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In Situ Gelling Ophthalmic Systems Containing Herbal Bioactive: A Novel Approach for Ocular Therapy

Archana Shaha¹, Anuradha Chivate^{2*}, Niranjan Chivate³

¹PhD Research Scholar, Krishna Vishwa Vidyapeeth, Krishna Institute of Pharmacy, Karad- 415539, Maharashtra, India

¹Assistant Professor, Department of Pharmacy Vishwakarma University, Kondhwa, Pune-411048, Maharashtra, India

²Department of Pharmacology, Krishna Institute of Pharmacy, Krishna Vishwa Vidyapeeth (Deemed to be University), Karad- 415539, Maharashtra, India.

³Department of Pharmaceutics, Krishna Charitable Trust's Krishna College of Pharmacy, Karad- 415539, Maharashtra, India

ABSTRACT: The globally known ocular diseases like dry eye syndrome, glaucoma, cataracts, conjunctivitis, diabetic retinopathy, and age-related macular degeneration—are leading causes of vision impairment. Conventionally available ocular formulations suffer from physiological barriers, such as high tear turnover, nasolacrimal drainage, and poor corneal permeability, resulting in low ocular bioavailability and poor patient compliance due to frequent dosing. Phytoconstituents offer significant therapeutic value via antioxidant, anti-inflammatory, antimicrobial, anti-angiogenic, and neuroprotective properties. Ophthalmic formulations that gel in situ offers enhanced precorneal residence time, improved ocular bioavailability, sustained drug release, reduced frequency of dosing and improved patient compliance. To provide a comprehensive review of phytoconstituents-loaded ocular in situ gelling systems, focusing on various methods used for formulation development, emerging polymers used and future perspectives for clinical translation and commercialization. A thorough literature survey regarding ocular in situ gelling systems incorporating phytoconstituents was synthesized and utilization of emerging smart polymers for in-situ ocular gel was discussed. Phytoconstituent based ocular in situ gels surmount the major ocular drug delivery constraints by enhancing precorneal residence time, sustained drug release, improving ocular bioavailability, and minimising dosing frequency to increase patient compliance. Advanced drug delivery techniques like nanotechnology, smart stimuli-responsive polymers, and AI optimization will aid to unlock the full therapeutic potential of phytoconstituents and facilitating their successful commercial translation

1. INTRODUCTION

1.1 Overview of Ocular Drug Delivery

The eye is a specialized organ that is highly protected to preserve the vision and prevent the entry of foreign materials. These barriers make it challenging to deliver drugs effectively. Ocular drug delivery is the administration of drugs to the eye for treating diseases of the anterior segment (cornea, conjunctiva, aqueous humor, iris and ciliary body) and posterior segment (retina, choroid, vitreous humor and optic nerve). The easiest and least invasive route of administration, with the highest acceptance by patients, is topical instillation as eye drops. [Ahmed I, Patton TF, 1985; Ahmed S et al 2023] Nonetheless, the effectiveness of conventional ophthalmic formulations is often hindered by the distinctive barriers of the eye's anatomy and physiology. The mechanisms of tear turnover, blinking, lacrimation, corneal epithelial tight junctions, conjunctival clearance, and nasolacrimal

drainage rapidly deplete administered drugs from the precorneal area at the ocular surface. As a result, the amount reaches the tissue to which the drug is targeted. Traditional eye drops make it to the eye to less than 5%. For delivery to the posterior segment, the outcome is poorer due to the blood-ocular barriers and their impact on bioavailability. The insufficient therapeutic effectiveness of drugs is due to impaired permeation through these barriers. Ocular drug delivery, depending on the target tissue and disease condition, should be carried out through topical, systemic, periocular, intravitreal and intracameral routes. Topical administration is the preferred route of administration for anterior segment disorders like conjunctivitis, glaucoma, dry eye syndrome, and corneal inflammation. Nevertheless, topical formulations are often not effective for diseases of the posterior segment like age-related macular degeneration and diabetic retinopathy due to poor penetration through ocular tissues. To solve the limitation of the eye, nanoparticles, liposome, niosome, ocular inserts, contact lens drug delivery system, and in situ gel forming system etc. have been developed. In situ gelling systems have garnered considerable attention because of their capacity to undergo a sol-to-gel transition in response to a physiological stimulus like pH, temperature, or ionic composition of the tear fluid. Sustained-release systems increase precorneal residence time, reduce nasolacrimal drainage and enhance drug bioavailability. The incorporation of herbal bioactives in situ gelling systems offers additional therapeutic advantages due to their antioxidant, anti-inflammatory, antimicrobial, and neuroprotective activities, making them a potential therapeutic agent in the management of ocular disorders. Consequently, the pursuit of new ocular drug delivery systems that can bypass both anatomical and physiological barriers continues to be an important aspect of pharmaceutical research. Herbal bioactives incorporated in in situ gelling ophthalmic systems can suitably augment therapeutic effectiveness with better patient compliance along with prolonged treatment of ocular disorders. [Ali Z et al 2023; Almeida H, 2020]

1.2 Global Burden of Ocular Diseases:

Eye disorders are a major public health problem globally. It is one of the leading causes of visual impairment and blindness worldwide. The World Health Organisation (WHO) estimates that at least 2.2 billion people around the world have a vision impairment or blindness. Of these, more than one billion cases could have been prevented or are still left untreated. The growing elderly population, accelerating urbanization, ever-increasing environmental pollution, extended hours on digital screens and rising numbers of patients suffering from chronic diseases like diabetes and hypertension are leading causes of eye disorders. Visual impairment has a remarkable effect on quality of life, productivity, autonomy, and mental health. It also places a heavy burden on the socioeconomic system and on health care provision worldwide. [Al-Kinani AA et al 2022]

1.2.1. Dry Eye Syndrome:

Dry eye syndrome, or dry eye disease, is a multifactorial disorder of the ocular surface characterized by tear film instability, an increase in tear osmolarity, inflammation, and pain in the eye sphere. One of the most prevalent eye disorders, depending on age, geography, and diagnostic criteria, affects 5–50% of the world's population. The increasing prevalence of dry eye disease can be attributed to the extensive use of digital devices, environmental contaminants, wearing contact lenses, and the age-related decline in tear production. Some of the common symptoms will be burning, irritation, redness, foreign body, blurred vision, photophobia, etc. Untreated dry eye disease and chronic ocular surface inflammation may lead to corneal damage and visual disturbances. The growing incidence of dry eye syndrome is increasingly demanding ocular drug delivery systems that can offer a comforting effect for prolonged periods. [Awwad S et al, 2022]

1.2.2 Glaucoma:

Glaucoma is a progressive optic neuropathy resulting in retinal ganglion cell degeneration and optic nerve damage that can cause irreversible vision loss. Worldwide, it is the second leading cause of blindness and the leading cause of irreversible blindness. Elevated intraocular pressure (IOP) is the most important modifiable risk factor for disease progression. The global estimates show that about 76 million individuals were diagnosed with glaucoma in 2020 and is expected to rise to over 111 million by 2040 owing to population aging. Primary open-angle glaucoma is the commonest glaucoma. As the disease is normally asymptomatic in its early stages, most of the individuals are diagnosed after considerable vision loss. Chronic administration of antiglaucoma medications will be required as glaucoma is a long-term treatment which calls for patient compliance. As a result, sustained-release ophthalmic formulations are quite popular these days.

1.2.3 Cataract

Cataract refers to the progressive opacification of the crystalline lens leading to visual impairment and ocular blindness, if untreated. Cataracts continue to be the most common cause of blindness worldwide, especially in low- and middle-income countries with limited access to surgical treatment. Age-related cataract is the most common type of cataract. It is mainly associated with oxidative stress, proteins' aggregation, and age-dependent degeneration of lens fibres. Excessive exposure to Ultraviolet Radiation, smoking, diabetes, prolonged use of corticosteroids are other risk factors. Even though cataract surgery is highly successful, the rising elderly population around the world continues to add a significant burden of visual impairment globally. Recent studies have shed light on the antioxidant and anti-inflammatory potential of therapeutic agents of herbal bioactives to delay cataract onset and oxidative damage to ocular tissues. [Barar J et al, 2008]

1.2.4 Conjunctivitis

Conjunctivitis, known as pink eye, is when the conjunctival membrane becomes inflamed due to bacterial, viral, allergic or irritant causes. Clinical practice most frequent ocular disease and affect people in all age groups. Infectious conjunctivitis is very contagious and contributes significantly to consultations worldwide. The clinical manifestations consist of conjunctival hyperaemia, pruritus, tearing, mucopurulent discharge of the eye, swelling, and ocular discomfort. Even though infections usually have a limited duration, severe and recurrent infections can involve the cornea and cause vision problems. The high occurrence and reoccurrence of conjunctivitis are reasons for ocular formulations that can maintain therapeutic drug concentrations at the ocular surface for a prolonged time. [Bourne RRA et al, 2021]

1.2.5 Age-Related Macular Degeneration:

Age-related macular degeneration (AMD) is a chronic degenerative condition that affects the macula, the central part of the retina that is responsible for sharp, detailed vision. Age-related macular degeneration (AMD) is responsible for the severe visual impairment of people 50 years and older in western countries. The disease is classified broadly into dry (atrophic) and wet (neovascular) form. The dry form comprises 85–90% of cases. Several factors can put individuals at greater risk of suffering from this condition. According to current estimates, AMD affected around 196 million people in 2020 and the prevalence is predicted to greatly increase in the upcoming decades. Age-related macular degeneration (AMD) is characterized by a progressive loss of central vision. This loss of vision has a significant impact on the performance of everyday activities, including reading, driving, and recognizing faces. As a result, significant research activities are taking place to develop new ocular delivery systems that can enhance retinal drug targeting and increase therapeutic efficacy. With the concerning increase in the incidence of ocular diseases, there is an urgent need for novel ophthalmic drug delivery systems which surpass ocular barriers, enhance drug bioavailability and provide sustained effects. In situ gelling systems with herbal bioactives are one of the best strategies to overcome challenges and enhance patient compliance. [Cholkar K et al 2013]

1.3 Challenges Associated with Conventional Ophthalmic Formulations:

Although conventional formulations like eye drops, ointment and suspensions are being used commonly, they have poor therapeutic efficacy. This is due to the special anatomic and physiological make-up of the eye. Ocular preparations that are administered topically account for over 90% of the products in the market due to their ease of administration, high patient acceptance, and non-invasiveness. Nevertheless, only a small percentage of drug reaches the target ocular tissue and the drug is rapidly cleared from the ocular surface. As a result, to maintain therapeutic drug concentrations, frequent dosing is required, which may lead to less compliance and increased adverse effects. The conventional ophthalmic formulations face the challenges such as rapid tear turnover, nasolacrimal drain, poor corneal permeability, and low ocular bioavailability. [Del Amo EM and Urtti A 2023; Fernández-Albarral JA et al 2020]

1.3.1 Rapid Tear Turnover

The tear film on the surface of the eye protects against environmental irritants and pathogens. Under normal physiological conditions, the human tear volume ranges from 7 to 10 μL while the common ophthalmic eye droplet delivers approximately 30–50 μL of ophthalmic formulation. Because the conjunctival sac can hold only small volume of fluid, excess formulation is quickly removed by the eyelid's blinks and tear drainage. As the tears turnover at a rate between approximately 1–3 $\mu\text{L}/\text{min}$, the drug is constantly diluted and removed from the precorneal area. A shortening of the contact time between drug and ocular surface, along with drug loss, can occur when reflex tearing sets in due to formulation irritation. As a result, there is very little

of the given dose that remains available for absorption. The rapid turnover of tears is one of the main causes of poor ocular drug retention and thus, treatment failure.

1.3.2 Nasolacrimal Drainage

The nasolacrimal system is a key barrier to drug delivery. After topical installation, the large portion of the instilled formulation is drained rapidly via the nasolacrimal duct to the nasal cavity. The drain of the drug reduces the residence time at the ocular surface and minimizes its absorption on the cornea. At the same time, it reduces therapeutic effect, nasolacrimal drainage may also contribute to the absorption of the drug, via the highly vascularized nasal mucosa. The aforementioned effect may lead to unwanted systemic adverse events especially among subjects under chronic ophthalmic therapy (cl. antiglaucoma drug). When you use β -blockers in glaucoma, they may cause adverse effects on other body parts. For example, it can enter systemic circulation via nasal absorption. Due to this, it can result in adverse respiratory or cardiovascular effects. Reducing nasolacrimal drainage is important to improve ocular drug bioavailability and minimize systemic exposure. [Flaxman SR et al 2017]

1.3.3 Poor Corneal Permeability:

The main route for drug absorption into the anterior segment of the eye is cornea. However, the unique multi-layer structure of cornea acts as an effective barrier for drug penetration. The cornea has three broad layers, namely epithelium, stroma, and endothelium. The cells of the exterior epithelium form a tight junction to impede the passage of hydrophilic molecules. On the contrary, the stromal layer has a high level of hydrophilicity preventing the diffusion of lipophilic agents. Successful penetration of the cornea requires a balance between hydrophilic and lipophilic properties. Drugs with undesirable physicochemical characteristics have poorly corneal permeability and cannot reach therapeutic concentrations in ocular tissues. Furthermore, corneal permeability can also be influenced significantly by all other factors like molecular weight, solubility, and ionization state. As a result, corneal barriers are one of the toughest obstacles to achieve for ophthalmic drug delivery research. [Flaxman SR et al 2017]

