Delivery of Worm-like Drug Carriers in Stenotic Mrcovessels: A Simulation Study

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Abstract. We present in this study two-dimensional numerical simulations of hydrodynamic interaction between red blood cells (RBCs) and worm-like drug carriers in a stenotic microvessel. The dynamics of the blood flow and large deformation of the RBC are fully resolved in the simulations using a fictitious domain/immersed boundary method. We find margination of worm-like drug carriers and this phenomenon depends on factors such as drug stiffness, RBC deformability, and flow velocity. In particular, the stiffer drug carriers has higher probability to migrate and stay in the cell free layer. In additional, tumbling is observed for drug carriers at near wall location and this behavior is not found for RBCs which suggests that the worm-like structure may play an important role. Our investigation provides an understanding of the hemodynamic effects of drug carriers in microcirculation and will help in clinical implementation of drug delivery.

Keywords: Drug delivery; red blood cells; worm-like drug carriers; stenotic microvessels.

1. Introduction

In recent years, people have focused their researches on the physicomechanical properties, such as shape, size, and stiffness of the drug carriers and utilize them for the development of drug delivery system [1, 2]. Both experimental and simulation studies suggest that the carrier's behavior in hemodynamic circulation, as well as drug-cell interactions for targeted delivery are significantly influenced by these parameters [3, 4]. Among the widely used drug delivery systems, polymer-based micelles have gained increasing clinical attention due to their potential as vehicles to deliver poorly soluble drugs [5]. Micelles can be synthesized into different shapes, such as spheres, rods, and worm-like structure. Micelle structure and morphology play a critical role in delivery performance and in regulating drug-cell interactions [6].

Worm-like micelles have shown great potential as drug carriers because they can take up drugs and possibly permeate tissues to targets. Particularly challenging is the study of their interactions with fluids, cells, and tissues, which are essential to predict the real *in vivo* behavior [7]. To this end, numerical and simulation studies have shown potential as a promising aid to the design of the nanomedicine [8].

Targeted drug delivery shows great advantages in treatment of stenosis because the drug efficacy may be increased by concentrating the drugs at the required location [9]. However, investigation of hemodynamics and transport behaviors of drug carriers in stenotic vessels is still far from sufficient. By simulating the motion and interaction with RBCs of worm-like drug carriers in stenotic microvessels in the present study, we hope to provide a deeper understanding into the factors that govern the biocirculation and biodistribution of drug carriers in microvessels, which must be considered in selecting parameters for the optimum drug system.

2. Methodology

2.1 Simulation Method.

Our simulations are based on the fictitious domain method (FDM) [10,11] to simulate the fluid flow in the irregular stenotic microvessel. The time evolution of the blood velocity is determined by

the Navier-Stokes equations and shape of the RBCs and the carriers is determined by the immersed boundary method (IBM) [12].

2.2 Modeling RBCs and Drug Carriers.

A plasma-cell-carrier system is considered to simulate the multiphase blood flow. The blood flow in the stenotic microvessel is solved by the fictitious domain method with the Navier-Stokes equations. The drug carriers are described as one-dimensional (1D) worm-like structure formed by deformable spherical beads. A fixed pressure gradient is enforced between inlet and outlet of the vessel to drive the blood flow. The RBC membrane is modeled by a spring and this model is also adopted for the drug carriers. The cell-fluid and carrier-fluid interactions are described by the immersed boundary method.

2.3 Simulation Setup.

Parameters used for the simulations are shown in Table 1. The size of the RBC is chosen to be the same as in ref. [13] and the spherical bead of the drug carrier is of radius 1μm. Initial configuration of RBCs and carriers at the beginning of the simulation is displayed in Fig. 1. The severity of the stenosis is 40% and this value will be varied in the further simulation studies.

Table 1.Simulation Parameters

Parameter	Value
Size of domain	70 μm×10 μm
Number of RBCs	12 (biconcave-shaped)
Number of drugs	3 (worm-like)
Spring constant of RBC	1.0×10^{-12} Nm (soft), 5.0×10^{-12} Nm (hard)
Spring constant of drug	1.0×10^{-12} Nm (soft), 2.0×10^{-12} Nm (medium soft), 5.0×10^{-12} Nm (hard)
Stenosis severity	40%

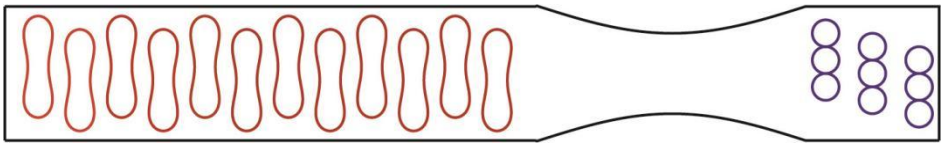

Fig. 1 Initial configuration of RBCs and worm-like drug carriers in the microvessel at the beginning of the simulation.

