IJPSR (2026), Volume 17, Issue 1 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 July 2025; received in revised form, 13 August 2025; accepted, 27 October 2025; published 01 January 2026

EMERGING TRENDS IN *IN-SITU* GELLING NANOTECHNOLOGY FOR OCULAR DRUG DELIVERY

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Keywords:

Polymer, Bioavailability, Ocular drug administration, *In-situ* gel, Ocular diseases

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ABSTRACT: The most serious health issues facing the world today are blindness and vision impairment, which have a significant financial and societal cost. Delivering drugs to specific ocular regions is challenging due to the eye anatomical and physiological elimination mechanisms. When drugs are instilled to the eye using traditional delivery systems, their ocular bioavailability is low. These methods can avoid the ocular obstacles that currently limit the effectiveness of conventional therapies. They can also provide a longer-lasting release of the drug, which reduces dosing frequency and improves patient compliance. Drug delivery techniques based on nanotechnology, including micelles, nanosuspensions, nanoparticles, colloidal emulsions, niosomes and cubosomes offer efficient alternatives to conventional eye therapy. These devices are being used to study treatments for conditions affecting the anterior portion of the eye. The several delivery methods based on nanotechnology that are being researched for the treatment of anterior eye disorders are covered in this paper. The present and promising advancements in *in-situ* gelling as a means of delivering ocular medication were reviewed and summarized in this paper.

INTRODUCTION: The human eye, a complex organ often called the window to the soul, is divided into two primary portions, the anterior and posterior. Each of these wide divisions corresponds to a certain eye disease situation. The anterior region of the eye is impacted by conditions such as conjunctivitis, glaucoma, blepharitis, and cataracts, whereas the posterior segment is known to be affected by diabetic retinopathy and age-related macular degeneration. Over 90% of ophthalmic medications are eye drops, yet because of their quick elimination, they have a low ocular bioavailability (<5%).

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.17(1).168-177

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.17(1).168-177

This includes Complex absorption obstacles such as the blood-aqueous barrier (BAB), blood-retinal barrier (BRB), and corneal barrier, as well as enzymatic breakdown, protein binding, systemic absorption, nasolacrimal drainage, and tear turnover [1]. For ocular drug administration, reaching and maintaining the optimal drug concentration in the eye is one of the main challenges. To extend medication retention in the ocular cavity, several formulations, including ointments, gels, eye drops, and inserts, have been investigated. Although they somewhat increase corneal contact time, their broad use is constrained by problems such as ointment-induced impaired vision and low patient compliance with inserts.

Because systemic drugs that target the eye frequently have limited tissue access, intravitreal and periocular routes are more effective treatments. Conventional ocular drug delivery faces significant precorneal drug loss due to nasolacrimal drainage,

leading to low bioavailability and the need for frequent dosing. Rapid drug clearance reduces the pharmacological effect, while systemic absorption through the nasolacrimal duct can cause potential systemic toxicity. To improve ocular medication residence duration, penetration, and bioavailability, a variety of delivery technologies have been developed in permeability enhancers, prodrugs, and carriers such liposomes, nanoparticles, and microneedles. Among these, *in-situ* gelling systems show promise by forming viscous, mucoadhesive gels upon exposure to stimuli like pH, temperature, or ions, improving drug retention and bioavailability on the eye's surface [2].

Anatomy of Eye: The eye is a sophisticated optical device that transforms light into electrical impulses by focusing and capturing it to create images. It is made up of three layers: the center pigmented layer, which comprises the choroid, ciliary body, and iris; the inner layer, which houses sensory components; and the outer fibrous sclera, which shields the eye and contains the transparent cornea **Fig. 1**. The concentration of medication in the aqueous humor is mostly determined by corneal permeability. Barrier resistance is mostly dependent on the stroma, epithelium, endothelium, Bowman's membrane, stroma, and Descemet's membrane, out of its six layers. While the lipoidal endothelium offers little barrier to drug diffusion, the epithelium restricts transcorneal diffusion for the majority of hydrophilic medicines.

