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AN INVESTIGATION OF THE REUSE OF LIQUID MEMBRANES AND THE USE OF A MULTIDRUG DONOR PHASE IN SOLUTE TRANSPORT

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ABSTRACT

Complex or multiple emulsions have been investigated for their potential use in pharmaceutics as both drug delivery and drug removal systems. Studies involving previously unused emulsions and single drug donor phases have been described in the literature. The subsequent uptake of solutes using one multiple emulsion or liquid membrane and the co-uptake of solutes from one donor phase were studied. The ability of liquid membranes to remove one solute following removal of another solute was studied for three systems using salicylic acid and phenobarbital at various temperatures. In each case it was observed that the liquid membrane was capable of subsequent drug uptake to varying degrees indicating that the previous use of liquid membranes does not materially affect their further use as sinks. The removal of two drugs from one donor phase using a liquid membrane was studied using acetylsalicylic acid, salicylic acid, and phenobarbital. These systems demonstrated the ability to remove two solutes simultaneously at rates which were of the same

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magnitude as those measured in single solute systems. The solute combination, initial molar concentration of each solute, and the liquid membrane oil/water ratio were found to influence the apparent rate constants and extent of removal for each drug in the donor phase.

INTRODUCTION

At the present time, reported studies in the literature pertaining to the use of complex or multiple emulsions in pharmaceutics are sparse. These systems, referred to as liquid membranes, have been proposed for use as sinks to trap drugs in the emergency treatment of drug overdose (1,2). The results of *in vitro* work to evaluate the potential usefulness of liquid membranes for the rapid removal of drug from the gastrointestinal tract showed that 95% of the phenobarbital present in the external aqueous phase of the water-in-oil-in-water system was removed within five minutes (2). The rate of acetylsalicylic acid uptake in a similar system was slightly faster (2). Although these results are quite encouraging, these studies did not address the possibility of the simultaneous or subsequent ingestion of two drugs in cases of overdose. Whereas Yang and Rhodes conducted extensive studies on the effect of formulation variables on the transport of solutes across liquid membranes (3), their work focused on systems with single solute donor phases. The present study was performed to examine the effect of solute combination and sequence in the removal of drugs from an external donor phase, the effect of initial molar concentration of each solute and liquid membrane oil/water ratio on the removal of two drugs from a single donor phase, and to investigate the ability of liquid membranes to be reused for the purpose of subsequent solute uptake using the model developed by Yang and Rhodes (3).

MATERIALS AND METHODS

Materials: The following materials were used: acetic acid[1], acetonitrile[2], acetylsalicylic acid[3], boric acid[4], hydrochloric

acid[5], methanol[1], phenobarbital[5], potassium chloride[6], potassium biphthalate , potassium phosphate monobasic[5], salicylic acid[3], sodium hydroxide[7]. The liquid membranes[8] used were composed of an internal aqueous phase of pH 10 buffer and an external oil phase. The oil phase consisted of a mixture of straight and branched chained alkyls and polyamino surfactants.

Preparation of Donor Phase Solutions: Standard donor phase solutions were prepared by dissolving drug in a 200 ml volumetric flask with either pH 2 (hydrochloric acid) buffer solution or 0.1N hydrochloric acid.

Sample Preparation: The sampling method used was that described by Rhodes and co-workers (3,4). Figure 1 depicts the experimental sequence used to investigate subsequent solute uptake. After the first single solute uptake experiment was completed, the remaining liquid membrane system (LMS I) was collected, measured, and mixed in a beaker until further use. LMS I was then mixed with a second single solute donor phase containing a different drug with subsequent sampling in the usual manner. In all cases collected samples were assayed by high pressure liquid chromatography (5,6).