3. Results and Discussion

3.1 Drug Carriers Motion and Margination.

We find that there are several observable dynamic states of cell-carrier interaction in the domain considered. Firstly, we observe that the both the RBCs and drug carriers are undergoing deformation and change their original shapes in blood flow. Sample snapshots that demonstrate these behaviors are shown in Fig. 2. In this figure, both the RBCs and the drug carriers deform their shape under the plasma flow and tend to accumulate in the center region of the vessel. Even though the stiffness of the drug carriers was the same as the RBCs, the RBCs move slightly faster than the drug carriers. The drug carriers have a high probability to attach to the membrane of the RBCs.

While in Fig. 3, the drug carrier are five times stiffer than the RBCs. Therefore they deform less and RBCs move around the drug carriers at a much higher velocity. The RBCs tend to move to the vessel walls in the micro blood flow while the RBCs are mostly accumulated in the center region of the vessel. This phenomenon is called margination of the drug carriers [14] and is an important consideration for nanocarrier design [2]. Margination enables carriers to establish contact point with

endothelial walls which favors carrier-cell binding and receptor-ligand interaction [15]. Our results suggest that the margination of worm-like carriers is affected by the stiffness of the carrier and the process is facilitated by increasing the carrier stiffness, ie., stiffer carriers marginate faster than their softer counterparts. Moreover, softer carriers are more easily to be trapped in the gap of RBCs and sometimes they are even attached to the membrane of the RBCs. The attachment of the drug carriers is significantly reduced by increasing the carrier stiffness. We also change the deformability of the RBCs and found that harder RBCs facilitate the margination and reduce the attachment of the worm-like drug carriers.

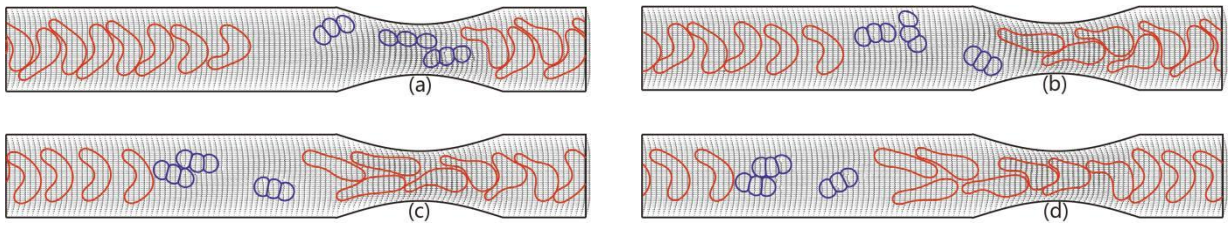

Fig. 2 Simulation results showing snapshots of worm-like drug carriers interacting with RBCs in blood flow. The drug carrier is of the same stiffness as the RBC. (a) t=10ms; (b) t=20ms; (c) t=30ms; (d) t=40ms.

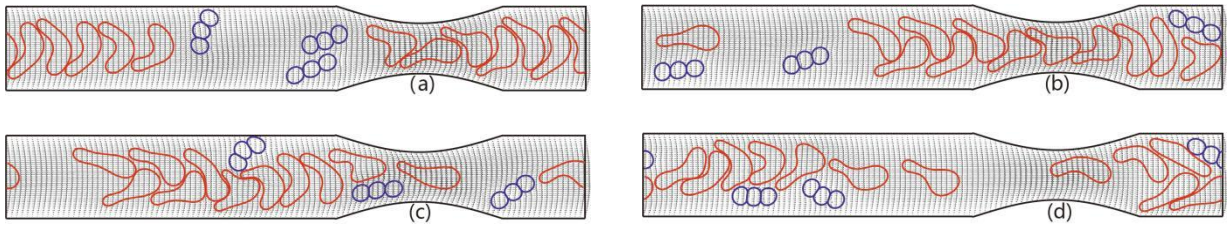

Fig. 3 Simulation results showing snapshots of worm-like drug carriers interacting with RBCs in blood flow. The drug carrier is five times harder than the RBC. (a) t=10ms; (b) t=20ms; (c) t=30ms; (d) t=40ms.

3.2 Tumbling of Drug Carriers.

Nonspherical carriers under flow exhibit tumbling and rolling dynamics, which is a more complex motion than lateral movement [2, 16]. Tumbling is another important phenomenon observed for the worm-like drug carrier in our study. Figure 4 shows typical tumbling process of a worm-like drug carrier (green colored carrier) in the domain considered. Note that tumbling is observed for drug carriers at near wall location and this behavior is not found for RBCs which suggests that the worm-like structure may play an important role.

