Steady State Diffusion of Oxygen in Red Blood Cell and Model Suspensions

Experimental measurements were made of the steady oxygen permeation rate through films of nonreactive and reactive dispersions, including suspensions of red blood cells. The data compare well with a theoretical analysis which incorporates a one-step reversible reaction within the dispersed phase. In the absence of reaction, the red cell permeability could be treated as that of a concentrated hemoglobin solution. For reactive suspensions of red cells or water-in-oil emulsions containing hemoglobin at 25°C, substantial facilitation of oxygen transport occurred when oxyhemoglobin gradients were steep, but both the data and the theory exhibited considerably less facilitation than would be suggested by an equilibrium analysis.

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SCOPE

The rate of oxygen transport in red blood cells and through whole blood is of biophysical and physiological interest. A quantitative understanding of this process is important in the design and analysis of extracorporeal blood oxygenators because the blood phase invariably constitutes the dominant resistance to mass transfer. The red cell contains a concentrated solution of hemoglobin in which the diffusion coefficient of oxygen is substantially reduced from its value in water or plasma, and it is surrounded by a membrane which may, in addition, offer a significant resistance to oxygen diffusion. Within the red cell, oxygen reacts reversibly with hemoglobin to form oxyhemoglobin, and the parallel diffusion of oxyhemoglobin may augment oxygen transport above that expected from purely physical diffusion. Although the topic is venerable, uncertainty still surrounds the relative importance of these factors.

Experimental measurements were made of steady state oxygen permeation through red blood cell and model suspensions. Results were compared with a theoretical model for oxygen transport through a dilute suspension of spheres in the interior of which the reaction $O_2 + Hb \rightleftarrows HbO_2$ occurs. The objectives were to assess the relative importance of the mechanisms influencing transport, in particular the extent of facilitated oxygen transport in the red cell, and to evaluate the adequacy of the theoretical model and available physicochemical parameters.

Measurements were made with one-dimensional supported vertical films of known thickness under quasi-steady conditions. Volume fraction of dispersed phase was varied over a wide range. Materials investigated included nonreactive synthetic dispersions of known physical properties, reactive synthetic water-in-oil emulsions of known particle size distribution containing hemoglobin solution in the dispersed phase, and suspensions of red cells in buffered isotonic saline exposed to oxygen partial pressure boundary conditions covering both reactive and nonreactive regimes. Nonreactive suspensions were employed to provide verification of theory and transport parameters without the additional complication of chemical reaction. Synthetic reactive emulsions were prepared with a hemoglobin concentration for which hemoglobin diffusivity was known more accurately than in the red cell; in addition, particle shape conformed exactly to that employed in the model.

CONCLUSIONS AND SIGNIFICANCE

Agreement between theory and data was excellent for nonreactive synthetic suspensions (Figure 4); the same was true for nonreactive red cell suspensions (Figure 5) when the red cell oxygen permeability was taken to be that of a hemoglobin solution at the same concentration as the red cell interior and the cell membrane resistance was ignored. The average permeability of red cell suspensions (Figures 7, 8, 9) depended upon oxygen partial pressure boundary conditions. Substantial facilitation occurred in the presence of a large oxyhemoglobin gradient relative to the oxygen gradient. The data fell midway between the predicted limits for a nonreactive suspension and for reaction equilibrium throughout the red cell. Agreement with a model which incorporated one-step oxygenation kinetics was surprisingly good; the data scattered between the curves predicted for spheres of 1 and 4 μm radius. Little facilitation occurred with oxyhemoglobin gradients simulating physiological conditions. With reactive synthetic emulsions (Figure 10), average permeability increased with particle size, thereby confirming a departure from reaction equilibrium in the dispersed phase. Agreement with theory was satisfactory, but the model underpredicted the average permeability somewhat. Better agreement can likely be achieved with an improved kinetic model. However, more accurate knowledge of the hemoglobin diffusion coefficient is required before definitive conclusions can be drawn.

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BACKGROUND

Augmentation of oxygen transport by hemoglobin and myoglobin solutions has been observed under transient (Klug et al., 1956*a*) and steady state (Wittenberg, 1959; Scholander, 1960) conditions. Numerous investigations (for reviews, see Wittenberg, 1970; Kreuzer, 1970; Schultz et al., 1974; Goddard et al., 1974) indicate that the phenomenon results from parallel diffusion of oxyhemoglobin; immobilized hemoglobin is unable to facilitate oxygen transport (Colton et al., 1973). Roughton and colleagues (Nicolson and Roughton, 1951; Longmuir and Roughton, 1952; Klug et al., 1956*b*) have contended that augmentation is insignificant at physiological hemoglobin concentration, but recent analyses (Moll, 1968; Kutchai, 1973; Spaan, 1973) employing more reliable diffusivity estimates suggest that facilitated transport can be significant during transient oxygen uptake or release by red cells.

Qualitative evidence for augmentation of steady state oxygen transport across layers of blood and packed red cells has been reported (Scholander, 1960; Hemmingsen, 1965; Moll, 1969). Measurements of Kutchai and Staub (1969) with packed red cells and hemoglobin solutions at 22°C suggest that oxygen and hemoglobin diffusivities are identical in intact red cells and in hemoglobin solutions of the same concentration, and that the oxygen-hemoglobin reaction is at equilibrium within the cell. By contrast, Keller and Friedlander (1966) argued, on the basis of prior analysis (Friedlander and Keller, 1965), that the oxygenation reaction is far from local equilibrium in a system of red cell dimensions. Spaeth and Friedlander (1967) reported higher oxygen flux during blood deoxygenation than predicted for a nonreactive suspension but less than that predicted if local equilibrium prevailed. Keller (1969) subsequently cited data indicating no facilitation in the red cell, even with large oxyhemoglobin gradients.

Measurements with a rapid reaction flow apparatus (for example, Hartridge and Roughton, 1927; Roughton, 1959; Forster, 1964) suggest that the red cell membrane is an important oxygen diffusion barrier, but these findings are clouded by the possibility of significant mass transfer resistance in the liquid surrounding the red cell (Koyama and Mochizuki, 1969; Mochizuki, 1970). Kreuzer and Yahr (1960) found no difference between oxygen uptake rates by layers of packed red cells and of hemoglobin solutions of identical concentration. Their results, and those of Kutchai and Staub (1969) and Stein et al. (1971), suggest that the oxygen diffusion resistance of the red cell membrane is insignificant.

