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RHEOLOGICAL EXAMINATION OF ERYTHROCYTE AGGREGATION IN THE PRESENCE OF LIPID-BASED FINE PARTICLES

The development of lipid-based fine particles as potential drug carriers requires a detailed investigation of the possible effects of these carriers on the rheological properties of blood. In this study, we investigated the influence of dynamic conditions on aggregate formation and stability in dispersions of lipid-based fine particles in whole blood under in vitro conditions. The rheological parameters of two concentrations of liposome dispersion and two concentrations of lipid emulsion in blood were examined. A micro–rheological model of aggregating dispersions is proposed in which the apparent viscosity is estimated as the sum of the hydrodynamic and structural parts which are correlated with system structural ordering in the flow. The dynamics of structural ordering of the aggregating system an considered by examining the evolution of the state of the system in phase space depending on the shear rate.
The addition of lipid-based particles induced aggregate formation in the blood, which was more pronounced at higher concentrations of lipid-based fine particles. Furthermore, larger and more stable aggregates are formed in liposome dispersions as compared to lipid emulsions in blood.

Key words: blood rheology, lipid based fine particles, aggregation in blood.

Lipid-based fine particles, such as liposomes and lipid emulsions, could be useful as potential drug carriers with a controlled release mechanism [1–7]. Investigation of the effects of the intravenous administration of such lipid-based drug carriers on the microcirculation directly or on factors that significantly influence the microcirculation is of major importance [8]. Intensified aggregation of erythrocytes and lipid based drug carriers could cause rheological problems such as higher blood viscosity and flow resistance, especially at low shear rates. Changes of the erythrocyte mobility and whole blood viscosity following the intravenous administration of heparin and fat were studied by Coran and Horwitz [8]. The authors observed an increase in the whole blood viscosity and a decrease in erythrocyte mobility in adult baboons given fat and heparin. Tsai and Wong [9] found significant changes in the aggregation of erythrocytes under *in vitro* conditions as a result of interactions with polymerized hemoglobin. The elucidation of bio–molecular interactions is of steadily increasing importance. Exact knowledge of the principles governing the strengths and formation of erythrocyte–lipid particle interactions is of the highest importance for the design and development of lipid-based drug carriers [10,11]. It is of fundamental interest to examine the influence of dynamic conditions on aggregate formation and stability. Rheological analyses are useful tools for the determination of lipid-based fine particle–blood interactions and aggregate stability under *in vitro* conditions.

The principal goal of this study was to investigate the influence of dynamic conditions on aggregate formation and stability in two types of dispersions of lipid-based fine particles: liposomes and lipid emulsion. The aim of this study was to determine some of the rheological parameters such as the hydrodynamic and structural part of the viscosity as functions of the shear rate and lipid-based particle concentrations. Such contributions to the viscosity were correlated with systems structural ordering in flow. In this study, the effects of lipid-based fine particles that can be used as drug carriers, on the blood rheology were investigated, while drug release into the outer environment was not the subject of this analysis.

THEORETICAL CONSIDERATIONS

Many authors have reported the non–Newtonian behavior of human blood and studied blood flow under various geometric or dynamic conditions [12–14]. The rheological behavior of blood can be examined using the apparent viscosity function, $\eta_{app}(\dot{\gamma}, \phi_p)$ according to the general equation:

$$\tau(\dot{\gamma}, \phi_p) = \eta_{app}(\dot{\gamma}, \phi_p)\,\dot{\gamma} \qquad (1)$$

where $\tau(\dot{\gamma}, \phi_p)$ is the shear stress and $\dot{\gamma}$ the shear rate and ϕ_p is the volume fraction of the particles. The apparent viscosity is the sum of various contributions. De Rooij et al. [15] as well as Potanin et al. [16] analyzed two contributions to the viscosity, i.e. hydrodynamic and structural:

$$\eta_{app}(\dot{\gamma}, \phi_p) = \eta_H(\dot{\gamma}, \phi_p) + \eta_S(\dot{\gamma}, \phi_p) \qquad (2)$$

