tional Defense Act Fellowship during the course of the work.

NOTATION

A = molar concentration of absorbed gas A
a = A/A_i, dimensionless concentration of A
B = molar concentration of absorbed gas B
b = B/B_i, dimensionless concentration of B
C = molar concentration of nonvolatile liquid reagent
c = C/C_o, dimensionless concentration of C
D = diffusion coefficient in the liquid
h = arbitrary constant
k = bimolecular reaction rate constant
k_L = mass transfer coefficient for the liquid phase
M = measure of the rate of the chemical reaction, or the ratio of diffusion time to reaction time in the film theory
m_A = $\nu_A A_i/C_o$, the ratio of the effective interfacial concentration of dissolved gas A to the concentration of liquid reagent; similarly for m_B
p = k_B/k_A, ratio of reaction rate constants
r_B = D_B/D_A, ratio of diffusion coefficients
r_C = D_C/D_A, ratio of diffusion coefficients
t = contact time
x = distance coordinate normal to the interface
x_L = film thickness in the film theory

Greek Symbols

β = parameter defined by Equation (15)
Δ = indication of difference
ζ = transformed distance coordinate in the penetration theory
η = dimensionless distance normal to the interface in the penetration theory
θ = dimensionless time for the penetration theory
κ = k_L/k_L', dimensionless mass transfer coefficient
ν = stoichiometric coefficient
ξ = x/x_L, dimensionless distance in the film theory
ϕ = reaction factor, the ratio of the liquid phase mass transfer coefficient to that for no reaction under otherwise similar conditions

Subscripts

i = interfacial conditions
o = bulk liquid concentration
A, B = reference to the two absorbed gases
C = reference to the nonvolatile liquid reagent
∞ = condition at very large M or θ

Superscripts

$\overline{\ }$ = average over contact time
* = reference to concentrations at the reaction plane
$'$ = asymptotic value, with first-order reaction
^{0} = physical absorption without chemical reaction

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Diffusion of Urea in Flowing Blood

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SCOPE

It is well recognized (*1*, *2*) that in hemodialysis for the replacement of renal function, the rate of removal of toxic molecules, particularly low molecular weight solutes, is often limited by transport within the blood. For this reason, application of mathematical models for the prediction of solute transport rates in hemodialyzers requires reasonably accurate knowledge of diffusion coefficients in flowing blood.

In an earlier study (*3*), diffusion coefficients of urea in stagnant plasma and red blood cell solutions were reported, and the latter were found to correlate well with the model of Fricke (*4*) for the electrical conductivity of a suspension of oblate ellipsoids. However, it has been suggested (*5*, *6*) that rotation and migration of red cells in the presence of a velocity gradient, and the resulting secondary fluid motion, may materially increase transport rates. Hence, application to flowing blood of results obtained in stagnant solutions requires verification.

The present work is concerned with measurement of the

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effective diffusion coefficient of urea in flowing blood and its dependence upon hematocrit. The primary objective is to determine if diffusion coefficients measured in stagnant blood can be applied to flowing blood and to see if there are any augmentation effects observed in flowing blood as shear rate is increased. An additional motivation for this study is to obtain data at low hematocrit. Measurements in stagnant blood are limited to moderate to high hematocrit because of difficulties with red cell sedimentation, but these problems are negligible in flowing blood.

A rigorous treatment of solute transport in whole blood is complex because it must include the influence of:

1. diffusion in plasma and the red cells
2. solute interaction with plasma proteins and hemoglobin and finite kinetics of these processes
3. permeability of the red cell membrane
4. solute partitioning between plasma and red cells
5. excluded volume of plasma proteins and red cells as well as the effects associated with multicomponent diffusion and shear-dependent phenomena.

Urea is a relatively ideal solute to study because its interactions with plasma proteins and hemoglobin are minimal, thereby permitting major simplifications in the analysis of the results obtained in this study.

SUMMARY

Experiments were carried out with a continuous flow, flat-plate dialyzer utilizing two parallel, rigidly supported semipermeable membranes. Blood-side concentrations into and out of the device were monitored as flow rate was varied. Mass transfer in the dialyzate phase was first characterized by replacing the membrane with a rigid interface of soluble material. Either membrane permeability or effective solute diffusion coefficient in blood could be determined (if the other parameter was known) by fitting experimental data to a theoretical model for transport in the device.

Membrane permeability was measured with aqueous solutions on the blood side using solutes of known diffusivity; these values were checked independently by another method (*7, 8*). Each sequence of runs was performed with the same membrane in place and without disassembling the device. First, the membrane permeability to sodium chloride was measured to verify the satisfactory operation of the device. Then urea permeability was determined. With all the necessary parameters now known, effective urea diffusion coefficients were evaluated in plasma and whole human blood solutions.

In the transport model employed here, we treat the blood as being homogeneous and write a single differential equation describing diffusion and convection of total urea in the blood. It is assumed that the effective diffusion coefficient evaluated on this basis may be compared with available treatments of transport through heterogeneous media. The effects of solute binding by proteins are included in the effective urea diffusion coefficient in plasma and in partition coefficients relating equilibrium solute concentrations in the various phases present. This simplified approach seems reasonable for urea because of the small binding effects and because the partition coefficients are near unity. However, this model implicitly assumes that all the urea within a given phase is equally diffusible. Hence, a more complete description may be required for solutes which interact to a greater extent with plasma proteins.

Measurements of membrane permeability to sodium chloride and independent determinations made with the same membrane material in a batch dialyzer agreed to within about 1%. Over the entire range of flow rates studied, experimental mass transfer rates (Figure 4) agreed, within experimental error, with the theoretically predicted values calculated using the known solute diffusivity, the measured membrane permeability, and the dialyzate mass transfer coefficient estimated from the correlation obtained in this study. Urea permeabilities were generally higher by 5 to 20% than the corresponding values estimated from the batch dialyzer results.

Urea diffusion measurements in flowing plasma agreed well with results for stagnant plasma. Experiments with flowing blood were carried out for five hematocrits ranging from about 16 to 47. The measured urea diffusion coefficient decreased with increasing hematocrit, falling from about 0.99×10^{-5} to 0.53×10^{-5} sq.cm./sec. over the range studied, at an average temperature of 27°C. In the region where the data overlap, the effective diffusion coefficient in flowing blood was not significantly different from that in stagnant media. The dependence upon hematocrit for volume fraction red cells ranging from about 0.3 to 0.7 conformed approximately to that predicted by the Fricke model for a heterogeneous suspension in which the dispersed phase is nearly impermeable (Figure 8).

