



Review Article

Emerging Trends and Technologies in Ocular Drug Delivery: A Comprehensive Review

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ABSTRACT

There are anatomical and physiological challenges in ocular drug delivery, particularly because of the human eye. Poor drug retention and penetration with conventional drug formulations like eye drops and ointments require multiple doses and poor patient adherence. In the last decade, new technologies have revolutionized the field of ocular therapeutics with the development of innovative drug delivery platforms for sustained, targeted and controlled release. This review covers recent developments of nanocarriers, liposomes, dendrimers, microneedles, hydrogels, contact lenses for drug delivery, in situ gels and implantable drug delivery systems for the eye. Discussions also include bioinspired and stimuli-responsive systems in which the release of the product can be customized upon demand, to optimize pharmacokinetic profiles. Furthermore, the article discusses the major regulatory implications, translation issues and future prospects of incorporating nanotechnology, biomaterials and smart drug delivery methods in the field of ophthalmology. The aim of this review is to provide a summary of the state of the art in the field of ocular drug delivery, highlight the trends, and support further research for more efficient, patient-friendly, and clinically translatable drug delivery solutions to the eye.

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INTRODUCTION**A Brief Overview of the Obstacles Facing Ophthalmology Drug Delivery**

The intricate architecture and robust defence systems of the eye make medication delivery to the eye a formidable obstacle in the field of Pharmaceutical Sciences. Eye drops have been the traditional formulation used for anterior segment diseases and are beset with a number of inherent limitations. They generally have a bioavailability of less than 5%, because they are rapidly and completely cleared through the blink and tears and shielding the cornea from the outside world. This short half-life requires frequent dosing which may result in patient non-adherence and sub-optimal therapeutic response [1-4].

The Eye's Anatomy and Physiology Obstacles

An extraordinarily complex and sensitive organ is the human eye. Fig. 1 illustrates the structure of the human eye. Human eyes are comprised of

the front and rear of the eye. All of these structures—the tear film, cornea, pupil, lens, and ciliary body—make up the anterior segment of the eye. The retina, optic nerve, vitreous humor, choroid, sclera, and conjunctiva make up the back of the eye.

The iris is an organ of vision that regulates the quantity of light that reaches the retina by adjusting the pupil size. In prenatal development of the iris texture is complete. A little, black hole called a pupil sits in the middle of the iris. Ambient light causes a change in pupil size. In the center of the spherical globe, behind the eye, you can see the retina, and the lens is the translucent part that focuses light on it. The ciliary body is made up of ciliary muscles, stroma, and epithelia (both pigmented and non-pigmented). Through the capillaries of the ciliary body, intersegmental connections are formed between the anterior and posterior segments. The transparent, gel-like, and avascular vitreous humour connects the retina to the eye lens. Hyaluronic acid, ions, collagen, and water make about 99.9 percent of it [5].

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Before the iris and pupil, at the front of the eye, you'll find the cornea. The cornea is the most abundantly supplied tissue in the body, receiving the great majority of its nerve impulses as sensory impulses from the ophthalmic branch of the trigeminal nerve. As a person grows older, their cornea maintains a pretty consistent horizontal diameter of around 11.5 mm and a vertical diameter of roughly 10.5 mm. The vitreous chamber encases the eye, in contrast to retinal tissue, which borders the inner space of the eye. The optic cup is the embryonic site from

which the retina of the vertebrae develops. The cornea and sclera that surround the retina safeguard it and keep it in position. The sclera is a continuous layer that lies just below the cornea. It helps to keep the eyeball in its proper form, protects it from both inside and outside influences, and even supports the insertions of the extraocular muscles. Collagen fibrils and glycoproteins form the bulk of the Sclera extracellular matrix [6]. Create the eye's anatomical barriers (Fig. 1).

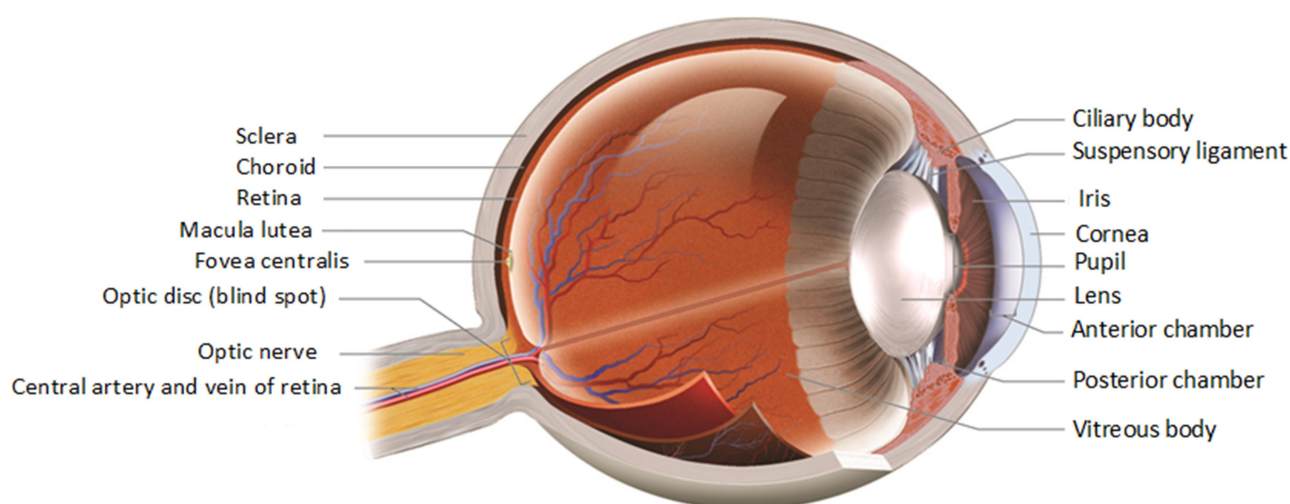


Figure 1: Anatomy Barrier of the Eye

Several Obstacles Make Drug Transport to the Eye Difficult, Such As the Following:

- It is not possible to stop the dosage form in a crisis.
- Visual impairment.
- Finds it difficult to put in and take out the dose form.
- Sometimes, when sleeping or washing the eyes, some of the medication might be lost.

The Current State of the Ocular Drug Delivery System

Current Situation Regarding Ocular Drug Delivery Systems

The primary ways in which an infection can occur are topically or systemically by the invasive route.

The physicochemical properties of the medicine, its therapeutic product formulation, the physiological condition of the various administration sites, and the kind of illness to be treated are the main elements that determine the route of drug administration.

Topical Route

Topical drops are the predominant form of eye drug delivery on the market as they are easy, inexpensive and most importantly convenient to use, also known as intravitreal injections and periocular injections can only be administered by a medical specialist. Topical applications have the disadvantage that at the active agent may not penetrate deeply enough, thus limiting therapeutic effects [7].

Systemic Route

Systemic applications can result in adequate therapeutic levels, but also are accompanied by undesirable systemic effects [8]. Two typical barriers to the systemic circulation of ophthalmic medications, one particular to the anterior portion of the eye and the other to the posterior, are the blood-retinal barrier (BRB) and the blood-aqueous barrier (BARB), respectively. Major issues arise with this method of administration because drugs given orally must withstand the hostile conditions of the digestive tract, and drugs given intravenously must contend with the lower blood flow to the eye

compared to the rest of the body, which prevents high levels of drug accumulation [9].

Intravitreal Routes

When treating disorders affecting the front and rear of the eye, intravitreal methods proved to be more effective. The intravitreal method shows promise for delivering large concentrations of drugs to the tissues behind the eye; nevertheless, complications such as endophthalmitis and retinal

detachment may restrict its use. The implant is either administered using an applicator or put into the vitreous via a sclerotomy incision; no sutures are used in this process. Controlled release formulations (e.g., liposomes, microspheres, implants) of drugs may also be introduced to the vitreous in order to extend the duration of therapeutic action [10]. Both osmosis and diffusion are described in Table 2, along with their similarities and differences.

Table 1: Application in Ocular Delivery, Method of Administration, Advantages and Disadvantages

Route	Benefits	Challenges	Applications
Topical Route	Good adherence from patients, easy to administer, and painless	The cornea functions as a barrier, efflux pumps, and a tear dilution and turnover rate that is less than 5%.	Eye infections such as blepharitis, scleritis, episcleritis, uveitis, and conjunctivitis
Systemic Route	Administration method that is both patient-friendly and painless	BAB, BRB, hazardous effects occur at large doses, BA <2%	Chronic uveitis, scleritis, episcleritis, and CMV retinitis
Intra-vitreous Route	Maintains medication levels, avoids BRB, and delivers directly to the vitreous and retina	Disconnection of the retina, bleeding, cataract, endophthalmitis, and noncompliance on the part of the patient	The following conditions are associated with AMD: PU, BRVO, CRVO, DME, CME, UME, and CMV retinitis

The Effectiveness and Disadvantages of Different Approaches are Compared and Contrasted

A low bioavailability is achieved with topical eye drops or systemically administered treatments. Injections cause significant tissue damage, many adverse effects, and poor therapeutic compliance; yet, they are therapeutically utilized to overcome the barrier qualities. Because they are noninvasive, easy to self-administer, and provide several future options, topical eye drops have several benefits over intravitreal injection. Medications applied topically have a lengthy travel ahead of them before they reach the posterior segment, the rear of the eye [11].

New Methods for Drug Delivery to the Eye Nanocarrier-Based Systems

• Liposome

The extended residence period for drug absorption makes liposomes, nanocarriers having an aqueous phase encased in a lipid bilayer similar to a cell membrane, a promising candidate for ocular drug delivery (Fig. 2). Because of this property, liposomes may encapsulate substances with a lipophilic and a hydrophilic nature. Typically, liposomal vesicles vary in size from 10 nm to 1 micrometer or even greater. Liposomes are constructed from unilamellar vesicles (ULVs) and multilamellar

vesicles (MLVs). The size of the vesicles allows for further classification of ULVs into three types: small (SUVs), gigantic (GUVs), and big (LUVs). Because of this, liposomes have been the subject of substantial research into drug delivery systems [12].