1.3.4 Low Ocular Bioavailability:

The reason for low ocular bioavailability is the various precorneal and corneal barriers encountered by conventional ophthalmic formulations. The bioavailability of a drug given into the eye is only 5%. Most of the drug is lost due to tear turnover, blink action, nasolacrimal drainage action and excessive absorption by surrounding non-target tissues. Due to the low bioavailability of conventional eye drops, the patient often has to administer the eye drops frequently. Constant use of a drug may not only increase the treatment cost and affect patient adherence to treatment but also increase exposure to preservatives which can cause ocular irritation and toxicity. Additionally, inadequate drug concentrations at the target site may hamper therapeutic efficacy, especially for chronic ocular diseases such as glaucoma, dry eye disease and ocular inflammation. In order to overcome these challenges, substantial efforts have been made to develop new ophthalmic drug delivery systems such as nanoparticles, liposomes, ocular inserts, contact lens-based systems and in situ gelling systems. Among these strategies, in situ gelling systems show promising application as the precorneal residence time can be enhanced, followed by loss of dosage, increased corneal permeation, and enhanced ocular bioavailability. Overall, the natural limitation of conventional ophthalmic formulations hampers effective ocular therapy. To enhance the therapeutic efficacy and patient compliance innovative delivery systems with extended residence time that augments bioavailability of the ocular drug is necessary. [Gaudana R et al, 2010]

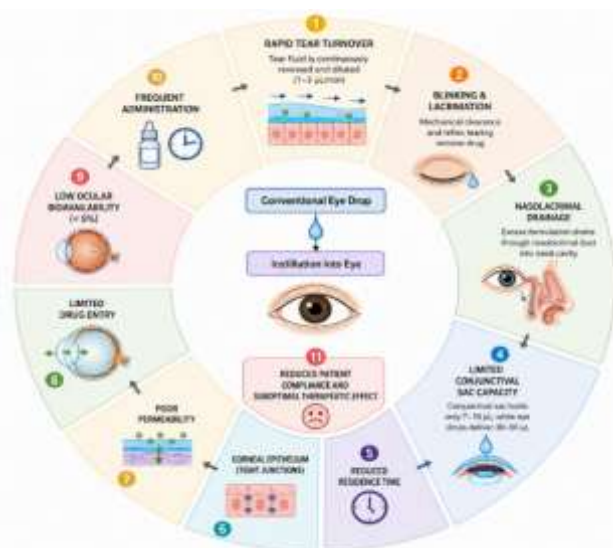


Figure 1. Barriers affecting ocular drug delivery and fate of conventional ophthalmic formulations following topical administration.

Table 1. Challenges Associated with Conventional Ophthalmic Formulations and Their Impact on Drug Delivery Performance [Gaudana R, Jwala J et al 2009; Ghate D, Edelhauser HF, 2006]

Challenge	Mechanism	Impact on Drug Delivery
Rapid Tear Turnover	Continuous renewal and dilution of tear fluid (1–3 $\mu\text{L}/\text{min}$) removes instilled drug from the ocular surface.	Reduced contact time and decreased drug absorption.
Blinking and Reflex Lacrimation	Mechanical clearance of drug solution and stimulation of excessive tear production.	Accelerated drug elimination and reduced residence time.
Nasolacrimal Drainage	Excess formulation drains through the nasolacrimal duct into the nasal cavity.	Loss of drug from ocular surface and potential systemic side effects.
Limited Conjunctival Sac Capacity	Eye can retain only 7–10 μL , whereas eye drops typically deliver 30–50 μL .	Significant drug wastage immediately after administration.
Poor Corneal Permeability	Corneal epithelium restricts hydrophilic drugs while stromal layer limits lipophilic drug diffusion.	Low penetration into intraocular tissues.
Ocular Surface Barriers	Presence of mucus layer, tear proteins, and epithelial tight junctions.	Restricted drug permeation and retention.
Blood–Ocular Barriers	Blood-aqueous and blood-retinal barriers prevent drug entry into ocular tissues.	Poor delivery to posterior ocular segments.
Low Ocular Bioavailability	Combined effect of precorneal and corneal barriers.	Less than 5% of administered drug reaches target tissues.
Frequent Dosing Requirement	Rapid drug clearance necessitates repeated administration.	Poor patient adherence and increased treatment burden.
Preservative-Related Toxicity	Long-term exposure to preservatives such as benzalkonium chloride.	Ocular irritation, inflammation, and reduced patient comfort.

1.4 Emergence of Herbal Therapeutics in Ocular Treatment

The expanding interest towards the herbal therapeutics has led to the development of alternative and complementary approaches for the management of ocular diseases. For centuries, herbal medicines are being used for the treatment of various eye disorders in traditional systems like Ayurveda, Traditional Chinese Medicine (TCM), Unani and other indigenous systems

of medicine. Recent years have also seen an increase in the scientific evidence which strongly supports the pharmacological activities of different plant-derived compounds. This has led to their quicker incorporation into modern ophthalmic formulations. The rising trend of using herbal therapeutics for the treatment of ocular diseases is mainly due to their various biological actions, good safety profiles, low cost, and ability to overcome the limitations of synthetic drugs. The onset of many ocular diseases due to redox imbalance is attributed mainly to oxidative stress, inflammation, microbial infection, and neurodegeneration. For example, dry eye disease (DED), glaucoma, cataract, conjunctivitis, diabetic retinopathy, and age-related macular degeneration are such diseases whose initiation and progression are influenced severely by these factors. Many phytochemicals have powerful antioxidant, anti-inflammatory, antimicrobial, antiangiogenic, and neuroprotective effects that can counteract these pathogenic mechanisms. [Gratieri T et al 2010; Gupta H et al 2011] Therefore causing agents considered useful in the treatment of ocular diseases. Curcumin is one of the most studied herbal substances. It is a polyphenolic component of *Curcuma longa* (turmeric). Curcumin has strong antioxidant and anti-inflammatory activities via the modulation of transcription factor nuclear factor-kappa B (NF- κ B) and cyclooxygenase (COX). Various cytokine-mediated signal pathways are regulated by curcumin action. Research shows that it is effective in the management of uveitis, diabetic retinopathy, corneal neovascularization, and age-related macular degeneration. Likewise, thymoquinone, the major bioactive component of *Nigella sativa* (black seed), has potent antioxidant, anti-inflammatory, and neuroprotective effects, and may thus have a role in preventing retinal degeneration and eye inflammation. [Gupta S and Vyas SP, 2020] Quercetin, resveratrol, berberine, lutein, zeaxanthin and epigallocatechin gallate (EGCG) are other significant phytochemicals. Quercetin has anti-allergic and anti-inflammatory effect which is useful in allergic conjunctivitis and dry eye disease. The naturally occurring polyphenol resveratrol present in grapes and berries exhibit antiangiogenic and neuroprotective activities appointed for the management of glaucoma and retinal disorders. Berberine with broad-spectrum microbiological activity may help treat eye infections. Lutein and zeaxanthin can be utilized in the progress of age-related macular degeneration. Lutein and zeaxanthin are capable of retaining for retinal protection. Lutein refers to the Xanthophylls and the zeaxanthin carotenoid. Although the herbal bioactives have a strong potential as a therapeutic product, their clinical application in the ocular therapy is usually limited to poor aqueous solubility, low stability, high precorneal elimination, and poor corneal penetration. [Hashemi H et al, 2020] Numerous phytoconstituents exhibit poor bioavailability as conventional eye drops owing to ocular barriers and rapid tear turnover. To tackle these difficulties, researchers have investigated sophisticated concepts such as nanoparticles, liposomes, niosomes, nanoemulsions, cubosomes, and in situ gelling systems. Ophthalmic polymer systems are developed to extend precorneal and ocular residence time of the drug molecules and therefore they will perform as a sustained release dosage form. In situ gelling ophthalmic systems have become more popular among these strategies because of their ability to increase precorneal residence time and give sustained release of herbal bioactives. These systems undergo a sol-to-gel transition in response to physiological stimuli like pH, temperature, or ionic composition of tear fluid. [Imam A et al, 2022] This enhances ocular bioavailability by reducing drug loss through nasolacrimal drainage. The incorporation of herbal bioactives in any delivery system imparts synergism which ensures a better bioavailability of the pharmacologically active extracts. This study's findings on the toxicity and potential therapeutic benefits of plant extracts are promising for pharmaceutical drug development with further studies and clinical trials. The utilization of advancement in ophthalmic delivery technologies along with herbal medicines will help treat chronic ocular diseases by reducing side effects and improving patient compliance. The ocular drug delivery of herbal bioactive-loaded systems might be the new land of opportunity for researchers. Research in medicines from plants with formulation science and nanotechnology will help develop newer ophthalmic products to cater to the unmet clinical needs of ocular disorders. [Koo H et al, 2011]

Table 2: Herbal Bioactives Investigated for Ocular Therapy and Their Pharmacological Activities [Kowluru RA and Kanwar M, 2007; Lee CM and Afshari NA, 2017]

Herbal Bioactive	Natural Source	Pharmacological Activity	Potential Ocular Application
Curcumin	<i>Curcuma longa</i>	Antioxidant, anti-inflammatory	Uveitis, AMD, diabetic retinopathy
Thymoquinone	<i>Nigella sativa</i>	Antioxidant, neuroprotective	Retinal disorders, dry eye
Quercetin	Fruits and vegetables	Anti-inflammatory, anti-allergic	Allergic conjunctivitis
Resveratrol	Grapes	Neuroprotective, antiangiogenic	Glaucoma, AMD

Berberine	<i>Berberis</i> spp.	Antimicrobial, anti-inflammatory	Ocular infections
Lutein	Marigold	Antioxidant	AMD prevention
Zeaxanthin	Corn, vegetables	Retinal protection	Macular degeneration
EGCG	Green tea	Anti-inflammatory, antioxidant	Corneal and retinal disorders

1.5 Scope and Objectives of the Review:

The rapid growth of ocular illnesses coupled with the drawback of regular ophthalmic preparation expanded the demand for new drug delivery systems to enhance therapeutic efficacy and patient compliance. Numerous currently existing synthetic preparations aimed for ocular disease treatment do offer therapeutic benefit but the bioavailability onto ocular surfaces being limited, increased precorneal elimination in addition to frequent dosages with adverse effects hampers the therapeutic outcomes. At the same time, increasing interest in natural therapeutics encouraged researchers to search for herbal bioactives as a safer and more biocompatible alternative for management of different eye diseases. Nevertheless, one of the major impediments in the ocular delivery of these phytoconstituents is their poor aqueous solubility, limited permeability across the cornea and quick clearance from the ocular surface. In the past few years, in situ gelling ophthalmic systems have been developed that can overcome many of the existing limitations of drug delivery. These formulations change their state from liquid to gel when subjected to specific physiological stimuli such as pH, heat or ions of tear fluid; thus, increasing precorneal residence time and result in better drug absorption. Combining these systems with herbal bioactives for sustained ocular bioavailability is one such innovative approach which can offer a dual advantage of bioavailability and bioactivity. [Loftsson T and Järvinen T,1999; Ludwig A, 2005]

The present review is an attempt to summarize the in-situ gelling systems containing herbal bioactives which have significance in ocular therapy. Review discusses anatomical and physiological barriers pertaining ocular drug delivery, requirement for prolonged ocular retention and limitations of conventional ophthalmic formulations. In addition, it also discusses critically the mechanisms and principles of in situ gel formation, various polymers used in ophthalmic gel systems and formulation strategies for the loading of herbal bioactives. The present review highlights the merit of plant-derived compounds for ocular disorders like dry eye syndrome (DES), glaucoma, cataract, conjunctivitis, diabetic retinopathy and age-related macular degeneration. Special emphasis is placed on curcumin, thymoquinone, quercetin, resveratrol, lutein, zeaxanthin, berberine and epigallocatechin gallate. Recent developments in the design of nano enabled in-situ gelling systems which include nanoparticles, liposomes, niosomes, cubosomes, nanoemulsions, etc. were reviewed to enhance the delivery of herbal therapeutics. Furthermore, the review shows various approaches for preparing and characterizing the herbal bioactive-loaded in situ gels employed like physicochemical characterization, rheological evaluation, gelation studies, drug release study, corneal permeation study, ocular irritation study and stability studies. The benefits and drawbacks of these delivery systems are evaluated, along with challenges associated with formulation development, standardization of herbal extracts, regulatory requirements and clinical translation. Finally, the review will focus on new trends and future perspectives on ocular drug delivery, including smart stimuli-responsive gels, multifunctional nanocarriers, personalized ophthalmic therapy, and AI-assisted formulation development. This summary article, through an overview of recent scientific findings as well as technological advances, will offer researchers, formulation scientists and clinicians an insight into the possible role of herbal bioactive-loaded in situ gelling systems in the delivery of ocular therapy. [Mandal S et al, 2010; Mitchell P et al, 2018]

The current review aims to provide information on ocular anatomy, physiological barriers and limitations of conventional ocular drug delivery systems. The article focuses on mechanisms for prolonged ocular retention and the in-situ gelling system that improves ocular bioavailability and in turn therapeutic efficacy. The present review discusses various polymers and stimuli-responsive mechanisms involved in ophthalmic in situ gel formation. It also describes the pharmacological activities and therapeutic potential of herbal bioactives in ocular disease management. Also, it appraises the formulation strategies, preparation methods and characterization techniques used in the development of herbal bioactive-loaded ophthalmic in situ gels. The review also discusses the benefits and shortcomings as well as the present challenges of these systems and advances in nanotechnology-based ocular drug delivery systems. Further, it identifies the research gaps, regulatory considerations, and future opportunities for the clinical translation and commercialization of herbal ophthalmic formulations. Ultimately, the review aims enhancing an evidence-based scientific approach to developing safe herbal-based ocular drug delivery systems that effective and patient-friendly. [Nabavi SF et al, 2015; Pang IH and Clark AF, 2020]

