Rheological Optimization in Ophthalmic Drug Products: A Comprehensive Review

***Najiya Ibrahim Nk[1], Dr. Manoj Kumar Singh[2], Dr. Uma Shankar[3], Dr. Mubeen Ghani[4].**

[1,4] Al Ameen College of Pharmacy, Hosur road, Bangalore 560027.
[2,3] MICROLABS Limited, Hosur road, Kudlu Bangalore 560068.

Najiya Ibrahim NK
Al-Ameen college of pharmacy
Hosur Road, (Near Lalbagh main gate) Bangalore - 560027
Tel.: +91-8547570736
E-mail: najiyank2000@gmail.com

Abstract:

Improving the rheological (flow-related) properties of ophthalmic drug formulations is essential for enhancing their effectiveness, safety, and patient comfort. The eye has unique barriers that make drug delivery challenging, as most of the medication is quickly washed away by blinking and tears. To overcome this, adjusting the viscosity and flow behaviour of eye drops, gels, and suspensions can help keep the drug on the eye surface longer, improving absorption and reducing the need for frequent dosing. This review discusses the importance of rheological properties such as viscosity, shear-thinning (viscosity decreases when blinking), and thixotropy (reversible thinning during use) in different ophthalmic formulations. Various thickening agents—such as carbomers, HPMC, hyaluronic acid, chitosan, and poloxamers—are examined for their ability to improve these properties. In addition, the review outlines key methods used to measure viscosity, including capillary viscometers, rotational viscometers (like Brookfield), rolling-ball viscometers, rheometers, and newer tools like the Smear-Bot. Each method's usefulness and limitations are compared.

The article also highlights recent advancements in formulation strategies and testing methods, showing how better control of rheology can lead to safer, more effective, and longer-lasting ophthalmic products. Through critical synthesis of recent scientific literature and regulatory guidelines, this article aims to inform and guide formulation scientists in the rational design and optimization of ophthalmic products with superior rheological performance and clinical relevance.

Keywords: Ophthalmic formulations, viscosity, rheology, shear-thinning, viscometer, polymers, bioavailability, eye drops, thixotropy, ophthalmic suspensions.

INTRODUCTION

Ophthalmic preparations (eye preparations) are sterile liquid, semi-solid, or solid preparations that may contain one or more active pharmaceutical ingredients. Ophthalmic products are designed to be applied to the eyelids, conjunctiva, or conjunctival sac.[1] The most popular dose type for patient-administered eye therapy is topical ophthalmic drops. Due to the intricate anatomy and physiology of the eyes, only a tiny percentage of the medication reaches the site of action, making efficient ocular delivery potentially difficult.

Suspensions and other ophthalmic drug products are complex and multipurpose pharmacological dosage forms that are frequently employed to extend drug retention on the ocular surface. They are defined by the dispersion of small solid particles inside a liquid medium, creating a biphasic system. Maintaining ideal pharmacokinetic and pharmacodynamic profiles requires a mechanism for controlled release and targeted distribution, which is provided by the suspended particles continued undissolved state. Higher ocular bioavailability is the consequence of API particles dissolving gradually over a longer length of time in the Cull de sac of the eyes when suspended. One important component of ophthalmic suspensions that affects both the dosage form's physical stability and therapeutic effectiveness is particle size. Ophthalmic suspensions usually have particle sizes no larger than 25 µm to prevent irritation of the eyes. [2]

The three major ways that rheology contributes to the functional features of lubricating eye formulations are by maximising ocular residence duration, minimising blink resistance, and forming a stable lubricating film that keeps the cornea and eyelid apart. Shear-thinning and shear-thickening behaviour, viscosity, and thixotropy are examples of rheological properties that impact the suspension's residence duration on the ocular surface, which in turn impacts medication absorption and bioavailability. The right viscosity is crucial for ophthalmic suspensions and gels to guarantee that the preparation stays in touch with the ocular surface for a prolonged amount of time, improving medication absorption and therapeutic impact.

An ophthalmic formulation with ideal rheological characteristics guarantees that the drug may be taken with ease and that it is thick enough to avoid washing out or draining from the eye too quickly. Shear thinning behaviour makes it easier to apply while keeping the protective, gel-like consistency on the surface of the eye at rest. This occurs when viscosity lowers under stress, such as blinking. Another advantage of thixotropic qualities is that they allow the formulation to regain its viscosity after application, extending its residence period.

