was estimated to be 0.0022 Å. using the observed value of 0.9.[27]

4. Beam Trap.—To see the benefits of using a beam trap, the experiment was carried out with the sector without the beam trap. The analysis of the photographs showed that the mean amplitude increased 0.002 Å. and index of resolution became 94%. But the value of $r_g(1)$ and r_{RD} were unchanged within the limits of experimental error.

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(25) The value of ρ was experimentally estimated to be 0.23.

(26) Due to the different form of this nozzle the correction is opposite to that proposed by Bartell (ref. 22).

(27) In this case the asymmetrical distribution was approximated by the symmetrical distribution with a shift of $\rho/2\sigma$.

DISPERSION CONDUCTIVITY THEORY APPLIED TO OXYGEN DIFFUSION IN BLOOD

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A theory is developed for calculating steady-state diffusion flux through a dispersion in which the diffusion coefficient in the dispersed phase is dependent on the concentration of the diffusing species. The theory is based on semitheoretical conductivity equations for dispersed systems. The theory when applied to oxygen flux in blood agrees qualitatively with available experimental data. There is also agreement with a previous treatment of oxygen flux in blood where whole blood is approximated first by alternate layers of hemoglobin and plasma transverse to the diffusion path and then parallel to it. The oxygen flux calculated from the dispersion equations lies between the flux for transverse and parallel layers, indicating the reliability of the results.

Introduction

Steady-state diffusion flux of a molecular species through a dispersion is normally calculated from Fick's first law by use of an effective diffusion coefficient for the dispersed system. This diffusion coefficient is a function of the diffusion coefficient for the diffusing species in the dispersed and continuous phases and the volume fraction of dispersed phase. Theoretical equations relating effective diffusion coefficient to these system parameters are useful only for very small volume fractions of dispersed spheres. There are, however, many semitheoretical and empirical equations for the effective diffusion coefficient of dispersions. Meredith and Tobias[1] have given a summary of these equations. Many of these equations are useful for dispersions of nonspherical particles and for large volume fractions of dispersed phase.

None of the equations mentioned can be applied to dispersions in which the diffusion coefficient, in the dispersed or continuous phase, is a function of concentration of diffusing species, and yet the most common and important dispersed system, namely blood, is just such a dispersion. In a previous publication[2] we showed how to calculate upper and lower limits for the effective diffusion coefficient for oxygen in blood. In that paper we pointed out how an estimate of the oxygen transport could be made by first assuming all the hemoglobin to be in layers parallel to the direction of oxygen diffusion and then transverse to this direction. These two limiting solutions must bracket the exact solution, and, since they lie close together for oxygen partial pressures of physiological interest, they should, we believe, represent a good approximation to the exact answer.

We will show here that a semitheoretical equation given by Meredith and Tobias[1] for calculating diffusion in a simple dispersion can be used for dispersions containing a dispersed phase in which the diffusion coefficient is concentration dependent. We will use blood as an example of this kind of system and show that the effective diffusion coefficient calculated in this way lies between the limits we have previously determined. Furthermore, this calculated effective diffusion coefficient for oxygen in blood is in at least qualitative agreement with experimental data in the literature.

Theory

Blood is a dispersion of red blood cells in a homogeneous protein solution called the plasma. The red blood cells in man are biconcave disks, 7 μ in diameter and 2 μ thick. The cell is a membrane envelope filled with a hemoglobin solution. An effective diffusion coefficient for oxygen diffusion through blood cannot be calculated from the conventional equations for effective diffusion coefficients of dispersions because the diffusion coefficient for oxygen in hemoglobin solution depends upon the mean oxygen pressure. Our approach, therefore, is to divide a barrier of blood into many thin layers. Across each thin layer we assume a constant oxygen concentration for the purpose of calculating the effective oxygen diffusion coefficient. Integration over many thin layers gives the oxygen flux for a given oxygen pressure gradient and therefore yields the oxygen diffusion coefficient.

