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HERBAL OPHTHALMIC DRUG DELIVERY: A COMPREHENSIVE REVIEW

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ABSTRACT

The purpose of the review is the Dry eye disease is a multifactorial disorder of the tear film and ocular surface that cause discomfort visual disturbance and potential damage to the eye. Ophthalmic treatment like hyaluronic acid based eye drop, hydroxypropylmetylcellulose, and nano emulsion provide temporary relief because of the poor drug bioavailability and ocular barriers. To overcome these there are herbal drug is used like Aloe Vera. Aloe Vera has many active constituents which include vitamin, enzyme, anthraquinone, and polysaccharide which give the anti- inflammatory, antioxidant, antimicrobial, and wound healing, which is helpful in the restore tear film, reduce inflammation and promote the corneal health in DES. Hence the aloe Vera based ophthalmic drug delivery gives safe, biocompatible, and conventional synthetic treatment for dry eye disease.

KEYWORDS: Herbal bioactives, Mucoadhesive polymer, Ocular diseases, Conventional ocular drug delivery.

INTRODUCTION

Ocular conditions and medicinal plants or traditional eye remedies A- ethnobotany as a major source of drugs

Ethnobotany is "any study pertaining to plants," according to Martin (1995), which describes how local people interact with their natural surroundings. Traditional herbal medicine, a

branch of ethnobotany, describes the medicinal benefits of herbal remedies that go beyond the active components of prescription drugs. The earliest known kind of medical care is traditional herbal medicine, which has been used in almost every civilization on the planet. based on methods for gathering plants at random and ethnomedicine in order to find novel pharmacologically bioactive compounds. Finding plants with beneficial therapeutic qualities requires the application of folklore from a wide range of civilizations. Even while plants have many traditional uses, only a small number of species have been tested for biological activity, and little is known about eye problems.[1]

The most popular technique for treating many eye disorders is topical delivery to the eye. Because of the eye's robust defenses, ocular medicines are only partially absorbed. Drainage, baseline lachrymation, reflex lachrymation, and blinking are a few of the mechanisms that remove dirt from the eye's surface. Additionally, the cornea's physiology, composition, and barrier function facilitate drug absorption. Effects that are toxic or extended exposure to very concentrated liquids can harm the eyes. The ocular dose form was further refined by the use of a mucoadhesive, which has proven useful in oral and mucosal applications. In one study, the relationship between mucins and synthetic and natural polymers was examined. Precorneal preparation was prolonged when there were interactions with the mucous layer or ocular structures. It was discovered that a number of mucoadhesive polymers improved drug absorption, sped up wound healing, and protected stem cells. Due to its enormous size and distinct physiology, the eye prevents medications from entering the proper ocular regions. For many years, effective topical administration has piqued the curiosity of researchers.

Increased drug residence time and appropriate ocular penetration have been their objectives.[2] The process by which the drug carrier system adheres to a particular biological substrate is called bioadhesion. Adhesion to the mucosal surface denotes mucoadhesion. The mucosal fluid is thought to play a significant role in the mucoadhesion phenomenon, which serves as a physical barrier or defense mechanism against chemical or biological stimuli from the outside world. Maintaining hemostasis, or the equilibrium of water and electrolytes, and clearing the eyes of debris are further benefits.[3] To enable the tear film to carry out its essential protective, nutritional, mechanical, and optical roles, ocular mucus helps the film adhere to the surface of the eye. Choosing mucoadhesive polymers that can form strong adhesive connections even at the low mucosal thickness encountered is necessary since ocular mucus is extremely thin.[4]

ROLE OF HERBAL COMPONENTS IN VARIOUS OCULAR DISEASES

An endless supply of biologically active substances has always been found in nature. People have looked to plants and animals for resources to heal eye conditions since the dawn of time. Nevertheless, controlled interventional investigations have shown that the safe use of plant and animal extracts was only possible after the Industrial Revolution. Developing medications that can lessen blindness from glaucoma and managing the pain associated with eye surgery are two of the main issues facing ocular pharmacology. A number of ocular hypotensive medicines, including physostigmine from the Physostigma venenosum plant, have been developed as a result of the search for a medication that may successfully reduce intraocular pressure and regulate the progression of glaucoma.

