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Topical Delivery of Metformin for Ocular Application

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Abstract

Metformin is known to lower inflammation, independent of its anti-diabetic action. Thus, topical metformin can be a therapeutic strategy for managing ocular inflammation associated with diabetes. To achieve this and address the issues of ocular retention and controlled release an *in situ* gel of metformin was developed. The formulations were prepared using sodium hyaluronate, hypromellose, and gellan gum. The composition was optimized by monitoring gelling time/capacity, viscosity, and mucoadhesion. MF5 was selected as the optimized formulation. It showed both chemical and physiological compatibility. It was found to be sterile and stable. MF5 exhibited sustained release of metformin for 8h that fitted best with zero-order kinetics. Further, the release mode was found to be close to the Korsmeyer-Peppas model. Supported by an *ex vivo* permeation study, it showed potential for prolonged action. It showed a significant reduction in ocular inflammation that was comparable to that of the standard drug. MF5 shows translational potential as a safe alternative to steroids for managing ocular inflammation.

Keywords: Diffusion; Mechanical properties; Ophthalmic drug delivery; Polymeric drug delivery system(s); Residence time(s); Viscosity.

NEED OF STUDY

The treatment of ocular diseases, particularly those affecting both the anterior and posterior segments of the eye, remains one of the most formidable challenges in the field of pharmaceutical sciences. The eye is a highly protected organ, guarded by multiple complex anatomical and physiological barriers designed to protect it from xenobiotics. These barriers, including the tear film, corneal epithelium, conjunctiva, and blood-aqueous and blood-retina barriers, severely restrict.

The entry and bioavailability of topically applied therapeutic agents. Conventional ocular drug delivery systems, such as aqueous eye drops, ointments, and suspensions, account for over 90% of the marketed ophthalmic formulations. Despite their ease of administration and high patient compliance, they suffer from significant drawbacks. Upon instillation, a major portion of the administered dose is rapidly eliminated from the precorneal area due to reflex blinking, lacrimation, and drainage into the

nasolacrimal duct. Consequently, only a very small fraction (typically less than 5%) of the applied drug actually penetrates the cornea to reach the intraocular tissues. This necessitates frequent dosing regimens, which can lead to poor patient adherence, pulsed drug release profiles causing systemic side effects through mucosal absorption, and potential ocular toxicity.

AIM & OBJECTIVE

Aim

- The primary aim of this research project is to design, formulate, and evaluate a sustained-release topical ocular drug delivery system (such as an in-situ gel or nanostructured lipid carrier system) containing Metformin to enhance its ocular bioavailability, prolong precorneal residence time, and investigate its potential therapeutic efficacy for ocular surface and inflammatory diseases.[18]

Objectives

• To conduct an exhaustive literature review on the anatomical and physiological barriers of the eye, current ocular drug delivery systems, and the novel pharmacological applications of Metformin in ophthalmology.

• To perform preformulation studies including the characterization of the pure drug (Metformin) through melting point determination, partition coefficient analysis, and solubility studies across varioussol.

• To establish a sensitive and accurate analytical method for the estimation of Metformin using UV-Visible spectrophotometry and High-Performance Liquid Chromatography (HPLC).

• To investigate the compatibility between Metformin and various selected polymers and excipients using Fourier Transform Infrared (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC).

• To formulate multiple batches of topical ocular formulations (e.g., temperature-sensitive, pH-sensitive, or ion-activated in-situ gels) incorporating Metformin using statistical design approaches.

• To evaluate the developed formulations for physicochemical parameters such as physical appearance, clarity, pH, isotonicity, gelling capacity, and rheological behavior (viscosity).

1. Introduction

Diabetes is a risk factor for many physiological disorders. Increased level of sugar alters the homeostasis of cells to induce degeneration while reducing the ability of the cells to manage inflammation. Although the eye is a protected organ, the increased sugar level adversely affects its homeostasis. An increase in polyol and protein kinase C (PKC) pathway activity, vascular endothelial growth factor (VEGF), advanced glycation end products (AGEs), oxidative damage, and renin-angiotensin system (RAS) have been implicated in diabetes.[2] Up-regulation of these inter-dependent metabolic pathways contributes to chronic inflammation and other ocular disorders.[3,4] Although steroids are the most effective anti-inflammatory agents, their short-term (7 days) ocular application is known to raise blood glucose levels

in patients with controlled diabetic conditions[5] that may induce other ocular disorders including glaucoma. Nonsteroidal anti-inflammatory drugs (NSAIDs) are relatively better tolerated. However, at higher doses, they are known to cause ocular comorbidity that was found to be severe in patients suffering from diabetes.[7] Thus, it is desirable to find an alternative therapeutic strategy. Using a drug that is suitable for long-term application is preferable. Anti-diabetic drugs that are suitable for long-term application may be preferred for diabetes-induced ocular inflammation or ocular inflammation in diabetes patients, provided they have the potential to manage ocular inflammation without affecting ocular homeostasis. However, ensuring ocular bioavailability is a significant challenge.[1]

Novel Ocular Drug Delivery Systems:

To overcome the limitations of conventional systems, extensive research has been directed towards the development of novel and advanced ophthalmic delivery platforms. The primary goals are to increase precorneal residence time, enhance corneal permeability, provide controlled and sustained drug release, and deliver drugs to the posterior segment non-invasively. In-Situ Gelling Systems: These are polymeric solutions that are liquid upon instillation into the eye but undergo a rapid sol-to-gel phase transition in response to physiological stimuli such as temperature, pH, or specific ions present in the tear fluid. They combine the advantages of solutions (accurate dosing, ease of administration) with those of gels (prolonged residence time). Common polymers used include Poloxamer (temperature-sensitive), Cellulose Acetate Phthalate (pH-sensitive), and Gellan Gum or Alginate (ion-sensitive).