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where $\eta_H(\dot{\gamma}, \phi_p)$ is the hydrodynamic contribution and $\eta_s(\dot{\gamma}, \phi_p)$ the structural contribution to the viscosity. The structural contribution to the viscosity included Brownian and inter–particle interaction contributions [16]:

$$\eta_s(\dot{\gamma}, \phi_p) \approx \frac{\xi(\dot{\gamma}, \phi_p)}{\dot{\gamma}} \quad (3)$$

where $\xi(\dot{\gamma}, \phi_p)$ is the total connection energy density, expressed as $\xi(\dot{\gamma}, \phi_p) \approx N_r(\dot{\gamma}, \phi_p)\, q k_e \Delta q$; $N_r(\dot{\gamma}, \phi_p)$ is the equilibrium number concentration of rigid inter–aggregate bonds per volume, and $q k_e \Delta q$ represents the elastic energy per bond between particles.

The hydrodynamic contribution to the viscosity of the dispersion is generally assumed to be related to the volume fraction of the particles and the viscosity of the medium, i.e. blood serum (μ_0). For whole blood, the red blood cell concentration has the major effect on the blood rheology in general [12,13]. The Roscoe and Brinkman equations [17,18] give the best approximation for blood viscosity modeling for all red blood cell concentrations:

$$\eta_H(\dot{\gamma}) = \mu_0 (1 - 2.5\alpha k \phi_p)^{-2.5} \text{ where } \alpha = \frac{\mu_i + 0.4\,\mu_o}{\mu_i + \mu_o} \quad (4)$$

where μ_i is the blood cell internal viscosity, μ_0 the medium viscosity, k the parameter representing the effects of poly–dispersity and ϕ_p the real particle volume fraction. These equations can also be applied to dispersions of lipid-based fine particles in whole blood [16]. In these cases, lipid-based particles and red blood cells form aggregates, which are considered to be flow units in the dispersions. Aggregates immobilize parts of the medium resulting in an effective volume fraction (ϕ_f), larger a the real particle volume fraction (ϕ_p) calculated from volumes of lipid-based particles and erythrocytes.

MODELING OF ERYTHROCYTE AGGREGATION IN THE PRESENCE LIPID-BASED FINE PARTICLES

We considered erythrocyte aggregation after the addition of lipid-based fine particles to blood. Much smaller lipid particles (200–400 nm) adsorbed onto the erythrocyte interfaces and formed dense layers causing erythrocyte aggregation. This aggregation will be weak, since the dense layer effectively decreases the strength of attraction. In paper I [19], erythrocyte–lipid particle interactions were analyzed using the phenomenological approach and now a more detailed model was investigated.

Our approach includes the consideration of the dynamics of structural ordering of the aggregating system in a flow field, by examining the evolution of the steady–states of the system in phase space depending on the shear rate. The state of the system is described by introducing the distribution function of activity of the erythrocyte surface (a) with values ranging between 0 and 1. An erythrocyte with the activity a=1 is free of bonding, while with the activity a=0 is totally bonded. The surface activity, as a scalar property of erythrocytes, is introduced to express many body interactions. System ordering in the flow field is described using the modified Langevin balance equation of motion in a flow field [20,21]. The balance equation represents the state of dynamic equilibrium between the local frictional forces, elastic driving forces and Brownian forces for the corresponding shear rate and volume fraction of erythrocytes:

$$\frac{da(\dot{\gamma}, \phi_p)}{d\dot{\gamma}} = K\varphi(\phi_p)\, a(\dot{\gamma}, \phi_p) + \Gamma(\dot{\gamma}) \quad (5)$$