Viscosity is an important component of ophthalmic preparations because it directly affects how long the formulation remains on the surface of the eye, increasing medication bioavailability by giving the active ingredient more time to be absorbed. Ophthalmic preparations such as drops, gels, and ointments require controlled viscosity to sustain prolonged contact with the eye, enhancing drug absorption and therapeutic effect. Viscosity-enhancing substances and highly viscous lubricants are frequently utilised to accomplish this. Within a few minutes, eye drops with a viscosity like that of natural tears are usually gone. To optimise bioavailability, ocular lubricants must have a high enough viscosity. After being applied to the eye, ophthalmic formulations are impacted by a few variables, such as dilution from tears, possible pH changes, and an increase in temperature from ambient levels to the eye's temperature, which varies from 32.9°C to 36°C. The studies indicate that pH must be kept within the physiological range,

which is around 6.5-8, because it is essential for both the stability of the drug delivery system and patient comfort.[3] The formulation's performance and efficacy depend heavily on temperature and dilution, as viscosity decreases with increasing temperature.

Depending on whether viscosity and shear rate or liquid composition is connected, a system is classified as either a Newtonian flow or a non-Newtonian flow. When a system's viscosity depends on the liquid's composition, temperature, and pressure but is not affected by shear rate, it is said to exhibit Newtonian flow behaviour. The viscosity is shown to rise with increasing pressure while decreasing with increasing temperature. There is no constant viscosity in non-Newtonian systems because the viscosity of non-Newtonian fluids varies with the rate of shear.[4]

The viscosity of ocular preparations is greatly impacted by the shear rate produced by eye blinking, which in turn impacts the preparations' functionality and therapeutic efficacy. When the eyelids move across the tear film and any applied formulation, blinking produces a high-shear environment on the ocular surface. Shear rates resulting from eyelid closure and opening range from 4000 to 20000 1/s. To facilitate better dispersion and less resistance while blinking, many ophthalmic formulations are made to have shear-thinning, which means that their viscosity reduces under high shear rates. The high shear rate produced by each blink causes the tear film to be mechanically disrupted, which lowers the viscosity of the applied formulation.[5] Consequently, the formulation is applied thinner to the eye, making it more prone to discharge.

The internal resistance of a fluid to flow is measured by dynamic viscosity, sometimes referred to as absolute viscosity. It is the amount of tangential force per unit area needed to move two horizontal planes at the same speed while keeping them apart by one unit in a fluid. It stands for a liquid's viscous force. It is represented by the symbol μ and is defined as the ratio of shear stress to shear strain. Dynamic viscosity has a CGS unit of poise (P) and a SI unit of Ns/m^2.

The ratio of dynamic viscosity to fluid density is known as kinematic viscosity. It depicts the fluid's viscous and inertia forces and does not directly involve any force, in contrast to dynamic viscosity. The dynamic viscosity of a fluid is divided by its mass density to calculate its kinematic viscosity. Denoted by the symbol ν, it is considered a more fundamental property, particularly useful in scenarios where both inertia and viscous forces are significant.

When describing the rheological behaviour of ophthalmic formulations including polymers, intrinsic and relative viscosity are critical characteristics. The study of polymer chemistry, which examines the structure and characteristics of polymers, uses intrinsic viscosity determination. It is defined as the limiting value of the reduced viscosity, η_i/c or the inherent viscosity, ηinh, at infinite dilution of the polymer,[6] i.e. the reduced viscosity $(\eta-\eta_0)/\eta_0 c(=\eta_{sp}/c)$ at infinite dilution, where η_0 and η_{sp} denote the solvent viscosity and the specific viscosity, respectively. A polymer's inherent viscosity determines its actual viscosity-enhancing characteristics, regardless of its concentration in solution. Different regression models might be applied depending on the polymer under investigation. The many regression models that are being used include Martin, Huggins, Kraemer, and Schulz-Blaschke.[7] A crucial factor to consider when evaluating undissolved polymers is the relative viscosity. It is calculated by dividing the viscosity of the pure solvent (η_0) by the viscosity of the polymer solution (η). The basis for determining other characteristics that are important for polymer quality management is the relative viscosity, or η_r.[8]

$$\eta_r = \frac{\eta}{\eta_0}$$

Viscometers are frequently employed as precise tools to measure a fluid's resistance to flow. Depending on the formulation's characteristics and the level of precision needed, many kinds of viscometers are used, including capillary, rotating, falling ball, and rolling ball viscometers.

VISCOSIFIERS

Viscosity enhancers prolong the drug's precorneal residence duration at the ocular location, increasing ocular bioavailability. The duration of the drug's interaction with the ocular surface is extended by the inclusion of viscosity modifiers.[9] For the best therapeutic and cosmetic efficacy, these compounds are essential for increasing formulation stability, prolonging drug residence duration, and supplying the appropriate texture. Natural polymers (Xanthan gum), semi-synthetic polymers (Carboxymethyl cellulose), synthetic polymers (Poloxamer), and inorganic viscosifiers are the different categories of viscosifiers based on where they come from.