We have shown[3] that the oxygen flux per unit area through a thin barrier of hemoglobin solution is given by

$$J = \frac{D_A' a \Delta P}{\Delta x} + D_E \frac{\partial f(P)}{\partial P} \frac{\Delta P}{\Delta x} \qquad (1)$$

where J is the flux per unit area and ΔP a small oxygen

(1) R. E. Meredith and C. W. Tobias, "Advances in Electrochemistry and Electrochemical Engineering," Vol. 2, C. W. Tobias, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, p. 15.

(2) R. C. La Force and I. Fatt, *Trans. Faraday Soc.*, **58**, 1451 (1962).

(3) I. Fatt and R. C. La Force, *Science*, **133**, 1919 (1961).

pressure differential across a barrier of thickness Δx. The diffusion coefficients for dissolved oxygen and oxyhemoglobin are D_A' and D_E, respectively, and the concentration of dissolved oxygen is equal to its partial pressure multiplied by the constant a. The concentration of oxyhemoglobin is not related to oxygen partial pressure by a constant, however, but by the factor $\partial f(P)/\partial P$ where $f(P)$ is the familiar hemoglobin–oxyhemoglobin dissociation curve.

From eq. 1 we may define a conductivity coefficient for oxygen flux as

$$D_A'a + D_E \frac{\partial f(P)}{\partial P} = k_d \qquad (2)$$

It is important to keep in mind that k_d is pressure dependent through the $\partial f(P)/\partial P$ term. An analogous coefficient for plasma is simply

$$D_A a = k_c \qquad (3)$$

We now consider whole blood to be a suspension of oblate spheroids of hemoglobin having conductivity k_d in plasma which has a conductivity k_c. For this calculation we assume that the red blood cell membrane is infinitely conductive to oxygen. We will later show the effect of the cell membrane if it has a finite oxygen conductivity.

Meredith and Tobias[1] have shown that an earlier equation of Bruggeman, based on an extension of Maxwell's treatment of the conductivity of a suspension of spheres, can be modified to give an expression for the conductivity of a dispersion of oblate spheroids of conductivity k_d dispersed in a continuous medium of conductivity k_c. We assume here that the red blood cell is approximately an oblate spheroid. Meredith's equation is

$$\phi = \frac{\left(\frac{k_m}{k_c} - \frac{k_d}{k_c}\right)\left(\frac{k_m}{k_c} + \alpha\frac{k_d}{k_c}\right)^{\gamma}}{\left(1 - \frac{k_d}{k_c}\right)\left(1 + \alpha\frac{k_d}{k_c}\right)^{\gamma}}\left(\frac{k_m}{k_c}\right)^{\beta} \qquad (4)$$

where k_m is the conductivity of the dispersion and ϕ the volume fraction of plasma. The volume fraction of oblate spheroids is $1 - \phi$. We shall use this result directly, making allowance for the fact that k_d is pressure dependent.

From microscopic observations and from electrical conductivity data on whole dog's blood[4] we can assume that the red blood cells are oblate spheroids with an axial ratio between 3 and 4.5. α, β, and γ were taken for convenience in calculation as 1.182, $-1/6$, and $-1/3$, respectively. The choice of these constants is somewhat arbitrary because we are using eq. 4 for particles, biconcave disks, and at particle concentrations for which this theoretical equation has not been checked against experimental data. However, the constants need only be known approximately because we are more interested here in the relation of oxygen conductivity of dispersion to oxygen pressure than in the absolute value of the conductivity. Meredith and Tobias[1] show that in the limiting case $k_d/k_c = 0$, and at $\phi = 0.50$ the electrical conductivity of a dispersion of spheres is only 20% greater than that of dog's blood. For $k_d/k_c \geq 1$, the situation existing for oxygen conductivity of a dispersion of red blood cells, the conductivity of a dispersion of nonspherical particles is

(4) H. Fricke, *Phys. Rev.*, **24**, 575 (1924).

