International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Issue 3, 2022

Review Article

NOVEL APPROACHES IN OCULAR DRUG DELIVERY-A REVOLUTION

AYUSHI KAUSHIK[a], RUPA MAZUMDER[a]*, SWARUPANJALI PADHI[a], AVIJIT MAZUMDER[a], RAJAT BUDHORI[a], MANORMA[a], SWARNALI DAS PAUL[b]

[a]Noida Institute of Engineering and Technology (Pharmacy Institute), 19, Knowledge Park-2, Institutional Area, Greater Noida, Uttar Pradesh 201306, India, [b]SSTC-SSGI-FPS, Bhilai, Chhattisgarh, 490020, India
Email: rupa_mazumder@rediffmail.com

Received: 04 Jan 2022, Revised and Accepted: 12 Mar 2022

ABSTRACT

Conveying the therapeutic agent to the human eye has been a struggling task for formulators and scientists because of the complicated arrangement of the eye. The therapeutic agents needed to deliver the drugs to specific sites of the eye require the crossing of various ocular barriers, which act as hitches for drug delivery. Conventional preparations present in the market do not achieve the desired therapeutic results due to their lower bioavailability, less retention time, or difficulty in reaching the site of action. In a need to overcome the challenges with these preparations, various modern technologies are being applied to address the same with outstanding results. The purpose of the present review is to focus on several innovative approaches, *viz.*, the development of novel ocular drug delivery systems including liposomes, niosomes, nano-wafers, cubosomes, microneedles, dendrimers, and many others, adopted to combat various ocular diseases. In the present review, various novel formulations and drug delivery approaches have been taken into consideration, as developed, and reported by various scientists and researchers working in the field of ocular drug delivery systems.

Keywords: Ocular barriers, Novel delivery, Nanowafers, Cubosomes, Microneedles, Cell therapy, Implants

DOI: https://dx.doi.org/10.22159/ijap.2022v14i3.44045. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

The human eye is an extremely Byzantine and delicate part consisting of numerous anatomical and physiological barriers, required to be focused while designing for targeting the eye [1]. A brief anatomical overview of the eye shows that it can be partitioned into two primary areas comprising of anterior and posterior sections, each section encountering with variety of ailments [2]. The presence of different defensive hindrances, along with the anatomical and physiological highlights, has offered a big impediment for formulators and researchers in delivering the therapeutic agents to the eye [3]. The definitive motivation behind any type of ocular drug conveyance is to limit dose recurrence, sustain curative drug concentration at the active site, and resolve different ocular hindrances. Most essentially, no detrimental effect should be seen in the eye through the drug delivery process and the fabricated delivery system should increase the availability of the drugs at the site [4]. Even though being patient-compliant and noninvasive, conventional formulations, such as eye drops, have been the least beneficial and the cause of the same may be attributed to the limited surface area, tear turnover, protein binding, nasolacrimal voidance, enzyme deprivation, and penetration barriers like corneal, blood-fluid and blood-retinal barrier and minimal contact time resulting in decreased ocular biodistribution (<5%), hence, struggling to convey ample amount of drug to the retinal tissues because of the existence of assorted expulsion restrictions. The downside of the low bioavailability of therapeutics can also be attributed to the time the medication is left on the eye's surface, which impacts the achievement pace of the therapy [5, 6]. In the current decades, there has been a progressive improvement in ophthalmic medication delivery with the development of revolutionary delivery systems and by, culminating in newer clinical interventions for eye disorders [4]. Developments of the plan and exploratory investigation of new formulations have geared towards expanding the residence period in the ocular region, as well as creating intact and competent frameworks that are fit for maximizing permeation by various methods [5, 6]. To achieve the desired therapeutic outcome, many new methods of drug delivery are employed to ensure the bioavailability of the medicine in ocular drug delivery.

The fusion of nanotechnology and ophthalmic drug delivery has paved the way designed for precise and focused approaches [7]. Paul *et al.* (2012) has reported an interesting overview on patented nanotechnology used for ocular drug delivery in Recent Patents on Nanomedicine journal. Modern developments in nanotechnology have made a major prospect for the successful delivery of both poorly soluble and permeable drugs into the human eye. Colloidal systems, for example, can be developed to enhance the solubility of water-insoluble drugs, allowing topical as well as intravitreal drug delivery [8]. A drug administration technique based on nanocarriers has been extensively studied to improve the ocular bioavailability of inappropriately soluble medicines and has been shown to be successful.

We searched the studies in three English databases, including PubMed, Google Scholar and Elsevier website, for the last ten years to find all papers regarding ocular drug delivery systems. Papers with any language having an English abstract were included in the first step of the search. We used the following words and terms including: "ocular drug delivery latest approaches", "novel formulations for ocular delivery of drugs", "cubosomes preparation for ocular delivery", "niosomes", "liposomes formulation for ocular drug delivery", "in situ gels", "nanowafers", "microneedles preparation for ocular drug delivery". Inclusion criteria in the present study were the studies assessing the conventional and novel approaches included so far in the formulation and type of administration of the ocular drug delivery systems, highlighting the revolutionary newer approaches, but the papers with insufficient data, the abstract without full text, in conformity between methods and results, the inappropriate explanation of the findings were excluded from this review.

Novel approaches for ocular drug delivery

Liposomes

They are lipid-containing vesicular structures made of phospholipid bilayers entrapping an aqueous core [9]. Phospholipids are amphiphilic, having hydrophilic heads and hydrophobic tails. The hydrophilic section comprises more phosphoric acid bundled with water-soluble molecules, while the hydrophobic section comprises of two fatty acid chains. Liposomal structures are categorized according to their size and phospholipid bilayers. They can be labeled as small unilamellar (10-100 nm), large unilamellar (100-300 nm), and multilamellar (>300 nm). The existence of lipid layers

and an aqueous core makes their structure unique and helps in the incorporation of both hydrophilic and lipophilic materials within the structure. The lipid membrane fuses with other cell membranes to discharge the material to supply the required drug molecules to the site, where it is to be utilized [10].

The biocompatibility of liposomes is greater than that of a polymer-based device. The amphiphilic design of corneal membranes can serve as an impediment for the transport of drugs. For the drug preparation to penetrate the cornea it ought to have stability between its lipophilicity and hydrophilicity and as liposomes are amphipathic molecules with strong biocompatibility, they can be used to overcome the penetration problem. As the cornea is charged negatively and is much more permeable to cations than anions at normal pH, the cationic formulations easily infiltrate the cornea more than the anionic ones. Modifications of the surface load of liposomes by inserting cationic lipids can confer attractive properties, *i.e.*, they may lead to an improved precorneal residence time of the drug [7]. Schaeffer and Krohn (1982) have explored the impact of the colloid charge on corneal absorption *in vitro* by monitoring 14C-liposomal phosphatidylcholine and 14C-encapsulated penicillin and observed that absorption of liposomes by the cornea has occurred in the order, positive>negative>neutral. A four-fold rise in penicillin G transcorneal flow has been found to occur with the most powerful formulation, *i.e.*, positive SUV. The bioavailability of tropicamide, as evaluated by its dilatory pupil reaction, has been shown to be more potent in positively charged liposomes than that in the subsequent neutral preparation. The addition of a cationic charge to the vesicles has led to the enhancement of the viscosity of the formulation, *i.e.*, the residence time of the drug, to the eye surface [2].

