# Use of Solubility Parameters for the Preparation of Hemodialysis Membranes

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## Synopsis

The solvent mixtures of acetone and ethanol (swelling agent) were selected for the preparation of cellulose acetate dialysis membranes using the solubility parameter concept. Increased concentration of ethanol or decreased concentration of cellulose acetate in the formulation resulted in membranes with higher dialysis rate constants but with decreased tensile strengths. The membranes prepared from 20 g of cellulose acetate per 100 ml of mixed solvent of 59.9 mole-% acetone and 40.1 mole-% ethanol were comparable to Cuprophane membrane but were better than those prepared by using formamide as a swelling agent.

## INTRODUCTION

The idea of hemodialysis was described by Abel et al.[1] in 1913, but it was Kolff and Berk[2] who in 1944, using cellulose membranes, developed the rotating-drum-type artificial kidney and used it clinically. Since that time a number of different types of artificial kidneys such as the parallel plate kiil,[3] the twin coil developed by Kolff and Watschinger,[4] and the hollow fiber[5] have been in clinical use. These changes in the original device have been incorporated to improve the performance of the kidney. Basically, the idea remains the same wherein blood flows on one side of the membrane and dialyzate on the other side, and metabolites in the blood permeate across the membrane into the dialyzate solution. A different approach to the artificial kidney was conceived and developed by Chang who used semipermeable microcapsules.[6-8] The design, performance, characteristics, and results of laboratory and clinical trials have been described in detail elsewhere.[7-12]

At present, a large amount of research on the development of optimal dialysis membranes for use either in standard hemodialyzers or in the microcapsule artificial kidneys is being carried out. Since artificial kidneys are used at frequent intervals over long periods of time, any trace amount of toxic substances is undesirable. This may limit the feasibility of using the great variety of membrane technology available. This paper reports on a study of the feasibility of substituting solvents which are normally used for the preparation of dialysis membranes with nontoxic solvents in order to prepare membranes containing no traces of any potentially toxic material. For this purpose, the solubility parameter concept used by Klein and Smith[13] in selecting the solvents for the preparation of asymetric membranes was used. A brief introduction to the solubility parameter concept is given below.

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## Solubility Parameters Concept

General background and the application of the solubility parameters for the formulation of solutions have been described in the literature.[14−17]  In brief, for solution to occur between two components, the enthalpy of mixing $\Delta H_m$ (or overall heat of mixing $\Delta E_m$) should be minimum.

$$\Delta H_m = \Delta E_m = V_m \left[ \left( \frac{\Delta E_1}{V_1} \right)^{1/2} - \left( \frac{\Delta E_2}{V_2} \right)^{1/2} \right]^2 \phi_1 \phi_2 \qquad (1)$$

where $V_m$ is the total volume of the mixture, $\phi_1$ and $\phi_2$ are the volume fractions, $\Delta E_1$ and $\Delta E_2$ are the energies of vaporization, and $V_1$ and $V_2$ are the molar volumes of the components 1 and 2.  $(\Delta E/V)^{1/2}$ is the cohesive energy density (CED) and has been assigned the symbol $\delta$, called the solubility parameter.  Thus,

$$\delta_1 = \left( \frac{\Delta E_1}{V_1} \right)^{1/2} \qquad (2)$$

$$\delta_2 = \left( \frac{\Delta E_2}{V_2} \right)^{1/2} \qquad (3)$$

Therefore, as seen from eq. (1), for solubility to occur $\delta_1$ and $\delta_2$ should be nearly equal.  Further refinement of the solubility parameter concept assumes that the energy of vaporization, and hence the solubility parameter, is made up by contributions from dispersion forces, polar interactions, and hydrogen bonding forces.  Thus,

$$\frac{\Delta E}{V} = \frac{\Delta E_d}{V} + \frac{\Delta E_p}{V} + \frac{\Delta E_h}{V} \qquad (4)$$

and

$$\delta^2 = \delta_d{}^2 + \delta_p{}^2 + \delta_h{}^2 \qquad (5)$$

where $\delta_d$, $\delta_p$, and $\delta_h$ are the component solubility parameters, arising from the contributions of dispersion forces, polar interactions, and the hydrogen bonding forces, respectively.  For solubility to occur, component $\delta$ values for solute and solvent should be nearly equal.  As $\delta_d$ is nearly constant for all the solvents, $\delta_p$ and $\delta_h$ are more significant.