The thin, vascularized mucous membrane that borders the inner eyelids and covers the anterior sclera is called the conjunctiva. The conjunctiva collects much more tear fluid than the cornea when medicine is administered topically. Its goblet cells create a mucus layer that acts as an infection-prevention barrier while hydrating, cleaning, and lubricating the corneal and conjunctival surfaces.

Aqueous humor, the transparent fluid in the eye's anterior and posterior chambers, nourishes the cornea, removes waste, and maintains intraocular pressure to preserve the cornea's shape. It has a pH of 7.2 and high ascorbate content. The sclera, the white part of the eye, is elastic and collagen-based, allowing higher permeability to hydrophilic substances than the cornea and conjunctiva. The retina, a complex structure of vascular, glial, and neural cells, acts as a significant barrier to drug delivery, especially for larger molecules [3].

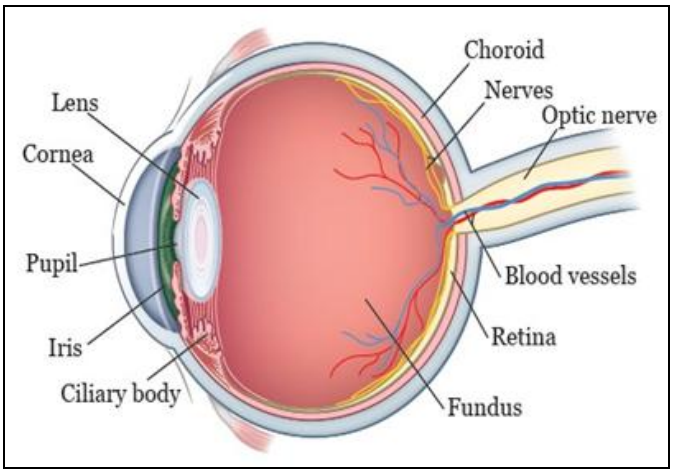

FIG. 1: STRUCTURE AND FUNCTION OF EYE

Diseases Affecting Ocular System:

Conjunctiva: eye is the inflammation of the conjunctiva. Conjunctivitis is commonly caused on by allergies, and chemicals. Contact lens patients are more susceptible to allergic conjunctivitis, especially if they don't change their lenses regularly. Staphylococcal, streptococcal, and infectious viruses that grow during the common cold are responsible for the majority of cases of infectious conjunctivitis [4].

Fungal Keratitis: Since a healthy cornea normally resists fungal infections, fungal keratitis happens when corneal damage occurs. Fungi such as Candida glabrata and Candida albicans are the cause of it. Fungi are responsible for 40% of cases of infectious keratitis in impoverished countries. Systemic diseases like diabetes or HIV as well as ocular variables like contact lenses or trauma are risk factors. Corneal ulcers, redness, blurred vision, and stromal infiltrates are among the symptoms, which are frequently connected to inflammation and changed miRNA expression. Bacteria, viruses, and Acanthamoeba can also cause infectious keratitis [5].

Glaucoma: A group of disorders known as glaucoma can damage and eventually cause blindness by gradually destroying the optic nerves. Open-angle glaucoma is more prevalent and long-lasting than closed-angle glaucoma, which is painful and acute. Early detection and treatment are essential for preventing vision loss [6].

Cataract: They are caused by cloudiness in the lens of the eye, and risk factors include UV exposure, smoking, poor diet, heredity, and diabetes. There are three forms of cataracts: posterior subcapsular, cortical, and nuclear [7].

Retinoblastoma: Unilateral (60%) retinoblastoma is caused by mutations in the RB1 tumor suppressor gene, which codes for the retinoblastoma protein. According to recent research, the development of angiogenic blood vessels and the release of proangiogenic substances are essential for both its advancement and management [8].

Diabetic Retinopathy (DR): Diabetic retinopathy (DR) affects all type I diabetics and 60% of type II diabetics after 20 years. It results from oxidative damage and inflammation caused by pro-inflammatory mediators in hyperglycaemic conditions. DR is classified into proliferative and non-proliferative types, both leading to gradual retinal deterioration [9].