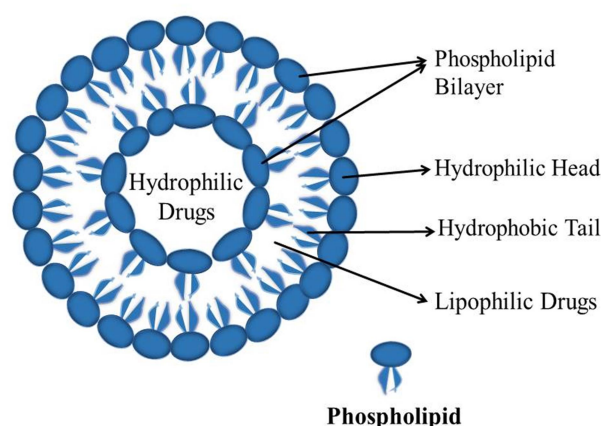


Figure 2: Structure of Liposome

Problems with the retina and vitreal condensation have resulted after intravitreal injection of liposomes. Several researchers in the last several decades have shown that liposomal formulations are an effective way to deliver medications to the eye. To further increase their retention duration on the ocular surface, a well-known technique involves modifying the

liposomal surface with mucoadhesive polymers, such as hyaluronic acid [13]. Fig. 2 illustrates liposome.

• Niosome

A novel medication delivery device called a niosomes is a vesicle with a non-ionic surface active agent bi-layer. Niosomes (Fig. 3) can be easily prepared with a hydrophilic or lipophilic or amphoteric drug. It is a new controlled ocular drug delivery system other than liposome to solve the sterilization, large scale production and stability issues [14]. It also has an improvement on the ability of the drug to adhere to or retain in the eye. Niosome made up of non-ionic surfactant has greater stability as drug carrier when compared with liposomes and are relatively inexpensive when compared to liposomes [15]. The above mentioned characteristics make niosomes suitable for ophthalmic application with drugs to be delivered to the ocular site such as gentamicin, diclofenac sodium, acetazolamide, timolol etc. for the treatment of eye disease. Some of the drug loading techniques are; active loading and passive loading [16]. When the medication is encapsulated passively during hydration, this is known as passive drug loading. The use of a trans-membrane gradient in the encapsulation of medicinal compounds is known as active loading. Niosomes are more cost-effective and need less time to prepare than liposomes, making the formulation process simpler [17]. Fig. 3 shows a niosome.

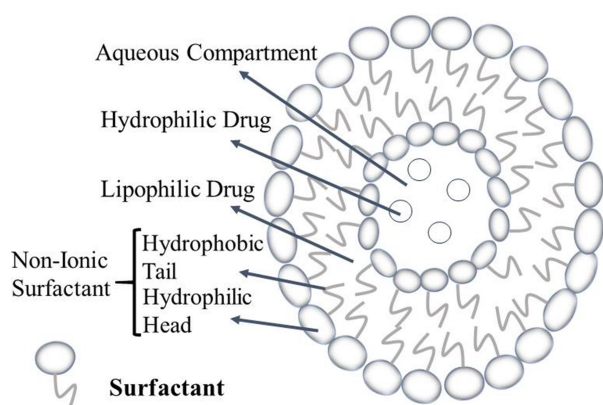


Figure 3: Structure of Niosome

• Solid Lipid Nanoparticle

The first mention of SLNs goes back to Citation Müller and Lucks (1996). Since then they have gained interest among scientists as a popular, non-toxic, stable and reliable particulate drug delivery vehicle [18]. SLNs are made from

physiologically accepted biocompatible excipients (similar to liposomes and Nano emulsion. The SLNs have a small size range (100 to 200 nm) and a wide size range (about 10 to 200 nm) [19]. In SLN, the medication is mostly present in a molecular form, such as between the glycerides' fatty acid chains (see Fig. 4). Because of this, these drug-loaded carriers work well when given intravenously [20-22]. There has been much research and development into SLN formulations for administration via the parenteral, oral, pulmonary, ophthalmic, and cutaneous routes [23]. There has been a lot of research on SLNs as a means of transporting large molecules, such as DNA, oligonucleotides, and proteins [24, 25]. Two of the SLNs' claimed production methods, emulsion and high-pressure homogenization (HPH), have already been used in medium- and large-scale manufacturing. Solid lipid nanoparticles (SLNs) have a stable matrix for drug encapsulation in their core, which is a lipid that stays solid at room temperature. The phospholipid layer around the core further enhances the nanoparticles' stability and biocompatibility [26]. The regulated release, reduced immunological responses, and prolonged ocular surface residence duration of the active molecules are all advantages of this unique structure. [27]. The Illustrate Solid Lipid Nanoparticles are shown in Fig. 4.

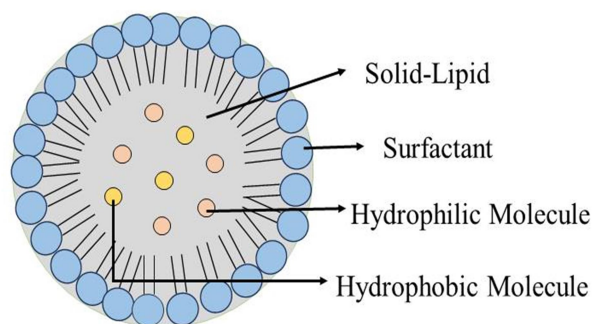


Figure 4: Interconnected solid lipid particles make up solid lipid nanoparticles.

• Polymeric Nanoparticle

Nanoparticles made of polymer and NPs, or polymeric nanoparticles, are particles with a size between 1 and 1000 nm. These NPs include active chemicals that are either embedded in the polymer or attached to its surface [28] (Refer Fig. 5). The polymeric nanoparticles loaded with drugs (Drug loaded polymeric nanoparticles) have several attractive properties including biodegradability, nontoxicity, biocompatibility

and muco-adhesiveness. These submicron particles are more advantageous than conventional ophthalmic dosage forms for improving bioavailability without causing any visual disturbances [29]. One of the strategies employed for enhancing the absorption of drugs across the biological membrane is the use of polymeric nanoparticles. A number of polymers are advantageous because they are biodegradable and may decompose into harmless substances in the body [30]. When designing an ocular implant, biodegradability is crucial since it gets rid of the need to manually remove the drug delivery system after it's finished working [31]. The size of this type of nanocarriers is usually between 100-500nm and can be further classified into 2 types of Nanostructures: nanospheres and Nano capsules (NCs). An improved alternative, polymeric nanoparticle (NPs) improve the rate at which drugs given topically reach the eyes [32-34].

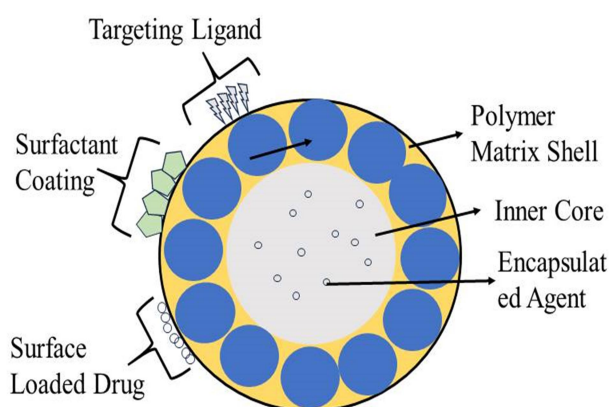


Figure 5: Structure of Polymeric Nanoparticle

• Nano Emulsion

The emulsion which is prepared by using the amphiphilic surfactant of the dimensions 20 to 500nm with two immiscible liquids (water and oil) is called Nano emulsion (NEs) (Fig. 6). They are transparent, have a high bioavailability and have a longer shelf life. Pharmaceuticals that are lipophilic or have low solubility in water may have their ocular bioavailability increased with the use of nano emulsions.

Nano emulsions for the eyes need additional ingredients such as preservatives, tonicity modifiers, buffers, viscosity modifiers, antioxidants, and API solubilizers because of the specificity of the application location [35-37]. The three varieties of nanoemulsions may be classified according to the oil and water components. The oil-in-water (O/W)

nanoemulsion is the first one. Second, there's the W/O nanoemulsion, which stands for water in oil. Third, there's the bi-continuous nanoemulsion, which has oil and water microdomains scattered throughout [38].

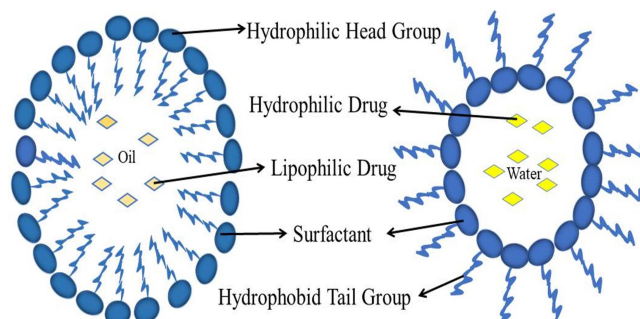


Figure 6: The structure of Nano Emulsion

• Micelle

The molecular weights of the blocks used to construct the core and corona determine the size and shape of the generated Micelle, which may range from 10 to 1000 nm [36]. Micelles are an encouraging new drug delivery system for treating anterior and posterior segment eye diseases including glaucoma, AMD, diabetic retinopathy, and dry eye syndrome. Their core-shell shape is the result of amphiphilic block polymers a self-administering in water with hydrophobic and hydrophilic block co-polymers [39].