At the lowest hematocrit, the measured diffusion coefficient was higher than that predicted by the Fricke model, and it increased with increasing blood flow rate. The difference between the measured and predicted values was about 2×10^{-6} sq.cm./sec. at a wall shear rate of about 50 $sec.^{-1}$ This observation may result from a shear-induced augmentation mechanism.

PREVIOUS WORK

Previous research dealing with transport of organic compounds in whole blood is limited to the initial *in vivo* results of Babb et al. (*9*) who examined various solutes at a single hematocrit. Studies of oxygen transport in flowing (*10* to *14*) and stagnant (*15, 16*) blood, while indicating the possibility of a shear-rate dependent diffusivity (*17*), are contradictory and cannot be directly compared to the problem of interest here because of the complicating nonlinear source-sink effects associated with the reaction of oxygen with hemoglobin.

THEORY

The system of interest consists of a dilute solution of constant physical properties (blood) in fully developed laminar flow in a semi-infinite flat duct. At a point in the channel ($z = 0$), the solution of initially uniform concentration contacts semipermeable membranes, characterized by a constant solute permeability P_m, which are bathed externally by dialyzate of uniform bulk solute concentration c_o and constant mass transfer coefficient k_d. At the shear rates employed in this study, blood behaves like a Newtonian fluid (*18*). Assuming steady state con-

ditions, an absence of convection through the wall, homogeneous fluids with no sources or sinks, and ignoring axial diffusion, which is reasonable for the conditions studied (19), the equation of change is

$$\frac{3}{2}\bar{v}\left(1-4\frac{r^2}{h^2}\right)\frac{\partial c}{\partial z}=D\frac{\partial^2 c}{\partial r^2} \tag{1}$$

with boundary conditions

$$z\leq 0 \quad \text{all } r \quad c=c_i \tag{2}$$

$$\text{all } z \quad r=0 \quad \frac{\partial c}{\partial r}=0 \tag{3}$$

$$\text{all } z \quad r=\frac{h}{2} \quad -D\frac{\partial c}{\partial r}=\frac{k_w}{K_{B/D}}(c-K_{B/D}c_o) \tag{4}$$

where D is the solute diffusion coefficient in blood and, from additivity of resistances,

$$\frac{1}{k_w}=\frac{1}{P_m}+\frac{1}{k_d} \tag{5}$$

The boundary condition at the wall, Equation (4), is different from that employed by previous investigators (20) in that it contains $K_{B/D}$, the equilibrium solute partition coefficient between blood and dialyzate. This is necessary because blood and dialyzate (equivalent to saline or water) are dissimilar fluids, and at equilibrium the concentration in each phase may differ. With plasma employed on the blood-side, the partition coefficient becomes $K_{P/D}$, and with aqueous solutions the partition coefficient is essentially unity.

$K_{B/D}$ is a complex function of the red blood cell volume fraction, the red cell-plasma solute partition coefficient, and solute interactions with proteins in plasma and in the red cell. Both $K_{B/D}$ and $K_{P/D}$ may be concentration dependent. A more detailed discussion of these parameters can be found elsewhere (3). $K_{B/D}$ may be calculated from

$$K_{B/D}=K_{B/P}K_{P/D} \tag{6}$$

In the region where solute binding by proteins is proportional to the free solute concentration (of primary interest in this study), one finds (3)

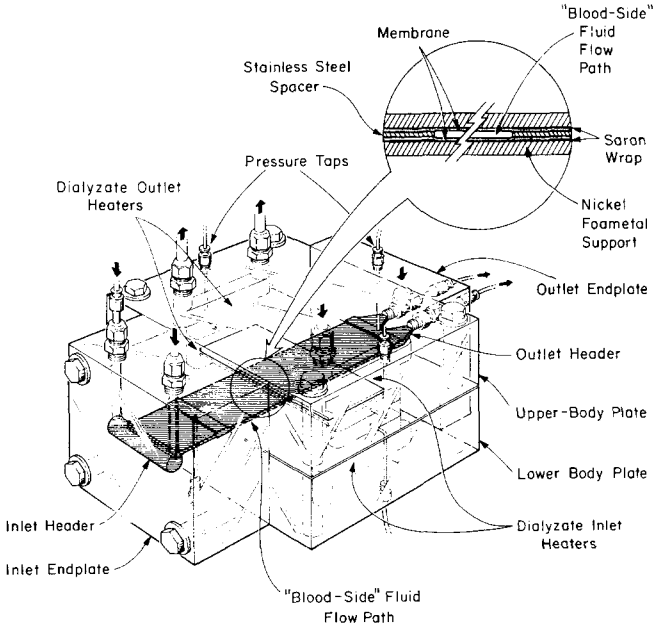

Fig. 1. Phantom view of flat plate flow dialyzer.

$$K_{B/P}=1-\phi+\phi K_{RC/P} \tag{7}$$

$$K_{P/D}=1+k_p-\phi_P \tag{8}$$

From data for urea in the literature (3), $K_{RC/P}\simeq 0.859$, $k_p\simeq 0.096$, and $\phi_p\simeq 0.079$, whence $K_{B/P}\simeq 1-0.141\phi$, $K_{P/D}\simeq 1.017$, and $K_{B/D}\simeq 1.017-0.143\phi$. Hence, the partition coefficients for urea do not depart greatly from unity, although this is not necessarily true for many solutes of potential interest in hemodialysis. Where a large amount of binding occurs, this treatment may prove inadequate, and separate terms accounting for transport of free and bound species may be required.

In dimensionless form, Equations (1) through (4) become

$$\frac{3}{2}(1-4y^2)\frac{\partial\theta}{\partial x}=\frac{\partial^2\theta}{\partial y^2} \tag{9}$$

$$x\leq 0 \quad \text{all } y \quad \theta=1 \tag{10}$$

$$\text{all } x \quad y=0 \quad \frac{\partial\theta}{\partial y}=0 \tag{11}$$

$$\text{all } x \quad y=\frac{1}{2} \quad -\frac{\partial\theta}{\partial y}=N_{Sh_w}\theta \tag{12}$$

The solution to Equation (9) and its associated boundary conditions is given in detail elsewhere (21) and will not be discussed here. For the dimensionless mixing-cup concentration, one finds

$$\theta_m=f\left(\frac{zD}{\bar{v}h^2},\frac{k_w h}{K_{B/D}D}\right) \tag{13}$$

Hence, from knowledge of the channel height and length, average blood velocity, blood-dialyzate partition coefficient, and dialyzate mass transfer coefficient, one can fit the experimentally measured value of θ_m to the theoretical solution to determine the diffusion coefficient or the wall mass transfer coefficient (and hence the membrane permeability), if one or the other parameter is known.