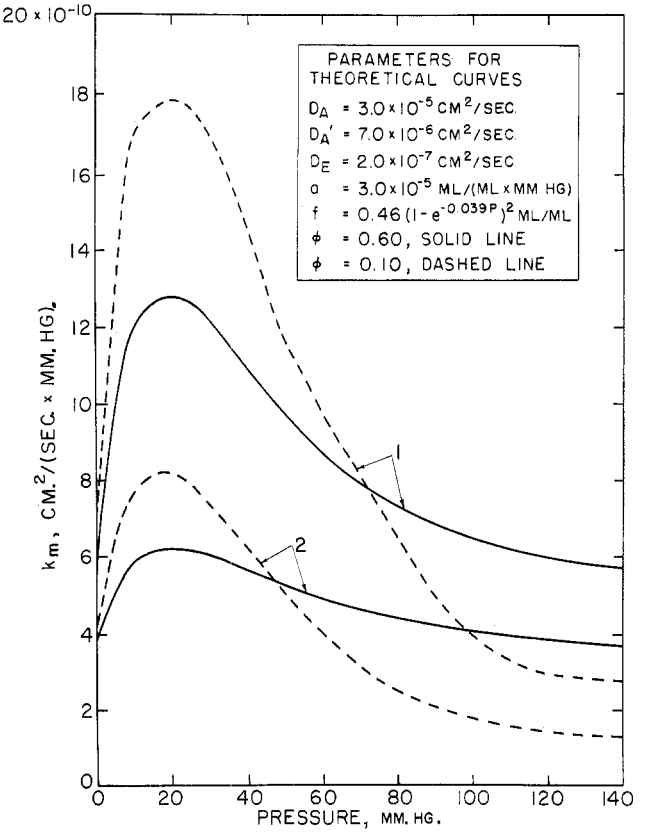

Fig. 1.—Conductivity of a dispersion as a function of pressure for whole blood: solid curves are for normal whole blood; dashed curves are for a paste of red cells; curves labeled 1 are for cells without membrane; curves labeled 2 are for cells with membrane.

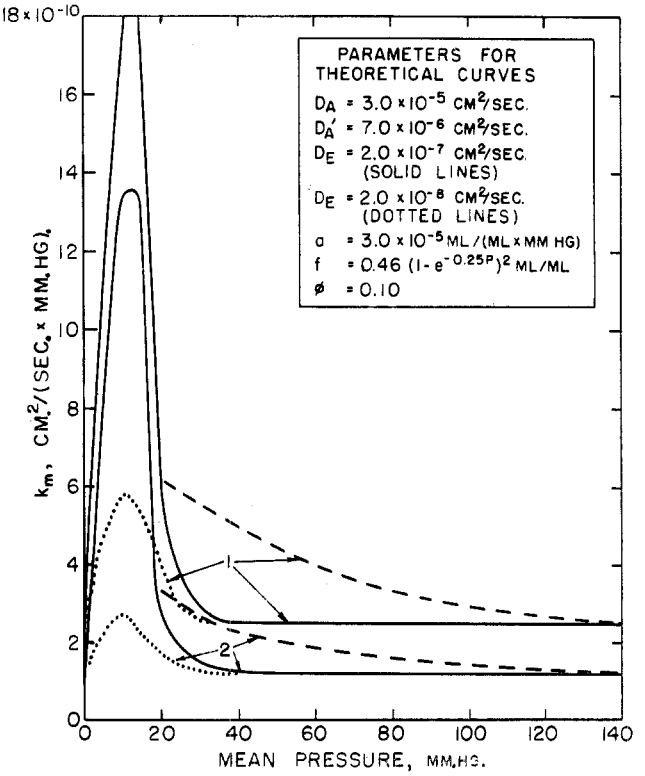

Fig. 2.—Conductivity of a red cell paste as a function of pressure calculated from eq. 4 and 8 compared to Scholander's data, dashed curve: curves labeled 1 are for cells without membrane; curves labeled 2 are for cells with membrane.

