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Review article

Formulation of microemulsion of netarsudil for glaucoma

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ABSTRACT

Glaucoma is still one of the leading causes of irreversible blindness worldwide, affecting an estimated 80 million people. The disease is defined by a progressive damage to the optic nerve and is often associated with an increase in intra-ocular pressure (IOP). Classical pharmacotherapy includes the different classes of IOP-lowering agents. The recently approved Rho kinase inhibitor Netarsudil is a major therapeutic advance due to its novel mechanism of action targeting the trabecular meshwork outflow pathway. However, conventional ophthalmic formulations suffer from serious limitations like low corneal bioavailability (0.1-5%), rapid precorneal clearance and dose-dependent side effects like conjunctival hyperaemia . Microemulsion based pharmaceutical delivery systems offer a promising platform to overcome these problems by enhanced permeation, prolonged ocular residence time and improved solubility of drugs. This review systematically surveys the literature on ocular delivery of Netarsudil using microemulsions, focusing on formulation approaches, characterisation parameters, optimisation strategies and therapeutic potential.

Keywords: Glaucoma, Microemulsion of netarsudil for ocular drug delivery, Rho kinase inhibitor.

INTRODUCTION

The eye is a complicated and highly specialised organ of sense. The organ of vision. Eye disorders are a broad range of diseases affecting different anatomical structures from the outer cornea to the inner retina and optic nerve. These include relatively minor conditions such as dry eye and conjunctivitis, to sight-threatening diseases like glaucoma, age-related macular degeneration, diabetic retinopathy and cataracts.

According to the World Health Organisation (WHO), approximately 2.2 billion people globally suffer from some form of vision impairment, and at least 1 billion of these are preventable or untreated [1,2]. Eye disorders significantly impact quality of life, economic productivity and health care systems worldwide. Vision loss and eye disorders place a large economic burden that includes direct medical costs, lost productivity, and reduced quality of life.

Glaucoma: pathophysiology and clinical significance

Glaucoma is a chronic, progressive and potentially blinding ocular disease that is associated with damage to the optic nerve, usually in the presence of elevated intraocular pressure (IOP). It is one of the leading causes of irreversible blindness in the world and a major public health problem [3,4]. The disease is usually asymptomatic at an early stage, which prevents early diagnosis and, as a rule, leads to delayed treatment. As the condition progresses, it causes progressive loss of peripheral vision and eventually central vision if left untreated [5–7].

Glaucoma is multifactorial and has a complex pathophysiology. The most important risk factor is increased intraocular pressure, which is brought about by an imbalance between the production and drainage of aqueous humour. The aqueous humour is produced continuously by the ciliary body and drained through two major pathways: the trabecular meshwork (conventional pathway) and the uveoscleral pathway (unconventional pathway). Glaucomatous conditions are associated with increased resistance to outflow of aqueous humour, particularly in the trabecular meshwork, resulting in raised intraocular pressure. Over time, this increased pressure leads to mechanical stress and reduced blood supply to the optic nerve, resulting in irreversible damage [8–10].

Some populations are more prone to get glaucoma than others. Open-angle glaucoma is the most common form of glaucoma. Studies have shown that glaucoma prevalence varies widely in terms of demographics and geography [11–15]. The prevalence of primary open-angle glaucoma in the Netherlands was 1.1% in the Rotterdam Study and in Australia, 3.0% in the Blue Mountains Eye Study. In addition, normal-tension glaucoma, an optic nerve disease that occurs despite normal IOP, presents additional diagnostic and therapeutic challenges [16–20].

Current pharmacological management

The pharmacological management of glaucoma is primarily achieved using topical ophthalmic formulations like eye drops. Several classes of drugs are used, including beta-blockers, prostaglandin analogues, alpha agonists, carbonic anhydrase inhibitors and more recently Rho kinase inhibitors.

The only therapy that is of benefit is to lower the intraocular pressure, whether it is primary open-angle glaucoma or ocular hypertension. Conventional pharmacotherapy includes:

Prostaglandin analogues: Enhance uveoscleral outflow

Beta-blockers: Reduce aqueous humor production

Alpha-agonists: Both reduce production and enhance outflow

Carbonic anhydrase inhibitors: Reduce aqueous humor production.