RESULTS AND DISCUSSION

Evaluation of Subsequent Solute Uptake: The ability of liquid membranes to remove one solute from an external aqueous phase following removal of another solute was studied for three systems

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[1]Fisher Scientific Company, Fairlawn, NJ

[2]Waters Associates, Milford, MA

[3]Aldrich Chemical Company, Milwaukee, WI

[4]Allied Chemical, Morristown, NJ

[5]Mallinckrodt Chemical Works, New York, NY

[6]J. T. Baker Chemical Company, Phillipsburg, NJ

[7]Amend Drug and Chemical Company, Inc., Irvington, NJ

[8]Exxon Research and Engineering Company, Linden, NJ

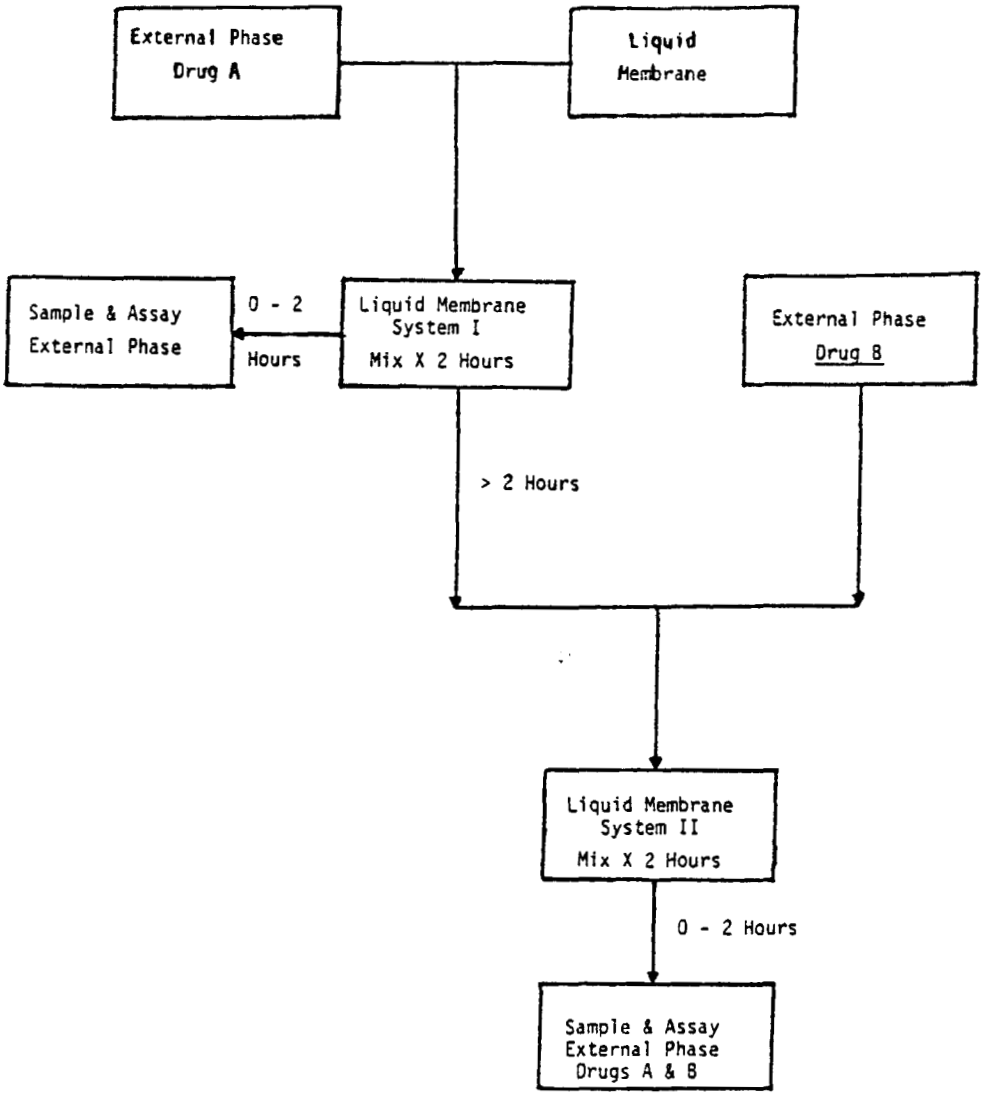

FIGURE 1: Experimental Sequence for Subsequent Uptake of Solutes

(Table I). In each case it was observed that the liquid membrane was capable of subsequent solute uptake to varying degrees. In the first system the uptake of phenobarbital following the removal of salicylic acid at 50°C was slow and incomplete, whereas the removal of salicylic acid from the external aqueous phase subsequent to phenobarbital at both 37.5 and 45°C was

TABLE I

Subsequent Uptake of Solutes

Initial Solute(g/l)	Subsequent Solute(g/l)	Temperature	Uptake of Subsequent Solute
Salicylic Acid 1.0	Phenobarbital 1.2	50°C	Steady but incomplete uptake
Phenobarbital 0.6	Salicylic Acid 1.0	37.5°C	Steady, complete uptake
Phenobarbital 0.6	Salicylic Acid 1.0	45°C	Steady, complete uptake

steady and essentially complete. The high temperature in the former case may be responsible for some alteration in the permeability of the liquid membrane and thus incomplete uptake of phenobarbital.

Evaluation of Co-uptake of Solutes from One Donor Phase:

1. Co-uptake of solutes with different initial molar concentrations - Table II lists the combinations of solutes and their initial concentrations in pH 2 buffer used to study the co-uptake of solutes with different initial molar concentrations. The mean apparent rate constants for the co-uptake of these drug combinations were calculated and are presented in Table II. As can be seen from these results, the liquid membrane was capable of the simultaneous uptake of drugs. The apparent rate constants and the extent of drug uptake differed for each drug in solution with another drug. The mean percent of each drug remaining in the external aqueous phase at 120 minutes can be found in Table II.