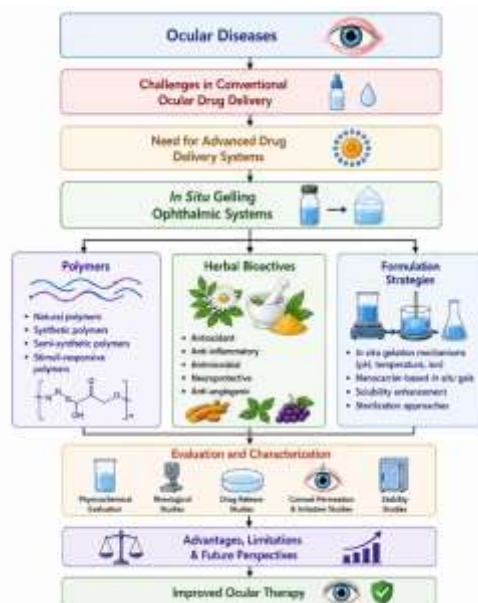


Figure 2: Scope of the Review Article

2. OCULAR ANATOMY AND NEED FOR PROLONGED OCULAR RETENTION:

2.1 Anatomy and Physiology of the Eye: The organ of sight is eye which help us to see. The retina, which is multi-layer architecture that includes various kinds of tissues and compartments, is an anatomical structure that converts light into signals which get transmitted to the brain. The diameter of human eye is nearly 24 mm, which is divided into anterior (front) and posterior (back) segments. The anatomical barriers separating these segments help to maintain the homeostasis within the eye and also affect drug uptake and distribution. A thorough understanding of the eye's anatomy and physiology is critical for developing effective drug delivery systems for the eye. Such systems are aimed at augmenting drug retention and bioavailability. [Patel A et al, 2013]

2.1.1 Anterior Segment of the Eye:

The eye's anterior segment stretches from the cornea to the crystalline lens and primarily facilitates the refractive power of the eye. The eye is composed of the cornea, conjunctiva, aqueous humor, iris, ciliary body, anterior segment, posterior segment and lens. Most conventional ocular formulations target site this. The cornea, which is the transparent outermost layer of the eye, acts as a shield against external particles and offers almost two-third of the eye's refractive power. The eye can be divided into 3 coats or layers which include the three of the following. The corneal epithelium's tight junctions restrict hydrophilic drug penetration while the stromal layer blocks lipophilic diffusion. Hence, the cornea is a significant barrier in the ocular drug delivery system. Conjunctiva is a thin, transparent, highly vascularised mucous membrane that covers the sclera and inner eyelids (palpebral conjunctiva). It is responsible for maintaining the tear film and also play an important role in the defence mechanism against infections. Due to its highly vascularised nature, drugs applied to conjunctiva may absorb systemically. A clear colourless transudate in anterior and posterior chamber of eye is called aqueous humor. It provides nutrients to avascular tissue. Because of the aqueous humor's continuous turnover, it also affects the distribution and elimination of ophthalmic drugs. The structures of the iris and ciliary body are important therapeutic targets in the treatment of the eye disease Glaucoma. The iris controls the amount of light entering the eyes by changing the size of the pupil. Meanwhile, the ciliary body produces the aqueous humour and alters the shape of the lens that allow for visual accommodation. The lens is a transparent biconvex structure located behind the iris. It helps focus incident light rays on the retina. Moreover, it aids in accommodation. Cataract development is caused by age-related changes and oxidative damage to lens proteins, which is a leading cause of non-reversible blindness globally. [Patel DK et al 2022; Patravale VB et al 2021]

2.1.2 Posterior Segment of the Eye:

The eye's posterior segment is about two-thirds of the eyeball in volume. It includes all of the vitreous humor, retina, macula, choroid, sclera and optic nerve. This section will generate and transmit visual signals to the corresponding centers in the brain. This area may be affected by significant eye diseases which are difficult to treat because of the presence of barriers limiting drug penetration. The amount of space occupied by the vitreous humor inside the eye is quite large and it occupies a huge 80% volume of the eye. Furthermore, it is a transparent jelly-like substance which is mostly made up of water along with the presence of a variety of collagen and hyaluronic acid. It maintains the shape of the eye and enables light to be transmitted to the retina. The retina is a specialized neural tissue whose overall structure and organization allows for the conversion of light energy into electrical impulses through the action of photoreceptor cells, bipolar cells, ganglion cells and other supporting neurons. Retinal diseases like diabetic retinopathy, retinal degeneration, and age-related macular degeneration (AMD) are one of the principal causes of visual disability globally. The macula, positioned at the center of the retina, allows for high acuity vision. It also enables the perception of colors. The degeneration of the macula results in a form of blindness known as age-related macular degeneration. The choroid is an area that lies between the retina and sclera. It is a highly vascularized structure which supplies the outer retinal tissues with oxygen and nutrients. In addition, it is also imperative for retinal metabolism. However, with the extensive blood flow also comes the rapid clearance of the drugs due to the same mechanism. The white outer covering of the eye is known as sclera. Sclera is made up of dense fibrous tissue and it provides support to the intraocular tissues. Scleral Route for Posterior Ocular Drug Delivery has been studied. The optic nerve is important for the communication of retinal ganglion cell visual information to the brain, and its progressive degeneration is a feature of glaucoma and many other neurodegenerative ocular diseases. The eyes' anatomy and physiology pose challenges for drug delivery to the eyes (the eye) of patients. Topical formulations may target the anterior segment successfully, but drug delivery to the posterior segment is a challenge because of the anatomical and physiological barriers. The low ocular bioavailability of drugs is due to the corneal epithelium, blood–aqueous barrier, blood–retinal barrier, vitreous humor, etc. The limitations of conventional drug delivery systems have led to the development of advanced ophthalmic drug delivery systems (nanoparticles, ocular inserts, intravitreal formulations, and in situ gelling systems) that improve drug bioavailability and retention in the ocular delivery system. These novel drug delivery systems promise improved therapeutic efficacy over their conventional counterparts. It is essential to understand ocular anatomy and physiology for the rational design and development of effective formulation which can overcome ocular barriers and optimize the treatment. [Pescosolido N et al 2014; Quigley HA and Broman AT, 2006]

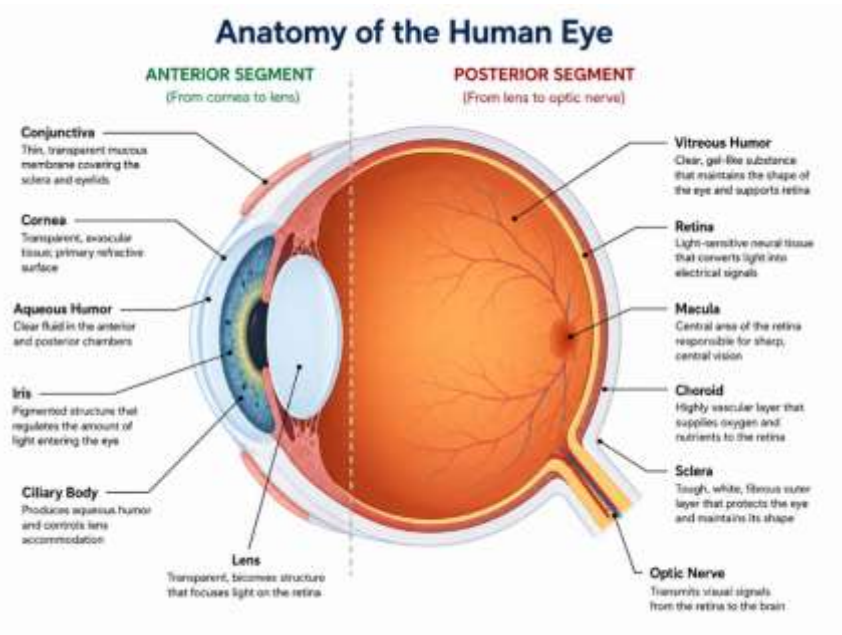


Figure 3. Anatomy of the Human Eye Showing Anterior and Posterior Segments

Table 2. Anatomical Components of the Eye and Their Relevance in Ocular Drug Delivery [Remington LA, 2021]

Ocular Structure	Segment	Function	Relevance in Drug Delivery
Cornea	Anterior	Light refraction	Major permeability barrier
Conjunctiva	Anterior	Protection and lubrication	Alternative absorption route
Aqueous Humor	Anterior	Nutrient transport	Influences drug distribution
Iris/Ciliary Body	Anterior	Light regulation and aqueous humor production	Target in glaucoma therapy
Lens	Anterior	Light focusing	Target in cataract prevention
Vitreous Humor	Posterior	Maintains ocular shape	Affects posterior drug diffusion
Retina	Posterior	Phototransduction	Target for retinal diseases
Macula	Posterior	Central vision	Target in AMD
Choroid	Posterior	Nutrient supply	Influences drug clearance
Sclera	Posterior	Structural support	Potential drug delivery route
Optic Nerve	Posterior	Visual signal transmission	Target in glaucoma

2.2 Ocular Barriers Affecting Drug Delivery:

The eye possesses a series of highly specialized anatomical and physiological barriers that protect ocular tissues from environmental insults, pathogens, and toxic substances. Although these barriers are essential for maintaining ocular homeostasis and visual function, they significantly hinder the delivery of therapeutic agents to both anterior and posterior ocular segments. As a result, only a small fraction of the administered drug reaches the target site, leading to poor therapeutic efficacy and low ocular bioavailability. Ocular barriers can be broadly classified into static barriers, dynamic barriers, and blood–ocular barriers. [Rodríguez Villanueva J and Rodríguez Villanueva L, 2024]

2.2.1 Static Barriers:

Components of the eye that do not move and that may not be all the time but at certain times will impede passage of the drug will be the static barriers. The ocular tissues absorb therapeutic substances, which are restricted through various barriers. These barriers include the cornea, conjunctiva and sclera. The most part of the ocular drug absorption following the topical application is the cornea. It has five important layers, epithelium– Bowman’s membrane– stroma– Descemet’s membrane and endothelium. The tight junctions between its epithelial cells make the corneal epithelium the major permeability barrier among several barriers. Due to the hydrophobic nature of epithelium, hydrophilic compounds cannot penetrate the epithelium layer while the stroma layer limits the hydrophobic compounds. Drugs, in general, should have balanced hydrophilic–lipophilic properties for optimal corneal permeation. The conjunctiva, a smooth and thin mucous membrane with many blood vessels, coats the sclera and the eyelid. The sclera, unlike the cornea, has a larger surface area and is relatively permeable and can allow uptake of larger molecules. The blood and lymphatic vessels are highly extensive, which facilitates systemic absorption and the rapid clearance of drugs from the body. As such, very little of a drug may reach the intraocular tissues. The sclera forms the outer covering of the eye. It is a dense connective tissue which made up of collagen fibres. It helps to maintain the shape of the eye. Because of its porous structure and relatively large surface area, the sclera has been extensively researched as an alternative route for posterior ocular drug delivery. The molecular size, lipophilicity, and electrical charge affect the process of drug diffusion through the sclera. The scleral permeability of drugs is higher than corneal permeability. However, due to additional barriers in deeper ocular tissues, the drug often does not efficiently reach the retina and vitreous. Consequently, these static barriers affect the efficacy of ocular drug delivery systems and create a hurdle to achieving sufficient therapeutic concentrations in the eye. [Sasaki H et al, 2021; Silva B et al, 2020]

2.2.2 Dynamic Barriers:

Dynamic barriers are physiological mechanisms that continuously remove drugs instilled at the eye's surface and hence reduce drug residence time and ocular absorption. The first defence mechanism of the eye is the tear film, which is continuously renewed by tear secretion and drainage at a normal turnover rate of 1-3 $\mu\text{L}/\text{min}$. Standard eye drops generally release a volume of 30-50 μL of the formulation. This considerable instilled volume far exceeds the holding capacity of the conjunctival sac. Thus, its dilution and elimination happen almost instantaneously. Consequently, the drug contact time at the cornea is less. Hence, poor ocular bioavailability is observed. Blinking is another protective mechanism helping to distribute tears evenly across the eye and remove particles. Humans blink 12–20 times every minute. This involuntary act removes drug formulations that have been administered and mechanically clear the precorneal area. As a result, drug retention is considerably reduced, impacting therapeutic efficacy. Lacrimation (i.e. tears produced by the lacrimal glands) can be reflexively induced by an ophthalmic formulation due to a non-physiological low pH or the presence of preservatives or any other irritating ingredient in the formulation. Reflex tearing allows increased volume of tears to wash over the ocular surface, creating a situation that will expedite dilution and elimination of the drug from the ocular surface. Thus, a substantial part of the instilled dose is already lost and not able to be absorbed adequately before it happens. Together, these dynamic barriers play a significant role in limiting the success of topical ocular drug delivery systems as well as their low bioavailability. [Singh RM et al 2014; Souto EB et al 2021]

2.2.3 Blood–Ocular Barriers:

Blood-ocular barriers are exceptionally specialized physiological barriers that regulate the passage of molecules between the blood circulation and ocular tissues, thus maintaining ocular immune privilege, tissue homeostasis and visual function. The eye provides defense against harmful substances. At the same time, these barriers also hinder the delivery of drugs to the intraocular parts. The blood-aqueous barrier, or BAB, is a structure made of cells that is located in the ciliary body epithelium and the blood vessels of the iris. The AB prevents certain substances from passing freely from the blood to the aqueous humor. The non-pigmented ciliary epithelium's tight junctions block many drugs and macromolecules from entering the anterior chamber, which results in relatively low drug concentrations in the anterior structures of the eye after systemic administration. Though inflammation temporarily disrupts the integrity of the BAB and enhances drug permeability, it, however, still remains a major hurdle in ocular drug delivery under physiological conditions. The blood-retinal barrier (BRB) is one of the most impermeable ocular barriers that prevents the movement of macrophages from the blood to the retina. It has two components. The blood-retinal barrier itself, made of retinal capillary endothelial cells connected by tight junctions, is the inner blood-retinal barrier. The outer blood-retinal barrier consists of retinal pigment epithelial (RPE) cells connected by tight junctions. As a result of these structures, the ingress of drugs, toxins, and circulating molecules is prevented into retinal tissues. Necessary for maintaining retinal functioning, the BRB does present a major obstacle in the treatment of posterior segment disorders especially diabetic retinopathy, age-related macular degeneration, and retinal degeneration. As a result, the posterior section of the eye requires the use of intravitreal injections, nanoparticles, liposomes, ocular implants, in situ gelling systems, and other sophisticated drug delivery systems for achieving therapeutic drug concentration. [Stapleton F et al, 2017; Tham YC et al, 2014]

