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Analytical model for effects of shear rate on rouleau size and blood viscosity

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Abstract

In this paper, a theoretical model is proposed by using the reversible kinetic equation of colloid coagulation to reveal the effects of erythrocyte aggregation and shear rate on the rouleau size and the blood viscosity. With this model, shear rate $\dot{\gamma}$ dependences of the average size of rouleaux n_c and the viscosity η in concentrated red blood cell suspension are derived analytically. In this model, we consider not only the shear rate effect but also the rouleau size effect on the aggregation and degradation mechanism. By comparing with experimental results obtained by Shiga et al., some theoretical parameters have been determined. The variation of rate of rouleau formation with shear rate derived in our model is in fairly good agreement with the experimental results, and the viscosity of the concentrated red cell suspension derived in our model showing shear thinning agrees qualitatively with the experimental results obtained by Chien and Sung.

Keywords: Viscosity of blood; Colloid coagulation; Rouleaux; Blood; Red cells; Shear rate; Aggregation

One of the properties of blood is its non-Newtonian viscosity, i.e., the shear rate dependence of the viscosity. The understanding of blood viscosity is not only of physical importance, but also of clinical importance. For example, the increase in blood viscosity may cause a slow-down in blood circulation and reduce capillary perfusion and cause ischemia, necrosis or tissue infarction. Many theoretical and experimental papers have been published, but there is still no satisfactory expression for the viscosity of blood. The popular expression is Casson's equation for pigment–oil suspensions of the printing ink type. But at very low shear rate, blood does not obey Casson's equation. One of the important factors affecting the viscosity of blood is red cell aggregation, forming rouleaux, especially at low shear rate. Although there are some explanations of rouleaux formations, the detailed mechanism is still absent. The basic object of the present paper is to reveal the shear rate dependence of rouleau size and viscosity from the microscopic point of view, and to some extent, to study the mechanism of rouleaux formation.

Whole blood consists of three kinds of cells and

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plasma. The greatest proportion of the cells are red cells, the haematocrit or volume fraction of red blood cell suspension $\phi = 0.45$, and they have a great influence on blood viscosity. The presence of white cells and platelets does not make a measurable change in the viscosity of the whole blood. The plasma can be treated as a Newtonian medium with viscosity $\eta_0 = 1.2$ cp. So when we derive blood viscosity, we may consider the blood as a suspension of red cells in a Newtonian medium. For simplicity, we assume the red cells to be oblate spheroids with axes ratio $p_0 = a/b = 0.28$, where a is half of the maximum thickness of a red cell ($a = 1.2$ μm), b is its maximum radius ($b = 4.25$ μm). These cells may aggregate into rouleaux. The aggregation of red cells is a dynamic and reversible process, and rouleaux can easily be broken by external forces. It is known that several factors may influence the aggregation in in vitro laboratory preparation, including the concentration of plasma macromolecules, the balance between attractive and repulsive forces, the shape and deformability of red cells, the haematocrit, the temperature, and the pH value, which affects the volume of red cells. Under flow conditions, the formation and break-up of aggregates are governed by another factor, specifically the shear forces [1]. At low shear rate, the aggregation of red cells tends to increase. However, as the shear rate increases, the size of the aggregates decreases [2–4].

Suppose the suspension of red cells is subjected to a simple shearing motion. A rouleau containing i cells is termed as an i-mer, and the number of i-mers per unit volume at time t is denoted as $C_i(t)$, then the total number of red cells per unit volume is given by

$$N_0 = \sum_{i=1}^{\infty} iC_i(t) \tag{1}$$

and the total number of rouleaux per unit volume is

$$M(t) = \sum_{i=1}^{\infty} C_i(t) \tag{2}$$

We treat the rouleaux formation and degradation process as one of polymerization and fragmentation of colloid, so we may apply the reversible kinetic equation of colloid coagulation to the rate of change of the number of i-mers. It follows that [5,6]:

$$\begin{aligned} dC_k/dt = {} & 1/2 \sum_{i=1}^{k-1} K_{ik-i} S_{ik-i} C_i C_{k-i} \\ & - \sum_{j=1}^{\infty} K_{kj} S_{kj} C_k C_j \\ & - 1/2 \sum_{i=1}^{k-1} F_{ik-i} C_k + \sum_{j=1}^{\infty} F_{kj} C_{k+j} \end{aligned} \tag{3}$$

where K_{ij} is the aggregation rate which indicates the rate of aggregation between an i-mer and a j-mer, and F_{ij} is the degradation rate which indicates the rate of the formation of an i-mer and a j-mer by breaking up an $(i+j)$-mer. They satisfy the following relations:

$$K_{ij} = K_{ji} \tag{4}$$

$$F_{ij} = F_{ji} \tag{5}$$

S_{ij} is the sticking probability which indicates the probability of formation of a single $(i+j)$-mer after the collision between an i-mer and a j-mer. The first term of the right hand side of Eq. 3 indicates the increasing rate of the number of k-mers by collisions between smaller ones and the second term refers to the decreasing rate of the number of k-mers by collisions with other rouleaux. The third term describes the disruption of a k-mer by shearing force, and the last one represents the increasing rate of the number k-mers by disruption of larger ones.

From Eqs. 3 and 2 one can derive the rate of change of the total number of rouleaux per unit volume as

$$\begin{aligned} dM(t)/dt = {} & d/dt \sum_k C_k(t) \\ = {} & -1/2 \sum_{k=1}^{\infty} \sum_{j=1}^{\infty} K_{kj} S_{kj} C_k C_j \\ & + 1/2 \sum_{k=1}^{\infty} \sum_{i=1}^{k-1} F_{ik-i} C_k \end{aligned} \tag{6}$$

In order to derive the total number of rouleaux $M(t)$ and the average rouleau size, we must specify F_{ij} and K_{ij}. There are many factors which determine

the value of F_{ij} and K_{ij}. In principle, K_{ij} and F_{ij} should be determined in terms of the theory of non-equilibrium statistical mechanics concerning the knowledge of the hydrodynamic and potential interactions between the particles and their Brownian motion.

If we only consider the shear rate dependence of F_{ij} and K_{ij}, one might set [6]

$$K_{ij} = K_g = d_1\dot{\gamma} + d_2 \tag{7}$$

$$F_{ij} = K_d = d_3\dot{\gamma} \tag{8}$$

where $\dot{\gamma}$ is the shear rate, and d_1, d_2, d_3 are constants.

The sticking probability S_{ij} has the following form [6]:

$$S_{ij} \equiv S = 1 \text{ for } \dot{\gamma} \le \dot{\gamma}_c$$

$$= \dot{\gamma}_c/\dot{\gamma} \text{ for } \dot{\gamma}_c \ge \dot{\gamma} \tag{9}$$

where $\dot{\gamma}_c$ is a critical shear rate at which the time needed for one rouleau to pass through another becomes equal to a characteristic time t_c.

To improve this model, we include the effects of rouleau size on the formation and degradation of red cells. The aggregation and degradation probabilities for a large rouleau are higher than that for a smaller one. For aggregation rate K_{ij}, we suppose that

$$K_{ij} = (\alpha + \beta ij) K_g \tag{10}$$

with

$$K_g = d_1\dot{\gamma} + d_2$$

where α and β are constants. The term α represents the effect of two aggregates colliding in the direction of the red cell thickness. When two aggregates collide in the lateral direction, the aggregation rate K_{ij} should be proportional to the rouleaux sizes of i-mer and j-mer. So $(\alpha + \beta ij)$ is the simplest combination of these effects. When $\alpha = 1$ and $\beta = 0$, Eq. 10 reduces to Eq. 7.

