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Understanding particle margination in blood flow – A step toward optimized drug delivery systems

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ABSTRACT

Targeted delivery of drugs and imaging agents is very promising to develop new strategies for the treatment of various diseases such as cancer. For an efficient targeted adhesion, the particles have to migrate toward the walls in blood flow – a process referred to as margination. Due to a huge diversity of available carriers, a good understanding of their margination properties in blood flow depending on various flow conditions and particle properties is required. We employ a particle-based mesoscopic hydrodynamic simulation approach to investigate the margination of different carriers for a wide range of hematocrits (volume fraction of red blood cells) and flow rates. Our results show that margination strongly depends on the thickness of the available free space close to the wall, the so-called red blood cell-free layer (RBC-FL), in comparison to the carrier size. The carriers with a few micrometers in size are comparable with the RBC-FL thickness and marginate better than their sub-micrometer counterparts. Deformable carriers, in general, show worse margination properties than rigid particles. Particle margination is also found to be most pronounced in small channels with a characteristic size comparable to blood capillaries. Finally, different margination mechanisms are discussed.

1. Introduction

One of the major causes of human death in the world is cancer; for instance, about 8 million people died from cancer in 2012 [1]. Although significant progress has been achieved in developing treatments for cancer, the impact on patient survival remains rather moderate [2]. Therefore, the development of early detection and therapy strategies for cancer is under active research. One of the ideas with a great potential in this area is the targeted delivery of drugs and imaging agents through micro- and nano-particles [2]. A very challenging task is to design suitable carriers which would meet several demands including good adhesion properties to targeted sites in blood flow, efficient transport through the biological barriers (e.g., vessel walls, interstitial space, and cell membranes), and low clearance by various defense mechanisms of the body [3–7]. Proposed solutions are polymer conjugates, which are already in clinical use [8,9], fabricated nano-particles [9,10], and self-assembled structures from lipids or block copolymers forming liposomes, polymersomes, or worm-like micelles [9]. All these micro- and nano-carriers differ in shape, size, and deformability. Furthermore, the circulatory system of humans consists of blood vessels which vary from several centimeters to a few micrometers with a wide range of flow rates. Hence, to identify advantages and disadvantages of various particles for vascular drug delivery, their behavior in blood flow for different flow rates, hematocrits (i.e., volume fraction of red blood cells), vessel diameters, particle sizes, shapes, and deformability needs to be better understood.

Blood is a complex fluid which consists of red blood cells (RBCs), white blood cells (WBCs), platelets, and the blood plasma. The physiological systemic hematocrit is in the range 37%–54%, varying for males and females [11]. The local hematocrit in microcirculation can be even lower and depends on the vessel diameter [12,13]. Experimental [14–19], theoretical [20–22], and numerical [23–26] studies have shown that vesicles and RBCs experience a lift force acting away from a wall due to the hydrodynamic interactions with the wall and the RBC shape and deformability. Consequently, RBCs in blood flow migrate toward the center of a vessel and close to the wall a region depleted of RBCs develops, called the RBC-free layer (RBC-FL). In contrast, WBCs and platelets migrate toward vessel walls, which is referred to as margination [27–30]. The margination of WBCs and platelets is mediated by RBCs and appears to be important for these cells, since in order to perform their biological function they must have a possibility to adhere to the wall. Thus, margination can be thought of as a necessary precondition for the wall adhesion.

In similarity with WBCs and platelets, the margination process in blood flow is also expected to occur for micro- and nano-particles. Experiments [31] on margination of rigid platelet-like particles in channels with a characteristic size within 50 μm–200 μm have shown that a significant number of the particles gets accumulated

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near a wall if the hematocrit is larger than about 7% and the accumulation is enhanced with increasing hematocrit. Recent microfluidic experiments [32] have shown that rigid spheres with the size of 2 μm display a significantly higher adhesion density than particles with a size of 200 nm–500 nm. Thus, available experiments already show that there exists a strong dependence of particle margination on hematocrit, flow rate, and carrier size. Numerical simulations of blood flow are ideally suited to explore the margination trends for a wide range of conditions and to better understand the corresponding mechanisms.