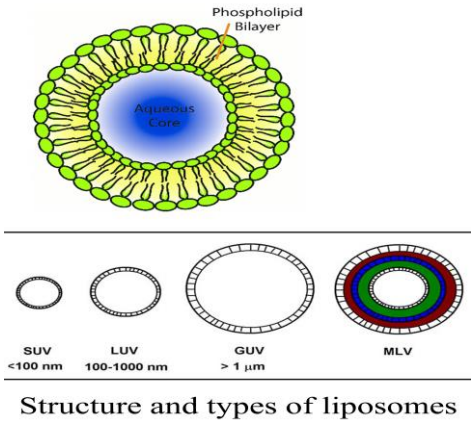

Fig. 1: Liposome structure and types [2]

Table 1: Experimented data for liposomal formulations

Liposomal formulations	Description/Results	Reference
Liposomes of Coenzyme Q10 (CoQ10) coated with trimethyl chitosan.	Mucoadhesion techniques enhanced the time of residency in the precorneal tissue portion of the rabbit eye.	[11]
Timolol maleate gelatinized liposome treatment	Metwally AA *et al.* demonstrated that this therapy resulted in reduced intraocular pressure (IOP) when examined *in vivo* on glaucomatous rabbit's eyes.	[12]
Ganciclovir liposomes	This showed a 2-10 times the elevated concentration of drug in sclera and cornea relative to ganciclovir solution.	[13]
C6-ceramide filled in liposomes	Demonstrated to be equipped for treatment of inflammation of the front portion of the eye.	[14]
Azithromycin liposomes	Tang X *et al.* researched *in vivo* pharmacodynamics trials in rats discovered a decline in manifestations of dry eye infection.	[15]

Cubosomes

Cubosomes are disjunct, bicontinuous, nanostructured (100–300 nm), self-assembled cubic liquid crystalline phase particles [16]. Their design involves bicontinuous, curved lipid bilayers illustrating the three-dimensional honeycombed configuration, which gives them improved stabilization under an aqueous environment. They are composed principally of amphiphilic lipids, stabilizer/surfactant, and water. Surfactants offer colloidal stabilization to the prepared cubosomes. The cubic arrangement of cubosomes contains various channels of water inside them. As a result of being comprised of amphiphilic lipids and having watery ducts, they are capable of incorporating a variety of molecules with moderately greater stacking proficiency [17]. They have been shown to perk up the ocular bioavailability of the drugs loaded in them as they have a longer residence time at the corneal surface [18]. One of the major limitations of cubosomes is their contribution to drug leakage and low drug loading efficiency during processing, preservation, and transport, thereby serving as a barrier to drug stability and thereby restricting their use [19].

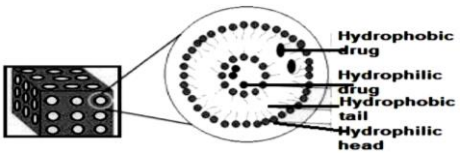

Fig. 2: Structure of cubosomes [17]

Table 2: Components of cubosomes

Amphiphilic lipids	Surfactants	References
Glyceryl mono-oleate (GMO) Phytantriol (PHYT)	Poloxamer 407	[17]

Table 3: Experimented data for cubosomes

Drug	Pharmacological uses	Description	References
Ketorolac	Non-steroidal anti-inflammatory drug (NSAID) for relief from itching eyes caused by seasonal allergies.	High corneal permeability	[18]
Flurbiprofen	NSAID for ocular inflammation treatment.	Less ocular Irritation	[20]
Timolol maleate (for targeting glaucoma)	A non-selective beta-blocker drug used for glaucoma treatment.	Demonstrated reduced IOP when compared with the eye drops available commercially. Increased corneal penetration along with prolonged retention time was also seen	[21]

Nanowafers

The nano wafer is a mini disc-like membrane containing nano-reservoirs of drugs [22]. They can usually be placed with a fingertip on the surface of the eye and endure constant flickering without being displaced, which is contrary to topical eye drops [23]. The time of residence of the drug at the eye surface and subsequent absorption in the nearby tissue is increased by gradual drug release

from the nano wafer. While nano wafers are in the evolving stage, they can treat subsequent eye diseases [23].

In this research, hydrogel-forming carboxymethyl cellulose (CMC) was chosen to facilitate easy adherence and retentiveness of the nano wafer on an ocular surface due to its mucoadhesive characteristic [22]. CMC also facilitated the reepithelialization of the cornea by attaching it to the matrix proteins [24]. This insightful platform integrated both nanofabrication and techniques of drug delivery. It has been able to further improve effective therapy for dry eye conditions by showing sustained delivery of dexamethasone [22, 25, 26].

Fig. 3: Nanowafer ocular drug delivery: (A) Image showing a corneal implanted nanowafer; (B) Drug diffusion into the corneal tissue [23]

Cell therapies-encapsulated cell technology (ECT)

Mechanisms of biomedical implementation of therapeutic agent delivery on a cellular level have opened up new possibilities for the pharmacological utility of self-cells. Innovation of ECT employs the use of entanglement via semi-permeable membranes of genetically engineered cells, with the motive of separating them from the presenter's body [23].

Encapsulation is done to impart the encapsulated cells with an immune-privileged atmosphere to operate their functions. The ECT drug supply network is intended to ensure selective permeability, where nutrients and oxygen can be dispersed for cell nutrition, while necessary therapeutics and waste can be sprayed away. Two of the Neurotech Pharmaceuticals ECT products have been exposed to clinical research. They are NT-501, also called Renexus®, which delivers ciliary neurotrophic factor (CNTF), and NT-503, which conveys a soluble anti-vascular endothelial growth factor (VEGF) receptor protein [27]. NT-501 allows for the continuous supply of CNTF for implant encapsulating human retinal pigment (RPE) cells [28]. NT-503 has been shown to ooze soluble VEGF receptor proteins for an extended time and has demonstrated notably elevated VEGF neutralization (~20-30 times superior) [29, 30]. ECT appears as an appealing way to monitor release and to ensure the delivery of long-term biopharmaceuticals into the eye.

Microneedles

The drug delivery technology via microneedles was first used to resolve the stratum corneum barrier and utilized as a transdermal drug delivery system [31]. Researchers were inspired by the efficacy of microneedles on transdermal structures and investigated them for use in ocular therapy for the anterior and posterior segments of an eye [4].

Microneedles have micro projections that make their nature minimally invasive. They are slightly invasive and can be developed to deliver medicine throughout a significant period relative to conventional hypodermic needles. Therefore, repetitive administration would not be needed [32]. Applying microneedles to biological membranes will contribute to the microdimensional transport pathways and improve therapeutic agent permeability across membrane barriers. They are commonly classified into 4 types according to their delivery processes [33].

For the treatment of glaucoma, in the anterior section of the eye, Jiang *et al.* (2007) used coated stainless-steel microneedles. They used intrasclerally administered pilocarpine and improved the drug absorption rate by around 45 times [32]. Song *et al.,* (2015) had engineered a pen-style microneedle to allow simple penetration into a small eye tissue target area, where a durable SU-8 resin-based microneedle was created and connected to a macro-scale applicator for the development of the microneedle pen. The model drugs used for dip coat were Rhodamine B, Evans blue, or sunitinib malate along with various polymer carriers. The microneedle pen has been shown to allow for precise positioning of the drug inside the stromal membrane of the cornea, which is otherwise hard to achieve during topical application of the drug because of the presence of the corneal epithelium [34]. An attempt was made by Gilger *et al.* (2013) to supply triamcinolone acetonide (TA), using microneedles to treat the posterior uveitis present in the suprachoroidal space (SCS). The supply of TA to SCS by microneedles, showed no indication of any toxicity, thereby showing efficacy and safety in drug delivery [35].

Nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs)

At the start of the 1990s, SLNs have been developed as an alternative carrier system to emulsions and polymeric nanoparticles for controlled drug delivery [36]. SLNs are usually distinguished by a solid lipid center, which can be maintained in an aqueous dispersion medium by surfactants. They can load both lipophilic as well as hydrophilic molecules within themselves [37]. They offer many benefits such as exceptional biocompatibility, site-specific supply of drugs, improved drug steadiness, higher surface area with smaller particle sizes, elevated drug entrapment with convenient particle sizes, as required, carrier prevention, low manufacturing costs, and many others [38]. To conquer the problems of SLNs, NLCs have been created. As NLCs are made from a solid-liquid lipid combination and have a nonideal crystalline state, they resist the expulsion of the drug by stopping lipid crystallization [39]. NLCs comprise of different spatial lipids (for instance, glycerides) and subsequently, have a more extensive distance between the fatty acid chains of glycerides and general unstructured crystals. Therefore, they are capable of upholding higher drug accommodation [40]. Such nanoparticulate systems can be employed as a workable vehicle to treat ocular infections and can convey the medicine to the ophthalmic tissues present in both the anterior and posterior chambers of the eye [41, 42]. Suresh *et al.* (2011), has explained the lipophilic ion pair of timolol, incorporated as a submicron emulsion and a potential ocular drug delivery system.

Table 4: List of constituents

Constituents	Examples	References
Lipids	Beeswax, Stearic acid, Cholesterol, Caprylic/capric triglyceride.	[40]
Surfactant or Emulsifiers	Phosphatidylcholine, Soy and Egg lecithin, Poloxamer, Polysorbate 80	
Co-surfactants	Sodium dodecyl sulfate, Tyloxopol, Butanol	
Cryoprotectant	Gelatin, Glucose, Lactose, Sorbitol, Polyvinyl pyrrolidone	
Preservative	Thiomersal	
Charge modifiers	Dipalmitoyl phosphatidylcholine, Stearylamine	

Niosomes

Niosomes are nano-sized lamellar structures formed with the composition of nonionic surfactant and cholesterol which are subsequently hydrated in aqueous media [43]. The pharmaceutical and cosmetic uses of niosomal and liposomal vesicular systems are identical, but they are chemically distinct in structural units. Niosomes are composed of surfactants, while liposomes are built of phospholipids, which ensures that niosomes have better durability and lack certain liposomal drawbacks, *i.e.*, high prices, poor supply, and differing in purity issues [44].

Because of the special composition of the niosomes, both hydrophilic and hydrophobic resources can be enclosed in the core

and bilayer shells, respectively [45, 46]. They are graded depending on the size or number of bilayers as small unilamellar vesicles, large-unilamellar vesicles, or multilamellar vesicles [47]. Niosomes can control and enhance the physical properties of pharmaceuticals, such as viscosity, film strength, and spreading of films.

Bioadhesive-coated acetazolamide niosomal preparations prepared using Span60, cholesterol, diacetyl phosphate, or stearylamine, are promising for the reduction of intraocular pressure in contrast to the marketed formulations [48]. Natamycin-packed niosomes coated with trimethyl chitosan (TMC), have been prepared for fungal keratitis (FK). The altered TMC-niosomes extend drug retention into the ocular cavity, as they have a greater mucoadhesive capacity. Prolonged medicine releases up to 12 h have been seen in the niosomal formulae. The coated formulation increases drug permeation and drug accumulation in tissues deeper than the uncoated niosomes [49].

Table 5: Experimental data for niosomes

Drug	Disease	Surfactant	Results	References
Naltrexone	Diabetic keratopathy	Span 60	No irritation and good corneal tolerability were shown by niosomal formulations.	[50]
Voriconazole	Fungal keratitis	Span 40, 60	The entrapment productivity level of the preparation was greater than 49 percent. *In-situ* gel preparation showed delayed drug delivery for 8 h.	[51]
Corneal graft rejection	Tacrolimus	Poloxamer 188	Delayed the duration of residence of medicine and declined the clearance rate of the medicine in aqueous humor.	[52]
Atenolol	Glaucoma	Span 60 Cholesterol	The entrapment efficiency percentage of formulated niosomes was 80.7%. Preparation showed prolonged drug release and intraocular pressure reducing activity was found to be for>8 h inside the *in-situ* gel.	[53]

Spanlastics

Spanlastics are contemporary nanovesicular structures built of nonionic surfactants and Spans. Unlike niosomes, spanlastics lack cholesterol in their structure. These are ductile and multilamellar, contributing to better trapping efficiency as compared to niosomes [17]. Of particular interest for ophthalmic nanodevice formulators are the spanlastics drug delivery skills and their penetration-enhancing traits [54].

Kakkar and Kaur (2011) were the first ones to set the spanlastics**.** The preparation of spanlastics filled with ketoconazole, using Span 60 and Tween 80 as edge activators, was demonstrated by these authors. The spanlastics produced were first examined for physical characterization, in contrast to niosomes (cholesterol-based) and the results indicated better spanlastic values (drug content 9.9% and % entrapment over 68%) [17].

The corneal permeability was further tested on the porcine cornea and spanlastics (67% permeation) permeated slightly more than the niosomes (32%). As a final comment, the drugs could be offered to be delivered to the posterior section of the eye via spanlastics [55].

Iontophoresis

Iontophoresis is a noninvasive procedure requiring the application of a slight electric current to increase the penetration of an ionized substance in the tissue. For many drugs, including hormones, antibiotics, antivirals, and macromolecules, iontophoresis has been shown to boost transscleral permeability. Transscleral iontophoresis provides choroids and the retina to elevated concentrations with minimum adverse reactions [56, 57]**.** Wirtz in 1908 first recorded iontophoresis in eyes. He researched drugs for iontophoresis for the topical supply of zinc salts for the treatment of corneal ulcers and keratitis [58]. Over the last few years, a growing number of experiments on iontophoresis have been conducted to include delivery of macromolecules [59], small molecules [60], and nanocarriers [61, 62] to the human eye.

Lam *et al.*, 1991 have shown that RNA and DNA molecules up to 8 million Daltons size can be conveyed across sclera using iontophoresis [63]. However, they have used electric fields on human cadaver eyes for a prolonged time. Epithelial edema, decreased endothelial cells, inflammatory penetration, and burns, depending upon the site of use, current density, and duration, are the detrimental effects of iontophoresis [64]. Eyecups are one of the most popular iontophoretic instruments which are used in the iontophoretic method to provide drugs by filling the solution into cups. EyeGate® has been first invented by the Optis group (Paris, French) and further developed in EyeGate II by EyeGate Pharmaceuticals Inc. It is a ring-shaped silicon sensor with a 0.5 cm^2 contact area and 13 mm inner diameter for trans-scleral iontophoresis (Waltham, MA, USA) [33]. It is currently being tested in clinical trials for the treatment of anterior uveitis (Phase 3) [65], dry eye syndrome (Phase 3) [66], and prevention in patients who have undergone cataract surgery (Phase 2)**.**

Hydrogels and in situ gels

This system consists of net structures made of water-soluble polymers with varying chemical and physical properties [67]. Hydrogels can swell and hold solvents inside a cross-connected gel system for a possible continuous supply of the drugs [68]. Notable hydrogel characteristics such as hydrophilicity, durability, and elasticity make them an acceptable choice for the ocular delivery of drugs [69]. Hydrogels, due to their porous nature, soft texture, and more water content, are appropriate for enclosing aqueous-soluble drugs, such as peptides, proteins, and other drugs within their structure. The high aqueous content and delicate nature of hydrogel contribute to a prompt discharge of biomolecules from the gel matrix, which, in general, may affect the hydrogel's injectability. In situ hydrogel for bevacizumab, a supra-VEGF injection in the suprachoroidal space, has demonstrated the sustainability of the delivery of therapeutic drugs for over 60 d to treat choroidal neovascularization. This has been generated and manufactured effectively through the invention of combining polycaprolactone and hydroxyl methacrylate [70]. Paul *et al.* (2017) have described different novel gels and their applications for drug delivery in their Nanostructures for Drug Delivery book. This chapter provides a good insight into the mechanism, application, and basic principles of different gels.