The Ocular Administration Routes [10-13]:

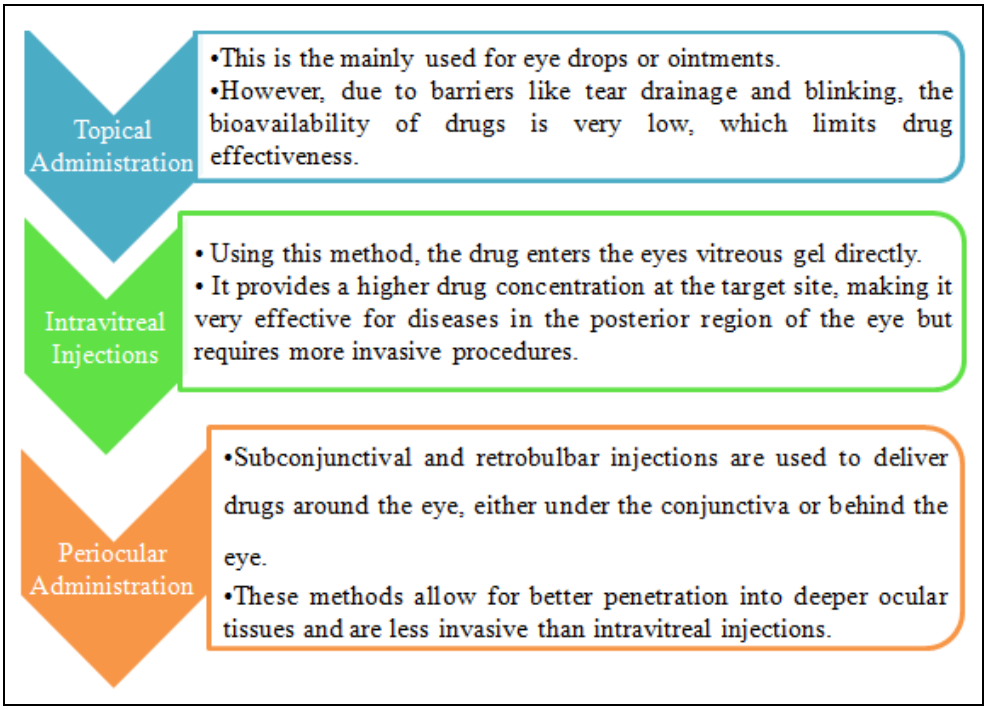

FIG. 2: ROUTES OF OCULAR DRUG ADMINISTRATION

***In-situ* Gelling System:** Ophthalmic *in-situ* gelling is made of environmentally sensitive polymers that will undergo structural changes in response to slight variations in environmental parameters such as pH, temperature, and ionic strength. Through delayed drug release, these gels enhance patient compliance through enhancing bioavailability, reducing dosage frequency, and reducing systemic absorption.

Significance of *In-situ* Gelling Systems: The 'Sol-Gel transition' that takes place while n-situ gels are administered allows for regulated and extended drug release. The required dosage and frequency of administration are reduced by the delayed medication release. *In-situ* gels precise dose and controlled drug release minimize adverse effects and prevent drug aggregation. Improved bioavailability and a decrease in the amount of medication needed. Gel formation promotes longer medication retention and better tissue contact. *In-situ* gel systems improves patient adherence.

The *In-situ* Gelling Technique has the Following Advantages over Traditional Ocular Formulations: *In-situ* ocular gels are a novel and promising method of ocular medication administration since they have many advantages over traditional ocular formulations.

Minimized Systemic Absorption: The *in-situ* ocular gels reduce the chance of systemic

medication absorption because they can remain localized inside the eye and on the ocular surface.

Prolonged Retention: One of the main advantages of in situ ocular gels is the ability to change from a liquid to a gel-like phase on contact with the ocular surface.

Increased Bioavailability: Improved drug absorption and bioavailability are made possible by the extended contact time that in situ ocular gels provide. A more regulated and extended delivery profile is made possible by the gel's sustained release of the drugs, which minimizes the need for regular administration and enhances the therapeutic effects.

Improved Patient Adherence: As they are quickly disappear from the eye, conventional ocular formulations must to be administered constantly. By lowering the frequency of administration, in situ ocular gels can increase patient compliance.

