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Review Article

Ocular Drug Delivery of Phytoconstituents: Barriers and Challenges

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ABSTRACT

Medicinal plants have been used in many parts of the world for thousands of years as a common remedy for many human diseases. Herbal material continues to be used as a primary medicinal source in rural areas of developing countries. The eye is one of the most delicate organs of the body. Conjunctivitis, cataracts, glaucoma, ocular allergies, ocular inflammation, uveitis, etc. are the most common diseases of the eye. Because of the availability of novel formulation approaches a huge number of herbal drugs are used for the treatment of ocular diseases. Due to safety, efficacy, and lesser side effects herbal medicines gaining popularity and it is growing day by day. This review article discusses the barriers to ocular drug delivery and the challenges experienced in producing herbal medicines.

INTRODUCTION

In ancient times, natural extracts and herbal materials were consumed by people for curing ophthalmic diseases [1]. These herbal materials contain hundreds of Phytoconstituents which work at the same time against various diseases. The topical use of the macerated fruit of Atropa Belladonna by the Egyptians is the first known use of a naturally derived agent to treat ophthalmic diseases [2]. The discovery of drugs that are capable of reducing intraocular pressure(IOP), thereby controlling the progression of glaucoma, was one of the most important research findings that stimulated interest in molecules extracted from plants [2]. Carl Koller in 1884 clinically demonstrated the analgesic properties of cocaine in the eye. The discovery of the anaesthetic property of cocaine, a milestone in the history of ocular pharmacology, only occurred in the late 19th century [3]. From then on, exponential growth in the plant-derived drug has been observed due to the growth of the pharmaceutical industry as it continues seeking discoveries and new markets. Recently, scientists are actively involved in the research and development of a novel formulation approach for delivering herbal drugs [1].

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The production of nano dosage forms (polymeric nanoparticles and nanocapsules, liposomes, solid lipid nanoparticles, Phytosomes, nanoemulsion, etc.) in photo-formulation research has many advantages for herbal drugs, including improved pharmacological activity, improved distribution of tissue macrophages, improved stability, sustained delivery, protection from physical and chemical degradation.

Current Scenario of the Herbal Ophthalmic Market

The world ophthalmic medications market share was esteemed at USD 31.0 billion in 2019 and is expected to grow at a CAGR of 5.0 per cent from 2019-2027. One of the main market drivers is an increase in macular degeneration, the pervasiveness of presbyopia, and diabetic retinopathy. According to the WHO (World Health Organization), roughly 2.2 billion individuals were visually impaired in 2019. Similarly, more than 39 million people reported vision loss, almost 188.5 million people experienced mild vision impairment, and more than 217 million people experienced moderate to extreme vision impairment. In recent years, drug delivery systems in ophthalmic therapy have undergone significant technological developments and thus remain a primary growth factor for the industry.

According to the report published by Polaris Market Research, the worldwide market size for Herbal Medicine is expected to grow at USD 411.2 billion by the year 2026 and is foreseen to develop at a CAGR of 20.5 percent from 2020 to 2026. A higher level of government support and funding amount for research and development is boosting the market development. Different factors such as minimal or no side effects of traditional medicines, increased use by the global population and easy accessibility will contribute to market developments over the forecast period. Natural sources of drugs are the basic source of treatment for relieving different illnesses. The National Center for Biotechnology Information indicated that between 70%-80% of the world's population favored conventional medications for various disease treatments. Furthermore, it has been revealed that customer spending on conventional medicines has expanded to USD 7.5 billion. In addition, this growing interest will additionally support the business development somewhere in the range of 2020 and 2026.

The herbal ophthalmic product market was showing promising growth and increased interest among consumers seeking natural and holistic eye care solutions. With a broader shift toward natural and holistic healthcare solutions, consumers were increasingly looking for herbal and plant-based alternatives to traditional pharmaceutical products for eye care.Increased awareness about eye health and the importance of preventive measures, especially with the growing prevalence of digital device usage, has driven the demand for products that promote eye wellness. Herbal ophthalmic products were often perceived as having fewer side effects compared to synthetic eye drops and medications, which can sometimes cause irritation or allergic reactions. Many herbal eye drops and washes were positioned as a natural alternative to artificial tears, offering relief from dry eyes and eye strain. Consumers were becoming more conscientious about the ingredients in the products they use, and herbal products often offered transparency regarding the source and composition of ingredients.