The use of diverse gelling polymers is among the most promising ways to resolve issues in traditional ophthalmic formulations [8, 71, 72]. Because overly viscous preparations can source an unfamiliar sensation in the eye and can be the cause of blurred vision, the ideal thickness and rheological profile of these preparations must be determined [73]. In situ gels are polymeric solutions that change from sol to gel stage to frame viscoelastic gel transformation in response to environmental stimuli [74]. The pseudoplastic quality of in situ gel shaping polymers aids in limiting the intrusion of squinting of the eyelids. The drug can be broken down or scattered into the in situ gelling polymer solution and as a result of conformal changes in physiological conditions, undergoes a phase transition into the conjunctival cul-de-sac to form viscoelastic gels [75–77]. Singh *et al.* (2017) have reported an interesting study on neomycin sulfate-loaded in situ ophthalmic gels for the treatment of various bacterial eye infections.

The in situ gels can be further divided depending upon the type of biological stimuli, *i.e.*, it can be temperature, pH triggered and ions triggered [78].

Temperature-sensitive in situ gelling systems (IGS)

Thermoresponsive IGS is the most primeval, yet at the same time, the most usually employed IGS for drug delivery to the eye [79].

These preparations respond to a shift in temperature as an outer boost, *i.e.,* when the temperature acts as an external stimulus [78)]. IGS can be shifted above room temperature to a gel state, ideally at precorneal temperature. On the other hand, the IGS formed which has a 35 °C gel transition temperature corresponding to the precorneal temperature [76]. The sol-to-gel transition temperature is acknowledged as the lowest critical solution temperature (LCST) [78]. Underneath LCST, the arrangement of the gelling polymer stays in the fluid state [80].

Polymers

Poloxamers (Pluronic)

They are nonionic triblock of type ABA, consisting of a core polyurethane hydrophobic chain (propylene oxide), fringed by 2 polyurethane hydrophilic chains (ethylene oxide). They are arranged as PEO-PPO-PEO [78]. It is termed 'pluronic' commercially. Poloxamer acts like a viscous liquid at room temperature (~25 °C) and becomes a translucent gel, when the temperature rises, *i.e.*, up to 35±2 °C. It forms a thin, small micellar subunit at low temperatures and increases the viscosity with temperature resulting in swelling into a large micellar network [79].

To understand the transformation step at a higher temperature, the main potential mechanisms were proposed: the incremental polymer desolvation enhanced micellar agglomeration and expanded polymer network interconnection [81]. The pluronic copolymers are currently present in the market in various grades with varying physical shapes and molecular weights. Depending on the physical definition, the grading is given as "L-liquid," "P-paste" and "F-floves" [82].

The mainly researched polymer in pharmaceutical science is the pluronic F127 amongst the various available classes [78]. Pluronic F-127 or Poloxamer 407 (P407) is an ethylene oxide (70%), which makes a significant contribution to its hydrophilic properties. Furthermore, F-127 has preferable solubility in hot water than in cold water because of hydrogen connections at low temperatures [82, 83].

Table 6: Experimental data for poloxamer polymer

Drug	Polymers	Major findings	References
Pluronic F127, Poly(ethyleneglycol) (PEG), Polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), methyl cellulose (MC), Hydroxypropyl methylcellulose (HPMC)	Pilocarpine hydrochloride	Along with MC and HPMC shows controlled release	[84]
Poloxamer 407 and poloxamer P188	Methazolamide	Greater drug retaining capability compared to the eyedrops.	[85]
Pluronic F127, Pluronic F68, Sodium hyaluronate	Sparfloxacin	Showed sustained release up to 24 h	[86]
Poloxamer 407 and Poloxamer 188	Dorzolamide hydrochloride	The improved pharmacological effect, more rapid onset of action	[87]
Pluronic F127, Pluronic F68, hyaluronic acid (HA)	Acyclovir	Rheological synergism between poloxamers/HA gel. Prolonged drug release up to 6 h	[88]
Pluronic (PF-127 and PF-68) and Na-Alginate	Ofloxacin	In *in vivo* examination of rabbits, Pluronic F127 maintained higher retention performance than Pluronic F68 by 20 percent (w/w).	[89]

Xyloglucan

Xyloglucan is a polysaccharide extracted from tamarind seeds, which exhibits thermal reversible gel-forming properties in dilute aqueous solution if partially degraded by β-galactosidase [90]. It represents its function in drug bioavailability [91] since it can make large ionic complexes with medicine which allows the drug to exhibit longer effects than traditional ophthalmic solutions [92].

As a gelling agent for the preparation of pilocarpine chloride formed by Miyazaki *et al.* (2001), enzyme-degraded xyloglucan has been used. In comparison with the rheological properties, 2% xyloglucan gel power equals 25% PF-127. This is an advancement of xyloglucan since it can be put to use in a considerably smaller amount than PF-127 in formulations. For more than 6 h, Xyloglucan-based IGS has demonstrated continuous drug release. Miosis has been affected by the formulation of 1.5% xyloglucan for at least 4 h, as occurred with 25% PF-127 [93].

pH-sensitive in situ gelling system

These systems are pH-induced preparations that translate into a gel form, e. g., cellulose acetate phthalate, and carbopol when exposed to the pH of the lachrymal fluid [77]. pH-sensitive polymers either contain weak acid or basic groups in the backbone of the polymer that releases the proton in response to an alteration in pH or embraces a free proton. Hydrophobic association, electrostatic, and hydrogen linkage occur at a particular pH and thereby contribute to the conformational swelling of the polymer. This causes the sol to gel transformation to pH [94].

Polymers

Chitosan

It is a deacetylated chitin substance that is famous for its mucoadhesive properties. In the production of in situ gels, this polymer has been widely studied. Chitosan is a pH-based cationic polymer. Chitosan stays transparent at an acidic pH (under its pKa 6.2) and is transformed into a soft gel at a higher pH (physiological pH) [78]. It is biologically degradable and nontoxic. It shows pseudo-plasticity as well as viscoelasticity. The mucoadhesive activity of chitosan comes from the ionic association between the chitosan amino positive group and mucin residues of negative sialic acid. It is employed in artificial tear formulations as a viscosity boosting tool for its bioadhesive, hydrophilic and strong propagation properties [95].

Carbopol

It is also known as a polyacrylic acid polymer that displays a transformation from sol to gel in an aqueous medium by raising pH over its pKa [96]. Four main reasons responsible for its mucoadhesive quality are: electrostatic interaction, hydrophobic interaction, hydrogen bonding, and interdiffusion [97]. Carbopol is a coiled molecule that is acidic. Once scattered into the water, the carboxylic molecule group partly separates to form a flexible spiral.