EXPERIMENTAL METHODS

The flat plate flow dialyzer, shown in phantom view in Figure 1, was a modification of the basic design described by Grimsrud and Babb (20), incorporating a highly porous metal support to keep the membranes flat and parallel. Particular attention was paid to the design of the inlet header to insure a uniformly flat transverse velocity profile. The main body of the dialyzer was composed of two virtually identical lucite blocks, with 5 in. × 2 in. × ⅛ in. channels milled into the center of one face on each. A precut piece of low-density nickel foametal (General Electric Co., Metallurgical Products Division) was coated with adhesive, inserted into each channel, and the entire assembly machined flat.

The dialyzer was assembled in a horizontal position and was operated vertically so that air was not trapped in the headers. A sandwich arangement was built up on one block in the order: saran (Dow Chemical Co.) wrap, wet membrane, stainless steel spacer, wet membrane, saran wrap, followed by the second lucite block. The saran wrap was used under the spacers to minimize puncturing of the membrane by the support. The membranes were sprayed with water during assembly to prevent drying. All films were smoothed flat by hand, and all items in the sandwich arrangement were prepunched with holes to fit over positioning dowels in the bottom plate which aligned with holes in the top dialyzer plate.

The flow path of blood-side fluid was a rectangular channel with large aspect ratio defined by the membranes and spacers, 8 in. long and 2 in. wide. Total channel thickness was calculated as the sum of the spacer and saran wrap thicknesses. Dialyzate flow in the foametal was perpendicular to the blood flow, and the area available for solute transfer was a 2-in.-square region defined by the cross-over of the blood channel

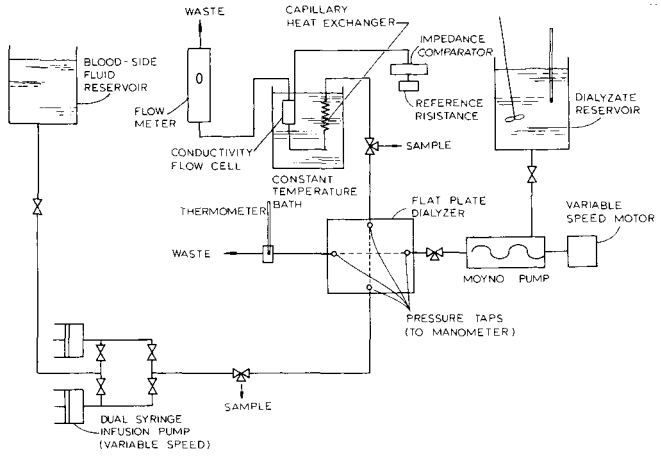

Fig. 2. Schematic diagram of dialyzer flow system.

and the dialyzate channel. The entrance length for blood velocity profile development was 2 in. and an additional 2 in. was allotted beyond the mass transfer section to eliminate any disturbances caused by the outlet section.

The overall flow system is shown schematically in Figure 2. The blood-side fluid was pumped from a reservoir and then through the dialyzer by means of a continuous, variable speed, reciprocating syringe pump (Harvard Apparatus Co.). Three-way valves were positioned at the inlet and outlet for sampling. Dialyzate was pumped from a reservoir to the dialyzer by a Moyno screw pump with a variable speed motor and then sent to waste in a single-pass operation. Both pumps were calibrated and were accurate to about 1%. During any single run, dialyzate flow rate was held constant at about 400 or 600 ml./min. and blood-side fluid flow rate was varied over a wide range, from as low as 0.6 ml./min. to as high as 120 ml./min.

All experiments were made with commercial cellophane membranes (Bemberg Cuprophane PT-150) from a single batch. Membranes were soaked in distilled water for at least 2 hr. prior to use and the dialyzate contained 200 ppm. formaldehyde as a bacteriocide. Thickness measurements were made with a sensitive micrometer (Ames dial comparator, Model 412) from which readings could be estimated to 0.01 mil. The wet membranes ranged in thickness from about 1.0 to 1.15 mils; other physical properties were the same as those previously described (*8*).

Each series of runs with a single membrane followed a standard procedure. First, isotonic saline (0.15M sodium chloride) on the blood side was dialyzed against distilled water as dialyzate. Sodium chloride diffusivity in water was evaluated from published data (*22, 23*) at the mean film concentration, and the measured membrane permeability was compared with results obtained with a batch dialyzer. This was used to check the performance of each assembly [in a fashion analogous to the "calibration" of channel height suggested by Babb et al. (*9*)] and, if satisfactory, was followed by radioactively labelled urea-C^{14} (New England Nuclear Corp.) in isotonic saline, plasma, and human blood solutions. The urea diffusion coefficient in water at infinite dilution and its dependence on temperature were taken from the data of Longsworth (*24*).

Plasma and blood samples used in this study were obtained from O^+ male donors in good health at the blood bank of the Massachusetts General Hospital in Boston and were stored in standard vinyl bags containing ACD solution at 4°C. for up to 2 weeks. Hematocrit was varied by addition of plasma or packed red cells and was determined by centrifugation in heparinized glass capillary tubes at 17,000 g. for 5 min. Volume fraction red cells were calculated as 0.96 times the hematocrit (*25*).

Concentration measurements were made on the blood-side, and dialyzate concentrations were calculated by a mass balance. The dialyzate concentration was always so low that θ_m could be calculated as c_m/c_i. When sodium chloride was dialyzed, the outlet stream was sent through a conductivity flow cell located in a constant temperature bath (± 0.05°C.). Urea concentration was measured in triplicate with liquid scintillation counting. Details of the scintillation counting are given elsewhere (*3, 26*). Typically, 1-ml. samples were analyzed with aqueous solutions and 0.2-ml. samples with plasma and blood. The relative standard error of a single concentration determination, evaluated by repetitive measurements and a propagation of error analysis, was as follows: sodium chloride in water, 0.1%; urea in saline, 0.75%; urea in plasma, 1.25%; and urea in blood, 2.0%.