Quantitative investigations are few. Studies with blood in laminar flow (Weissman and Mockros, 1967; Spaeth and Friedlander, 1967; Buckles et al., 1968; Colton and Drake, 1971) have yielded estimates of effective oxygen diffusivities, but these results may be influenced by shear induced augmentation effects (Keller, 1971; Colton, 1976). Marx et al. (1960) reported a single diffusivity from measurements of oxygen uptake rates by a stagnant horizontal layer of initially deoxygenated whole blood. The diffusivities measured by Hershey and Karhan (1968), also under transient conditions, were uniformly higher than those subsequently reported by Stein et al. (1971) from steady state measurements across films of red cells. Both studies were carried out at high oxygen partial pressures to ensure complete oxyhemoglobin saturation.

The model of Fricke (1924) for conduction in a dilute suspension of randomly oriented oblate spheroids has been applied to transport of oxygen (Buckles et al., 1968; Spaeth, 1970; Stein et al., 1971) and of ionic (Chilcote, 1971) and organic (Colton et al., 1970, 1971) solutes in blood under nonreactive conditions. The model derived by Maxwell (1881) for a dilute suspension of spheres and the model of Fricke give similar numerical estimates when applied to the red cell (Stein et al., 1971). La Force and Fatt (1962) incorporated the effect of equilibrium facilitation into the permeability of the red cell in models comprised of series or parallel arrangements of plasma and hemoglobin solution; later (Fatt and La Force, 1963) they used a semitheoretical expression (Meredith and Tobias, 1962) for a suspension of oblate spheroids. Spaeth and Friedlander (1967) similarly incorporated equilibrium facilitation into the model of Fricke. Departure of the oxygenation reaction from equilibrium has not previously been explicitly considered as a factor which influences the rate of steady state oxygen transport in red cell suspensions.

THEORY

In a previous paper (Stroeve et al., 1976*a*), we have developed a general analysis for steady state diffusion through a heterogeneous dispersion in which a carrier species contained within the dispersed and/or continuous phases reversibly reacts with the permeating solute. The analysis incorporates finite-reaction kinetics and a resistance to interphase transport of the permeating solute. For the present study we consider a dilute random dispersion of spheres of volume fraction ϕ, radius a, and oxygen permeability P_d situated in a continuous phase of oxygen permeability P_c with no interfacial resistance. The sphere diameter is assumed to be small compared to the overall thickness L of the dispersion. The interior of each sphere contains a solution of hemoglobin which undergoes reaction with oxygen according to the simple bimolecular scheme

$$O_2 + Hb \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HbO_2 \tag{1}$$

for which $K = k_1/k_{-1}$ is the equilibrium constant. The diffusivities of Hb and HbO_2 are taken to be equal.

One-step kinetics has had widespread use in describing oxygen uptake and release (Gibson, 1959), although it leads to a hyperbolic, rather than sigmoidal, oxyhemoglobin saturation curve, and it is an oversimplification of the true mechanism. The four-step scheme of Adair (1925) is more accurate and has been employed to describe transport in hemoglobin solution (Meldon et al., 1973; Stroeve, 1973). We have retained use of Equation (1) to assess its utility for predictive purpose because of its advantages of simplicity and the availability of kinetic parameters for a range of experimental conditions (Bauer, 1971).

From Stroeve et al. (1976*a*), the solution for the effective permeability of the suspension P_{eff} is

$$\frac{P_{eff}}{P_c} = \frac{2 - 2\phi + \rho(1+F)(1+2\phi)}{2 + \phi + \rho(1+F)(1-\phi)} \tag{2}$$

where

$$\rho = \frac{P_d}{P_c} \tag{3}$$

$$P_{eff} = D_{eff}\alpha_{eff} \tag{4}$$

$$\alpha_{eff} = \phi\alpha_d + (1-\phi)\alpha_c \tag{5}$$

$$F = \frac{F_{eq}\gamma}{1 + F_{eq}(1-\gamma)} \tag{6}$$

TABLE 1. RESULTS WITH HOMOGENEOUS MATERIALS, 25°C

Material	Measured oxygen permeability (P) $\frac{\text{cm}^3\ (\text{STP})}{\text{cm} \times \text{s} \times \text{atm}} \times 10^7$	Calculated diffusion coefficient* $\frac{\text{cm}^2}{\text{s}} \times 10^5$	Literature value
MEM-213 membrane	12.0		$P_m = 12.1 \times 10^{-7}$ (General Electric Co.)
Distilled water	6.27 ± 0.18	2.22 ± 0.06	$D_{O_2} = 2.13 \times 10^{-5}$ (Goldstick and Fatt, 1970)
Isotonic phosphate buffer	6.00 ± 0.12	2.20 ± 0.04	$D_{O_2} = 2.07 \times 10^{-5}$ (Isotonic saline, Goldstick and Fatt, 1970)

* Calculated from permeability with α = 0.0283 cm³(STP)/(cm³ × atm) for oxygen in distilled water and 0.0272 cm³(STP)/(cm³ × atm) in isotonic saline (Altman and Dittmer, 1971).

$$\gamma = \frac{\left(3\frac{\lambda^2}{a^2} + 1\right)\tanh\left(\frac{a}{\lambda}\right) - 3\frac{\lambda}{a}}{\left(2\frac{\lambda^2}{a^2} + 1\right)\tanh\left(\frac{a}{\lambda}\right) - 2\frac{\lambda}{a}} \tag{7}$$

$$\lambda = \left[\frac{k_1\alpha_d p^* + k_{-1}}{D_{Hb}} + \frac{k_1 k_{-1}\alpha_d C_T}{P_d(k_1\alpha_d p^* + k_{-1})}\right]^{-1/2} \tag{8}$$

As $a/\lambda \to 0$, physical diffusion dominates, F approaches zero, and Equation (2) then reduces to the relation derived by Maxwell (1881). As $a/\lambda \to \infty$, the reaction approaches equilibrium everywhere within the sphere, and F attains its maximum value

$$F_{eq} = \frac{D_{Hb}KC_T}{D_{O_2}(1 + K\alpha_d p^*)^2} \tag{9}$$

The derivation of Equation (2) proceeded via the linearization of Friedlander and Keller (1965) which is valid (Smith et al., 1973) so long as the difference in partial pressure across each sphere is small compared to the local value at its center p^*. Since P_{eff} is a function of p^*, the average permeability which obtains when a finite partial pressure difference $p_1 - p_2$ is imposed across the suspension is given by

$$\bar{P}_{eff} = \frac{\int_{p_2}^{p_1} P_{eff}\,dp}{p_1 - p_2} \tag{10}$$

Evaluation of $\bar{P}_{eff}$ requires numerical integration except for the equilibrium limit which has been obtained in closed form (Stroeve et al., 1976*a*).

