P. Chaturvedi and S.R. Shah (2024) Int. J. Appl. Sci. Biotechnol. Vol 12(1): 46-53.
DOI: 10.3126/ijasbt.v12i1.64057

ISSN (Online): 2091-2609
DOI Prefix: 10.3126/ijasbt

International Journal of Applied Sciences and Biotechnology (IJASBT)

Research Article

Assessing the Clinical Outcomes of Voxelotor Treatment in Patients with Sickle Cell Disease

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Article Information

Received: 15 February 2024
Revised version received: 25 March 2024
Accepted: 27 March 2024
Published: 31 March 2024

Cite this article as:
P. Chaturvedi and S.R. Shah. (2024) Int. J. Appl. Sci. Biotechnol. Vol 12(1): 46-53.
DOI: 10.3126/ijasbt.v12i1.64057

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Peer reviewed under authority of IJASBT
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Abstract

The results of Voxelotor treatment in Sickle Cell Disease, as assessed through clinical outcomes, demonstrated its efficacy in reducing hemolysis and improving hemoglobin levels. This effect can be attributed to Voxelotor's inhibition of HbS polymerization, thereby restoring the deformability and compliance of sickle RBCs. Our mathematical model provided mechanistic insights into how altered rheological properties of sickle RBCs impact their flow dynamics in microcirculation. Specifically, we observed that Voxelotor-induced improvements in RBC deformability and compliance lead to enhanced plasma film height in capillaries, promoting smoother blood flow and reducing the risk of vaso-occlusive events. We established a direct relationship between the molecular mechanism of Voxelotor action and its clinical outcomes. The mathematical model served as a bridge, elucidating how Voxelotor-induced changes in sickle RBC mechanics translate to improved microcirculatory flow and reduced vaso-occlusion. This holistic understanding not only validates the therapeutic efficacy of Voxelotor but also underscores the importance of considering biomechanical factors in evaluating treatment outcomes in SCD. Furthermore, this study highlighted the relevance of microfluidics based diagnostic tools in assessing the efficacy of Voxelotor treatment. By leveraging insights from our mathematical model, microfluidics devices can be designed to mimic physiological conditions and effectively evaluate the deformability of sickle RBCs before and after treatment. This integrated approach not only facilitates the development of personalized therapeutic interventions but also accelerates the translation of novel treatments, such as Voxelotor, from preclinical studies to clinical practice for the management of Sickle Cell Disease.

Keywords: Hemorheology, Rheological Properties, Vaso-Occlusion, Viscoelasticity, Hemoglobin Polymerization, Deformability, Endothelial Interaction, Computational Modeling, Voxelotor

Introduction

Red Blood Cells (RBCs) are unique structures composed of a viscoelastic membrane filled with an incompressible viscous fluid. Despite their small size, they can smoothly navigate through tiny blood vessels, carrying essential oxygen and nutrients to tissues while regulating vital processes. Hemoglobinopathy refers to a group of genetic disorders affecting hemoglobin, which is the protein responsible for carrying oxygen in red blood cells. Sickle Cell Disease (SCD) is one such disorder, characterized by abnormal, crescent-shaped red blood cells that lead to