where $K = \frac{R^2}{D_0}$ is the structural relaxation time, $D_0 = \frac{k_B}{6\pi\mu_0 R}$ the Stokes–Einstein diffusion coefficient, k_B the Boltzmann constant, T temperature, and $\varphi(\phi_p)$ the relaxation time correction due to the increase of the total particle concentration (erythrocytes+lipid-based particles). The structural relaxations in colloidal dispersions are governed by a slow diffusive process. In concentrated dispersions particle diffusion is slower due to the hydrodynamics and Brownian interactions between the suspended particles. The quantity $K\varphi(\phi_p)$ represents the corrected relaxation time which corresponds to the short–time diffusion coefficient [22]. The second term in eq. 5, $\Gamma(\dot{\gamma})$ – Brownian force, denotes a δ–correlated Gaussian noise with the zero mean . Eq. (5) is solved by introducing the initial condition:

For $\dot{\gamma} = 0$, the system is in a uniform state defined as $a(\dot{\gamma} = 0) = a_0$. The initial averaged particle activity (a_o) is assumed to be equal 0.5.

Solving eq. (5) yields:

$$a(\dot{\gamma}, \phi_p) = a_0 e^{K\varphi(\phi_p)\dot{\gamma}} + \int_0^{\dot{\gamma}} \Gamma(\dot{\gamma}')\, e^{-K\varphi(\phi_p)(\dot{\gamma}-\dot{\gamma}')}\, d\dot{\gamma}' \quad (6)$$

After solving eq. (5), we must to average over all the possible realizations:

$$\langle a(\dot{\gamma}, \phi_p) \rangle = a_0 e^{-K\varphi(\phi_p)\dot{\gamma}} \quad (7)$$

The steady–state of the examined aggregating system is expressed by the averaged activity for given shear rate. For further analysis, it is necessary to relate the structural and hydrodynamic contributions to the viscosity with an averaged, steady system activity. The effective adhesion energy is expressed as:

$$w_{eff}(\dot{\gamma}, \phi_p) = w_0 4R^2\pi \left(1 - \langle a(\dot{\gamma}, \phi_p) \rangle\right) \quad (8)$$

where w_0 is the specific adhesion energy per erythrocyte surface and R is the erythrocyte radius. The structural part of the viscosity is further expressed by replacing the connection energy density in eq. 3 by the form:

$$\xi(\dot{\gamma},\phi_p) = w_{eff}(\dot{\gamma},\phi_p)\, N_T \quad (9)$$

where N_T is the erythrocyte number concentration.

The hydrodynamic contribution to viscosity is expressed using eq. 4 in the following form:

$$\eta_H(\dot{\gamma}) = \mu_0 \left(1 - \phi_f(\dot{\gamma})\right)^{-2.5} \quad (10)$$

where $\phi_f(\dot{\gamma})$ is the effective volume fraction of particles (erythrocytes+lipid particles). The effective volume fraction of particles, as well as the hydrodynamic part of the viscosity can increase, decrease or stay constant with shear rate, depending on which process is dominant in system structural ordering. Such processes are particle and/or aggregate orientation and deformation in a flow field, as well as, aggregation and disagregation.

EXPERIMENTAL METHODOLOGY

In this study, the following dispersions of liposomes and lipid emulsions, listed as drug carrier systems, were used:

(1) 9% and 18% v/v liposomes with an average particle diameter of 350 nm, prepared in our laboratory by a standard procedure from a de-oiled soya lecithin fraction with 70% of phosphatidylcholine (PC) [23],

(2) 10% and 20% v/v lipid emulsions of soya oil dispersed in an aqueous phase – with an average particle diameter of 200 nm; prepared in our laboratory by a standard procedure [24].

Since the focus of this research was the rheological behavior of fine particles in blood and not drug release from the particles, no drugs were included in the experiments.

The volumetric and cumulative size distributions were determined by laser scattering, with a 2602–LC particle analyzer (Cillas, Alcatel, France) according to the log–normal distribution model.