As a pH-sensitive polymer, the pH of the solution increases the swelling of the polymer. In an acidic environment, owing to hydrogen bonding, electrostatic repulsion occurs between anionic groups as the pH increases, resulting in swelling of gel [98].

Ion sensitive in situ gel system

Tear fluid contains various ions in it (Na+, Ca2+and Mg2+). This gelling system creates a cross-link with the mentioned cations and thus forms a gel on the eye surface that leads to extended corneal contact time [91, 104].

Polymers

Gellan Gum

It is an anionic heteropolysaccharide, composed of molar backbone 2:1:1 molar glucose, glucuronic acid, and rhamnose, which are joined together to create a unit of tetrasaccharides [78]. It is

produced by the "sphingomonas elodea" which is a microbe [97, 98]. The gellan gum is accessible under the name of Gelrite®, which in the existence of mono-or divalent cations and undergoes gelation. Tear fluid electrolytes, in particular Na+, Mg2+, and Ca2+cations, are well known to prompt polymer gel-forming on introduction as a liquid solution in the cul-de-sac [81].

Table 7: Experimental data for carbopol polymer

Ingredients/polymers	Drug	Key findings	References
Carbopol 980NF Na	Dexamethasone	Sustained-release with amplified bioavailability.	[98]
Carboxy methylcellulose (CMC), 2-Hydroxypropyl-β-cyclodextrin (HP-β-CD)			
Carbopol or HPMC	Moxifloxacin	Precorneal residence time is increased along with increased ocular bioavailability.	[99]
Carbopol 974P, HPMC E4M	Baicalin	Area under the curve (AUC) and maximum concentration (C_{max}) values were elevated as compared with the drug solution	[100]
Chitosan, HPMC	Timolol maleate	Clear noticeable data of enhanced retention of in situ gel.	[101]
Carbopol 934P	Norfloxacin	Adequate mucoadhesive, antibacterial activity, and safe from ocular irritancy.	[102]
Ca Alginate along with HPMC K4M	Ciprofloxacin	Supplementary advantage of sustained drug release.	[103]

Table 8: Experimental data for gellan gum

Polymers	Drug	Key findings	References
Gellan Gum	Perfloxacin mesylate	Sustained release up to 12 h. Formulation reported being stable for more than 2 y.	[105]
Gellan Gum	Indomethacin	Sustained-release up to 8 h. Improved clinical symptoms of uveitis-induced rabbits.	[106]
Gellan Gum along with Carrageenan	Antisense oligodeoxynucleotide	The maximum diminution in wound size, tiniest stromal edema	[107]
Na alginate	Pilocarpine hydrochloride	Slow-release up to 24 h. IOP-lowering effect up to 10 h in comparison with simple drug solution (3 h)	[108]
Gellan gum with HPMC or carbopol	Acetazolamide	Better therapeutic efficacy and decreased IOP were observed when compared with marketed eye drops.	[109]

Polymeric nanoparticles

Polymer nanoparticles are designed to incorporate medicines that are enclosed or scattered in the polymer matrix and are formed as nanocapsules or nanospheres [110]. It ranges between 10 nm and 1000 nm [111]. Nanospheric polymers have a central matrix of the polymer in which medications can be either applied to the surface of the polymer or drawn into the matrix. Nanocapsules are developed in such a way that they have a solid polymeric wall and a liquid phase in the center [112]. These polymeric features allow them to be possible nanocarriers, since a drug molecule may be coupled on the surface or enclosed inside and distributed at a high concentration at a certain target site with low systematical toxicity [111].

Nanoparticles are commonly composed of lipids, collagen, natural or synthetic polymers, such as albumin, sodium alginate, and polycaprolactone for the ophthalmic supply of medicines. Nanoparticles are formulated as nanospheres or nanocapsules. In nanocapsules, the medicine is confined to the polymer shell while it is spread evenly across the polymeric matrix in nanospheres. Nanoparticles have gained attention in the distribution of ocular drug products in recent decades and many scientists have tried to create drug-loaded nanoparticles on both the anterior and posterior segments of the human eye [113–120].

During *in vivo* studies, Kumar and Amita, 2015 found that amikacin sulfate including polymeric nanoparticles of chlorotrimethyl-ammonium methacrylate produced high levels of corneal binding, resulting in better medicinal retention in the cornea [121]. Qiu *et al.* (2019) have created fenofibrates filled PLGA-nanoparticles that are intravitreally injected into the eyes of diabetic rats. Consequently, retinal vascular leakage suppression, VEGF suppression, and retinal leukocytosis inhibition were observed [122].

Musumeci *et al.* (2013) recorded the most efficient melatonin-powered PLGA-PEG nanoparticles and showed a substantial decrease in intraocular pressure (IOP) in comparison to PLGA-nanoparticles filled with melatonin and the aqueous solution of concentration equal to that of rabbit's eye. It was hypothesized that the decreased zeta potential of PLGA-PEG nanoparticles permitted longer and improved interactions between nanoparticles and the ocular surface, which resulted in a higher, hypotensive long-term impact [123].

Nanosuspension

Nanosuspension is a promised carrier device for the distribution of badly water-soluble drug products [124]. In addition to preventing a high degree of ophthalmic osmolarity, the distinctive existence of nanosuspension solves the saturation or solubility-related problems of hydrophobic medications in tear fluids while holding medicine in a cul-de-sac for a prolonged along with sustained drug release [125]. Moreover, the drugs which were prepared with PLGA for nanosuspension have shown increased precorneal tolerance and eye permeation. Drugs embedded in lyophilized nanosuspensions have also been found to be more soluble than the traditional ones [117].

Kassem *et al.* (2007) designed nanosuspensions for certain water-insoluble glucocorticoid medications by high-pressure homogenization processes (hydrocortisone and prednisolone). Developed formulations were examined for the micro-and nanosize range particle size and the viscosity effect on albino rabbits have been investigated. The nanosuspension increased the rate and volume of absorption of ophthalmic drugs and the strength of drug activity. The span of drug activity depended significantly on viscosity**.** The betaxolol nanosuspension with ion exchange resin was permitted and was available commercially. The 0.25-percent betaxolol containing cationic exchange resin in the cul-de-sac improved the time of medicine residency [126]. Paul *et al.* (2011 and 2013) had developed amphotericin B nanosuspension for the treatment of fungal keratitis with different eudragit polymers. The results showed promising penetration and drug retention of the system to the eye in both cases. They further developed a method of analysis of residual solvent in ocular nanosuspension [48].

Dendrimers

Dendrimers have a broad range of therapeutic uses, such as improved solvent solutions, improved delivery of DNA and oligonucleotides, targeting drugs at particular receptor sites, and the

ability to imitate drug development systems as a carrier [127]. Previously, bioadhesive polymers, including polyacrylic acid, have been used for prolongation of contact time to boost medicine delivery into the eye. The blurring of the precorneal region of vision and the development of a veil giving rise to visual distortion, limit the utilization of this polymer [128]. To address such restrictions, polyamide amine (PAMAM) dendrimers have been added to it. The use of PAMAM dendrimers in the ocular trajectory is significant. PAMAM dendrimers have physicochemical properties that are congruent with ocular formulations [127].