Eventually, eye surgery was made possible by the anesthetic qualities of cocaine, which was isolated from Erythroxylon cocaine. In an effort to find compounds that may offer extra advantages to eye tissue and vision, a number of novel natural compounds have been studied. Research in this area has increased due to new findings of plant extracts and animal tissues having anti- inflammatory, wound-healing, antibacterial, antioxidant, anticancer, and antiangiogenic qualities. The pharmaceutical industry continues to look for novel active molecules from natural sources and to review previously identified natively derived compounds, even with technological advancements in drug synthesis. This review article concentrates on the bioactive chemicals having scientifically demonstrated advantages for ocular tissues, despite the fact that many naturally occurring compounds are known.

Herbal extracts have long been used to treat ophthalmic disorders. The first documented use of a natural remedy for an eye condition was the topical use of the macerated fruit of the Atropa belladonna by the Egyptians. However, scientific research in physiology and pharmacology as well as technological advancements in the pharmaceutical industry during the 19th and 20th centuries were necessary for the development of safer and more effective ophthalmic medications.[5] The natural antioxidant, anti-inflammatory, and nutritional qualities of medicinal plants including fennel, lemon, saffron, cornelian cherry, green tea, turmeric, grapes, celery, and dandelion offer great promise for improving visual function and preventing eye disorders. An all-natural method of preserving eye health and improving vision is to consume these plants. It is possible to draw the conclusion that these medicinal plants have promise as supplemental therapies and preventative measures for improving vision and protecting ocular health from aging and environmental damage according to the

natural substances found in them. Incorporating these plants can greatly support and improve eye health, especially when paired with a nutritious and well-balanced diet.[6]

DRY EYE DISEASE

An ocular surface and tear film multifactorial disease, dry eye syndrome (DES) causes decreased tear production, discomfort, and visual disruption along with possible ocular surface damage. DES is linked to inflammation of the ocular surface, increased tear osmolarity, and tear film instability.[7] The natural components of human tears and antioxidants are typically absent from tear replacements used to treat DED. But they can be added to with natural active substances, such as herbs, and their derivatives to increase a product's medicinal potential.[8]

RETINOPATHY

The crude prevalence of diabetic retinopathy-related visual impairment and blindness increased globally between 1990 and 2015, primarily due to the rising prevalence of type 2 diabetes, especially in low- and middle-income countries.[9] About 30 to 40% of people with diabetes mellitus develop diabetic retinopathy (DR), the main visual consequence of the disease. Over 100 million people worldwide have DR, which is a major cause of blindness and visual impairment, particularly in working-age adults.[10] Blindness or vision impairment can result from retinopathy, a secondary injury of retinal neurons and vascular cells brought on by metabolic/cardiovascular disease or radiation exposure. It may be possible to avoid early-stage retinopathy over the long run by using certain bioactive chemicals derived from plants.

The unstable polyphenols and carotenoids found in these botanicals necessitate technological advancements for specific ocular applications. Hydrogels and other polymers can be used to bioprint wearable ocular devices, such as contact lenses, implants, and inserts, which can help advance non-invasive delivery of bioactive compounds directly to the eyes. Computational and AI-assisted methods are novel approaches for bioprospecting bioactive compounds and protein targets specific to retinopathy pathways to expedite clinical validation for drug development and save costs on experimental resources and time.

The benefits of herbal-based compounds for the treatment of early retinopathy are highlighted by computational, experimental, and clinical studies. These compounds are inexpensive, widely available, and have few side effects. They can be taken as supplements or through diet, and they are especially effective against oxidative stress, inflammation, apoptosis,

angiogenesis, and deficiencies in visual function. Particularly, polyphenols and carotenoids were the primary bioactive substances helpful in the treatment of early retinopathy. The bioaccumulation of macular carotenoids (lutein and zeaxanthin, which make up 80–90% of the total carotenoids) in the retina and macular following consumption of foods or supplements high in carotenoid has been linked to improvements in eye functions, indicating its significance in maintaining and promoting overall eye health. Moreover, developments in polymers such as hydrogel formulations and encapsulations have laid the groundwork for a variety of uses, allowing the delivery of innovative medications for ailments other than retinopathy and maybe treating more difficult illnesses.