The rheological parameters were measured after the addition of lipid-based fine particles (liposomes or lipid emulsions) to heparinized blood of a healthy subject under the same experimental conditions (temperature and shear rate range). The experimental groups and calculated real volume fractions of the particles (lipid-based particles + erythrocytes) are presented in Table 1. The investigated final concentrations of lipid-based fine particles in the blood were comparable to those in similar *in vitro* studies of aggregation in blood [9,25].

Table 1. Experimental design

Experimental group	1 ml additive	2 ml whole blood	ϕ_p
1	9% v/v liposome dispersion	+	0.23
2	18% v/v liposome dispersion	+	0.26
3	10% v/v lipid emulsion	+	0.23
4	20% v/v lipid emulsion	+	0.27
5	saline (pH=7.5)	+	0.20

The instrument used was the HAAKE RV20 with its CV100 Couette measuring–system especially suited for measurements of whole blood and plasma viscosity [26]. The measuring system of CV100 is constructed in such a why that the inner cylinder is firmly centered with respect to the outer one and supported by a compressed–air–bearing cylinder by means of an air bearing, which provides extreme sensitivity of the instrument.

All the experimental measurements were repeated 5 times at 37°C and shear rates ranged from 20 to 200 s^{-1}. The sample volume was 3 cm^3 and the experiment duration 1 min for one cycle.

RESULTS AND DISCUSSION

The apparent viscosity (η_{app}) of the dispersions of liposomes or lipid emulsion in whole blood and of the control an a function of the shear rate ($\dot{\gamma}$) are presented in Figure 1. The solid curves are the model curves.

The experimentally obtained apparent viscosities decrease more rapidly for the lipid emulsion than for liposome in blood, indicating that liposome–erythrocyte aggregates are much more stable than lipid emulsion–erythrocyte aggregates. This assumption is in accordance with the conclusions of our previous paper I [19]. Liposomes are highly bonded on erythrocyte surfaces, more than lipid emulsion drops.

The experimental data for both liposome concentrations, as well as for both lipid emulsion concentrations in the blood were compared with the rheological behavior of the control (Figure 1). The control represents non–aggregating erythrocyte

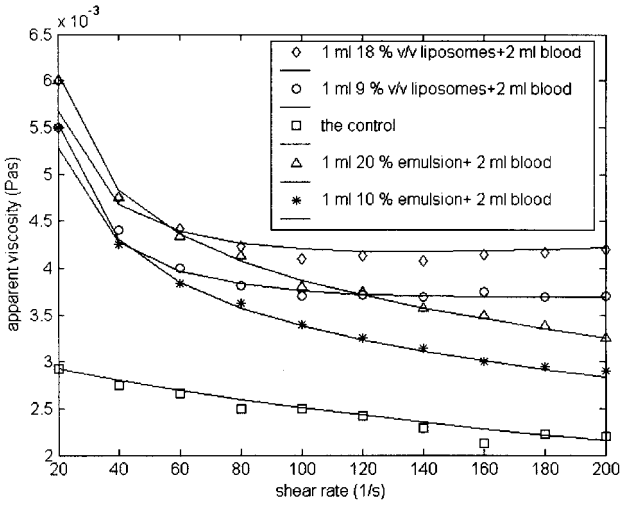

Figure 1. Experimental data for the apparent viscosities as functions of the shear rate for different concentrations of liposome dispersions and lipid emulsions in blood and the control.

dispersion (heparinized stabilization) with the same erythrocyte concentration as the other experimental group with added lipid particles. The medium viscosity, μ_0, (from eqs. 4 and 10) for all the experimental conditions was equal to $1.2x10^{-3}$ Pas. The apparent viscosity of the control was equal to the hydrodynamic contribution to the viscosity (eq. 10). The structural part of the viscosity was neglected due to system stabilization. The effective volume fractions of erythrocytes were obtained from eq. 10 by introducing experimental values of the apparent viscosities for the control. The effective volume fraction (ϕ_f) for the initial experimental shear rate of $\dot{\gamma}_0 = 20\ s^{-1}$ was equal to 0.30 and decreased due to erythrocyte orientation and deformation in the flow field to a value of 0.22 for a shear rate of 200 s^{-1}, while the real volume fraction of erythrocytes (ϕ_p) was equal to 0.20.