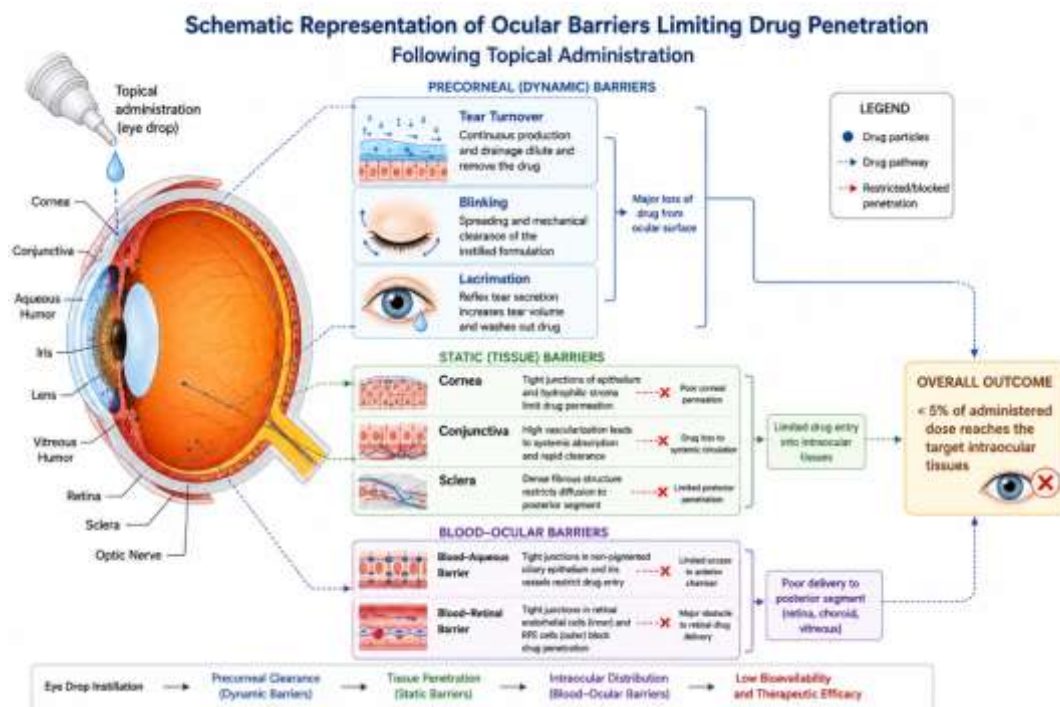


Figure 4. Schematic Representation of Ocular Barriers Limiting Drug Penetration Following Topical Administration

Collectively, static barriers, dynamic barriers, and blood–ocular barriers significantly reduce ocular drug absorption and contribute to the extremely low bioavailability of conventional ophthalmic formulations. It has been estimated that less than 5% of a topically administered dose reaches intraocular tissues. Therefore, overcoming these barriers remains one of the primary objectives in the development of advanced ophthalmic drug delivery systems. Novel approaches such as mucoadhesive formulations, nanocarriers, ocular inserts, and in situ gelling systems have demonstrated considerable potential in enhancing drug retention, improving tissue penetration, and achieving sustained therapeutic effects.

Table 3. Ocular Barriers Affecting Drug Delivery and Their Impact on Drug Absorption [Torchilin VP, 2014; Urtti A, 2006]

Barrier Type	Barrier	Function	Impact on Drug Delivery
Static	Cornea	Protects eye and refracts light	Major permeability barrier
Static	Conjunctiva	Lubrication and immune defense	Systemic absorption and drug loss
Static	Sclera	Structural support	Restricts posterior drug transport
Dynamic	Tear Turnover	Maintains tear film	Rapid drug dilution and elimination
Dynamic	Blinking	Ocular surface protection	Mechanical clearance of formulation
Dynamic	Lacrimation	Tear secretion	Accelerated drug washout
Blood–Ocular	Blood–Aqueous Barrier	Controls aqueous humor composition	Restricts drug entry into anterior chamber
Blood–Ocular	Blood–Retinal Barrier	Maintains retinal homeostasis	Major obstacle to retinal drug delivery

2.3 Need for Prolonged Ocular Retention:

Rapid clearance from the ocular surface due to tear turnover, blink, lacrimation and nasolacrimal drainage is one of the major limitations in ocular drug-delivery systems. This process decreases the residence time of a drug, leading to poor ocular bioavailability. As a result, more advanced drug delivery systems such as in situ gelling formulations are being developed for ocular retention, drug absorption, prolonged therapeutic effect, lesser dosing frequency and better patient compliance.

2.3.1 Enhanced Residence Time: Enhanced residence time means increasing the time that the formulation remains on the ocular surface before being washed away by tears and blinking. Medication Vanishing within Minutes in Eye Drops Denies Drug Absorption. In-situ gel formation extends the ocular contact-time, thereby enhancing drug permeation and the efficacy of the drug.

2.3.2 Improved Bioavailability: Ocular bioavailability refers to the fraction of a given drug reaching the target ocular tissues in therapeutic concentrations. The bioavailability of conventional or traditional formulations is low due to precorneal loss, anatomical barrier and poor permeability to ocular tissues. Holding back of the solution in the cul-de-sac enhances the absorption of the drug through the cornea and conjunctiva leading to enhanced therapeutic effects with reduced side effects.

2.3.3 Sustained Drug Release: When the drug gets cleared rapidly from the eye, it calls for frequent applications of the conventional eye drop. Prolonged-retention systems afford effective drug levels for longer durations thereby curtailing repeated dosing. This makes treatment plans easier and patients more comfortable.

2.3.4 Reduced Dosing Frequency: Successful ocular therapy relies heavily on patient compliance, especially for chronic diseases with long-term therapy. The ineffective treatment due to poor adherence is due to the frequent dosing schedule and repeated instillation. Formulations that lead to prolong-retention are more convenient, promote adherence, and result in efficacy.

2.3.5 Better Patient Compliance: Prolong ocular retention overcomes the restrictions of conventional ophthalmic formulations and further increases the drug residence time and absorption. It incorporates bioavailability, provides sustained release and reduces dosing frequency. Such advantages allow for better patient compliance and overall therapeutic performance of ocular drug delivery.

Overall, prolonged ocular retention plays a crucial role in overcoming the limitations of conventional ophthalmic formulations. The superior therapeutic performance of a pharmaceutical formulation can be attributed to enhanced residence time, improved bioavailability, sustained drug release, reduced dosing frequency and better patient compliance. As a result of these advantages, there is a development of new ocular drug delivery systems. In situ gelling formulations are one such system, which has shown great promise to deliver synthetic drugs and herbal bioactives for ocular diseases effectively. [Willoughby CE et al, 2010; Wong WL et al, 2014; World Health Organization 2019]



Figure 5. Benefits of Prolonged Ocular Retention in Ophthalmic Drug Delivery

Table 4. Importance of Prolonged Ocular Retention in Ophthalmic Drug Delivery [Yadav KS et al, 2019]

Benefit	Description	Therapeutic Impact
Enhanced Residence Time	Increases contact time of formulation with ocular tissues	Greater drug absorption
Improved Bioavailability	Increases fraction of drug reaching target tissues	Enhanced therapeutic efficacy
Sustained Drug Release	Provides controlled and prolonged drug delivery	Stable therapeutic concentrations
Reduced Dosing Frequency	Minimizes need for repeated administration	Improved treatment convenience
Better Patient Compliance	Simplifies dosing regimen and improves adherence	Better clinical outcomes

3. In Situ Gelling Ophthalmic Systems: In situ gelling ocular systems are drug delivery systems administered as liquid dosage formulations which as per the physiological conditions of the eye, gel. An eye drop controlled drug delivery system is easy to administer and also possesses prolonged ocular retention and sustained release characteristics like gels. The eye's pH, temperature, or ions can bring about the sol-to-gel transition in PNIPAM. Usually, for the fabrication of in situ gel forming implants, generally used are polymers like Carbopol® (pH-sensitive), Poloxamer 407 (temperature-sensitive), and gellan gum or sodium alginate (ion-sensitive). The gel formed is able to enhance ocular residence time, inhibit precorneal drug loss, increase bioavailability and provide controlled release. Consequently, in situ gels improve the efficacy of medication and decrease the dosage frequency, which in turn increases patient compliance. As a result, in situ gel has a possibility for delivering synthetic drugs and herbal bioactives in ocular disorders. [Yang Y and Lockwood A, 2022]

Table 5. Characteristics of In Situ Gelling Ophthalmic Systems

Parameter	Conventional Eye Drops	In Situ Gelling Systems
Physical State	Liquid	Liquid → Gel
Residence Time	Short	Prolonged
Drug Release	Immediate	Sustained
Bioavailability	Low (<5%)	Improved
Dosing Frequency	Frequent	Reduced
Patient Compliance	Moderate	High
Therapeutic Efficacy	Limited	Enhanced

3.2 Mechanism of Sol-to-Gel Transition:

The fundamental principle of in situ gelling ophthalmic systems is the sol-to-gel transition. These formulations are given as low-viscosity liquids that quickly turn into semi-solid gels when they come in contact with physiological conditions in the eye. As a result of this transformation the formation of a three-dimensional polymeric network occurs which localizes the drug at the site of administration and ensures sustained drug release. When the physicochemical properties of polymers are altered by stimuli such as pH, temperature, ionic concentration or combination of any of these, gel formation occurs. When interacting with tear fluid, the polymer chains swell, ionize, aggregate or crosslink increasing the viscosity and forming a gel. The gel that results from this reaction prevents ocular residency for long duration along reduces precorneal drug loss, improves corneal contact, and increases ocular bioavailability. Once the liquid formulation is administered, it interacts with the ocular physiological conditions to form the gel matrix by interacting with each other and entrapping drug, which gets released over prolonged period. [Zhang K et al, 2024] The tear fluid pH (7.4) induces gelation of pH-sensitive in situ gelling systems. These formulations are typically made at an acidic pH at which the polymer remains soluble. When the substance is put on the polymer, there is ionization of functional groups which leads to the repulsion of these groups and swelling of the substance, resulting in the formation of gel. Polymers that are also pH-sensitive, include Carbopol®, polyacrylic acid, and polycarbophil.

[Lang JC, 1995] In situ gelling systems that are temperature-sensitive use thermo-responsive polymers that are liquid at room temperatures but gels at the temperature of the ocular surface (34–35°C). The interconnection of polymer chains due to polymer dehydration and enhanced hydrophobic interactions caused polymer aggregation that leads to gelation. Thermosensitive polymers include Poloxamer 407, Poloxamer 188, and Pluronic® F127. Ion-sensitive in situ gelling systems utilize the interaction of polymers with ions that are already available in the tear fluid. Sodium, calcium, and magnesium ions are examples of ions present. The ions induce crosslinking of ionic kinds amongst polymer chains causing formation of gel quickly. Gellan gum, sodium alginate and pectin are common ion-sensitive polymers with high ocular compatibility and extended retention time. [Saettone MF, Salminen L, 1995] Multi-stimuli responsive in situ gelling formulations employ more than one mechanism of gelation to enhance gel strength, prolong retention, and allow controlled drug release. These sophisticated formulations offer advanced therapeutic efficacy by reacting to pH, temperature, and ionic strength. Examples include polymer mixes like Carbopol® with HPMC, Carbopol® with Poloxamer, and gellan gum with chitosan. These outperform single stimulus systems regarding ocular retention and drug delivery efficiency. [Mitra AK, et al, 2003]

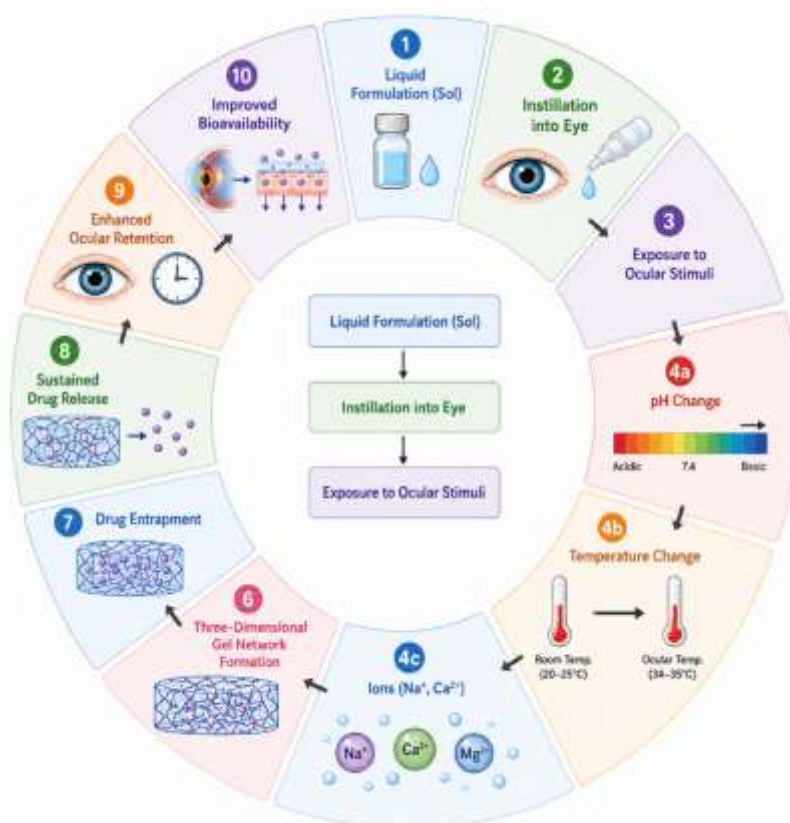


Figure 7. Mechanism of Sol-to-Gel Transition in Ophthalmic in Situ Gelling Systems

The sol-to-gel transition mechanism is crucial for the success of in situ ophthalmic systems because it combines the advantages of liquid and gel formulations in a single dosage form. The liquid state facilitates easy administration, while the gel state provides prolonged ocular retention and sustained drug release. Consequently, these systems improve bioavailability, reduce dosing frequency, enhance patient compliance, and increase therapeutic efficacy. For herbal bioactive-loaded formulations, the sol-to-gel transition further enhances the retention and delivery of phytoconstituents that typically suffer from poor solubility and rapid ocular clearance. Therefore, understanding the mechanisms governing gel formation is essential for the rational design of effective in situ gelling ophthalmic systems.