For a linear chain, a k-mer has $(k-1)$ bonds, we assume that all bonds are equally breakable, so the total rate of k-mer's break-up, $1/2\Sigma_i F_{ik-i}$ is proportional to the number of bonds, i.e.,

$$1/2\sum_i F_{ik-i} = K_d(k-1) \tag{11}$$

with

$$K_d = d_3\dot{\gamma}$$

Substituting Eqs. 10 and 11 into Eq. 6, one finds

$$dM(t)/dt = -1/2K_g \sum_{k=1}^{\infty}\sum_{j=1}^{\infty}(\alpha + \beta kj) S_{kj} C_k C_j + K_d \sum_{k=1}^{\infty}(k-1)C_k \tag{12}$$

Substituting Eqs. 1 and 2 into Eq. 12, we get

$$dM(t)/dt = -K_g \alpha S M^2(t)/2 - K_d M(t) + K_d N_0 - K_g \beta S N_0^2/2 \tag{13}$$

Integrating Eq. 13, and noting that $M(0) = N_0$, one gets

$$M(t) = \frac{(N_0 - M_1)M_2 - (N_0 - M_2)M_1 e^{-\lambda t}}{(N_0 - M_1) - (N_0 - M_2)e^{-\lambda t}} \tag{14}$$

where

$$M_1 = -\frac{1}{\alpha K_g S}\left\{K_d + \left[K_d^2 + 2\alpha K_g S N_0 (K_d - K_g \beta S N_0/2)\right]^{1/2}\right\} \tag{15}$$

$$M_2 = -\frac{1}{\alpha K_g S}\left\{K_d - \left[K_d^2 + 2\alpha K_g S N_0 (K_d - K_g \beta S N_0/2)\right]^{1/2}\right\} \tag{16}$$

$$\lambda = -\alpha K_g S(M_1 - M_2)/2 \tag{17}$$

The important quantity which is used in deriving the viscosity of blood is the average size of rouleaux, i.e., the average number of cells within a single rouleau

$$n(t) = N_0/M(t) \tag{18}$$

In order to compare quantitatively our theoretical model with the experimental results of Shiga et al. [7] and thus to determine parameters d_1, d_2, d_3, α, and β, we calculate the rate of rouleau formation dn/dt. dn/dt is a function of t, and we choose $[dn/dt]_{t_1}$ as the rate of rouleau formation at a time

t_1 when $M(t_1) = N_0/2$. Introducing dimensionless time τ as $\tau = t\dot{\gamma}_c$, we have

$$\left[\frac{dn}{d\tau}\right]_{\tau=\tau_1} = 2\left[N_0(d_1\dot{\gamma} + d_2)\left(\frac{1}{4}\alpha + \beta\right) - d_3\dot{\gamma}\right] / \dot{\gamma}_c \quad \dot{\gamma} \le \dot{\gamma}_c$$

$$= 2N_0(d_1 + d_2/\dot{\gamma})\left(\frac{1}{4}\alpha + \beta\right) - 2d_3\dot{\gamma}/\dot{\gamma}_c \quad \dot{\gamma} \ge \dot{\gamma}_c \tag{19}$$

The curve in Fig. 1 shows the rate of rouleau formation $dn/d\tau$ normalized by a maximum value

$$[dn/d\tau]_{max} = 2N_0(d_1 + d_2/\dot{\gamma}_c)\left(\frac{1}{4}\alpha + \beta\right) - 2d_3$$

against the shear rate normalized by $\dot{\gamma}_c$. The small triangles in Fig. 1 are the experimental data of Shiga [7] taken from [6], in which the normalized rate of rouleau formation is denoted by V/V_c as a function of the reduced shear rate $\dot{\gamma}/\dot{\gamma}_c$, and the critical shear rate is $\dot{\gamma}_c = 5.78\ s^{-1}$, at which the rate of rouleau formation V has a maximum value $V_c = 17.9\ \mu m^2\ s^{-1}$. From this figure it can be seen that our theoretical result agrees fairly well with the experiment, by choosing appropriate values of parameters. The haematocrit of red cell suspension is taken to be