Basic ocular anatomy and physiology:

The eye is one of the most complicated organs of the body, consisting of three chambers anterior, anterior-posterior, and vitreous or postrenal [4, 5]. The human eye is spherical, with a diameter of about 23nm [6]. The amount and quality of light entering the eye are controlled and filtered by the pupil, which dilated and contracts according to requirements. Between the iris and cornea, the anterior chamber is located and between the lens and the iris, the posterior chamber is located. The vitreous humor is surrounded by the retina. It also has three main layers; fibrous layer, vascular layer, and neural layer. The fibrous layer is the outer layer of the eye consists of white, opaque sclera and the clear transparent cornea. The vascular layer is the middle layer consists of the ciliary body, choroid, and iris [6, 7].

The inner layer contains the retina, which is an extension of the central nervous system (CNS). The visible part of the sclera is covered by a transparent mucous membrane called the conjunctiva. The inner layer of the eye is the retina. It is a complex and layered structure of neurons that captures and processes the light.

Barriers to Ocular Drug Delivery

Depending on the target site, medication can be delivered into the eye through anterior and posterior segment routes. After passing the tear film and lacrimal fluid to the appropriate target locations, drugs are faced with several membrane barriers located in the cornea, conjunctiva, iris-ciliary body and, retina (shown in Fig.1), in which the epithelial and/or endothelial cells are sealed by the tight junctional constituents [8]. These barriers are discussed as follows:

Drug Loss from the Ocular Surface

After installation of the drug, the flow of lacrimal fluid eliminates the instilled compounds from the surface of the eye [9]. Although the turnover rate of lacrimal fluid is only around 1 μL/min, the excessive volume of the instilled fluid is rapidly transferred within a few minutes to the nasolacrimal duct [10]. Another source for the removal of non-productive drugs from the ocular surface is its systemic absorption rather than ocular absorption [10]. Systemic absorption is mostly directed through the conjunctival sac to the local blood capillaries or occurs after the flow of fluid to the nasal cavity [11, 12]. In any case, most of the small molecular weight drugs are quickly absorbed into the bloodstream in few minutes. This contrasts with the low ocular bioavailability of less than 5% [10]. Absorption of the drug into the bloodstream extensively decreases the concentration of the drug in a lacrimal fluid. Therefore, constant drug release from the solid delivery system to lacrimal fluid may lead only to 10% ocular bioavailability, since most of the drug is cleared by the local systemic absorption.

Lacrimal Fluid-Ocular Barrier

Corneal epithelium prevents the absorption of the drug from tear fluid into the eye. When epithelial cells mature, the corneal barrier begins to form [10]. They migrate from the central area of the cornea to the apical surface. The most apical hydrophilic corneal epithelial cells form the tight junction which limits the permeation of paracellular drugs [10, 13]. Therefore, lipophilic drugs show higher permeability in the cornea than hydrophilic drugs [11]. Despite the tightness of the corneal epithelium, the main route of drug penetration from the lacrimal fluid to the aqueous humor is transcorneal permeation. (Fig. 1) In other words, compared to that of the cornea, we can say that conjunctiva has leaky epithelium and also has 20 times greater surface area than the cornea that supports rapid systemic absorption [11]. Recently, drug absorption has gained increasing attention through the bulbar conjunctiva, as the conjunctiva is often relatively permeable to hydrophilic and large molecules [14]. Therefore it can act as an absorption route for larger bio-organic compounds such as proteins and peptides. Medications used clinically are usually tiny and slightly lipophilic. Therefore the corneal route is currently dominant at present [10]. In the two membranes, cornea and conjunctiva, the principle of passive diffusion has been thoroughly studied, but the role of active transporters is poorly studied [10].