Solubility parameters for solvents can be determined[14] from such physical constants as heat of vaporization, thermal coefficients (expansion and compressibility), surface tension, etc., but this is not always possible for the high molecular weight polymers as the required physical data may be lacking or cannot be obtained.  Therefore, solubility diagrams appear to be the answer.  For most applications, a two-dimensional diagram with $\delta_p$ and $\delta_h$ as the axes is sufficient. A region of solubility is then defined by actual solubility measurements in different solvents.  For a more accurate description, a three-dimensional diagram with $\delta_d$, $\delta_p$, and $\delta_h$ as the axes may be made.

The solubility parameters of the mixed solvents may be calculated from the relation[17]

$$\delta_{\text{mix}} = \frac{x_1 V_1 \delta_1 + x_2 V_2 \delta_2}{x_1 V_1 + x_2 V_2} \qquad (6)$$

where $x_1$ and $x_2$ are the mole fractions of the two components.

## MATERIALS AND METHODS

The cellulose acetate (CA) used was Eastman Kodak 40-25. All the solvents used were of C.P. grade.

To obtain the solubility diagram, 1 g of CA was mixed with 10 ml of each of the solvents tested. After mixing for 5 days, the solubility of CA was examined.

For preparing membranes, unless stated otherwise, a 20 g-% CA solution in the mixed solvents of acetone and ethanol was used. The CA solution was degassed by centrifugation at 2000 rpm for $1/2$ hr in a centrifuge (International Centrifuge, model UV) according to the method of Huang and Jarvis.[18] Most of the membranes were cast with a doctor's knife on a float glass plate with a knife to glass plate clearance of $2.5 \times 10^{-2}$ cm. As soon as the membrane had been cast, it was gelled in ice cold water. The glass plate, placed in a tray, had metal railings arranged loosely around it to prevent the water from flowing directly over the casted membrane. This prevented the formation of ripples or wrinkles on the membrane. Furthermore, this procedure cuts down the time between the casting of the membrane and subsequent gelling, this time being less than 5 sec. The membranes thus prepared were washed throughly and then stored under water.

For comparison purposes, the membranes were prepared using formamide as a swelling agent. The formulation used was cellulose acetate (20.2 g), acetone (32.6 g), and formamide (54 ml), the one used by Mason.[19] After preparation of these membranes by the above described procedure, these were also stored under water.

A simple sketch of the dialysis cell is shown in Figure 1. It consisted of two concentric circular cells. The membrane was clamped on the lower open end of
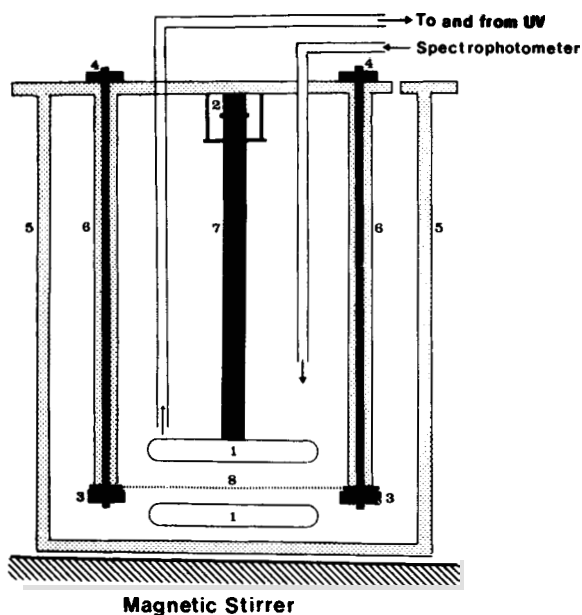


Fig. 1. A simple sketch of the dialysis cell. The various components are (1) magnetic bars (5 cm × 0.8 cm), upper one connected to bearings (2) and 0.3 cm above the membrane, (3) stainless steel flange with inside diameter of 5.9 cm, (4) nuts and bolts, (5) wall of outer cell, (6) wall of inner cell, (7) connecting rod, (8) membrane.

the inner cell. For stirring, two magnetic bars, one in each compartment, were used. In the outer compartment, it was resting on the bottom of the cell, whereas in the inner cell, it was suspended from the top cover. The dialysis cell was placed on a magnetic stirrer. During an experimental run, the bars were rotated at about 200 rpm. The speed was checked by stroboscope (General Radio Company, type 1531-A).