EXPERIMENTAL METHODS

Materials

Experiments were carried out with nonreactive aqueous dispersions and oil-in-water emulsions which covered a wide range in ρ and which were compatible with the apparatus. Dispersions of Teflon 120 FEP (fluorinated ethylenepropylene) and of Teflon 30 TFE (tetrafluorothylene) in aqueous media containing 5 to 7% (w/v) surfactantes were obtained from E. I. duPont de Nemours and Co. Dispersions of polystrene latex beads were prepared by emulsion polymerization of styrene monomer using the procedure in Table 1 of Woods et al. (1968). Volume fraction dispersed phase was varied by addition or removal of continuous phase (the latter by centrifugation of the dispersion) and was evaluated from the densities of the dispersion and continuous phase as determined by pycnometry. Particle size was evaluated by electron microscopy.

Emulsions were prepared with an emulsator (Becher, 1967) consisting of two syringes connected by a double-hubbed needle through which the mixture to be emulsified was repeatedly passed. The following systems were employed: castor oil (Fisher Chemical Co.) castor oil with 10% (v/v) Span 80 surfactant (ICI America, Inc.), and Wesson vegetable oil (Hunt-Wesson Foods, Inc.), all in aqueous solution containing 10% (v/v) Tween 40 Surfactant (ICI America, Inc.,); and P1D fluorocarbon (perfluoro-1,4-diisopropoxybutane, Allied Chemical Co.) in aqueous solution containing 50 g Pluronic F68 surfactant (BASF Wyandotte Corp.)/l of water. Droplet size was measured by optical microscopy. Details of emulsion preparation are available (Stroeve, 1973).

Blood from O^+ donors in good health was obtained from the blood bank of Massachusetts General Hospital (Boston, Mass.), stored in standard vinyl bags containing ACD solution at 4°C, and used within 7 days of collection. The blood was centrifuged at 5 000 × g for 15 min at 4°C, and the plasma and buffy coat were discarded. The red cells were washed four times with phosphate buffer (pH 7.2) made isotonic to plasma with sodium chloride, recentrifuged, and then diluted to the desired hematocrit with buffer (final pH about 7.0). The entire preparation procedure required 2 hr. Hematocrit was determined by centrifugation in heparinized glass capillary tubes at 17 000 × g for 5 min and measurement of the resulting heights of packed red cells and plasma. Hematocrit was remeasured after permeation experiments; in no case did hemolysis account for more than 1% of the original red cells. To inhibit bacterial growth, all plastic ware contacting blood was rinsed with 1% (v/v) formaldehyde solution and with saline prior to use, and 0.01% (w/v) streptomycin sulfate (Richterich, 1969) was added to red cell suspensions.

Oxyhemoglobin saturation curves at 25°C were measured in parallel with the permeation experiments. Aliquots were placed in stoppered flasks and exposed to a flow of humidified air or humidified nitrogen under gentle agitation at 25°C. After equilibration, small volumes of fully saturated and fully deoxygenated suspensions were mixed to produce specified saturations between 0 and 100%. Oxyhemoglobin saturation was measured with an IL 182 CO-Oximeter (Instrumentation Laboratory, Inc.); pH, p_{O_2}, and p_{CO_2} were measured with a BSM Blood Micro System (Radiometer).

Hemoglobin solutions were prepared from washed packed red cells by three cycles of freeze thawing in a salt-ice slush at −10°C. The solution was centrifuged at 11 000 × g for 30 min to remove red cell stroma; the supernatant was then diluted as needed with isotonic phosphate buffer. Hemoglobin was converted to nonreactive methemoglobin when desired by addition of 1.05 moles of potassium ferricyanide/mole of heme (Antonini and Brunori, 1971). Total hemoglobin concentration was measured by the cyanmethemoglobin method (Richterich, 1969). The measured hemoglobin concentration in the red cells was its normal value, 33 ± 1 g/100 ml solution.

Reactive synthetic water-in-oil emulsions of known but polydisperse size distribution were studied to permit a quantitative test of theory. The aqueous phase (pH 7.0) contained 16.3 g hemoglobin/100 ml solution so as to maximize facilitation while providing a more accurate estimate of oxygen diffusivity than is possible at physiological concentration. The oil phase was similar to that used for preparing liquid-surfactant membranes (Li and May, 1972): 90% (v/v) S100N (a mixture containing primarily paraffins, naphthenes, and

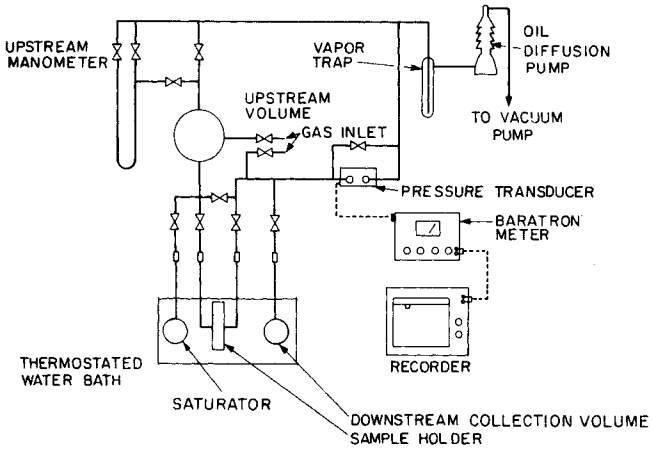

Fig. 1. Schematic diagram of experimental permeation apparatus.

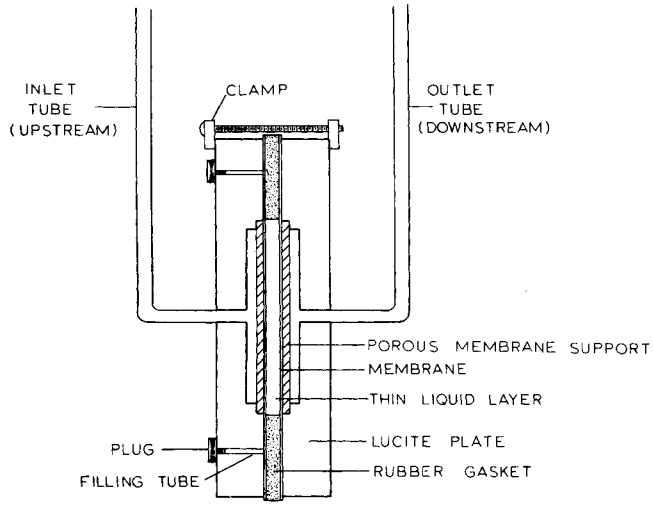

Fig. 2. Schematic diagram of sample holder.

aromatics) and 5% ENJ-3029 (a high molecular weight amine), both manufactured by Enjay Chemical Co.; and 5% Span 80. A fine emulsion (40 ml total volume) was prepared by dropwise addition of hemoglobin solution to the oil in a 100 ml beaker agitated by a 3 cm diameter turbine impeller at 400 rev/min, after which the system was agitated at 1 000 rev/min for 7 min. After standing 30 min, the foamy layer was skimmed off. A coarse emulsion was prepared by substituting a 4 cm diameter magnetically driven stirring bar and by agitating at 400 rev/min for 8 min after addition of hemoglobin solution. Particle size distribution was evaluated by measuring more than 500 particles via optical microscopy. Emulsification caused some deactivation of the hemoglobin, perhaps from denaturation at the water-oil interface; the remaining activity was measured by the Van Slyke gasometric technique (Van Slyke and Neill, 1924).