The Blood Ocular Barrier

The blood ocular barrier protects the eye from xenobiotics in the bloodstream [10]. These barriers are consisting of two parts: blood-retinal barrier and blood-aqueous barrier(Shown in Fig. 1) [10]. Between the blood and the eye, there is a physical barrier that plays a key role in the penetration of drugs, elimination and removal of drugs from the ophthalmic route, and maintenance of homeostatic control[15]. The anterior portion of the blood eye barrier is comprised of the endothelial cells in the uvia [10]. This barrier prevents plasma albumin from entering the aqueous humor and prevents plasma hydrophilic drugs from entering the aqueous humor [10]. The integrity of this barrier can be disrupted by inflammation, allowing the unrestricted delivery of drugs to the anterior portion. In reality, the permeability of this barrier is poorly characterized [10]. The posterior barrier between the eye and the plasma stream consists of the retinal pigment epithelium (RPT) and retinal capillaries resulting in a tight wall junction [11].

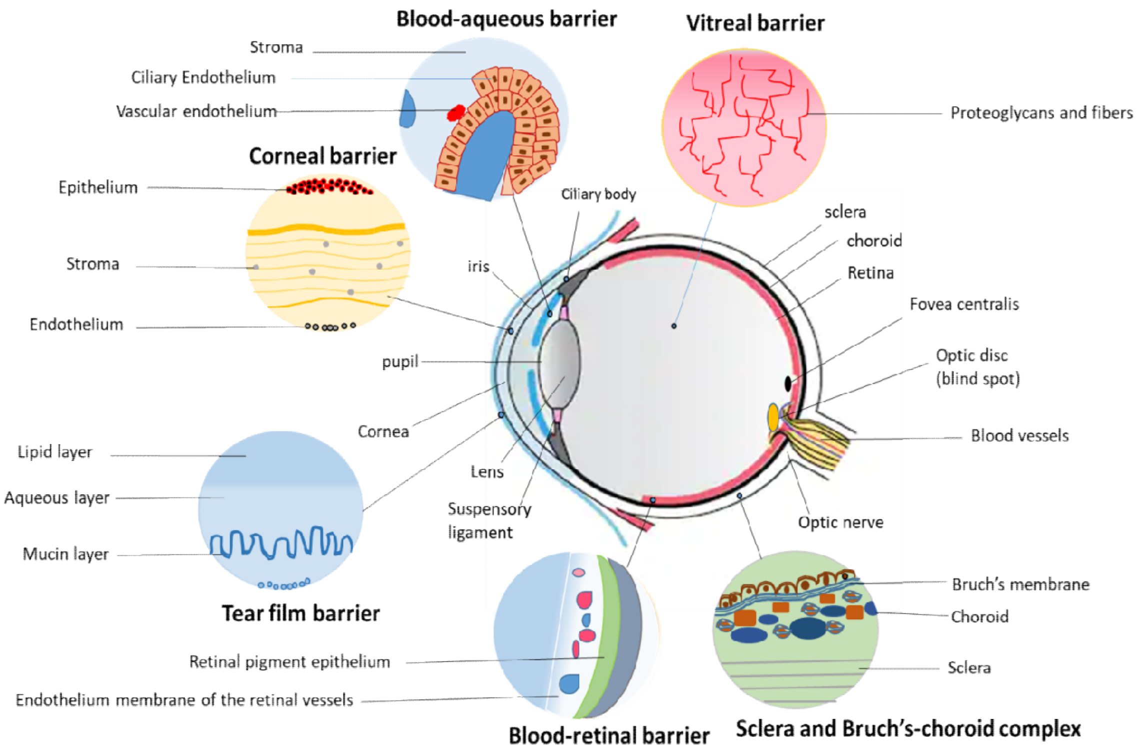

Figure 1: Barriers to ocular drug delivery

Choroid vasculature consists of extensive blood flow and leaky walls, due to which easy drug access takes place in the extravascular choroidal space, but due to the presence of RPE and retinal endothelium, their distribution in the retina is again restricted [11]. The blood-aqueous barrier is an anterior segment barrier that is non-porous (104 A°) and isotonic membrane (Dernouchamps and Heremans 1975; Dernouchamps and Michiels 1977) composed by the ciliary epithelium and the capillaries of iris [15, 16]. The aqueous humor is secreted by the non-pigmented epithelium of the ciliary body [15]. The permeability of the blood-aqueous barrier is controlled by the sodium, chloride, and bicarbonate transport and by the physical-chemical properties of the drugs. Passages from the aqueous humor to the blood of the hydrophilic molecules are active and passive for lipophilic molecules [16]. An epithelial barrier and an endothelial barrier make up the blood-aqueous barrier. The epithelial barrier consists of a close junction between the ciliary epithelial cells that are not pigmented and form a channel for free molecular diffusion [16]. The iris vessels contain a protein similar to the tight junctions of the epithelium and form the endothelial barrier [16].

Sclera and Bruch's Choroid Complex

