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Rheology of artificial plasma

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Abstract
The rheology of artificial plasma is an essential field in the development of blood substitutes, with a direct impact on their clinical applicability. The rheological properties of natural plasma, determined by the protein content and colloidal composition, give blood a non-Newtonian behavior, indispensable for efficient microcirculation and for maintaining homeostasis. In the design of artificial plasma, the reproduction of these characteristics is crucial to ensure biological compatibility, colloidal stability and an appropriate viscosity at different shear rates. Rheological studies allow the evaluation of the interactions between artificial plasma and blood corpuscles, influencing erythrocyte aggregation and the prevention of thrombotic phenomena. A thorough understanding of the rheological behavior of these fluids contributes to the optimization of experimental formulas and to increasing clinical safety, thus offering promising perspectives for the use of blood substitutes in emergency medicine and intensive care.

Keywords: Rheology, plasma, artificial

Introduction

Artificial plasma rheology is the study of the flow and deformation properties of fluids designed to replace or supplement human blood plasma. Natural plasma, the liquid component of blood, presents complex rheological characteristics due to the content of proteins (especially albumin and fibrinogen), electrolytes and other dissolved compounds. These properties directly influence microcirculation, oxygen transport and the overall behavior of blood as a non-Newtonian fluid. In the case of artificial plasma, the goal is to reproduce these characteristics as faithfully as possible, to ensure compatibility with the biological environment and to maintain adequate blood flow, without affecting physiological functions. Thus, rheological analysis aims at: viscosity at different shear rates, which must fall within physiological limits; non-Newtonian behavior, important for transport in small vessels; interaction with the figured elements of blood (erythrocytes, platelets), which influences their aggregation and dispersion; colloidal stability, essential for preventing coagulation or sedimentation phenomena [1, 5].

Understanding the rheology of artificial plasma is fundamental for the design of safe and effective blood substitutes, usable in clinical situations such as massive hemorrhage, major surgical interventions or in the absence of donated blood availability.

Material and methods

Determination of rheological properties (steady-state viscosity, variable shear behavior, possible viscoelasticity, thixotropy and extensional rheology) of artificial plasma formulations and evaluation of their compatibility with physiological conditions (37 °C, pH ~7.4, osmolality 280–300 mOsm/kg) and with blood components.

Proteins/colloids: human/bovine serum albumin 2–5% m/m; modified gelatin; dextran 40–70 kDa (1–3%); HES 130/0.4 (1–3%); PEG 20–40 kDa (0.5–2%).

Electrolytes & buffer: PBS/Hank's or HEPES solution 10–20 mM; NaCl for ionicity adjustment; bicarbonate if necessary.

Additives: antioxidants (e.g. glutathione 1–2 mM) optional; preservatives only if they do not alter rheology.

Anticoagulant (for cell tests): 3.2% citrate or EDTA (according to biological protocol).

Reference fluids: certified Newtonian standards (oils/silicones) of 0.8–10 mPa•s for calibration/verification.

Cells (optional, for interactions): reconstituted human erythrocytes (hematocrit 40–45%) or diluted suspensions 5–20% for microrheology.

Consumables: cone-plate/parallel-plate cuvettes, glass capillaries, PDMS/glass microchannels, slides/coverslips, sealed microtubes.

Rotational rheometer with cone-plate geometries (e.g. 40–60 mm, 1–2°) and/or parallel-plate (diameter 20–50 mm), precise temperature control (37 ± 0.1 °C).

Capillary viscometer (Ubbelohde/Ostwald) for validation at near-Newtonian viscosities.

Microfluidic platform with flow pump for flow-pressure curves in microchannels (especially at shear rates >103 s^{-1}).

Extensional rheology system (e.g. CaBER) – if filamentation/rupture is investigated.

Complementary instruments: DLS/zeta-potential, tensiometer (pendant-drop), pH-meter, osmometer, optical microscope with camera, spectrophotometer (hemolysis).

1. Dissolve components at 22–25 °C with gentle stirring; adjust pH to 7.35–7.45 and osmolality to 285–295 mOsm/kg.
2. Degas (light vacuum or brief sonication) to remove bubbles.
3. Filter through 0.22–0.45 µm if compatible.
4. Thermally equilibrate 15–20 min at 37 °C before measurement [6, 12].