CHITOSAN

N-acetylglucosamine and glucosamine combine to form the positively charged mucopolysaccharide known as chitosan. It was thought that chitosan, a viscosity enhancer, might open intracellular cells and epithelial tight junction barrier cells. Without compromising viability, it raises cell permeability. More medications are carried through the cornea because of this enhanced permeability. It also possesses mucoadhesive qualities and is naturally biodegradable. Accelerated keratocyte migration promotes quicker corneal repair by speeding up collagen production and wound healing. The ocular mucosa's medication bioavailability was improved using chitosan nanoparticles. The benefits of adding penetration enhancers, such chitosan, to microspheres include increased bioavailability and retention duration because to the closer contact with the mucous layer, as well as precise drug delivery to the eye area. Polycationic chitosan compounds that are soluble at the physiological pH of tear fluid improve penetration when applied topically, raising the therapeutic preparation's viscosity and permeability.[9]

XANTHAN GUM

One polysaccharide that is utilised as an efficient thickening agent is xanthan gum. The gum solutions' high viscosity at low shear rates can aid colloidal systems in maintaining stability over time.[9] A liquid's viscosity can be significantly increased by adding 1% xanthan gum. But when shear rates rise, xanthan gum solutions' viscosity falls, a phenomenon referred to as shear thinning or pseudoplasticity.

HYALURONIC ACID

High molecular weight hyaluronic acid is a non-immunogenic glycosaminoglycan polymer that is used in ocular medicine for several purposes. Their main benefits are their viscoelasticity and mucin-like biophysical properties, which enable sustained hydration and retention.[9]

CARBOXYMETHYL CELLULOSE

High molecular weight polysaccharide carboxymethylcellulose is one of the most often employed viscous polymers in artificial tears to achieve the extended duration of ocular surface residence. Due to its muco-adhesiveness and viscosity, CMC has a lengthy retention period on the surface of the eye.[9]

HYDROXYPROPYLMETHYLCELLULOSE

A semisynthetic, inert, viscoelastic polymer, hydroxypropyl methylcellulose (HPMC) is utilised in eye drops and as an excipient and controlled-delivery ingredient in oral medications. Numerous test techniques are available for Hypromellose solution because to its non-Newtonian nature and pseudoplastic, or more precisely, thixotropic, behaviour, and the outcomes of various techniques and viscosimeters may not always agree with one another.[10]

HYDROXYETHYL CELLULOSE

One type of biopolymer with a low charge density is hydroxyethyl cellulose, a water-soluble, non-ionic cellulose derivative. It is made by adding hydroxyethyl groups to cellulose, which etherifies it and improves its solubility and functional qualities. Typically used at concentrations ranging from 0.5% to 2%, hydroxyethyl cellulose serves as an effective viscosity-modifying agent and binder in pharmaceutical formulations. It is essential in ophthalmic preparations because it enhances the consistency and retention of eye drops and has also been shown to improve the strength of dry tears, providing the patient with more comfort and therapeutic advantages [11].

CARBOMER

A high molecular weight polymer used as a viscosity enhancer is polyacrylic acid, also known as carbomer (Carbopol). Mostly made up of polymerised acrylic acid monomers, carbomers are a class of crosslinked polyacrylic acid derivatives. Even at very moderate usage levels, they effectively increase viscosity in aqueous environments. When employed at just 0.5% w/w, the majority of carbomers may create viscosities of 10,000–60,000 cP. As a result, carbomers are often used in a wide range of goods as aqueous phase thickeners. Nonetheless, carbomers' actual usefulness stems from their capacity to provide formulas a high yield value.[12] Of its many pharmaceutical-grade forms, Carbopol 934P is a highly refined version created especially for use in ocular formulations, such as gels and ointments. The rheological features of this polymer are pH-responsive; at pH values below 5.5, it exists as a low-viscosity liquid,

but when the pH rises over this threshold, it passes through a phase transition to form a semi-solid gel. Because of this property, Carbopol is a perfect gelling agent for pharmaceutical formulations, especially in ophthalmic applications where bio-adhesion and controlled viscosity are crucial for drug administration and extended ocular residence duration.[13]

POLOXAMER

The FDA has allowed the use of Poloxamers 188 and 407, which are synthetic, non-ionic, and amphiphilic polymers, in several industrial, medicinal, and cosmetic goods. These polymers are frequently utilised as inactive components in a variety of eye drop formulations due to their surfactant qualities, biocompatibility, non-toxicity, and biodegradability. Poloxamers create colloidal solutions when dissolved in water at low concentrations, which aid in lowering surface tension and enhancing medication absorption. Poloxamers remain liquid at lower temperatures (~4 °C) or room temperature (~20 °C) at concentrations greater than 15% (w/w), but at eye temperature (~32 °C), they transform into a clear, colourless gel. Higher concentrations of Poloxamers lengthen the retention period on the eye, however the high concentrations required for in situ gel formation might irritate the eye. To get around this, materials like cellulose are added to lower the necessary concentration of Poloxamers while preserving the gel's characteristics.[13]

TYLOXAPOL

Tyloxapol is an alkyl aryl polyether alcohol-type non-ionic liquid polymer. It facilitates liquefaction by acting as a surfactant. Niosomes, or liposomes based on non-ionic surfactants, are developed using tyloxapol for application in drug delivery systems.[14]