The addition of lipid-based particles into the blood indicated aggregate formation. The hydrodynamic part of viscosity was interpreted using eq. 10. The effective volume fractions of such systems are expressed in the form: $\phi_f(\dot{\gamma}) = \phi_f * e^{m(\dot{\gamma}-\dot{\gamma}_0)}$, where m is the coefficient which could be (1) $m > 0$ for the case when the aggregates become more compact and embed a higher volume of medium with the increase of shear rate and (2) $m < 0$ for the case that the aggregates break in the flow. If coefficient m is positive the effective volume fraction of the particles, as well as the hydrodynamic part of the viscosity increase with shear rate. For the case that coefficient m is negative, the effective volume fraction of the particles and the corresponding hydrodynamic part of the viscosity decrease with shear rate. The effective volume fraction of the particles (erythrocytes+lipid particles) $\phi_f(\dot{\gamma}_0) = \phi_f *$, where $\dot{\gamma}_0 = 20\ s^{-1}$ is the initial experimental value of the shear rate. The values of ϕ_f * are supposed to be the sum of the real volume fraction of the added lipid particles and the effective volume fraction of erythrocytes for the control, $\phi_{f(erythrocyte)}(\dot{\gamma}_0) = 0.30$ and expressed as $\phi_f* = \phi_{f(erythrocyte)}(\dot{\gamma}_0) + \phi_{p(lipids)}$. The values of coefficient (m) for various experimental groups with added lipid particles are presented in Table 2.

Tabela 2. Response of the model parameters to experimental group changes

Exp. group	$\phi_f(\dot{\gamma}_0=20\ s^{-1})$	m	φ (ϕ_p)	w_0 (J/m^2)
1	0.33	$3.5x10^{-4}$	1.3±0.2	$1x10^{-7}$
2	0.36	$3.0x10^{-4}$	1.5±0.2	$1x10^{-7}$
3	0.33	$-1.2x10^{-3}$	1.3±0.2	$1x10^{-8}$
4	0.37	$-1.0x10^{-3}$	1.5±0.2	$1x10^{-8}$
5	0.30	$-2.0x10^{-3}$	1.1±0.2	–

The values of coefficient (m) for both liposome concentrations in the blood are positive, indicating an increase of the effective volume fraction of the particles, as well as the corresponding hydrodynamic contribution to the viscosity with shear rate. The aggregates become more compact and embed a higher volume of fluid due to the action of the flow field. The phenomenon is more pronounced for higher liposome concentrations, which corresponds to higher a value of coefficient (m). Approximately the same concentrations of lipid emulsion in the blood have shown quite different rheological behavior as compared to liposome dispersions. The values of coefficient (m) for both lipid emulsion concentrations in the blood are negative indicating a decrease of the effective volume fraction of the particles, as well as the hydrodynamic contribution to the viscosity with shear rate. In such cases aggregate break up could be expected.

The averaged activity of the erythrocytes <a> for $\dot{\gamma} = 0$ (boundary condition 2) is obtained by a fitting procedure and is equal to 0.5 for all the experimental groups with added lipid particles. Structural ordering without flow is carried out by Brownian mechanisms. The model introduced the supposition that all systems with added lipid particles are approximately in the same state. The specific adhesion energy per erythrocyte surface (w_0) was obtained by a fitting procedure from eq. 8 and is equal to 10^{-7} J/m^2 for liposome adhesion and 10^{-8} J/m^2 for lipid emulsion adhesion on the erythrocyte surface, which corresponds to weak adhesion [10,11] (Table 2). Liposomes are stable bi–layer vesicles which interact with erythrocyte surface by hydrophilic bonds [10,11]. Lipid emulsion droplets are non–stable mono–layer vesicles which can mechanically disrupt and interact with the erythrocyte surface by, hydrophilic and hydrophobic bonds simulthaneously. Hydrophilic bonds are stronger than hydrophobic bonds. The structural part of the viscosity was obtained from eq. 3 by substituting the connection energy density from eq. 9. The structural part of the viscosity decrease for all systems with added lipid particles with shear rate, indicating shear thinning behavior.