Although herbal supplementation has potential for preventing disease, especially in the early stages, its translational applicability for treating established disorders is limited. It is not appropriate as a primary therapeutic intervention due to its delayed beginning of effect, substantial inter-individual variability in bioavailability, and reliance on dietary and lifestyle factors. Instead, long-term preventative measures in public health and nutrition programs aimed at at-risk groups have the most translational benefit.[11]

GLAUCOMA

The term glaucoma, which comes from the Greek glaukós, which means "green" or "light grey", refers to a range of illnesses with varying pathophysiologies, risk factors, symptoms, therapies, and prognoses. A common characteristic of both is the gradual degeneration of the optic nerve, which includes progressive excavation of the optic disc, thinning of the retinal nerve Fiber layer, and loss of retinal ganglion cells.[12] Traditionally, topical medication in the form of eye drops is the first line of treatment. These medications either promote outflow from the eye or decrease the generation of aqueous humour.[13]

To create formulations that incorporate well-known herbal constituents and an efficient eye drop. Our hypothesis was that, in accordance with recent glaucoma studies, this formulation may lower intraocular pressure (IOP), lessen oxidative stress and inflammation, and offer neuroprotection, hence delaying the development of irreversible visual neuropathy. This work is limited by its brief trial period and use of a single rodent model. Extended investigations and the application of these results to populations of glaucoma patients in humans might be beneficial for future research. Finally, our structural, molecular, and functional investigations show that the herbal formulation shows great therapeutic promise as an eye drop treatment and

has strong protective benefits against the development of glaucoma.[14] GBE and bilberry have been investigated as potential neuroprotective drugs for the treatment of glaucoma. Both are appealing options since they are reasonably priced, easily accessible, and safe. The data pertaining to their effectiveness, however, is mixed. Their impact on glaucomatous VF alteration is unclear.

It has been demonstrated that medical marijuana's potential to reduce intraocular pressure has positive impacts on the treatment of glaucoma. But because this effect is transient and necessitates several daily dosages, patients run the danger of developing cannabis use disorder. Since there is presently no proof that using medicinal marijuana in any form can change the course of glaucoma, its short duration of action, wide range of adverse effects, and risk for addiction make it unsuitable as a standard of treatment for treating glaucoma patients. Glaucoma, in general, is a chronic, diverse group of illnesses that is not always controlled by the medications that are already on the market. There is great promise for using medicinal herbs to treat glaucoma since some of them can work by protecting retinal ganglion cells. The data is inconclusive, despite the strong theoretical justification and preliminary clinical support for the advantageous effects of GBE and bilberry as supplemental treatments. Studies examining the impact of GBE, bilberry, and marijuana on the progression of glaucoma in contrast to the currently available pharmacological medicines are also lacking. Future research on the potential of medicinal plants for glaucoma treatment must involve larger sample sizes and longer time frames.[15]

AGE-RELATED MACULAR DEGENARATION (AMD)

The gradual loss of macular pigment or photoreceptors is the cause of AMD, a chronic retinal disease. It is one of the main reasons why older adults over 50 experience vision loss or impairment. Age, arteriosclerosis, family history, hypertension, hypercholesterolemia, obesity, and smoking are the main risk factors. Numerous risk factors, including advanced age, smoking, air pollution, high blood sugar (hyperglycaemia), elevated metabolic rates, and exposure to light, might result in age-related eye illnesses. These risk factors contribute to oxidative stress by generating unregulated reactive oxygen species (ROS). Based on scientific evidence, dietary plant- based natural products may be helpful in managing, treating, and preventing age-related eye problems. Depicts the probable processes by which dietary plant-based natural compounds guard against age-related eye disorders. Because dietary plant natural products have the ability to scavenge free radicals and decrease enzymes involved in

the generation of reactive oxygen species, they have shown both preventative and therapeutic effects. The oxidation reaction that takes place in photoreceptor cells is neutralized, and the antioxidant defense mechanism is enhanced.

They've also demonstrated the ability to increase ocular blood flow, control inflammatory indicators and the blood-retinal barrier, and lessen opacification of the suppressed lens and retinal pigment epithelium apoptosis. A summary of the advantageous benefits of the dietary plant natural products under study can be seen below.

In addition to lowering intraocular pressure (IOP) and raising antioxidant activity, caffeine also decreases the activities of SOD, CAT, and MDA.