blockages in blood vessels, causing various complications. This distortion of RBCs arises from a specific genetic mutation in the β-globin gene, resulting in the formation of abnormal hemoglobin when oxygen levels are low. These sickled cells become fragile, less flexible, and prone to sticking to blood vessel walls, contributing to the obstruction of blood flow and the subsequent damage to tissues (Kato *et al.*, 2018; Schechter, 2008). SCD is a significant global health concern, imposing substantial physical burdens on individuals, families, and communities. While treatments such as stem cell transplantation and gene therapy offer hope for some patients, diagnosing SCD typically involves expensive and specialized laboratory tests like electrophoresis and genotyping. To address the need for more accessible diagnostic methods, researchers have turned to microfluidic platforms. These platforms utilize microscale channels and chambers to mimic physiological conditions and allow for the observation and analysis of cellular interactions, including RBC adhesion to endothelial surfaces or other biomimetic substrates. By integrating various biochemical and biophysical cues within the microfluidic devices, researchers can assess the adhesion behavior of RBCs under controlled conditions, providing valuable insights into disease mechanisms such as sickle cell disease and facilitating the development of diagnostic tools and therapeutic interventions (Kohne, 2011; Secomb, 2017; Ye *et al.*, 2017). These platforms offer advantages such as rapid screening of RBC deformability at a lower cost. Microfluidic systems manipulate small volumes of fluids within microscale channels, making them highly efficient and cost-effective tools for studying cell biology. Given the urgent need for point-of-care markers to assess disease activity, microfluidic technologies hold promises for providing real-time insights into SCD progression. In summary, microfluidic systems offer innovative solutions for studying the biomechanical properties of RBCs and advancing diagnostic capabilities for diseases like SCD. Their ability to manipulate small fluid volumes efficiently makes them invaluable tools in cell biology research and clinical diagnostics (Kavanagh *et al.*, 2022; Secomb, 2019; Zhang, 2018). Fig.1 shows morphology of normal and sickle red blood cells in the blood.

Numerous studies have investigated the molecular mechanisms underlying Sickle Cell Disease (SCD) and its clinical manifestations, with notable advancements in microfluidic technology. The introduction of the SCD biochip has enabled the quantitative evaluation of red blood cell (RBC) adhesion to endothelium-associated proteins. These investigations have revealed various factors affecting blood rheology, including flow viscosity, vessel geometry, RBC aggregation, and pressure gradient, all contributing to flow of blood obstruction and vaso-occlusion. Characterization of the viscoelastic properties of sickle RBCs has demonstrated their higher elastic modulus compared to normal RBCs, shedding light on their altered mechanical behaviour (Sadique and Shah, 2022; Schechter, 2008; Shah, 2022). Moreover, there has been a focus on the increased adherence of sickle RBCs to endothelial cells, implicating this adhesion in the pathophysiology of SCD. Subsequent studies have delved deeper, quantifying the strength of sickle RBC-endothelial adhesion and exploring the influence of plasma factors on this interaction. Investigations using optical tweezers have provided insights into the deformability of individual sickle cells, particularly in overcrowded flowing suspensions. To comprehend flow patterns and deformation of sickle RBCs in microvessels, studies have turned to capillary flow dynamics. RBCs typically travel in a single-file fashion within capillaries (Fig. 2), filling the lumen nearly completely (Ballas and Mohandas, 2004; Chaturvedi *et al.*, 2023; Fernández, 2020).