Purity of the urea-C^{14} was greater than 99% as determined by the supplier using radiochromatography. The material used in this study was from the same lot as that used in the batch dialyzer studies (*8*). In the period (about six months) between these sets of experiments, the tracer solute, in sterilized aqueous solution with 100 ppm. formaldehyde, was stored in aseptic vials at 4°C.

All experiments were conducted at ambient temperature. Temperature was measured with a thermometer at the dialyzate outlet, and the entire system was assumed to be in thermal equilibrium with this value. During a single run, temperature remained constant to within ± 1°C.

Pressure taps were located so as to monitor the blood-side, dialyzate side, and transmembrane pressure drops with a mercury manometer. Whenever possible, transmembrane pressure was maintained high enough to keep the membranes flat but sufficiently low so that ultrafiltration was negligible. However, at low blood-side flow rate, the pressure difference between the blood-side inlet and the dialyzate inlet decreased to about zero. Since the flow paths were in cross-flow, the corner of the membranes near the blood-side outlet and dialyzate inlet was exposed to a higher pressure on the dialyzate side, causing the membranes to distend and collapse upon themselves. This reduced the area available for transport and produced shunting of the blood-side fluid and a drastic drop in mass transfer performance. This phenomenon imposed a constraint on the minimum blood-side flow rate.

Measurements of dialyzate mass transfer coefficients were carried out with one dialyzer body plate, with the membrane "sandwich" and the other lucite plate replaced by an aluminum plate containing an insert of compressed benzoic acid. The benzoic acid covered a 2 in. by 2 in. square, duplicating the area and position of the mass transfer section of the dialyzer as normally assembled. The solution pumped through the system initially contained 0.002M benzoic acid. The outlet concentration was monitored with the conductivity cell, and all experiments were performed at 25°C. Mass transfer coefficients were calculated from the log-mean concentration driving force based on inlet and outlet conditions:

$$k_d = \frac{Q_d}{wL} \ln \left[\frac{c_w - c_i}{c_w - c} \right] \qquad (14)$$

The concentration c_w at the wall was taken to be the saturation concentration, as obtained from Seidell's (*27*) data. Values of the molecular diffusion coefficient of benzoic acid in water as a function of concentration and temperature were taken from the results of Chang (*28*). Diffusivity was evaluated at the average of the wall and outlet concentrations. Pressure drop measurements for flow through the foametal were also made with a blank plate bolted to the dialyzer plate.

Similar dialyzate mass transfer experiments were carried out with one half of the Babb-Grimsrud (B-G) test dialyzer (*29*), for which an aluminum plate of the proper dimensions was constructed. The foametal employed in the B-G cell was substantially identical to that employed in this study, except that it was one half as thick (1/16 in.).

DATA ANALYSIS

Grimsrud, Babb, and coworkers (*9, 20, 29*) have proposed a number of techniques for determining membrane permeability or solute diffusivity with a flat plate dialyzer. For the purposes of this study, these methods were found (*26*) to be either experimentally difficult or too limiting in the constraints imposed by their simplifying approximations to obtain accurate results. Instead, the data were

fitted exactly to the theoretical solution, and systematic errors associated with an approximate solution were eliminated.

The technique employed was as follows: An initial estimate was made for the unknown parameter, k_w or D. The true values of these variables were then defined as

$$(k_w)_{\text{true}} = \alpha_1 (k_w)_{\text{est}} \tag{15}$$

$$(D)_{\text{true}} = \alpha_2 (D)_{\text{est}} \tag{16}$$

whereupon the true values of N_{Sh_w} and x became

$$N_{Sh_w} = \frac{\alpha_1 k_w h}{\alpha_2 K_{B/D} D} \tag{17}$$

$$x = \frac{\alpha_2 z D}{\bar{v} h^2} \tag{18}$$

Initially, α_1 and α_2 were set equal to 1.0, and the correction factor corresponding to the known parameter was kept at unity for the entire procedure. The dimensionless mixing-cup concentration, denoted by θ_m', was calculated from the theoretical model, and an objective function was defined relating the difference between the experimentally measured and theoretically calculated values

$$F = |\theta_m - \theta_m'| \tag{19}$$

The evaluation then reduced to a minimization problem, i.e., finding α_1 or α_2, and hence the true value of k_w or D, such that $F = 0$. Assuming k_d to be known accurately, the true value of P_m was obtained from Equation (5).

In principle, using a least-squares criterion, both α_1 and α_2 could be obtained by simultaneously fitting two or more data points, or either parameter could be obtained by simultaneously fitting all the data from a single run. However, a sensitivity error analysis (*26*) revealed that such a procedure would be imprecise. Fortunately, for each set of runs, one parameter could be regarded as known and each data point was individually fitted to the theoretical results. If no systematic trends with changes in flow rate or time were observed, the individual estimates were pooled and data points more than 1.5 standard deviations from the mean were eliminated, yielding a best estimate of the parameter for the entire run.

This technique required multiple evaluations of the objective function and hence θ_m'. The data were analyzed on a digital computer using a golden section search for minimization of F. The evaluation of θ_m' featured an optimum search for the first eigenvalue and least-squares polynomial fits for the higher eigenvalues. This gave values of θ_m' accurate to 0.01% in several seconds' computer time on an IBM 360/65 computer. Additional details are available (*26*).

The initial estimates for membrane permeability to sodium chloride and urea were obtained from independent measurements made with a batch dialyzer using membranes from the same batch (*7, 8*). At the concentration employed in this study, where Donnan exclusion effects are negligible (*7*), the effective diffusion coefficient of sodium chloride in water-swollen Cuprophane PT-150 is given by an Arrhenius-type relationship,

$$D_{\text{eff}} = D_o \exp(-E/RT) \tag{20}$$

where $D_o = 1.11 \pm 0.16 \times 10^{-3}$ sq. cm./sec. and $E = 3560 \pm 690$ cal./mole, °K. For a membrane of thickness t_m, the permeability is given by

$$P_m = \frac{D_{\text{eff}}}{t_m} \tag{21}$$

For urea permeation, $D_{\text{eff}} = 0.286 \times 10^{-5}$ sq. cm./sec. at 37°C. The activation energy for urea was assumed to be the same as for sodium chloride because no other data were available, in which case $D_o = 0.925 \pm 0.133 \times 10^{-3}$ sq. cm./sec.

Urea diffusion coefficients in plasma and whole blood solutions were initially estimated from measurements previously made in stagnant solutions (*3*) and were extrapolated to different hematocrits, where necessary, using the Fricke model.

