane rupture depends upon molecular structure of the solute and other physico-chemical properties of liquid membrane systems.

In order to establish the reproducibility of the data, a second replicate was carried out for methyl

p-hydroxybenzoate and ethyl p-hydroxybenzoate. Figures 14 and 15 show the two replicates for methyl p-hydroxybenzoate and ethyl p-hydroxybenzoate respectively. As one can see from these two figures, the data was quite reproducible. The reproducibility of this technique of solute uptake by liquid membranes was also demonstrated by Yang (30). With five replicants of phenobarbital uptake, the technique was proven to be quite reproducible.

A second replicate of acetylsalicylic acid was performed at the end of the study to test whether or not the liquid membrane used was stable enough through the entire period of study. The first replicate was carried out at the begining of the study. A comparision of these two replicates of acetylsalicylic acid is presented in Figure 16. These two replicates showed no significant difference in the uptake of acetylsalicylic acid, confirming the liquid membrane formulation was stable over a period of four months. Further, this is also an indication of reproducibility of the technique.

In conclusion, the molecular structure of a solute plays an important role in its uptake by the liquid membranes. Surfactants contained in the liquid membrane formulation can significantly alter the partition coefficients and uptake rates of the solutes. The position of a phenolic group in a solute is an important factor in its transport across the membranes. If present along with a carboxylic group, it can increase the solubility of the

solute in the membrane by forming intramolecular hydrogen bonding with carboxylic group. By analysing the data by a sophisticated kinetic model containing micro-rate constants, basic mechanisms of solute transport across the liquid membranes can be understood. This model enables us to explain why monoexponential or biexponential kinetics were followed for different solutes. Thus, this investigation serves the purpose of delineating the factors governing the solute transport across liquid membranes.

V. REFERENCES

1. "Remington's Pharmaceutical Sciences", Mack Publishing Co. Easton, Penn., 14th ed., (1970) p. 334.

2. Lachman, L., Lieberman, H. A., and Kanig, J. L., 'The Theory and Practice of Industiral Pharmacy", Lea & Febiger, Philadelphia, (1970) p. 472.

3. Becher, P., "Emulsions; Theory and Practice", Reinhold Publishing Corporation, 2nd ed., (1965) p. 169.

4. Li, N. N., U. S. Pat. 3, 410, 794 (Nov. 12, 1968).

5. Li, N. N., and Shrier, A. L., "Recent Developments in Separation Sciences", Vol. 1, CRC Press, Cleveland, Ohio, 1972, Chapter 9.

6. Li, N. N., Ind. Eng. Chem. Process Des, Dev., 10, 215 (1971).

7. Asher, W. J., Bovee, K. C., Frankenfeld, J. W., Hamilton, R. W., Henderson, I. W., Holtzapple, P. G., and Li, N. N., Kidney Int., 7, S-409 (1975).

8. Rhodes, C. T., Frankenfeld, J. W., and Fuller, G. C., "Use of Liquid Membrane Technology in the Oral Treatment of Drug Overdose", Symposium on Separation and Encapsulation by Liquid Membranes, Am. Chem. Soc. Centennial Meeting, New York, April 6, 1976.

9. Frankenfeld, J. W., Fuller, G. C., and Rhodes, C. T., "Potential Use of Liquid Membranes for Emergency Treatment of Drug Overdose', Drug Development Communications 2, 405 (1976).

10. Chiang, C-W., Fuller, G. C., Frankenfeld, J. W., and Rhodes, C. T., J. Pharm. Sci., 67, 63-66 (1978).

11. Kitagawa, T., Nishikawa, Y., Frankenfeld, J. W., and Li, N. N., "Waste Water Treatment by a Liquid Membrane Process", Environ. Sci. Technology II, 602 (1977).

12. Cahn, R. P., and Li, N. N., "Separation of Pherol from Waste Water by the Liquid Membrane Technique", Separation Science 9, 505, (1974).

13. "FDA Poison Control Statistics for 1971," National Clearinghouse for Poison Control Centers, Washington D. C., 1972.

