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POTENTIAL USE OF LIQUID MEMBRANES FOR EMERGENCY TREATMENT OF DRUG OVERDOSE*

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ABSTRACT

Several liquid membrane formulations were evaluated for the absorption of model drugs from two different donor solutions. Up to 95% of both phenobarbital and aspirin (acetylsalicylic acid) were removed from pH 2 donors and more than 85% of the former from a pH 7 donor in

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five minutes or less. The uptake of drug was found to be diffusion limited and to follow first order kinetics. The viscosity of the oil phase of the membrane is the most important rate determining parameter.

INTRODUCTION

Poisoning fatalities account for 3% of all accidental deaths and 26% of all suicides in the United States (1). Recent estimates of 15 to 20 non-fatal suicides for each successful attempt suggest that the total number of such poisonings are in excess of one million per year (2). The data available for 1968 implicates the barbiturates in 75% of suicides by drugs or 50% of all suicides by chemicals (1). The salicylates have been established as the principal agent in accidental poisoning but unlike the barbiturates they do not represent a major cause of death (3). A large percentage of accidental poisonings involve children under the age of five. Many of these are caused by aspirin because of its ready availability. The identification of this hazard and subsequent counter measures (smaller package size and "child proof" closures) have resulted in a significant reduction in childhood fatalities. Nevertheless, this remains a significant problem with regard to non-fatal poisoning.

The present modes of emergency treatment are aimed at removal of the drug from the body by one of two general methods:

(a) Invasive, e.g. peritoneal dialysis, a technique of limited efficiency which is both expensive and sometimes hazardous.

(b) Noninvasive, e.g. ingestion of absorbants such as activated charcoal or administration of emetics.

These methods of limited effectiveness for some drugs, contradicted in many instances and unpleasant in the extreme.

Liquid membranes which were invented by Li in 1966 (4) are water-in-oil-in-water emulsions which have been used for removal of toxins from body fluids and have been suggested as agents for the slow release of encapsulated drugs (drug delivery) under physiological conditions (6). Our experience with liquid membranes suggests they may also be valuable as alternative methods for the emergency treatment of drug overdose. This paper describes the rationale for this assertion as well as the results of some preliminary in vitro experiments in the removal of model drugs from various donor systems.

MATERIALS AND METHODS

Two oils were used as the diluent for the membrane phase, Solvent 100 Neutral (S100N) an isoparaffinic, dewaxed oil of relatively high viscosity and Norpar-13, a non-viscous, normal paraffinic solvent. The viscosity of the membrane formulations was adjusted by mixing the two solvents; the more Norpar-13 the less viscous the membrane. The surfactant used was ENJ-3029, a proprietary emulsifier of the polyamine type. Standard buffer solutions of the biphthalate-phosphoric acid (pH = 2.0), sodium and potassium phosphate (pH = 7.0), NaOH-KCl- boric acid (pH = 8.0) and tri and di-sodium phosphate (pH = 12.0) type were employed.

The equipment used was quite simple, consisting of a mixer and stirrer. The emulsions were made up by adding, dropwise, the reagent to be encapsulated to a rapidly stirred solution of the emulsifier in the oil mixture. The resulting emulsions were contacted by slow stirring at room temperature with an equal quantity of donor solutions consisting of 0.60 g/l of phenobarbital or 1.0 g/l of acetylsalicylic acid in pH 2.0 or pH 7.0 buffer solutions. The uptake of drug was monitored by

analyzing the donor phase for phenobarbital (240 nm) or acetylsalicylic (240 nm and 278 nm) using a Beckman DB UV Spectrophotometer.

RESULTS AND DISCUSSION

The Liquid Membrane Concept. A schematic diagram of a liquid membrane (LM) globule is shown in Figure 1. The example shown is an aqueous base-in-oil system which can be used to remove acidic drugs such as barbiturates and salicylates. The unionized drug, having significant oil solubility, permeates from the aqueous donor phase through the oil membrane into the basic inner phase where it is trapped in the form of an oil-insoluble anion. In actual practice the emulsion can absorb the drug from either the stomach or small intestine. After a short residence time the emulsion would be voided from the gastrointestinal tract similar to mineral oil, carrying the absorbed drug along with it.