Curcumin suppresses oxidative stress, lowers pro-inflammatory cytokines, inhibits lipid peroxidation, reactive oxygen species, and vascular endothelial growth factor, inhibits DNA damage by reducing NFkB activation, and increases antioxidant enzymes.

Epigallocatechin gallate (EGCG) lessens vascular leakage and permeability in VEGF, decreases angiogenesis, VEGF, reactive oxygen species, and retinal ganglion cell apoptosis. It also guards against mitochondrial dysfunction. Reduces oxidative stress and inflammation with lycopene.

RPE cells are protected by quercetin, which also reduces pro-inflammatory chemicals, ROS, VEGF, and neuronal death. Reseveratrol decreases inflammatory chemicals, raises glutathione (GSH), controls oxidative stress, reactive oxygen species, vascular endothelial growth factor, and lipid peroxidation.[16]

Herbal Bioactives Used in Ophthalmic Applications

Approximately 200 plant species have been reported to support the treatment of eye issues globally, and certain plant species have been promoted for their ophthalmic effects in Traditional Indian Medicine.[17] According to data from the World Health Organization (WHO), at least 75% of people worldwide receive their medical care from medicinal herbs. The pharmacognosy, chemistry, pharmacology, and clinical therapeutics of Ayurvedic and Chinese therapeutic systems are actually covered in outstanding research publications regarding medicinal plants.[18]

- **Aloe Vera**

Aloe vera is a type of aloe that is especially well-liked for its therapeutic qualities. Vera means true in Latin, and Aloe vera is derived from the Arabic term "Alloeh," which means brilliant bitter substance. Two millennia ago, aloe vera was considered the universal remedy by Greek scientists. "The plant of immortality" is how the Egyptians referred to aloe. Aloe is grown in more than 550 species worldwide. Only two species are being cultivated economically, though, with Aloe barbadensis Miller and Aloe aborescens Miller being the most often used. Mexico, the nations of the Pacific Rim, India, South America, Central America, the Caribbean, Australia, and Africa are habitats for aloe.

Aloe plants have rosette-shaped leaves that develop from the base. Mature plants typically reach a length of 28 to 36 inches, although they can reach heights of 2 and a half to 4 feet. Each plant typically has 12 to 16 leaves, which can weigh up to three pounds when fully grown. There are three layers in every leaf: A transparent inner gel that is composed of glucomannans, amino acids, lipids, sterols, and vitamins make up the remaining 99% water.

Anthraquinones and glycosides can be found in the bitter yellow sap that makes up the intermediate layer of latex. The rind, a thick outer layer of 15–20 cells, is protective and produces proteins and carbs. Every six to eight weeks, the plants can be harvested by removing three to four leaves from each plant.[19]

The therapeutic and medical benefits of aloe vera are numerous. Ancient writings such as the Sharangadhar Samita, Kaiydeva Nigantu, and Bhavprakash Nigantu have all noted the medicinal benefits of aloe vera. Numerous illnesses, including Vrana, Kustha, Gulma, Pliharoga, Yakritvridhi, Kaphaja Jwara, Granthi, Agnidagdha, Vishaphota, Pita-rakta vikar, Chuddraroga, and others, have been treated using the herb (Aloe vera) suggested in the clinical investigation. Aloe vera may help treat dry eye, inflammation, skin disorders, and other conditions, according to a number of experimental and clinical investigations. This medication was chosen to evaluate dry eye symptoms in light of these considerations.[20]