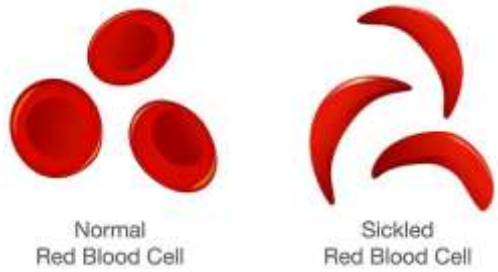

Fig.1: Normal and sickle red blood cells in the blood

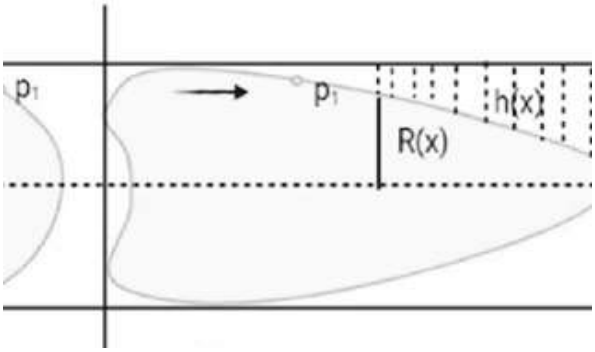

Fig. 2: Diagram of single red cell in capillary surrounded by tissue

Lubrication theory has been instrumental in describing the squeezing flow between RBCs and capillary walls, providing valuable insights into microcirculatory phenomena. Overall, these studies have significantly advanced our knowledge of SCD pathophysiology and microvascular dynamics, paving the way for improved diagnostics and therapeutic interventions. The culmination of these studies provides a comprehensive understanding of the intricate factors influencing red blood cell (RBC) behavior and blood flow dynamics within microvessels, offering crucial insights into the pathophysiology of Sickle Cell Disease (SCD). Researchers have extensively explored the prediction of blood rheological properties, particularly

in capillaries with diameters less than 8μm, using a fundamental approach. Various investigations, including those by have extended continuum models to incorporate impact of plasmatic layer close to the wall in microcirculation. Earlier studies characterized RBCs as flexible circular sheets deformed into hollow thimble shapes, analyzing their relationship with parameters such as cell diameter, capillary spacing, pressure gradient, and cell velocity in microcirculation. Some researchers have assumed a parabolic shape for undeformed RBCs near the wall, with cell deformation proportional to local pressure. The axisymmetric geometry of RBCs in capillary flow at low velocities has been thoroughly examined (Alapan *et al.*, 2016; Chaturvedi *et al*., 2021; Pearson *et al*., 2014).

Quantitative theoretical models have been developed to establish links between RBC mechanics and blood flow properties in capillaries, approximating plasma flow using lubrication theory. Furthermore, a biomechanical model for microcirculation flow has been devised, specifically considering the rheological characteristics of sickle blood in capillaries. These collective efforts have significantly advanced our understanding of microvascular dynamics, providing critical insights into the underlying mechanisms of SCD and paving the way for potential diagnostic and therapeutic innovations. In this paper, our primary focus was on understanding the flow of blood within capillaries, specifically examining how red blood cells deform and move through these tiny blood vessels. To describe flow within the capillaries, we made several assumptions. We treated the plasma (the liquid part of blood) as a continuous medium, meaning we viewed it as a smooth and continuous substance. We applied the laws of continuum mechanics to analyze its behaviour (Alapan, 2016; Carden and Little, 2019; Dongaonka, 2018). The motion of plasma were derived from the Navier-Stokes equations, which describe fluid flow, and the continuity equation, which ensures that the amount of plasma remains constant as it flows through the capillaries. Since blood is incompressible, meaning its volume doesn't change, we included the continuity equation to reflect this property. We considered the flow of red blood cells in a single file through the capillaries, treating the capillary as a cylindrical duct with axisymmetric geometry. We also took into account the presence of a lubricating film between the red blood cells and the walls of the capillary. This film, described by Lighthill, is formed due to the compliance (flexibility) of cells and capillary walls, and pressure difference within flow. To analyze the flow patterns, we used lubrication theory, which is applicable at very low Reynolds numbers and neglects inertial effects. In disease conditions, such as sickle cell disease, where adhesion between red blood cells and capillary walls occurs, we introduced a slip effect into the model to account for this adhesion. Overall, our study aimed to understand how highly viscous liquid-filled membranes, such as red blood cells, move within narrow capillaries, and we developed a mathematical model to describe this phenomenon (Carvalho *et al.,* 2016; Gladwin and Vichinsky, 2008; Sadique and Shah, 2022).

Mathematical Formulation

Assumptions of a mathematical model developed to study the behavior of red blood cells (RBCs) within a two-dimensional Cartesian geometry of a capillary, as represented in (Fig.2) (Howard et al., 2018). Here's a breakdown of each point:

***Similar Size to Capillary and Deformation*:** The RBC is assumed to have a diameter comparable to that of the capillary. Additionally, it is expected to deform in response to fluid stresses acting upon it, exhibiting compliance with the flow conditions within the capillary.