RESULTS

Dialyzate Transport Characterization

Pressure drop measurements made for flow through the foametal showed that, in the range of dialyzate flow rates employed in this study, pressure drop increased with the square of the velocity. This indicated the predominance of kinetic energy losses, which may be attributable to boundary layer separation during flow over the nickel filaments and sudden changes in flow direction, accompanied by secondary flows, as the fluid flows through the tortuous paths of the porous media. The result of these phenomena would be to mix the fluid somewhat, giving it the characteristics of turbulent flow, and consequently to increase mass transfer in the dialyzate phase above that expected if the foametal were not present.

Mass transfer coefficients were measured in the dialyzate phase with the membrane replaced by a plate of benzoic acid and with foametal first removed. The results (*26*) at low flow rate agreed with the Leveque solution for flow over a flat plate with constant concentration boundary conditions (*21*). As flow rate increased, there was a systematic departure from the Leveque solution, presumably because fully developed laminar flow was not established.

With foametal in place, mass transfer coefficients were higher by a factor of about 2.5 to 3.0. The B-G test cell, with its smaller dialyzate channel thickness, yielded mass transfer coefficients higher by 75 to 100% than the dialyzer used in this study. The results are summarized in Figure 3 and correlated in the form

$$\frac{k_d h_d}{D} = A \left(\frac{h_d \bar{u} \rho}{\mu} \right)^b \left(\frac{\nu}{D} \right)^{1/3} \tag{20}$$

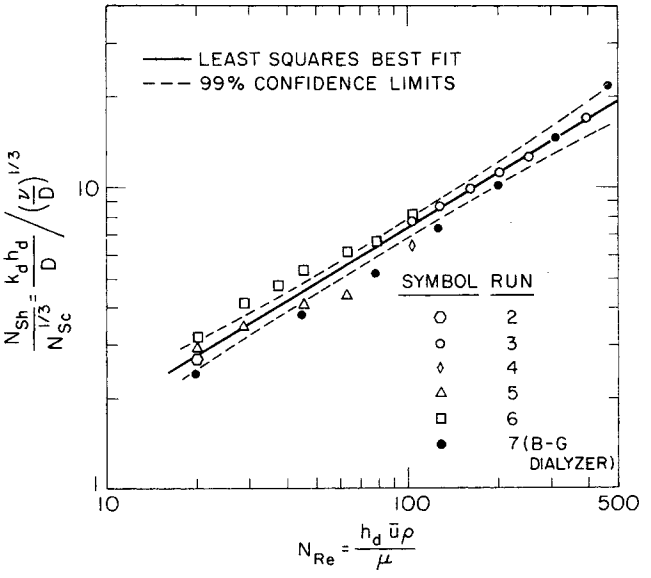

Fig. 3. Dialyzate mass transfer with foametal. $N_{Sh}/Sc^{1/3}$ as a function of N_{Re}.

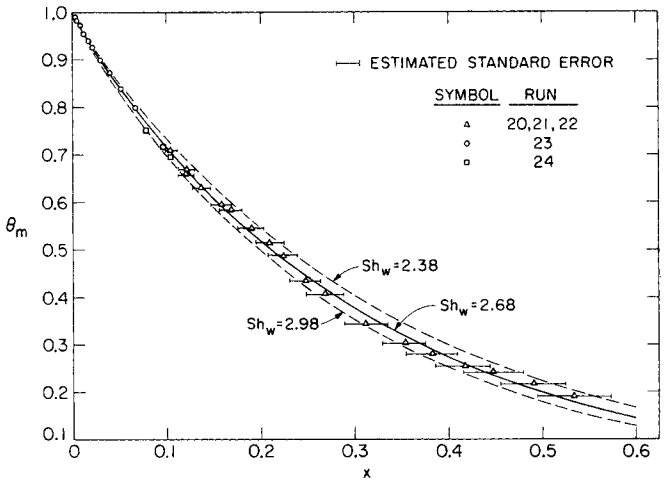

Fig. 4. θ_m as a function of x, sodium chloride in water. Best fit $N_{Sh_w} = 2.68 \pm 0.30$.

The constants and their standard deviations, determined by a linear regression analysis, are:

$$A = 0.460 \pm 0.052$$

$$b = 0.601 \pm 0.026$$

No correction was made for the fractional area occupied by the foametal supports (6.4%) in calculating k_d from experimental data, nor was any made in subsequent analysis using estimates obtained from Equation (20). The one-third power dependency on Schmidt number was not tested in this study but is a reasonable assumption in view of its widespread applicability in both laminar and turbulent flow over a flat plate (*31*). Changing the characteristic length from h_d to L_d (length of dialyzate channel) in Equation (20) gave a correlation between the results for the two dialyzers nearly as good as that in Figure 3. Hence, Equation (20), while valid for the two dialyzers studied, may not be generalizable to similar devices in which the foametal geometry is significantly different.

For the purposes of subsequent data analysis, it is assumed that k_d is constant over the length of the mass transfer section and independent of the wall boundary condition; i.e., the presence of a membrane with a finite resistance to transport does not alter k_d.If the dialyzate flow were laminar, either assumption could involve a serious error (*21*). However, flow through the foametal bears significant similarities to turbulent flow, and in this regime the changes of the local mass transfer coefficient in the entrance region and the effects of N_{Sh_w} are greatly reduced. Consequently, the error introduced by these assumptions should be quite small.

Membrane Permeability

The approach followed in this study was first to measure the membrane permeability to sodium chloride and urea using aqueous solutions with known solute diffusivities on the blood side. This was then followed by effective diffusion coefficient determinations in plasma and/or blood using the same membrane and without dismantling the dialyzer. In order to obtain reasonable error bounds on the measured parameters, maximum sensitivity required that the wall be the major mass transfer resistance ($N_{Sh_w} \lesssim 4$) for permeability evaluation (and that the membrane resistance R_m be much greater than the dialyzate resistance R_d) while the blood-side resistance should be limiting ($N_{Sh_w} \gtrsim 4$) for diffusion coefficient determination. This was accomplished for urea by employing a spacer of thickness 20.16 mils, which with the two saran wrap films (each 0.47-mil thick) gave a total blood channel thickness of 21.1 mils.