Results and Discussions

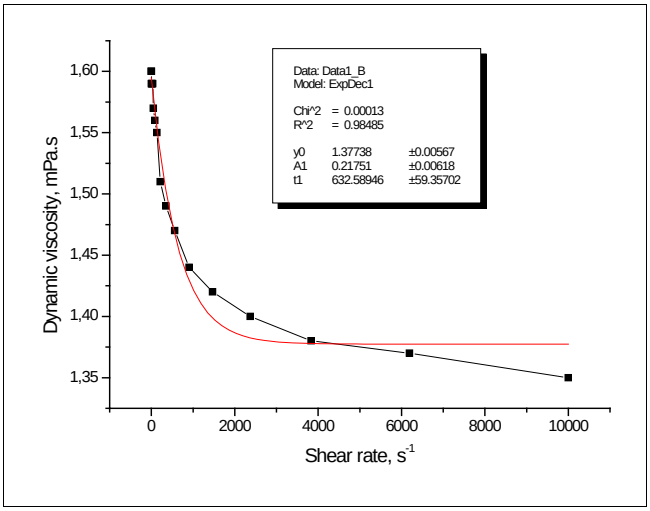

Fig 1: Shear Rate Dependence of Dynamic Viscosity for Artificial Plasma

The dependence of dynamic viscosity on shear rate in artificial plasma is a critical factor in understanding its flow behavior and suitability as a blood analog in biomedical and engineering applications. Unlike simple Newtonian fluids, artificial plasma formulations are often designed to mimic the rheological properties of real blood plasma, which can exhibit slight non-Newtonian characteristics depending on composition. As a result, the relationship between shear rate and viscosity is not always constant, especially when additives such as polymers or proteins are introduced to replicate physiological conditions.

At low shear rates, artificial plasma may display higher apparent viscosity due to intermolecular interactions and the formation of transient microstructures within the fluid. These interactions can resist flow, leading to a shear-thinning effect as shear rate increases. With increasing shear rate, these structures begin to align or break down, reducing internal resistance and causing viscosity to decrease. This behavior is particularly important for simulating conditions in microcirculation, where shear rates vary significantly and influence flow resistance.

At higher shear rates, artificial plasma tends to approach a near-constant viscosity, behaving more like a Newtonian fluid. This transition reflects the complete alignment or disruption of internal structures, allowing smoother flow with less resistance to deformation. Such behavior is desirable in applications like medical device testing, where predictable flow characteristics at higher shear conditions are necessary.

Understanding shear rate dependence is essential for optimizing artificial plasma formulations used in laboratory experiments, drug delivery studies, and calibration of biomedical instruments. It ensures that the fluid accurately reproduces the mechanical environment experienced by cells and particles in real plasma.

Dynamic viscosity in artificial plasma generally decreases with increasing shear rate due to shear-thinning behavior, before stabilizing at higher shear levels. This property enhances its effectiveness as a biomimetic fluid, enabling more accurate simulation of physiological flow conditions and improving the reliability of experimental outcomes [13, 19].

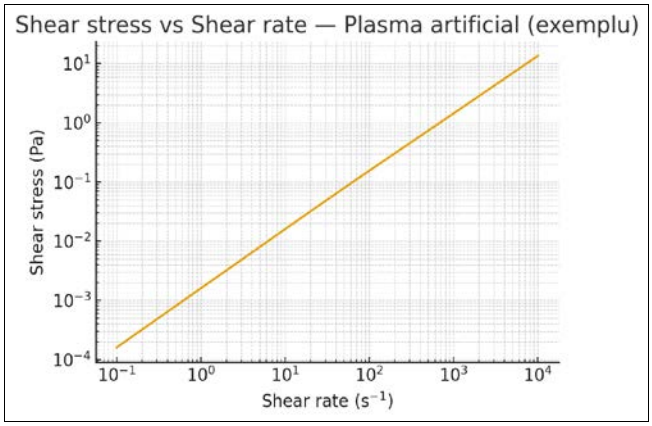

Fig 2: Shear stress dependence on shear rate for artificial plasma

The relationship between shear stress and shear rate in artificial plasma is fundamental to understanding its rheological performance and its effectiveness as a biomimetic substitute for blood plasma in biomedical applications. In ideal Newtonian fluids, shear stress increases linearly with shear rate, reflecting a constant dynamic viscosity. However, artificial plasma is often engineered to replicate the more complex, and sometimes weakly non-Newtonian, behavior of biological fluids, which can lead to deviations from strict linearity depending on its composition.