***Incompressible Fluid Model*:** The RBC is modeled as containing an incompressible fluid within its structure, implying that changes in volume due to deformation do not affect the fluid density inside the RBC.

***Axis-Symmetric Deformation*:** Deformation of the RBC is assumed to occur axis-symmetrically, meaning that the shape changes are uniform around the axis passing through the center of the cell.

Single File Flow: The flow of RBCs through the capillary is constrained to single-file motion, with each RBC moving sequentially through the capillary without overtaking or interacting with neighboring cells.

***Neglect of Wall and Cell Interactions*:** Interactions between the RBCs and the endothelial wall of the capillary, as well as interactions between adjacent RBCs, are neglected in the model. This simplification allows for a focus on the core mechanics of RBC flow within the capillary.

***Frame of Reference*:** The model utilizes a reference frame aligned with the plasma flow, located outside the red blood cell (RBC). This choice of reference frame facilitates the analysis of RBC dynamics relative to the surrounding fluid flow.

These assumptions lay the foundation for the mathematical model, enabling the investigation of RBC behavior within the microenvironment of a capillary. While simplifications are made to streamline the analysis, and provided valuable insights into the fundamental principles governing RBC dynamics in microcirculation.

Formulation of the problem

The governing equation for how plasma moves in the capillary are described by two main formulas: the Navier-Stokes equations and the continuity equation. These equations explain how fluids (like plasma) flow. They take into account factors such as pressure, viscosity (how sticky the fluid is), and velocity (how fast the blood is moving). These equations help researchers and scientists understand

how plasma moves through blood vessels and how different forces affect its flow. The continuity equation, on the other hand, is like a equation for how much plasma stays the same as it moves through the blood vessels. It basically says that the amount of plasma going into a particular area of a blood vessel should be the same as the amount coming out of that area. This equation helps scientists make sure they're accurately tracking the movement of plasma throughout the body (Kumar, 2022; Leithner, 2012; Pedley and Pitt-Francis, 2007; Sadique and Shah, 2023).

Together, these equations provide the foundation for understanding how plasma flows in the bloodstream and are essential for studying blood circulation and how it affects overall health and bodily functions (Sadique and Shah, 2022). The set of Navier-Stokes equations describing the motion at a certain point in the fluid can be expressed as:

$$\frac{Du'}{Dt} = -\frac{1}{\rho}\nabla P' + \frac{\mu}{\rho}\nabla^2 u' \tag{1}$$

$$\frac{\partial u'}{\partial x'} + \frac{\partial v'}{\partial y'} = 0 \tag{2}$$

In the capillary, the coordinates (x, y) represent the Cartesian position of any point, with x and y axes aligned along and across the capillary, respectively. The velocities in these directions are denoted as u' and v'.

The motion is governed by the following assumptions: We consider a one-directional flow, where the velocities are represented as (u', v') = (u', 0). Lubrication theory is utilized to elucidate gradual movement of plasma between red blood cell and tissue wall. Due to thinness of fluid layer between cell and wall, application of lubrication theory allows us to simplify the Stokes equations into the Reynolds equation (Shah, *et al*., 2023, Szafraniec, 2022).

Therefore, the Eq. describing the motion may be expressed:

$$\frac{\partial P'}{\partial y'} = 0 \tag{3}$$

$$-\frac{\partial P'}{\partial x'} + \mu\frac{\partial^2 u'}{\partial y'^2} = 0 \tag{4}$$