Metformin and its Potential in Ophthalmology:

Metformin (1,1-dimethylbiguanide) is the first-line oral hypoglycemic medication used worldwide for the management of type 2 diabetes mellitus. Its primary mechanism of action involves the inhibition of hepatic gluconeogenesis and the enhancement of peripheral insulin sensitivity, primarily mediated through the activation of AMP-activated protein kinase (AMPK). In recent years, the concept of drug repurposing has brought metformin into the spotlight for a variety of non-diabetic indications, including cancer, cardiovascular diseases, aging, and neurodegenerative disorders. In the realm of ophthalmology, an accumulating body of preclinical and epidemiological evidence suggests that metformin possesses significant pleiotropic effects that can be leveraged to treat several severe ocular morbidities. Diabetic Retinopathy (DR): DR is a microvascular complication of diabetes and a leading cause of blindness. Metformin has been shown to protect retinal capillary endothelial cells, reduce vascular hyperpermeability, and inhibit inflammatory cytokine production. Its activation of AMPK helps restore cellular energy homeostasis and mitigates oxidative stress in the retina. Age-Related Macular Degeneration (AMD): AMD is characterized by the degeneration of the macula, leading to central vision loss. Metformin has demonstrated anti-angiogenic properties, inhibiting the proliferation and migration of endothelial cells, which is crucial in managing neovascular (wet) AMD. Additionally, it protects retinal pigment epithelial (RPE) cells from oxidative damage, a key factor in the pathogenesis of dry AMD. Dry Eye Disease and Ocular Inflammation: The anti-inflammatory effects of metformin, mediated by the inhibition of the NF-κB pathway, make it a potential therapeutic agent for managing inflammatory conditions of the ocular surface, including severe dry eye syndrome and uveitis.[3]

Rationale for Topical Delivery of Metformin:

While the therapeutic potential of metformin in ocular diseases is evident, delivering it effectively remains a significant hurdle. Oral administration necessitates high systemic doses to achieve adequate concentrations in the eye, which can lead to adverse systemic effects, including gastrointestinal disturbances and, rarely, lactic acidosis. Furthermore, for patients without diabetes who suffer from AMD or other inflammatory ocular diseases, systemic administration of an anti-diabetic drug is clinically inappropriate and risky.

Therefore, the localized, topical ocular delivery of metformin represents a highly logical and necessary approach. By applying the drug directly to the eye, high local tissue concentrations can be achieved while minimizing systemic exposure. However, metformin is a highly water-soluble (hydrophilic) compound with low membrane permeability (BCS Class III). It struggles to cross the lipophilic corneal epithelium efficiently when administered as a simple aqueous solution. To overcome this, formulating metformin into an advanced delivery system, such as a polymeric nanoparticle-loaded in-situ gel, is proposed. The nanocarriers can encapsulate the hydrophilic drug, mask its physicochemical properties, and facilitate its transcorneal penetration.

Types Of Ocular Delivery Systems:

The field of ocular drug delivery has witnessed a paradigm shift from traditional dosage forms to sophisticated, targeted, and controlled-release systems. To fully appreciate the rationale behind selecting an in-situ gelling nanoparticulate system for metformin, it is essential to review the broad spectrum of ocular delivery systems currently available or under investigation. These systems can be broadly categorized into conventional systems, vesicular systems, particulate systems, controlled-release devices, and advanced polymeric systems.

Conventional Ocular Delivery Systems:

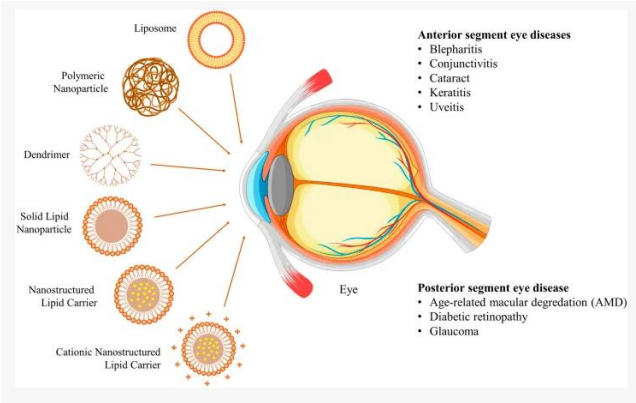
major limitation is the extremely short precorneal contact time. Reflex blinking and the rapid turnover of tears wash the formulation away within a few minutes, resulting in a bioavailability of merely 1% to 5%. To compensate, frequent dosing is required, which often leads to patient non-compliance and systemic side effects due to the drainage of the drug into the nasolacrimal duct.

Suspensions

Suspensions are utilized for active pharmaceutical ingredients that exhibit poor aqueous solubility. The drug particles are dispersed in an aqueous vehicle. The dissolution of these particles provides a slightly prolonged release compared to solutions. However, the particle size must be meticulously controlled (typically less than 10 µm) to avoid foreign body sensation, irritation, and reflex tearing upon instillation. Polymorphism and physical stability (caking, settling) are significant formulation challenges associated with ophthalmic suspensions.