Although the example shown is restricted to one method of drug binding (pH control) a variety of other trapping agents are possible, some very general and some site specific for various drug types. These alternate binding agents include: (a) plasma proteins (b) activated charcoal and (c) specific drug antibodies. In addition, additives may be incorporated in the oil phase of the membrane to enhance solubility and diffusion rates. For example, NO_3^- and PO_4^{-3}, anions which cannot normally permeate through oil membranes, have been successfully removed from aqueous solutions by incorporating an appropriate anion transport facilitator (7,8).

The emulsions prepared as described above are nearly colorless and have the consistency of a milk shake. They have been successfully fed to dogs with no apparent ill effects (5). The membranes could be administered orally or, to comatose patients, with the aid of stomach

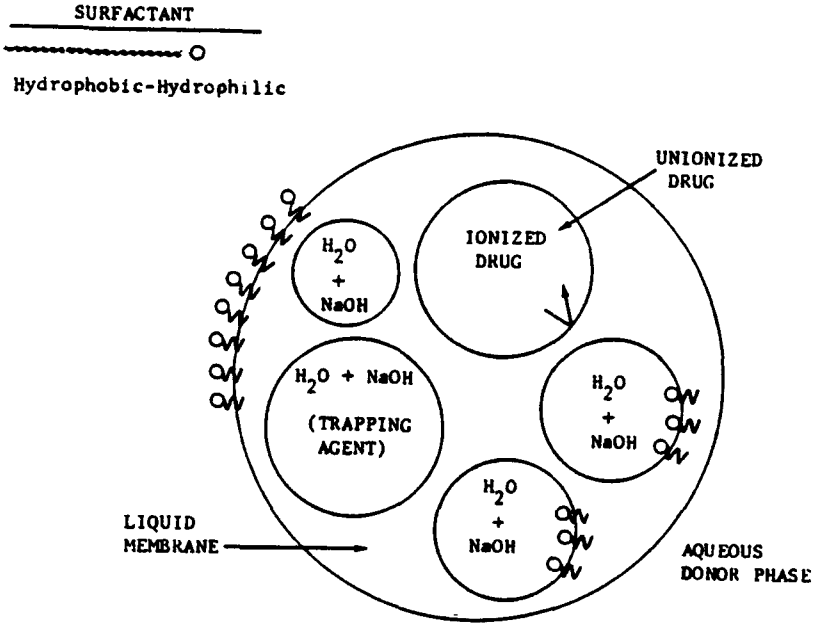

FIGURE 1

Schematic Diagram of Liquid Membrane System For Drug Removal

tubes. Use of stomach tubes would also allow the device to be delivered directly to the small intestine.

The results of in vitro liquid membrane extraction studies using phenobarbital and acetylsalicylic acid as model drugs are given in Figures 2-5. Figure 2 shows extraction curves for phenobarbital with three different membrane formulations all with 0.1N NaOH as the internal trapping agent. In the most favorable case 95% of the drug was removed from the donor phase in five minutes at a treat ratio (emulsion/donor) of 1/1. Essentially all of the drug was removed in 10 minutes. The three formulations shown differ largely in viscosity. The more "Norpar" the less viscous the membrane and the more rapid the absorption of the drug. The stability of the membrane toward rupture and leakage, however,