ANALYTICAL METHOD: VISCOMETER

Viscosity is measured using a variety of experimental methods, each of which is appropriate for a particular fluid type and set of application requirements. The kind of fluid, the sensitivity of the shear rate, and the needs of the application all influence the choice of viscometry method. Based on their flow characteristics, fluids are often categorised as Newtonian or non-Newtonian. Regardless of the applied shear rate, Newtonian fluids have a constant viscosity, which means that their flow characteristics don't alter under various circumstances. Non-Newtonian fluids, on the other hand, exhibit viscosity changes based on shear rate; under stress, they may thicken (shear-thickening) or thin (shear-thinning).[4] The majority of ophthalmic formulations, including gels and suspensions, have shear-thinning behaviour, which means that when shear increases, their viscosity reduces. This property makes instillation easier while preserving ocular retention. Capillary viscometry, rotational viscometry, and oscillatory rheometer are the experimental methods used to measure the viscosity of ophthalmic formulations. Capillary viscometers, like the Ostwald and Ubbelohde viscometers, are appropriate for Newtonian fluids since they measure the amount of time it takes for a liquid to flow through a small tube under gravity. Rotational viscometers, however, are recommended for ophthalmic compositions that show shear-thinning behaviour.[5] Viscosity may be measured

at various shear rates using devices like the Brookfield and cone-and-plate viscometers, which offer important information on how the formulation flows under physiological circumstances like blinking and eye movement. We can optimise ophthalmic formulations to strike a compromise between longer ocular retention and simplicity of administration by characterising viscosity over a range of shear speeds.

A capillary viscometer is a straightforward and popular tool for determining the viscosity of fluids, especially Newtonian fluids. It works based on laminar flow and measures how long it takes a fluid to move through a capillary tube when pressure or gravity is applied. Poiseuille's law, which links flow rate to fluid viscosity, tube size, and pressure differential, is used to calculate the viscosity.[15] The Ostwald and Ubbelohde viscometers are common capillary viscometers; a common version that aligns the bulb in the same vertical axis is the Cannon-Fenske viscometer. By shearing the fluid between a revolving and a stationary surface, rotational viscometers—which may be used with both Newtonian and non-Newtonian fluids—measure viscosity. A cylinder's rotational deflection indicates its viscosity. These include cone and plate viscometers, in which a narrow-angled cone rotates close to a flat plate, guaranteeing a constant shear rate, and cup and bob viscometers, which are composed of an inner revolving bob and an outer stationary cup, producing a viscous drag proportionate to the fluid's viscosity. The cup and bob viscometers are either based on the Couette or Searle concept. The Stormer and Brookfield viscometers are examples of the Searle type, in which the bob spins while the cup stays stationary, while the cup rotates while the bob stays stationary. By measuring how long it takes a ball of a certain size and density to fall down a liquid-filled tube under gravity, the falling ball viscometer determines viscosity using Newton's equation of motion and the Hoppler principle. Gravity pulls the ball downward, while buoyancy and friction serve as opposing forces. For consistency, the measurement can be repeated by flipping the tube. [16]

FORD CUP

Figure 1: Ford Cup

Ford cups are simple gravity devices that allow a known volume of liquid to flow through an aperture at the bottom of the device on a timed basis. The kinematic viscosity, which is measured in stokes or centistokes, is proportional to the flow rate under ideal circumstances. This is determined by the liquid's specific gravity. Maintaining the temperature of the cup and liquid is crucial when retesting liquids and using a Ford cup since ambient temperature

significantly affects viscosity as well as flow rate. It is frequently applied to fluids with low viscosity. [17]

OSTWALD VISCOMETER

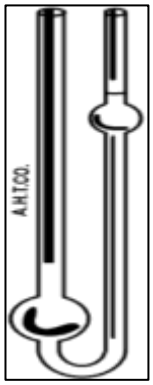

Figure 2: Ostwald Viscometer

It is a simple U-tube viscometer, used to measure the viscosity of the liquid with a known density. The Ostwald viscometer is not suitable for non-Newtonian fluids because their viscosity changes with shear rate under applied force. Since the Ostwald viscometer measures viscosity under fixed geometry and flow conditions, it cannot account for these changes. As a result, a single viscosity value obtained from the Ostwald viscometer is insufficient to accurately characterize the fluid's rheological behaviour.