Table 6. Types of Sol-to-Gel Transition Mechanisms in Ophthalmic in Situ Gels [Kaur IP and Kakkar S, 2014; Diebold Y and Calonge M, 2010]

Triggering Mechanism	Stimulus	Principle of Gelation	Common Polymers
pH-Triggered	Tear fluid pH (≈ 7.4)	Polymer ionization and swelling	Carbopol®, Polycarbophil
Temperature-Triggered	Ocular temperature ($34\text{--}35^\circ\text{C}$)	Polymer aggregation and micellization	Poloxamer 407, Pluronic F127
Ion-Triggered	Na^+ , Ca^{2+} , Mg^{2+} ions in tears	Ionic crosslinking	Gellan gum, Sodium alginate
Multi-Stimuli Responsive	Combination of pH, temperature, and ions	Multiple gelation mechanisms	Polymer combinations

3.3 Classification of In Situ Gelling Systems

The type of physiological stimulus that induces the sol-to-gel transition characterizes in situ gelling ophthalmic systems. Structural variations in polymers brought on by these stimuli can lead to gel formation at the ocular surface. In situ gels are classified as pH-triggered, temperature-triggered, ion-activated and multi-stimuli responsive systems based on gelation mechanism. Specific polymers are utilized in each category to ensure a prolonged ocular retention, sustained release with enhanced bioavailability. [Varela-Fernández R et al, 2020]

3.3.1 pH-triggered systems: pH-based in situ gels are developed from the polymers, which gel at a particular pH value. These formulations are prepared at an acidic pH at which the polymer remains in solution and gels at physiological pH of tear fluid (about 7.4). Ionization of polymeric functional groups leads to swelling of the polymers and the formation of a gel network through gelation. Carbopol® is a very common polymer in the market that is used due to its excellent mucoadhesive property, when exposed to pH, it gels rapidly. It has a prolonged ocular retention and ensures an extended drug release. [Yellepeddi VK, Palakurthi S, 2016] Other frequently used polymers are polycarbophil, polyacrylic acid, acrylic acid copolymers, which enhances precorneal retention as well as formulation stability.

3.3.2 Systems Triggered by Temperature: Temperature-sensitive in situ gels are liquid at a lower temperature, but they ionically gel upon contact with the ocular surface that is in the range of ($34\text{--}35^\circ\text{C}$). Due to dehydration of the polymer chains and enhanced hydrophobic interactions polymer aggregates and gels form. Both Pluronic® F127 and Poloxamer 407 have been identified as the most common thermoresponsive polymers owing to their biocompatibility, ease of administration, reversible gelation behavior and ability to provide sustained drug release. These systems provide ease of application and rapid gel formation post-instillation, thus enhancing ocular retention and therapeutic activity. [Sultana Y et al, 2005]

3.3.3 Ion-activated in situ gelling systems: These are those that gel with a presence of an ion such as sodium, calcium magnesium etc. which are found in tear fluid. The interaction of these ions with polymer strands causes ionic cross-linking and quick formed gel. The most used ion sensitive polymers are gellan gum and sodium alginate owing to their excellent biocompatibility, transparency, mucoadhesive properties and sustained drug release. The gelation systems of drugs occur when they come in contact with tear fluid almost instantaneously which enhances ocular contact and bioavailability of drug.

3.3.4 Multi-Stimuli Responsive Systems: Advanced in situ gels are multi-stimuli responsive systems that respond to more than one physiological stimulus such as pH, temperature and ionic conditions. Polymeric systems are made of different types of polymers which leads to more stable and stronger gel through intense polymer network formation with better gel strength ocular retention and drug release control. Combinations of polymers commonly used are Carbopol® with HPMC, Poloxamer 407 or sodium alginate, gellan gum with chitosan. Since single-stimulus systems' features are more binding, they expect therapeutic improvement. A novel drug delivery method utilized gel containing both synthetic and bioactive herbal components.

This method is based on incorporation of nanoparticles, liposomes and other nanocarriers in multi-stimuli responsive gels. [Rathore KS and Nema RK, 2009; Patel RB et al, 2010]

Table 7. Classification of Ophthalmic In Situ Gelling Systems

Type of System	Triggering Stimulus	Mechanism of Gelation	Representative Polymers
pH-Triggered	Tear fluid pH (≈ 7.4)	Polymer ionization and swelling	Carbopol®, Polycarbophil
Temperature-Triggered	Ocular temperature ($34\text{--}35^\circ\text{C}$)	Micellization and polymer aggregation	Poloxamer 407, Pluronic® F127
Ion-Activated	Na^+ , Ca^{2+} , Mg^{2+} ions	Ionic crosslinking	Gellan gum, Sodium alginate
Multi-Stimuli Responsive	Combination of pH, temperature, ions	Multiple gelation mechanisms	Polymer combinations

3.4 Advantages of In Situ Gelling Systems Over Conventional Eye Drops

Eye drops or ophthalmic formulations are the most commonly used dosage form for the treatment of ocular diseases due to their simplicity, ease of administration and acceptance by patients. The therapeutic success of these drugs is compromised due to their rapid precorneal clearance, low corneal permeability, low ocular bioavailability and frequent dosing. In situ gelling ophthalmic systems have emerged as a promising alternative to overcome these limitations. These formulations are administered as liquids and gel upon contact with physiological triggers present in the ocular environment. These properties improve ocular retention and therapeutic performance. [Hornof M et al, 2005]

3.4.1 Prolonged Precorneal Residence Time

One of the major advantages of in situ gelling systems is their ability to remain on the ocular surface for a long time. Conventional eye drops are removed rapidly within minutes of administration by blinking, tear turnover and nasolacrimal drainage. In contrast, in situ gels undergo a transformation after instillation into viscous gels, which helps in resisting the rapid elimination of drugs and enables prolonged contact with the ocular tissues. By increasing residence time, it allows additional bursts of drug permeability through the cornea and conjunctiva aiding drug absorption. [Hämäläinen KM et al, 1997]

3.4.2 Improved Ocular Bioavailability

One of the major advantages of in situ gelling systems is their ability to remain on the ocular surface for a long time. Conventional eye drops are removed rapidly within minutes of administration by blinking, tear turnover and nasolacrimal drainage. In contrast, in situ gels undergo a transformation after instillation into viscous gels, which helps in resisting the rapid elimination of drugs and enables prolonged contact with the ocular tissues. By increasing residence time, it allows additional bursts of drug permeability through the cornea and conjunctiva aiding drug absorption. [Hämäläinen KM et al, 1997]

3.4.3 Sustained and Controlled Drug Release

Conventional eye drops typically produce a rapid burst release followed by a sharp decline in drug concentration due to rapid clearance. Such fluctuations may lead to inconsistent therapeutic effects. In situ gelling systems form a three-dimensional polymeric network that acts as a drug reservoir. Drug molecules are gradually released from the gel matrix over an extended period, providing sustained and controlled drug delivery. This controlled release profile helps maintain therapeutic drug concentrations and minimizes concentration-related adverse effects.

3.4.4 Reduced Nasolacrimal Drainage

Most of a typical eye drop drains via the nasolacrimal duct shortly after application. This drainage reduces the availability of ocular drugs; further, it may lead to their absorption and side effects systemically. The in-situ gels have been designed in such

a way that they can increase in viscosity to restrict drainage through the nasolacrimal pathway thus having a considerable effect on local drug retention with the restriction in systemic exposure. [Prausnitz MR and Noonan JS, 1998]

3.4.5 Reduced Dosing Frequency

Because standard eye drops are quickly removed from the eye surface, frequent applications are often necessary to maintain therapeutic concentrations. Reducing patient compliance due to inconvenience of multiple daily dosing. The kinetic of sustained release of in situ gels helps in maintaining therapeutic levels of the drug for a longer duration and reducing the frequency of application. This benefit is particularly significant for chronic diseases (such as glaucoma, dry eye disease and allergic conjunctivitis) requiring long-term treatment. [Prausnitz MR and Noonan JS, 1998]

3.4.6 Enhanced Patient Compliance

Patient's compliance is a most important determinant of the therapeutic success in ophthalmology. Due to frequent dosing regimens and repeated administration, compliance is usually poor. This is especially true in the elderly and patients with chronic ocular disorders. In situ gelling systems improve patient compliance by reducing the number of doses and enhancing comfort. Improved adherence helps achieve better clinical outcomes and disease control. [Prausnitz MR and Noonan JS, 1998]

3.4.7 Improved Therapeutic Efficacy

In situ gelling substances are not presented as ocular insert or preformed gels but as viscous liquid. The property enables easy instillation that is similar to conventional eye drops and prevents the discomfort associated with a highly viscous formulation. The transformation from liquid to gel only occurs at the time of application, which makes it easy to use and effective for a prolonged period.

3.4.8 Ease of Administration

Unlike preformed gels or ocular inserts, in situ gelling systems are administered as low-viscosity liquids. This property allows easy instillation similar to conventional eye drops while avoiding the discomfort associated with highly viscous formulations. The transition from liquid to gel occurs only after administration, providing both convenience and prolonged therapeutic action. [Prausnitz MR and Noonan JS, 1998]

3.4.9 Reduced Systemic Side Effects

Systemic absorption of ophthalmic drugs through the nasal mucosa may lead to undesirable adverse effects, particularly during chronic therapy. By reducing nasolacrimal drainage and improving local drug retention, in situ gels decrease systemic drug exposure and minimize the risk of systemic toxicity. This advantage is especially important for drugs used in glaucoma treatment, where systemic absorption can affect cardiovascular and respiratory function. [Prausnitz MR and Noonan JS, 1998]

3.4.10 Suitability for Herbal Bioactive Delivery

Many herbal bioactives, including curcumin, thymoquinone, quercetin, and resveratrol, exhibit poor aqueous solubility and low ocular bioavailability. In situ gelling systems provide an effective platform for delivering these compounds by enhancing retention, improving stability, and enabling sustained release. Furthermore, the combination of herbal therapeutics with advanced gel-forming systems offers a promising approach for achieving improved ocular therapy with reduced adverse effects. [Prausnitz MR and Noonan JS, 1998] Overall, in situ gelling ophthalmic systems successfully combine the convenience of eye drops with the prolonged retention characteristics of gels. Their ability to enhance bioavailability, sustain drug release, reduce dosing frequency, and improve patient compliance makes them superior to conventional ophthalmic formulations. Consequently, these systems have become one of the most extensively investigated strategies for modern ocular drug delivery.

Table 8. Comparison Between Conventional Eye Drops and In Situ Gelling Ophthalmic Systems [Maurice DM and Mishima S, 1984]

Parameter	Conventional Eye Drops	In Situ Gelling Systems
Physical State After Administration	Liquid	Liquid → Gel
Ocular Residence Time	Very Short	Prolonged

Bioavailability	Low (<5%)	Improved
Drug Release Pattern	Immediate Release	Sustained Release
Nasolacrimal Drainage	High	Reduced
Dosing Frequency	Frequent	Reduced
Patient Compliance	Moderate	High
Systemic Side Effects	Higher	Lower
Therapeutic Efficacy	Limited	Enhanced
Suitability for Herbal Bioactives	Limited	Excellent

4. POLYMERS USED IN OPHTHALMIC IN SITU GELS [SCHOENWALD RD, 1990]

Polymers are the key components of ophthalmic in situ gelling systems and play a vital role in determining gelation behavior, viscosity, mucoadhesion, drug release, ocular retention, and therapeutic efficacy. The selection of an appropriate polymer is essential for achieving the desired sol-to-gel transition under physiological ocular conditions. Based on their origin and chemical nature, polymers used in ophthalmic in situ gels are broadly classified into natural, semi-synthetic, and synthetic polymers.

4.1 Natural Polymers [Hughes PM et al, 2005]

Natural polymers are widely used in ocular drug delivery because of their excellent biocompatibility, biodegradability, low toxicity, and mucoadhesive properties. Most natural polymers are polysaccharides capable of forming gels in response to physiological stimuli. Sodium alginate, obtained from brown algae, undergoes ion-induced gelation in the presence of calcium ions in tear fluid, providing sustained drug release and improved ocular bioavailability. Gellan gum, produced by *Sphingomonas elodea*, forms transparent gels through ionic interactions with tear electrolytes and is extensively used in ophthalmic formulations due to its excellent clarity and retention properties. Chitosan, derived from chitin, possesses strong mucoadhesive and permeation-enhancing properties because of its cationic nature, making it useful for ocular nanoparticles and herbal bioactive delivery systems. Other natural polymers such as pectin, xanthan gum, and guar gum are also utilized for their gel-forming, viscosity-enhancing, and ocular retention capabilities.