The large open space of the human sclera is around 16.3cm^2 and mainly consists of an extracellular matrix composed of fibrils collagen and glycoproteins. In general, the sclera is more porous to solutes than to the conjunctiva and cornea, especially to hydrophilic compounds because transscleral diffusion is the main material of diffusion through an aqueous medium. Proteoglycans or porous spaces (25 to 300 nm in diameter) within the collagen network rather than diffusion across cellular membranes [17, 18]. Like other tissues, scleral permeability is strongly dependent on the molecular weight of the compounds, with macromolecules with lower permeability than tiny molecules [19]. The molecular radius tends to be a better predictor of macromolecule permeability for sclera (e.g. dextrans and proteins) than the MW. However, For e.g., the scleral permeability of dextran with 70kDa was not significantly greater than for a dextran with 150kDa, whereas a globular protein with a molecular radius of 5.23nm was more permeable than a linear dextran of the same molecular weight, but with a molecular radius of 8.25nm [10]. Transscleral permeability is also strongly affected by the charge of molecules. Positively charged molecules have lower permeability through sclera compared to permeation across the cornea than those with negative charges, as the proteoglycan matrix of the sclera, is negatively charged, which leads to the binding of positively charged solutes and hinders the transport of them through the tissue [17]. A significant dynamic barrier is a choroid, as it is a highly vascularized and innervated tissue that supplies blood to the retina. It consists of a network of fenestrated capillaries and is protected by a thin (2 to 4μm) Bruch's membrane. It is a pentalamellar, elastic membrane that also represents the retinal pigment endothelium basement membrane (RPE) [10]. The Bruch's-choroid (BC) complex is a more critical barrier to transscleral drug delivery than the sclera itself, as it is more discriminatory, particularly for positively charged lipophilic drugs, due to the binding of the solute to the tissue, thus forming a slow-release drug depot in the BC complex [10]. Additionally, molecular size also affects the permeability of the BC complex with hydrophilic carboxyfluorescein and dextrans and has shown an exponential decrease with increasing molecular radius in bovine tissues [18].

Metabolism in Ocular Tissues

In the pigmented epithelium and ciliary bodies, drugs containing aromatic hydrocarbons are metabolized to their corresponding epoxides and phenols, or further metabolized by other enzymes present in the eye [20]. Hayakawa et al. demonstrated that poor peptides and insulin uptake is due to increased metabolism during conjunctival permeation in albino rabbits. Schoenwald et. al. demonstrated that clearance via aqueous humor turnover is significantly lower when compared to the rest of the clearance pathways, indicating that a majority of the drugs are eliminated via metabolic pathways [21, 22].