Vandamme and Brobeck, 2005 had analyzed the effects of PAMAM dendrimers on pilocarpine and tropicamide and found that because of increased bioadhesion and sustainable drug release, bioavailability was enhanced. PEGylation of dendrimer surfaces might further enhance the drug delivery using dendrimers. Dendrimers might adjust drug delivery by choosing the optimum corresponding surface groups (carboxylic, amines, and hydroxyl), or by specifying the dendrimer's size or molecular weight. Yaruz *et al.* (2013) described a thorough analysis of the dendrimer form, properties, and ocular application of dendrimeric supplies. A PAMAM dendrimer gel with PEG-acrylate strands filled with timolol or brimonidine was developed by Holden *et al.* [129]. PEG-acrylate chains bound together and developed a solution when exposed to light. This gel was innocuous and had shown mucoadhesive properties in the epithelium stroma. It also has helped in improving drug bioavailability. In *in vitro*, the drug exhibited a sustained-release effect. It was 72 h for brimonidine and 56 h for timolol due to PEG-network drug traps and drug encapsulation. However, drugs were released more rapidly after 1.5 h from eye drops, thereby not exhibiting sustained release, and the eye drops had not been released continuously [129].

Implants

Implants are intended to produce controlled drug release over a longer period. This system helps to avoid frequent intraocular doses and complications [130, 131]. Although implanting is intrusive, the associated benefits such as the continued release of drugs, the discharge of local medication to the diseased site, decreased complications associated with adverse effects, and the capacity to bypass the blood-retinal barrier has increased the appeal of these systems [131, 132]. Polymers used in implants are present as biodegradable or non-biodegradable, hydrophobic or hydrophilic. Through the body's enzymatic and non-enzymatic reactions, biodegradable polymers eventually become soluble, whereas non-biodegradable polymers are not metabolized and eroded within the body [133].

Biodegradable implants

The monolithic or binder type of biodegradable implants is usually categorized. The formulations of such implants make it complicated for the optimum release of drugs when compared with the non-biodegradable implant reservoir. However, no removal of biodegradable implants is required. The drug can be released through such implants using zero-order kinetics. This implant manufacturing procedure requires heating and drying. Drugs that quickly decay during these processes are, therefore not an appropriate choice for use in such implants, such as biologically active proteins [133]. The most popular polymers used in the manufacture of these implants are polyglycolic acid, polylactic acid, and polycaprolactones [130]. E. g., SurodexTM and Ozurdex® are developed respectively for the continued delivery of dexamethasone for intraocular inflammatory and macular edema treatment [132]**.** Dhaka *et al.*, 2020, reported the preparation and assessment methods of ocular inserts containing sulbactum. They also reported good controlled ocular delivery of the drug from this insert.

Non-biodegradable implants

The long-lasting release of non-biodegradable implants is accomplished by nearly zero-order release kinetics [132]**.** There is no first adverse explosion of the drugs in the non-biodegradable polymer device that is superior to the biodegradable polymer. The device cannot be biodegraded, and therefore the empty devices must be removed in 5-8 mo after implantation [133]. For the manufacture of these, polymers, such as ethylene-vinyl acetate and polyvinyl alcohol are used. Examples of commercialized non-biodegradable implants include Vitrasert® and Retisert® [130].

CONCLUSION

There are a variety of formulation approaches for delivering drugs into the human eye. Yet, drug delivery stays a stumper and a task for researchers because of the complicated human eye structure. The impediments of existing formulations for ophthalmic diseases incorporate low drug bioavailability, no explicitness, and reduced retention time. To defeat such restrictions, various novel approaches have been created in ocular drug delivery systems, for example, nanoparticles, liposomes, microneedles, niosomes, nanowafers, and some more. Nanotechnology is profiting the patient by limiting the numerous side effects which have been associated with conventional therapies. Current research shows that nanotechnology can substitute conventional drug delivery methods as a prior choice for the treatment of eye disorders.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declare none

REFERENCES

1. Bachu RD, Chowdhury P, Al-Saedi ZHF, Karla PK, Boddu SHS. Ocular drug delivery barriers-role of nanocarriers in the treatment of anterior segment ocular diseases. Pharmaceutics. 2018 Feb 27;10(1):28. doi: 10.3390/pharmaceutics10010028, PMID 29495528.
2. Souto EB, Dias-Ferreira J, Lopez Machado A, Ettcheto M, Cano A, Camins Espuny AC, Espina M, Garcia ML, Sanchez Lopez E. Advanced formulation approaches for ocular drug delivery: state-of-the-art and recent patents. Pharmaceutics. 2019 Sep 6;11(9):460. doi: 10.3390/pharmaceutics11090460, PMID 31500106.
3. Liu S, Jones L, Gu FX. Nanomaterials for ocular drug delivery. Macromol Biosci. 2012 May;12(5):608-20. doi: 10.1002/mabi.201100419, PMID 22508445.
4. Gote V, Sikder S, Sicotte J, Pal D. Ocular drug delivery: present innovations and future challenges. J Pharmacol Exp Ther. 2019 Sep;370(3):602-24. doi: 10.1124/jpet.119.256933, PMID 31072813.
5. Nagai N. Design of novel ophthalmic formulation containing drug nanoparticles and its usefulness as anti-glaucoma drugs. Yakugaku Zasshi. 2016;136(10):1385-90. doi: 10.1248/yakushi.16-00089, PMID 27725388.
6. Tiwari R, Pandey V, Asati S, Soni V, Jain D. Therapeutic challenges in ocular delivery of lipid-based emulsion. Egypt J Basic Appl Sci. 2018;5(2):121-9. doi: 10.1016/j.ejbas.2018.04.001.
7. Suri R, Beg S, Kohli K. Target strategies for drug delivery bypassing ocular barriers. J Drug Deliv Sci Technol. 2020;55. doi: 10.1016/j.jddst.2019.101389, PMID 101389.
8. Nagarwal RC, Kant S, Singh PN, Maiti P, Pandit JK. Polymeric nanoparticulate system: a potential approach for ocular drug delivery. J Control Release. 2009 May 21;136(1):2-13. doi: 10.1016/j.jconrel.2008.12.018. PMID 19331856.
9. Kadian R. Nanoparticles: A promising drug delivery approach. Asian J Pharm Clin Res. 2018;11(1):30. doi: 10.22159/ajpcr.2017.v11i1.22035.
10. Kumari B. Ocular drug delivery system: approaches to improve ocular bioavailability. GSC Biol Pharm Sci. 2019;6(3):1-10. doi: 10.30574/gscbps.2019.6.3.0030.
11. Zhang J, Wang S. Topical use of coenzyme Q10-loaded liposomes coated with trimethyl chitosan: tolerance, precorneal retention and anti-cataract effect. Int J Pharm. 2009 May 8;372(1-2):66-75. doi: 10.1016/j.ijpharm.2009.01.001. PMID 19437594.