Ointments and Creams

Ophthalmic ointments are formulated using a semisolid base, typically composed of white petrolatum, mineral oil, and lanolin. Their lipophilic nature and high viscosity enable them to resist tear washout, thereby significantly increasing the precorneal residence time and providing sustained drug release. Despite these advantages, their clinical utility is severely limited by patient discomfort. Upon application, they cause a thick film to form over the cornea, leading to blurred vision. Consequently, ointments are generally reserved for nighttime application or for treating severe exterior ocular infections where vision clarity is temporarily secondary.[3]



Eyes Anatomy

- IRIS IRIS
- Control size of pupil and hence amount of light entering.
- PUPIL
- Central opening in iris.
- Pathway for drug movement of posterior parts.
- EYE
- LENS

ANATOMY AND PHYSIOLOGY OF THE EYE:

- The human eye is a highly complex, exquisitely specialized, and unique organ, structurally designed to capture light and process visual information. However, from a pharmacological and drug delivery perspective, it presents one of the most formidable challenges. The eye is anatomically divided into two primary segments: the anterior segment and the posterior segment. The human eye is a highly complex, exquisitely specialized, and unique organ, structurally designed to capture light and process visual information. However, from a pharmacological and drug delivery perspective, it presents one of the most formidable challenges. The eye is anatomically divided into two primary segments: the anterior segment and the posterior segment. The human eye is a highly complex, exquisitely specialized, and unique organ, structurally designed to capture light and process visual information. .

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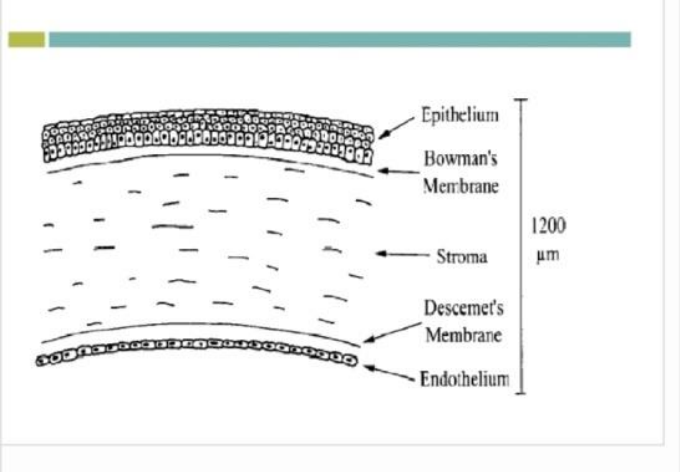
- The anterior segment comprises the cornea, conjunctiva, aqueous humor, iris, ciliary body, and lens. The cornea acts as the principal barrier for topically applied drugs. It is a transparent, avascular tissue consisting of five distinct layers: the epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium. The lipophilic nature of the corneal epithelium and endothelium, coupled with the hydrophilic nature of the thick corneal stroma, necessitates that a drug molecule possess a precise balance of lipophilicity and hydrophilicity (amphiphilic nature) to successfully traverse the intact cornea. The anterior segment comprises the cornea, conjunctiva, aqueous humor, iris, ciliary body, and lens. The cornea acts as the principal barrier for topically applied drugs. It is a transparent, avascular tissue consisting of five distinct layers: the epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium. The lipophilic nature of the corneal epithelium and endothelium, coupled with the hydrophilic nature of the thick corneal stroma, necessitates that a drug molecule possess a precise balance of lipophilicity and hydrophilicity (amphiphilic nature) to successfully traverse the intact cornea.

Mechanism of Ocular Drug Absorption:

- After application of drug on the surface of the eye, it must cross Several barriers to reach intraocular tissues.
- Drug absorption in the eye mainly occurs by two pathways:
- Comeal Absorption
- Non-corneal Absorption

Corneal Absorption:

- Drug passes through the cornea reaches aqueous humor then acts as on anterior eye tissues (e.g., in's, cilliary body).
- The cornea has three main layers affecting absorption:
- Epithellium
- Stroma
- Endothelium



Bowman's Membrane;

Bowman's membrane is an acellular thin layer made of collagen fibrils.

Anteriorly it is separated from the epithelium by a basement membrane.

It does not offer high diffusional resistance and as such it is not a rate limiting barrier

Stroma;

This corneal layer is a highly organized structure constituting 90% of the cornea.

It consists of parallel collagenous lamellae.

Between the lamellae lies the modified fibroblast known as keratocytes.

The stromal layer becomes a limiting barrier for permeationof lipophilic drug

Minimal resistance to hydrophilic drugs

Blood Retinal Barrier:

- The blood - retinal bamier is a physiological barrier that controls the movement of susbstances blw the blood and the retina.
- It protects the retina from harmful substances and maintains a stable environment for retina function.
- There are two main parts:
- @Inner Blood - Retinal Barrier: Formed by tight junctions blw endothelial cells of retinal capillaries.
- Outer Blood - Retinal Bamier: Formed by retinal pigment epithelial (RPE) cells with tight junctions blw them.