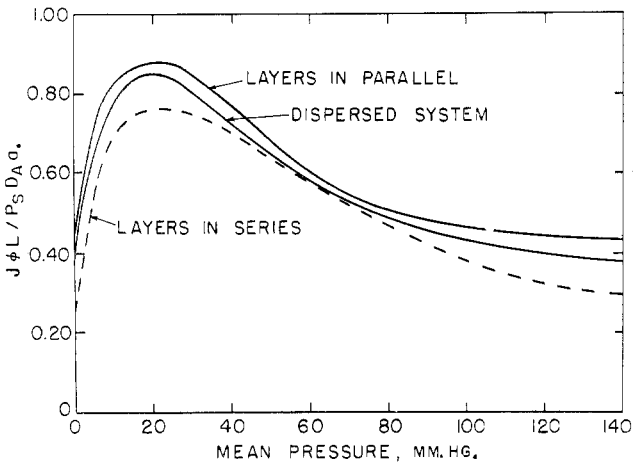

Fig. 3.—Dimensionless flux parameter as a function of mean pressure for a dispersion of hemoglobin with no cell membrane and with parameters shown in Fig. 1, for $\phi = 0.60$.

greater than that for spherical particles. However, the difference is not strongly dependent upon α, β, and γ because of the location of α in eq. 4 and because β and γ are fractional exponents.

Equation 4 must be evaluated by numerical techniques.

The values of k_d and k_c used in evaluating eq. 4 were calculated from eq. 2 and 3 using parameters which we presented in our previous work on oxygen transport in whole blood.[2] These parameters are reproduced here in the inserts of Fig. 1 and 2. Equation 4 was then solved by a trial and error procedure on a high-speed digital computer. As mentioned before, k_d will be pressure dependent because of the S-shaped dependence of $f(P)$ on P and k_m will, therefore, also be pressure dependent. We may numerically calculate the dependence of k_m on P by using, as suggested by Visser,[5] the following semiempirical expression for $f(P)$ to evaluate $\partial f(P)/\partial P$.

$$f(P) = 0.46(1 - e^{-0.039P})^2 \qquad (5)$$

The numerical coefficients in this equation give $f(P)$ for normal conditions in the human body. A plot of k_m *vs.* P for whole blood with $D_E = 2.0 \times 10^{-7}$ cm.^{2}/sec. and at body conditions is shown by the solid curves in Fig. 1. The dashed curves are for a cell volume fraction of 0.90 and demonstrate the effect of an increase in cell content. The effect of the choice of D_E will be discussed later.

Having k_m as a function of P, we can now calculate the oxygen flux J as a function of pressure drop $P_2 - P_1$ and layer thickness L for a layer of whole blood. The equation for steady-state conductivity under these conditions is

$$LJ = \int_{P_1}^{P_2} k_m \, dP \qquad (6)$$

Equation 6 may be evaluated from the curves in Fig. 1 by numerical integration. For convenience in calculation we have written eq. 6 in terms of a dimensionless flux parameter $J\phi L/P_s D_A a$ as follows.

$$\frac{J\phi L}{P_s D_A a} = \frac{\phi}{P_s D_A a} \int_{P_1}^{P_2} k_m \, dP \qquad (7)$$

(5) B. F. Visser and A. H. J. Maas, *Phys. Med. Biol.*, **3**, 264 (1959).

where $P_s = P_2 - P_1$. Some of our results will be presented in terms of this dimensionless flux.