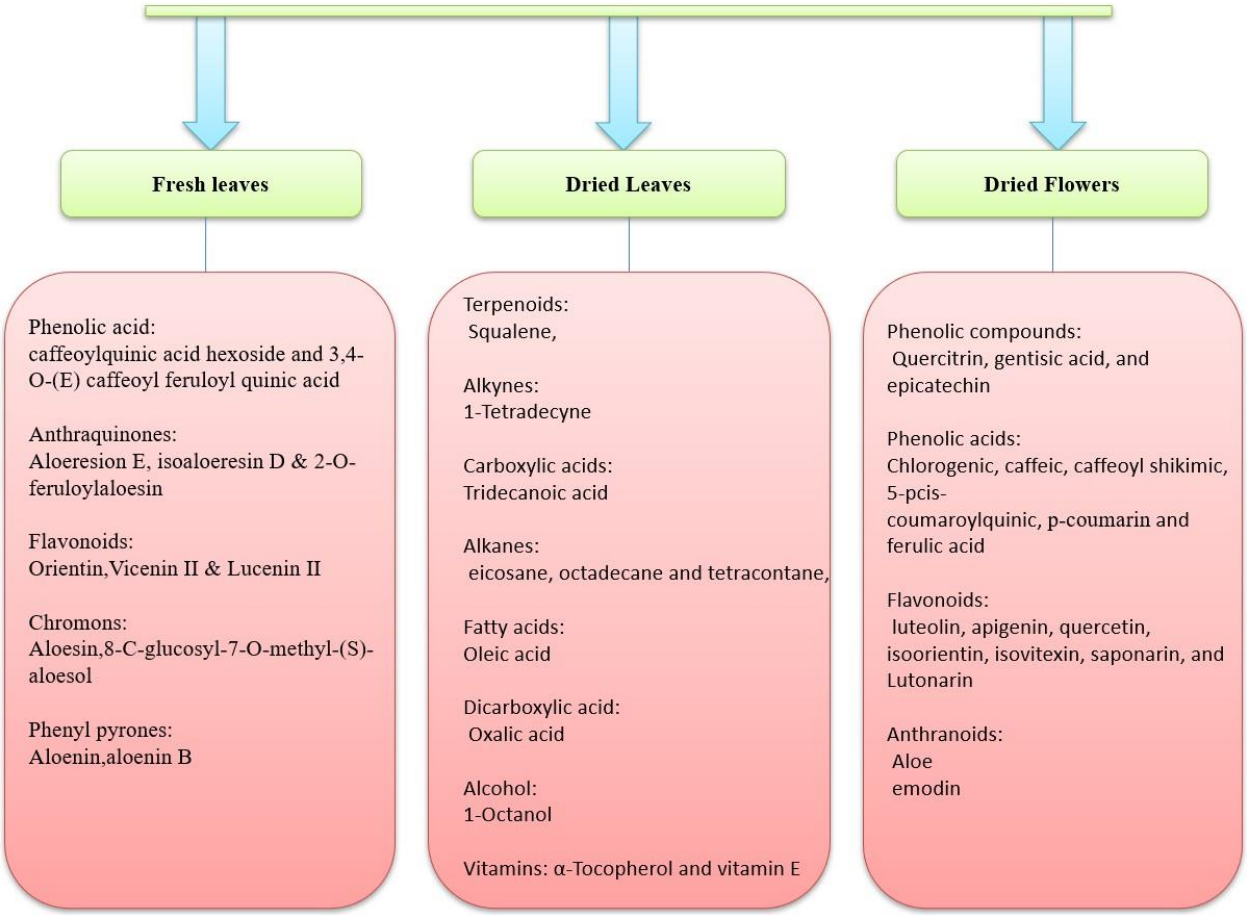

Figure 1: Chemical constituents present in Aloe vera.

- **Garlic (Allium Sativum Linn)**

A popular spice found all throughout the world, garlic (Allium sativum L.) belongs to the Alliaceae family. It is utilized in traditional medicine to prevent and treat a variety of illnesses and ailments in addition to being a nutritional component.[21] Numerous human and animal studies have noted the medicinal qualities of this edible herb, which is also commonly used as a seasoning and flavouring.[22]

A species of onion belonging to the Allium genus, Allium sativum is often referred to as ajo or gallic. A common seasoning in Asia, Africa, and Europe, it is native to central Asia and has long been a mainstay in the Mediterranean region.[23] Supplementing with garlic may help individuals with diabetic macular oedema by improving visual acuity, lowering CMT and IOP, and possibly serving as an adjuvant treatment. Patients with diabetes experienced satisfactory tolerance to garlic, and no notable side effects that would have disrupted the safety profile were noted.[24]

- **Turmeric**

The primary ingredient of turmeric (Curcuma longa, a flowering plant belonging to the ginger family, Zingiberaceae), curcumin[1,7-bis-(4-hydroxy-3-methoxyphenyl) -hepta-1,6-diene-3,5-dione], is recognized to have a variety of pharmacological effects, especially anti-inflammatory and antioxidant qualities. Given that many eye disorders, including diabetic retinopathy (DR), age-related macular degeneration (AMD), glaucoma, and anterior uveitis, have an underlying inflammatory process.[25] According to preliminary experiments, surfactants and cosolvents can effectively solubilize curcuminoids in aqueous media by solubilizing them up to 200 mg w/v. To improve the curcuminoids' water solubility, the current technique coats them with surfactants and a cosolvent.