Micelles have the ability to make hydrophobic or lipophilic substances more soluble in water (Fig. 7). they have been studied to help transport drugs to the back of the eye from the front, without the need for intrusive injections, and they provide a lot of advantages for formulations that treat the front of the eye. Research on the topical distribution of rapamycin to the back of the eye has shown that this is feasible [40].

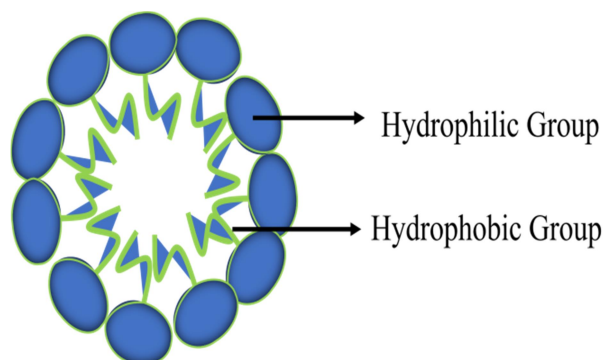


Figure 7: The Micelle Structure

Table 2: Other Forms of the Drug Delivery System Along With Their Pros and Cons

Drug Delivery System	Characteristics	Advantages	Disadvantages
Liposomes	Lipid bilayer vesicles	Capture biocompatible medications that are both hydrophilic and lipophilic	Potential for burst discharge and stability concerns
Niosomes	Vacuum-encased non-ionic surfactants	A stable and inexpensive substitute for liposomes	Less effective encapsulation
Solid Lipid Nanoparticles (50-1000nm)	One example of a drug carrier is the solid lipid nanoparticle, or SLN.	enhanced bioavailability, protection for labile drugs, controlled release, and making them good for oral, dermal	primarily low loading capacity for hydrophilic drugs,
Polymeric Nanoparticles	Efficient, customizable release	Tissue targeting, biocompatibility, sustained delivery	Intricacy of production, expense
Dendrimers	<i>Short and branched processes</i> that taper off further from the cell body	The extensive branching increases the surface area available to receive a large number of synaptic inputs from other neurons.	Their short length and tapering structure mean that signals can attenuate more with distance compared to axons, which are long and uniform
Nano emulsions	They are often transparent or translucent.	Small droplet size reduces gravitational force, preventing creaming, sedimentation, flocculation, and coalescence during storage	The equipment and processes required (e.g., high-pressure homogenization, micro fluidization) can be expensive for industrial-scale production.
Micelles	Amphiphilic nanostructures	Sustained release is ideal for lipophilic medications.	Uncertainty in dilution and short half-life

Microneedle-Mediated Delivery

The idea of MNs was first conceived in the 1960 s and was first patented by the Alza Corporation in 1971. A novel minimally invasive technology termed microneedles (MNs) has been established in recent years to pinpoint the exact location of a drug formulation within the eye's target tissues more precisely than a hypodermic needle. Mi-crones, patches with an array of micron-scale needles <1 mm [41]. Various types of microneedles have been used extensively for ocular applications, including hollow, solid (coated), dissolving microneedles and bio-inspired microneedles. By safely piercing the stratum corneum—the outermost layer of skin—MNs, a network of tiny needles, may transdermally dispense drugs [42].

The diffusion of drugs loaded in the microneedles through the dissolution of the microneedle matrix is allowed to be free because of these micro needles. Even though changing the matrix's composition may alter the pace of drug release—a subject that many researchers are interested in—the drug is only passively distributed throughout the body once the microneedle dissolves and it is introduced. As a treatment for long-term health problems, infinitesimally invasive' microneedles are being researched for their ability to provide

medications in a focused and sustained manner. It has been determined by the FDA that, microneedling devices create many small holes in the skin [43].

Hydrogel

The administration of medications to the eye has seen a plethora of recent advancements, since it is notoriously tough to treat. Drug transport and tissue engineering are only two of the many medicinal applications of hydrogels that have prompted much research into the material. Being three-dimensional networks of hydrophilic polymer chains with a high water-holding capacity, hydrogels may be composed of a wide variety of chemical compounds and tailored to exhibit a wide range of physical characteristics. This capacity can be achieved through physical or chemical cross-linking [44]. The important cross-links within the structure of the hydrogels make them take up a considerable amount of water and, unlike the other dosage forms and materials developed for ophthalmic use such as colloidal drug delivery systems and polymeric implants, do not dissolve in the surrounding aqueous environment but rather swell. Not only may hydrogels integrate a variety of ophthalmic medicines, but can also be kept in the eye, have less side effects due to systemic absorption, and

are well-tolerated compared to traditional pharmaceutical formulations like ointments [45].

• *In Situ Forming System*

In situ hydrogels in the intraocular drops are subject to a sol-gel transition due to environmental stimuli, like pH, temperature, ions etc., in the cul-de-sac. The composition was tweaked to make the medicinal chemicals stay in touch with the corneal layer for longer and reduce the frequency of delivery [46]. In situ gelling delivery devices for ocular drug delivery improves anterior eye disease by providing an easy, safe, repeat dose drug delivery system. A) Swelling and diffusion processes as physical mechanisms, b) ionic solutions, enzymatic activities, photo-initiated processes as chemical mechanisms, and c) in situ formation due to these two processes. A major issue with in-situ gels is their response to changes in temperature, pH and ion. Compared to traditional eye drops, in situ gelling systems are known to have a more prolonged pharmacological action [47].

3.4 Contact Lens-Based Drug Delivery

A contact lens (CL) is a small, curved piece of plastic that covers the eye's cornea and helps with nearsightedness or farsightedness as well as for protection. Many other interesting technologies such as drug loaded contact lenses have been of interest as an alternative way to deliver eye medications there. The present drawbacks of conventional administration techniques in the eye pose new problem to the ocular medication delivery system, however, contact lenses are soon gaining ground. Scientists have developed drug delivery systems for contact lenses that might extend the lens's retention time on the eye to allow more time for the drug to penetrate the cornea, boost its bioavailability, and improve effectiveness and convenience of treatment [48]. Ophthalmic medication delivery contact lenses have exploded in popularity because to their many useful features, such as longer wear time and 50% bioavailability. These elements such as composition of the ophthalmic medication to be included on the contact lens, thickness of the lens and amount of water in the polymeric network, affect the quality of the contact lens. There is a thin layer of fluid (post lens tear film) between the cornea and the contacts. In the form of fluid to the eye, this fluid is incompatible with other fluids found in the eye. Typically it will take about 30 minutes for the mixture to mix with the external tear film (the layer on the outside of the

contact lens). So, the ophthalmic medications produced by SCL may stay on the cornea for 30 minutes or more [49].

Ocular Inserts and Implants

Depending on their chemical and physical characteristics, ocular inserts may be bio-erodible, soluble, or insoluble. Improving the preparation's contact time with the conjunctival tissue is the main goal of the ophthalmic inserts. This, in turn, enables slower release which can be used in either topical or systemic treatment. One large issue with ocular inserts is the 'solidity' perceived by the patient – that is, they feel the insert in their eyes – and is often quite sensitive, and feels like an 'extraneous body'. This can be a really tough challenge for a patient to adhere with the treatment [50]. The various forms of micelles, vesicles, nanoparticles (NPs) or microspheres have been incorporated into the formulation of OIs to facilitate the loading, release and bioavailability of a drug. The components comprise a polymeric support, which can or cannot contain the drug(s) distributed on the surface of the polymeric support or solubilizers inside it. The inserts can be used for topical and therapeutic use. Ocular inserts are meant to deliver medicines in three different ways: diffusion, osmosis, or erosion. Connector preparation methods include simple and flexible electrospinning method to prepare a film of nano fibers with a new function and also three methods—solvent casting, glass paper and melt method—for preparing ocular inserts [51]. Ocular implants can be generally divided into biodegradable and non-biodegradable type based on the rate controlling polymers or systems used. The non-biodegradable implants have the advantage of delivering long term release of drug (up to several years) for longer period of time but the downside is that they require to be replaced or removed after the drug is exhausted. By contrast, there are a number of advantages to biodegradable implants: they can be shaped to different forms; they could be implanted outside the hospital; they do not need to be removed after use; and they might be used to lengthen the drug's half-life [52].

Gene and Cell-Based Delivery Platforms

Efforts to repair corneal injury by the transplantation of limbal stem cells (LSCs) were the first use of cell treatments in ophthalmology in the early 1989s. Cells, or derivatives like erythrocytes, platelets, stem cells, dendritic cells, or extracellular vesicles, are viable delivery

systems that could serve as a drug delivery platform and are interesting and promising alternatives for other Nano systems like nanoparticles. A limitation of gene delivery is that the therapeutic gene is hard to deliver to the desired cells in the retina [53]. Although various methods are being explored to deliver the drug in the eye, there is no optimal delivery system that can reliably and effectively get the drug to the target cells in all patients. Several approaches are being attempted toward gene delivery; they include the delivery of genes encoding for vascular endothelial growth factor receptors and for small interfering RNA (siRNA) that targets the VEGF mRNA. Recently, gene therapy was demonstrated to be an effective means to decrease the expression of VEGF in the retina, possibly decreasing the number of injections required [54]. In contrast to allogeneic cell treatment, which employs donor cells, autologous cell therapy makes use of the patient's own cells. Another branch of contemporary cell treatments is the genetic engineering of cells. Finally, there is a third subcategory that involves the cellular encapsulation and release of extracellular vehicles (EVs), including as transcription factors, microRNA, and membrane proteins. When it comes to ocular disorders, gene therapy may be used for more than only studying disease pathophysiology's; it can also be utilized to test how well it works as a treatment [55, 56].