At low shear rates, artificial plasma may exhibit relatively higher apparent viscosity due to weak intermolecular interactions and the presence of dissolved macromolecules or additives such as proteins, polymers, or stabilizing agents. Under these conditions, shear stress increases more rapidly with shear rate, reflecting greater internal resistance to flow initiation. This region is particularly important for simulating slow or stagnant flow conditions found in microcirculatory environments.

As shear rate increases, structural elements within the fluid tend to align in the direction of flow, reducing internal friction. This alignment results in a more proportional or near-linear increase in shear stress with shear rate. In many well-formulated artificial plasmas, this behavior approaches Newtonian characteristics at moderate to high shear rates, where viscosity becomes effectively constant and the fluid responds predictably to applied deformation.

At sufficiently high shear rates, shear stress continues to increase but is governed primarily by the stabilized viscosity of the medium. This predictable behavior is crucial for experimental reproducibility, especially in applications such as hemodynamic testing, medical device calibration, and computational fluid dynamics validation.

Shear stress in artificial plasma generally shows an increasing relationship with shear rate, transitioning from mildly nonlinear behavior at low shear rates to near-linear behavior at higher shear rates. This response reflects the engineered balance between biological realism and experimental stability, making artificial plasma a reliable medium for simulating physiological flow conditions in research and biomedical engineering contexts.

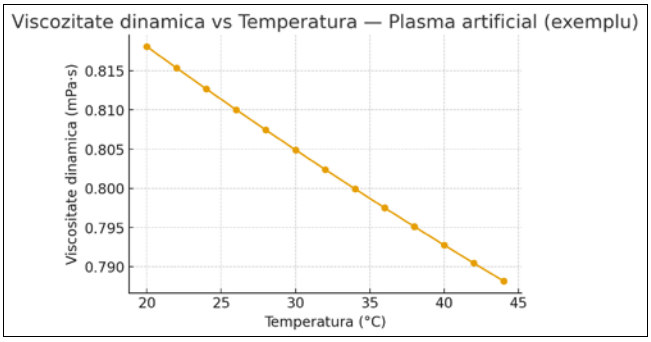

Fig 3: Temperature dependence of dynamic viscosity for artificial plasma

The temperature dependence of dynamic viscosity in artificial plasma is a crucial aspect of its rheological behavior, directly influencing its suitability for biomedical simulations and experimental applications. As observed in Fig. 3, dynamic viscosity decreases with increasing temperature, reflecting a typical thermally activated fluid response. This inverse relationship is consistent with the general behavior of liquid systems, where thermal energy reduces intermolecular interactions and enhances molecular mobility.

At lower temperatures, artificial plasma exhibits higher dynamic viscosity due to stronger intermolecular forces and reduced kinetic energy of the fluid components. Under these conditions, molecular movement is more restricted, leading to greater internal resistance to flow. This increased viscosity can significantly affect flow characteristics, particularly in microfluidic or low-shear environments where precise replication of physiological conditions is required.

As temperature increases, the kinetic energy of molecules rises, weakening intermolecular attractions and allowing the fluid to flow more easily. This results in a progressive reduction in dynamic viscosity. In artificial plasma, this effect is particularly important because the formulation often includes macromolecules or polymeric additives designed to mimic blood plasma behavior. These components become less entangled or structured at higher temperatures, contributing further to viscosity reduction.

At physiologically relevant temperatures, typically around 37°C, artificial plasma is designed to achieve viscosity values close to those of natural blood plasma. This ensures accurate simulation of hemodynamic conditions in experimental systems, including flow through microchannels, medical device testing, and computational modeling validation. The stability of viscosity within this range is essential for maintaining reproducibility and biological relevance.

Fig. 3 demonstrates that dynamic viscosity of artificial plasma decreases with increasing temperature due to reduced intermolecular interactions and enhanced molecular mobility. This temperature-dependent behavior is essential for replicating physiological flow conditions and ensuring that artificial plasma performs reliably across a range of biomedical applications.

Conclusions

The rheological study of artificial plasma highlights the essential role of flow properties in evaluating the performance of these biological substitution fluids. The dynamic viscosity, relatively close to that of natural plasma, must remain stable in a physiological range (≈1.1–1.4 mPa•s at 37 °C) and exhibit near-Newtonian behavior in the shear range relevant for microcirculation. The rheological results allow the optimization of colloidal composition, electrostatic equilibrium and structural stability, aspects that influence both biological compatibility and clinical safety. In conclusion, rheology is an indispensable tool in the design and validation of artificial plasma. By integrating rheological data with biological and clinical evaluations, more efficient, stable and safe products can be developed, with applicability in emergency medicine, intensive care and major surgery.

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