Enhanced Therapeutic Effect: Improved therapeutic efficacy can arise from in-situ ocular gels' prolonged drug release. This is especially helpful while treating long-term eye disorders, because maintaining a steady drug concentration is essential to effectively managing this condition.

Role of *In-situ* Gelation for Ocular Drug Delivery: The anterior regions of the eye, where tight junctions prevent drug penetration, might be possible with in-situ gelling. Longer medication exposure and better penetration into the internal compartments of the eye. When in situ gels come into contact with the ocular surface, they change phases from a liquid to a gel-like condition, which enables the treatment remain inside the junctions for prolonged periods of time. Drug adhesion to the ocular surface is additionally improved by the viscoelastic nature of *in-situ* gels, which enhances drug penetration through tight junctions. *In-situ* gels can be formulated with specific polymers and additives to enhance medication delivery. This method allows for targeted drug administration, reducing the possibility of systemic absorption and potential adverse effects.

Mechanisms of Gelling System: Temperature, pH, and ion-activated systems are some of the factors that can lead to *in-situ* gel formation. Polymers with alkaline groups that transition from sol to gel as the pH changes are used in pH-induced systems. Ionic concentration changes, usually brought on by tear fluid cations like Na+, Mg2+, and Ca2+, are the basis of ion-activated systems, also known as osmotically created gels. Photo-polymerization and enzymatic cross-linking are further methods[14]. There are numerous techniques for in-situ gel medication delivery.

Approaches for *In-situ* Gel Drug Delivery:

Thermally Trigged System: When it comes to environment-sensitive polymer process, thermosensitive polymer hydrogels are arguably the greatest extent researched class in drug formulation development. One appealing method for approaching in-situ formation is the usage of polymers, where the temperature increase causes the transition from sol-gel. For such systems, ambient and physiological temperatures represent the appropriate critical temperature range. This allows for clinical manipulation and eliminates the need for an external heat source the body itself serves as the trigger in order to activate the trigger [15].

pH Controlled *In-situ* Gelation Systems: This *in-situ* gelation is made up of pH-sensitive polymers, which are polyelectrolytes with an alkaline group that react to changes in the surrounding environment by either accepting or releasing protons. When the pH is lower (4.4), the mixture exists as a standard solution, but at pH 7.4, which is the pH of tear fluid, it gels. In ophthalmic preparation, polyacrylic acid, Carbopol 940and cellulose acetate phthalate are the most often utilized pH-responsive polymers [16].

Ion-triggered Gelation System: Ion activated in-situ gelaion devices produce a gel on the surface of the eye that extends corneal contact duration by reacting with the cations in tear fluid. In ocular formulations, ion-activated polymers such gellan gum and sodium alginates are frequently utilized [17].

Multi-responsive Gelation System: Combining polymers with different gelling approaches has recently enhanced ocular *in-situ* gelling systems, improving patient compliance and therapeutic efficacy. Using sodium alginate (ion-activated) and methylcellulose (pH-activated), for example, a

sparfloxacinloaded in-situ gel remained in sol form at pH 4.7 and converted to gel at pH 7.4. Compared to eye drops, this formulation showed an important increase in corneal permeability in *ex-vivo* testing and prolonged drug release over 24 hours [18].

Nanocarrier-Based Drug Delivery Systems: To treat eye diseases, nanocarriers such as liposomes, noisomes, dendrimers, nanosuspensions, nanoemulsions, nanoparticles, and micelles have been developed. While these nanoocular delivery systems have greater bioavailability, their efficacy and safety depend on careful excipient selection and formulation processes.

Composition of *In-situ* Gel: The main components of ocular delivery nanocarriers consist of polymers, lipids, stabilizers, and chemical compounds (drugs, peptides, or phytochemicals).