Phytoconstituents

Herbal medicines or medicinal plants have made unquestionable contributions from ancient civilizations and established one of the bases for health care in nearly all cultures around the world [23]. The use of medicinal plants is an essential part of any traditional system of medicines that are carried out in different ways in different human cultures [24]. Despite their extensive practice as medicinal products, the interest of communities in herbal medicines is increasing with a special focus on their pharmaceuticals, clinical, and economic significance. Herbal medicines are well known for their vast variety of biological features and diversity of chemical structures. This makes herbal medicines more desirable as the main element for the creation of new drugs. Owing to their importance in modern medicines, they are of greater interest [25]. The development of powerful analytical instruments and technologies such as, material science, bioinformatics, computer-aided screening, and cell biology have acquired rapid growth in the field of clinical and analytical characterization. These tools and technologies open up new opportunities for categorizing and characterizing a single chemical moiety. Thus, conventional herbal preparations have been left over, considering their utility, and cannot be seen as an endpoint. Relevant Phytoconstituents are isolated in place and characterized by the respective drug analogs synthesized. These Phytoconstituents are none more than the chemical moieties that naturally appear in plants and are responsible for different organoleptic and therapeutics [26]. Specifically, these chemical moieties are secondary metabolites such as alkaloids, glycosides, polyphenolic compounds, etc. Phytoconstituents and their health-related consequences were carefully examined in this century. Due to their role in the prevention of major life-threatening diseases such as cancer, cardiovascular disorder, and respiratory infections, their therapeutic findings are of crucial importance. Today, these diseases are leading causes of death, indicating that Phytoconstituents will prove to be of interest to the scientific community. Based on practical health benefits such as anti-oxidant, anti-inflammatory, and immuno-modulatory, Phytoconstituents may act as an herb additive and/or a replacement therapy [27].

Table 1: Phytochemicals used in various ocular diseases

Sr.no.	Common name/ Botanical name	Family	Applications in ocular disease	Ref
1.	Abelmoschusmoschatusmedik	Malvaceae	Eye diseases	[1]
2.	Abelmoschusesculentus (L.)/ Okra	Malvaceae	Conjunctivitis	[27]
3.	Acacia Nilotica L./Kikar	Mimosaceae	Burning sensation in eyes	[28]
4.	AdeniummultiflorumKoltzsch/ Impala lily	Apocynaceae	Sore eyes	[29, 30]
5.	AdhatodaVasica (L.) (Adulsa)	Acanthaceae	eye disorders	[31]
6.	Allium sativum L./ Garlic	Liliaceae	Ophthalmology, sore eyes	[1]
7.	Alstoniaboonei De Wild/ Indian Devil tree	Apocynaceae	Eye problems	[32]
8.	Atropa Belladonna L./ Deadly nightshade	Solanaceae	Iritis	[1]
9.	BixaOrellana L. Annatto	Bixaceae	Eye infection	[1]
10.	Bothrioclineugandensis (S. Moore) M.G. Gilbert/ Gnathostomata	Astraceae	Blindness, Conjunctivitis	[33]
11.	Calophylluminophyllum L. Oil nut tree	Clusiaceae	Eye ailment	[32]
12.	Daturametel L. /Datura	Solanaceae	To enlarge pupil	[29]
13.	Daucuscarota Linn. / Carrot	Umbelliferae	Glaucoma, eye sight	[34]
14.	FicusthonningiiBlume / Bark-cloth fig	Moraceae	Blindness, Conjunctivitis and related eye infection	[33]
15.	ZizyphusmauritianaLamk/ Ber	Rhamnaceae	Sty of eye	[35]

Challenges Related to Phytoconstituents

Ocular drug delivery, especially for phytoconstituents, presents several challenges due to the unique anatomy and physiology of the eye. These challenges can limit the effectiveness of phytoconstituents in treating eye conditions. Designing suitable ophthalmic formulations (e.g., eye drops, ointments, gels), that can effectively deliver phytoconstituents to the eye while ensuring patient comfort and safety can be challenging. Achieving precise dosage control with phytoconstituents is crucial to avoid under- or overdosing, which can lead to ineffective treatment or adverse effects. Many ocular conditions require sustained drug release to maintain therapeutic levels over time. Achieving this with phytoconstituents can be challenging due to their natural variability and potential degradation. Ensuring consistent quality and standardization of phytoconstituents in ocular formulations can be difficult due to variations in plant sourcing and extraction methods [36].

Regulatory Challenges for Herbal Drugs for Ocular Administration

As defined, a food supplement is a substance which is taken in and is meant to supplement the diet and contains the 'nutritional ingredient'. The nutritional components of these products may include minerals, herbs, vitamins, and other plant parts that the body needs [37]. Any other toxicity studies are usually not needed under the DSHEA (Dietary Supplement Health and Education Act) if the herb has been on the market before 1994[3]. To this purpose, the FDA bears the burden of proving that herbal medicines or "dietary ingredients" are toxic or unsafe to use. In many countries, the major additional challenge is that regulatory knowledge on herbal medicines is often not discussed between regulators and Health surveillance or Canters of Pharmacovigilance. Meeting regulatory requirements for ophthalmic drug products can be complex, particularly for phytoconstituents, which may not have well-established safety and efficacy profiles [36].