To begin the working of Ostwald viscometer, fill the reservoir tube with water until it reaches the designated mark, labelled ac C. Use a suction bulb to draw the liquid up through the capillary tube until it aligns with mark A. Finally, use a stopwatch to measure the time it takes for the liquid to descend from mark A to mark B, recording the starting time at mark A and the ending time at mark B. [15] Viscosity is calculated by the equation:

$$\eta_1 = \eta_2 \frac{\rho_1 t_1}{\rho_2 t_2}$$

Were,

η1 = viscosity of the sample solution

η2 = viscosity of the water

p1 = density of the sample

p2 = density of water

t1 = time taken to flow from Mark A to Mark B of the sample in seconds

t2 = time taken to flow from Mark A to Mark B of the water in seconds

UBBELOHDE VISCOMETER

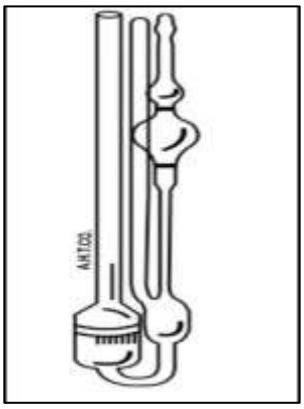

Figure 3: Ubbelohde Viscometer

Ubbelohde viscometer is a modified version of Ostwald's viscometer, used to test liquids with high viscosity cellulosic polymer solution. The instrument consists of two bulbs: the reservoir bulb, located at the lower-level and the measuring bulb, connected by a capillary tube, with an additional air vent. The reservoir bulb is initially filled with liquid, taking precaution to prevent it from entering the air hose. The viscometer is then submerged in a temperature-controlled liquid bath to ensure the liquid inside reaches thermal equilibrium with bath. A rubber tube attached to the air tube is used to suction the liquid to the measuring bulb. Once the liquid has been transferred, the rubber tube must be sealed to prevent it from leaking back into the reservoir. The liquid is then allowed to fall when the rubber tube has been loosened. The time taken for the liquid to flow between two markers in the measuring bulb is recorded to calculate the flow rate. It provides accurate readings regardless of the volume of liquid used.[15]

Viscosity is calculated by the equation:

Kinematic viscosity,

$$\nu = \kappa \times t$$

Were,

ν = kinematic viscosity

k = viscometer constant

t = flow time

This equation is used, if the viscosity constant is known.

The viscometer constant, k, in mm2 / s2 is calculated using the equation:

$$\kappa = \frac{\eta}{(\rho \times t)}$$

Were,

η = known viscosity of the liquid (mPa.s)

ρ = density of the liquid (g/mL)

t = flow time for the liquid to pass from the upper mark to the lower mark (s)

If the density of the fluid is known at the temperature of the viscosity measurement, then the Newtonian viscosity, η, in mPa. s, is calculated using the equation:

$$\eta = \nu \times \rho$$

Were,

ρ = density of the liquid (g/mL)

BROOKFIELD VISCOMETER

Figure 4: Brookfield Viscometer

It is a widely used viscometer for measuring the viscosity of non-Newtonian as well as Newtonian fluids. They are operated based on the principal of rotational viscometry and measures the torque required to rotate a spindle immersed in the test fluid at a constant speed. The resistance to the spindle's rotation (Shear stress) is directly proportional to the viscosity of fluid. It is mainly used for non-Newtonian fluids that exhibit shear-dependent viscosity. The Brookfield viscometer uses spindles of various shapes and sizes to measure the viscosity of fluids. The operation involves selecting an appropriate spindle and speed to ensure accurate readings within the instrument's operating range. Their geometry influences the shear rate applied to the fluid, allowing for accurate determination of viscosity across a wide range of applications. The minimum viscosity range is measured with the largest spindle at the highest speed, while the maximum range requires the smallest spindle at the slowest speed. Spindles are classified as types L, R, and H, designed for low, medium-to-high, and high-viscosity fluids, respectively.[18]

LOVIS 2000 M/ME

Figure 5: Lovis 2000 M/ME

Lovis 2000 M/ME is a rolling-ball viscometer, measures the rolling time of a ball through transparent and opaque liquids based on Hoeppler's falling ball principle. It measures the dynamic viscosity and relative viscosity from only 100 µL of sample. The device operates across a wide temperature range from -30 °C to 100 °C (-22 °F to 212 °F), accommodating

diverse experimental conditions. Its broad viscosity measurement range, spanning from 0.3 mPa·s to 10,000 mPa·s, makes it suitable for various applications. With high accuracy and a variable inclination angle, the micro-viscometer is ideal for testing shear-dependent flow behaviour, providing precise and reliable data for complex fluid analyses. [19]

RHEOMETER

A Rheometer is a laboratory device used to measure the way in which a viscous fluid (a liquid, suspension or slurry) flows in response to applied forces. It is used for those fluids which cannot be defined by a single value of viscosity and therefore require more parameters to be set and measured than is the case for a viscometer.[20] Depending on the functioning and geometry, Rheometer can be classified into three categories. Rheometers that regulate the applied shear stress or shear strain are known as rotational or shear rheometers, whereas rheometers that apply extensional stress or extensional strain are extensional rheometers. A rotational viscometer is a device used to determine viscosity, thixotropy, shear stress, and shear strain by applying a specific force to a sample and observing how it reacts, along with measuring the force the sample exerts back on the instrument. Rotational rheometers are classified into three types based on their measuring systems: concentric cylinder, cone and plate, and parallel plate.[21] Extensional rheometer is typically used to analyze materials undergoing tensile deformation, which commonly occurs during various processing techniques such as injection molding, fiber spinning, extrusion, blow molding, and coating flows.[22] Additionally, capillary viscometers are utilized to determine the shear viscosity and elasticity of highly viscous materials, particularly under high shear rate conditions.