TABLE 1: COMPOSITION OF *IN-SITU* GEL

Sr. no	Pharmaceutical Agent	Examples	Ref. no
1	Bioactive Agent	Dicolfenac, azithromycin, moxifloxacin, ciprofloxacin, gemifloxacin, vancomycin, voriconazole, Amphotericin B, acyclovir, curcumin, glycyrrhizin, naringenin.	19-22
2	Polymers	Chitosan, alginate, gelllan gum, hydroxypropyl methylcellulose, polyethylene glycol, polylactic co glycolic acid, polyglycolic acid, polyvinyl alcohol, polyacrylic acid.	23
3	Lipids	Triglycerides, cholesterol, stearic acid, oleic acid, phospholipids.	24
4	Surfactants	Tween, span, poloxamers, propylene glycol, glycerol, ethanol.	25

Ocular Nanomedicine Delivery Systems: Ocular nanomedicine delivery systems used to treat eye disorders are shown in **Fig. 3.**

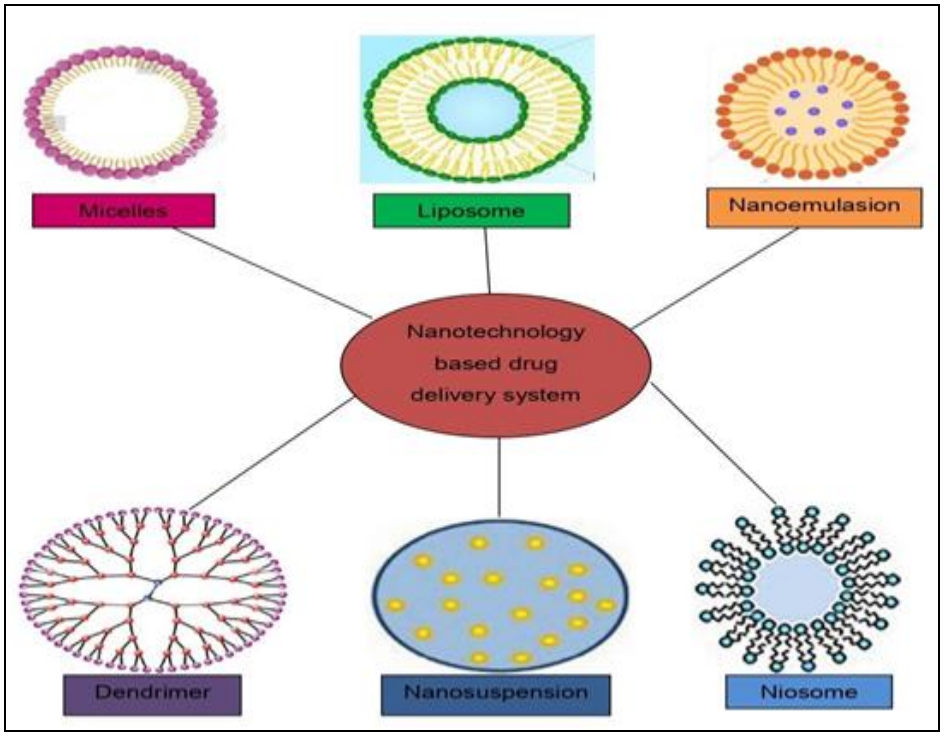

FIG. 3: NANOMEDICINE DELIVERY SYSTEMS FOR OCULAR APPLICATION

Nanomicelles: Colloidal carrier systems known as micellar system. When a specific concentration or temperature is reached, amphiphilic surfactants, also known as diblock polymers, self-assemble in liquids to form micelles. In an aqueous solution, normal micelles function well as carriers for hydrophobic medications, while reversed micelles can be used to transport hydrophilic pharmaceuticals. Micelles are a suitable option for medications that target the ocular tissues because they increase the permeability of pharmaceuticals administered topically to the cornea [26].

Nanosuspension: Colloidal systems containing insoluble drug particles dispersed in a medium and stabilized with polymers or surfactants are known as nanosuspensions. Aqueous dispersions of hydrophobic medicines are formulated and delivered to the intraocular tissues using nanosuspensions. Stabilizers, whether they natural, synthetic, or hybrid, are frequently employed in the creation of ocular nanosuspensions. The drawbacks of nanosuspensions in treating ocular illnesses include physical instability (e.g., sedimentation) and toxicity due to surfactant usage. Better bioavailability was demonstrated by the polymeric nanosuspension [27].