BARRIERS ARE BROADLY CLASSIFIED AS:

1)Anatomical barriers:

When a dosage form is topically administered there are two routes of entry, either through the cornes or via the non-corneal route. The cornea is very tight multilayered tissue that is mainly composed of five sections Epithelium, bowman's membrane, stroma, descent's membrane and endothelium.[5]

- Corneal cross section
- Pavement pitheliur
- sayers
- Bowman's layer
- Strome

2) Descemet's Endothelius:

Out of these it is the epithelium which acts as the principal barrier. These 5-6 layers of columnar epithelial cells with very tight junctions create high Para cellular resistance of 12-16 Kilom it acts as a major barrier to hydrophilic drug transport through intercellular spaces. On the other hand stroma, which consists of multiple layers of hexagonally, arranged collagen fibers contaising aqueous pores or channels allow hydrophilic drugs to easily pass through but it acts as a significant barrier for lipophilic drugs. Thus for a drug to have optimum bioavailability, it should have the right balance between lipophilicity and hydrophilicity. The remaining layers are leaky and do not act as significant barriers. Non-corneal route by passes the cornea and involves movement across conjunctiva and sclera. This route is important for large especially and hydrophilic molecules such as peptides, proteins and siRNA (small or short interfering RNA) The conjunctiva is more permeable than cornca especially for hydrophilic molecules due to much lower expression of tight junction proteins relative to corneal epithelium, ligh vascularity of the limbul area renders this route not suitable for drug delivery as the blood vessels remove a large fraction of absorbed dose. Only a small frationof the dove reaches the vitreous[6]

3) Physiological barriers:

The eye's primary line of defense is its tear film Binavailability of topical administered drugs is further redared by precorneal factors such as solution drainage, tears dilution, tear turnover, and increased lacrimation.

The lacrimal fluid is an isotonic aqueous solution containing a misture of proteins (such as lysozyme) as well as lipids Following topical application, lacrimation is significantly increased leading to dilation of administered dose This in turn lowers drug concentration beading to diminished drug absorption Rapid dearance from the precorneal area by lacrimation and through nasolacrimal drainage and spillage further redures contact time between the tissue and drug molecules This in turn lowers the exact time for absorption leading to reduced bioavailability The average tear volume is 7-9 ul. with a turnover rate of 16% per minute Thus drugs administered as eye drops need to be isobaeic and non irritating to prevent significant precorneal loss.

4) Blood-ecular barrier

The Hood-ocular barrier normally keeps most drugs out of the eye. However inflammation breaks down this harrier allowing drugs and large molecules to penetrate into the eye.

METHODS TO OVERCOME BARRIERS

I. Viscosity enhancers

Viscosity increasing polymers are usually added to ophthalmic drug solutions on the premise that an increased vehicle viscosity should comespond to a slower elimination from the preocular area, which lead to improved precorneal residence time and hence a greater transcomeal penetration of the drug into the anterior chamber.

The polymers used include polyvinyl alcohol (PVA),

polyvinylpyrrolidone (PVP),

methylcellulose (MC hydroxyl ethyl cellulose,

hydrowyl propyl methyl cellulose (HPMC),

hydroxyl propyl cellulose[7]

II. Penetration enhancers

The transport characteristics across the cornea can be maximized by increasing the permeability of the

comesl epithelial membrane

So, one of the approaches used to improve ophthalmic drug bioavailability les in increasing transiently the permeability characteristics of the comes with appropriate substances known as penetration enhancers or absorption promoters it has disadvantages like ocular imitation and toxicity. The transport process from the comes to the receptor site is a rate-limiting step, and permeation enhancers increase corneal uptake by modifying the integrity of the corneal epithelum Eg, cetyl pyridinium chloride, benzalkonium chloride, parabens, tween 20.

IMPLANTS:

The aim of designing an intraocular implant is to prolong the activity of the drug, along with its controlled release by using a polymer or polymer system. An injectable delivery system of drug, like liposomes and nanoparticles, is easy to administer, but having limitation that after insertion, it becomes difficult to retract those particles during any complication, like toxic responses. So it is beneficial to use implants for balancing the rate and duration of drug release. Removal of ocular implants is easy and can be removed by surgical intervention. Implants can be categorized into two types haced characteristics.

Implants can be categorized into two types based on the characteristics of the polymer(s) used

Nonbiodegradable implants:

They do not dissolve to any significant extent and are not even eroded in vivo Biodegradable implants as They mostly dissolve in vivo with soluble components by processes such enzymatic or nonenzymatic degradations . Examples of marketed implants used worldwide have been cited in.Approaches for posterior segment drug delivery Intravitreal injections Approaches for posterior segment drug delivery.

Intravitreal injections:

Research reports reveal that intravitreal injections for the posterior segment are gaining worldwide popularity as a drug delivery system, over the past few years.

Injections are directly given into the posterior segment via pars plana for delivering drugs to overcome all barriers. A number of studies have been conducted to find out the pharmacokinetic parameters of antiviral agents, like ganciclovir foscarnet and cidofovir antibiotics: Cefazolin amikacin, moxifloxacin ceftizoxime, ceftriaxone ceftazidime clindamycin and gentamicin steroids: dexamethasone triamcinolone acetonide and monoclonal antibodies, such as bevacizumab following intravitreal injections. If the molecular weight of the drug is very high, vitreal retention times seem to be higher as well. Molecules that are larger, i.e., linear>40 kDa and globular molecules>70 kDa seem to have long retention time due to the presence of tight barriers around the vitreous humor . So, this route is preferable for higher molecular weight drugs (>500 Da) and also having longer half-lives. First-order rate kinetics is mainly responsible for the elimination of residues out of the vitreous humour .Even the drug delivery through intravitreal injections can be gained by increasing concentrations of drugs in neural.[5]

Periocular route:

Periocular region is the region surrounding the eye. Among all the present routes, the periocular route is least painful and a promising route for delivery of the drug to the posterior segment of the eye. In drug delivery through periocular route, the drug is placed in the nearest position to sclera; as a result, vitreal drug levels can be noticed after 20-30 min. Periocular delivery includes retrobulbar, peribulbar, subtenon and subconjunctival routes.