12. Hathout RM, Gad HA, Abdel Hafez SM, Nasser N, Khalil N, Ateyya T, Amr A, Yasser N, Nasr S, Metwally AA. Gelatinized core liposomes: A new trojan horse for the development of a novel timolol maleate glaucoma medication. Int J Pharm. 2019 Feb 10;556:192-9. doi: 10.1016/j.ijpharm.2018.12.015. PMID 30553005.
13. Shen Y, Tu J. Preparation and ocular pharmacokinetics of ganciclovir liposomes. AAPS J. 2007 Dec 7;9(3):E371-7. doi: 10.1208/aapsj0903044, PMID 18170984.
14. Sun Y, Fox T, Adhikary G, Kester M, Pearlman E. Inhibition of corneal inflammation by liposomal delivery of short-chain, C-6 ceramide. J Leukoc Biol. 2008 Jun;83(6):1512-21. doi: 10.1189/jlb.0108076, PMID 18372342.
15. Ren T, Lin X, Zhang Q, You D, Liu X, Tao X, Gou J, Zhang Y, Yin T, He H, Tang X. Encapsulation of azithromycin ion pair in liposome for enhancing ocular delivery and therapeutic efficacy on dry eye. Mol Pharm. 2018 Nov 5;15(11):4862-71. doi: 10.1021/acs.molpharmaceut.8b00516. PMID 30251864.
16. Dhadwal A, Sharma DR, Pandit V, Ashawat MS, Kumar P. Cubosomes: A novel carrier for transdermal drug delivery. J Drug Delivery Ther. 2020;10(1):123-30. doi: 10.22270/jddt.v10i1.3814.
17. Lalu L, Tambe V, Pradhan D, Nayak K, Bagchi S, Maheshwari R, Kalia K, Tekade RK. Novel nanosystems for the treatment of ocular inflammation: current paradigms and future research directions. J Control Release. 2017 Dec 28;268:19-39. doi: 10.1016/j.jconrel.2017.07.035. PMID 28756272.
18. Ali Z, Sharma P, Warsi M. Fabrication and evaluation of ketorolac loaded Cubosome for ocular drug delivery. J App Pharm Sci. 2016;6:204-8. doi: 10.7324/JAPS.2016.60930.
19. Hartnett TE, O'Connor AJ, Ladewig K. Cubosomes and other potential ocular drug delivery vehicles for macromolecular therapeutics. Expert Opin Drug Deliv. 2015;12(9):1513-26. doi: 10.1517/17425247.2015.1021680, PMID 25745885.
20. Priyanka P, Sri Rekha M, Devi AS. Review on formulation and evaluation of solid lipid nanoparticles for vaginal application. Int J Pharm Pharm Sci. 2022:1-8. doi: 10.22159/ijpps.2022v14i1.42595.
21. Huang J, Peng T, Li Y, Zhan Z, Zeng Y, Huang Y, Pan X, Wu CY, Wu C. Ocular Cubosome drug delivery system for timolol maleate: preparation, characterization, cytotoxicity, ex vivo, and *in vivo* evaluation. AAPS PharmSciTech. 2017 Nov;18(8):2919-26. doi: 10.1208/s12249-017-0763-8, PMID 28429294.
22. Coursey TG, Henriksson JT, Marcano DC, Shin CS, Isenhart LC, Ahmed F, De Paiva CS, Pflugfelder SC, Acharya G. Dexamethasone nanowafer as an effective therapy for dry eye disease. J Control Release. 2015 Sep 10;213:168-74. doi: 10.1016/j.jconrel.2015.07.007. PMID 26184051.
23. Mandal A, Pal D, Agrahari V, Trinh HM, Joseph M, Mitra AK. Ocular delivery of proteins and peptides: challenges and novel formulation approaches. Adv Drug Deliv Rev. 2018 Feb 15;126:67-95. doi: 10.1016/j.addr.2018.01.008. PMID 29339145.
24. Garrett Q, Simmons PA, Xu S, Vehige J, Zhao Z, Ehrmann K, Willcox M. Carboxymethylcellulose binds to human corneal epithelial cells and is a modulator of corneal epithelial wound healing. Invest Ophthalmol Vis Sci. 2007 Apr;48(4):1559-67. doi: 10.1167/iovs.06-0848, PMID 17389485.
25. Coursey TG, Henriksson JT, Marcano DC, Shin CS, Isenhart LC, Ahmed F, De Paiva CS, Pflugfelder SC, Acharya G. Dexamethasone nanowafer as an effective therapy for dry eye disease. J Control Release. 2015 Sep 10;213:168-74. doi: 10.1016/j.jconrel.2015.07.007. PMID 26184051.
26. Marcano DC, Shin CS, Lee B, Isenhart LC, Liu X, Li F, Jester JV, Pflugfelder SC, Simpson J, Acharya G. Synergistic cysteamine delivery nanowafer as an efficacious treatment modality for corneal cystinosis. Mol Pharm. 2016 Oct 3;13(10):3468-77. doi: 10.1021/acs.molpharmaceut.6b00488. PMID 27571217.
27. Wong FSY, Tsang KK, Lo ACY. Delivery of therapeutics to posterior eye segment: cell-encapsulating systems. Neural Regen Res. 2017 Apr;12(4):576-77. doi: 10.4103/1673-5374.205093, PMID 28553333.
28. Emerich DF, Thanos CG. NT-501: an ophthalmic implant of polymer-encapsulated ciliary neurotrophic factor-producing cells. Curr Opin Mol Ther. 2008 Oct;10(5):506-15. PMID 18830926.
29. Kuno N, Fujii S. Biodegradable intraocular therapies for retinal disorders: progress to date. Drugs Aging. 2010 Feb 1;27(2):117-34. doi: 10.2165/11530970-000000000-00000, PMID 20104938.
30. Barar J, Aghanejad A, Fathi M, Omidi Y. Advanced drug delivery and targeting technologies for the ocular diseases. BioImpacts. 2016;6(1):49-67. doi: 10.15171/bi.2016.07. PMID 27340624.
31. Lee JW, Park JH, Prausnitz MR. Dissolving microneedles for transdermal drug delivery. Biomaterials. 2008 May;29(13):2113-24. doi: 10.1016/j.biomaterials.2007.12.048, PMID 18261792.
32. Jiang J, Gill HS, Ghate D, McCarey BE, Patel SR, Edelhauser HF, Prausnitz MR. Coated microneedles for drug delivery to the eye. Invest Ophthalmol Vis Sci. 2007 Sep;48(9):4038-43. doi: 10.1167/iovs.07-0066, PMID 17724185.
33. Huang D, Chen YS, Rupenthal ID. Overcoming ocular drug delivery barriers through the use of physical forces. Adv Drug Deliv Rev. 2018 Feb 15;126:96-112. doi: 10.1016/j.addr.2017.09.008. PMID 28916492.
34. Song HB, Lee KJ, Seo IH, Lee JY, Lee SM, Kim JH, Kim JH, Ryu W. Impact insertion of transfer-molded microneedle for localized and minimally invasive ocular drug delivery. J Control Release. 2015 Jul 10;209:272-9. doi: 10.1016/j.jconrel.2015.04.041. PMID 25937320.
35. Gilger BC, Abarca EM, Salmon JH, Patel S. Treatment of acute posterior uveitis in a porcine model by injection of triamcinolone acetonide into the suprachoroidal space using microneedles. Invest Ophthalmol Vis Sci. 2013 Apr 3;54(4):2483-92. doi: 10.1167/iovs.13-11747, PMID 23532526.
36. Ustundag Okur N, Homan Gokce E. Lipid nanoparticles for ocular drug delivery. Int J Ophthal Res. 2015;1(3):77-82. doi: 10.17554/j.issn.2409-5680.2015.01.29.
37. Sanchez Lopez E, Espina M, Doktorovova S, Souto EB, Garcia ML. Lipid nanoparticles (SLN, NLC): overcoming the anatomical and physiological barriers of the eye- Part I- Barriers and determining factors in ocular delivery. Eur J Pharm Biopharm. 2017;110:70-5. doi: 10.1016/j.ejpb.2016.10.009. PMID 27789358.
38. Pandey V, Gajbhiye KR, Soni V. Lactoferrin-appended solid lipid nanoparticles of paclitaxel for effective management of bronchogenic carcinoma. Drug Deliv. 2015 Feb;22(2):199-205. doi: 10.3109/10717544.2013.877100, PMID 24467582.
39. Manjunath K, Reddy JS, Venkateswarlu V. Solid lipid nanoparticles as drug delivery systems. Methods Find Exp Clin Pharmacol. 2005 Mar;27(2):127-44. doi: 10.1358/mf.2005.27.2.876286, PMID 15834465.
40. Mishra V, Bansal KK, Verma A, Yadav N, Thakur S, Sudhakar K, Rosenholm JM. Solid lipid nanoparticles: emerging colloidal Nano drug delivery systems. Pharmaceutics. 2018 Oct 18;10(4):191. doi: 10.3390/pharmaceutics10040191, PMID 30340327.
41. Tekade RK, Maheshwari R, Tekade M, Chougule MB. Solid lipid nanoparticles for targeting and delivery of drugs and genes. Nanotechnol-Based Approaches Target Deliv Drugs Genes. 2017:256-86.
42. Balguri SP, Adelli GR, Majumdar S. Topical ophthalmic lipid nanoparticle formulations (SLN, NLC) of indomethacin for delivery to the posterior segment ocular tissues. Eur J Pharm Biopharm. 2016 Dec;109:224-35. doi: 10.1016/j.ejpb.2016.10.015. PMID 27793755.
43. Wagh VD, Deshmukh OJ. Itraconazole niosomes drug delivery system and its antimycotic activity against Candida albicans. ISRN Pharm. 2012;2012:653465. doi: 10.5402/2012/653465, PMID 23378932.
44. Jain N, Verma A. Preformulation studies of pilocarpine hydrochloride as niosomal gels for ocular drug delivery. Asian J Pharm Clin Res. 2020:149-55. doi: 10.22159/ajpcr.2020.v13i6.37523.