Colloidal Emulsions: Water colloidal dispersions in oil either oil within water that are stabilized by a surfactant and have thermodynamic stability. In terms of formulation elements, microemulsion and nanoemulsion are comparable, but their stability is different. Nanoemulsion is thermodynamically unstable even though it is thermodynamically stable [28].

Nanoparticles: Nanoparticles are frequently utilized to deliver treatments to the anterior eye because they can target particular ocular tissues and get beyond physiological barriers. Their diameters range from 50 to 400 nm. Nanoparticles are often coated with mucoadhesive polymers like chitosan, polyethylene glycol, or hyaluronic acid to improve the nanocarrier's residence time on the cornea and conjunctiva. An innovative eye drop made of cerium oxide-loaded glycol chitosan nanoparticles [29].

Liposomes : Liposomes are hydrophilic core-containing bilayered vesicular structures made of phospholipids. Based on the size and quantity of bilayers, liposomes can be divided into several kinds. These three kinds of liposomes are multilamellar, large unilamellar, and tiny unilamellar. They are very compatible with biological systems because of their structure, which is comparable to that of cell membranes. Liposomes have generated a lot of interest because of their biocompatibility and biodegradability. Liposomes can also be used to distribute ophthalmic medications that have a high molecular weight and limited solubility [30].

Dendrimer: A dendrimer is a delivery device based on polymeric nanotechnology that has a branching structure structured like a star. These nanosystems operate as arise surface groups and have strong drug encapsulation and conjugation capabilities. Pharmaceutical active substances can be conjugated to the dendrimer's surface or contained in its core. The functional groups connected to the polyamidoamine dendrimer carboxylic and hydroxyl determine the dendrimer generations (G1, G2, G3, G4, and G5). Dendrimers are advantageous because to their tiny size, easy preparation, drug targeting, and potential to be functionalized. Furthermore, dendrimers are great drug delivery vehicles for the eyes because of their monodispersity, high encapsulation rate, and enhanced aqueous solubility. However, there are a few disadvantages to using dendrimers in ophthalmology [31].

Niosomes: Niosomes are amphiphilic non-ionic surfactant bilayers assembled into stable vesicular delivery systems. Because non-ionic surfactants are used, they are biocompatible and have low toxicity. As such, they present a great deal of promise as superior medication delivery carrier systems for the eyes. In addition, niosomes have been used for improved medication bioavailability, prolonged drug release, and targeted administration. Azithromycin-loaded chitosan-coated niosomes have also been studied as a possible drug delivery mechanism to boost the antibacterial agent's retention duration and ocular bioavailability. They created the chitosan-coated azithromycin niosomes using the thin film hydration process [32].

Marketed Formulations of Conventional Ocular Dosage Form:

TABLE 2: COMMONLY USED OCULAR MEDICATIONS

Ocular Dosage Form	Marketed Formulation	Drug	Indication	Advantages	Disadvantages
Solutions	Betnisol N Ciplox	Betamithasone Ciprofloxacine	Eye infection Conjunctivitis	Convenient. No effect on vision of patient.	Non-sustained action. Rapid drainage.
Suspensions	Pred Fort	Prednisolone	Anti-allergic	Patient	Loss of both solution

	Nevanac	acetate Nepafenac	Anti-inflammatory	compliance. Slow dissolution of drug.	and suspended solids. Performance depends on drug properties.
Emulsions	Restasis Enpred	Cyclosporine Difluprednate	Dry eye	Prolonged release of drug from vehicle.	Patient noncompliance. Blurred vision.
Ointments	Acivir eye Chloromycetin	Acyclovir Chlorampthenicol palmitate	Eye infection Conjunctivitis	Improve drug stability. Inhibition of dilution by tears.	Poor patient compliance. Blurred vision.
Gels	GenTeal	Hydroxypropyl methylcellulose	Dry eye	Less blurred vision. Comfortable.	No rate control on diffusion. Matted eyelids after use.

Evaluation of *In-situ* Gel[33-36]:

***In-vitro* Dissolution Study:** Dialysis membrane can use to *in-vitro* dissolution study. The formulations were administered at 37°C in 500 ml of water. 5 ml samples were collected out at specified times, replaced with new medium, and to a UV-visible spectrophotometer analysis to determine the drug content. To determine the drug release kinetics and mechanism, the data was entered into mathematical models (zero-order, first-order, and Higuchi).