Retrobulbar injection;

Retrobulbar injection consists of drug solution deposition into retrobulbar space within the muscle cone. This route is used when the formulation needs to be in direct contact with the macular region. These injections are mostly given through specific 23 gauge sharp, 1.5-inch needle with a rounded tip and a 10 bend.

Peribulbar injection;

Peribulbar injections are used for lowering the risk of injury to intraorbital structures related to retrobulbar administration during cataract surgery. The injection is given in the quadrant between the inferior and the lateral of the orbit using a 26-gauge half-inch disposable needle .

retina; side effects like retinal detachment due to repeated injections, retinal hemorrhage, endophthalmitis and other toxicities in the retina occurs because of more concentrations upon bolus dose administration that can cause patient's non-compliance . Ausayakhun et al. (2005), have found in their study, that the cytomegalovirus (CMV) retinitis can be controlled by using intravitreal ganciclovir (2 mg in 0.1 ml per) and the reported data has shown that 60% of the treated eyes have remained stable, 13% have shown improvement and 26% have shown a reduction in visual acuity [88]. However, a retinal detachment has been noticed in 6%, intravitreal hemorrhages observed in 1% and endophthalmitis observed in 1% of treated eyes. So we can observe from the study that the problems associated with intravitreal injections should be taken into consideration . A number of other studies have also been carried out for similar findings, which have stated that the intravitreal injections are useful, but not good for posterior segment.[8]

diseases Development in designing of drug delivery system and surgical procedures has led to the development of intravitreal implants that can be instilled inside the vitreous chamber for a longer duration. The difference between intravitreal injections and intravitreal implants is their administration time. Injections can be taken 2 or 3 times a week and preferably can be changed every month, respectively

Subconjunctival injection:

The conjunctiva is a membrane that covers the sclera. The injection administered as a drug solution below the conjunctiva follows minimally invasive technique for delivering a drug to the posterior segment of the eye. About 500 µl of a drug solution as dosage form is injected into the subconjunctival area (bulbar conjunctiva) using a 25/30 gauge, 30 mm long needle. Subconjunctival injection can be used in critical conditions in which a molecule diffuses directly through sclera .

Subtenon injection;

The Tenon's capsule is a facial sheath of connective tissue sandwiched between the conjunctiva and episcleral plexus. The episcleral or subtenon's space is a void space between the tenon's capsule and sclera . Subtenon injection is used to administer the drug in contact with sclera for prolonged periods because of its vascular nature.technologies. According to the reported studies, an ocular delivery system includes liposomes and nanoparticles in droppable gels and liposomes and nanoparticles coated with bioadhesive polymers. The challenges to be faced by topical ocular drug delivery systems in the future are:

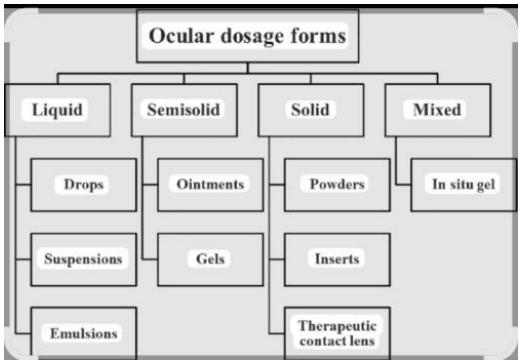
The ocular route enhances bioavailability not more then 15 to 20% of the administered dose.

Most of the marketed ocular formulations are highly non-specific. So, it needs to focus on the development of new drug candidates initially intended for ocular use.

Further studies need to be carried out for exploring the non-corneal routes, mainly for ionic/water-soluble contents and drug molecules with a preferential corneal absorption (and minimum absorption through nasal mucosa) should be explored.[9]

Further researches are needed for suitable designing and packaging of the delivery systems. Several scientific and technological advancements need to progress in this field. Mainly the advancement in nanotechnology and biomaterials science may provide new technologies to improve ophthalmic drug delivery systems.

CLASSIFICATION OF OCULAR DRUG DELIVERY SYSTEM :



CONVENTIONAL DELIVERY SYSTEMS

- These are traditional, widely used formulations that are generally easy to manufacture but suffer from low bioavailability (<5%) due to rapid drainage.
- Liquid Dosage Forms: The most common type. Includes solutions (clear liquids), suspensions (dispersed particles), and emulsions (oil-water mixtures).
- Semi-Solid Dosage Forms: Provide longer contact time. Includes ointments (petrolatum-based) and gels (mucoadhesive polymers).
- Intraocular Injections: Direct delivery
- into the eye, such as intravitreal (into the vitreous humor) or intracameral (into the anterior chamber) injections.[10]

Novel/Advanced Delivery Systems

These systems are designed to overcome ocular barriers, increase drug residence time, and provide controlled release.

Vesicular Systems

Microscopic carriers that encapsulate drugs to improve penetration:

Liposomes: Lipid-based vesicles.