From Table II it can be shown that essentially complete uptake had occurred by the end of the experimental run for acetylsalicylic and salicylic acid in a donor phase containing both solutes. However, 25.24% and 33.78% of the initial total of phenobarbital remained in the external aqueous phase when this drug was removed from a donor phase which also contained acetylsalicylic and salicylic acids, respectively.

The highest apparent rate constants were calculated for salicylic acid in a donor phase which contained either acetylsalicylic acid or phenobarbital. Although the mean apparent rate constant describing the uptake of salicylic acid from a multisolute external aqueous phase containing acetylsalicylic acid was less than that for salicylic acid in a single component system (7) (32.27×10^{-2} (min^{-1}) versus 49.67×10^{-2} (min^{-1})), the mean apparent β rate constant for salicylic acid in an external aqueous phase with phenobarbital was greater (59.79×10^{-2} (min^{-1}) versus 49.67×10^{-2} (min^{-1})). Additional

TABLE II

Mean Apparent Rate Constants and Mean Percent of Drug I Remaining in External Aqueous Phase at 120 Minutes After Co-uptake with Drug II When Initial Molar Concentrations are Different

Drug I		Drug II	Mean Apparent Rate Constants for Drug II	Mean Percent Drug I
Acetylsalicylic Acid 5.6 mM	1.	Phenobarbital 2.5 mM	11.41 (β)	1. < 1.00
	2.	Salicylic Acid 7.2 mM	6.75 (β)	2. < 1.00
Salicylic Acid 7.2 mM	1.	Phenobarbital 2.5 mM	59.79 (β)	1. < 1.00
	2.	Acetylsalicylic Acid 7.2 mM	32.27 (β)	2. < 1.00
Phenobarbital 2.5 mM	1.	Salicylic Acid 7.2 mM	1.25*(β)	1. 33.78
	2.	Acetylsalicylic Acid 5.6 mM	6.65 (α), 1.24 (β)	2. 25.24

*One Run

data would be useful in determining the statistical significance of the differences in these rate constants.