14. US-DHEW, National Center for Health Statistics, 1968.

15. Wallace, H. W., Asher, W. J., Zubrow, M. T., Stein, T. P., and Brooks, H., "Liquid Membrane Oxygenator", J. Thorac. Cardiovasc. Surg. 66, 887 (1973).

16. Wallace, H. W., Stein, T. P., and Asher, W. J., "Evaluation of Fluorochemicals for Liquid Membrane Oxygenation", Fed. Proc. 34, 1506 (1975).

17. May, S. W., and Li, N. N., Enzyme Engineering, Pye, E. K., and Wingard, L. B., eds., Plenum Press, New York (1974).

18. May, S. W., and Li, N. N., "The Immobilization of Urease using Liquid-Surfactant Membranes", Biochem. Biophys. Res. Commun., 47, 1179 (1972).

19. Martin, A. N., Swarbrick, J., and Cammarata, A., "Physical Pharmacy", Lea and Febiger, Philadelphia, 2ed., (1969) p. 237.

20. "Remington's Pharmaceutical Sciences", Mack Publishing Company, Easton, Penn. 14th ed., (1970) p. 394.

21. Martin, A. N., Swarbrick, J., and Cammarata, A., "Physical Pharmacy", Lea and Febiger, Philadelphia, 2ed., (1969) p. 314.

22. Willard, H. H., Merritt Jr., L. L., and Dean, J. A., "Instrumental Methods of Analysis", D. Van Nostrand Company, New York, 5th ed., (1974) p. 83.

23. "AUTOAN" Computer Program, Publications Distributions Service, 675 East University Avenue, Ann Arbor, Michigan.

24. "NONLIN" Computer Program, Metzler, C. M., The Upjohn Company, Kalmazoo, Michigan.

25. Meites, Louis., ed., "Hand Book of Analytical Chemistry", 1st ed. (1963) McGraw-Hill, New York., p. 12-75.

26. "Martindale, The Extra Pharmacopoeia", The Pharmaceutical Press London, 26th ed., (1972).

27. "Remington's Pharmaceutical Sciences", Mack Publishing Company, Easton, Penn. 15th ed., (1975) p. 1048.

28. "Atlas of Spectral Data and Physical Constants for Organic Compounds", Vol. II, 2ed., (1975) CRC Press, Cleveland, Ohio.

29. "Isolation and Identification of Drugs", Ed. Clarke, E. G. C., The Pharmaceutical Press, London (1969).

30. Yang, T. T., "Study of the Effect of Variation of the Physical and Chemical Properties of Liquid membrane Systems on Their Ability to Function as Sinks", Masters Thesis, Univ. of R. I., 1979, Personal Communication.

VI. BIBLIOGRAPHY

Asher, W. J., Bovee, K. C., Frankenfeld, J. W., Hamilton, F. W., Henderson, L. W., Holtzapple, P. G., and Li, N. N., Kidney Int., 7, S-409 (1975).

"Atlas of Spectral Data and Physical Constants for Organic Compounds", Vol. II, 2ed., (1975) CRC Press, Cleveland, Ohio.

"AUTOAN" Computer Program, Publications Distributions Service, 675 East University Avenue, Ann Arbor, Michigan.

Becher, P., "Emulsions; Theory and Practice", Reinhold Publishing Corporation, 2nd ed., (1965) p. 169.

Cahn, R. P., and Li, N. N., "Separation of Phenol from Waste Water by the Liquid Membrane Technique", Separation Science 9, 505, (1974).

Chiang, C-W., Fuller, G. C., Frankenfeld, J. W., and Rhodes, C. T., J. Pharm. Sci., 67, 63-66 (1978).

Clarke, E. G. C., Ed., "Isolation and Identification of Drugs", The Pharmaceutical Press, London (1969).

"FDA Poison Control Statistics for 1971," National Clearinghouse for Poison Control Centers, Washington D. C., 1972.

Frankenfeld, J. W., Fuller, G. C., and Rhodes, C. T., "Potential Use of Liquid Membranes for Emergency Treatment of Drug Overdose', Drug Development Communications 2, 405 (1976).