Smart and Stimuli-Responsive Drug Delivery System

A class of polymers known as stimuli-responsive polymers may undergo rapid physicochemical changes in response to environmental cues. The unique properties and controlled release capabilities of these polymers have made them a primary focus in drug delivery systems and biological applications. Among the class of smart platforms, stimuli-responsive delivery system has received more attention due to its immense potential to treat and alleviate many disease conditions of the eyes. Their biocompatibility, biodegradability, peculiar secondary conformation, different functionalities and reduced side effects and stimuli-enhanced therapeutic efficacy are all attractive features for the attraction. Alterations in shape or form may be induced by either internal or external forces, including but not limited to heat, acidity, enzymes, glucose, reactive oxygen species (ROS), magnetic fields, ultrasound, light, biorthogonal processes, or phase transitions [57].

System Sensitive To pH, Temperature, And Light

Target-Specific pH-Responsive Drug Delivery:

To provide target-specific drug delivery, pH-responsive polymers may be engineered to possess a particular pKa value. The polymeric system is affected by chemical and physical changes that occur with variations in pH, which in turn cause the release of the medication. Polymers that react to variations in pH levels in the surrounding environment are called pH-responsive polymers. (A) Polymers with ionizable moieties and (B) Polymers with acid-labile linkages are the two main categories into which they fall [58]. Polyelectrolytes with acidic or basic groups in repeating units are called polymers. In environments with an increasing pH, it swells, although weak basic group polymers (polybases) do the exact reverse. Particularly noteworthy are the properties of pH-responsive particles, which show promise for tailored oral medication administration. Because of these factors, PH-responsive medication delivery systems are a potential way to make oral BNZ treatment work better. The cancer cells have a pH of 5–6, whereas the extracellular pH is 7.4, because of the fast and rapid cell multiplication and lactic acid generation. Using a carrier molecule that reacts only to acidic pH could be one of the most effective ways to precisely release medications and subsequently precisely cytotoxic to the cancer cells [59, 60].

Temperature-Triggered and Thermo-Responsive System

Thermo-responsive nanocarriers are among the most studied types of smart nanoparticles (NPs) in the last few decades. Pathological lesions may be heated either externally (by externally delivered heat) or internally (by a naturally higher temperature). Some temperature stimuli are internal, like core body temperature or elevated temperatures caused by tumour or diseases, while others are external, like heat delivered from a magnet, a light source, or a sound wave. Since polymers only gel at temperatures higher than their LCST (60°C), those having a lower LCST are more likely to find use in biomedical settings. Thermodynamically speaking, the sol-gel transition at the LCST of a thermo-responsive polymer is quite similar to the temperature-dependent protein folding process. As a precaution against potential eye irritation caused by the coldness of the product, thermo-responsive or temperature responsive polymers must have the ability to gel at

temperatures higher than room temperature and undergo the gel-sol transition at temperatures lower than the pre-corneal temperature. There is an upper and lower critical solution temperature for these polymers, and at both high and low temperatures, they exhibit a miscibility gap [61].

Light-Responsive System

Such biomaterials show promise for therapeutic drug and nucleic acid delivery because to the tunable/precise payload distribution, which might be helpful in treating a range of diseases. One possible use for light-responsive devices is as biomimetic sensors or actuators. There are three potential wavelengths of light: infrared (NIR, 700-1000 nm), visible (Vis, 400-700 nm), and ultraviolet (UV, 200-400 nm). Ultraviolet light is very powerful, yet it is both phototoxicity and unable to penetrate living tissue. The processes of light-responsive nanocarriers for small molecules and polymers, ultraviolet light (UV) and visible light (Vis), and near-infrared light (NIR) will be discussed, as will the most recent advances in light-responsive nanoplatfroms for controlled drug release. Minimally invasive distribution of payload to the posterior eye segment is possible using light-responsive drug release devices, which may lessen the invasiveness of the surgery. Converting sol-gel more quickly than other stimuli like pH, temperature, and ion-triggered in situ gel, a light-responsive system may precisely construct the system's structure in terms of porosity and hardness, ensuring the implants' integrity. Using a light-responsive method, the implant may stay in the vitreous for longer and less medication will diffuse from the polymer matrix. There is a decrease in the harmful consequences of the payload.4.2 A Sensitive Enzyme-Responsive and Magnetic System [62, 63].

Enzyme-Triggered and Magnetic Responsive System

An innovative method of medication administration enzyme-responsive drug delivery systems (ERDDS), use the precise action of enzymes to release medications at predetermined locations. Enzymatic alterations may take place in both healthy and unhealthy states, and these systems react accordingly. An important class of drug delivery techniques in nanomedicine, enzyme-responsive nanomaterials have been extensively researched and used for controlled drug release, and they have gained remarkable progress [64]. The

foundation of enzyme-triggered drug delivery systems is enzyme-sensitive polymers. The release of medications from these polymers requires enzymes. When enzymes are involved, the release of drugs occurs in two stages. First, there's the ocular microenvironment-specific enzyme activity, which changes the physical and chemical properties of the encapsulated drug's polymer and ultimately causes drug release [63, 65]. The second part of enzyme-responsive drug release is that it's possible for the nanocarriers to become unstable and release their payloads due to changes in the internal interactions of the nanomaterials that contain them. In order to accomplish enzyme-mediated medication release at the location of inflammation, which is mostly associated with metabolic and biological processes, enzymes might be used [65]. Precise control of the initial release of enzyme-responsive drug delivery systems is the primary problem when deploying these systems [66].

Magnetic-Responsive System

The utilization of magnetic fields has several applications in healthcare, one of which is the diagnostic tool known as magnetic resonance imaging (MRI). Though it is still in its infancy as a technology, magnetic fields are already showing great promise in the realm of medicine delivery. Targeted drug delivery involves using an external magnetic field to release the drug, and thermal sensitive carriers release the payload by applying the heat created by the magnetic mediator. These two methods are often connected with drug release under the influence of magnetic fields. As for the second mechanism, it is thought to be a magnetocaloric phenomena, which means it is a two-part release event induced by a magnetic field and a thermos response [67]. Systems with magnetic responsiveness characteristics include magnetic-responsive hydrogels; however, they have only been partially investigated for the purpose of creating a mechanical reaction to a magnetic field; their principal use is in MRI scans of the human body. Magnetic responsive drug delivery systems are one kind of medication administration device that might react to magnetic fields. A controlled insulin release, where the magnetic field controls the release of insulin to treat diabetes, is one example of targeting, where magnetic fields lead drug carriers to their target area; another application of these systems is magnetothermal therapy, which uses magnetic fields to release medications; and finally, there are magnetically

guided delivery systems [68, 69]. The use of colloidal carriers such as β -cyclodextrins, liposomes, micelles, or solid nanoparticles encases magnetic nanoparticles. These nanoparticles can then be exposed to an external

magnetic field, which, after a few seconds, releases the drug at the target site. This process is particularly useful in cancer therapy when hyperthermia is the goal [66].

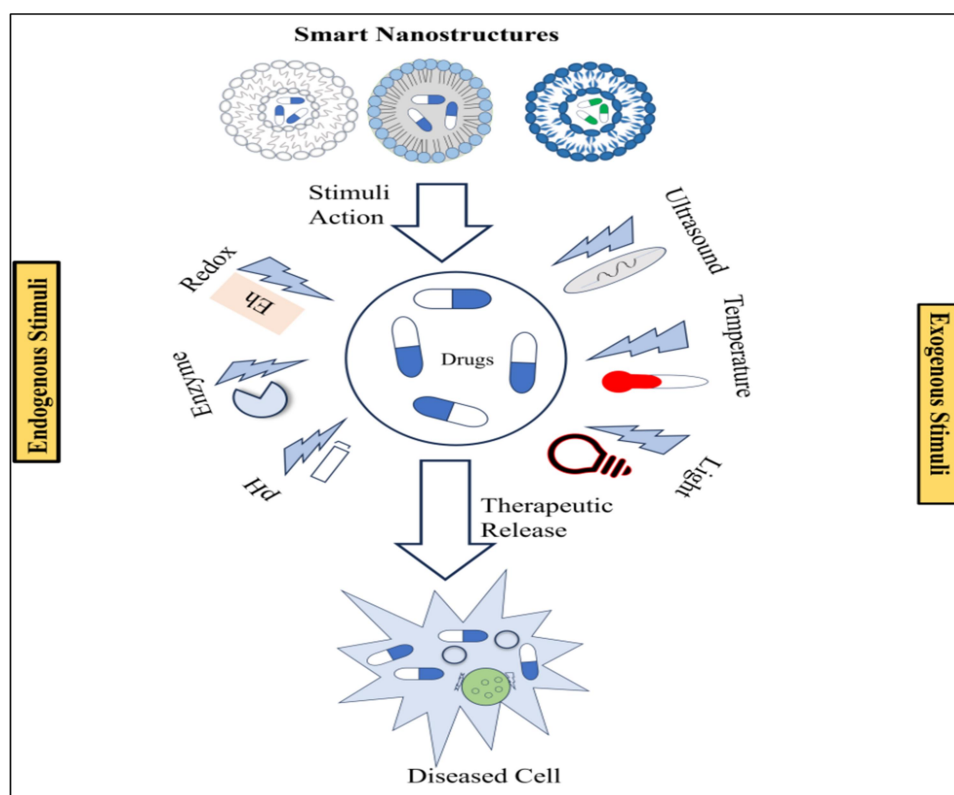


Figure 8: Different Stimuli-Responsive Schematic Representation

Bio-inspired and Biomimetic Approaches

Bio-inspired Approaches:

There are a number of benefits to using bio-inspired nano-structured systems, including reduced risk, simplified preparation, and lower overall costs. These systems could find use in nano-technology as a drug agent to improve the solubility of drugs that aren't very water-soluble, or as an agent to achieve a reduction in drug regimen through well-controlled sustained release profiles [70]. The application of Bio-inspired tunable optics and photonics is a new frontier in adaptive, efficient management of light, which is inspired by phenomena in biological systems. The concept of nanocarriers inspired from biological systems and structures is becoming an exciting field for drug delivery, as natural systems improve the critical challenges of therapeutic systems [71].