Figure 6: Rheometer

ANALYTICAL METHODS REPORTED IN LITERATURE FOR DETERMINATION OF VISCOSITY IN OPTHALMIC PREPARATION.

Anh Vo et al., (2020) examined the impact of formulation and process parameters on the quality attributes of brinzolamide ophthalmic suspensions. They evaluated three milling techniques—probe sonication, micro-fluidization, and planetary centrifugal media milling—for manufacturing. Planetary centrifugal media milling produced the narrowest particle size distribution and was deemed the most effective lab-scale technique. They investigated the

effects of shear rate, shear time, and carbomer concentration on the suspension's rheological properties using a Box-Behnken design.[2]

Rahman et al., (2012) analyzed the impact of temperature, pH, and dilution on the viscosity of four ocular lubricants. Using Ostwald capillary viscometers, kinematic viscosity was measured at temperatures ranging from 22°C to 40°C and across pH values of 5–8. Results revealed that viscosity significantly decreased with rising temperatures and dilution but remained unaffected by pH. For instance, POLYMER SAMPLES 0.4% showed a 36% viscosity reduction between 22°C and 35°C. At 32°C, only POLYMER SAMPLES and carboxymethylcellulose sodium/glycerin retained adequate viscosity for precorneal residence. The findings highlighted viscosity's instability under physiological conditions, suggesting the need for more stable formulations.[3]

Kapadia et al., (2022) investigated the shear viscosity and temperature-dependent behaviour of 12 commercial ocular lubricants to inform eye drop prescribing and development for dry eye disease. Viscosity measurements were conducted at clinically relevant temperatures (4.3°C, 24.6°C, 34.5°C) using a rheometer. Results showed that higher temperatures reduced viscosities, with a significant average change of −48% from 4.3°C to 24.6°C and −21% from 24.6°C to 34.5°C. All lubricants exhibited shear-thinning behaviour, with viscosities well-approximated by a power-law model. The study highlighted the importance of considering rheological properties at physiological shear rates and temperatures to enhance ocular surface retention and patient comfort.[5]

Lee CH et al., (2009) reviewed the characterization of thixotropic properties, examining factors influencing these properties, including pH, temperature, polymer concentrations, polymer modifications, polymer combinations, and the addition of cations or excipients and explored the relationships between the rheological properties of thixotropic formulations and their effects on controlled drug delivery across various routes, such as oral, topical, ophthalmic, dental, and mucosal administration, as well as their pharmacological efficacy.[24]

Muhammad Akram et al., (2010) developed a new Prednisolone acetate (1%) ophthalmic suspension to improve drug contact at the site of action. The formulation was optimized based on physiological, physicochemical, and pharmaceutical parameters, with particle size maintained between 1-3 micrometres. Viscosity enhancers, preservatives, and chelating agents were used to extend transient residence time and ensure antimicrobial preservation. The results demonstrated that the new Prednisolone acetate suspension was more effective in suppressing corneal inflammation compared to a 1.0% Prednisolone phosphate solution.[25]

Uddin et al., (2017) reviewed the quality control (QC) processes for ophthalmic pharmaceuticals, emphasizing that consistent and predictable therapeutic performance is essential for drug quality. The review highlighted the role of pharmacopoeias, such as IP, BP, and USP, which provide standards and testing methods for drugs. It aimed to outline the QC tests for these ophthalmic products as required by different pharmacopoeias.[26]

Vooturi SK et al., (2020) investigated the impact of particle size and viscosity on the topical ocular bioavailability of budesonide, a corticosteroid. The suspensions were characterized for particle size, viscosity, and osmolality, and administered to rabbits. The concentration of budesonide in the aqueous humour was analyzed, with C_{max}, T_{max}, and AUC (0–6h) values. The study found that the suspensions were not bioequivalent, and higher viscosity was associated with improved bioavailability of budesonide from the micro-suspension formulation.[27]

Toropainen E et al., (2021) described the impact of particle size and viscosity on the bioavailability of indomethacin in ocular suspensions. They examined seven formulations, including experimental suspensions with two particle sizes (0.37–1.33 µm and 3.12–3.50 µm) and three viscosities (1.3, 7.0, and 15 mPa), along with one commercial suspension. Smaller particle sizes enhanced ocular absorption, as indicated by higher AUC values in the aqueous humour. Higher viscosity increased ocular absorption by 3.4–4.3-fold for suspensions with similar particle sizes. These findings highlighted that both particle size and viscosity are crucial for drug retention and dissolution, thus influencing ocular drug absorption and bioequivalence.[28]