The effect of the cell membrane on steady-state oxygen transport in whole blood may also be estimated. Data from studies[6] of oxygen diffusion through red blood cells indicate that the properties of the membrane surrounding the cell are such as to reduce oxygen flux through the cell to 40% of the flux in the absence of a membrane. Furthermore, oxygen flux in the membrane material depends only on oxygen pressure differential and not on mean oxygen pressure. Under these conditions the effect of the membrane on oxygen diffusion can be taken into account simply by multiplying k_d in eq. 4 by 0.40. Equation 4 now becomes

$$\phi = \left(\frac{\frac{k_m}{k_c} - \frac{0.40\,k_d}{k_c}}{1 - \frac{0.40\,k_d}{k_c}}\right)\left(\frac{\frac{k_m}{k_c} + \alpha\frac{0.40k_d}{k_c}}{1 + \alpha\frac{0.40k_d}{k_c}}\right)^{\gamma}\left(\frac{k_m}{k_c}\right)^{\beta} \qquad (8)$$

Equation 8 may also be evaluated by a trial and error procedure, thereby giving k_m for a suspension in plasma of oblate spheroids each containing a hemoglobin solution surrounded by a membrane. The effect of the membrane is to increase the resistance to the transport of oxygen through the spheroids. Figure 1 shows the effect of cell membrane on k_m for whole blood, $\phi = 0.60$, and for a red cell paste, $\phi = 0.10$, both at body conditions, and for $D_E = 2.0 \times 10^{-7}$ cm.^{2}/sec.

Discussion

Figure 1 shows that the effective conductivity of whole blood to oxygen is oxygen pressure dependent. k_m is at maximum where the slope is maximum on the S-shaped relation between oxygen content and pressure for hemoglobin. The effect of the cell membrane is to lower the conductivity, but the general shape remains the same. Note, however, that for $\phi = 0.60$ the ratio between k_m at high oxygen pressures, 140 mm. or above, to k_m at the peak is about 1.7 for cells with membranes and 2.2 for cells without membranes. This difference may offer a means for using experimental data to test the effect of the cell membrane. Unfortunately there is only one set of experimental data in the literature which can be used to test the theoretical curves in Fig. 1. Scholander[7] measured the ratio of oxygen to nitrogen flux at different air pressure gradients through a "paste" of washed, human red blood cells smeared on filter paper. The downstream side was always a "vacuum" (containing only water vapor). His flux ratio, presented in his Fig. 4, can be shown by a simple argument to be equivalent to our k_m multiplied by a constant. Let Scholander's ratio be J_{O_2}/J_{N_2}, then

$$\frac{J_{O_2}}{J_{N_2}} = \frac{k_m \Delta P_{O_2}}{k_{N_2} \Delta P_{N_2}} \qquad (9)$$

where k_{N_2} is the diffusion conductivity to nitrogen. But since at the downstream side $P_{O_2} = P_{N_2} = 0$

$$\frac{J_{O_2}}{J_{N_2}} = \frac{k_m P_{O_2}}{k_{N_2} P_{N_2}} \qquad (10)$$

(6) F. J. W. Roughton, "Progress in Biophysics and Biophysical Chemistry," Vol. 9, Pergamon Press, London, 1959, p. 55.

(7) P. F. Scholander, *Science*, **131**, 585 (1960).

For air $P_{O_2} = 0.25P_{N_2}$. For blood constituents k_{N_2} is not a function of pressure, therefore

$$\frac{J_{O_2}}{J_{N_2}} = \text{constant} \times k_m \qquad (11)$$

Scholander's paste was about 10% plasma,[8] $\phi = 0.10$, and the flux measurement was made at room temperature, about 25°, and in the absence of carbon dioxide. For these conditions the pH may rise to about 8 and the coefficient of P in eq. 5 is then about -0.25. A plot of the theoretical k_m from eq. 4 and 8 for these conditions is shown by the solid lines in Fig. 2 for $D_E = 2.0 \times 10^{-7}$ cm.²/sec., and by the dotted lines for $D_E = 2.0 \times 10^{-8}$ cm.²/sec. The effect of the increase in the coefficient of P in eq. 5 can be seen by comparing the dashed curves in Fig. 1 with the solid curves in Fig. 2. The increase in the coefficient does not greatly change the position of the curve on the vertical scale but does cause the peak to be sharper and the flat portion to be longer. For coefficients much larger than 0.25 the curve will tend to become flat over most of the pressure range with a sharp spike at about 15 mm.