Biomimetic Approaches:

The concept of taking ideas from nature for inspiration is seeing use for a long time and not new to this study or any trend. It is sometimes referred to as "intellectual structure" in Japan

and "smart material" in the USA. Mimicking these efficient mechanisms for focusing adjustment, as found in biological eyes, has allowed humans to learn how to design imaging system to keep its vision sharp over long and short-range distances [72]. Biomimetic design not only means maintaining the original shape of a bio-model, but also validates and verifies this mimicking shape. Taking cues from the natural world and applying biological principles to the creation of technological solutions is known as biomimetic s, bio-inspiration, or biomimetic design [73].

Progress in Materials and Fabrication Techniques

Natural Fiber, Biodegradable, and Biocompatible Polymers

The eye is a challenging target for medication administration due to its unique anatomical and physiological characteristics. An optomedic delivery method for physiologically essential compounds has been shown to be biodegradable polymers. One possible carrier for this is biodegradable polymeric NPs, which might reduce the frequency of dosing and prolong the

drug's half-life by blocking its interaction with proteins and enzymes in the blood [74]. Natural biodegradable polymers, for instance, offer a variety of properties and potential applications; they have all found their way into the eye medication industry. b) Polyanhydrides (PAs), poly-lactic acid (PLGA), polycaprolactone, and other synthetic biodegradable polymers; and c) Hybrid biodegradable polymers, such as PLGA/collagen or PLGA/chitosan [75]. The discovery of biodegradable polymers occurred a long time ago. Subsequently, a plethora of biomaterials were developed, which had far-reaching effects in areas such as controlled drug delivery, regenerative medicine, orthopaedics, and long-term implants [76].

3D Printing and Micro fabrication Technologies

In 1986, the 3D printing technique had its beginnings. In recent years, 3D printing analysis has attracted tremendous interest and has been applied at a scale never seen before, due to the development of technology. In the last decade, particularly from early 2000s, 3D bio printing with cells and bio-molecules has been successfully used for tissue engineering to directly 3D print living systems that mimic the activity of real living systems. Rapid prototyping and product development have both benefited greatly from the advent of three-dimensional (3D) printing in the hardware manufacturing industry [77]. 3D printing is one of the additively manufactured technique, which create custom constructs that are designed by computer-based design (CAD) software and stacked together layer by layer. Digital images from medical imaging techniques like computed tomography (CT), magnetic resonance imaging (MRI), and 3D scans may inform the development of individualized 3D designs and equipment for each patient [78]. Many new kinds of 3D printing technology have emerged, each with its own set of advantages and disadvantages. There are three broad categories into which the ASTM classified 3D printing technology; 1) Binder jetting is a reactive admixture process (RAP) that uses a liquid binder to selectively deposit it into a bed of powder ingredients. 2) Directed energy deposition: This additive manufacturing technology creates components layer by layer using a moving build platform and continuous-drive deposition of thermoplastic material. Subsequent heating stages complete the process. The third method is material extrusion, which is a kind of additive manufacturing that involves

the mechanical extrusion of liquid thermoplastic material in successive layers on a moving build platform. fourthly, powder bed fusion, in which a material is spread out on a bed of powder and melted using an electron beam, 5) Laminating sheets: In the lamination process, a construction platform is used to cut the coated material using a regulated laser. In accordance with ASTM Standards, materials jetting is a 3D printing method that selectively deposits building material drop by drop. In material jetting, the dpi/print head sprays a stream of photo-hardened (UV) material onto the part, which then hardens into a resolved part. In vat photopolymerization, UV resins are exposed to a UV laser and solidify at the exposure site [79]. A powerful laser beam is used in the selective laser sintering (SLS) technique of three-dimensional printing to melt and mix powdered materials like metal or plastic (often nylon). After every printed layer is finished, the plastic powder is spread over the layer that the laser has cut. Laser light melts and fuses the powder particles with the prior layer as they melt and fuse with the new layer [80].

Clinical and Regulatory Standpoint

Drug discovery and drug development depend on decades of strong science research, cross-functional team efforts, and clinical evidences crossing back and forth, develop validation of the integrative sciences. Therapeutic proteins intended for intraocular usage must first pass through convoluted regulatory processes before they can be developed and licensed. For new medications to be safe, effective, and of high quality, they must pass stringent inspections by the FDA and the EMA, respectively [81].

Contamination Control

The choice of suitable animal models for the relevant eye anatomy and physiology, and the design of the experiments are crucial to ensure the 'relevancy' of feasibility assessment and high chances of successful translation. Many preclinical studies that report small molecule or protein delivery via topical application successfully targets the retina have relied on rodent models. Similarly advantages include an existing well accepted pharmacological models and practical factors of cost and availability. These advantages are readily apparent when one considers the vast anatomical variations between the human and rodent eyes, as well as how the pharmacodynamic response to a medication may be affected by its distribution and elimination in

each [82]. Hence, efficacy data obtained in rodent models should be taken with a pinch of salt.

Preclinical evaluation should strive to:

- Determine the local tolerance of formulation.
- Determine if there is any injury, inflammation or irritation present
- Memorize characteristics of drug distribution in the eye
- Check for likely systemic exposure
- Determine dose-related toxicity
- Have preservatives, excipients and nanoparticles in the formulation to be safe for eye use [83].

Multiple studies have found that the right preclinical animal model is key in highlighting that even medications successful in preclinical studies have failed in clinical trials and at the patient level when administered topically. Following, pre-clinical models were translated to a human in a clear and defined hypothesis. The human PK was obtained from the monkey model by scaling distribution volume and both clearances (linear and non-linear) by the body weight with a single allometric proportion of 1 [84].

General Guidelines for Formulation of Ophthalmics from FDA and EMA:

Both the US Food and Drug Administration and the European Medicines Agency (EMA) need research including in vivo and in vitro analyses before they will approve a generic product. To make sure the reference medication and the test product are "same," the FDA has issued guidelines for some products that provide both in-vitro (IVRT) and in-vivo (clinical endpoint study or drug metabolite and pharmacokinetic study, DMPK) options [85]. Draft recommendations from the FDA address:

- Preventing goods from being adulterated requires a strong visual inspection program in addition to meeting CGMP criteria.
- Under USP General Chapter <771> ocular Products - Quality Tests, the majority of ocular medication products with USP-identified names must adhere to the particle matter criteria. The aforementioned USP 65 General Chapter should also be followed by any compendial ophthalmic medication products.

- The suggested maximum allowable levels of leachable ingredients in ophthalmic medication products are as follows, expressed in parts per million (ppm):
 - Reporting limit: 1 ppm.
 - 10 parts per million is the identifying level.
 - The cutoff for qualifying is 20 parts per million.
- As an additional quality control measure, in-vitro drug release/dissolution testing may be used for some ophthalmic dosage forms.
- Guidelines for the development, distribution, and use of container closure systems (CCSs)" was the subject of the book.
- "Recommendations for stability studies"[86] is an evaluation of stability studies.

Out of all the published Draft Guidelines and/or applicable Pharmacopoeia standards concerning the quality of cutaneous goods, the ones that have yet to be released are: 1) Regarding the skin care product's quality. 2) Topical equivalency testing substances—as an alternative to therapeutic equivalency tests including clinical endpoints. The effectiveness and safety of a cutaneous product may be significantly affected by changes to its formulation, dosage form, administration technique, or manufacturing process, according to current standards [87].

Here are some broad points to keep in mind while evaluating the quality of ophthalmics—drug treatments for the eyes—and their topical administration—including ointments, gels, creams, and liquid dosage forms including solutions, suspensions, and emulsions. More specifically, the instructions cover:

- Microbiological considerations.
- Examining Extracted and Leachable Substances, Impure Materials, and Degradation Products: We will go over several methods.
- As an alternative for quality control, in vitro drug release/dissolution testing may be performed on some ophthalmic dosage forms.
- Some suggestions on the construction, distribution, and administration of CCSs.
- Suggested investigations into stability [88].

There is currently no comprehensive guidance from EMA on the development of ophthalmic

products. On the other hand, topical or locally acting products and sterile goods both have pertinent EMA recommendations. Important ones include:

Sterilisation of the Active Substance, Excipient, and Primary Container of Medicinal Products: A Guideline

- The information about the sterilization method that may be used for sterile pharmaceutical goods are provided in the EMA guideline (EMA/CHMP/CVMP/QWP/850374/2015).
- EMA's Quality Guidelines hub contains several guidelines that are pertinent to formulation, packaging, stability, impurities etc.
- Additionally, EMA provides its input in the Quality Q&A (Part 2), where eye drop specific questions such as specification setting, sterility, stability, container systems etc. are answered.
- Medical Device Quality Requirements is a proposed guideline from the European Medicines Agency (EMA). (May 2019) [88] for drug-device combination products (such as ophthalmic products with specialized droppers).

Marketed and Pipeline Products

An array of new hepatic eye disease therapies for glaucoma, dry eye syndrome, retinal illnesses, and infections of the eye have contributed to the current explosion in ocular therapeutics. Products currently on the market have been developed to further improve treatment outcomes in consideration of their ocular bioavailability, safety and patient convenience. In glaucoma and ocular hypertension, the global prevalence of glaucoma makes it the leading cause of vision impairment. Common treatment options include medications in three categories: Analogues (Sipetaprost, Omidoprost Isopropyl, latanoprost, bimatoprost), NO-Donors (Latanoprostene Bunod (Vyzulta ®) NCX 470) and timolol [89].

DED is a very prevalent eye disease. Symptoms of DED can differ from patient to patient, but often include itching, sight changes (merging eyes, difficulty focusing, blurred vision), mucous discharge, ocular irritation, a decrease in tear meniscus and/or a decrease in tear break-up time, and eyes which are made more sensitive when exposed to light. Treatment will help improve the symptoms make it, although it is not

a cure Omega-3 and omega-6, Azithromycin, tetracycline [90], tacrolimus, generously apply Restasis® cyclosporine A.