An ophthalmic eye drop dispenser that contains an ophthalmic (topical) composition that includes a therapeutically effective quantity of a pharmaceutically acceptable surfactant or cosolvent, as well as an effective amount of natural or synthetic curcuminoids, to effectively increase the solubility of the naturally active or synthetic component(s) used to prepare the composition(s).

This disclosure's composition(s) is effective in extending the therapeutic duration and have no negative side effects.[26]

Curcumin's effects on the eyes are not yet being studied in human trials. Given that curcumin has showed promise in previous animal research, this is the next obvious step.

Future research contrasting conventional therapies like AREDs vitamins with curcumin particles or oral curcumin should next be conducted.[27]

Mucoadhesive polymers For Ocular Delivery

Penetration enhancers and mucoadhesive polymers that raise the tear film's viscosity are two strategies that use lower concentrations of active ingredients to produce more noticeable therapeutic benefits while minimizing undesirable systemic effects.[28] The tendency of substances, particularly medications, to draw in and stick to the body's mucosal membranes results in mucoadhesion, which extends the duration of residence after topical ocular administration. The mucoadhesion of an ocular drug delivery vehicle (DDV) is influenced by a number of parameters, including the tears' composition, physiochemical characteristics, and structure. A successful mucoadhesive DDV needs to come into close contact with the mucous

membrane and pierce it deeply enough to establish a robust interaction between the particles and the mucin network.[29]

Mucin, a glycoprotein secreted by the cornea's goblet cells, creates the thin film layer that covers the cornea's surface. Mucin may absorb 40–80 times its weight in water and is composed of a lengthy straight-chain peptide with many oligosaccharide chains attached. Organic and inorganic (synthetic) mucoadhesive polymers attach to mucin and remain in close contact to it for as long as it is present, enabling appealing medication delivery. Numerous researchers have developed methods for describing the bioadhesion of a broad range of polymers. Robinson claims that polyanions are more poisonous and bioadhesive than polycations.[30]

Polymer application is a popular tactic for long-term ocular medication delivery. When the viscosity is raised, but not to a significant degree, the eye drop's residence period on the surface of the eye is extended without causing any negative effects like irritation or visual disorders.[31] Dry tablets with dexamethasone-loaded micelles embedded in an alginate matrix that are delivered using a particular preocular applicator. They showed that, in comparison to the commercially available eyedrop formulation Maxidex®, which is based on dexamethasone, the usage of this technology could boost the ocular drug bioavailability by 2.6 times. Fenofibrate was also administered by PLGA/PVA NPs, which demonstrated therapeutic benefits for neovascular age- related macular degeneration and diabetic retinopathy. created PLGA NPs with bevacizumab as a treatment for age-related macular degeneration using polyvinylpyrrolidone. Despite the fact that this release might be modified by altering the drug/polymer ratio, this system demonstrated a sustained drug-release for more than 91 days. Chitosan (CH), a naturally occurring hydrophilic cationic polysaccharide, is another often utilized polymer for creating micelles for ocular administration. This polymer is perfect for medication delivery in the mucosa and ocular regions due to its excellant mucoadhesion and penetration qualities.[32]

Sr No.	Polymers	Application in Ocular Drug Delivery System	References
1	Chitosan	Antibacterial , Mucoadhesive , permeability enhancer	44
2	Scleroglucan	viscosifying agent	45
3	Sodium alginate	Mucoadhesive, controlled-release qualities and low cellular toxicity, wound healing, and tissue recovery	46, 47

4	xanthan gum	Enhancing the viscosity of solutions, thereby prolonging contact time	48
5	Gellan gum	Anti-glaucoma, Anti-inflammatory, Antibiotic, Bacterial conjuctivitis, bacterial keratitis, Fungal keratitis	49

A common polycationic hydrophilic polymer in ocular formulations is chitosan (CH). It possesses bioadhesive qualities, a cationic charge, and permeability-enhancing qualities. The safety of chitosan in ocular administration has been the subject of several investigations. At pH >6.5, it can transform into hydrogel when it comes into touch with physiologically induced tear fluid.