Niosomes: Non-ionic surfactant-based vesicles.

Pharmacosomes: Lipid-drug

Particulate Systems

Ultrafine particles (10-1000 nm) that can be targeted to specific tissues:

Nanoparticles & Nanospheres: For sustained release and protection of sensitive drugs.

Microparticles: Larger than nanoparticles, used for long-term delivery.[11]

SIDE EFFET OF OCULAR DRUGS DELEVARY SYSTEM :

- **Eye Conditions:** Delivery of medications over months to treat conditions like glaucoma (reducing intraocular pressure) and wet age-related macular degeneration (AMD) using sustained-release implants or intracameral/intravitreal injections.
- **Inflammation and Infection Control:** Targeted delivery of corticosteroids, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs) for conditions like uveitis, bacterial keratitis, or postoperative inflammation.[12]
- **Drug Delivery to the Posterior Segment:** Specialized systems bypass the eye's protective barriers to treat vitreoretinal diseases, such as diabetic retinopathy or macular edema.
- **Dry Eye Management:** Use of lubricating, anti-inflammatory, or tear-stimulating agents, including mucoadhesive gels or contact lenses that release drugs, to improve tear film stability and ocular comfort.
- **Pre- and Post-operative Care:** Application of mydriatics (pupil dilation), miotics (pupil constriction), and anesthetics during ocular surgery.
- **Non-Surgical Cataract Treatment:** Research-based nanoformulations (e.g., liposomes, nanoparticles) aim to deliver antioxidants to the lens, targeting oxidative stress and preventing protein aggregation.
- **Common Ocular Drug Delivery SystemsTraditional:** Eye drops, suspensions, and emulsions (represent >95% of products).
- **Advanced/Novel:In situ Gels:** Liquid upon instillation but form a gel in the eye for longer residence time.Implants: Biodegradable or non-biodegradable, such as the Susvimo port delivery system for Lucentis (ranibizumab).
- **Ocular Inserts:** Solid devices placed in the conjunctival sac to provide long-term release.Nanotechnology: Liposomes and nanoparticles for targeted delivery

ADVANTAGE :

- Provides locallized drug action in the eye.
- Reduced systemic side effects.
- Improved bicavailability compared to conventional drops.
- Sustained & controlled drug release possible.
- Better patient compliance.
- Can be used for posterior segment targeting.
- **Targeted Concentration:** Delivers the drug directly to the cornea, conjunctiva, and anterior chamber.
- **Bypassing Barriers:** Avoids the **blood-aqueous barrier** and **blood-retinal barrier** that often prevent systemic drugs from reaching therapeutic levels in the eye.

DISADVANTAGE

- Limited drug permeability through ocular barriers.
- Short residence time for topical formulations.
- Invasive methods (like instraocular injections) may cause discomfort.
- Risk of infection or irritation.
- Complex & costly manufacturing techniques.

VISCOSITY:

increasing polymers are highly preferred additive in the ophthalmic hydroxylpropyl formulations due to their properties of enhancing viscosity and thereby imparting benefit to the penetration of the drug into the anterior chamber of the eye by lowering the elimination rate from the preocular area, resulting in increase in precorneal residence time and transcorneal penetration, but having very fewer effects for enhancing bioavailability in human beings. Examples of polymers are polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, hydroxylethylcellulose, methylcellulose (HPMC) and hydroxypropyl cellulose As per Saettone et al. (1984), in their study of tropicamide solution, by using PVA, HPMC, and PVP solution, at concentrations yielding the same viscosity of 20 cst, PVA has been reported to be the most effective among all, probably due to the adhesive property of PVA and its capability to enhance the thickness of the precorneal tear film . Saettone et al. (1982) have stated in their study that the retention of drug in the precorneal tear film does not strictly belong to vehicle viscosity, but also with surface spreading properties of the vehicle and to the capability of a polymer

IONTOPHORESIS;

Ocular iontophoresis is one of the growing fields in research due to its noninvasive nature of delivering drugs to both the anterior and posterior segments of eye. Iontophoresis is defined as a noninvasive procedure for the transfer of ionized drugs via membranes with low electrical current.

The drugs can move across the membranes by two ways, migration and electro-osmosis. Ocular iontophoresis, categorized as transcorneal, corneoscleral, or trans-scleral . is considered as one of the most attractive options. OcuPhor™™™™ system has been designed with the help of an applicator, dispersive electrode and a dose controller for trans scleral iontophoresis . The device works, as it releases the active drug moiety into retina-choroid. Another similar device being made known by name called Visulex™, which allows specific transport of ionized molecules through the sclera. Antibiotics, which are successfully used, are gentamycin, tobramycin, and ciprofloxacin, but not vancomycin, due to its high molecular weight Fruitful results of delivery have been observed with drugs such as dexamethasone and antisense ODNs .[14]

Advantages:

- It can overcome the major side effects caused by intraocular injections and implants .
- Disease that might be cured using iontophoresis includes fungal keratitis, uveitis, retinitis, retinoblastoma, proliferative vitreal retinopathy and various retinal degenerations .

Disadvantages:

- As there is a chance of burns and pains because of excessive current density, it should be used in such a manner that it takes a short period for delivering the drug.
- Drug should be in ionic form and have sufficient concentration because of high molecular weight, i.e., 8 000-12 000.