It is quite common for elderly individuals to have some kind of abnormality of their retina that is a result of neovascular formation. Anti-VEGF drugs (cervical shunt, including Ranibizumab, bevacizumab, and aflibercept).

Viral infection of the eye is a prevalent condition and is common in all parts of the world. Ganciclovir, foscarnet, cidofovir, fomivirsen, boric acid, citric acid, sodium derivatives of perborate and bicarbonate, boric acid, and stabilize oxychloro complex are some of the infectious disorders that these eye drops are used to treat.

Drugs that treat allergic conjunctivitis, such as olopatadine (Patanol) and ketotifen, are used to treat allergic conjunctivitis. Bepotastine is the latest available dual activity agent in Canada and there are significant differences in the bioavailability of Bepotastine versus Azelastine [91].

Ocular therapies are continuously being developed and advanced to address unmet medical needs. Bispecific antibodies like fARTICimab, which bind to both VEGF and Ang-2, are at late stage development for retinal disorders with anti-VEGF gene therapies like RGX-314 in clinical development for sustained anti-VEGF delivery. New topical treatments such as latanoprostene bunod are also being explored in glaucoma, while new therapies such as NOV03 (perfluorohexyloctane) are explored in dry eye disease. Also, there has been great progress in eye disease with several gene therapies (voretigene neparvovec (Luxturna) is approved for inherited retinal syndromes). Ongoing efforts in pipelines of sustained release intravitreal implants, RNA/gene-based therapeutics, novel small molecule compounds that enhance ocular bioavailability, reduce system exposure, and provide therapeutic solutions in diseases with limited available treatment options [92].

Facing Some Difficulties and Looking Ahead

In the first review, we covered the eye's architecture and natural defence, as well as the difficulties of administering medications and therapies to the eye, especially in the posterior segment due to ocular obstacles and the wide variety of disorders that might affect it. There has been a plethora of research on the topic of

retinal medication delivery of ocular medicines during the last decade. Indeed, the commercial market has significantly grown after the advent of anti-VEGF drugs [93]. Scientists' potential setbacks in targeted drug delivery in the eyes are complicated by the multiple barriers found in the eye. However, much effort has been made to date and the trends are ongoing in the search for so called 'ocular' drug delivery and in search of biocompatible, safe, and effective therapeutic drug delivery techniques. Contact lenses, aqueous gels, MNs, dendrimers, nanomicelles, microemulsions, nanosuspensions, dendrimers, liposomes, and other novel drug delivery methods have the potential to greatly enhance the effectiveness of existing therapies. Future ocular drug delivery systems should prioritize patient compliance, especially in light of the promising developments in gene delivery and exosomes technology for pharmaceutical distribution [94]. One alternative to focused ocular delivery is to combine simpler systems with more complicated ones; for example, a dual delivery system with nanoparticles embedded in hydroxy gel and a light-responsive system might be developed in this way. The creation of dual-release controlled DDSs for use in the eyes has been the subject of very few papers in academic journals. As far as we are aware, there have been very few reports on the creation of ocular applications using dual release controlled DDSs. It is also natural for NIR-DDS to grow into theranostic nanomedicine, which combines diagnostic and therapeutic capabilities [95, 96].

Difficulties in Crossing Eyes and Scaling Up Production

These formulations need to be scalable and reproducible to be successful. No matter the size, from lab to pilot to industrial, the formulation must be rock solid. While nano-medicine's approval was a watershed event, improvements in scale up technology and Quality by Design (QbD) techniques have greatly enhanced the commercialization of nanomedicine. [97-99]. There are several steps involved in bringing a nanomedicine product from the lab to the consumer level. Some of these factors include the material's properties, its GRAS status, the toxicological features of its size and shape, the nanocarriers' biodegradability, the large-scale balancing of the system's many components, and so on [98].

When medications encounter drug barriers, their distribution is impeded and their bioavailability

is reduced. To address these eye diseases, scientists have developed various drug delivery systems with the goal of increasing the bioavailability of these drugs in the eye. These systems include emulsions, ointments, suspensions, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, in situ thermosensitive gels for the eye, and contact lenses [98, 99].

Process Management, Quality and Risk Control

The main difficulty with the adherence of the patient to the therapy used in ophthalmology, is the need for numerous installations over years in cases of glaucoma. In one such study, ~30% of cases with glaucoma reported their not being adherent with glaucoma medications, many of which were related to side effects of preservatives in glaucoma eye drops, which may help increase adherence with preservative-free glaucoma eye drops [100]. Due to the low absorption rate, the traditional drop may need frequent administration for optimal results; also, some of the medicine is lost via tear drainage and turnover, adding unnecessary treatment load to the patient's treatment regimen. In response to this, new products like the drug eluting contact lens, which provide continuous drug delivery (lasting hours or days) and increases in bioavailability, as well as decreases the frequency of drops to maintain comfort and adherence, have been developed. Patient tailored or personalized ocular therapies are also on the rise, such as the customization of engineered exosomes for the individual genetic profile of a patient, using disease-specific biomarkers, which allows more precise and safer therapies delivery, also reducing contamination risk and dropout due to irritants. In total, the use of sustained-release systems, preservative free formulations and tailored treatment approaches has great potential to increase patient compliance and therapeutic success for ocular diseases over time. Advances in genomics and nanotechnology - continuing their stellar progress toward the goal of enriching our approach to patient care - range from diagnosis and prognosis, to targeting and personalizing therapeutics [101, 102].

Integration with Digital Health and Smart Diagnostics to Be Performed

The first application that digital tools could be used to assist in healthcare would be in analysing medical images -- whether retinal images and scans or even the scan of the eyes -- subsequently identifying the first symptoms of

illnesses like diabetic retinopathy or macular degeneration by forecasting the real tiniest change in the eye tissue. As an example, DeepMind is using an algorithm to identify over 50 eye disorders with the same level of accuracy as a trained eye doctor, [103]. Affordable healthcare would be accessible to a bigger portion of the global population with the aid of this healthcare application. Primary care settings or distant locations may benefit from automated AI-based screening systems that non-specialists can employ for initial screening. This not only aids in getting patients at risk for subsequent examinations done quickly, but it also helps to lighten an ophthalmologist's burden. Wearable technology and illness monitoring may be used in conjunction with this to follow the progression of diseases [104]. Wearable technology, such as smart contact lenses, allows glaucoma sufferers to have their intraocular pressure monitored continuously. These gadgets may also notify the patient and healthcare provider of any changes that might suggest their condition is becoming worse, so they can take action quickly. All the way through the pharmaceutical development process, from the beginning to the end, these technologies can handle massive volumes of data. To identify targets for a wide range of pathophysiology's AI can sift through mountains of biochemical and pharmacological data. New targets to visit these recognised places may be found using all this data. Artificial intelligence models may aid in the early phases of drug development by predicting which active compounds will target which molecular targets in a variety of ophthalmic illnesses [105].

REFERENCES

- [1] Chakorkar SS, Mulla JA. Cubosome-based Corticosteroids Drug Delivery System for Sustained Ocular Delivery: A Pharmacokinetic Investigation. Indian Journal of Pharmaceutical Education and Research. 2024 May 27;58(2s): s502-14.
- [2] Mali JD, Mulla JA. Ocular drug delivery system: A review. World Journal of Drug Targeting. 2023;1(1):9-24.
- [3] Chakorkar S, Mulla JA. Cubosomal Drug Delivery System: Promising Approach for Ocular Drug Delivery of Corticosteroids. Eur. Chem. Bull. 2023; 12:13850-81.
- [4] Chakorkar SS, Mulla JA. A novel corticosteroid cubosomes–for ocular drug delivery. Indo Am J Pharm Res. 2020;10(06):322-8.
- [5] S. Ahmed, M. M. Amin, and S. Sayed, Ocular Drug Delivery: a Comprehensive Review, AAPS Pharm SciTech, 2023;24:66.
- [6] C. E. Willoughby, D. Ponzin, S. Ferrari, A. Lobo, K. Landau, and Y. Omid, Anatomy and physiology of the human eye: Effects of muco polysaccharidoses disease on structure and function – a review, Clinical & Experimental Ophthalmology, 2010;38(1), pp. 2–11.
- [7] Raj, Vishal Kumar, Rupa Mazumder, and Monika Madhra. Ocular Drug Delivery System: Challenges and Approaches. International Journal of Applied Pharmaceutics, 2020;12:5 49–57.
- [8] Nguyen, Q. D. editors. Retinal Pharmacotherapeutics. Karger Medical and Scientific Publishe 2015;55.
- [9] Guidi, Lorenzo, Maria Grazia Cascone, and Elisabetta Rosellini. Light-Responsive Polymeric Nanoparticles for Retinal Drug Delivery: Design Cues, Challenges and Future Perspectives. Heliyon, 2024;10(5).
- [10] Cholkar, Kishore, Aswani Dutt Vadlapudi, Hoang M. Trinh, and Ashim K. Mitra. Compositions, Formulation, Pharmacology, Pharmacokinetic, and Toxicity of Topical, Periocular, and Intravitreal Ophthalmic Drugs. Methods in Pharmacology and Toxicology, Springer, 2013;91–118.
- [11] Huang, W. C., A Novel Eye Drop Formulation for Potential Treatment of Neovascular Age-Related Macular Degeneration. Translational Vision Science & Technology, 2021;10(14) 23.
- [12] Patole PJ, Mulla JA. Liposomal In Situ Gel: A Novel Approach for the Treatment of Parkinson's Disease via Intranasal Drug Delivery. Research Journal of Pharmaceutical Dosage Forms and Technology. 2025 Mar 10;17(1):53-62.
- [13] Shingate DM, Mulla JA. Exploring Liposomes: Comprehensive Classification, Preparation Techniques, and Composition Insights. Indian Journal of Novel Drug Delivery. 2024;16(2):80-90.
- [14] Kumbhar AV, Thorat PA, Mulla JAS. Development and assessment of risperidone-loaded niosomal *in situ* gel for nasal drug delivery. Indian Drugs. 2025;62(12):41-50.
- [15] Rane KA, Mulla JA. Hyaluronic Acid-Coated Niosomes: A Promising Drug Delivery System with Potential Applications. Indian Journal of Novel Drug Delivery. 2024;16(1):11-9.