However, conventional eye drop formulations face several limitations that reduce their overall therapeutic effectiveness, including poor patient adherence, limited bioavailability, and adverse effects [21–25].

Netarsudil

Mechanism of action

Netarsudil is a novel antiglaucoma drug used in the management of ocular hypertension and open-angle glaucoma. It belongs to the class of Rho kinase (ROCK) inhibitors and represents an advanced therapeutic approach for lowering intraocular pressure.

Table 1: Physicochemical properties of Netarsudil

Property	Description
Chemical Name	[4-[(2S)-3-Amino-1-(isoquinolin-6-ylamino)-1-oxopropan-2-yl]phenyl] methyl 2,4-dimethylbenzate
Molecular Formula	$C_{28}H_{27}N_3O_3$
Molecular Weight	453.542 g·mol^{-1}
Solubility	Freely soluble in water; soluble in methanol
Physical Appearance	White to light yellow crystalline powder
Half-life	16-17 hours

Chemically, Netarsudil is presented as Netarsudil dimesylate and possesses lipophilic properties which enable it to penetrate into ocular tissues. The drug acts locally within ocular tissues and exerts its pharmacological effect primarily on the trabecular meshwork, which is the main site responsible for aqueous humor drainage.

Netarsudil lowers intraocular pressure through multiple mechanisms:

ROCK inhibition: Relaxes trabecular meshwork cells and reduces cellular stiffness, increasing aqueous humor outflow through the conventional drainage pathway

Episcleral venous pressure reduction: Decreases episcleral venous pressure, further contributing to IOP reduction

Norepinephrine transporter inhibition: Reduces aqueous humor production [26–30].

The 2017 FDA approval of Netarsudil ophthalmic solution 0.02% (Rhopressa®) marked a paradigm shift in glaucoma management. Netarsudil is a new dual ROCK and norepinephrine transporter (NET) inhibitor that acts on trabecular meshwork and Schlemm's canal cells, the main sites of outflow resistance in glaucoma. Netarsudil increases conventional outflow facility by reducing actin stress fibres and focal adhesions in TM cells, decreasing contractility and extracellular matrix deposition [30–33].

Clinical efficacy and safety

Netarsudil has shown significant IOP-lowering efficacy in clinical trials. The ROCKET-2 study also assessed the long-term safety and ocular hypotensive efficacy of Netarsudil ophthalmic solution and confirmed its therapeutic potential in glaucoma management.

The drug is particularly useful in patients needing long-term control of intraocular pressure. Netarsudil targets the trabecular meshwork pathway, the primary site of resistance to aqueous humour outflow, setting it apart from many common antiglaucoma medications. Its once-daily dosing regimen also increases patient convenience and treatment adherence.

Netarsudil can be used alone or together with other glaucoma medicines to help control the pressure better. Because of its novel mechanism of action, it is considered beneficial in patients who have inadequate response to traditional therapies such as beta-blockers or prostaglandin analogues.

Limitations of conventional formulations

However, conventional ophthalmic delivery of Netarsudil has various limitations despite its therapeutic potential. The human eye presents unique anatomical and physiological barriers to drug absorption such as:

Corneal epithelial barrier

Turnover of tears

Nasolacrimal drainage

Automatic eye blinking

Thus, only a small percentage (generally less than 5%) of the administered drug reaches the intraocular tissues. Fast precorneal clearance results in a short residence time and requires frequent dosing, which may reduce patient compliance.

The corneal barriers, tear turnover, nasolacrimal drainage and non-productive absorption usually lead to a bioavailability of

only 0.1% to 5% when drugs are applied topically into the aqueous humour. Furthermore, conjunctival hyperemia occurs in up to 53% of patients, and corneal verticillata develops in 15–20% of users, contributing to discontinuation rates approaching 20% after three years of topical therapy. Additionally, the use of preservatives in eye drops may cause irritation and discomfort, further affecting adherence to therapy [34–36].

Microemulsion technology in ocular drug delivery

Definition and characteristics

Microemulsions are thermodynamically stable, isotropic systems of oil, water, surfactant and co-surfactant. They are characterised by their small droplet size (usually from 10 to 100 nm), which provides a large surface area for drug absorption and enhances permeability across biological membranes.