As per the reference [20,26, 29], the thickness h' of fluid film comprising plasma between tissue and cell wall is denoted:

$$h' = (\alpha+\beta)(P' - P'_0) + \frac{x'^2}{4a} \tag{5}$$

In the given context, P' represents the local pressure within the fluid film region, while P_0' denotes the reference pressure. The parameter 'a' corresponds to the length of the initially considered parabolic shape, that relates the curvature 'k' of pellet at its maximum diameter. Parameters α and β denote the radial compliances of cell and tube, respectively, which only appear in a linear combination α+β. This combination (α+β) represents additional deformation due to increased pressure within the lubricating film between the cell and inner tube wall. Additionally, U_0 and V_0 signify the reference velocities of the cell and plasma, respectively, when the cell is propelled along tube due to pressure difference, with velocity U_0 utilized for non-dimensionalizing the system of equations to derive the solution for the equation of motion. Therefore, It is assumed that dynamics of lubricating film are nearly identical to cell velocity. The model incorporates increased adhesion between the cell and capillary wall by elevating the slip parameter (n). Upon applying a non-dimensional scheme, we obtain:

$$x = \frac{x'}{H}, y = \frac{y'}{H},\ P = \frac{P'}{\rho {V_0}^2},$$

$$u = \frac{u'}{V_0},\ P_0 = \frac{P_0'}{\rho {V_0}^2},\ v = \frac{v'}{V_0},$$

$$R_e = \frac{\rho V_0 H}{\mu},$$

$$n = \frac{n'}{H} \tag{6}$$

In this scenario, H denotes the radius (internal) of capillary, while Re represents the Reynolds number, which signifies the ratio of inertial forces to viscous forces. Considering the boundary conditions, we encounter:

$$\begin{Bmatrix} u' = U_0 & at & y' = h' \\ u' = -n'\frac{\partial u'}{\partial y'} & at & y' = 0 \end{Bmatrix} \tag{7}$$

The non-dimensional representation of the governing equations and the thickness of the fluid film can be expressed as follows:

Formulas (3), (4), and (5) represent;

$$\frac{dP}{dy} = 0 \tag{8}$$

$$\frac{dP}{dx} = R_e\frac{\partial^2 u}{\partial y^2} \tag{9}$$

Dimensionless fluid film thickness

$$h = b\left(\frac{P}{P_0} - 1\right) + ex^2$$

(10)

Radial compliance of the cell $b = \frac{(\alpha+\beta)'\rho {V_0}^2 P_0}{H}$

Deformation parameter $e = \frac{l^2}{4aH}$

The boundary and matching conditions in dimensionless form are expressed as:

$$\begin{Bmatrix} u = \frac{U_0}{V_0} & at & y = h \\ u = -n\frac{\partial u}{\partial y} & at & y = 0 \end{Bmatrix} \quad (11)$$

The set of equation of motion was simplified by utilizing the aforementioned boundary conditions, yielding the solution for axial velocity as presented below:

$$u = R_e \frac{dP}{dx}\left[y^2 - h^2\left[\frac{y-n}{h-n}\right]\right] + \frac{U_0}{V_0}\left[\frac{y-n}{h-n}\right] \quad (12)$$

Results and Discussion

Red blood cells (RBCs) exhibit complex behavior due to their viscoelastic membrane filled with incompressible viscous fluid. Despite their small size, RBCs can efficiently navigate through microvessels, delivering oxygen and nutrients to tissues while regulating various physiological processes. However, in the case of sickle cell disease (SCD), which is an inherited monogenic disorder, the flow mechanics of RBCs undergo significant alterations. This study explores the flow mechanics of RBCs within capillaries, considering variations in rheological parameters as outlined in Table 1.