CONCLUSIONS

In this study, we investigated the effects of dynamic conditions on aggregate formation and stability in dispersions of lipid-based fine particles under *in vitro* conditions. Examination of the aggregate stability in shear flow has a practical aspect from the standpoint of controlled drug delivery. The estimation of lipid-based particle–blood interactions and aggregate stability as functions of the shear rate could be realized by determining the rheological parameters of the dispersions such as the hydrodynamic and structural

contribution to the apparent viscosity by the proposed mathematical model. The rheological parameters depend on system structural ordering in the flow. The dynamics of system structural ordering were examined in terms of the evolution of the system states in phase space. The states of the system were described by introducing the distribution function of activity of the erythrocyte surface (a) with values ranaging between 0 and 1. The hydrodynamic contribution to the viscosity decreases with shear rate and the values of coefficient (m) are negative, for both lipid emulsion concentrations in the blood and for the control, indicating erythrocyte ordering and aggregate break up in the flow. For both liposome concentrations in the blood, the values of coefficient (m) are positive and the hydrodynamic part of the viscosity increases with shear rate, indicating an increase of aggregate compactness. Erythrocyte–liposome aggregates embedded the volume of the medium. The structural part of the viscosity decreases with shear rate for all the experimental systems indicating shear thinning behavior. These results indicate the formation of more stable aggregates in liposome dispersions as compared to lipid emulsions in the blood within the experimental range of shear rates.

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NOTATION

$\dot{\gamma}$ – shear rate (1/s)
ϕ_p – real volume fraction of the particles (–)
ϕ_f – effective volume fraction of the particles (–)
η_{app} – apparent viscosity of the dispersion (Pas)
η_H – hydrodynamic contribution to the viscosity (Pas)
η_s – structural contribution to the viscosity (Pas)
μ_0 – viscosity of the medium (Pas)
μ_i – viscosity inside the particle (Pas)
τ – shear stress (Pa)
a – activity of the erythrocyte surface (–)
N_t – total number of erythrocytes (–)
R – erythrocyte radius (m)

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IZVOD

REOLOŠKO ISPITIVANJE AGREGACIJE ERITROCITA U PRISUSTVU LIPIDNIH ČESTICA

(Naučni rad)

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Razvoj lipidnih čestica za primenu kao nosači lekova zahteva dodatno ispitivanje efekata koje ovi nosači imaju na reološke osobine krvi. U ovoj studiji je ispitivan uticaj dinamičkih uslova na formiranje agregata i njihovu stabilnost u disperzijama lipidnih čestica u krvi, u uslovima in vitro. Određivani su reološki parametri za dve koncentracije lipoyoma i lipidne emulzije u krvi. U radu je predložen mikro–reološki model za agregirajuće disperzije kod koga se prividna viskoznost izražava kao suma hidrodinamičkog i strukturnog dela koji se povezuju sa strukturnim uređivanjem u toku. Razmatrana je dinamika strukturnog uređivanja aggregišućeg sistemaispitivanjem evolucije sistema u faznom prostoru u zavisnosti od brzine smicanja.
Dodavanje lipidnih čestica krvi izazivaju formiranje agregata, što je više izraženo pri većim koncentracijama lipidnih čestica. Veći i znatno stabilniji agregati se formiraju u disperzijama lipozoma nego u disperzijama lipidnih emulzija.

Ključne reči: reologija krvi, lipidi, fine čestice, aglomeracija.