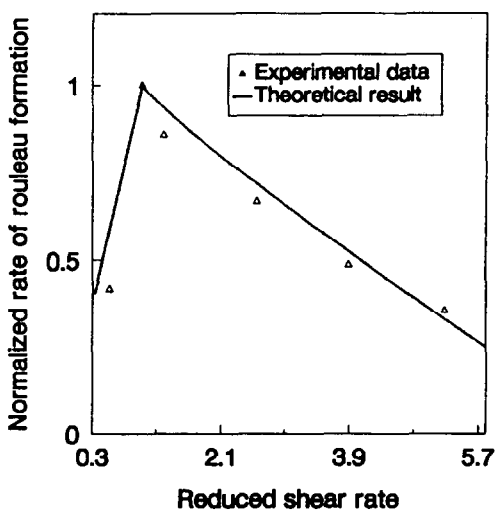

Fig. 1. Variation of normalized rate of rouleau formation with reduced shear rate, with $N_0 = 4.96 \times 10^{-3}\ \mu m^{-3}$, $d_1 = 3.03 \times 10^3\ \mu m^3$, $d_2 = 1.83 \times 10^3\ \mu\ m^3\ s^{-1}$, $d_3 = 1.00$, $\alpha/4 + \beta = 0.5$.

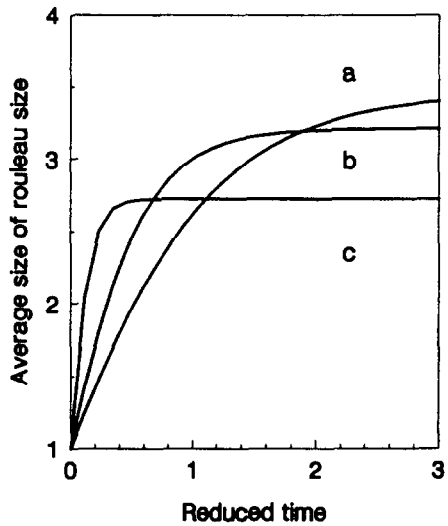

Fig. 2. Variation of the average size of rouleaux $n(t)$ with reduced time τ, with $N_0 = 4.96 \times 10^{-3}\ \mu m^{-3}$, $d_1 = 3.03 \times 10^3\ \mu m^3$, $d_2 = 1.83 \times 10^3\ \mu m^3\ s^{-1}$, $d_3 = 1.00$, $\alpha/4 + \beta = 0.5$, $\alpha = 3.0$, $\beta = -0.25$. (a) $\dot{\gamma} = 0.01$, (b) $\dot{\gamma} = 0.5$, (c) $\dot{\gamma} = 6.0$

0.45, according to Eq. 24 (see below), we have $N_0 = 4.96 \times 10^{-3}\ \mu m^{-3}$. Values of parameters obtained by fitting the experimental data are bounded by the following relations: $d_1 R/Q = 115$, $d_2 R/Q = 69.5$, $d_3/Q = 0.076$, where $R = \alpha/4 + \beta$, Q is a parameter. In Fig. 1, we choose $d_3 = 1.0$, $R = 0.5$, then it follows that $d_1 = 3.03 \times 10^3\ \mu m^3$, $d_2 = 1.83 \times 10^3\ \mu m^3\ s^{-1}$.

The time course of the average size of rouleaux is shown in Fig. 2. It is shown that it increases with time from single cell at $t = 0$, $n_0 = 1$, until reaches its equilibrium size $n_e = N_0/M_e$.