Apparatus

Gas permeation rates were measured with the apparatus shown in Figure 1. The material under study was supported vertically in a sample holder between two chambers, and a sample of the continuous phase was placed in the saturator to prevent evaporation from the liquid film. The system was first evacuated to the vapor pressure of the continuous phase, and the leak rate in the downstream volume (25 cm^3) was determined. During this period, virtually all carbon dioxide was removed from the red cell suspensions. After equilibration at the desired downstream partial pressure of the permeating gas, the partial pressure in the upstream volume (about 3 000 cm^3) was increased, and the downstream partial pressure was monitored with a Baratron Type 77 capacitance manometer (MKS Instruments) sensitive to ± 1 μm Hg. The upstream pressure, which changed minimally during the course of a run, was measured with a mercury manometer and read to within 0.1 mm Hg with a cathetometer. After an initial transient period, but before a substantial pressure increase occurred, the system became quasisteady, and the rate of pressure increase was independent of time. Oxygen partial pressure was calculated by subtracting the known continuous phase vapor pressure and the pressure rise due to leakage (less than 5% of the total) from the measured total pressure.

All experiments were carried out at 25°C unless otherwise specified. The sample holder, saturator, and downstream collection volume were placed in a constant temperature water bath maintained within ± 0.001°C by a YSI Model 72 proportional temperature controller (Cole-Parmer); temperature change was measured to the same precision with a Beckman differential thermometer. Precise temperature control was necessary to prevent variation in vapor pressure for the liquid in the saturator. The remainder of the vacuum apparatus was enclosed in an insulated wooden box maintained about 3°C above the water bath temperature to prevent liquid condensation in the apparatus, especially in the capacitance manometer pressure sensing head.

Details of the sample holder are shown in Figure 2. The liquid film was contained in a volume defined by a rubber gasket placed between two identical MEM-213 silicone-polycarbonate membranes (General Electric Co.) of 25 or 50 μm thickness. The membranes were supported by disks of low-density (91% void fraction) nickel foametal (General Electric Co.) inserted in Plexiglas plates. All contacting surfaces were first coated with a thin film of silicone vacuum grease, and the entire assembly was tightly clamped between metal plates. The desired liquid film thickness (450 to 2 200 μm) was assured by placing circular metal spacers in holes around the periphery of the slightly thicker gasket. The area available for transport was 25.5 cm^2. Liquid was introduced into and removed from the assembled sample holder through two filling ports with a syringe. The membrane was punctured and liquid was passed through a slot in the rubber gasket; filling was carried out slowly to prevent entrapment of bubbles.

A vertical film was selected so that any sedimentation or creaming occurred in a direction perpendicular to that of gas transport. Significant phase separation occurred in some systems with $\phi < 0.4$. The sample was redispersed just prior to introduction of the permeating gas by rotating the sample holder 180 deg. around its axis. In no case was the height of clear continuous phase at the end of a run more than 10% of the total film height.

The mass transfer resistances of the gas phases and the porous foametal supports were negligible in comparison to that of the liquid film. The contribution of the membranes was small but finite, and the partial pressure drop Δp_m across each membrane was calculated from

$$N = \frac{P_m}{L_m} A \Delta p_m \tag{11}$$

The calculated gas partial pressure at each liquid-membrane interface was then used to evaluate the average film permeability from

$$N = \frac{\overline{P}_{eff}}{L} A(p_1 - p_2) \tag{12}$$

RESULTS AND DISCUSSION

Homogeneous Materials

Results with homogeneous materials are summarized in Table 1. The measured oxygen permeability of the MEM-213 membranes agreed well with the value reported by the manufacturer. The permeability of distilled water and of isotonic phosphate buffer was measured with a variety of film thicknesses (655 to 2 330 μm) and p_{O_2} driving forces (15 to 190 mm Hg). The calculated diffusion coefficients were in good agreement with those of Goldstick and Fatt (1970) and within the range of reported values, 1.87 to 2.44 $\times 10^{-5}$ cm^2/s (Goldstick and Fatt, 1970).

Table 2. Properties of Nonreactive Synthetic Suspensions, 25°C

System number	Dispersed phase	Permeability $cm^3(STP)/(s \times cm \times atm) \times 10^7$ P_d	P_c	Particle size $\bar{d}_v \pm \sigma_v$, μm
1	Polystyrene latex	0.0913 Robb (1971)	6.02	0.12 ± 0.008
2	Teflon 120 FEP	0.967† Pasternak, et al.	112†	0.20 ± 0.02
3	Teflon 30 TFE	0.890† Pasternak, et al. (1970, 1971)	130†	0.05 to 0.5*
4	Castor oil	2.55	5.42	10 (range 1 to 15)
5	Castor oil 10% Span 80	2.76	5.42	9 ± 4
6	Vegetable oil	9.09	5.42	10 ± 4
7	P1D fluorocarbon	200 ± 30	6.02	11 ± 4

* Particles formed irregular flakelike aggregates extending up to 10 μm in their longest dimension.
† Carbon dioxide permeation.