Challenges in Safety and Efficacy Assessment

The fact cannot be contradicted by anyone that the requirements, as well as the research protocols, specifications, and methods needed to assess the safety and effectiveness of herbal medicines, are much more complex than those required for traditional or orthodox pharmaceuticals [38]. More than hundreds of natural constituents may be found in a single herbal medicine or medicinal plant, and a mixed herbal medicinal product may contain several times the amount of one. Analysis of such single active constituents may be practically impossible, especially when a plant-based product is a combination of two or more herbs. Some phytoconstituents may cause irritation or allergic reactions in the eye, making it essential to assess their safety and tolerability [38].

Challenges Regarding Quality Control of Medicinal Plants

The quality of the starting materials used in the production of plant-based medicinal products is an important determinant of drug safety and effectiveness of medicines. The quality of raw material is dependent on intrinsic(genetic) as well as extrinsic factors like environmental conditions, good agricultural, and good collection practices for medicinal plants, including plant selection and cultivation [36]. It is a combination of several factors that make it difficult for herbal medicines to carry out quality controls on the raw materials [38]. According to Good Manufacturing Practice (GMP), Proper identification of species of medicinal plants, special storage and special cleaning methods for different materials are important criteria for quality control of starting materials. Quality control of finished herbal medicines, particularly mixtures of herbal products, is a major challenge [37]. As a result, the overall requirements and quality control methods for finished plant-based products remain far complex than for other pharmaceutical products. To ensure the safety and efficacy of herbal medicinal products, the WHO continues to support quality assurance and control measures such as the Specification of national quality and standards for herbal materials, GMP, labelling, and manufacturing licensing schemes [36].

Challenges in Monitoring Safety of Medicinal Products

Issues related to the increase in the use of natural or herbal medicines or products in developing countries have been addressed in recent years. Also, the dependency of many people living in developing countries on plants as a major source of medicines, combined with poor regulation of herbal medicines in most countries, and the occurrence of high-profile safety issues have raised awareness of the need to monitor safety and understand the possible harmful and potential benefits associated with the use of herbal media [36]. A variety of causes are responsible for adverse effects resulting from the use of herbal medicinal products, including the use of incorrect plant species, adulteration of herbal products, undeclared medicines, contamination, overdose, abuse of herbal medicines by health care providers, or consumers, and the use of herbal medicinal products with other medicinal products. There is a lack of proper knowledge of the importance of taxonomic botany and documentation among most herbal medicine manufacturers, and this causes particular difficulties in identifying and collecting medicinal plants used for herbal remedies [36]. To overcome the confusion caused by common names, one should adopt the most commonly used binomial names for herbal medicines. For example, Artemisia absinthium L., with at least 11 common names, contains an active narcotic derivative. Effective monitoring of plant-based drugs would also require effective monitoring of the Collaboration between phytochemists, pharmacologists, botanists, and other important stakeholders [36].

CONCLUSION

Phytoconstituents have the potential to offer alternative or complementary treatment options for various ocular conditions, including dry eye, glaucoma, and age-related macular degeneration. However, ocular barriers protect eyes from various external factors, including dust, microbes, and potentially harmful substances. Understanding these barriers is essential in the development of ophthalmic drugs and in the treatment of ocular conditions, as they can influence the delivery and effectiveness of medications and therapeutic agents including phytoconstituents.

To address numerous challenges of ocular drug delivery of phytoconstituents various strategies, such as nanotechnology, microemulsions, nanoparticles, liposomes, and prodrug approaches reported. Additionally, preclinical and clinical studies are essential to assess the safety and efficacy of these formulations in treating specific ocular conditions. Collaborative efforts of pharmacologists, pharmacists, ophthalmologists, and experts in phytochemistry are crucial to developing effective phytoconstituent-based ocular drug delivery systems.

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