A Model for the Controlled Release of Nano-encapsulated Tissue Plasminogen Activator Using Shear-Activation

M. Jalaal\(^1\), K. Letchford\(^2\), and B. Stoeber\(^1\)

\(^1\)Department of Mechanical Engineering, University of British Columbia, B.C., V6T 1Z4, Canada; \(^2\)Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, B.C., V6T 1Z3, Canada

m_jalaal@yahoo.com

ABSTRACT SUMMARY

A model is presented for the controlled release of Tissue Plasminogen Activator tPA from nanoparticles using shear stress as trigger. The present model resolves blood flow in a partially blocked vessel, motion of micro-scale particles (aggregated nano-particles), and the subsequent release of nano-particles encapsulating tPA due to shear activation. Assumptions and results are described and a number of comments are made for further development of this class of nano-medicine.

INTRODUCTION

Cardiovascular disease is a leading cause of death in the United States, with over 137,000 death annually. Furthermore, it is also a leading cause of long-term disabilities with associated costs of over $53 billion [1]. Tissue plasminogen activator, tPA (a protein involved in the disruption of blood clots) is a major treatment in the category of thrombolytic therapy for ischemic strokes. tPA is an enzyme that catalyzes the conversion of inactive plasminogen to active plasmin (the major source of clot breakdown). Subsequently, tPA dissolves the blood clots and allows blood flow to return to the affected areas, thus preventing further damage. tPA has revolutionized treatment of strokes, heart attacks, and pulmonary embolisms; however, the success rate is low and different side effects such as bleeding are caused due to overdosing [2]. Very recently, Korin et al. [3] presented a promising technique for targeting tPA to clots to reduce the side effects while restoring blood flow to the normal state. The proposed scenario is based on high shear stress caused by vascular obstruction such that micro-particles (~2-5\(\mu\)m) made by aggregation of nano-particles (~180\(\mu\)m), encapsulating tPA, break down in the high-shear stress region close to a clot, resulting in the dispersion of the nano-particles and subsequently release of tPA. The current study presents a model of this shear-activated drug delivery employing computational fluid dynamics. The main goal is to obtain a reliable generic model to describe the mechanism of shear-activated nanoparticle dispersion for different clot and vessel geometries and subsequent clot removal. This model can be used to study phenomena, which are difficult to visualize in experiments and might be essential for further development of this novel type of triggered controlled release.

METHODOLOGY

Direct numerical simulation is used for the modeling. Figure 1 demonstrates the schematic view of the problem.

Figure 1. Schematic of a partially blocked vessel. The vessel is 80\(\mu\)m height, and 78% blocked. The diameter of micro particle is 2\(\mu\)m.

Main assumptions are: 2D incompressible Newtonian behavior of blood, non-deformable vessel, and half-circle geometry of clot. In the high shear zone, the particle breaks apart and releases the nanoparticles. The diffusion of encapsulated drug through the nano-particles is not considered. The incompressible Navier-Stokes equations

\[
\rho \frac{\partial \mathbf{u}}{\partial t} + \nabla \cdot (\mathbf{u} \mathbf{u}) + \nabla p = -\nabla \cdot (2\mu \mathbf{D}),
\]

and the diffusion equation

\[
\nabla \cdot \mathbf{u} = 0
\]
\( \partial_t c = \nabla \cdot (D \nabla c) - \nabla \cdot (uc) \) 

are solved, with the velocity vector \( u \), density \( \rho \), pressure \( p \), viscosity \( \mu \), nano-particle concentration \( c \), diffusion constant \( D \) and deformation tensor \( D \), where \( D \) is a function of shear stress (zero for \( \tau < \tau_{crit} \), and a finite value, \( D_{crit} \) for \( \tau \geq \tau_{crit} \)). A minimum grid resolution of order of 10 nm is needed to correctly resolve the diffusion of particles. To address this challenge, an adaptive Cartesian grid generation is used (see figure 2).

Figure 2. An example of grid adaption around particle and clot. Smallest grid is 15 nm.

The current numerical technique makes the current model computationally feasible. Details of numerical simulation can be found in [4].

RESULTS AND DISCUSSION

Due to partially blockage of the vessel, shear stress increases near the clot (see figure 3).

Figure 3. Red area shows the domain with shear rate higher than the activation threshold. The Reynolds number is 80 and \( \tau_{crit} = 10 \text{e}5 \text{ s}^{-1} \) [4].

It is expected that in the high shear area the micro tPA carrier deaggregates and releases nano particles. Figure 4 illustrates an example of dispersion of tPA with time.

Figure 4. Release of tPA particles in shear activation zone. a) A microparticle reaches the high shear zone; b) nano-particles rapidly diffuse and c) move downstream, d) some of the particles are trapped in the recirculation zone.

Dotted line shows the path of maximum concentration of nano-particles.

The current model successfully resolves the motion, shear activation, and diffusion of nano-particles carrying tPA in a vessel with stenosis. The model can be developed for more complex geometries to investigate the influence of vessel curves and other obstruction geometries on the release of drugs. A more complete model should include the influence of the micro-particles on the fluid flow. Our results (not presented here) show that the shear activation zone can be varied in presence of rigid particles. Moreover, the diffusion of tPA molecules through nano-particles and their reaction with plasminogen should be added. Finally, the clot-busting should be included for a complete model. Figure 5 shows an example of our preliminary results for the clot removal modeling using Volume of Fluid technique [4]. This part of research is in progress.

Figure 5. Clot busting simulation.

CONCLUSIONS

The idea of control release of tPA particles using shear activation can revolutionize emergency stroke treatment. However, there is plenty of investigation ahead before the clinical applications. In the present study, a model is presented to obtain more detail on mechanism of shear activation and influence of geometries.

REFERENCES