Kitagawa, T., Nishikawa, Y., Frankenfeld, J. W., and Li, N. N., "Waste Water Treatment by a Liquid Membrane Process", Environ. Sci. Technology II, 602 (1977).

Lachman, L., Lieberman, H. A., and Kanig, J. L., 'The Theory and Practice of Industiral Pharmacy", Lea & Febiger, Philadelphia, (1970) p. 472.

Li, N. N., and Shrier, A. I., "Recent Developments in Separation Sciences", Vol. 1, CRC Press, Cleveland, Ohio, 1972, Chapter 9.

Li, N. N., Ind. Eng. Chem. Process Des, Dev., 10, 215 (1971).

Li, N. N., U. S. Pat. 3, 410, 794 (Nov. 12, 1968).

Martin, A. N., Swarbrick, J., and Cammarata, A., "Physical Pharmacy", Lea and Febiger, Philadelphia, 2ed., (1969) p. 237, 314.

"Martindale, The Extra Pharmacopoeia", The Pharmaceutical Press London, 26th ed., (1972).

May, S. W., and Li, N. N., Enzyme Engineering, Pye, E. K., and Wingard, L. B., eds., Plenum Press, New York (1974).

May, S. W., and Li, N. N., "The Immobilization of Urease using Liquid-Surfactant Membranes", Biochem. Biophys. Res. Commun., 47, 1179 (1972).

Meites, Louis., ed., "Hand Book of Analytical Chemistry", 1st ed. (1963) McGraw-Hill, New York., p. 12-75.

Metzler, C. M., "NONLIN" Computer Program, The Upjohn Company, Kalmazoo, Michigan.

"Remington's Pharmaceutical Sciences", Mack Publishing Co. Easton, Penn., 14th ed., (1970) p. 334, 394.

"Remington's Pharmaceutical Sciences", Mack Publishing Company, Easton, Penn. 15th ed., (1975) p. 1048.

Rhodes, C. T., Frankenfeld, J. W., and Fuller, G. C., "Use of Liquid Membrane Technology in the Oral Treatment of Drug Overdose", Symposium on Separation and Encapsulation by Liquid Membranes, Am. Chem. Soc. Centennial Meeting, New York, April 6, 1976.

US-DHEW, National Center for Health Statistics, 1968.

Wallace, H. W., Asher, W. J., Zubrow, M. I., Stein, T. P., and Brooks, H., "Liquid Membrane Oxygenator", J. Thorac. Cardiovasc. Surg. 66, 887 (1973).

Wallace, H. W., Stein, T. P., and Asher, W. J., "Evalution of Flurochemicals for Liquid Membrane Oxygenation", Fed. Proc. 34, 1506 (1975).

Willard, H. H., Merritt Jr., L. L., and Dean, J. A., "Instrumental Methods of Analysis", D. Van Nostrand Company, New York, 5th ed., (1974) p. 83.

Yang, T. T., "Study of the Effect of Variation of the Physical and Chemical Properties of Liquid membrane Systems on Their Ability to Function as Sinks", Masters Thesis, Univ. of R. I., 1979, Personal Communication.

VII. APPENDIX

Fortran subroutine to fit the data to equations 9,10,11.

```
      SUBROUTINE DFUNC(F,P,CON,VAL,X,I,J,ISPEC,XVEC,Y,W,NOBS)
      IMPLICIT REAL*8(A-H,K,C-Z)
      DIMENSION NOBS(1),ISPEC(1),P(1),VAL(1),CON(1),Y(1),
                                             W(1),XVEC(1)
      PART=CON(1)
      K1=P(1)
      K2=K1/PART
      K3=P(2)
      K4=0.0            (OR K4=P(3))
      A=VAL(1)
      B=VAL(2)
      C=VAL(3)
      IF(J.EQ.0) RETURN
      GO TO (1,2,3),J
1     F=K2*B-K1*A
      RETURN
2     F=K1*A+K4*C-(K3+K2)*B
      RETURN
3     F=K3*B-K4*C
      RETURN
      END
```