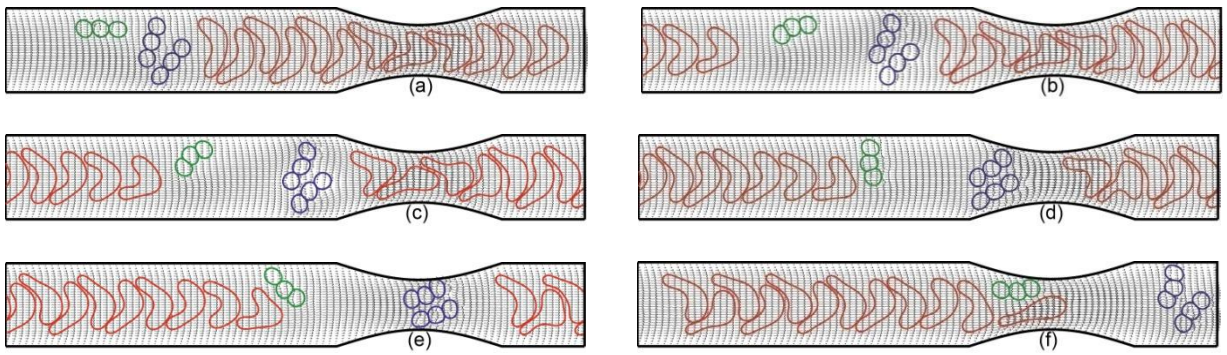

Fig. 4 Typical tumbling process of a worm-like drug carrier (green colored carrier) in the stenotic microvessel. (a) t=3.5ms; (b) t=5.5ms; (c) t=6.5ms; (d) t=7.5ms; (e) t=8.5ms; (f) t=10.5ms.

3.3 Blood Flow Velocity.

The effect of flow velocity is studied and it is found that the drug carriers have a high probability to marginate at higher flow rate in the stenotic microvessel.

The blood flow velocity at the outlet of the microvessel is also studied under various conditions and the results are shown in Fig. 5. Due to the low concentration of the drug carriers, the influence of the drug stiffness on the blood velocity is not significant. However, the simulation shows that the RBC stiffness has a nonnegligible influence and the velocity of blood decreases significantly at the outlet of the vessel for the blood with stiffer RBCs.

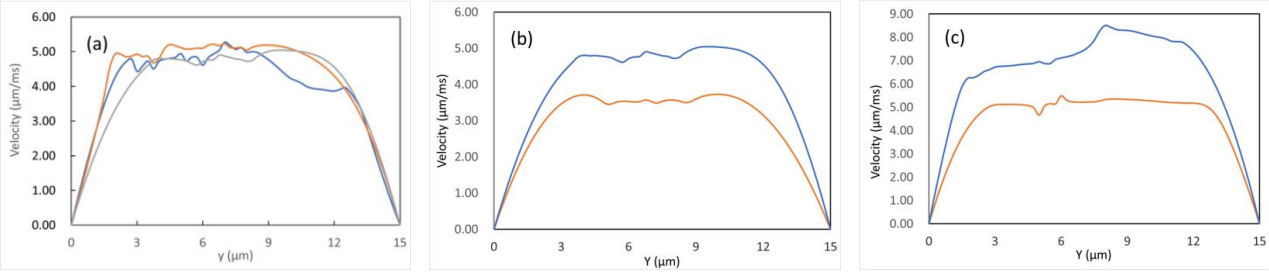

Fig. 5 (a) Effect of drug stiffness on the blood flow velocity at the outlet of the vessel. Blue line: hard drug; Grey line: medium soft drug; Orange line: soft drug. (b) Effect of RBC stiffness on the blood flow velocity at the outlet of the vessel under low axial pressure gradient. Blue line: soft RBC; Orange line: hard RBC. (c) Effect of RBC stiffness on the blood flow velocity at the outlet of the vessel under high axial pressure gradient. Blue line: soft RBC; Orange line: hard RBC.

4. Conclusions

The present simulation study shows several characteristics of worm-like drug carriers in stenotic microvessels, including margination and tumbling behaviors and cell-drug interactions. Our simulation suggests that carrier margination in blood flow depends on carrier stiffness, RBC deformability, and flow rate. The results show that stiffer carriers have a higher margination probability in comparison to the softer ones. Moreover, tumbling of carriers happens at near vessel wall locations and is only observed for the drug carriers while the RBCs tend to accumulated at the center region of the blood vessel. This different behavior of RBCs and drug carriers is due to the different structure of them so that the RBCs undergo large deformation and tumbling is not likely to happen. Current study is of potential relevance to clinical implementation in nano-drug delivery in stenotic microvessels and hopefully advances our understanding of the delivery performance of worm-like drug carriers and its influence factors, and provide hints to the synthesize of the effective drug delivery systems.

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