The important features of microemulsions are:

Thermodynamical stability

Transparency to light

Low viscosity

Formation spontane

Small size of droplets

Advantages of microemulsion-based ocular delivery

Microemulsions have several advantages for ocular drug delivery:

Enhanced Permeation: Nanosized droplets offer better penetration through the corneal epithelium, thus increasing the bioavailability of the drug. The presence of surfactants and co-surfactants can also change membrane fluidity and decrease interfacial tension, thus improving permeability.

Improved Solubility: Microemulsions may improve the solubility of poorly soluble drugs in water, making them good vehicles for lipophilic compounds such as Netarsudil.

Extended Residence Time: The transparent and low-viscosity nature of microemulsions guarantees patient comfort and ease of administration. Prolonged residence time can be achieved by including mucoadhesive agents or optimising the formulation composition.

Sustained Release: Microemulsions can protect the drug from degradation and offer a controlled release profile, which is advantageous for maintaining therapeutic drug levels over an extended period.

Fewer Doses: The extended residence time allows for continuous drug release and decreases the frequency of dosing, thus improving patient compliance.

Patient Comfort: Microemulsions' transparency and low viscosity provide patient comfort and ease of administration, which are important in ophthalmic preparations.

Mechanism of enhanced ocular bioavailability

The authors Hegde et al. highlighted the significance of microemulsions in ocular drug delivery and stated that they could be used to overcome the physiological barriers associated with conventional eye drops. The small droplet size and low surface tension of microemulsions allowed them to spread better on the corneal surface and to enhance drug penetration through ocular tissues, according to the authors.

Moreover, the surfactants and co-surfactants in the formulation can change the membrane fluidity and increase the permeability. Furthermore, microemulsions have been reported to increase precorneal retention and delay drug elimination, thereby increasing ocular bioavailability.

Gautam and Kesavan reviewed the development of microemulsions for ocular drug delivery and described that these systems may improve the drug retention time, corneal permeation and therapeutic efficacy. According to the authors, the nanosized droplets in microemulsions provide a larger interfacial area for drug absorption, while the surfactant system reduces interfacial tension and promotes spontaneous formation of stable formulations [37–40].

Formulation development of microemulsions

Selection of components

The formulation of a stable and effective microemulsion requires careful selection of its components, including the oil phase, surfactant, and co-surfactant.

Oil phase

The choice of oil is crucial as it determines the solubilization capacity of the drug. One of the important factors in the development of a successful ocular microemulsion is to choose a suitable oil phase. The oil phase is crucial for solubilising lipophilic drugs and for the formulation's drug-loading capacity.

Oils such as oleic acid, castor oil, isopropyl myristate and Capryol are frequently used in ophthalmic microemulsions due to their compatibility and penetration enhancer properties. In particular, oleic acid has been studied extensively for improving membrane fluidity and enhancing drug permeation through biological membranes.

Surfactants

Surfactants are a key component of microemulsion systems, as they lower the interfacial tension between the oil and water phases, and stabilise the nanosized droplets. The surfactants are selected according to their emulsifying ability and safety to the eye.

Nonionic surfactants are usually preferred in ophthalmic preparations because of their lower toxicity and better biocompatibility. Nonionic surfactants such as Tween 80, Cremophor EL, and Poloxamers are generally preferred in ocular formulations because of their lower toxicity and irritancy compared to ionic surfactants.

Co-surfactants

The co-surfactants aid in reducing the interfacial tension and increase the flexibility of the interfacial film, leading to the spontaneous formation of microemulsions. Co-surfactants like polyethene glycol (PEG 400), ethanol and propylene glycol increase the flexibility of the interfacial film and promote spontaneous formation of microemulsions.

Pseudoternary phase diagrams

Construction of pseudo-ternary phase diagrams is an important step in the determination of the microemulsion region and optimisation of the ratios of components. Pseudoternary phase diagrams are extensively used in the formulation development to find the microemulsion region and to optimise the component concentrations.

These diagrams give us useful information on the phase behaviour of oil, surfactant, co-surfactant and water systems. By constructing phase diagrams at different ratios, researchers can find the composition range that gives stable microemulsions with the desirable physicochemical properties.