The outer cell contained 210 ml of the solution of creatinine and the inner 75 ml of deionized and degassed water. These volumes were selected so as to yield no hydrostatic pressure difference between the two compartments. The appearance of creatinine in the inner cell was monitored continuously by recirculating the solution through the flow cells placed in the UV spectrophotometer (Beckman, model G25). Flow rate was about 35 ml/min. and the dead volume of connecting tubing and the flow cell was about 6 ml. The wavelength used was 232 m$\mu$. The dialysis rate constant $k$ was calculated using the relation[20]

$$\frac{2.303 \, Y_1 Y_2}{A(Y_1 + Y_2)} \log \frac{(C_2 - C_1)_0}{(C_2 - C_1)_t} = kt \tag{7}$$

where $A$ is the area of the membrane used, $(C_2 - C_1)_0$ and $(C_2 - C_1)_t$ are the concentration differences between the two compartments at zero and at any time $t$; and $Y_1$ and $Y_2$ are the solution volumes in the inner and outer cells, respectively.

The dialysis rate constant $k$ was calculated from the slope of the plot of the left hand side against time $t$.

Thicknesses of the membranes were measured with a precision micrometer. Water contents of the membranes were found gravimetrically from the loss of water when these were heated at 90°C under vacuum overnight. As membranes are hygroscopic, after drying these were cooled in a desiccator and then weighed.

The tensile strength measurements were made using an Instron Testing Machine, (table model). The membranes were always under water. Specially designed clamps were used for holding the membranes. Instron cross-head speed, i.e. rate of extension was 0.5 cm/min.

## RESULTS AND DISCUSSION

For the solubility diagram, the solution of CA in different solvents was examined for solubility. A clear, gel-free solution indicated solubility whereas other conditions, such as partial solubility, highly swollen polymer, etc., were marked insoluble. This visual inspection technique has been used by Hansen[21] and appears to be sufficient for obtaining a solubility diagram. The $\delta_p$ and $\delta_h$ values of the solvents for the solubility diagram (Fig. 2) were obtained from the literature.[15,16] The region of solubility is enclosed by the graph. For preparing the solution of CA, any one solvent or mixture of solvents could be selected with the condition that their solubility parameters lie within the solubility region defined in Figure 2. The solvent mixtures of acetone and ethanol selected are shown in Table I along with the solubility parameters calculated by using eq. (6). These solubility parameters are also shown in Figure 2 by points S1 to S5. They all lie within the solubility region and on the line joining the points representing the solubility parameters of acetone and ethanol. As is seen from Figure 2, with the increased ethanol concentration, the solvent composition in the polymer solution approaches the boundary of the solubility region. Therefore, (1)

TABLE I
Effect of Swelling Agent (Ethanol) on the Membrane Water Contents

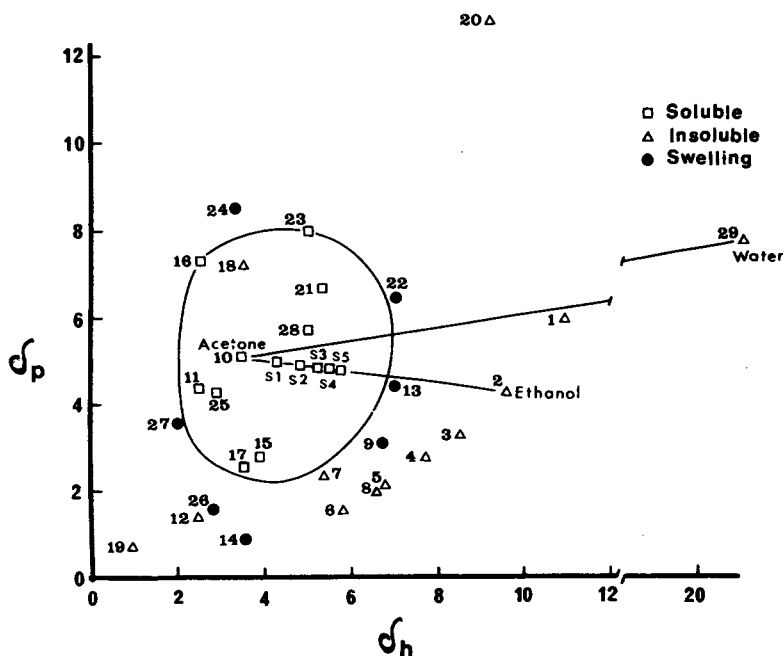| Membrane code no. | Mixed solvent | | Calculated values of mixed solvents | | Membrane water contents, wt-% |
|---|---|---|---|---|---|
| | Ethanol, mole-% | Acetone, mole-% | $\delta_p$ | $\delta_h$ | |
| CA-24 | 20 | 80 | 4.99 | 4.23 | 50.7 |
| CA-23 | 30 | 70 | 4.93 | 4.69 | 50.3 |
| CA-22 | 40 | 60 | 4.86 | 5.20 | 53.4 |
| CA-25 | 46.6 | 53.4 | 4.83 | 5.47 | 61.2 |
| CA-21 | 50 | 50 | 4.79 | 5.75 | 65.8 |