Recent numerical simulations have considered segregation of a binary mixture of spherical elastic capsules in shear and channel flow [33–35]. Simulations for different capsule sizes have shown that in binary mixtures of particles, the large particles migrate toward the center and the small ones toward the wall if the volume fraction of the small ones is low. Furthermore, floppy particles tend to migrate to the center in a binary mixture together with rigid particles. Simulations of WBCs in two dimensions (2D) [36,37] and three dimensions (3D) [38] have shown that WBCs are subject to strong margination for $H_t \approx 0.2$–0.4 and the venular range of flow rates, characterized by the pseudo-shear rates $\bar{\dot{\gamma}} \lesssim 80\,\mathrm{s}^{-1}$ in small vessels [39,40]. Platelet margination has been studied in 2D for two shear rates, two hematocrit values ($H_t = 0.2$ and $H_t = 0.4$), and two sizes (0.75 μm and 1.5 μm) of rigid particles [41] in a 50 μm wide channel. The results indicate that platelet margination increases with hematocrit, shear rate, and particle size. A similar trend is observed in another 2D and 3D simulation study of particles between 0.25 μm and 1 μm in a 20 μm wide channel [42], demonstrating that the margination is significantly worse for sub-micrometer particles in comparison to larger carriers in agreement with experimental findings [32]. This numerical investigation has also shown that an oblate discoidal shape has advantages for drug delivery systems compared to spheres. Other 3D simulations [43] have focused on the dependence of platelet margination on hematocrit, their aspect ratio, and different viscosities between the inner and outer fluids of RBCs. The simulation results have shown that margination of rigid particles increases with increasing hematocrit and that the RBC viscosity contrast influences margination as well. Additionally, the study indicated that discs marginate slower than spherical particles. Furthermore, platelet margination in blood flow has been studied numerically for different shear rates and hematocrit values of $H_t = 0.1$ and $H_t = 0.2$ [44,45] for rigid discoidal and spherical particles in a channel of 34 μm. In these investigations, an increase of margination with hematocrit has been observed and related to the different RBC-FL thickness.

In this paper, we systematically investigate the dependence of margination on particle size for a wide range of hematocrit values and flow rates using a 3D model system. In this context, we concentrate on the margination into a thin layer near the wall, where particle adhesion to the wall would be possible. Thus, we assess the adhesion potential of particles in blood flow depending on various carrier and flow properties. In addition, we employ 2D simulations to study the effect of particle deformability on its margination properties. Finally, we consider blood flow and particle margination in channels of several widths. Our results from 3D simulations further support the observations that particles with a few micrometers in size marginate significantly better than their sub-micrometer counterparts. Deformable carriers are in general worse than rigid particles; however, they may marginate slightly better at high H_t values and low shear rates, where their deformability aids them to fit better within a relatively narrow RBC-FL at such conditions. Furthermore, the margination of particles is found to be most efficient in small channels with the sizes corresponding to capillaries in the human microvasculature. Finally, we will also discuss the physical mechanisms of margination and the relation between particle margination, its physical properties, and the thickness of the RBC-FL.

2. Methods and models

2.1. Simulation methods

Two particle-based hydrodynamic simulation approaches, the dissipative particle dynamics (DPD) [46,47] method and the smoothed dissipative particle dynamics method with angular momentum conservation (SDPD+a) [48], have been employed. DPD has mainly been used for 2D simulations and SDPD+a for 3D simulations. An advantage of SDPD is the possibility to directly control the fluid compressibility and viscosity in comparison to DPD, where these quantities need to be pre-calculated in a separate simulation. In both methods, the system is represented by a collection of N_p point particles. These particles interact locally through three pairwise additive forces: a conservative force $\mathbf{F}^{\mathrm{C}}$, a dissipative or drag force $\mathbf{F}^{\mathrm{D}}$, and a random $\mathbf{F}^{\mathrm{R}}$ force. Hence, the total force $\mathbf{f_i}$ on particle i exerted by all neighboring particles j is given by