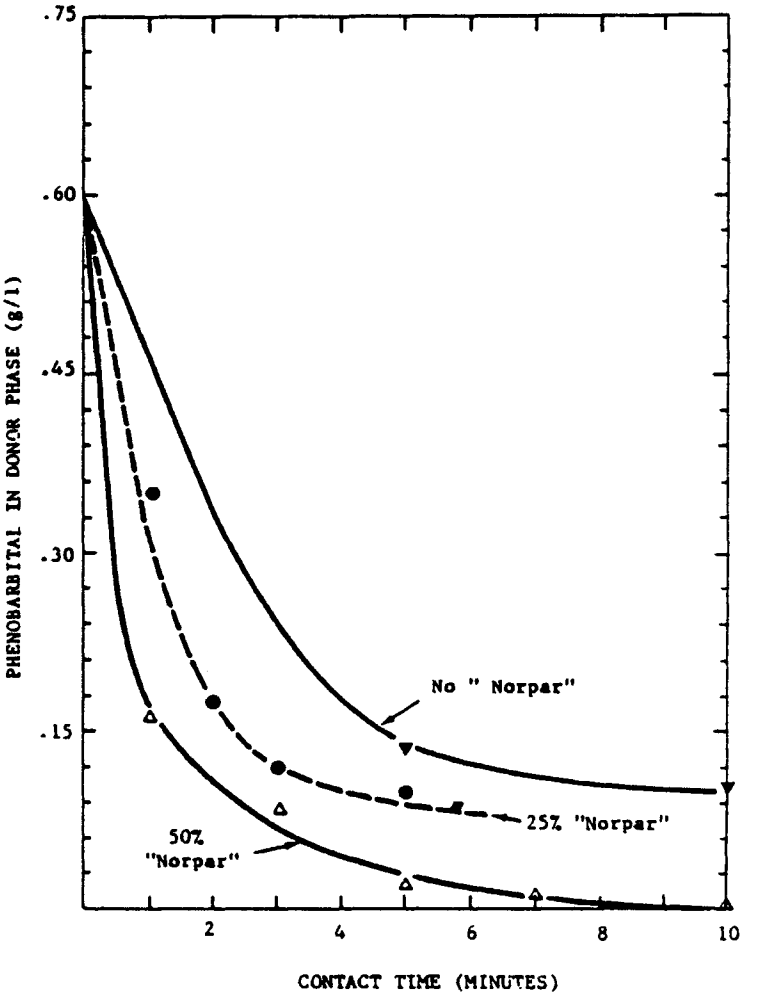

FIGURE 2

Effect of Membrane Viscosity on Removal of Phenobarbital From pH 2 Donor

increases with viscosity. Formulations containing more than 50% "Norpar" were found to be too unstable for use under the conditions of the test.

The effect of donor pH on extraction efficiency is illustrated by the curves in Figure 3. A expected for a weak acid, phenobarbital