A possible explanation for former case described above may be based on the similarity in chemical structure of acetylsalicylic and salicylic acids. As previously observed for both of the drugs in single solute system, increasing the initial concentration of drug in the external aqueous phase resulted in a decreased apparent β rate constant (7). It was speculated that increasing the initial concentration resulted in an alteration of the surfactant properties at the liquid membrane/internal aqueous phase interface.

In the case of co-uptake of acetylsalicylic and salicylic acids, this mixture of drugs in one donor phase may have had the same effect as increasing the concentration of one of these drugs alone in the external donor phase. Thus, the decrease in the apparent β rate constant was observed for salicylic acid.

The increased mean apparent β rate constant for salicylic acid in the presence of phenobarbital may possibly be a result of an interaction between phenobarbital and the surfactant at both interfaces to produce an alteration in the properties of the liquid membrane. This could favor the transport of salicylic acid into both the liquid membrane and the internal donor phase. In addition this alteration may increase the micro rate constant controlling the transport of salicylic acid into the liquid membrane with an increase in the apparent β rate constant for the system resulting.

It is interesting to note that essentially the same phenomena occurred with the co-uptake of acetylsalicylic acid and phenobarbital. The mean apparent β rate constant for acetylsalicylic acid was lower when it was in a multicomponent donor phase with salicylic acid than with phenobarbital (6.75×10^{-2} (min^{-1}) versus 11.41×10^{-2} (min^{-1})). The apparent β rate constant for phenobarbital in a multicomponent system with acetylsalicylic acid was similar to that obtained for phenobarbital in a co-uptake situation with salicylic acid (1.24

x 10^{-2} (min^{-1}) versus 1.25 x 10^{-2} (min^{-1})).

2. Co-uptake of Solutes with Equimolar Initial Concentrations - The effect of concentration on co-uptake was further studied by exposing liquid membrane to an external donor phase containing equimolar concentrations of two solutes (see Table III). System I consisted of equimolar concentrations of salicylic and acetylsalicylic acids (5.6 mM) while System II contained salicylic acid and phenobarbital at 2.5 mM concentrations. Table III lists the mean apparent rate constants for each drug and the mean percent of drug remaining in the external aqueous phase after 120 minutes.

In System I both acetylsalicylic and salicylic acid were essentially completely removed from the external donor phase after 120 minutes. The mean apparent β rate constant for salicylic acid in this system was approximately equal to the rate constant for this drug when alone in the external donor phase (7) (49.10 x 10^{-2} (min^{-1}) versus 49.67 x 10^{-2} (min^{-1})). This rate constant was greater than that for salicylic acid in a non-equimolar multicomponent systems with acetylsalicylic acid (49.10 x 10^{-2} (min^{-1}) versus 32.27 x 10^{-2} (min^{-1})). Moreover the mean apparent β rate constant for acetylsalicylic acid in System I was approximately the same as that calculated for this drug in a non-equimolar multicomponent system with salicylic acid (6.95 x 10^{-2} (min^{-1}) versus 6.75 x 10^{-2} (min^{-1})).

The total molar concentration of solute in the external donor phase with acetylsalicylic and salicylic acids in equimolar concentrations was less than the total molar concentration of solute in the previous co-uptake system for these two drugs (11.2 mM versus 12.8 mM of solute). As previously observed for these two solutes in single component systems, a decrease in concentration resulted in increased mean apparent β rate constants (7). The mean apparent β rate constants obtained for the present system seem to support the proposed speculations of membrane surface property alterations and changes in the size of the

TABLE III

Mean Apparent β Rate Constants for the Co-uptake of Solutes in Equimolar Initial Concentrations in a Multicomponent System and Mean Percent Remaining in the External Aqueous Phase at 120 Minutes

System	Solutes and Molar Concentration (mM)		Mean Apparent β Rate Constant x 10^{-2} (min^{-1})	Mean Percent Remaining in External Aqueous Phase at 120 Minutes
I	Salicylic Acid	5.6	49.10 (2)*	< 1.00
	Acetylsalicylic Acid	5.6	6.95 (2)	< 1.00
II	Salicylic Acid	2.5	---**	< 1.00
	Phenobarbital	2.5	3.41 (2)	9.48

*Number of Runs.