4.2 Semi-Synthetic Polymers [Ranta VP et al, 2010]

Chemically modified cellulose derivatives that is known as semi-synthetic polymer are extensively used as viscosity enhancer, stabilizer and release modifier for ophthalmic formulation. Hydroxypropyl methylcellulose (HPMC) is among the most used polymers due to its safety profile, film-forming ability and sustained drug release properties. Methylcellulose (MC) has a viscosity that varies with temperature and has a lubricant effect on the ocular surface. Hydroxypropyl cellulose or HPC increases viscosity of formulation and controls drug-release. Carboxymethyl cellulose or CMC is widely used in artificial tears and dry eye therapy due to its superior hydration and lubricating properties. These polymers are often used with other gelling agents for better use of formulations.

4.3 Synthetic Polymers [Eljarrat-Binstock E and Domb AJ, 2006]

Synthetic polymers provide precise control over gelation behavior, mechanical strength, and drug release characteristics. Carbopol® is a pH-sensitive crosslinked polyacrylic acid polymer that undergoes gel formation at physiological tear pH, offering excellent mucoadhesion and prolonged ocular retention. Poloxamers, particularly Poloxamer 407 and Poloxamer 188, are thermoresponsive triblock copolymers that remain liquid at room temperature and form gels at ocular temperature, making them ideal for temperature-sensitive ophthalmic systems. Polyvinyl alcohol (PVA) is another synthetic polymer commonly used as a viscosity enhancer and lubricant due to its transparency, ocular compatibility, and film-forming properties.

4.4 Criteria for Polymer Selection [Janoria KG et al, 2007]

The successful development of ophthalmic in situ gels depends largely on the appropriate selection of polymers. An ideal polymer should be biocompatible, non-toxic, non-irritating, and capable of undergoing gelation under ocular physiological

conditions. It should provide suitable viscosity, muco-adhesion, controlled drug release, optical clarity, and formulation stability while being compatible with sterilization processes and regulatory requirements. For herbal bioactive-loaded formulations, additional considerations include compatibility with phytoconstituents, enhancement of drug solubility and permeability, and protection against degradation.

4.5 Recent Advances in Smart and Stimuli-Responsive Polymers [Bourlais CL et al, 1998]

Recent progression in polymer science has led to smart and stimuli-responsive polymers, which have the capacity to respond to physiological stimuli such as pH, temperature, ionic strength, etc. Some examples of pH-responsive polymers are Carbopol® and polycarbophil, whereas those of thermoresponsive polymers include Poloxamer 407 and Pluronic® F127. Also, gellan gum and sodium alginate are examples of ion-responsive polymers. These sophisticated dual and multi responsive systems give enhanced gel strength and prolonged ocular retention due to the unique combination of Carbopol®, Poloxamer, chitosan, and gellan gum. This gives superior control on drug release. In addition, the enhanced ocular delivery of drugs by nanocarriers like nanoparticles, liposomes, niosomes, cubosomes and nanoemulsions into smart gel matrices. Novel technologies like self-healing hydrogels, bioinspired polymers, injectable hydrogels, AI-aided polymer optimization and herbal nanogel systems are likely to shape the advanced ocular formulations in the future. The emergence smart and stimuli-responsive polymers have advanced ocular drug delivery dramatically and is also expected to have an important place in future ophthalmic formulations. More particularly the development of an herbal bioactive-loaded in-situ gelling system.

Table 9. Polymers Used in Ophthalmic In Situ Gelling Systems

Polymer	Category	Gelation Mechanism	Major Function
Sodium Alginate	Natural	Ion-sensitive	Sustained release
Gellan Gum	Natural	Ion-sensitive	Rapid gelation
Chitosan	Natural	pH-sensitive/Mucoadhesive	Permeation enhancement
Pectin	Natural	Ion-sensitive	Controlled release
Xanthan Gum	Natural	Viscosity enhancement	Ocular retention
Guar Gum	Natural	Thickening agent	Lubrication
HPMC	Semi-synthetic	Viscosity modifier	Sustained release
MC	Semi-synthetic	Thickening agent	Lubrication
HPC	Semi-synthetic	Film-forming	Controlled release
CMC	Semi-synthetic	Hydration enhancer	Artificial tears
Carbopol®	Synthetic	pH-sensitive	Muco-adhesion
Poloxamer 407	Synthetic	Thermosensitive	In situ gelation
Polyvinyl Alcohol	Synthetic	Viscosity enhancer	Ocular lubrication

5. HERBAL BIOACTIVES FOR EYE DISEASES [GUPTA C, CHAUHAN A, 2012]

5.1 Importance of Herbal Therapeutics in Ophthalmology

Herbal therapeutics have gained significant attention in ophthalmology due to their diverse pharmacological activities and favorable safety profiles. Traditionally used in systems such as Ayurveda, Traditional Chinese Medicine, and Unani medicine, many plant-derived bioactives have demonstrated potential in the prevention and treatment of ocular diseases including dry eye syndrome, glaucoma, cataract, diabetic retinopathy, uveitis, and age-related macular degeneration. These compounds possess antioxidant, anti-inflammatory, antimicrobial, antiangiogenic, and neuroprotective properties that target multiple pathological pathways involved in ocular disorders. [Cholkar K et al, 2013] Unlike conventional synthetic drugs that often act on a single

target, herbal bioactives can modulate several biological pathways simultaneously. Compounds such as curcumin, resveratrol, thymoquinone, quercetin, lutein, and EGCG help reduce oxidative stress, suppress inflammation, protect retinal neurons, and improve ocular health. Some phytoconstituents also exhibit antimicrobial activity against pathogens responsible for ocular infections, making them promising alternatives or adjuncts to conventional therapies. Despite their therapeutic potential, many herbal bioactives suffer from poor aqueous solubility, low stability, limited corneal permeability, and rapid elimination from the ocular surface. To overcome these limitations, advanced drug delivery systems such as nanoparticles, liposomes, nanoemulsions, and in situ gelling formulations have been developed. Among these, ophthalmic in situ gels are particularly promising because they prolong ocular residence time, provide sustained drug release, and enhance the bioavailability of herbal compounds. Therefore, the integration of herbal therapeutics with advanced ocular delivery systems offers a promising strategy for developing safe, effective, and patient-friendly treatments for various eye diseases. [Sahoo SK et al, 2008]

5.2 Major Herbal Bioactives and Their Therapeutic Potential

5.2.1 Curcumin

Curcumin, a polyphenolic compound obtained from *Curcuma longa* (turmeric), possesses potent antioxidant and anti-inflammatory properties. It exerts therapeutic effects by scavenging reactive oxygen species (ROS), inhibiting NF- κ B activation, suppressing inflammatory cytokines, and reducing VEGF expression. Curcumin has shown potential in the management of diabetic retinopathy, age-related macular degeneration (AMD), uveitis, corneal neovascularization, and cataract prevention. However, its clinical application is limited by poor aqueous solubility, low bioavailability, and rapid degradation. [Koo OM et al, 2005]

5.2.2 Thymoquinone

Thymoquinone is the principal bioactive constituent of *Nigella sativa* (black seed) and exhibits strong antioxidant, anti-inflammatory, and neuroprotective activities. It reduces oxidative stress by enhancing endogenous antioxidant defenses and suppressing inflammatory mediators associated with retinal and corneal damage. Thymoquinone has demonstrated therapeutic potential in dry eye syndrome, glaucoma, retinal degeneration, corneal inflammation, and diabetic retinopathy through mechanisms such as ROS scavenging, anti-apoptotic action, and neuroprotection. [Kompella UB et al, 2013]

5.2.3 Quercetin

Quercetin is a naturally occurring flavonoid widely distributed in fruits, vegetables, and medicinal plants. It possesses significant antioxidant, anti-inflammatory, and anti-allergic activities and protects ocular tissues from oxidative stress. Quercetin inhibits histamine release and inflammatory cytokines, making it beneficial in the treatment of allergic conjunctivitis, dry eye disease, corneal inflammation, and retinal oxidative injury while providing corneal protection and reducing inflammatory responses. [Kompella UB et al, 2013]

5.2.4 Resveratrol

Resveratrol is a polyphenolic stilbene found in grapes, berries, peanuts, and red wine. It has gained attention for its neuroprotective, antioxidant, anti-inflammatory, and antiangiogenic properties. By activating SIRT1 pathways, reducing oxidative stress, and inhibiting VEGF expression, resveratrol protects retinal neurons and may be useful in the management of glaucoma, AMD, diabetic retinopathy, and retinal degeneration. [Kassem MA et al, 2014]

5.2.5 Berberine

Berberine is an isoquinoline alkaloid isolated from plants of the *Berberis* genus and is known for its broad-spectrum antimicrobial, antioxidant, and anti-inflammatory activities. It inhibits microbial growth, reduces inflammation, and protects retinal tissues from oxidative damage. Berberine has shown promise in treating bacterial conjunctivitis, ocular infections, corneal inflammation, and diabetic retinopathy, with the added advantage of low toxicity. [Kassem MA et al, 2014]

5.2.6 Lutein

Lutein is a xanthophyll carotenoid naturally present in green leafy vegetables and marigold flowers and is a major pigment of the macular region of the retina. It protects retinal tissues by filtering harmful blue light and reducing oxidative stress. Lutein

has been widely investigated for age-related macular degeneration, cataract prevention, and retinal degeneration owing to its antioxidant and retinal protective effects. [Aggarwal D and Kaur IP, 2005]

5.2.7 Zeaxanthin

Zeaxanthin is an important macular carotenoid that accumulates in retinal tissues and protects the eye from photooxidative damage. Similar to lutein, it enhances macular health, improves visual performance, and safeguards photoreceptor cells against degeneration. Its therapeutic potential has been explored in AMD, retinal degeneration, and visual function improvement through its antioxidant and retinal protective mechanisms. [Aggarwal D and Kaur IP, 2005]

5.2.8 Epigallocatechin Gallate (EGCG)

Epigallocatechin gallate (EGCG), the most abundant catechin found in green tea (*Camellia sinensis*), exhibits strong antioxidant, anti-inflammatory, and antiangiogenic properties. It protects ocular tissues by scavenging free radicals, inhibiting VEGF expression, and suppressing inflammatory pathways. EGCG has demonstrated therapeutic potential in dry eye syndrome, corneal inflammation, diabetic retinopathy, and retinal degeneration. [Li J et al, 2013]

5.2.9 Rutin

Rutin is a flavonoid glycoside commonly found in citrus fruits, buckwheat, and several medicinal plants. It possesses antioxidant, anti-inflammatory, and vaso-protective activities that help protect retinal tissues and microvasculature. Rutin strengthens capillary walls, improves microcirculation, and reduces oxidative damage, making it potentially beneficial in diabetic retinopathy, retinal vascular disorders, and ocular inflammatory conditions. [Li J et al, 2013]

5.2.10 Catechins

Catechins are polyphenolic compounds abundantly present in green tea and include epicatechin, epigallocatechin, epicatechin gallate, and EGCG. These compounds exhibit potent antioxidant, antimicrobial, and anti-inflammatory activities that contribute to ocular protection. Catechins have shown potential in the management of ocular infections, corneal disorders, dry eye syndrome, and retinal oxidative injury through free radical scavenging, antimicrobial action, and inhibition of inflammatory mediators. [Wagh VD et al, 2009]

Significance of Herbal Bioactives in Ocular Therapy

Herbal bioactives provide multifaceted therapeutic benefits through antioxidant, anti-inflammatory, antimicrobial, neuroprotective, and antiangiogenic mechanisms, making them promising candidates for ocular disease management. However, their clinical application is often limited by poor aqueous solubility, low stability, and restricted ocular permeability. Advanced delivery systems such as nanoparticles, liposomes, cubosomes, nanoemulsions, and in situ gelling formulations have therefore been developed to improve their ocular bioavailability, prolong retention time, and enhance therapeutic efficacy. The combination of herbal bioactives with ophthalmic in situ gelling systems offers a promising approach for achieving sustained drug release and improved treatment outcomes in various ocular disorders.