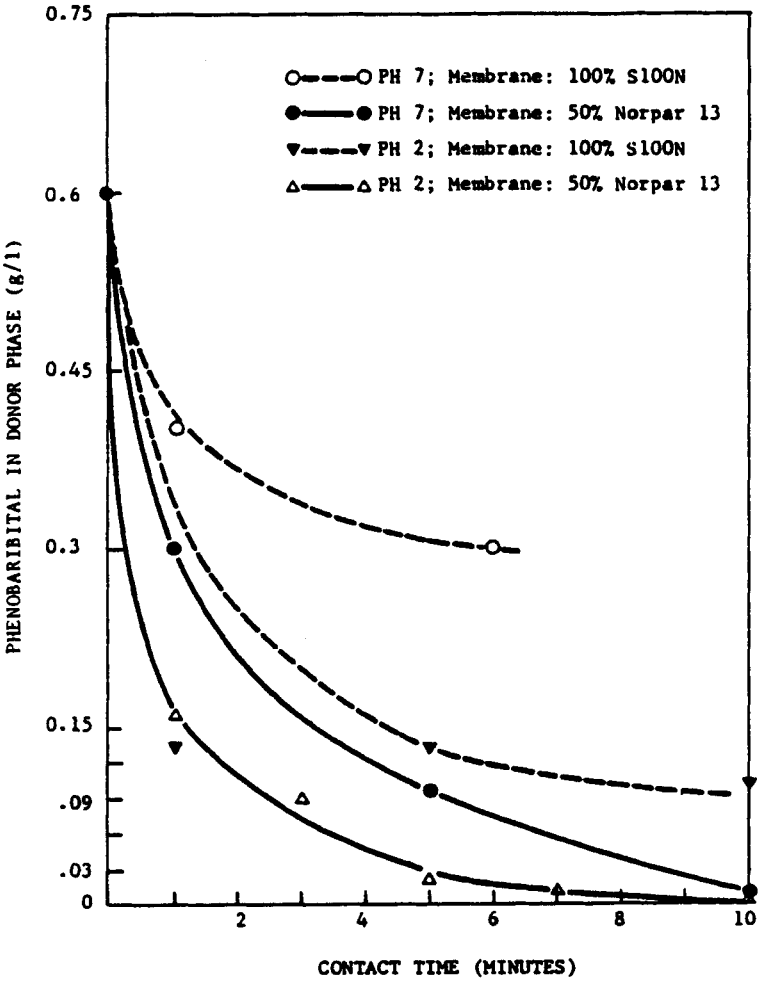

FIGURE 3

Uptake of Phenobarbital From Various Donor Solutions

(pKa = 7.3) is extracted less rapidly from the pH 7 donor than at pH 2. Nevertheless, about 85% of the drug is removed in five minutes and more than 95% in ten minutes even at pH 7. The effect of reduced membrane viscosity is accentuated at the higher pH; a five-fold increase in rate is observed by adding 50% "Norpar" to the membrane system.

The uptake of acetylsalicylic acid from an acidic donor solution is shown in Figure 4. This drug is extracted slightly more rapidly than phenobarbital under comparable conditions. An improvement of some ten-fold

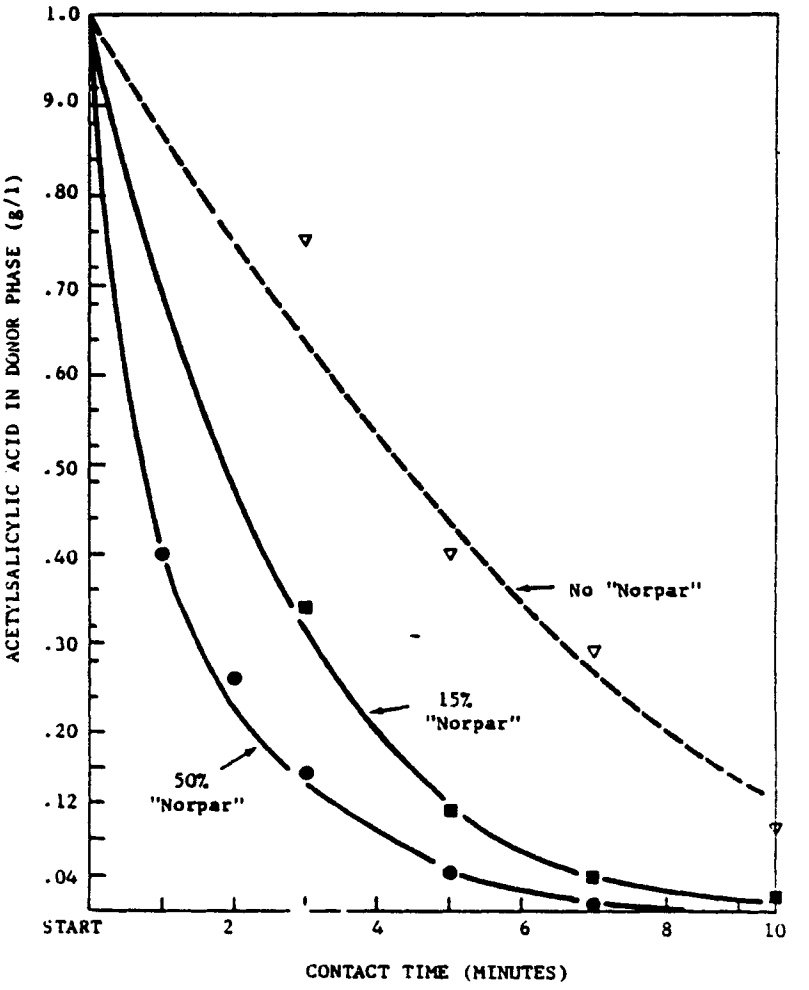

FIGURE 4

Uptake of Acetylsalicylic Acid From pH 2 Donor;
Effect of Membrane Viscosity (Trapping Agent: 0.1N NaOH)

in extraction rate for acetylsalicylic acid is achieved by adding 50% "Norpar" to the formulation. On the other hand, the rate is quite insensitive to the base strength of the trapping agent. This is illustrated by the extraction curves in Figure 5. An increase in pH from 8 to 13 (represented by 0.1N NaOH) has only a minor effect on efficiency of extraction. The membranes shown in Figure 5 contained 15% "Norpar" to reduce viscosity. This represents a good compromise in stability and rapid extraction rates for acetylsalicylic acid.