- [16] Mane RK, Mulla JAS. A comprehensive review on niosomes: Composition, methods of preparation, characterization and potential applications. *World Journal of Nanoparticle Research*. 2023;1(1):35-44.
- [17] Shewale SS, Mulla JA. Non-Ionic Surfactant Vesicle (Niosome): A Novel Drug Delivery System. *Indian Journal of Novel Drug Delivery*. 2022;14(3):129-37.
- [18] Maiti D, Inamdar MN, Almuqbil M, Suresh S, Asdaq SM, Alshehri S, Al Arfaj SA, Alamri AM, Aldohyan MM, Alqahtani MT, Alosaimi TM. Evaluation of solid-lipid nanoparticles formulation of methotrexate for anti-psoriatic activity. *Saudi Pharmaceutical Journal*. 2023 Jun 1;31(6):834-44.
- [19] Mulla JA, Hiremath SP, Sharma NK. Repaglinide loaded solid lipid nanoparticles: design and characterization. *RGUHS J Pharm Sci*. 2012 Oct;2(4):41-9.
- [20] Mulla JA, Khazi MI, Khan AY, Khazi IA. Design, Characterization and In vitro Evaluation of Imidazole [2, 1-b] [1, 3, 4] thiadiazole Derivative Loaded Solid Lipid Nanoparticles. *Drug Invention Today*. 2012 Aug 1;4(8).
- [21] Mulla JS, Khazi IM, Sharma NK, Hiremath SP, Jamakandi VG. Solid lipid nanoparticles: methods of preparation. *Indian J Nov Drug Deliv*. 2011;3(3):170-5.
- [22] Panchamukhi SI, Mulla JA, Shetty NS, Khazi MI, Khan AY, Kalashetti MB, Khazi IA. Benzothieno [3, 2-e] [1, 2, 4] triazolo [4, 3-c] pyrimidines: Synthesis, Characterization, Antimicrobial Activity, and Incorporation into Solid Lipid Nanoparticles. *Archive der Pharmacies*. 2011 Jun;344(6):358-65.
- [23] Mulla JS, Khazi IM, Sharma NK. Solid lipid nanoparticles: Measures of characterization. *Indian Journal of Novel Drug delivery*. 2011;3(4):259-64.
- [24] Mulla AS, Shetty NS, Panchmukhi SI, Khazi IA. Formulation, characterization and in vitro evaluation of novel thienopyrimidies and triazolothienopyrimidies loaded solid lipid nanoparticles. *International Journal of Research in Ayurveda and Pharmacy*. 2010; 1:192-200.
- [25] Mulla JS, Khazi IM, Jamakandi VG. Solid lipid nanoparticles: Potential applications. *Indian J Nov Drug Deliv*. 2010; 2:82-7.
- [26] Mulla JA, Suresh S, Khazi IA. Formulation, characterization and in vitro evaluation of methotrexate solid lipid nanoparticles. *Research Journal of Pharmacy and Technology*. 2009;2(4):685-9.
- [27] Mulla JS, Khazi IM. Influence of process variables on particle size of solid lipid nanoparticles. *Indian Journal of Novel Drug Delivery*. 2009;1(1):47-9.
- [28] Mujawar NK, Mulla JAS. Targeted Drug Delivery: Revolutionizing Breast Cancer Treatment with Lipid Polymer Hybrid Nanoparticles. *Research Journal of Pharmacy and Technology*. 2025;18(12):6129-6136.
- [29] Sushant Laxman Pawar, Jameel Ahmed S Mulla. Lipomes as Hybrid Nanocarrier: Innovation in Targeted and Controlled Drug Delivery. *Indian Journal of Novel Drug Delivery*. 2025;17(3):150-164.
- [30] Mujawar N, Mulla JAS. Lipid Hybrid Nanoparticles in Cancer Therapy: A Promising Nanotechnology-Based Drug Delivery System. *International Journal of Pharmaceutical Sciences and Drug Research*. 2025;17(4):371-387.
- [31] Priyanka Jadhav, Jameel Ahmed S Mulla. Unlocking Nano sponges Potential: An Overview of Formulation Strategies, Assessment Approaches and Emerging applications. *Indian Journal of Novel Drug Delivery*. 2024;16(3):130-136.
- [32] Mulla JA. Nano-based drug delivery systems: A comprehensive review of design, mechanisms and applications. *World J Pharm*. 2024;1(1):1-1.
- [33] Mulla JA. Molecular pharmacology of nanocarrier based drug delivery systems: Mechanisms, targets, and therapeutic implications. *World Journal of Molecular Pharmacology*. 2024;1(1):16-23.
- [34] Mulla JA, Kapse MV. Exploring nanomedicine in cancer: Diagnosis, treatment and its potential applications. *IP Journal of Diagnostic Pathology and Oncology*. 2024;9(2):86-94.
- [35] Mulla JA, Chalke PM, Londhe SP, Patil MA, Nalawade SN, Sawant RR. Design and Optimization of Nano sponges of Poorly Soluble Voriconazole Using Central Composite Design. *Indian Journal of Novel Drug Delivery*. 2023;15(4):189-99.
- [36] Shirke SN, Mulla JA. Intranasal nano emulsion for brain targeting: A review. *Indian Journal of Novel Drug Delivery*. 2023;15(1):1-1.
- [37] Dhahir, Rasha Khalid Nano emulsions as Ophthalmic Drug Delivery Systems.

- Turkish Journal of Pharmaceutical Sciences Oct. 2021;18(5):652-64.
- [38] Sutradhar, Kumar Bishwajit, and Md. Lutful Amin. Nano emulsions: Increasing Possibilities in Drug Delivery. *European Journal of Nanomedicine*, 2013;5(2):97-110.
- [39] Mandal, Abhirup Polymeric Micelles for Ocular Drug Delivery: From Structural Frameworks to Recent Preclinical Studies. *Journal of Controlled Release* 2017;24(8):96-116.
- [40] Formica, Maria-Luiza Development and Optimization of Acetazolamide-Loaded Soluplus®-Based Polymeric Micelles for the Treatment of Glaucoma. *Pharmacia*, 2025;72.
- [41] Yadav, Jayanthi, Microneedles for Advanced Ocular Drug Delivery. *Journal of Drug Delivery Science and Technology*, Aug. 2022;74 103577.
- [42] Jiang, Xiao, Hu Zhao, and Wei Li. Microneedle-Mediated Transdermal Delivery of Drug-Carrying Nanoparticles. *Frontiers in Bioengineering and Biotechnology*, 2022;10 840395.
- [43] Rojekar, Satish Revolutionizing Eye Care: Exploring the Potential of Microneedle Drug Delivery. *Pharmaceutics*, 30 Oct. 2024;16(11):1398.
- [44] Date RB, Mulla JAS. Nano sponges Loaded Hydrogels for Anti-Inflammatory Drug Delivery: Characterization Evaluation and Applications. *Asian Journal of Pharmaceutical Research*. 2026;16(1):27-32.
- [45] Kadam SS, Mulla JA. Design, Development and Evaluation of Etodolac Loaded Chitosan based Nano-gel for Topical Drug Delivery. *Hacettepe University Journal of the Faculty of Pharmacy*. 2025;45(2):146-161.
- [46] Dubald, Marion Ophthalmic Drug Delivery Systems for Antibiotherapy—A Review. *Pharmaceutics* 13 Jan. 2018;10(1):10.
- [47] Rojekar, Satish Revolutionizing Eye Care: Exploring the Potential of Microneedle Drug Delivery. *Pharmaceutics* Oct. 2024;16(11):1398.
- [48] Miller, L. J., and L. Cuttler. The Endocrine Effects of Inhaled Corticosteroids. *Journal of Pediatric Endocrinology*, 2013;26(2):65–73.
- [49] Rykowska, Iwona, Iwona Nowak, and Rafał Nowak. Soft Contact Lenses as Drug Delivery Systems: A Review. *Molecules*, 2021;26(18):5577.
- [50] Kumari, Anita Ocular Inserts—Advancement in Therapy of Eye Diseases. *Journal of Advanced Pharmaceutical Technology & Research*, 2010;1(3):291–296.
- [51] Omer, Safaa, and Romána Zelkó. A Systematic Review of Drug-Loaded Electrospun Transferosome-based Ophthalmic Inserts. *Pharmaceutics*, 2021;13(10):1637.
- [52] Giri, Bhupendra Raj Advancements in Ocular Therapy: A Review of Emerging Drug Delivery Approaches and Pharmaceutical Technologies. *Pharmaceutics*, 2024;16(10):1325.
- [53] Naik KK, Ashok B, Naik N, Mulla JA, Prakasha A. DNA binding, anti-inflammatory and analgesic evaluation of metal complexes of N/S/O donor ligands; Synthesis, spectral characterization. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 2015 Apr 15; 141:88-93.
- [54] Rathi, Aman Sohan, and Akash P. Dhoke. A Comprehensive Review of Innovations for Diabetic Retinopathy and Next-Generation Intraocular Drug Delivery. *International Journal of Science and Technology* 2025;1 Article 1504.
- [55] Shrivastava, Nikhil, and Shikha Saxena. An Update Review on Novel Advanced Ocular Drug Delivery System. *International Journal of Pharmaceutical Sciences Review and Research*, 2012;15(2):64–70.
- [56] Shah, S., and R. Garg. Artificial Intelligence in Remote Patient Monitoring: Opportunities and Challenges. *Remote Patient Monitoring* 2024;7:29.
- [57] García-Peñalosa, Cecilia, and Jean-François Wen. Redistribution and Occupational Choice. *Comprehensive Economic Policy*, 2022;60:100541.
- [58] Tan, Rachel Yie Hang pH Responsive Polyurethane for the Advancement of Biomedical and Drug Delivery. *Polymers*, 2022;14(9):1672.
- [59] Augustine, Rimesh, pH-Responsive Polypeptide-Based Smart Nano-Carriers for Theragnostic Applications. *Molecules*, 2019;24(16):2961.
- [60] Chatterjee, Sudipta, and Patrick Chi-leung Hui. Review of Applications and Future Prospects of Stimuli-Responsive Hydrogel Based on Thermo-Responsive Bio polymers