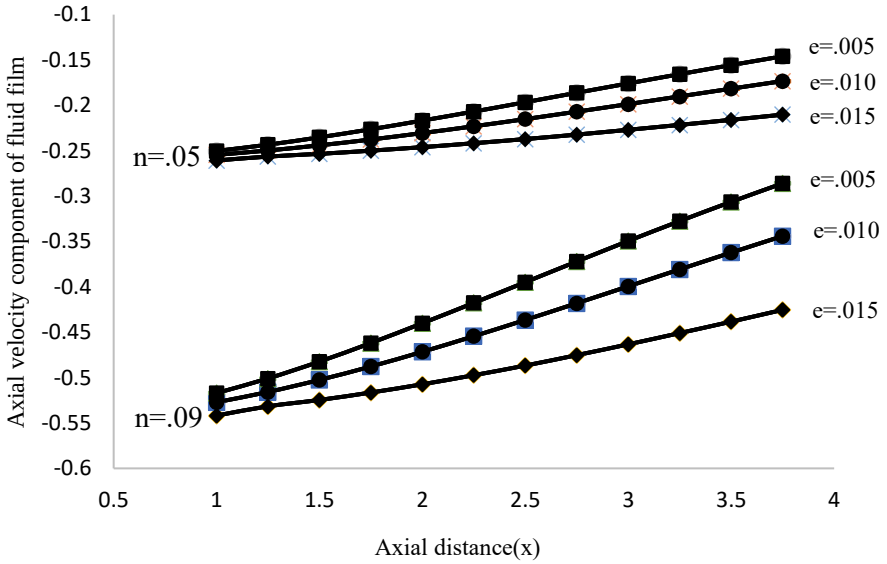

Fig. 3: Changes in the axial velocity component were observed for various slip parameters across different axial distances, considering different deformation parameters at a pressure of P=2.

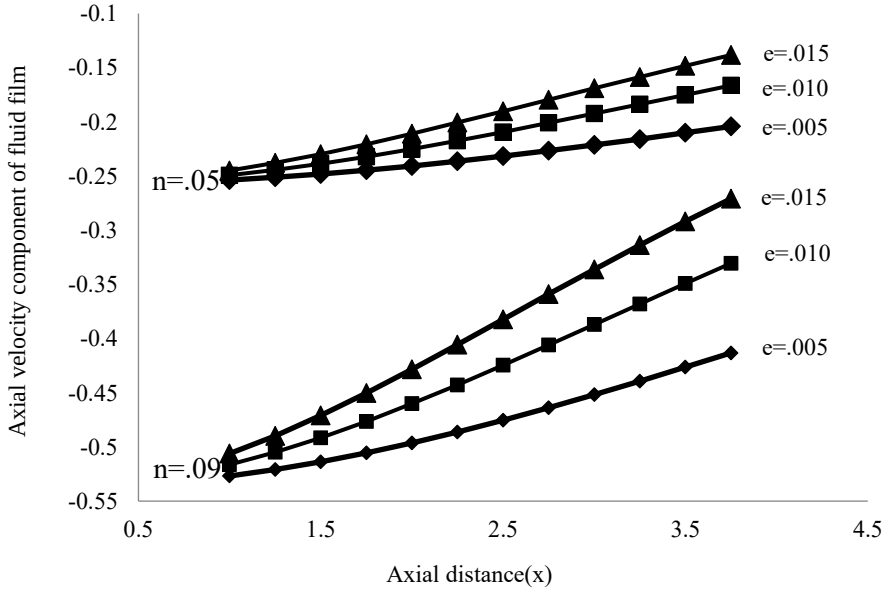

Fig. 4: Alterations in the axial velocity component were examined across varying axial distances for different slip parameters, considering different deformation parameters at a pressure of P=3.

Table 1. Parameter's Values

Parameters	Details	References No.
Pressure Drop, (P)	4	[23]
Ratio of local pressure in fluid region with reference to pressure in capillary, (P/P_0)	6.877	[25]
Ratio of the velocities of the cell to plasma, U_0/V_0	1.67	[18]
Reynolds number, (R_e)	0.25	[28]
Slip parameter (healthy flow) (n)	0.05	[29]
Deformation Parameter, (e)	0.005, 0.010, 0.015	[29]
Radial Compliance of normal red cell, μm/mb	0.06	[28]