LITERATURE REVIEW

A comprehensive review of literature is an indispensable prerequisite for defining the rationale, scope, and direction of any research endeavor. The subsequent section delineates the significant scientific contributions made by various researchers in the domains of ocular drug delivery systems and the therapeutic repurposing of Metformin.

1. Literature Review

Smith et al. (2001) conducted a pivotal study focusing on the formulation parameters governing the precorneal residence time of topical ophthalmic preparations. The authors utilized gamma scintigraphy to track the clearance of radiolabeled formulations from the human eye. Their findings conclusively demonstrated that increasing the viscosity of the formulation up to a threshold of 50 cPs significantly improved the retention time, whereas higher viscosities resulted in reflex tearing and rapid washout. Smith et al. (2001) conducted a pivotal study focusing on the formulation parameters governing the precorneal residence time of topical ophthalmic preparations.

2.Literature Review

Furthermore, this study explored the use of mucoadhesive polymers such as chitosan and hyaluronic acid. The researchers established that cationic polymers, owing to their electrostatic interaction with the negatively charged mucin layer of the tear film, exhibited superior bioadhesion compared to non-ionic or anionic polymers. This foundational research paved the way for the development of modern polymeric in-situ gelling systems and nanoparticle-based therapies designed to mitigate precorneal drug loss. Furthermore, this study explored the use of mucoadhesive polymers such as chitosan and hyaluronic acid.

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MATERIALS AND METHODS

- **Materials**
- Metformin Hydrochloride (API) - Procured as a gift sample from Biocon Ltd., Bangalore.
- Poloxamer 407 (Pluronic F127) - Sigma-Aldrich, USA.
- Sodium Alginate - Loba Chemie, Mumbai.
- Hydroxypropyl Methylcellulose (HPMC K4M) - Colorcon Asia Pvt Ltd.
- Benzalkonium Chloride - S D Fine-Chem Ltd., Mumbai.
- Simulated Tear Fluid (STF) components (NaCl, NaHCO3, CaCl2) - Merck Life Science.
- Dialysis Membrane (Molecular weight cutoff 12,000-14,000 Da) - HiMedia Laboratories.
- HPLC grade solvents (Methanol, Acetonitrile, Water) - Fisher Scientific.[20]

- **Preformulation Studies**

Preformulation testing is the primary step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The objective of preformulation studies is to develop a portfolio of information about the drug substance, which serves as a set of parameters against which formulations can be designed and evaluated. Preformulation testing is the primary step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

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physical and chemical properties of a drug substance alone and when combined with excipients. The objective of preformulation studies is to develop a portfolio of information about the drug substance, which **Formulation Development:**

Preparation of In-Situ Gelling System: The in-situ gelling formulations were prepared using the cold method. Briefly, an accurately weighed quantity of Metformin was dissolved in a specified volume of distilled water. The required amount of the temperature-sensitive polymer (e.g., Poloxamer 407) was added slowly to the aqueous drug solution under continuous magnetic stirring to prevent the formation of lumps. The dispersion was then kept in a refrigerator at 4°C for 24 hours to ensure complete swelling and dissolution of the polymer, resulting in a clear, viscous solution. Preparation of In-Situ Gelling System: The in-situ gelling formulations were prepared using the cold method. Briefly, an accurately weighed quantity of Metformin was dissolved in a specified volume of distilled water.

EVALUATION PARAMETERS

Determination of pH: The physiological pH of tear fluid is approximately 7.4. Therefore, ophthalmic preparations should ideally be formulated around this pH to prevent irritation, excessive tearing, and subsequent drainage of the instilled dose. The pH of all formulated batches was measured using a calibrated digital pH meter at room temperature. Determination of pH: The physiological pH of tear fluid is approximately 7.4. Therefore, ophthalmic preparations should ideally be formulated around this pH to prevent irritation, excessive tearing, and subsequent drainage of the instilled dose. The pH of all formulated batches was measured using a calibrated digital pH meter at room temperature. Determination of pH: The physiological pH of tear fluid is approximately 7.4. Therefore, ophthalmic preparations should ideally be formulated around this pH to prevent irritation, excessive tearing, and subsequent drainage of the instilled dose. The pH of all formulated batches was measured using a calibrated digital pH meter at room temperature. Determination of pH: The physiological pH of tear fluid is approximately 7.4. Therefore, ophthalmic preparations should ideally be formulated around this pH to prevent irritation, excessive tearing, and subsequent drainage of the instilled dose. The pH of all formulated batches was measured using a calibrated digital pH meter at room temperature. [27,28]

CHEMICAL INSTUMENT PROCEDURE IN DETAIL :

1. Preservatives

Used in multi-dose eye drops to prevent microbial growth.

Benzalkonium Chloride (BAK): Most common, but can cause ocular surface toxicity with long-term use

Purite / Stabilized Oxychloro

Complex: Breaks down into water and oxygen in the eye, less irritating

Sodium Perborate: Oxidizes on

contact with eye, converts to water and oxygen

Preservative-free: Used in single-dose vials to avoid toxicity

Company : Polymers for Implants/Inserts & Viscosity Enhancers

Company : Ashland Global Holdings Inc. - USA

Products: HPMC, HPC, PVP, Carbomer, PVA

Brand names: Klucel, Benecel, Aquarius

2. Viscosity Enhancers

Increase residence time of the drug on the ocular surface by thickening the formulation.