Considering the reversible process of rouleaux formation and degradation, one may expect a constant distribution of rouleaux size in steady state under constant shear rate. The average size of rouleaux in dynamic equilibrium is obtained from Eqs. 14 and 18,

$$n_e = N_0/M_2 \tag{20}$$

or

$$n_e = \frac{\alpha N_0 S(d_1\dot{\gamma} + d_2)}{(h_1\dot{\gamma}^2 + h_2\dot{\gamma} + h_3)^{1/2} - d_3\dot{\gamma}} \tag{21}$$

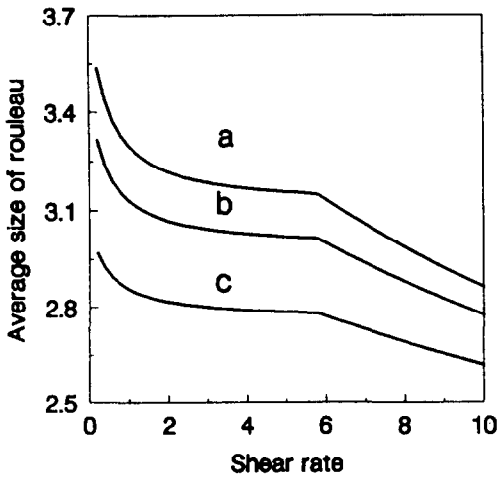

Fig. 3. Relation between average size of rouleaux n_e and shear rate $\dot{\gamma}$ with $N_0 = 4.96\times10^{-3}$ μm^{-3}, $d_1 = 3.03\times10^{3}$ μm^3, $d_2 = 1.83\times10^{3}$ μm^3 s^{-1}, $d_3 = 1.00$, $\alpha/4+\beta = 0.5$. (a) $\alpha = 2.8$, $\beta = -0.2$. (b) $\alpha = 3.0$, $\beta = -0.25$. (c) $\alpha = 3.5$, $\beta = -0.375$.

where

$$h_1 = d_3^2 + 2\alpha d_1 d_3 S N_0 - \alpha\beta d_1^2 S^2 N_0^2 \quad (22a)$$

$$h_2 = 2\alpha d_2 d_3 S N_0 - 2\alpha\beta d_1 d_2 S^2 N_0^2 \quad (22b)$$

$$h_3 = -\alpha\beta d_2^2 S^2 N_0^2 \quad (22c)$$

In order to make Eq. 21 meaningful for $\dot{\gamma} = 0$, we must have $\alpha\beta \leq 0$. The relationship between n_e and $\dot{\gamma}$ is shown in Fig. 3, which shows that the average size of rouleaux decreases with increasing shear rate, which coincides with the experimental results found by Chien [2], Schmid-Schönbein et al. [3] and Snabre et al. [4].

Red cell suspension is a multi-disperse system which contains many rouleaux of various sizes. In order to simplify the problem, we assume in the following that this suspension is a mono-disperse system which contains M_e rouleaux of the same size n_e per unit volume. Furthermore, we shall still treat these rouleaux as oblate spheroids with axes ratio

$$p = d/b = n_e p_0 \quad (23)$$

According to the above assumption, the haematocrit or volume fraction of red blood cell suspension is given by

$$\phi = 4/3\pi d b^2 M_e = 4/3\pi a b^2 N_0 \quad (24)$$

According to [8], the apparent viscosity of dilute suspension of oblate spheroids is given by

$$\eta = \eta_0\{1 + \tilde{a}(p)\phi\} \quad (25)$$

There are several expressions for $\tilde{a}(p)$, among which we are interested in the one for the steady state, so we choose [8]

$$\tilde{a}(p) = 2\left(1 - \frac{1}{5p^2}\right) \quad (26)$$

Hence,

$$\eta = \eta_0\{1 + a(n_e)\phi\} \quad (27)$$

where

$$a(n_e) = 2\left(1 - \frac{1}{5p_0^2 n_e^2}\right) \quad (28)$$

Eq. 27 is applicable only to very dilute suspension. In order to derive the viscosity of concentrated suspension, we make use of Brinkman's method [9]. Consider the addition of a small amount of rouleaux to a suspension of volume fraction ϕ. Let the amount added be $\delta\phi$ per $(1 - \delta\phi)$ of the original suspension. We assume that the new suspension may be treated as a very dilute suspension of volume frac-