Additionally, it inhibits the likelihood of infection following ocular injection and has antimicrobial properties.[33]

Conventional Ocular Drug Delivery

Figure 2: Conventional Ocular Drug Delivery.

Topical solutions, one of the traditional drug delivery methods used to treat ocular illnesses, have a bioavailability of less than 5% because of significant precorneal loss. Suspensions,

gels, and ointments are used to reduce precorneal loss. As drug administration to the ocular tissues advanced, several new drug delivery mechanisms were created.[34] Eye drops, ointments, emulsions, suspensions, and polymeric gels are some of the common ocular medication delivery methods available on the market.[35]

EYE DROP

Numerous experimental investigations have been carried out by various writers to demonstrate the actions of various Ophthacare substances and components. Eight herbs are combined to make ophthacare. It is a translucent, colourless, and odourless aqueous extract of these eight plants: Carum copticum seeds: 0.60% w/v; Terminalia beberica fruits: 0.65% w/v; Emblica officinalis fruits: 1.30% w/v; Curcuma longa rhizome: 1.30% w/v; Ocimum sanctum leaves: 1.30% w/v; Rosa damascena petals: 1.10% w/v; Cinnamomum camphora crystals: 0.5% w/v; Meldespumapum honey: 3.70% w/v. Gas chromatography is used to standardise the formulation through fingerprint analysis.

In an open prospective multicenter clinical trial, patients with a variety of ocular conditions—including conjunctivitis, conjunctival xerosis (dry eye), acute dacryocystitis, degenerative conditions (pterygium or pinguecula), and postoperative cataract patients—were given a herbal eye drop preparation called Ophthacare. This preparation contains the fundamentals of several herbs that have been traditionally used in the Ayurvedic medical system since ancient times. Carum copticum, Terminalia bellirica, Emblica officinalis, Curcuma longa, Ocimum sanctum, Cinnamomum camphora, Rosa damascena, and Meldespumapum are a few of them. It has been reported that these herbs have anti-inflammatory and anti-infective qualities.[36]

CONTACT LENSES

The dynamic portion of the eye's optical system, the crystalline lens, is located behind the iris and is in charge of focussing the picture onto the retina. The presence of any lens opacities or lack of transparency is what defines a cataract. Reduced contrast sensitivity, colour disruption, glare, and reduced vision are the most typical signs of cataract. Lens changes may also be indicators of ageing and systemic health in the general population. Cataracts are divided into three traditional kinds based on the type of lens opacities: cortical, posterior subcapsular, and nuclear. These kinds can also be linked to one another, and can eventually lead to complete lens opacification if left untreated. Age, diabetes, steroid usage, trauma, and family history are some of the most frequent causes of cataracts in adults. Additionally,

congenital cataracts are quite common.[37] Ocular disorders offer a special potential and challenge for the development of new treatments.

The eye's accessibility, compartmentalization, immunological privilege, and size make it a unique target for therapy. Numerous therapeutic delivery approaches that affect long-term efficacy, toxicity, invasiveness, and delivery range are being studied for eye illnesses. Although gene, cell, and antibody treatment as well as the administration of nanoparticles directly address diseased areas, their length of therapeutic delivery may be restricted, and their effects may be localized. On the other hand, ocular implants and contact lenses can more successfully provide long-lasting and extensive therapy delivery; yet, they may cause the medicines to become more diluted, which could lead to decreased efficacy. Typically used for vision correction, contact lenses offer a possible effective non-invasive topical drug delivery approach for the eye, especially for the delivery of therapy-loaded nanoparticles. Contact lenses are placed on top of the cornea's aqueous layer.[38]

EYE OINTMENT

to ascertain whether applying 5% tea tree oil ointment (TTOO) to the lids can alleviate the irritation in the eyes that is linked to ocular demodicosis. After four weeks of treatment with chlortetracycline hydrochloride eye ointment lid massage, twenty-four patients with ocular irritation and Demodex switched to TTOO for an additional four weeks. Every two weeks, they were evaluated, and the severity of their itching was rated as 0, 1, 2, or 3. A comparison was made between the changes in itching ratings and Demodex numbers.