Destruel et al., (2023) developed and evaluated an innovative in situ gelling ophthalmic drug delivery system using Gellan gum and hydroxyethyl cellulose. The study focused on the delivery of phenylephrine and tropicamide, addressing ocular administration challenges. Physicochemical and rheological properties, including gelation capacity and viscosity, were analyzed, and a novel method assessed gel resistance under simulated eye blinking. Muco-adhesion was confirmed through tensile strength and rheological synergism tests. In vivo studies on rabbits using a fluorescent dye demonstrated prolonged precorneal retention compared to conventional eye drops. The findings highlighted strong in vitro/in vivo correlations, suggesting improved ocular residence time.[29]

Vilimi et al. (2023) highlighted the significance of viscosity measurement in pharmaceutical formulations, noting its influence on stability, drug release, bioavailability, and injectability. They emphasized that traditional rotational viscometers, though widely used, face limitations in handling non-Newtonian materials like gels and require large sample volumes. Recent advances in microfluidics allow viscosity determination using sub-milliliter samples with precise shear rate control and stable temperature regulation, offering rapid and accurate analysis. Antal et al. (2022) reported that microfluidic rheology provides distinct advantages in pharmaceutical applications, particularly for injectable formulations, due to its efficiency and minimal sample requirement. Despite these benefits, the adoption of microfluidics-based viscometers in routine pharmaceutical analysis remains limited, warranting further exploration and standardization in practice. [30]

CONCLUSION:

Rheological optimization is a cornerstone in the design and development of ophthalmic drug products. The viscosity and flow behavior of formulations are not merely physical parameters, but critical quality attributes that determine stability, drug release, ocular residence time,

bioavailability, and ultimately therapeutic success. An optimal rheological profile improves patient comfort by reducing irritation, ensures ease of administration, and enhances compliance, especially in long-term therapies. Traditional viscometric approaches have provided valuable insights, yet recent advancements such as microfluidic rheology enable faster, more precise measurements using minimal sample volumes, making them highly advantageous for modern pharmaceutical research. Integrating rheological characterization at the early stages of formulation development is therefore essential for ensuring safety, efficacy, and robustness of ophthalmic dosage forms. Future research should focus on expanding the pharmaceutical application of advanced rheological tools and establishing regulatory acceptance to standardize their role in drug development.

***REFERENCES*:**

1. (PDF) Sterile Ophthalmic Preparations and Contamination Control [Internet]. ResearchGate Available from: https://www.researchgate.net/publication/265377388_Sterile_Ophthalmic_Preparations_and_Contamination_Control
2. Vo A, Feng X, Patel D, Mohammad A, Kozak D, Choi S. Factors affecting the particle size distribution and rheology of brinzolamide ophthalmic suspensions. Int J of Pharm. 2020 586:119495
3. Rahman MQ, Chuah K-S, Macdonald ECA, Trusler JPM, Ramaesh K. The effect of pH, dilution, and temperature on the viscosity of ocular lubricants—shift in rheological parameters and potential clinical significance. Eye. 2012 Oct 19;26(12):1579–84.
4. Non-Newtonian fluid [Internet]. Wikipedia, The Free Encyclopaedia. 2025. Available from: https://en.wikipedia.org/w/index.php?title=Non-Newtonian_fluid&oldid=1273623358
5. Kapadia W, Qin N, Zhao P, Phan CM, Haines L, Jones L, et al. Shear-Thinning and Temperature-Dependent Viscosity Relationships of Contemporary Ocular Lubricants. Translational Vision Science & Technology. 2022 Mar 2;11(3):1
6. 'intrinsic viscosity' in IUPAC Compendium of Chemical Terminology, 5th ed. International Union of Pure and Applied Chemistry; 2025. Online version 5.0.0, 2025. https://doi.org/10.1351/goldbook.I03140
7. Intrinsic viscosity determination [Internet]. Anton Paar. [cited 2025 Apr 14]. Available from: https://wiki.anton-paar.com/en/intrinsic-viscosity-determination/
8. Basics of viscometry [Internet]. Anton Paar. [cited 2025 Apr 14]. Available from: https://wiki.anton-paar.com/en/basic-of-viscometry/
9. Pk P, Rd R, Sr J. A review on topical ophthalmic drug delivery system: Reference to viscosity enhancer. Polymer w medicine [Internet]. 2024 Mar 27 [cited 2024 Jun 19]; Available from: https://pubmed.ncbi.nlm.nih.gov/38533624/
10. ”Hypromellose,” *wikipedia*, 13-Jan-2023. [Online]. Available:https://en.wikipedia.org/wiki/Hypromellose. [Accessed: 31-Jan-2023]