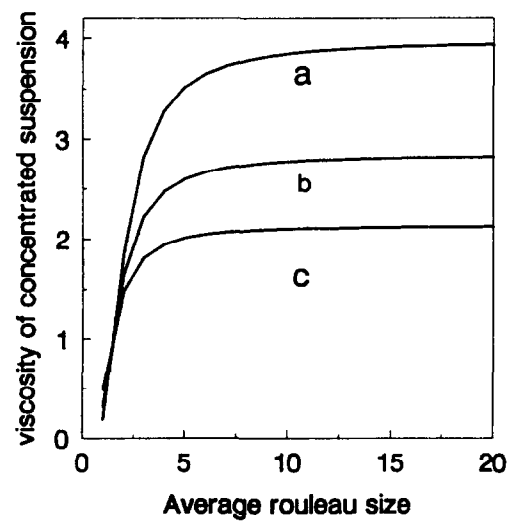

Fig. 4. Relation between viscosity η and average rouleaux size n_e, with $p_0 = 0.28$, $\eta_0 = 1.2$ cp, (a) $\phi = 0.45$; (b) $\phi = 0.35$; (c) $\phi = 0.25$.

tion $\delta\phi$, the original suspension now forming the continuous medium. The true volume fraction ϕ' of the new suspension is given by

$$\phi' = \phi(1 - \delta\phi) + \delta\phi \tag{29}$$

i.e., the increase in the true concentration is

$$d\phi = \phi' - \phi = \delta\phi(1 - \phi)$$

i.e.,

$$\delta\phi = \frac{d\phi}{1 - \phi}$$

Let the viscosity of the original suspension be η, which is now taken as the viscosity of the medium of the new suspension. From Eq. 27, the viscosity η' of the new suspension is

$$\eta' = \eta\{1 + a(n_e)\,\delta\phi\}$$

Writing $d\eta = \eta' - \eta$, $\delta\phi = d\phi/(1 - \phi)$, we get

$$\frac{d\eta}{\eta} = a(n_e)\frac{d\phi}{1 - \phi} \tag{30}$$

Integrating Eq. 30 and noting that $\eta = \eta_0$, when $\phi = 0$, we get

$$\eta = \frac{\eta_0}{(1 - \phi)^{a(n_e)}} \tag{31}$$

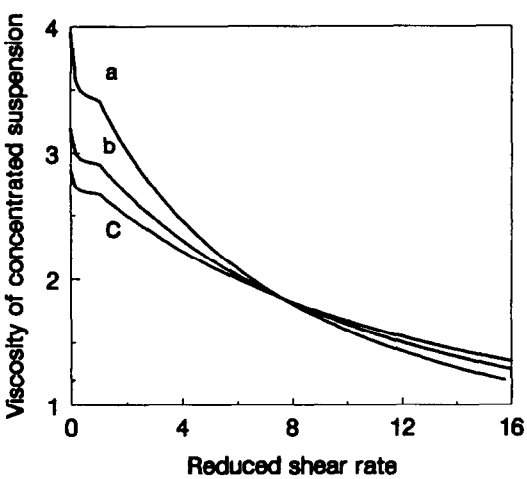

Fig. 5. Shear rate dependence of viscosity in concentrated suspension, with $p_0 = 0.28$, $\phi = 0.45$, $\eta_0 = 1.2$ cp, $N_0 = 4.96 \times 10^{-3}$ μm^{-3}, $d_1 = 3.03 \times 10^3$ μm^3, $d_2 = 1.83 \times 10^3$ μm^3 s^{-1}, $d_3 = 1.0$, $\alpha/4 + \beta = 0.5$. (a) $\alpha = 2.01$, $\beta = -0.0025$. (b) $\alpha = 2.8$, $\beta = -0.2$. (c) $\alpha = 3.5$, $\beta = -0.375$.