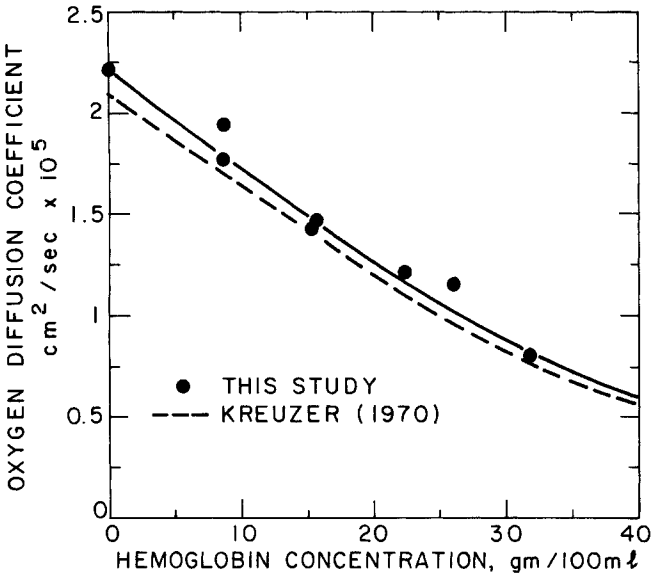

Fig. 3. Oxygen diffusion coefficient in hemoglobin solution, 25°C, pH 7.0. Dashed curve represents recommended values of Kreuzer (1970). Solid curve represents Kreuzer's correlation adjusted to a diffusivity of 2.20×10^{-5} cm²/s in isotonic saline.

Physical properties of the nonreactive synthetic suspensions are tabulated in Table 2. Permeabilities of the dispersed and continuous phases were measured individually in this study unless otherwise indicated. Oxygen transport was studied in all cases except for the Teflon dispersions with which carbon dioxide was employed.

Oxygen permeability was measured for several buffered solutions of increasing hemoglobin concentration in which the hemoglobin had been inactivated by conversion to methemoglobin. Oxygen solubility was estimated by linear interpolation between the value for isotonic saline, 0.0272 cm^3 (STP)/(cm^3 × atm), and that for red cells (33% (w/v) hemoglobin), 0.0276 cm^3 (STP)/(cm^3 × atm), as given by Altman and Ditmer (1971). Oxygen diffusivities calculated from these experiments are shown in Figure 3. Kreuzer (1970) reviewed the available data for oxygen diffusion through hemoglobin solution. His recommended correlation, which adjusted all data to a saline diffusivity of 2.07×10^{-5} cm²/s (Goldstick and Fatt, 1970) is also plotted in Figure 3 and is uniformly about 6% lower than the results of this study. At 33% (w/v), oxygen permeability is estimated to be 2.05×10^{-7} cm^3(STP)/(cm × s × atm). The measured permeability of distilled water and of 15.4% (w/v) hemoglobin solution did not change significantly from 25° to 37°C, indicating that the decrease in solubility (Altman and Dittmer, 1971) was balanced by an increase in diffusivity.

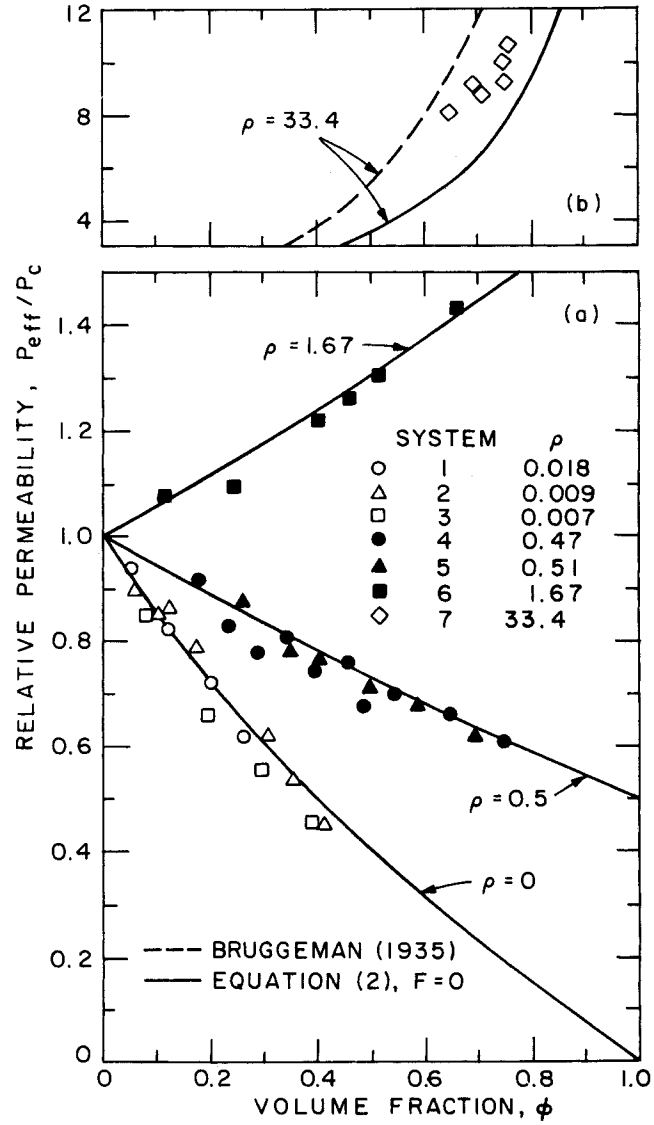

Fig. 4. Relative permeability of nonreactive synthetic suspensions, 25°C. System number refers to Table 2.

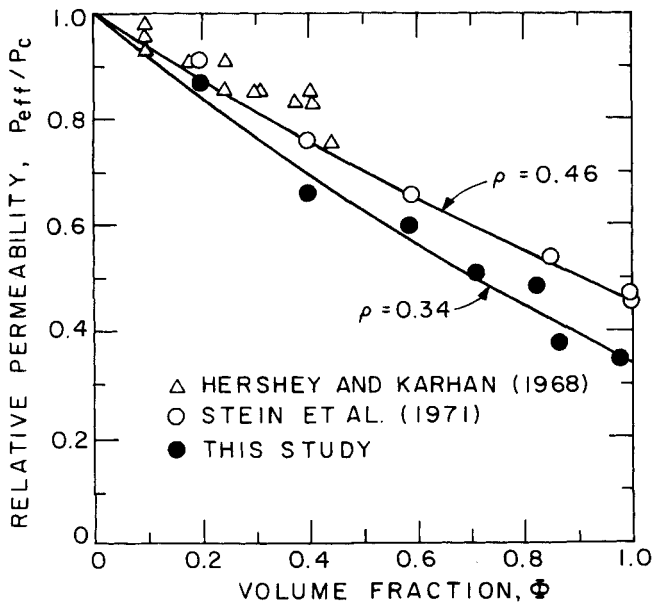

Fig. 5. Relative permeability of nonreactive red cell suspensions (this study: 25°C, pH 7.0, p_1 = 200 mm Hg, p_2 = 50 mm Hg).