Fig. 2. Solubility diagram for cellulose acetate. Solvents used: (1) methanol, (2) ethanol, (3) propanol, (4) butanol, (5) 1-pentanol, (6) 1-octanol, (7) 2-octanol, (8) cyclohexanol, (9) benzyl alcohol, (10) acetone, (11) methyl ethyl ketone, (12) diethyl ether, (13) ethylene glycol monoethyl ether, (14) dioxane, (15) tetrahydrofuran, (16) furfural, (17) ethyl acetate, (18) ethyl sulfate, (19) toluene, (20) formamide, (21) N,N-dimethyl formamide, (22) diethylene triamine, (23) dimethyl sulfoxide, (24) acrylonitrile, (25) pyridine, (26) chloroform, (27) 1,2-dichloro ethane, (28) acetic anhydride, (29) water.

decreasing amounts of water need to diffuse into the cast membranes for the gellation to occur, and (2) decreasing amounts of solvents would be able to diffuse out before gellation sets in. These two simultaneous phenomena would result in swollen membranes in which membrane structure did not collapse due to the loss of solvents.[22-24] Results of membrane-water-content measurements, given in Table I, indicate increasing water content with increasing ethanol concentration, showing thereby that the membranes are indeed more swollen with higher ethanol concentrations.

A natural question arises as to whether the membranes were asymmetrical. As mentioned in the Experimental section, the time between casting a membrane
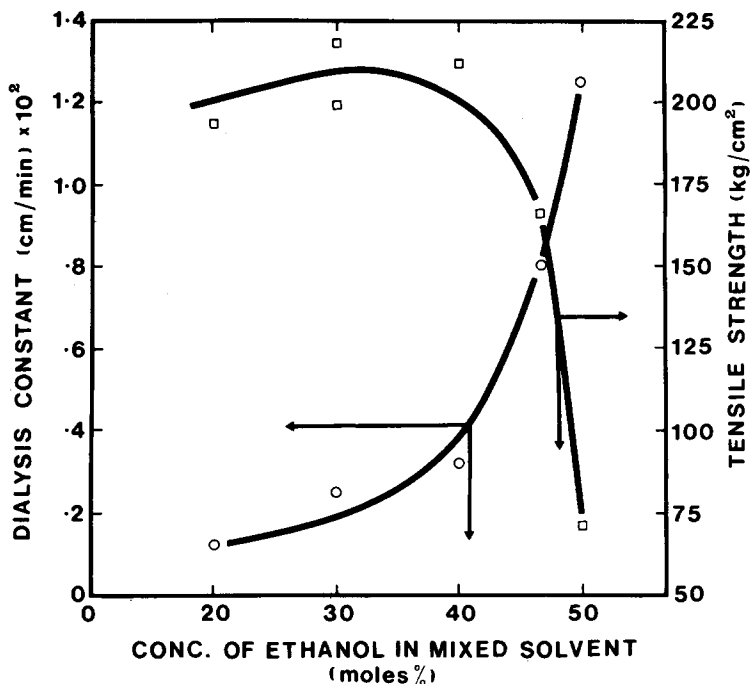
Fig. 3. Effect of swelling agent concentration on the dialysis rate constant and the tensile strength of the membrane.

and its subsequent gelling with ice cold water was less than 5 sec. It was hoped this would avoid formation of asymmetric membranes. The dialysis rate constant of membrane CA-21 was checked from both sides. It was $1.25 \times 10^{-2}$ cm/min when the air-exposed surface was in contact with creatinine solution, and $1.17 \times 10^{-2}$ cm/min when the membrane was reversed. These two dialysis rate constants are within experimental error and are not considered significantly different. Thus, it would appear that the membranes prepared were essentially symmetrical as far as the transport characteristics were concerned.