Combined results of five different runs under virtually identical conditions, with isotonic saline dialyzed against distilled water at 25.8°C. and $Q_d = 617$ cc./min. are illustrated in Figure 4, where the dimensionless mixing cup concentration is plotted as a function of dimensionless length. The solid curve is the theoretical solution for the composite, best-fit value of N_{Sh_w}, 2.68, and the dashed curves correspond to this wall Sherwood number plus or minus the standard deviation in N_{Sh_w} estimated from a propagation of error analysis. Similarly, the error flags on the data points were obtained from a propagation of error analysis.

Over the entire plotted range, the agreement between the experimental data and best-fit theoretical curve is excellent, and all the data points lie within the region bounded by the dashed curves. A large and systematic deviation between the theoretical curve and the experimental data, as observed by Grimsrud and Babb (*20*), was not found in this study.

Initial estimates for the mass transfer resistances were $R_m = 17.4$ min./cm. and $R_d = 5.1$ min./cm., giving $R_w = 22.5$ min./cm.; D was estimated to be 1.48×10^{-5} sq. cm./sec. Minimization of F for each of the data points and pooling the results gave an average value for α_1 of 1.0084. Substitution into Equation (5) gave a true value for the membrane resistance of 17.2 min./cm., about 1% lower than the value estimated from the batch dialyzer results. Such excellent agreement for sodium chloride was obtained throughout this study.

Figure 5 illustrates typical results obtained with urea in isotonic saline for a single run at 25.9°C. and $Q_d = 617$ cc./min. Parameter estimates were $R_m = 20.1$ min./cm., $R_d = 5.5$ min./cm., $R_w = 25.6$ min./cm. and $D = 1.41 \times 10^{-5}$ sq. cm./sec. Minimization of F and pooling the results gave $\alpha_1 = 1.104$, i.e., the value of N_{Sh_w} which best fit the data, 2.73 ± 0.31, was 10.4% higher than the

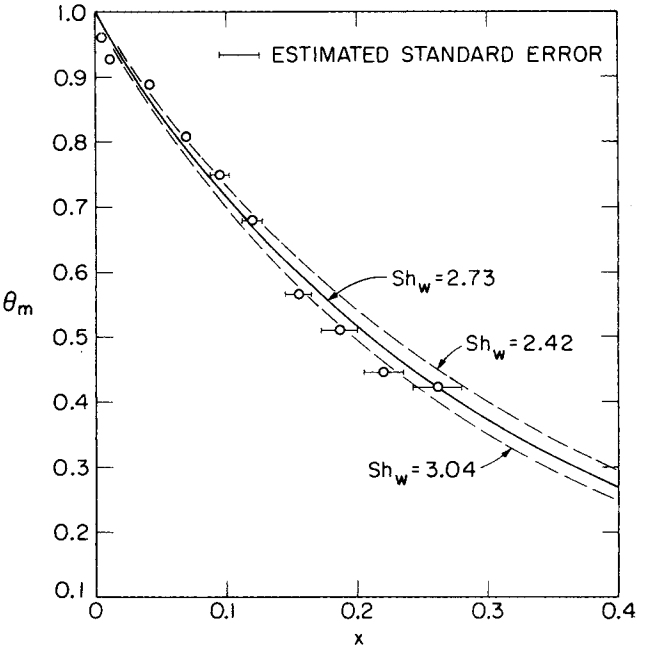

Fig. 5. θ_m as a function of x, urea in isotonic saline. Best fit $N_{Sh_w} = 2.73 \pm 0.31$.

original estimate. Assuming R_d to be correctly estimated, Equation (5) gave $R_m = 17.7$ min./cm., almost 14% lower than the value extrapolated from the batch dialyzer results. This run was typical of the urea permeability determinations, with the measured permeability ranging from 5 to 20% higher than the batch dialyzer value. The reason for this is not clear. A likely possibility is that the extrapolation from 37°C. to about 25°C., using the activation energy evaluated with sodium chloride, was not quite correct. Degradation of the tracer solute during storage between the batch dialyzer experiments and this study is also possible, although permeability measurements with the batch dialyzer, separated by long intervals, showed no systematic change with time. In any event, the permeability measured with the flow dialyzer was taken to be the true value for subsequent diffusion coefficient measurements.

Diffusion in Plasma and Blood

Several runs were made with urea in whole human serum. Representative results are shown in Figure 6 for a run at 27.3°C. with $Q_d = 394$ cc./min., $R_m = 15.3$ min./cm., $R_d = 7.0$ min./cm., $R_w = 22.3$ min./cm., and $K_{P/D} = 1.017$. The best fit estimate of the pooled results gave $D = 1.16 \pm 0.12 \times 10^{-5}$ sq. cm./sec. and $N_{Sh_w} = 3.27 \pm 0.42$. The average of 29 measurements made with stagnant plasma using the capillary technique at 37°C. (3) gave 0.807 ± 0.080 for the ratio between the diffusion coefficient of urea in plasma and in water (isotonic saline). At 27.3°C., the diffusivity of urea in water is 1.45×10^{-5} sq. cm./sec. Assuming the ratio of 0.807 to be independent of temperature, one obtains an estimate for the diffusion coefficient in plasma of $1.17 \pm 0.12 \times 10^{-5}$ sq. cm./sec., in excellent agreement with the results of this study.

Five runs were made with fresh blood solutions with hematocrits ranging from 16.0 to 46.9 (32). At the lowest flow rates, some settling of red blood cells was noted in the blood inlet header. However, the hematocrit measured at the blood outlet for any single data point never deviated more than ±1 hematocrit unit from the mean value. The data for blood showed more scatter and had a larger associated error estimate than the aqueous solutions because of the decreased precision in the concentration measurement.

Figure 7 shows the results obtained with whole human blood at a hematocrit of 35.6. The experiment was run at 25.8°C. with $Q_d = 394$ cc./min., $R_m = 17.7$ min./cm., $R_d = 7.1$ min./cm., $R_w = 24.9$ min./cm., and $K_{B/D} = 0.968$. The best-fit pooled estimate gave $D = 0.614 \pm 0.087 \times 10^{-5}$ sq. cm./sec. and $N_{Sh_w} = 6.04 \pm 1.10$. Despite the increased scatter, the data points agree well with the best-fit theoretical curve and lie within the limits of the dotted curves

The results from all five blood runs are summarized in Table 1. The measured urea diffusion coefficient decreased with increasing hematocrit, falling from 0.991 to 0.526×10^{-5} sq. cm./sec., over the range of hematocrits studied. During the run at a hematocrit of 37.8, blood flowrate was maintained constant for 90 min. and samples periodically taken. No significant change with time was noted. Following the 32.5 hematocrit run, isotonic saline was dialyzed against distilled water, yielding the same membrane permeability as before the run. This suggests that any deposition of proteins or formed elements which occurred on the membrane surface had little effect on urea transport. This is consistent with observations made with the batch dialyzer (8).