Table 11. Major Herbal Bioactives and Their Therapeutic Potential in Ocular Diseases [Vyas SP and Khar RK, 2012]

Herbal Bioactive	Natural Source	Major Pharmacological Activity	Potential Ocular Applications
Curcumin	<i>Curcuma longa</i>	Antioxidant, Anti-inflammatory	AMD, Uveitis, Diabetic Retinopathy
Thymoquinone	<i>Nigella sativa</i>	Antioxidant, Neuroprotective	Glaucoma, Dry Eye
Quercetin	Fruits and Vegetables	Anti-allergic, Antioxidant	Allergic Conjunctivitis
Resveratrol	Grapes	Neuroprotective, Antiangiogenic	AMD, Glaucoma
Berberine	<i>Berberis</i> spp.	Antimicrobial, Anti-inflammatory	Ocular Infections
Lutein	Marigold	Antioxidant	AMD Prevention
Zeaxanthin	Corn, Vegetables	Retinal Protection	Macular Disorders

EGCG	Green Tea	Antioxidant, Anti-inflammatory	Dry Eye, Retinal Disorders
Rutin	Citrus Fruits	Vasoprotective, Antioxidant	Diabetic Retinopathy
Catechins	Green Tea	Antioxidant, Antimicrobial	Corneal and Retinal Disorders

5.3 Mechanisms of Action of Herbal Bioactives in Ocular Diseases:

The therapeutic efficacy of herbal bioactives in ocular diseases is largely attributed to their ability to modulate multiple pathological pathways simultaneously. Ocular disorders such as dry eye syndrome, glaucoma, cataract, conjunctivitis, diabetic retinopathy, and age-related macular degeneration are associated with oxidative stress, inflammation, microbial infections, abnormal angiogenesis, and neurodegeneration. Herbal phytoconstituents possess diverse pharmacological activities that target these mechanisms and provide comprehensive protection to ocular tissues. [Peppas NA et al, 2000; Huang Y et al, 2000]

Antioxidant activity is one of the most important mechanisms of herbal bioactives. The eye is continuously exposed to light, oxygen, and environmental pollutants, leading to the generation of reactive oxygen species (ROS) and oxidative stress. Herbal compounds such as curcumin, thymoquinone, quercetin, resveratrol, lutein, zeaxanthin, EGCG, and rutin protect ocular tissues by scavenging free radicals, inhibiting lipid peroxidation, enhancing endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, and reducing oxidative stress-induced cellular damage. These effects are beneficial in conditions such as cataract, diabetic retinopathy, glaucoma, retinal degeneration, and age-related macular degeneration. [Hoffman AS, 2012]

Anti-inflammatory activity plays a crucial role in the management of ocular disorders characterized by chronic inflammation. Herbal bioactives suppress inflammatory pathways by inhibiting NF- κ B activation, reducing pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, and decreasing the production of prostaglandins and leukotrienes. Phytoconstituents including curcumin, thymoquinone, EGCG, resveratrol, and quercetin effectively reduce inflammation and tissue damage in dry eye syndrome, allergic conjunctivitis, uveitis, corneal inflammation, and post-surgical ocular conditions. [Hoffman AS, 2012]

Antimicrobial activity is another important property of many herbal compounds. Plant-derived bioactives can inhibit the growth of bacteria, fungi, and viruses through disruption of microbial cell membranes, inhibition of enzyme systems, prevention of biofilm formation, and interference with microbial DNA replication. Compounds such as berberine, curcumin, catechins, EGCG, and neem-derived constituents have demonstrated broad-spectrum antimicrobial activity and may be useful in the treatment of bacterial conjunctivitis, keratitis, blepharitis, and other ocular infections.

Anti-angiogenic activity is particularly important in retinal disorders characterized by abnormal blood vessel formation. Herbal bioactives can inhibit angiogenesis by suppressing vascular endothelial growth factor (VEGF) expression, reducing endothelial cell proliferation, decreasing vascular permeability, and preventing neovascular membrane formation. Curcumin, resveratrol, EGCG, and quercetin have shown significant anti-angiogenic effects and may be beneficial in diabetic retinopathy, wet age-related macular degeneration, corneal neovascularization, and retinal vascular disorders. [Qiu Y and Park K, 2012]

Neuroprotective activity contributes to the prevention of retinal and optic nerve degeneration. Herbal compounds protect retinal ganglion cells and photoreceptors by reducing oxidative stress, inhibiting neuronal apoptosis, preserving mitochondrial function, regulating calcium homeostasis, and enhancing neuronal survival pathways. Bioactives such as resveratrol, thymoquinone, curcumin, quercetin, and *Ginkgo biloba* extract have demonstrated promising neuroprotective effects in glaucoma, retinal degeneration, optic neuropathy, diabetic retinopathy, and ischemic retinal injury. [Caló E and Khutoryanskiy VV, 2015] Overall, herbal bioactives offer a multifactorial therapeutic approach by simultaneously targeting oxidative stress, inflammation, infection, angiogenesis, and neurodegeneration. This pleiotropic mode of action makes them attractive candidates for the management of complex ocular diseases. Furthermore, incorporation of these phytoconstituents into advanced ophthalmic delivery systems such as in situ gels, nanoparticles, liposomes, and cubosomes can significantly improve their ocular bioavailability, retention time, and therapeutic efficacy. [Khutoryanskiy VV, 2011]

Table 12. Mechanisms of Action of Herbal Bioactives in Ocular Therapy [Khutoryanskiy VV, 2014]

Mechanism	Major Targets	Representative Herbal Bioactives	Ocular Diseases Benefited
Antioxidant	ROS, lipid peroxidation	Curcumin, Thymoquinone, Lutein, Zeaxanthin	Cataract, AMD, Glaucoma
Anti-inflammatory	NF- κ B, TNF- α , IL-6, COX-2	Curcumin, EGCG, Resveratrol	Dry Eye, Uveitis
Antimicrobial	Bacteria, fungi, viruses	Berberine, Catechins, EGCG	Conjunctivitis, Keratitis
Anti-angiogenic	VEGF, endothelial proliferation	Resveratrol, Curcumin, EGCG	AMD, Diabetic Retinopathy
Neuroprotective	Retinal ganglion cells, optic nerve	Thymoquinone, Resveratrol, Curcumin	Glaucoma, Retinal Disorders

5.4 Herbal Bioactives in Specific Ocular Diseases:

Table 13. Herbal Bioactives and Their Applications in Specific Ocular Diseases

Ocular Disease	Major Herbal Bioactives	Primary Mechanism	Therapeutic Outcome
Dry Eye Syndrome	Curcumin, Thymoquinone, EGCG, Quercetin	Anti-inflammatory, Antioxidant	Improved tear film stability
Glaucoma	Resveratrol, Thymoquinone, Curcumin	Neuroprotective, Antioxidant	Retinal ganglion cell protection
Cataract	Curcumin, Lutein, Zeaxanthin, Quercetin	Antioxidant	Delayed cataract progression
Corneal Inflammation	Curcumin, EGCG, Thymoquinone	Anti-inflammatory	Enhanced corneal healing
Conjunctivitis	Berberine, Curcumin, Quercetin, Catechins	Antimicrobial, Anti-inflammatory	Reduced infection and inflammation
AMD	Lutein, Zeaxanthin, Resveratrol, Curcumin	Antioxidant, Antiangiogenic	Macular protection
Diabetic Retinopathy	Curcumin, Resveratrol, Rutin, Thymoquinone, EGCG	Antioxidant, Antiangiogenic	Retinal protection

Herbal bioactives have shown significant therapeutic potential in the management of various ocular diseases due to their antioxidant, anti-inflammatory, antimicrobial, antiangiogenic, and neuroprotective properties. In dry eye syndrome, compounds such as curcumin, thymoquinone, EGCG, and quercetin help reduce ocular surface inflammation, improve tear film stability, enhance tear secretion, and promote corneal healing. In glaucoma, neuroprotective phytoconstituents including resveratrol, thymoquinone, curcumin, and *Ginkgo biloba* extract protect retinal ganglion cells, reduce oxidative stress, improve ocular blood flow, and help preserve visual function. Cataract formation, which is largely associated with oxidative damage to lens proteins, may be delayed by antioxidants such as curcumin, lutein, zeaxanthin, and quercetin that protect lens epithelial cells and maintain lens transparency. Herbal bioactives also play an important role in the treatment of corneal inflammation and conjunctivitis. Curcumin, EGCG, thymoquinone, and quercetin reduce inflammatory responses, promote tissue repair, accelerate corneal healing, and prevent corneal scarring. In conjunctivitis, berberine, curcumin, quercetin, catechins, and EGCG exhibit

antimicrobial, anti-inflammatory, and anti-allergic activities that help suppress infection, reduce redness, and alleviate ocular discomfort. In age-related macular degeneration (AMD), lutein and zeaxanthin protect retinal tissues by filtering harmful blue light and reducing oxidative stress, while resveratrol and curcumin provide antiangiogenic and neuroprotective effects that help preserve macular integrity and visual performance. [Soni V et al, 2015; Kumar S and Himmelstein KJ, 1995]

Diabetic retinopathy, a major microvascular complication of diabetes, is characterized by retinal inflammation, oxidative stress, vascular leakage, and neovascularization. Herbal bioactives such as curcumin, resveratrol, rutin, thymoquinone, and EGCG target multiple pathogenic pathways by reducing oxidative damage, suppressing inflammatory cytokines, protecting retinal microvasculature, inhibiting VEGF-mediated neovascularization, and preventing retinal neuronal degeneration. Overall, the ability of herbal bioactives to simultaneously target oxidative stress, inflammation, infection, angiogenesis, and neurodegeneration makes them highly promising candidates for ocular therapy. However, challenges such as poor solubility, low stability, and limited ocular bioavailability often restrict their clinical application. Therefore, incorporation of these phytoconstituents into advanced ophthalmic delivery systems, particularly in situ gelling formulations, offers an effective strategy for improving drug retention, bioavailability, and therapeutic outcomes in various ocular diseases.

6. PREPARATION METHODS OF HERBAL BIOACTIVE-LOADED IN SITU GELS [Lin HR and Sung KC, 2000; Miyazaki S et al, 1999; Carlfors J et al, 1998]

Herbal bioactive-loaded ophthalmic in situ gels can be prepared using various techniques depending upon the physicochemical properties of the polymer and the active used. The simplest technique is the direct dispersion method. In this method, the polymer is dispersed in an aqueous medium which is then continuously stirred until complete hydration occurs. The bioactive of a given herb along with other excipients are then added. The cold method is a good technique for thermosensitive polymers like Poloxamer 407 and Pluronic® F127, wherein the formulation components are mixed under refrigeration in order to prevent the gelation from occurring too early as well as the polymer from completely hydrating. The hydration process of the polymer is accomplished before incorporating the drug. Swelling and Hydration of polymeric materials such as HPMC, Carbopol®, sodium alginate, and chitosan are first carried out to give uniform consistency and viscosity. [Balasubramaniam J et al, 2003; Zhidong L et al, 2008; Ruel-Gariépy E, Leroux JC, 2004; Choi HG et al, 1998] The process improves the stability of the formulation. It is the method of solvent evaporation which is generally adopted for the preparation of nanoparticles or polymeric carrier of poorly water-soluble phytoconstituents. After preparation, the prepared polymeric nanoparticles or carriers are incorporated into the gel system to enhance the drug encapsulation, stability and controlled release characteristics. Recent developments in nano-enabled in situ gelling systems that utilize polymers with gel forming capacity have improved ocular retention, permeability and bioavailability through nanotechnology. This includes in situ gels loaded with nanoparticles, liposomal gel, niosomal gel, cubosomal gel and nanoemulsion gel. Systems allow for deeper penetration in cornea, enhancement protection of herbal bioactives from degradation, controlled drug release and better therapeutic impact. Nano enabled methods can be used to treat poorly soluble compounds like curcumin, thymoquinone, quercetin, and resveratrol, as ocular bioavailability of such compounds in conventional formulations is poor.

Table 14. Preparation Methods for Herbal Bioactive-Loaded In Situ Gels

Method	Principle	Suitable Systems	Advantages
Direct Dispersion	Direct polymer dissolution	Simple gels	Easy and economical
Cold Method	Low-temperature hydration	Poloxamer systems	Prevents premature gelation
Polymer Hydration	Controlled polymer swelling	Carbopol, HPMC systems	Uniform viscosity
Solvent Evaporation	Organic solvent removal	Nanoparticles	High encapsulation
Nano-enabled Approaches	Nanocarrier incorporation	Advanced systems	Enhanced bioavailability

Ophthalmic formulations must meet the requirement of sterility. The presence of microbial contaminants can cause severe ocular infections and vision-threatening complications. Autoclaving, membrane filtration, gamma irradiation and aseptic processing are sterilization methods. The sterilization process selected is based on the stability of the polymeric system and the

sensitivity of the herbal bioactive. Aside from being sterile, ophthalmic formulation must have proper pH, isotonicity, clarity, freedom from particulate matter, ocular safety and adequate storage stability. Medicinal agents are prescribed based on their physicochemical properties including solubility, melting point, pKa, hydrophobicity. The selection of a suitable preparation and sterilization method affects the physicochemical properties, drug release behaviour, ocular retention and therapeutic performance of the formulation. [Balakrishnan P et al, 2009]

7. EVALUATION PARAMETERS

The assessment of the quality, safety, efficacy and patient acceptability of herbal bioactive-loaded ophthalmic in situ gelling systems. The characterization of the developed formulation should include the analysis of its physicochemical properties, gelation characteristics, rheological properties, mucoadhesive strength, in vitro drug release profile, corneal permeation, ocular compatibility, stability, and in vivo therapeutic efficacy. Physicochemical evaluation includes appearance, clarity, pH, drug content, and also osmolality. An ophthalmic formulation that is ideal must be clear and homogenous without contamination. It must have a pH in an acceptable range of 6.5–7.4. Furthermore, an ophthalmic formulation must have uniform drug content and same osmolality as that of tear fluid which is between 280 and 320 mOsm/kg. Studies of gelation assess whether something can convert from a liquid to a gel under physiological conditions. Important parameters are gelation temperature, gelation time, gel strength, and gel capacity. Thermosensitive systems should gel at the ocular surface temperature (34–35°C). Also, the gelation has to be rapid along with adequate gel strength to stop precorneal drainage as well as lasting drug release. The gel capacity is determined by observing the formation and persistence of the gel in simulated tear fluid. It indicates the ability of the formulation to retain in the eye for a longer time. Rheological evaluation is carried out to determine viscosity and flow before gel and after gel formation. An ideal in situ gel formulation should show low viscosity before application for easy instillation and high viscosity after gelation for maximum ocular retention. While the in situ ophthalmic gels exhibit pseudoplastic or shear-thinning behavior, it is convenient for the patient and also provides prolonged contact with ocular tissue. [Gupta A and Gupta V, 2019] Mucoadhesive strength is a measure of the ability of the formulation to adhere to the ocular mucosal surface. Made stronger adhesion to mucous membranes which increases residence time and reduces drug loss and enhances ocular bioavailability. In vitro drug release studies of herbal bioactives from the gel matrix can be carried out using techniques such as Franz diffusion cells or dialysis membrane methods. Testing for the release studies is usually done using simulated tear fluid or phosphate-buffered saline and follows a kinetic model such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Such studies help assess the sustained release characteristics of the formulation and optimize polymer used. The ex vivo corneal permeation study evaluates drug transport across biological corneal tissues such as goat, rabbit, porcine or bovine cornea using a Franz diffusion cell apparatus. Parameters flux, corrosion retention, and drug accumulation, permeability co-efficient is assessed to estimate its in vivo absorption the efficiency of formulation permeation-enhancing. It is a safety requirement to carry out ocular irritation assessment of the substance. Either the HET-CAM (Hen's Egg Test–Chorioallantoic Membrane) method or traditional Draize eye irritation test must be used. The formulation may be examined for redness, swelling, hemorrhage, corneal opacity, and any other ocular reaction which is adverse. Stability studies are carried out as per ICH guidelines to see the ability of the formulation to maintain its quality. Under long-term and accelerated storage conditions, various parameters like appearance, pH, drug content, viscosity, gelation behavior, and sterility are monitored. Evaluation of stability assesses shelf life, formulation robustness and commercial viability. Ultimately, an in vivo study reveals all the information with respect to ocular absorption, distribution, therapeutic efficacy and safety. The analysis of pharmacokinetic parameters such as C_{max}, T_{max}, AUC, half-life, and mean residence time is conducted using HPLC or LC-MS/MS analytical techniques, while the pharmacodynamic analysis consists of therapeutic outcomes like lowering of intraocular pressure, increase in tear production, anti-inflammatory effect and retinal protection. All these evaluation parameters are necessary for establishing the quality, safety, efficacy and clinical applicability of advanced herbal bioactive-loaded ophthalmic in situ gelling systems. [Vinardell MP and Mitjans M, 2008]