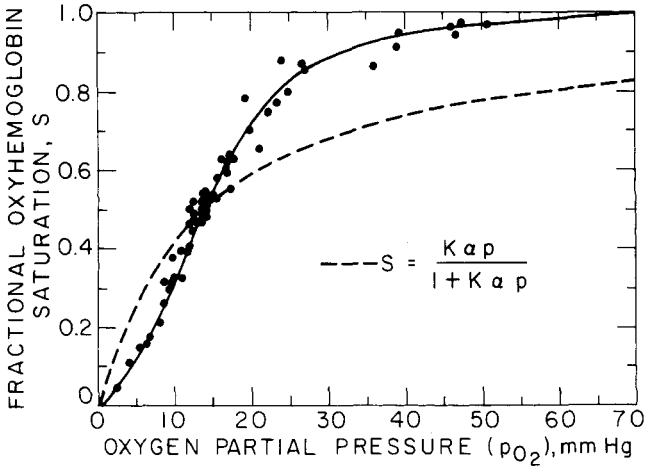

Fig. 6. Oxyhemoglobin saturation curve for red cell suspensions, 25°C, pH 7.0. Hyperbolic curve (dashed) corresponding to one-step kinetics computed with parameters in Table 3.

Nonreactive Suspensions

The results of permeation experiments with the nonreactive synthetic suspensions are summarized in Figure 4. The data in Figure 4*a* conform well to the predictions of Maxwell's equation. The data for PID fluorocarbon emulsion (Figure 4*b*), for which ρ = 33.4, fall between the predictions of Maxwell and of Bruggeman (1935). Similar behavior has been observed with other systems (Meredith and Tobias, 1962) when $\rho >> 1$. The results in Figure 4 indicate that Maxwell's equation provides accurate prediction even at large values of ϕ, except when ρ is substantially greater than unity.

Experiments for which the downstream oxygen partial pressure was above 50 mm Hg so that hemoglobin was fully saturated and therefore nonreactive were also carried out with red cell suspensions. The results are shown in Figure 5, along with a theoretical prediction calculated from the assumptions that the permeability of a 33% (w/v) hemoglobin solution is representative of the red cell interior and that the relative resistance of the red cell membrane is negligible. The excellent agreement between theory and data substantiates both assumptions and supports the finding of others (Kreuzer and Yahr, 1960; Kutchai and Staub, 1969; Stein et al., 1971) that the red cell membrane is not an important barrier to oxygen transport.

Also plotted in Figure 5 for comparison are the results of Hershey and Karhan (1968) and of Stein et al. (1971). Agreement with the latter study is satisfactory; the higher value of ρ reflects the lower hemoglobin concentration, 31.6% (w/v), found in the red cells they employed, as well as the lower permeability of their continuous phase (agar gel). The relative permeabilities measured by Hershey and Karhan are higher than either of the other studies. The disparity may result from the effect of sedimentation in a thin horizontal film, a likely possibility of which the authors were aware. The curves in Figure 5 were calculated for a suspension of spheres, whereas the human red cell is a biconcave disk with a diameter of 8.5 μm and maximum and minimum thicknesses of 2.4 and 1.0 μm, respectively (Whittam, 1964). However, Stein et al. (1971) showed that the effect of dispersed phase shape variation was relatively insignificant over the parameter range of interest here.

Reactive Suspensions

The saturation curve for all reactive suspensions is shown in Figure 6; it demonstrates consistent behavior between samples. Also plotted is the hyperbolic saturation curve which corresponds to a one-step reaction scheme with the kinetic parameters listed in Table 3.

Results from three sets of experiments with reactive red cell suspensions, in which p_2 was less than 5 mm Hg and p_1 was varied, are compared with theoretical pre-

Table 3. Properties of Reactive Suspensions, 25°C

Parameter	Red cell suspensions	Reactive emulsions	Source
Hemoglobin, % (w/v)	33	16.3	
C_T, moles heme/l	2.04×10^{-2}	1.01×10^{-2}	
D_{Hb}, cm²/s	7×10^{-8}	2.25×10^{-7}	Kreuzer (1970)
P_d, cm³(STP)/(cm × s × atm)	2.05×10^{-7}	4.03×10^{-7}	This study
P_c, cm³(STP)/(cm × s × atm)	6.00×10^{-7}	7.05×10^{-7}	This study
α_d, cm³(STP)/(cm³ × atm)	0.0276	0.0274	Altman and Dittmer (1971)
k_1, l/(mole × s)	3×10^6	3×10^6	Hartridge and Roughton (1925)
k_{-1}, s^{-1}	68.5*	68.5*	
Particle size, μm	Fine Emulsion	Coarse Emulsion	
Range	1 to 6	2.5 to 50	
$\bar{d}_n \pm \sigma_n$	2.5 ± 0.9	9.3 ± 8.7	
$\bar{d}_v \pm \sigma_v$	3.8 ± 1.4	33.2 ± 12.5	
Hemoglobin activity remaining, % of original	46	58	

* Calculated from $k_1 p_{50}/k_{-1} = 1$, as suggested by Bauer (1971).

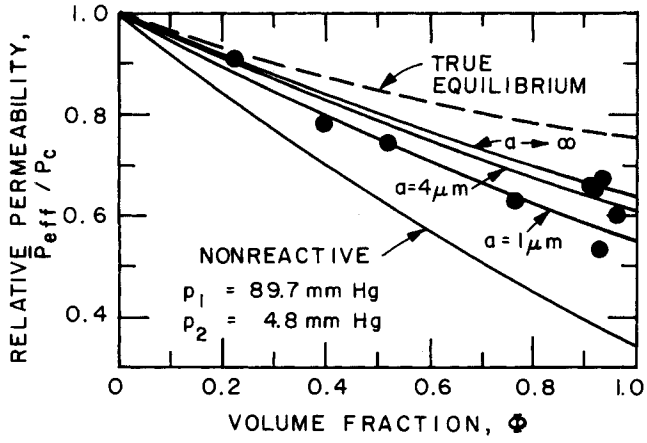

Fig. 7. Relative permeability of reactive red cell suspensions, 25°C, pH 7.0.