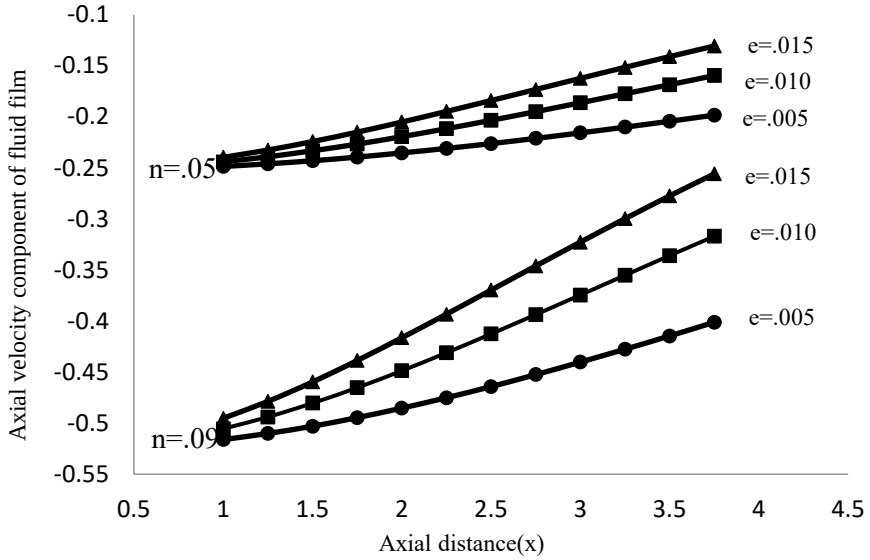

Fig. 5: The changes in the axial velocity component were analyzed concerning different axial distances, considering various slip parameters and deformation parameters at a pressure of P=4.

The investigation involves deriving expressions for the fluid film plasma height (h) and forward flow velocity in capillary, taking into account variable cell compliance and incorporating deformation and slip parameters (e, n) to simulate the behavior of less deformable and adherent RBCs. A key finding of the model is the dependence of plasma film height between cell and wall on factors such as cell deformation, pressure, and a linear combination of radial compliance of cell and tube. The results include expressions for forward flow velocity in capillary, derived from equation (12), which provides insights into the flow of plasma with the cell. Overall, this study contributes to our understanding of the intricate flow mechanics of RBCs, particularly in the context of SCD. By elucidating the factors influencing RBC behavior within capillaries and providing mathematical expressions for key parameters, this research enhances our knowledge of the pathophysiology of SCD and offers valuable insights for potential therapeutic interventions and diagnostic approaches (Siddiqui et al., (2013, 2015) Telen, 2016).

Fig. 3, 4 and 5 show that how the speed of blood flow changes in a capillary under different conditions. Specifically, it focusses on how the flow speed varies with different levels of deformation and slip.

- Deformation parameter: This refers to how much the shape of the red blood cells changes as they move through the capillary. A higher deformation parameter means the cells change shape more.
- Slip parameter: This represents how easily the red blood cells slide along the walls of the capillary. A higher slip parameter means the cells have more difficulty sliding.

The figures show that when the slip parameter is set to 0.09 (which indicates more difficulty sliding), there is a significant reduction in flow speed compared to when it's set to 0.05 (which indicates easier sliding). This reduction in speed suggests that higher slip parameters oppose the motion of the blood, creating resistance. This resistance is consistent with what Mishra and colleagues found in their research. They observed that higher slip parameters result in increased resistance to blood flow, slowing it down. Similarly, Hebbel and his team noted that sickle red blood cells tend to stick more to the walls of blood vessels, which also increases resistance to flow during circulation (Secomb, 2017, Kumar et al. 2024).