Scholander's experimental data can be compared to our theoretical curves in Fig. 2 by matching theory and experiment at 140 mm. oxygen pressure to give the lower dashed curve in Fig. 2. All that can be said is that there is qualitative agreement.

If we assume that in Scholander's data the cell membrane does not hinder movement of oxygen, we can match his data at 140 mm. to our theoretical curve for cells without membrane. Scholander's data are then shown as the upper dashed curve in Fig. 2. Again there is qualitative agreement so that it is not possible from this treatment to evaluate quantitatively the effect of cell membrane on oxygen movement through the cell. There appears, however, to be somewhat better agreement between the experimental and theoretical curves when the theory includes a cell membrane, giving evidence that there is some effect due to the membrane.

Figure 3 shows the dimensionless flux parameter $J\phi L/P_s D_A a$ as a function of mean oxygen pressure, when the oxygen pressure gradient is 10 mm., for the dispersed system as calculated from eq. 4 and compares this curve with our previous results.[2] The flux parameter calculated here from integration of the Meredith–Tobias dispersion equation falls as it should between the curves for alternate layers of hemoglobin and plasma in series and in parallel.

One of the parameters of whole blood not yet well known is D_E, the diffusion coefficient of oxyhemoglobin in the hemoglobin solution found in the red blood cell. The comparison of Scholander's experimental data to theory using both $D_E = 2.0 \times 10^{-7}$ and 2.0×10^{-8} cm.²/sec. as shown in Fig. 2 does not permit a choice of D_E for whole blood. Additional diffusion data on whole blood, preferably a direct measurement of D_E, are needed.

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(8) P. F. Scholander, private communication.

KINETICS OF ION EXCHANGE IN THE CHELATING RESIN BIO-CHELEX 100. I. THE EXCHANGE OF THE ALKALINE EARTH IONS

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The exchange of the cations Ca, Sr, and Mg on the chelating resin Bio-chelex 100 in the hydrogen form was studied. The slow step which determines the rate of exchange of these ions is diffusion through the resin particle. The diffusion coefficients at two temperatures and the activation energies for the various cations were calculated.

Introduction

The chelating resin Bio-chelex 100 consists of a cross-linked polystyrene matrix with iminodiacetic acid, $R\text{–}N(CH_2COOH)_2$, as the functional group. In some preliminary experiments it was found that in acid solutions the resin can act as an anion exchanger at the nitrogen atom and thus may enable the study of chloro complexes. Sorption of copper chloride was studied at various concentrations of hydrochloric acid. It was shown that $CuCl_4^{2-}$ was sorbed rapidly at high concentrations of acid,[1] but very slowly in the absence of hydrochloric acid, *i.e.*, in weak acid and neutral solutions. It therefore appears that the sorption of copper proceeds by two different exchange reactions, the one an anion-exchange reaction in concentrated acid solutions and the other a very slow exchange by chelation. To explain these results, the kinetics of the exchange on the hydrogen form of the resin were studied. The cations used in this study were the alkaline earths which are known to give weak complexes with iminodiacetate in solution, and copper, which gives a very strong complex with the same anion. A kinetic study on the similar Dowex A-1 resin was effected by Turse and Rieman.[2] These authors worked with the sodium form of the resin, concluding that the slow step is the chemical exchange reaction for cations giving a chelate with the resin, while when nonchelating cations such as the alkaline ions were used, the slow step is diffusion through the particle. Schwarz[3] studied the kinetics of isotope exchange on the same Dowex A-1, Na form resin for the sodium and zinc ions in

(1) G. Markovits and C. Heitner-Wirguin, unpublished results.

(2) R. Turse and W. Rieman, III, *J. Phys. Chem.*, **65**, 1821 (1961).

(3) A. Schwarz, Thesis, Israel Institute of Technology, Haifa, 1962.