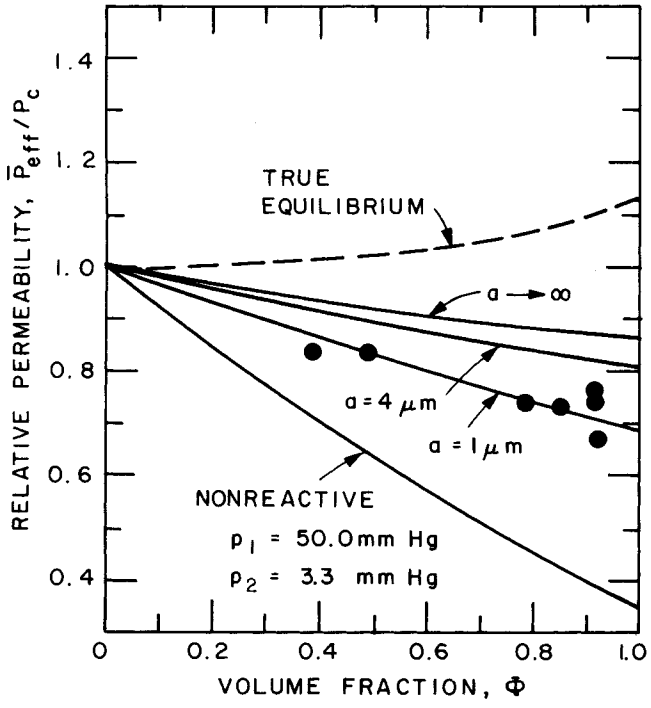

Fig. 8. Relative permeability of reactive red cell suspensions, 25°C, pH 7.0.

diction in Figures 7, 8, and 9. The lower curve in each figure is for a nonreactive suspension (Figure 5). The uppermost curve (dashed) represents the true equilibrium limit when the reaction is at equilibrium throughout each red cell; in that case F_{eq} is evaluated from

$$(F_{eq})_{true} = \frac{D_{Hb}C_T}{P_d}\frac{dS}{dp} \qquad (13)$$

where dS/dp was evaluated from the analytical relation proposed by Margaria (1963) which was fitted to the oxyhemoglobin saturation curve, Figure 6. The remaining solid curves are calculated from the theory presented earlier for one-step oxygenation kinetics and correspond, in descending order, to the equilibrium limit ($a \to \infty$) and to the nonequilibrium regime for spheres of two different radii (4.0 and 1.0 μm) which bound the physical dimensions of the red cell.

Parameters employed in the theoretical calculations are tabulated in Table 2. Uncertainty is greatest for D_{Hb} at physiological concentration. Measurements for 33 ± 2 g hemoglobin/100 ml range from about 3×10^{-8} cm²/s (Adams and Fatt, 1967) to about 1.5×10^{-7}

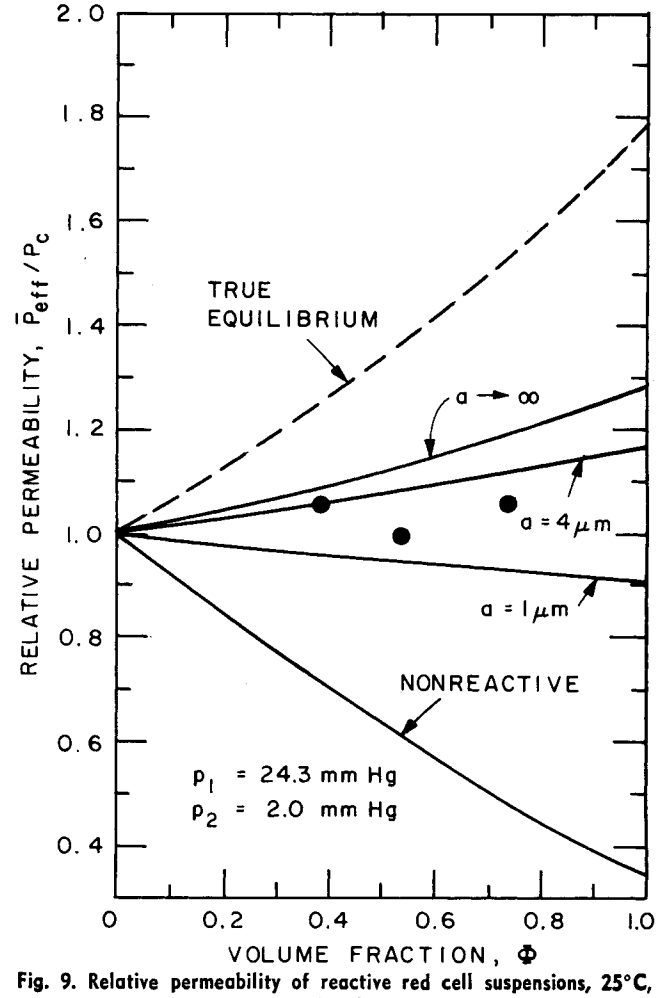

Fig. 9. Relative permeability of reactive red cell suspensions, 25°C, pH 7.0.

cm²/s (Keller et al., 1971). We have employed the compromise value recommended by Kreuzer (1970). The backward rate constant k_{-1} was selected so that the hyperbolic saturation curve intersects the true saturation curve at p_{50}, the p_{O_2} where oxyhemoglobin is half saturated (see Figure 6).

The relative permeabilities in Figures 7, 8, and 9 are all greater than expected for a nonreactive suspension; they increase as p_1 decreases (and the gradient in oxyhemoglobin saturation increases), they fall midway between the limits of true reaction equilibrium and no effect of reaction, and they generally scatter between the curves for radii of 1 and 4 μm with one-step kinetics. These observations indicate that substantial facilitated transport of oxygen can occur in the red cell, and they suggest, subject to the uncertainty in D_{Hb}, that the oxygen-hemoglobin reaction is significantly departed from equilibrium. The difference in prediction between the two equilibrium calculations is a measure of the extent to which the saturation curve for one-step kinetics deviates from the measured curve. In view of this disparity, the agreement of the data with the nonequilibrium prediction of one-step kinetics is gratifying, and it suggests that the model and parameters employed have utility for predictive purposes.

Under conditions of normal physiological blood oxygenation, oxyhemoglobin saturation varies from about 75 to 100%. An experiment was carried out to simulate these conditions at 37°C with $p_1 = 100$ mm Hg, $p_2 = 35$ mm Hg, pH 6.85, hematocrit of 45, and zero partial pressure of carbon dioxide. The average permeability