11. Sciencedirect.com. [cited 2025 Jun 16]. Available from: https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/hydroxyethyl-cellulose
12. Profile of Carbomer [Internet]. Cosmetics & Toiletries. 2013. Available from: https://www.cosmeticsandtoiletries.com/cosmetic-ingredients/rheology-thickener/blog/21837741/profile-of-carbomer
13. Jumelle C, Gholizadeh S, Annabi N, Dana R. Advances and limitations of drug delivery systems formulated as eye drops. J Control Release [Internet]. 2020;321:1–22. Available from: http://dx.doi.org/10.1016/j.jconrel.2020.01.057
14. Sigmaaldrich.com. [cited 2025 Jun 16]. Available from: https://www.sigmaaldrich.com/IN/en/product/sigma/t8761?msockid=0ec09aaeba4d69d2 01e28994bbe06857
15. ⟨911⟩ viscosity—capillary methods [Internet]. Usp.org. [cited 2025 Feb 5]. Available from: https://doi.usp.org/USPNF/USPNF_M99700_02_01.html
16. ⟨913⟩ viscosity—rolling ball method [Internet]. Usp.org. [cited 2025 Feb 5]. Available from: https://doi.usp.org/USPNF/USPNF_M6237_01_01.html
17. Ford viscosity cup [Internet]. Wikipedia, The Free Encyclopaedia. 2024. Available from: https://en.wikipedia.org/w/index.php?title=Ford_viscosity_cup&oldid=1242470597
18. Brookfieldengineering.com. [cited 2025 Jan 29]. Availabl from: https://www.brookfieldengineering.com/-/media/ametekbrookfield/manuals/obsolete%20manuals/dial%20m85-150-p700.pdf?la=en&utm_.com
19. Rolling-ball viscometer: Lovis 2000 M/ME [Internet]. Anton Paar. [cited 2025 Jan 29]. Available from: https://www.anton-paar.com/in-en/products/details/rolling-ball-viscometer-lovis-2000-mme/srsltid=AfmBOooWv5vhlm5hh0eojweHSqmMo_f6nGXzouu07NA5TLmkexEdu g
20. Rheometer [Internet]. Wikipedia, The Free Encyclopedia. 2024. Available from: https://en.wikipedia.org/w/index.php?title=Rheometer&oldid=1260771842
21. Labcompare.com. Rotational Rheometer [Internet]. [cited 2025 Feb 5]. Available from: https://www.labcompare.com/Chemical-Analysis-Equipment/602-Rotational-Rheometer/
22. Wikipedia contributors. Rheometer [Internet]. Wikipedia, The Free Encyclopaedia. 2024. Available from: https://en.wikipedia.org/w/index.phptitle=Rheometer&oldid=1260771842
23. Mir MA, Tirumkudulu MS. A viscosity measurement technique for ultra-low sample volumes. Soft Matter [Internet]. 2024;20(22):4358–65. Available from: http://dx.doi.org/10.1039/d4sm00050a
24. Lee CH, Moturi V, Lee Y. Thixotropic property in pharmaceutical formulations. J Control Release. 2009;136 (2):88–98.
25. Akram M, Syed Baqir Shyum, Shahnaz Gauhar. Development of new ophthalmic suspension of 1% Prednisolone acetate. PubMed. 2010; 23(2):149–54.

26. Uddin M, Mamun A, Kabir M, Setu J, Zaman S, Begum Y. Quality Control Tests for Ophthalmic Pharmaceuticals: Pharmacopoeial Standards and Specifications. J Adv Med and Pharm Sci. 2017, 10;14(2):1–17.
27. Vooturi SK, David, Jiban Jyoti Panda, Choi S, Kim H, Yandrapu SK. Effect of Particle Size and Viscosity of Suspensions on Topical Ocular Bioavailability of Budesonide, Corticosteroid. J of Ocular Pharmacol and Ther. 2020; 36(6):404–09
28. Toropainen E, Fraser-Miller SJ, Novakovic D, Del Amo EM, Vellonen KS, Ruponen M. Bio pharmaceutics of Topical Ophthalmic Suspensions: Importance of Viscosity and Particle Size in Ocular Absorption of Indomethacin. Pharmaceutics. 2021; 26; 13(4):452
29. P. Destruel, Zeng N, Seguin J, Douat S, Rosa FM, Baudouin C, et al. Novel in situ gelling ophthalmic drug delivery system based on Gellan gum and hydroxyethyl cellulose: Innovative rheological characterization, in vitro and in vivo evidence of a sustained precorneal retention time. 2020 Jan 25;574:118734–4.
30. Vilimi, Z., Pápay, Z. E., Basa, B., Orekhova, X., Kállai-Szabó, N., & Antal, I. (2024). Microfluidic rheology: An innovative method for viscosity measurement of gels and various pharmaceuticals. Gels (Basel, Switzerland), 10(7), 464. https://doi.org/10.3390/gels10070464