$$\mathbf{f}_i = \sum_{j \neq i} \left(\mathbf{F}^{\mathrm{C}}_{ij} + \mathbf{F}^{\mathrm{D}}_{ij} + \mathbf{F}^{\mathrm{R}}_{ij} \right). \tag{1}$$

The conservative force $\mathbf{F}^{\mathrm{C}}$ controls the pressure and fluid compressibility, while the pair of dissipative $\mathbf{F}^{\mathrm{D}}$ and random $\mathbf{F}^{\mathrm{R}}$ forces defines a local thermostat in order to keep the system at a constant equilibrium temperature. The forces are local and vanish beyond a selected cut-off radius r_c in DPD or a smoothing length r_h in SDPD.

In DPD, the proposed forces act only along the separation vector $\mathbf{r_{ij}} = \mathbf{r_i} - \mathbf{r_j}$ of the particles [49–51]. In SDPD, the forces are derived through a discretization of the Navier–Stokes equation as for the smoothed particle hydrodynamics [52] method, while the incorporation of thermal fluctuations is similar to that in DPD [53]. The original SDPD formulation [53] did not satisfy angular momentum conservation, which is crucial in applications where fluids with different viscosities coexist [48]. To incorporate angular momentum conservation, an additional spin variable for every particle $\boldsymbol{\omega}_i$ has been introduced [48]. Therefore, the dissipative force $\mathbf{F}^D = \mathbf{F}^{D_L} + \mathbf{F}^{D_R}$ in SDPD+a is modified and consists of two force components, a translational friction $\mathbf{F}^{D_T}$ and a rotational friction $\mathbf{F}^{D_R}$. The time evolution of the position $\mathbf{r}$ and the translational velocity $\mathbf{v}$ in DPD and SDPD+a, as well as the angular velocity $\boldsymbol{\omega}$ in SDPD+a, of a particle i follows Newton's second law,

$$\dot{\mathbf{r}}_i = \mathbf{v}_i, \quad \dot{\mathbf{v}}_i = \sum_j \frac{1}{m_j} \mathbf{F}_{ij}, \quad \dot{\boldsymbol{\omega}}_i = \sum_j \frac{1}{I_j} \mathbf{N}_{ij}, \tag{2}$$

where m_j is the mass of particle j, I_j is the moment of inertia, and $\mathbf{N}_{ij} = -\mathbf{r}_{ij} \times \mathbf{F}_{ij}/2$ is the torque exerted by particle j on particle i. The equations of motion for both methods are integrated in time by the velocity-Verlet algorithm [54].

2.2. Model for RBCs and particles

Network models have been successfully used to model membranes of vesicles and RBCs filled with a cytosol [55–58]. Here, we employ a network model [57,58] to simulate both, the membranes of RBCs and drug carriers. In 3D, the network is defined by a 2D triangulated mesh on a membrane surface, see Fig. 1(a). The vertices are connected by N_s springs and form N_t triangles. The full potential energy of the system is given by

$$U = U_{\mathrm{spring}} + U_{\mathrm{bending}} + U_{\mathrm{area}} + U_{\mathrm{volume}}, \tag{3}$$

with a spring potential U_{spring}, a bending potential U_{bending}, and area and volume conservation constraints U_{area}, U_{volume}, respectively. For the RBCs, a membrane viscosity is also employed, which is necessary to mimic realistic rheological properties of an RBC membrane [58]. For model details we refer the reader to [57].

In 3D, RBCs are characterized by the effective diameter $D_r = \sqrt{A_0/\pi}$, where A_0 is the RBC surface area. Typical physiological values

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