- in Drug Delivery Systems. *Polymers*, 2021;13(13)2086.
- [61] Mohanty, D., Bakshi, V., Simharaju, N., Haque, M. A., & Sahoo, C. K. (2018). A review on *in situ gel*: A novel drug delivery system. *International Journal of Pharmaceutical Sciences Review and Research*, 50(1), 175–181.
- [62] Kundu, Sourabh, Gitika Kumari, and Dadi A. Srinivasarao. Emerging Drug Delivery Strategies for Glaucoma Therapy: Focus on Nanoparticles and Stimuli-Responsive Systems. *RSC Pharmaceutics*, 2025;2:1050–1077.
- [63] Dlodla, Siphokazi B. K. Current Advances in Nano-Based and Polymeric Stimuli-Responsive Drug Delivery Targeting the Ocular Microenvironment: A Review and Envisaged Future Perspectives. *Polymers* 2022;14(17)3580.
- [64] Hu, Quanyin, Prateek S. Katti, and Zhen Gu. Enzyme-Responsive Nanomaterials for Controlled Drug Delivery. *Nanoscale*, 2014;6(21):12273–12286.
- [65] Lee, Seulgi Cathepsin B-Responsive Liposomes for Controlled Anticancer Drug Delivery in Hep G2 Cells. *Pharmaceutics*, 2020;12(9):876.
- [66] Adepu, Shivakalyani, and Seeram Ramakrishna. Controlled Drug Delivery Systems: Current Status and Future Directions. *Molecules*, 2021;26(19):5905.
- [67] Raza, Ali, Endogenous and Exogenous Stimuli-Responsive Drug Delivery Systems for Programmed Site-Specific Release. *Molecules*, 2019;24(6):1117.
- [68] Pereira, Luís, Frederico Castelo Ferreira, Filipa Pires, and Carla A. M. Portugal. Magnetic-Responsive Liposomal Hydrogel Membranes for Controlled Release of Small Bioactive Molecules—An Insight into the Release Kinetics. *Membranes*, 2023;13(7):674.
- [69] Dave, Drashti. Stimuli-Responsive Drug Delivery Systems: Innovations in Personalized Medicine. 2023.
- [70] Chen, Xuan, Research Progress of Bioinspired Nano structured Systems for the Treatment of Ocular Disorders. *Pharmaceutics*, 2023;16(1):96.
- [71] Journal of Integrative and Complementary Medicine, 2024;30(1).
- [72] Zhang, L., Gu, F., and J. M. Chan. Nanoparticle-Mediated Drug Delivery and Gene Therapy. *International Journal of Nanomedicine*, 2015;10:1–15.
- [73] Banken, Elisabeth, and Johannes Oeffner. Biomimetics for Innovative and Future-Oriented Space Applications: A Review. *Frontiers in Space Technologies*, 2023;3 article 1000788.
- [74] Bhusari SR, Mulla JAS. Review on natural polymers and their applications. *World Journal of Green Pharmacy*. 2023;1(1):1-8.
- [75] Tsung, Ta-Hsin Biodegradable Polymer-Based Drug-Delivery Systems for Ocular Diseases. *International Journal of Molecular Sciences*, 2023;24(16)12976.
- [76] Lynch, Courtney, Advances in Biodegradable Nano-Sized Polymer-Based Ocular Drug Delivery. *Polymers*, 2019;11(8):1371.
- [77] Shirke SN, Mulaa JAS, Chavan PV. 3D printing in pharmaceuticals: A review. *World Journal of Applied Pharmaceutics*. 2023;1(1):1-6.
- [78] Lin, Neil, Maryse Gagnon, and Kevin Y. Wu. The Third Dimension of Eye Care: A Comprehensive Review of 3D Printing in Ophthalmology. *Hardware*, 2024;2(1):1–32.
- [79] Singh, V., and N. M. Patrikalakis. Bézier Curve-Based Singularity Analysis in CAD. *Computer-Aided Design and Applications*, 2019;16(2):243–248.
- [80] Lotale HH, Mulla JAS. Personalized medicine and 3D printing: A new era in drug delivery. *Journal of Pharmaceutical and Biological Sciences*. 2025;13(2):98–106.
- [81] Qiu, Tina Guanting, and Thomas V. Johnson. Defining the Problem in Ophthalmic Drug Development and Clinical Translation. *Frontiers in Pharmacology*, 2020;11:1040.
- [82] Zhang, Yan, Nanoparticle-Based Drug Delivery Systems for Cancer Therapy: Advances and Challenges. *International Journal of Nanomedicine*, 2024;19(1):123–145.
- [83] Kahn, James G., and Eric Marseille. The Evidence Base for Cost-Effectiveness of HIV Treatment and Care. *PLoS Medicine*, 2018;15(10):1002529.
- [84] Pignatello, Rosario, and Pietro Matricardi. Steering the Clinical Translation of Delivery Systems for Drugs and Health Products. *Pharmaceutics*, 2020;2(4)350.
- [85] Zhang, Y., Li, X., and Wang, J. A Novel Hybrid Model for Short-Term Load Forecasting Using Improved CEEMDAN and Temporal Convolutional Network. *Energy*, 2022;25(4): 124313.

- [86] United States Pharmacopeia. FDA's Draft Guidance on Topical Ophthalmic Drug Products and USP Standards. Quality Matters, 2024
- [87] European Medicines Agency. Guideline on Quality and Equivalence of Locally Applied and Locally Acting Cutaneous Products 2018;70(8):28
- [88] U.S. Food and Drug Administration. Quality Considerations for Topical Ophthalmic Drug Products. Draft Guidance, Dec. 2023.
- [89] Almeida, Ana J., Eliana B. Souto, and Ana M. Silva. Nanoparticles for Delivery of Therapeutic Peptides and Proteins. 2019;11(9):460.
- [90] Kumar, Vinay, Abul K. Abbas, and Jon C. Aster. Robbins Basic Pathology. 10th ed., Elsevier, 2019. PubMed Central
- [91] La Rosa, Mario, Allergic Conjunctivitis: A Comprehensive Review of the Literature. Italian Journal of Pediatrics, 2013;39(18)
- [92] Parekh, Bela, and Jai G. Parekh. Ocular Surface Disease Treatments in the Pipeline. Ophthalmology Management, May 2025;29(5):14–15.
- [93] Kim, Hyeong Min, and Se Joon Woo. Ocular Drug Delivery to the Retina: Current Innovations and Future Perspectives. Pharmaceutics, 2021;13(1):108.
- [94] Raj, Vishal Kumar, Rupa Mazumder, and Monika Madhra. Ocular Drug Delivery System: Challenges and Approaches. International Journal of Applied Pharmaceutics 2020;12(5):49–57.
- [95] Abdelrahman, A. M., and G. S. El-Feky. Light-responsive polymeric nanoparticles for retinal drug delivery: Design cues, challenges and future perspectives. Heliyon, 2024;10(12):26-47.
- [96] Kumar, Anil, Rajesh Singh, and Priya Sharma. Impact of Artificial Intelligence on Sustainable Agriculture: Opportunities and Challenges. Heliyon, 2024;10(12):26-47.
- [97] Gorantla, Srividya, Nanocarriers for ocular drug delivery: Current status and translational opportunity. RSC Advances, 2020;10(45):27835–27855.
- [98] Kumar, Vinay, Abul K. Abbas, and Jon C. Aster. Robbins and Cotran Pathological Basis of Disease. Indian Journal of Pathology and Microbiology, 2014;57(1):1–3.
- [99] Occhiutto, Marcelo L. Breakdown of the Blood-Ocular Barrier as a Strategy for the Systemic Use of Nano systems. Pharmaceutics, 2012;4(2):252–275.
- [100] Kumar, Amit, Anjali Singh, and Rajesh Singh. A Novel Hybrid Approach for COVID-19 Detection Using Chest X-Ray Images. Scientific Reports, , 2021;11(1):98-99
- [101] Zhang, Y., Li, X., Wang, J., and Chen, H. Nanoparticle-Based Drug Delivery Systems for Cancer Therapy: Advances and Challenges. International Journal of Nanomedicine 2024;19(1): 532074.
- [102] Ong, Frank S Personalized Medicine in Ophthalmology: From Pharmacogenetic Biomarkers to Therapeutic and Dosage Optimization. Journal of Personalized Medicine, 2013;3(1):40–69.
- [103] Bachu, Rinda Devi, Ocular Drug Delivery Barriers—Role of Nanocarriers in the Treatment of Anterior Segment Ocular Diseases. Pharmaceutics, 2018;10(1):28.
- [104] Zhang, Y Title of the Article. Nature Communications, , 2023;14(24):75.
- [105] Pushkaran, Anju Choorakottayil, and Alya A. Arabi. From Understanding Diseases to Drug Design: Can Artificial Intelligence Bridge the Gap Artificial Intelligence Review, 2024;57:86.