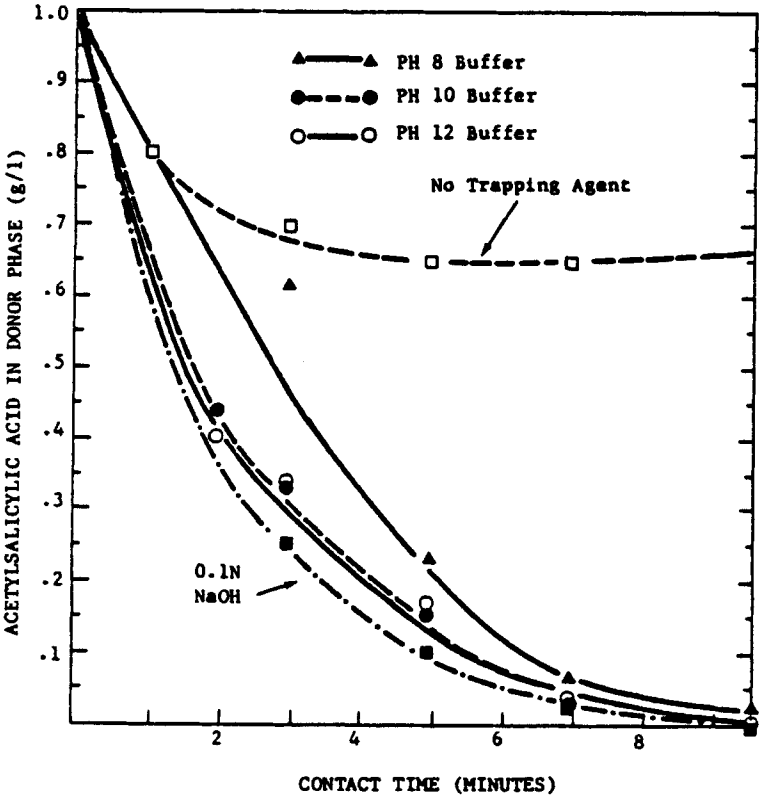

FIGURE 5

Effect of Base Strength on Efficiency of Trapping Acetylsalicylic Acid

The unique advantage of the liquid membrane concept is also illustrated by the curves in Figure 5. The top curve was obtained with a membrane formulation containing no encapsulated trapping agent. In this case, the drug is rapidly extracted from the donor phase until a concentration of about 700 mg/l is reached at which point no more is removed. This represents the equilibrium partitioning of the drug between the aqueous (donor) and oil phases. If an internal drug sink is provided, as in the other curves in Figure 5, the equilibrium is upset and essentially all the drug can be absorbed.

Reaction Kinetics. The results discussed above indicate that, althoug the capacity of the liquid membrane system is limited by the efficiency of the trapping agent, the rate of drug removal is dependent on the rate of diffusion through the membrane. In general, the thinner and less viscous the membrane the more rapid the uptake. Cahn and Li have discussed the reaction kinetics for non-facilitated transport through liquid membranes (9). The first order rate equation for a non-continuous process has the form:

$$\ln \frac{C \text{ in}}{C \text{ out}} = k_p \, (VE/VD)t \qquad \text{(Eqn. 1)}$$

where: C in = Concentration of drug in donor at start

C out = Concentration of drug after treatment

k_p = Permeation rate constant

VE/VD = Treat ratio

t = Contact time

Semi-log plots for some of the in vitro extraction data are shown for phenobarbital in Figure 6 and acetylsalicylic acid in Figure 7. Good first order plots are obtained, at least for the range of concentrations studied. Some first order rate constants, k_p, for extraction of these