Pseudo-ternary phase diagrams are used to optimise the ratio of these components to identify the region where a stable microemulsion can be formed [41-45].

Preparation methods

The most common method used to prepare microemulsion formulations is spontaneous emulsification or the aqueous titration method. The desired drug to be delivered is dissolved in the selected oil phase and mixed with surfactant and co-surfactant. Water is added dropwise with constant stirring until a clear and stable microemulsion is obtained. Different formulations can be prepared by varying component concentrations.

Characterization of microemulsion formulations

Characterization of the formulated microemulsion is an essential step to ensure its quality, stability, and performance. Parameters such as droplet size, zeta potential, viscosity, pH, refractive index, and drug content are evaluated to assess the physicochemical properties of the formulation.

Droplet size analysis

Droplet size analysis is particularly important because smaller droplets provide a larger surface area and better corneal permeation. Advanced techniques such as dynamic light scattering (DLS) and transmission electron microscopy (TEM) are used to determine droplet size and morphology [16,17].

Zeta potential

Zeta potential studies help assess the stability of the system. The zeta potential is a measure of the electrical charge present on the surface of the droplet and gives an idea about the physical stability of the formulation. In general, the greater the zeta potential (positive or negative), the greater the stability due to the electrostatic repulsion between the droplets.

Viscosity

Ocular retention characteristics are determined by viscosity measurements. The optimal viscosity provides adequate ocular surface contact time while maintaining patient comfort.

pH and osmolality

Another important parameter of ocular formulations is pH, as the eye is very sensitive to changes in pH. Ideally, ophthalmic formulations should be buffered to a pH of 6.0–7.4 to prevent irritation. The osmolality should be in the range of 280–320 mOsm/kg to be compatible with tear fluid.

Drug content determination

The analysis of drug content ensures that the drug is evenly distributed in the formulation. Drug content of formulations is determined by suitable analytical techniques such as UV spectroscopy or HPLC.

***In vitro* drug release studies**

In vitro drug release studies were carried out to assess the release profile of Netarsudil from the microemulsion system. These studies are useful to predict the in vivo performance of the formulation [46-49].

***Ex-vivo* corneal permeation studies**

Ex-vivo corneal permeation studies are performed to evaluate the drug release behaviour and permeation efficiency. The studies are useful in determining the ability of the formulation to transport the drug through the cornea.

Stability studies

Stability studies are important to ensure that the formulation is stable under different storage conditions. The studies include monitoring of changes in physical appearance, droplet size, drug content and pH over time. A stable formulation should have little change in these parameters, which implies that it is suitable for use over a long period of time [18,19].

Thermodynamic stability studies, such as heating-cooling cycles, centrifugation and freeze-thaw studies, are commonly used to evaluate the stability of microemulsions. Stable formulations should show no phase separation, precipitation, or significant changes in droplet size and drug content during storage.

Ocular barriers and challenges in drug delivery

The ocular route poses many challenges for effective drug delivery. Several anatomic and physiologic barriers exist to protect the eye and limit drug absorption. They are:

Epithelium of the conjunctiva

Blood-aqueous-barrier

Layers of the tear film

Cleaning the conjunctiva

Irrigation of the nasolacrimal duct

In most eye drops, the drug is washed away within minutes by the diluting effect of tears. Frequent blinking decreases the contact time of the drug with the ocular tissues. This complicates the

achievement of therapeutic levels at the site of action, particularly in chronic diseases, such as glaucoma, that require long-term treatment.

The corneal epithelium is a major barrier to drug absorption. The epithelium is made up of several layers of tightly packed cells, joined together by tight junctions that prevent hydrophilic and lipophilic drugs from passing through. The presence of efflux transporters further restricts drug permeation [50-52].

Advanced colloidal carrier systems

Researchers have investigated different novel ocular delivery systems like nanoparticles, liposomes, niosomes, nanoemulsions, in situ gels and microemulsions. Among these, microemulsions have several advantages such as easy preparation, transparency, high solubilisation efficiency and enhanced permeation characteristics [53].