All 24 patients reported itching ranging from 1 (n = 3), 2 (n = 15), and 3 (n = 6) for a duration of 2 weeks to 2 years prior to therapy, even if they had previously taken topical antibiotics, anti- inflammatory drugs, or antiallergy drugs. There were 5.5 6 1.6 demodex counts per 8 epilated lashes for all patients, but 4.6 6 1.5, 4.8 6 1.9, and 7.1 6 2.1 for patients with grade 1, grade 2, and grade 3 itching, respectively ($P < 0.05$ between grade 2 and grade 3). There were no changes in irritation and Demodex counts in all patients following four weeks of treatment with chlortetracycline hydrochloride eye ointment (P. 0.05). However, 16 patients experienced complete itching reduction following 5% TTOO treatment, whereas the remaining 8 patients experienced varying degrees of relief ($P < 0.01$). Overall, the number of Demodex dropped to 0.7 6 0.8 ($P < 0.01$).

Ocular itching is strongly associated with Demodex infestation, and regular lid massage with

5% TTOO reduces Demodex levels while also resolving symptoms. In spite of the positive outcomes of lowering Demodex counts and alleviating symptoms, this descriptive trial of treating Demodex- related ocular irritation with 5% TTOO did not entirely eradicate Demodex in all patients. The issue of illness recurrence requires more research using placebo and a longer follow-up period. Furthermore, we cannot yet rule out the possibility that some of the positive benefits seen here may possibly be due to TTO's well-known antibacterial and anti-inflammatory properties.[39]

Novel Topical Ocular Drug Delivery System

Despite the fact that traditional topical ocular medicines are now widely utilized, there are still certain issues with their application, effectiveness, and safety. As a result, several methods have been developed and examined. Utilizing nanotechnology in the ocular drug delivery system via nanoparticles and nanomicelles is one strategy. Ocular implants and liposomes are two further methods to enhance the ocular delivery mechanism.[40]

The bioavailability of medications is increased in front of your eyes using conventional techniques such liposomes, prodrugs, gels, consistency enhancers, and dispersion enhancers. In situ gels and implants are examples of contemporary methods that improve the drug's bioavailability in the eye and regulate its entry into the most developed area of the eye. Additionally, techniques including iontophoresis, subconjunctival injection, intravitreal injection, and the periocular cycle are employed to provide eye drops to the rear of the eye.[41]

Challenges & limitations in Ocular drug delivery system

For decades, a significant obstacle facing ocular scientists has been getting drugs into the right ocular tissues. Conventional formulations of drug solutions administered as topical drops had various disadvantages, which prompted the development of alternative carrier systems for ocular delivery. Researchers are working really hard on ocular research to create innovative medicine delivery methods that are safe and patient-friendly. At the moment, scientists are working very hard to enhance the in vivo performance of traditional formulations.[42]

Safety concerns: Although supplements and herbal medicines are generally thought to be safe, they can have negative effects or interfere with medications. For instance, taking too much vitamin A can be poisonous.

Standardization problems: Dosing and efficacy comparisons are made more difficult by variations in active ingredient concentrations. For instance, there are significant variations in the amount of curcumin present in turmeric preparations.

Regulatory Frameworks: Supplements and herbal treatments lack strict quality control procedures unlike pharmaceuticals, which increases the danger of adulteration and results in inconsistent efficacy.[43]

CONCLUSION

Because there are several ocular barriers in the anterior and posterior regions of the eye, managing ophthalmic disorders effectively is still a challenging task. To deliver the drug to the intended site of action, a variety of ocular methods of administration are employed, including topical, intraocular, periocular, and conjugation with ocular devices.

Through controlled and sustained drug delivery systems, a number of strategies and technologies have been used to reduce dosing intervals, administered doses, and adverse effects while improving ocular retention duration, drug penetration efficacy, and ocular bioavailability. These cutting-edge technologies may have a wide range of uses in the management and treatment of eye illnesses since they have demonstrated good biocompatibility and increased medication efficacy. More advancements in ocular medication delivery systems are anticipated in the future to increase patient compliance, maintain and improve eye health, and achieve better outcomes in the treatment of ocular disorders.[50]

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