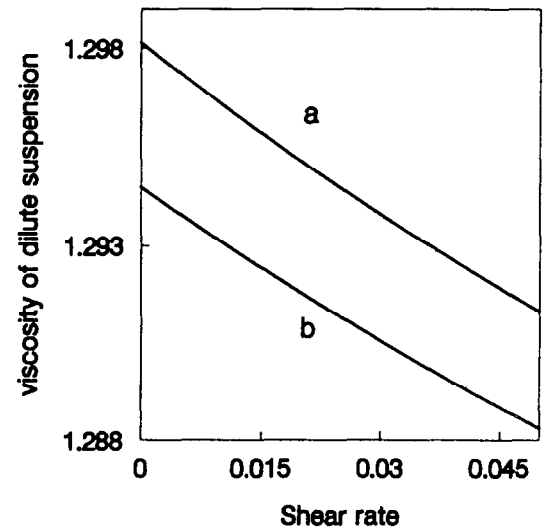

Fig. 6. Shear rate dependence of viscosity of dilute red cell suspension in the limit of low shear rate. $p_0 = 0.28$, $\phi = 0.05$, $\eta_0 = 1.2$ cp, $N_0 = 5.51 \times 10^{-4}$ μm^{-3}, $d_1 = 3.03 \times 10^3$ μm^3, $d_2 = 1.83 \times 10^3$ μm^3 s^{-1}, $d_3 = 1.0$, $\alpha/4 + \beta = 0.5$. (a) $\alpha = 2.8$, $\beta = -0.2$.(b) $\alpha = 3.0$, $\beta = -0.25$.

The relation between η and n_e is shown in Fig. 4, and Fig. 5 shows the relationship between η and the reduced shear rate. The viscosity increases with rouleau size and decreases with shear rate. Therefore, red cell aggregation increases blood viscosity [5,10] and the blood behaves as shear-thinning fluid, which agrees qualitatively with experimental results found by Healy and Joly [11] and Chien and Sung [12].

In the limit of dilute suspension, i.e., for very small ϕ, Eq. 31 can be written as

$$\eta = \eta_0\{1 + a(n_e)\,\phi + \ldots\}$$

Furthermore, for very low shear rate, from Eqs. 28 and 21, we have

$$a(n_e) = a(n_e(\dot\gamma)) = 2\left(1 - \frac{A\dot\gamma + h_3}{B\dot\gamma + D}\right) \tag{32}$$

where

$$A = h_2 - 2d_3h_3^{1/2},\quad B = 10d_1d_2\alpha^2p_0^2S^2N_0^2,$$

$$D = 5d_2^2\alpha^2p_0^2S^2N_0^2 \tag{33}$$

So the viscosity of blood at very low shear rate is given by

$$\eta = \eta_0 \left\{ 1 + 2 \left(1 - \frac{A\dot{\gamma} + h_3}{B\dot{\gamma} + D} \right) \phi \right\} \tag{34}$$

The shear rate dependence of viscosity for very low shear rate in the limit of dilute suspension is shown in Fig. 6. Compared with the Casson formula, which exhibits an infinite viscosity ($\eta \approx \dot{\gamma}^{-1/2}$) when $\dot{\gamma} \approx 0$, our calculation gives finite values of viscosity, which is consistent with experimental results [13].

In this paper we have tried to derive analytically the average size of rouleau and the viscosity of blood as a function of shear rate, with no approximation on large axis ratio p (i.e., very low shear rate assumption), using kinetic theory of colloidal coagulation, and to some extent, explain the effects of rouleaux formation mechanism on the blood viscosity. More rigorous results would need more exact expressions of K_{ij} and F_{ij}, and our theory must be modified by considering more complicated aggregates (instead of uniform aggregates) and hydrodynamic interactions between particles. Furthermore, the above result is the bulk behaviour of blood under flow conditions differing from those in the circulation. The rheological property of blood is different under different geometric and hydrodynamic conditions. Therefore, the same non-Newtonian properties of blood can lead to quite different rheological behaviour depending on actual conditions of flow.

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