Hydroxypropyl Methylcellulose (HPMC)

Polyvinyl Alcohol (PVA)

Carbomer / Carbopol

Sodium Hyaluronate: Also used for dry eye treatment

Company : DuPont / Dow Chemical - USA

Products: HPMC, PVA, Polyethylene Glycol

Brand names: METHOCEL, ELVANOL[29]

3. Permeation Enhancers

Improve drug penetration through the cornea and conjunctiva.

EDTA (Ethylene Diamine Tetraacetic Acid): Chelates calcium, loosens tight junctions

Cyclodextrins: Increase solubility and bioavailability

Chitosan: Natural polymer that enhances mucoadhesion and penetration

Company :Lubrizol Corporation - USA

Products: Carbomer, Polycarbophil

Brand names: Carbopol, Noveon

4. Polymers for Implants & Inserts

Used in sustained-release systems to control drug release over weeks to months.

PLGA (Poly Lactic-co-Glycolic Acid):

Biodegradable, used in Ozurdex implant

PVA (Polyvinyl Alcohol): Used in Ocusert inserts

Silicone: Non-biodegradable, used in Retisert implants

Hydrogels: Used in medicated contact lenses

Company : Evonik Industries - Germany

Products: PLGA, PLA for biodegradable implants

Brand names: RESOMER[30]

5. Buffers & pH Adjusters

Maintain pH around 6.5-7.6 to match tears and avoid stinging.

Phosphate Buffer, Citrate Buffer, Borate Buffer

Company : Corel Pharma Chem - India

Products: PLGA, PLA, Chitosan for sustained release

Sodium Hydroxide / HCI: For pH adjustment

6. Tonicity Adjusters

Make the formulation isotonic with tears to avoid irritation.

Tonicity Adjusters

Make the formulation isotonic with tears to avoid irritation.

Sodium Chloride

Dextrose, Mannitol

Company :Roquette Frères - France

Products: Hydroxypropyl Beta Cyclodextrin, Methyl Beta Cyclodextrin

Brand names: KLEPTOSE[31]

7. Active Pharmaceutical Ingredients (API)

The actual drugs delivered:

For Glaucoma: Timol, Latanoprost, Brimonidine

For Inflammation: Dexamethasone, Prednisolone Acetate

For AMD/Diabetic Retinopathy: Ranibizumab, Aflibercept - Anti-VEGF agents

For Infection: Moxifloxacin, Gatifloxacin

Company :Wacker Chemie AG - Germany

Products: Cyclodextrins, Cavamax, Cavasol.[32]

RESULT

primary results of modern Ocular Drug Delivery Systems (ODDS) include enhanced bioavailability, prolonged therapeutic action, and improved patient adherence. By overcoming physiological barriers like tear drainage and the blood-retinal barrier, advanced systems ensure more medication actually reaches and stays in the target tissue compared to conventional eye drops.

- **Organoleptic Properties and Preformulation**

The procured sample of Metformin Hydrochloride was found to be a white, crystalline, odorless powder. The melting point was determined to be 224-226°C, which is in close agreement with the official compendia, indicating the purity of the drug sample. The solubility profile revealed that the drug is freely soluble in water and slightly soluble in ethanol. The procured sample of Metformin Hydrochloride was found to be a white, crystalline, odorless powder. The melting point was determined to be 224-226°C, which is in close agreement with the official compendia, indicating the purity of the drug sample. The solubility profile revealed that the

DISCUSSION

Interpretation of Findings

The primary objective of this investigation was to formulate an ocular delivery system capable of circumventing the rapid precorneal clearance typical of conventional eye drops. Metformin was selected due to its emerging potential in treating ocular disorders via the AMPK activation pathway. The selection of the in-situ gelling platform was justified by its ability to be administered as a liquid (ensuring ease of instillation and dosage accuracy) and its subsequent transition into a gel in the cul-de-sac in response to physiological stimuli (temperature and pH).

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This is a highly desirable property for ocular delivery, as the sheer stress generated during blinking temporarily decreases the viscosity of the gel, spreading it evenly across the corneal surface, while the high resting viscosity prevents its drainage down the nasolacrimal duct. The rheological studies confirmed the pseudoplastic behavior of the formulations. This is a highly desirable property for ocular delivery, as the sheer stress generated during blinking temporarily decreases the viscosity of the gel, spreading it evenly across the corneal surface, while the high resting viscosity prevents its drainage down the nasolacrimal duct. The rheological studies confirmed the pseudoplastic behavior of the formulations. This is a highly desirable property for ocular delivery, as the sheer stress generated during blinking temporarily decreases the viscosity of the gel, spreading it evenly across the

Future Prospects

As challenges are more for eye as compared to the skin, so there is a need to focus more on non-invasive sustained drug release for eye disorders in both segments [103]. An ideal system is a system which should be able to administer an effective drug concentration at the targeted site for a prolonged period of time, while lowering systemic exposure. The output resulted from such systems, makes the system comfortable and easy to use.

Conclusions:

The current review identifies a unique regulatory mechanism in metformin-mediated defense against diabetic retinopathy. The potential of MET for ocular application is supported by the current study. The MF5 in situ gel demonstrated enhanced efficacy in reducing initial ocular inflammation and adjustment of crucial parameters for sustained release, bolstered by extended bleeding. Created using components that have been approved, MF5 exhibits promising results as a secure substitute for steroids in the treatment of ocular inflammation. This may stimulate additional research to apply it to other ocular conditions.

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