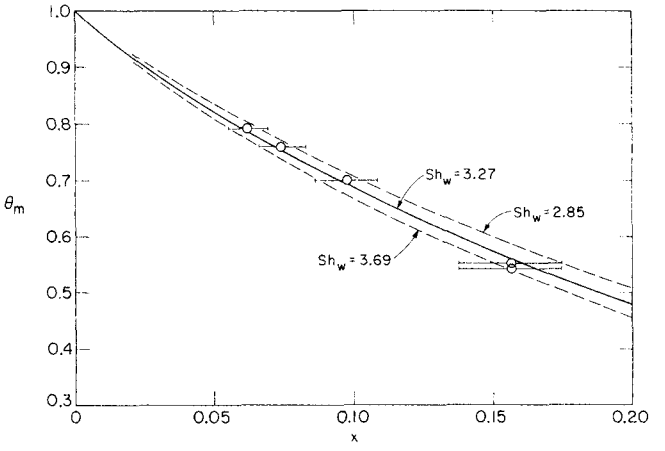

Fig. 6. θ_m as a function of x, urea in plasma. Best fit $N_{Sh_w} = 3.27 \pm 0.42$.

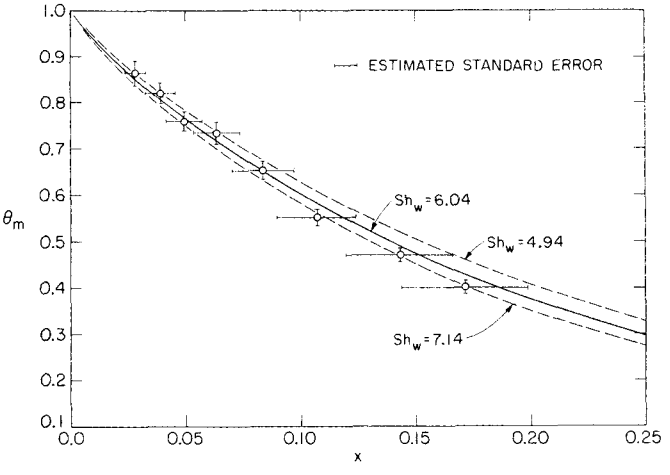

Fig. 7. θ_m as a function of x, urea in whole human blood (hematocrit 35.6). Best fit $N_{Sh_w} = 6.04 \pm 1.10$.

TABLE 1. DIFFUSION COEFFICIENT OF UREA IN FLOWING BLOOD AT VARIOUS HEMATOCRITS

T °C.	Hct.	R_m min./cm.	R_d min./cm.	R_w min./cm.	$K_{B/D}$	N_{Sh_w}* ± S.D.	D_B* ± S.D. sq. cm./sec. × 10^5	D_p** sq. cm./sec. × 10^5	$K_{B/P}$	ψ
26.9	16.0	15.4	7.1	22.4	0.995	4.04 ± .59	0.991 ± .069	1.16	0.978	0.834
27.4	32.5	15.2	7.0	22.2	0.972	6.05 ± .87	0.684 ± .086	1.18	0.956	0.557
25.8	35.6	17.7	7.1	24.9	0.968	6.04 ± 1.10	0.614 ± .087	1.13	0.952	0.516
26.2	37.8	15.6	7.2	22.8	0.965	6.41 ± .92	0.635 ± .059	1.14	0.949	0.527
28.2	46.9	15.0	6.9	21.9	0.953	8.16 ± 1.17	0.526 ± .034	1.20	0.936	0.411

* Best-fit estimate of pooled results for each run.
** $D_p = 0.807\ D_w$.

DISCUSSION

Of primary interest is the comparison of the results of this study with data obtained in stagnant media (3). Both sets of measurements are shown in Figure 8 and compared with the theoretical solution of Fricke (4) for transport in a suspension of oblate ellipsoids with an axial ratio of 4.25. The ordinate ψ represents the ratio of the permeability of the suspension to that of the suspending medium, i.e., the ratio of the diffusion coefficients in the suspension and the suspending medium multiplied by the partition coefficient between the two phases. Estimates for the latter quantity $K_{B/P}$ are given in Table 1 for each of the runs made in this study. The theoretical curves are plotted for a parametric variation of $Z = D_{RC}K_{RC/SM}/D_{SM}$, the ratio of the permeability of the red cell to that of the suspending medium. In this study, $K_{RC/SM} = K_{RC/P}$.

Several conclusions can be drawn from Figure 8. In the region where the data overlap, the effective diffusion coefficient in flowing blood is not significantly different, within experimental error, from the results in stagnant media when expressed in terms of ψ. At most, the data from flowing blood is 5 to 10% higher. Between volume fraction red cells of 0.3 and 0.7, the dependence of ψ on ϕ conforms approximately to that predicted by the Fricke model, with most of the data falling between the theoretical curves for $Z = 0.0$ and $Z = 0.05$. This range of the red cell-suspending medium permeability ratio is in accord with values calculated from published estimates of urea red cell permeability (3).

The sole exception to the generalizations above is the data point for the lowest hematocrit, which lies between the theoretical curves for $Z = 0.20$ and $Z = 0.25$. It is unlikely that this anomalously high value is related to an incorrect dependence of ψ on ϕ from the Fricke model as this run was the only one to show a systematic variation of effective diffusion coefficient with blood flow rate. Figure 9 contains a plot of diffusion coefficient fitted to each data point as a function of wall shear rate for the run at a hematocrit of 16.0. At the lowest shear rates, the diffusion coefficients are close to the values predicted by the Fricke model. As shear rate increases, the diffusion coefficient increases monotonically to a value about 20% higher than that predicted at a wall shear rate of about 50 sec.$^{-1}$.