The effect of swelling agent (ethanol) on the dialysis rate constant of the membrane for creatinine was studied and is shown in Figure 3. As is seen, the higher the concentration of the swelling agent, the higher the dialysis rate, the rate changing from $0.125 \times 10^{-2}$ cm/min at 20 mole-% ethanol to $1.25 \times 10^{-2}$ cm/min at 50 mole-% ethanol. This would be expected as higher concentrations of ethanol give more swollen membranes. Furthermore, this rate is not linear because more than one effect appears to contribute to giving the membranes with higher dialysis rates.[23] It has been shown by Fahey and Grethlein[24] that in the preparation of reverse osmosis CA membranes, their formulation and those of Manjikian et al.[25] all lie very close to the phase boundary of polymer solution and gellation point. This is in line with the present hypothesis that for obtaining highly swollen membranes, the formulation should be very close to the phase boundary separating solution and gelled state. It would be tempting to increase the swelling agent concentration for obtaining higher permeability rates, but the tensile strength, also shown in Figure 3, decreases with increasing amounts of ethanol, decreasing from a maximum of 218 kg/cm² at 30 mole-% ethanol to 60 kg/cm² at 50 mole-% ethanol. The maximum tensile strength at 30 mole-%
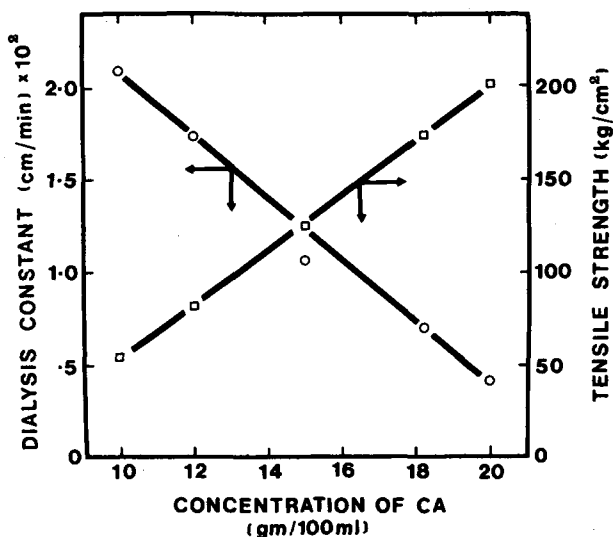
Fig. 4. Effect of CA concentration on the dialysis rate constant and the tensile strength of the membrane. Composition of the solvent used: ethanol, 40.9 mole-%; acetone, 59.1 mole-%.

ethanol may be due to the membrane to membrane variations. As much as ±10% variation in other properties such as permeability has been reported.[26]

As the ultimate goal was to be able to use cellulose acetate for the preparation of dialysis membranes for different applications, all the parameters were selected with this in mind. Thus, the membrane, besides having good permeability, should be strong enough to stand the stresses and strains of handling and the flow of blood over it. Therefore, a balance was made and the composition of the mixed solvent selected for subsequent work was acetone 59.1 mole-% and ethanol 40.9 mole-%.

Once the concentration of swelling agent in the solvent mixture had been decided, the concentration of cellulose acetate in the formulation was varied. The results of dialysis constant and tensile strength measurements are shown in Figure 4. It is seen that the dialysis rate decreases, whereas tensile strength increases with increasing CA concentration. It is evident that one property can be improved at the expense of the other. It is not desirable to have too low a concentration of CA in the formulation as this would yield incoherent membranes. Therefore, the concentration of CA selected was 20 g per 100 ml of mixed solvent (59.1 mole-% acetone and 40.9 mole-% ethanol). The membranes prepared from this formulation were compared with the (1) commercial Cuprophane and (2) the membranes prepared by using formamide as a swelling agent. Formulation and procedure for the preparation of membranes using formamide as a swelling agent have been described in the Experimental section. The dialysis rate constants for these membranes were found using the dialysis cell shown in Figure 1. As the thickness of the membranes were different, their permeability coefficients were obtained by multiplying the membrane thickness by the dialysis rate constant. The permeability coefficients were compared rather than the dialysis rate constants. The results obtained are given in Table II. It is seen that the membrane using ethanol as a swelling agent is comparable to the Cuprophane membrane, whereas the membrane using formamide as a swelling agent is a little less permeable.

| Membrane | Thickness of wet membrane, cm $\times 10^3$ | Dialysis rate constant, cm/min $\times 10^2$ | Permeability coefficient, cm$^2$/min $\times 10^6$ | Tensile strength, kg/cm$^2$ |
|---|---|---|---|---|
| CA using ethanol as swelling agent | 5.2 | 0.8 | 4.16 | 166 |
| Cuprophane | 2.5 | 1.71 | 4.28 | 131 |
| CA using formamide as swelling agent | 8.5 | 0.35 | 2.98 | 104 |

In conclusion, it appears possible to select solvents for preparing dialysis membranes by the use of solubility parameters. Furthermore, by changing their concentration, it should be possible to prepare membranes of varying permeabilities and tensile strengths.

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