This means that they are very small in size, have a large surface area and can be in close contact with the corneal epithelium, thus enhancing drug penetration and absorption. Surfactants and co-surfactants can also transiently alter the permeability of the membrane and improve the trans-corneal transport.

Extensive studies have been carried out on nanotechnology-based systems for drug delivery to the eye in recent years. Furthermore, Li et al. reported that ocular drug delivery remains challenging because of anatomical barriers and rapid drug clearance from the eye. Different nanocarrier systems such as nanoparticles, liposomes, nanoemulsions and microemulsions were described by the authors as developed for improving ocular bioavailability [54].

The nanosized systems greatly improve penetration into the cornea and provide sustained drug delivery, improving the therapeutic outcomes in glaucoma treatment, they found. Shen et al. also reported that the conventional hypotensive eye drops for the treatment of glaucoma have poor patient adherence and low bioavailability. In their review, they pointed out the role of nano- and micro-scale drug delivery mechanisms in enhanced ocular retention and controlled drug release. The study emphasized that advanced delivery systems have the potential to reduce dosing frequency and enhance patient compliance in glaucoma therapy.

Applications of microemulsions in ophthalmic delivery

Several studies have demonstrated the successful application of microemulsions for ocular delivery of various drugs. Researchers have reported the use of microemulsion systems of antiglaucoma agents, anti-inflammatory drugs, antibiotics and antifungal agents, which improve corneal permeation, prolong residence time and enhance therapeutic activity. The nanosized droplets, high drug loading capacity and ability to change membrane permeability have improved the performance of such systems. These results provide strong support for the usefulness of microemulsions as efficient ocular delivery systems for drugs.

Microemulsions for antiglaucoma drugs

Microemulsion formulations have been developed for various antiglaucoma agents, demonstrating improved therapeutic outcomes. The enhanced permeability and prolonged retention time offered by microemulsions make them particularly suitable for glaucoma therapy, where sustained IOP control is essential.

Microemulsions for anti-inflammatory drugs

Ocular inflammation is a common complication of many eye diseases. Microemulsion formulations of anti-inflammatory drugs have been shown to improve corneal permeation and therapeutic efficacy compared to conventional formulations.

Microemulsions for antimicrobial agents

Microemulsions have been successfully employed for ocular delivery of antibiotics and antifungal agents, demonstrating improved bioavailability and enhanced therapeutic activity against ocular infections.

Stability and sterility considerations

Sterility is an important consideration in ocular formulations as microbial contamination can result in serious ocular infections. Therefore, ophthalmic microemulsions should be prepared and stored under aseptic conditions.

Another important aspect of microemulsion formulations is stability. Ophthalmic preparations require long-term stability and sterility; therefore, formulations need to be evaluated under different storage conditions to ensure the maintenance of physicochemical properties and drug content.

In recent years, ocular nanotechnology has shown that microemulsion systems can be further modified with bioadhesive polymers, in-situ gelling agents and controlled release components for enhanced therapeutic outcomes [55].

CONCLUSION

Netarsudil represents a major step forward in glaucoma pharmacotherapy and has a unique ROCK-inhibiting mechanism of action that targets the conventional outflow pathway. But the limitations of commercial topical solutions, such as poor corneal bioavailability (0.1–5%), rapid precorneal clearance and dose-dependent hyperaemia, offer opportunities for formulation innovation.

Microemulsion technology is a scientifically rational approach to overcome these limitations by enhancing permeation, prolonging retention and possibly reducing the drug concentrations required. The literature clearly suggests that microemulsion systems have the potential to improve ocular drug delivery and overcome the limitations of conventional eye drops.

Successful development of Netarsudil microemulsion formulation is expected to increase corneal permeability, increase the ocular residence time, improve therapeutic efficacy and provide sustained control of intraocular pressure. Such a system may in future

enhance patient compliance and therapeutic efficiency in the treatment of glaucoma.

The microemulsion platform could be promising to achieve this goal with adequate optimisation and safety validation. The successful development of the optimised formulation could significantly contribute to the state of the art in ocular drug delivery research by improving therapeutic efficacy, enhancing patient adherence to treatment and providing better control of intra-ocular pressure in glaucoma patients.

Declaration

The author declares no conflicts of interest.

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