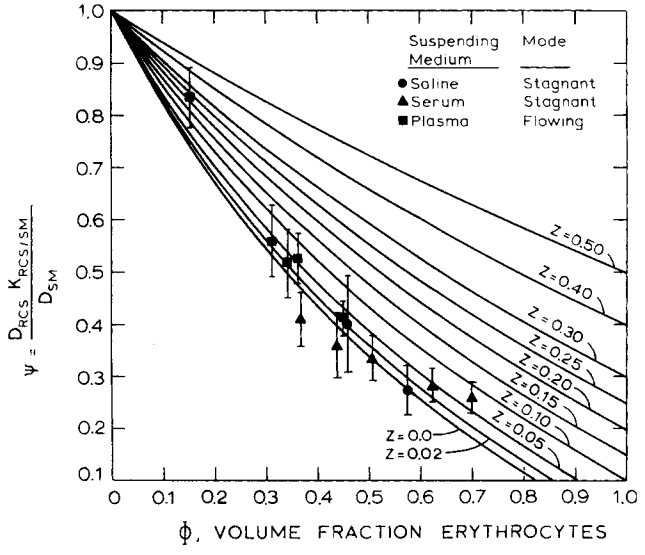

Fig. 8. Urea diffusivity reduction in red cell suspensions. Comparison between stagnant and flowing suspensions with Fricke model (oblate ellipsoid, axial ratio = 4.25). Data for stagnant solutions from reference (3).

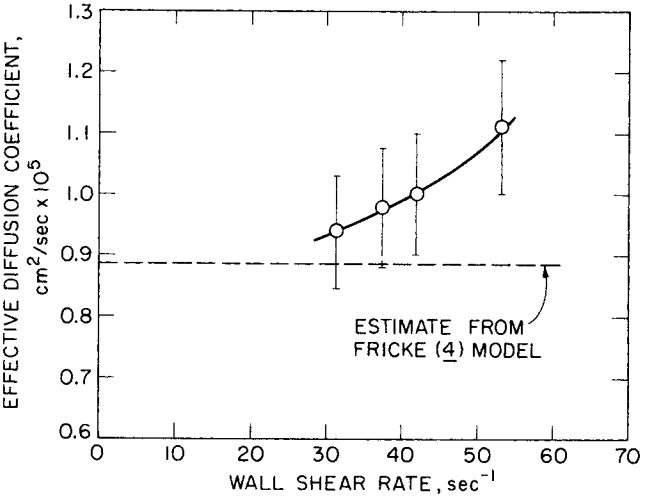

Fig. 9. Effective urea diffusion coefficient in blood, hematocrit 16.0, at 26.9°C. Fricke model estimate for $Z = 0$, $\phi = 0.152$, $K_{B/P} = 0.978$, oblate ellipsoid with axial ratio = 4.25.

The effect of particle motion on the diffusion of solutes in the flow of particulate suspensions is a complex and poorly understood phenomenon. It has been shown (33, 34) that, in a shear flow, particles rotate and translate in response to a velocity gradient. The secondary flows induced by such movements of the red cell may serve to augment the diffusive transport process, giving higher effective solute diffusion coefficients than that attributable to Brownian motion alone. Both theoretical and experimental results suggest that in flowing blood this mechanism may result in augmented transport of platelets (35, 36), oxygen (5, 37), and the red cell itself (6, 38).

In this study, a shear-rate dependent effective diffusion coefficient was observed only at the lowest hematocrit (16.0). The increment above the zero shear estimate was about 2×10^{-6} sq. cm./sec. at a wall shear rate of 50 sec.$^{-1}$. This value is within the range of order of magnitude estimates which have appeared in the literature (5, 38). The absence of a shear rate effect at higher hematocrits suggests that the augmenting mechanism is damped out by particle-particle interactions a higher red cell volume fractions.

In clinically employed hemodialyzers, wall shear rates are typically 10^2 sec.$^{-1}$ or higher, and solutes of higher molecular weight than urea are of interest. Furthermore, uremic patients are often anemic with hematocrits as low as 20 to 25. Under these conditions, the effect of augmented transport might be greater than that observed in this study. Hence, further research into this phenomenon with higher molecular weight solutes appears warranted.

In the theoretical model described above, it was tacitly assumed that the solute in plasma and the solute inside the red cell were in chemical equilibrium at the dialyzer outlet. In reference (3), an approximate model was derived describing transient diffusion in a slab of heterogeneous media with nonequilibrium between phases. By a simple change of variables, that model describes the system of interest here with plug flow and $N_{Sh_w} = \infty$. The results given there show that the equilibrium assumption is valid for urea under the conditions employed in this study, but that in similar experiments with higher molecular weight solutes, such as creatinine and uric acid, which permeate across the red cell membrane much more slowly, red cell concentrations at the dialyzer outlet would be far from equilibrium. Thus, further experiments with higher molecular weight solutes will require more complex analysis.

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NOTATION

c = concentration, g./ml.
D = diffusion coefficient, sq. cm./sec.
E = activation energy, cal./mole-°K.
F = objective function defined in Equation (19)
h = channel height, cm.
k = mass transfer coefficient, cm./sec.
k_p = overall plasma protein-binding coefficient (g. sorbed solute/ml. plasma)/(g. free solute/ml. protein-free plasma)
$K_{X/Y}$ = equilibrium solute partition coefficient between X (pure dispersed phase or heterogeneous medium) and Y (pure continuous phase)
L = channel length, cm.
P_m = membrane permeability, cm./sec.
r = transverse coordinate, cm.
R = mass transfer resistance, min./cm. or sec./cm.; ideal gas constant
N_{Sh_w} = wall Sherwood number, $\dfrac{k_w h}{K_{B/D} D}$
t_m = membrane thickness, cm.
T = temperature, °C. or °K.
$\bar{u}$ = mean dialyzate velocity, cm./sec.
$\bar{v}$ = mean blood-side velocity, cm./sec.
w = channel width
x = dimensionless coordinate, $zD/\bar{v}h^2$
y = dimensionless coordinate, r/h
z = axial coordinate, cm.
Z = ratio of permeability of red cell to that of suspending medium $K_{RC}D_{RC}/D_{SM}$

Greek Letters

α_1, α_2 = correction factors defined by Equations (15) and (16)
ϕ = volume fraction dispersed phase, e.g., red cells
ϕ_P = volume fraction proteins in plasma
θ = dimensionless concentration, $(C - K_{B/D}C_o)/(C_i - K_{B/D}C_o)$
μ = viscosity, poise
ν = kinematic viscosity, sq. cm./sec.
ρ = density, g./cc.
ψ = ratio of permeability of red cell suspension to that of suspending medium, $D_{RCS}K_{RCS/SM}/D_{SM}$

Subscripts

B = blood
d, D = dialyzate
m = mixing cup mean; membrane
o = outside wall (bulk dialyzate)
P = plasma
RC = red cell
RCS = red-cell suspension
SM = suspending medium
w = wall

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