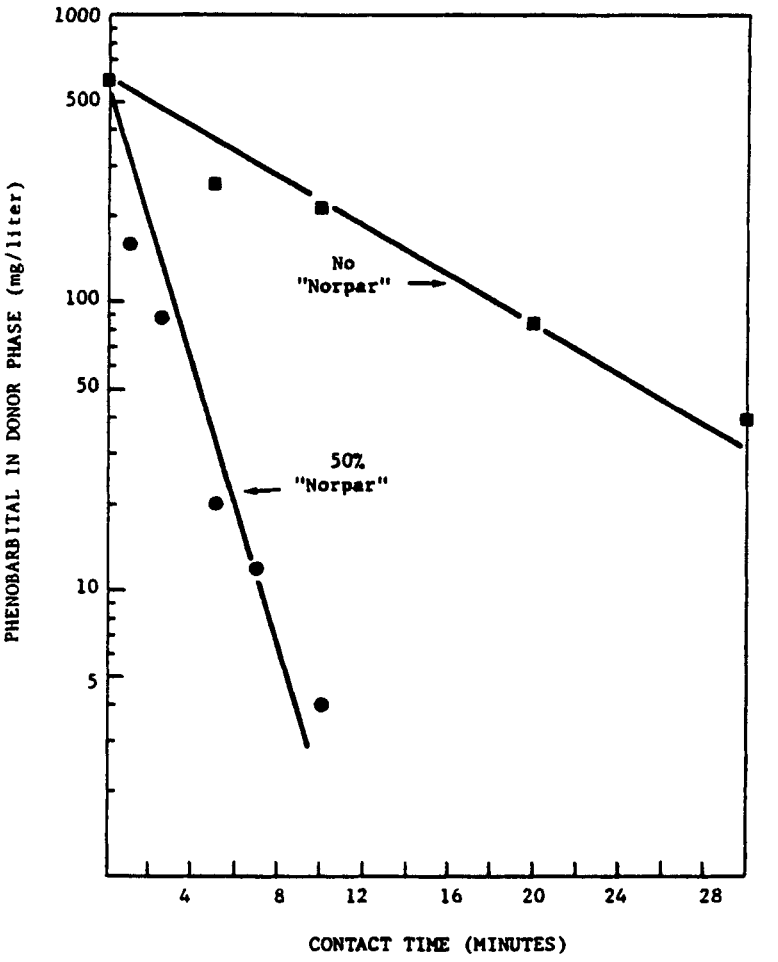

FIGURE 6

First Order Plot of Uptake of Phenobarbital From pH 2 Donor Solution

drugs over various time intervals are given in Table 1. The rate constants in both cases are quite consistent over the range of concentrations studied. The extraction rate for acetylsalicylic acid was greater than that of phenobarbital by more than a factor of two. This is also illustrated by the data shown in Table 2. The more acidic acetylsalicylic