Conversely, when the deformability parameter is increased (indicating greater flexibility of red cells), flow speed in

capillary increases. This suggests that the flexibility of the cells has a significant impact on flow speed, especially when combined with conditions that affect sliding along the walls. Overall, these findings provide insights into how different factors, such as cell shape and ability to slide, influence blood flow in the capillaries, which is crucial for understanding conditions like sickle cell disease and developing effective treatments. This mathematical model delves into the essential characteristics governing flow of red cells in capillaries, offering insights into the potential ramifications of abnormal biophysical factors on single-file flow. Through our investigation, we explored the flow dynamics of single red blood cells under abnormal physiological conditions, modulating rheological parameters to elucidate their implications for Sickle Cell Disease (SCD) pathophysiology. The microcirculatory blood flow is intricately linked to the biomechanical properties of red blood cells, particularly deformability and adhesiveness. Utilizing rheological parameters derived from published literature, we simulated disease conditions by varying these parameters to mimic the altered behavior of sickle red blood cells. Our results reveal that deformability and adhesiveness significantly influence plasma film height and forward flow velocity in capillaries (Leithner, et al., 2012; Pedley and Pitt-Francis, 2007). Notably, an increase in slip parameter, representing adhesion to endothelial cells, leads to a notable decrease in flow velocity, indicating its potential.

Furthermore, compliance of the cell affects plasma film height and velocity, with analytical expressions and simulation results corroborating these findings. Our focus then shifted to the flow of single cells in microchannels, where bio-mechanical properties play a crucial role. In SCD, the accumulation of less deform cells to endothelial layer contributes to vaso-occlusion in microvessels. Our study lays the groundwork for understanding the mechanisms underlying sickle cell occlusion and motivates further research into diagnostic applications. The use of lab-on-chip technology emerges as a promising approach for rapid screening of RBC deformability, holding significant potential as a diagnostic tool. Moreover, the incorporation of rheological properties of RBCs in microfluidic systems under physiological flow conditions offers valuable insights into SCD diagnosis. Advanced techniques such as machine learning in-silico models can further refine our understanding by exploring different forces and model variable paramaters in a suitable environment. In-silico studies hold the promise of contrasting sickle cell behavior with healthy RBCs, providing crucial insights into factors contributing to SCD pathogenesis (Kavanagh, *et al.*, 2022). This study paves the way for comprehensive investigations into SCD mechanisms and diagnostic approaches, with the potential to improve patient outcomes through early detection and targeted interventions.

Conclusion

The study on Voxelotor treatment in Sickle Cell Disease (SCD) patients has revealed promising insights into managing this complex condition. Acting as an HbS polymerization inhibitor, Voxelotor has demonstrated efficacy in reducing hemolysis and enhancing hemoglobin levels, potentially mitigating SCD-related complications and improving quality of life. However, it's crucial to recognize the underlying changes in sickle blood under low oxygen conditions, including a rightward shift in the oxy-hemoglobin dissociation curve, leading to reduced intracellular oxygen levels and affecting tissue oxygenation. This alters cell velocity and blood flow dynamics in microcirculation, with implications for vaso-occlusion. The study highlights the importance of factors like the height of the lubricating film between sickle RBCs and capillary walls in modulating blood flow behavior. Changes in deformation parameter and red cell compliance affect plasma film thickness, potentially leading to obstructed blood flow. Sickle RBCs show reduced compliance and increased adhesion to endothelial cells post-deoxygenation, heightening the risk of vaso-occlusion and tissue hypoxia. The findings provide valuable insights into SCD pathophysiology and potential therapeutic targets. They also inform the development of microfluidics-based diagnostic devices and screening tools for SCD. In silico modeling holds promise for further understanding single-cell flow dynamics, aiding in the development of targeted therapies and enhancing SCD diagnosis, treatment, and management.

Authors' Contribution

Both authors contributed equally at all stages of research and manuscript preparation. Final form of manuscript was approved by both.

Conflict of Interest

The authors declare that there is no conflict of interest with present publication.

Acknowledgement

The authors would like to thank the School of Computational and Integrative Sciences, Jawaharlal Nehru University, New Delhi-110067, (India) for providing facility of Bio-mathematical Lab. And also thankful for financial support to the DST/WOSA/PM-40/2021.

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