Viscosity and Rheological Study: This is a crucial metric for assessing the in situ gels. The Brookfield rheometer used to evaluate these characteristics of in situ forming drug delivery systems.

***In-vitro* Diffusion Studies:** In *in-vitro* diffusion tests, the drug release profile from formulations is determined using a Franz diffusion cell. The buffer solution is poured into the receptor compartment, which is kept at 37°C ±1°C and continuously stirred. The donor and receptor compartments are separated by a cellophane membrane. To prevent exposure to light, the donor cell is wrapped in aluminum foil and sealed with paraffin. To maintain sink conditions, 5 ml aliquots of buffer are taken out at predetermined intervals, replaced with new buffer, and subjected to spectrophotometric analysis. The drug release mechanism from in-situ gels is assessed using the Korsmeyer-Peppas equation and Higuchi's equation ($Q = Kt^{1/2}$).

Gel Strength: Based on the process of the gelling agent, a rheometer may assess gel parameters by making a certain volume of gel in a beaker from the sol form. A probe is gradually placed into the gel as the beaker filled with gel is raised at a predetermined pace. As the probe descends to varying depths beneath the gel surface, variations in its load are recorded.

Sol-Gel Transition Temperature: To determine the gelation temperature, we employed the tube tilting approach. Two milliliters of the chilled mixture were poured into a test tube. Gelation was defined as the point at which the formula's meniscus stopped moving when tilted through a 90-degree angle.

Gelling Capacity: A simulated tear fluid (STF) comprising a suitable quantity of distilled water, 0.67 g of sodium chloride, 0.2 g of sodium bicarbonate, and 0.008 g of calcium chloride dehydrate was used to test the gelling capacity. One hundred milliliters. We put two milliliters of freshly prepared STF in a test tube, added one drop of the solution, and let it equilibrate at 37^0 C. We visually examined the gel formation in addition to timing the gelation.

Irritation Studies: Six Albino rabbits participated in a Draize irritation experiment. The rabbit eye, or lower cul-de-sac of the conjunctiva, received 0.04 millilitres of the optimum formula. For a few seconds after application, the eyes were closed. After exposure, the rabbits' eyes are examined 1, 24, 48, and 72 hours later. The ocular abnormalities were evaluated using a grading system that takes into account changes to the iris, conjunctiva, cornea, redness, edema, wetness, and eyelids.

Bioavailability Study: Animals such as rats or rabbits that have been fasted for the whole night are used in pharmacokinetic research. The formulation is applied subcutaneously or intramuscularly, and 0.5 ml of blood is drawn at several points in time.

To determine the plasma drug concentrations, these samples are deproteinized with acetonitrile and subjected to analysis utilizing methods such as UV spectroscopy, mass spectrometry. Pharmacokinetic characteristics, including mean residence time, time to attain maximum concentration (tmax), and maximum plasma concentration, can be computed from the data.

Characterization of Drug Delivery Systems Based on Nanotecnology [37, 38]: Effective ocular medication delivery requires physicochemical and biological characterization, as well as formulation and process parameter optimization. This involves assessing particle size, entrapment efficiency, drug release, stability, and safety.

Particle size: Particle size are important characteristics of nanocarriers and important factors that affect their physical stability. Through dynamic light scattering, photon correlation spectroscopy is frequently used to investigate these characteristics [64]. Particles less than 10 μm should be used for ocular delivery because they are more easily absorbed by corneal epithelial cells, penetrate the mucin layer of the tear film more quickly, and cause less discomfort [65]. Although they are eliminated more quickly because they dissolve more quickly in tear fluid, smaller nanoparticles have higher aqueous humor absorption. Excipients and formulation techniques affect particle size.

Zeta Potential: A crucial component of nanoformulation stability and biological system interaction is zeta potential. Positively charged particles improve contact with the negatively charged ocular surface, while high values (> ±30 mV) guarantee stability through electrostatic repulsion. Through steric processes, particles having a zeta potential of less than 30 mV can also become stable.