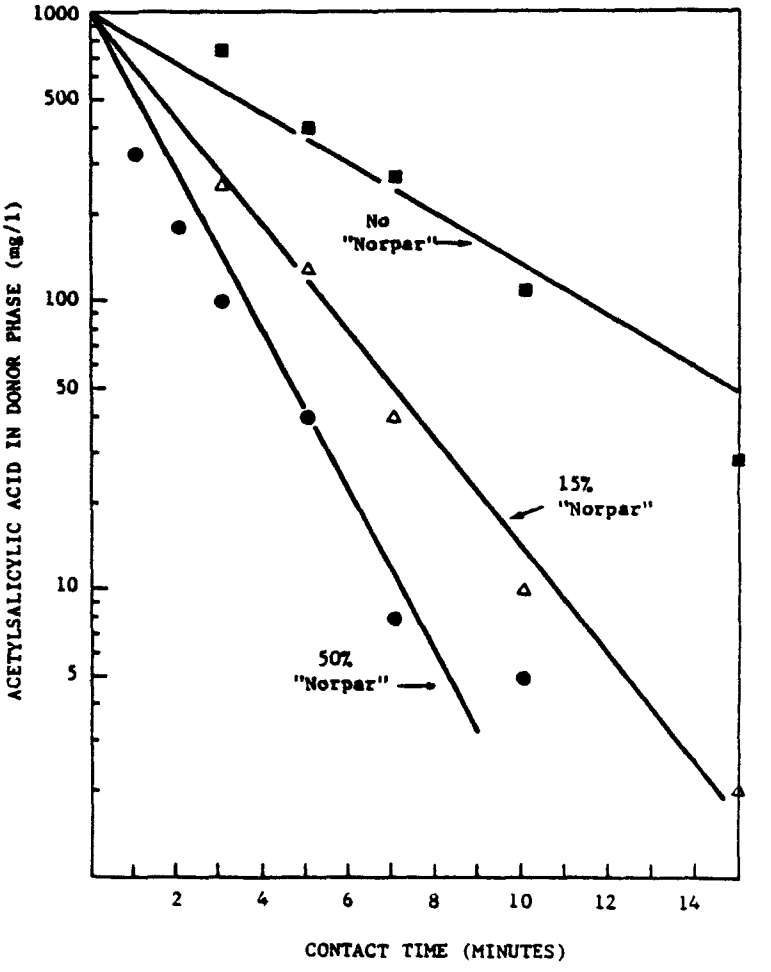

FIGURE 7

First Order Plot of Uptake of Acetylsalicylic Acid From pH 2 Donor Solution

acid is extracted more rapidly by all membrane formulations. However, the difference is more marked with the more viscous formulations where the rates for both drugs are lower. Addition of 50% of the less viscous solvent, Norpar-13, to the membrane enhances the rate of removal of phenobarbital by nearly six fold and that of acetylsalicylic acid by more

TABLE 1

FIRST ORDER RATE CONSTANTS FOR UPTAKE OF DRUGS FROM pH 2 DONOR SOLUTIONS*

Model Drug	Time Interval (min)	t(min)	C in/C out (ppm/ppm)	k_p (min^{-1})
Phenobarbital	0-5	5	600/260	0.15
	0-7	7	600/245	0.12
	0-10	10	600/150	0.13
	5-15	10	260/75	0.11
Acetysalicylic Acid	0-3	3	1000/250	0.42
	0-5	5	1000/130	0.37
	0-7	7	1000/40	0.42
	3-7	4	250/40	0.42
	0-10	10	1000/10	0.42

* Calculated from equation 1; VE/VW = 1.10; membrane: 83% S-100N, 15% Norpar-13, 2% surfactant.

TABLE 2

AVERAGE RATE CONSTANTS FOR UPTAKE OF MODEL DRUGS FROM pH 2 DONOR SYSTEMS USING VARIOUS MEMBRANE FORMULATIONS (1)

Drug	Membrane (2)	VE/VW	k_p (min^{-1})
Phenobarbital	98% S-100N	0.910	0.09
	83% S-100N 15% Norpar-13	0.910	0.14
	73% S-100N 25% Norpar-13	0.890	0.41
	48% S-100N 50% Norpar-13	0.886	0.51
Acetylsalicylic Acid	98% S-100N	0.910	0.18
	83% S-100N 15% Norpar-13	0.910	0.39
	48% S-100N 50% Norpar-13	0.886	0.62

(1) Determined graphically from first order plots.
(2) Each formulation contained two percent surfactant.

than three fold. It should be noted that the viscosity of the membrane is only one of the variables that affect the permeation rate. Others are temperature, emulsion/donor ratio, mixing efficiency and membrane thickness.

SUMMARY AND CONCLUSIONS

The results of these preliminary *in vitro* studies indicate that liquid membranes are capable of rapid uptake of model drugs from various donor systems. Under favorable conditions up to 95% of phenobarbital is removed in five minutes. Acetylsalicylic acid is extracted slightly faster. The system follows first order kinetics with the major rate determining parameter the viscosity of the oil used in membrane formulation. An increase in permeation rate in excess of five fold can be achieved by going to less viscous formulations. However, stability of the membrane toward rupture and leakage is adversely affected by reducing viscosity.

Additional *in vitro* work is planned to optimize membrane composition. This will be followed by *in vivo* studies in test animals, hopefully, followed by clinical trials to establish the safety and efficacy of the liquid membrane concept in humans.

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