Table 15. Evaluation Parameters for Herbal Bioactive-Loaded Ophthalmic in Situ Gels

Evaluation Parameter	Method	Purpose
Appearance & Clarity	Visual inspection	Physical quality assessment
pH	Digital pH meter	Ocular compatibility

Drug Content	UV/HPLC	Uniformity assessment
Osmolarity	Osmometer	Isotonicity evaluation
Gelation Temperature	Thermal analysis	Gelation behavior
Gel Strength	Texture analyzer	Mechanical stability
Viscosity	Brookfield viscometer	Rheological characterization
Muco-adhesion	Tensile method	Ocular retention
Drug Release	Franz diffusion cell	Release kinetics
Corneal Permeation	Ex vivo cornea model	Drug absorption
Irritation Assessment	HET-CAM, Draize test	Safety evaluation
Stability Studies	ICH protocols	Shelf-life determination
Pharmacokinetics	HPLC/LC-MS	Bioavailability assessment

8. ADVANTAGES AND LIMITATIONS

8.1 Advantages

The ophthalmic in situ gelling systems loaded with herbal bioactive have advantages over eye drops. By forming a gel upon administration, they increase ocular residence time, thereby decreasing precorneal drug loss and increasing corneal contact. Systems like these enhance the bioavailability in the eyes by increasing the absorption and retention factor of the drug at the site of action. The use of gel matrix helps in keeping the drug concentration at therapeutic level for a longer period of time. It also lessens the frequency of dosing. As a result, patients become more compliant and convenience improved in chronic eye diseases. Moreover, extended retention and regulated release improve therapeutic effectiveness while reducing systemic absorption and harmful effects. In general, these advantages make in situ gels a promising carrier of herbal bioactives for ocular therapy. [Luepke NP, 1985]

8.2 Limitations:

Herbal bioactive-loaded ophthalmic in situ gels have many challenges despite having advantages. Essentially, maintaining sterility is very critical and often difficult for most of the herbal and polymeric compounds as these are sensitive to sterilization. Formulation development is complicated by the need to optimize polymer concentration, viscosity, gelation behaviour and compatibility with herbal bioactives. It is also quite an expensive process. Under high concentration, certain polymers can cause eye irritation. The quality of the product may also be affected due to stability issues like oxidation, photodegradation, hydrolysis, and change in gel properties on storage. Moreover, the quality must be controlled and processes reproducible for scale-up and large-scale manufacturing, which all contributes to a rise in production costs. Obtaining complex regulatory approval for herbal materials is not easy as it involves extensive safety, efficacy, stability, and standardization data. In order for overcoming these limitations to attain successful commercialization and clinical application of ophthalmic in situ gelling systems. [Jain AK et al, 2013; Yellepeddi VK and Palakurthi S, 2016; Kumar R and Sinha VR, 2020]

Table 17. Limitations of Herbal Bioactive-Loaded Ophthalmic in Situ Gelling Systems

Limitation	Major Concern	Impact on Product Development
Sterility Challenges	Microbial contamination, sterilization sensitivity	Reduced product safety
Formulation Complexity	Multiple variables requiring optimization	Increased development time
Polymer-Related Irritation	Ocular discomfort and redness	Reduced patient acceptance
Stability Concerns	Drug degradation and viscosity changes	Reduced shelf life
Scale-Up Difficulties	Manufacturing reproducibility	Commercialization challenges
Regulatory Hurdles	Stringent approval requirements	Delayed market entry

9. Recent Advances and Emerging Trends:

Recent advancements in nanotechnology, biomaterials, polymer science, targeted delivery systems, and artificial intelligence are making an impact in the ophthalmic drug delivery space. The innovations are to beat the drawbacks of conventional eye drops like poor bioavailability, speedy clearance of drugs and limited ocular penetration. The combination of herb bioactives with sophisticated in situ gelling systems offer a potential strategy for improved ocular retention, sustained release of drug and therapeutic efficacy. In situ gels utilizing nanotechnology – including systems loaded with nanoparticles, liposomes, niosomes, cubosomes, and nanoemulsions – have been established as important means of improving the solubility, stability, permeability and bioavailability of poorly soluble herbal compounds including curcumin, thymoquinone, quercetin and resveratrol, and more. Multifunctional nanocarriers improve therapeutic efficacy through targeted delivery, controlled release, enhanced tissue penetration, and high drug-loading capacity. Their effectiveness has been demonstrated for the treatment of glaucoma, diabetic retinopathy, age-related macular degeneration, and ocular infections. The development of stimuli-responsive smart gels that respond to specific physiological triggers such as pH, temperature, ionic strength, etc. is very promising. These smart systems help improve a number of therapeutic treatment outcomes as they help to attain controlled release and site-specific release of drug along with prolonged ocular retention. The advanced approaches for biomaterials design like self-healing hydrogels, injectable hydrogels, biomimetic gels and bio responsive nanogels are predicted to play an important role in future ophthalmic therapies. [Kakkar S and Kaur IP, 2014; Bochot A and Fattal E., 2012; Natarajan JV et al, 2011] Treatments composed of multi-herbs are also in the spotlight. This is because it can induce multi-phytoconstituents which act synergistically to provide enhanced antioxidant, anti-inflammatory, neuroprotective, antiangiogenic etc. effects. Combinations like curcumin and resveratrol, thymoquinone, lutein, and zeaxanthin can give a broader therapeutic coverage and improved clinical outcomes. Furthermore, ocular delivery systems targeted, with the help of surface-modified nanocarriers, mucoadhesive polymers, and ligand-mediated targeting, enhance drug accumulation in specific ocular tissues such as retina, macula, optic nerve, and cornea along with reducing systemic exposure. Besides, ophthalmic formulation development is increasingly benefitting from artificial intelligence and machine learning to facilitate polymer selection, predict gelling behavior, model drug release profiles, design of nanocarriers, estimate stability, and QbD. A faster development process and lower research costs, along with improved formulation accuracy and accelerated commercialization. They aim to use innovative and emerging technologies to meet the growing demand for ocular bioavailability of herbal bioactive compounds. Overall, the future of ophthalmic drug delivery systems (DDPs) would be nanotechnology, smart biomaterials, targeted delivery strategies, combination phytotherapy and AI-based formulation design. The successful clinical translation of herbal bioactive-loaded in situ gelling systems should hold promise. [Wadhwa S et al, 2009]

10. FUTURE PERSPECTIVES:

The future of herbal bioactive system for Ophthalmic - in situ gelling formulation is the incorporation of phytopharmaceuticals and integration of advanced novel technologies such as nanotechnology, smart biomaterials, artificial intelligence (AI), targeted drug delivery and precision medicine. The most promising systems are manufactured in different carriers, with exceptional release pattern and controlled formulation and having demonstrated good results in animal models. However, successful clinical translation of these products would require extensive evaluation of the safety, efficacy, pharmacokinetics, stability, acceptability and regulatory requirements for human use. In the future, scientists should develop more standardized approaches that will bridge the gap between laboratory development and clinical application. This would involve planning for clinical trials and quality control. Standardization of herbal bioactives remains a critical requirement for successful commercialization. Plant source, cultivation conditions, harvesting practices, extraction methods, and storage can vary phytochemical composition and therapeutic performance. Advanced analytical techniques, such as HPLC fingerprinting, LC-MS/MS profiling, metabolomics, and chemometric analysis, are anticipated to play a key role in the establishment of batch-to-batch consistency, quality assurance (QA), and regulatory acceptance for herbal ophthalmic. The latest growth area in ophthalmology is personalized ocular therapy. The next generation formulations could be designed based on the individual patient characteristics including genetic make-up, disease progression, ocular physiology and drug response. The therapeutic outcomes of chronic ocular diseases can be improved and thereby the adverse effects reduced through precision formulation approaches combined with pharmacogenomic-guided therapies and digital monitoring. [Agarwal R et al, 2014] Theragnostic ophthalmic systems are multifunctional systems that can deliver therapeutic action while providing a diagnostic function in one platform. The introduction of these systems with herbal bioactives, nanocarriers and in situ gel matrices will help to diagnosis, monitor and treat diseases at the same time with imaging agents, fluorescent probes, or biosensors. Applications for such techniques might be especially beneficial for diabetic retinopathy, glaucoma, age-related macular degeneration, and other progressive eye diseases. [Kaur IP et al, 2008] Harmonized

regulations, standardization of herbal materials, stability testing over long durations, toxicological evaluation and strong clinical evidence will be needed for future commercialization of herbal ophthalmic formulations. The cooperation between the sectors and universities, as well as between the government and business, will shorten the development and marketing time of the products. The novel research areas such as intelligent nanocarriers, smart stimuli responsive hydrogels, gene and peptide delivery systems, artificial intelligence-based formulation design, green pharmaceutical technologies and biopolymers are likely to open up new avenues for advanced ophthalmic products. The next generation of ophthalmic therapeutics will largely involve the convergence of herbal medicine, nanotechnology, biomaterials, artificial intelligence and precision medicine. These advancements can improve the delivery, efficacy, safety, and patient acceptability of herbal bioactive-loaded in situ gelling systems that could play a pivotal role in preventing, diagnosing, and treating ocular disorders in the future. [Garg A et al, 2004]

11. CONCLUSION:

The use of in situ gel ophthalmic systems that are loaded with herbal bioactives may provide a better alternative than conventional ocular drug delivery. Ocular drug delivery has unique challenges, including rapid turnover of tears, nasolacrimal drainage, poor corneal permeability, and low ocular bioavailability, all of which considerably limit the therapeutic efficacy of conventional eye drops. In situ gelling systems are recognized as effective solutions that can overcome these barriers through prolonged precorneal residence, sustained drug release, enhanced bioavailability, and better patient compliance. A large variety of natural, semi-synthetic and synthetic polymers have been successfully employed in the formulation of stimuli-responsive ophthalmic gels, exhibiting sol-to-gel transition in response to a variety of physiological triggers such as pH, temperature and ionic strength. By giving a suitable milieu for the incorporation of herbal bioactives, these systems could manage the release of bioactive at ocular tissues. According to researchers, herbal bioactives and the respective compounds such as curcumin, thymoquinone, quercetin, resveratrol, berberine, lutein, zeaxanthin, epigallocatechin gallate, rutin and catechins have a huge therapeutic potential in the treatment of various ocular diseases. The antioxidant, anti-inflammatory, anti-microbial, anti-angiogenic and neuroprotective properties make them capable of targeting multiple pathologic pathways implicated in diseases such as dry eye disease, glaucoma, cataract, conjunctivitis, age-related macular degeneration, corneal inflammation and diabetic retinopathy. Still, their clinical utility is often restricted due to issues such as poor aqueous solubility, instability and limited ocular permeability. The use of these phytoconstituents in these systems can help to overcome these limitations and increase therapeutic efficacy. Recent developments in in situ gels, multifunctional nanocarriers, smart polymers, targeted ocular drug delivery systems, and AI-based formulation optimization in herbal ophthalmic therapeutics have shown great promise in recent years. The enhanced drug loading, targeting, retention, release, and personalization capabilities offered by these new medicines and technologies are substantial. While notable achievements have been made in this arena, serious challenges still exist such as standardization of herbal materials, large-scale manufacture, sterility assurance, long-term stability, regulatory approval and clinical validation. These challenges could be addressed through the collaboration of pharmacist scientists, clinicians, regulators, and industries in an interdisciplinary manner for the successful clinical translation and commercialization. Ultimately, herbal bioactive-loaded ophthalmic in situ gelling systems are likely to pave a promising way for ocular therapy. The capacity of these formulations to combine the therapeutic potential of natural products with innovative drug delivery systems opens up a new patient-friendly approach in the management of both anterior and posterior segment diseases. Future ophthalmic product research and technological innovations can be expected to develop safe, effective, and commercially viable products that can improve visual health and quality of life around the world.

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AUTHOR CONTRIBUTIONS

Dr. Anuradha Chivate: Conceptualization

Archana Shaha: Writing—Review & Editing

Dr. Niranjan Chivate: Data Curation, Formal Analysis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Ethical approval was not required for this study.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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