**Too rapid to calculate.

internal aqueous phase droplets. At this lower concentration alterations in the properties of the membrane are not as great as the more concentrated system and the internal aqueous phase droplets were not exposed to as much solute. This resulted in increased apparent β rate constants.

For System II the rate of salicylic acid uptake was too rapid to calculate a rate constant for the process. After two minutes less than one percent of the drug remained in the external donor phase. This rapid removal of salicylic acid was similar to both the removal of this drug from a single component 2.5 mM system (7) and from the previous salicylic acid/phenobarbital co-uptake system. The percent of phenobarbital remaining in the external aqueous phase after 120 minutes decreased as compared with the percent remaining in the previous salicylic acid/phenobarbital co-uptake system (9.48 versus 33.78).

In a co-uptake system, the rate constant and percent of phenobarbital remaining in the external aqueous phase appears to be affected by the total solute concentration in the donor phase. Speculation regarding the mechanisms involved as discussed previously with phenobarbital/salicylate uptake may be applied to this system. The effect of phenobarbital appears to be insignificant to the uptake of salicylic acid at these lower solute concentrations of the external aqueous phase. It is also possible that the lower concentration of solute in the external aqueous phase enhances the phenobarbital uptake in the same manner.

Effect of Liquid Membrane Oil/Water Ratio on the Co-uptake of Solutes: The effect of liquid membrane oil/water ratio on the co-uptake of phenobarbital (2.5 mM) and salicylic acid (7.2 mM) was studied using liquid membranes described in Table IV. For this situation two parameters must be considered - oil/water ratio of the membrane and the presence of two drugs in the external aqueous phase. Table IV lists the mean apparent β rate

TABLE IV

Mean Apparent β Rate Constants for the Co-uptake of Drugs as A Function of Liquid Membrane Oil/Water Ratio

Drug	Oil/Water Ratio	Mean Apparent β Rate Constant x 10^{-2} (min^{-1}) and Range	
Salicylic Acid	1:2	48.86 (2)*	44.56-53.16
	2:3	54.89 (2)	49.82-59.95
	1:1	59.79 (2)	55.19-64.38
	2:1	32.98 (2)	30.85-35.10
	3:1	26.99 (2)	26.98-27.01
Phenobarbital	1:2	2.28 (2)	2.14-2.41
	2:3	1.95 (2)	1.92-1.98
	1:1	1.25 (2)	1.03-1.48
	2:1	1.01 (2)	0.88-1.13
	3:1	0.72 (2)	0.70-0.74

*Number of Runs

constants for this process. In general, as the oil/water ratio increased, the uptake of drug by the system was slower. Increased membrane thickness would be expected to decrease the rate of drug transport.

As can be seen from Table IV, there appears to be an optimum oil/water ratio (1:1) for the uptake of salicylic acid from the multi-component system. As a general trend, the higher oil/water ratios gave a lower β rate constant. However, the range of apparent β rate constants varied widely at the lower oil/water ratios. Therefore, it was difficult to designate a specific order of decreasing apparent β rate constants for these three liquid membranes (1:2, 2:3, 1:1). Additional studies at the lower oil/water ratios may help clarify the order of rate constants in this situation.

Based on the previous results of co-uptake of phenobarbital and salicylic acid at one oil/water ratio (1:1), it was expected salicylic acid would behave similarly when the oil/water ratio was varied. In general this was the case.

In conclusion, the data presented here indicate that liquid membranes may be reused for the subsequent uptake of solutes and that liquid membranes show potential for use in the co-uptake of solutes from a single donor phase.

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