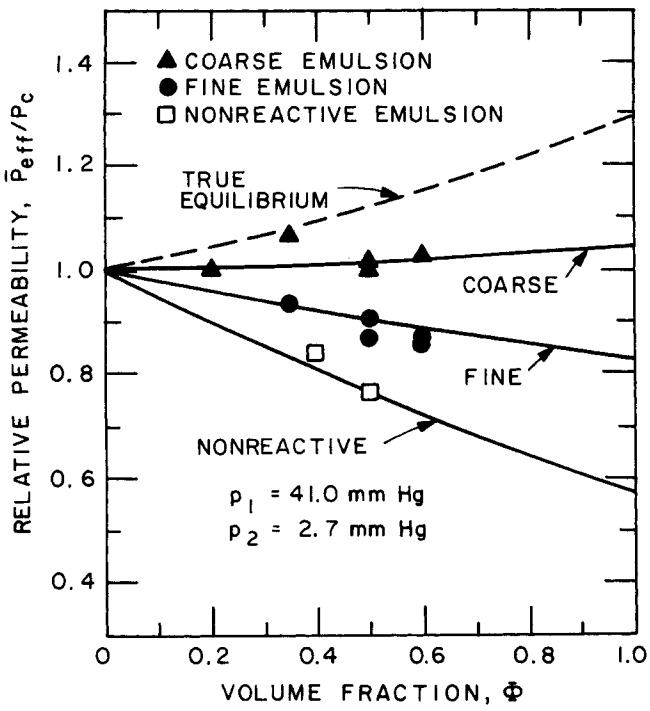

Fig. 10. Relative permeability of reactive synthetic suspensions, 25°C. True equilibrium plotted for amount of hemoglobin activity in coarse emulsion.

decreased from 4.05×10^{-7} to 3.89×10^{-7} cm³ (STP)/(cm × s × atm) when carbon monoxide was introduced into both gas chambers at a partial pressure of 20 mm Hg so as to render the red cell suspension nonreactive. The 4% increase under reactive conditions compares favorably with predicted enhancements of 8 and 10% for 1 and 4 μm radius, respectively (Stroeve, 1973). The predicted enhancement due to reaction effects in whole blood at 37°C is slightly larger, about 15% (Stroeve et al., 1976*b*), because of the lower oxygen permeability of plasma. Thus, facilitation of oxygen transport by red cells will be significant only when the oxyhemoglobin saturation gradient is steep, for example, in the case of hypoxia and in devices for blood deoxygenation (Colton and Drake, 1969).

Results with synthetic reactive emulsions are shown in Figure 10, and properties are tabulated in Table 3. D_{Hb} was estimated to be that for a 16.3% (w/v) solution, but the oxygen-combining capacity C_T was calculated for the hemoglobin activity actually measured with each emulsion, as described above. The saturation curve of the remaining active hemoglobin was the same as in Figure 6. The reduced uncertainty in D_{Hb}, as compared to that for the red cell interior, provides for a more accurate comparison between theory and data than is presently possible with red cell suspensions.

In the nonequilibrium regime, the facilitation factor F is a function of particle size. The procedure of Stroeve et al. (1976*a*) was employed for a distribution of particle sizes. The result is that Equation (2) is replaced by

$$\frac{P_{eff}}{P_c} = \frac{1 + 2\sum_i \phi(a_i)\dfrac{\rho[1+F(a_i)]-1}{\rho[1+F(a_i)]+2}}{1 - \sum_i \phi(a_i)\dfrac{\rho[1+F(a_i)]-1}{\rho[1+F(a_i)]+2}} \tag{14}$$

$F(a_i)$ is the dispersed phase facilitation factor, and $\phi(a_i)$ is the volume fraction, for spheres of mean radius a_i. $\phi(a_i)$ is evaluated from

$$\phi(a_i) = \frac{n_i a_i^3}{\sum_i n_i a_i^3}\phi \tag{15}$$

where n_i is the number of particles in the i^{th} interval of the size distribution of mean radius a_i. These expressions were evaluated from the measured particle size distributions (Tutunjian, 1973).

As with the red cell suspensions, the data in Figure 10 indicate significant facilitation of oxygen transport within the dispersed phase. Relative permeabilities for the reactive emulsions are greater than for the nonreactive case (data obtained after reaction with carbon monoxide) and increase with increasing mean particle size as the reaction approaches closer to equilibrium. The curve for true equilibrium again lies substantially above the prediction for one-step kinetics. Likewise, the data lie somewhat above theoretical prediction, but the agreement with the one-step kinetic model is nevertheless satisfactory.

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NOTATION

A = mass transfer area in sample holder
a = radius of particles in dispersed phase
a_i = mean radius of particles in i^{th} interval of size distribution
C_T = concentration of heme groups in dispersed phase (four times total hemoglobin concentration)
D_{O_2} = oxygen diffusion coefficient in dispersed phase
D_{Hb} = hemoglobin diffusion coefficient in dispersed phase
$\bar{d}_n$ = $\sum_i n_i d_i \Big/ \sum_i n_i$, number average particle size
$\bar{d}_v$ = $\sum_i n_i d_i^4 \Big/ \sum_i n_i d_i^3$, volume average particle size
F = facilitation factor, defined by Equation (6)
F_{eq} = equilibrium facilitation factor, defined by Equation (9) for one-step reaction scheme; true value defined by Equation (13)
K = k_1/k_{-1}, equilibrium association constant for Equation (1)
k_1 = forward rate constant for Equation (1)
k_{-1} = backward rate constant for Equation (1)
L = thickness of film across which permeation occurs
N = oxygen permeation rate
n_i = number of particles in i^{th} interval of size distribution
P = $D\alpha$, permeability
p = oxygen partial pressure
S = fractional saturation

Greek Letters

α = oxygen solubility
γ = function defined by Equation (7)

λ = reaction-diffusion length scale, defined by Equation (8)

ρ = P_d/P_c, ratio of permeabilities for dispersed and continuous phases

σ_n = $\left[\sum_i n_i(d_i - \bar{d}_n)^2 \Big/ \sum_i n_i \right]^{1/2}$, number average standard deviation

σ_v = $\left[\sum_i n_i d_i^3 (d_i - \bar{d}_v)^2 \Big/ \sum_i n_i d_i^3 \right]^{1/2}$, volume average standard deviation

ϕ = volume fraction dispersed phase (hematocrit/100 for red cell suspensions)

$\phi(a_i)$ = volume fraction dispersed particles of radius a_i

Subscripts

c = continuous phase

d = dispersed phase

eff = effective value for dispersion

m = membrane

1 = upstream membrane-liquid interface

2 = downstream membrane-liquid interface

Superscripts

* = local value, at center of spherical particle

$^-$ = average effective value for suspension as a whole (overbar)

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R & D NOTES

Turbulent Non-Newtonian Transport in a Circular Tube

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This work is concerned with turbulent heat or mass transfer in a circular tube to nonelastic fluids whose rheological behavior can be approximated by the power law model expressed as

$$\tau = K\left(\frac{du}{dy}\right)^n \qquad (1)$$

For the important case of large Prandtl numbers, an analytical expression for the heat transfer coefficient is derived. The asymptotic results obtained depend on the limiting behavior of the eddy diffusivity near the wall. An expression for the eddy diffusivity variation in the wall region derived by Notter and Sleicher (1971) was used in this work. This expression was derived from con-