Surface Morphology: Nanoparticle toxicity, cellular uptake, and biodistribution are all impacted by their surface shape. The best nanoparticles for improving medication performance are spherical ones. Transmission electron microscopy (TEM) offers information on internal structure, shape, and size, whereas scanning electron microscopy (SEM) shows surface structure and morphology.

Lipid Crystallinity: Powder X-ray diffractometry and differential scanning calorimetry are frequently used techniques to investigate the thermal behaviour and crystallinity of lipid nanoformulations. Lipid nanoparticle stability, drug loading, and release are all impacted by crystallinity Drug ejection during storage is one example of instability brought on by highly crystalline lipids.

Thermal Analysis: Using Shimadzu software for diffraction scanning calorimetry analysis. DSC scans of the every sample was weighed (10 mg) and heated between 50^0 and 300^0c at a scanning rate of 100 c/min while being supplied with dry nitrogen at a flow rate of 100 ml/min. For every sample, aluminum pans and lids were use. The DSC temperature scale and enthalpy Response were calibrated using pure water and indium.

Entrapment Efficiency: Entrapment efficiency in nanoformulations is assessed by centrifuging the entrapped medication for 10–30 minutes at 10,000–20,000 rpm. For high-dose formulations, high entrapment efficiency permits greater drug-to-excipient ratios, guarantees continuous drug release, and shields the drug from degradation. With drug solubility being the primary factor controlling drug loading, this improves biocompatibility.

Permeability Studies: The goal of developing nanocarriers is to provide prolonged and regulated medication delivery. A dialysis membrane containing phosphate buffer (pH 7.4) or artificial tear fluid is used as the release medium in in-vitro and ex-vivo investigations, which frequently include Franz diffusion cells. The membrane is continuously shaken at 37°C. Drug permeation analysis is used to determine parameters like the apparent permeability coefficient and steady-state flow.

Ocular Bioavailability: Topical ocular administration, which significantly boosts drug bioavailability, depends on ocular retention. Methods such as fluorescence imaging, gamma scintigraphy, and surface plasmon resonance spectroscopy are frequently employed for the *in-vivo* assessment of eye retention in nanoformulations.

Accelerated Stability Study: Nanocarrier stability problems include flocculation, creaming, coalescence, sedimentation, and Ostwald ripening. Changes in lipid crystallinity can cause physical instability in lipid nanoformulations.

Toxicity Study: Ocular epithelial cells can be killed by prolonged usage of certain cationic lipids, which are frequently used in nanoformulations. Ocular toxicity is detected by HEM-CAM test. A cytotoxicity assay measures the number of living cells after human corneal epithelial cells are grown with the test formulation for a few hours.

CONCLUSIONS: The eye is the most important and sensitive organ. Improved ocular bioavailability and therapeutic efficacy with less systemic absorption and toxicity are suggested by the majority of cytotoxicity and irritability studies that were analysed, which revealed no significant toxicity or negative effects from in-situ gel administration. Furthermore, *in-situ* gel may increase patient compliance because of its capacity to sustain medication release and reduce the frequency of administration. Polymers that are sensitive to pH, temperature, and ion concentration are used in *in-situ* gel formulations; combinations of stimuli-responsive polymers improve therapeutic efficacy and patient compliance.

Future formulations must concentrate on lowering dosage and administration frequency, enhancing drug release and action, extending eye contact, and limiting side effects, even though nanotechnology-based approaches have improved ocular drug delivery.

Future research must keep an eye on all the viewpoints of the usage of nanoformulations because of the stringent rules needed for the approval of ophthalmic medicines, even if some of these formulations are presently undergoing clinical trials.

ACKNOWLEDGEMENTS: The authors are thankful to Dr. Shivajirao Kadam College of Pharmacy Kasabe Digraj, India. The authors wish to acknowledge the support and contributions that facilitated the completion of this work.

CONFLICT OF INTEREST: The authors have no conflicts of interest regarding this investigation.

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How to cite this article:
Motugade S and Bhingardeve D: "Emerging trends in *in-situ* gelling nanotechnology for ocular drug delivery". Int J Pharm Sci & Res 2026; 17(1): 168-177. doi: 10.13040/IJPSR.0975-8232.17(1).168-177.