45. Rinaldi F, Del Favero E, Moeller J, Hanieh PN, Passeri D, Rossi M, Angeloni L, Venditti I, Marianecci C, Carafa M, Fratoddi I. Hydrophilic silver nanoparticles loaded into niosomes: physical-chemical characterization in view of biological applications. Nanomaterials (Basel). 2019 Aug 17;9(8):1177. doi: 10.3390/nano9081177, PMID 31426465.
46. Amoabediny G, Haghiralsadat F, Naderinezhad S, Helder MN, Akhoundi Kharanaghi E, Mohammadnejad Arough J, Zandieh Doulabi B. Overview of preparation methods of polymeric and lipid-based (niosome, solid lipid, liposome) nanoparticles: a comprehensive review. Int J Polym Mater Polym Biomater. 2018;67(6):383-400. doi: 10.1080/00914037.2017.1332623.
47. MS, MS, Panda SP, Buddha S, Kumari PVK, Rao YS. Proniosomes: A vesicular drug delivery system. Int J Curr Pharm Sci. 2021;32-36:32-6. doi: 10.22159/ijcpr.2021v13i6.1925.
48. Marianecci C, Di Marzio L, Rinaldi F, Celia C, Paolino D, Alhaique F, Esposito S, Carafa M. Niosomes from 80s to present: the state of the art. Adv Colloid Interface Sci. 2014 Mar;205:187-206. doi: 10.1016/j.cis.2013.11.018. PMID 24369107.
49. Verma A, Tiwari A, Saraf S, Panda PK, Jain A, Jain SK. Emerging potential of niosomes in ocular delivery. Expert Opin Drug Deliv. 2021 Jan;18(1):55-71. doi: 10.1080/17425247.2020.1822322, PMID 32903034.
50. Abdelkader H, Ismail S, Hussein A, Wu Z, Al-Kassas R, Alany RG. Conjunctival and corneal tolerability assessment of ocular naltrexone niosomes and their ingredients on the hen's egg chorioallantoic membrane and excised bovine cornea models. Int J Pharm. 2012 Aug 1;432(1-2):1-10. doi: 10.1016/j.ijpharm.2012.04.063. PMID 22575752.
51. Shukr MH. Novel in situ gelling ocular inserts for voriconazole-loaded niosomes: design, *in vitro* characterisation and *in vivo* evaluation of the ocular irritation and drug pharmacokinetics. J Microencapsul. 2016 Feb;33(1):71-9. doi: 10.3109/02652048.2015.1128489, PMID 26739851.
52. Shukr MH. Novel in situ gelling ocular inserts for voriconazole-loaded niosomes: design, *in vitro* characterisation and *in vivo* evaluation of the ocular irritation and drug pharmacokinetics. J Microencapsul. 2016 Feb;33(1):71-9. doi: 10.3109/02652048.2015.1128489, PMID 26739851.
53. Abu Hashim II, El-Dahan MS, Yusif RM, Abd-Elgawad AE, Arima H. Potential use of niosomal hydrogel as an ocular delivery system for atenolol. Biol Pharm Bull. 2014;37(4):541-51. doi: 10.1248/bpb.b13-00724. PMID 24694602.
54. Kaur IP, Singh M, Yadav M, Sandhu SK, Deol PK, Sharma G. Potential of nanomaterials as movers and packers for drug molecules. Solid State Phenom. 2014;222:159-78. doi: 10.4028/www.scientific.net/SSP.222.159.
55. Kakkar S, Kaur IP. Spanlastics-a novel nanovesicular carrier system for ocular delivery. Int J Pharm. 2011 Jul 15;413(1-2):202-10. doi: 10.1016/j.ijpharm.2011.04.027. PMID 21540093.
56. Sarraf D, Lee DA. The role of iontophoresis in ocular drug delivery. J Ocul Pharmacol. 1994 Spring;10(1):69-81. doi: 10.1089/jop.1994.10.69, PMID 8207346.
57. Ghate D, Edelhauser HF. Ocular drug delivery. Expert Opin Drug Deliv. 2006 Mar;3(2):275-87. doi: 10.1517/17425247.3.2.275, PMID 16506953.
58. Barza M, Peckman C, Baum J. Transscleral iontophoresis as an adjunctive treatment for experimental endophthalmitis. Arch Ophthalmol. 1987 Oct;105(10):1418-20. doi: 10.1001/archopht.1987.01060100120040, PMID 3499135.
59. Barza M, Peckman C, Baum J. Transscleral iontophoresis of cefazolin, ticarcillin, and gentamicin in the rabbit. Ophthalmology. 1986 Jan;93(1):133-9. doi: 10.1016/s0161-6420(86)33780-1, PMID 3951811.
60. Chopra P, Hao J, Li SK. Sustained-release micellar carrier systems for iontophoretic transport of dexamethasone across human sclera. J Control Release. 2012 May 30;160(1):96-104. doi: 10.1016/j.jconrel.2012.01.032. PMID 22306336.
61. Souza JG, Dias K, Silva SA, de Rezende LC, Rocha EM, Emery FS, Lopez RF. Transcorneal iontophoresis of dendrimers: PAMAM corneal penetration and dexamethasone delivery. J Control Release. 2015 Feb 28;200:115-24. doi: 10.1016/j.jconrel.2014.12.037. PMID 25553828.
62. Lam TT, Fu J, Tso MOM. Erratum. Graefe's Arch Clin Exp Ophthalmol. 1992;230(2):199. doi: 10.1007/BF00164665.
63. Parkinson TM, Ferguson E, Febbraro S, Bakhtyari A, King M, Mundasad M. Tolerance of ocular iontophoresis in healthy volunteers. J Ocul Pharmacol Ther. 2003 Apr;19(2):145-51. doi: 10.1089/108076803321637672, PMID 12804059.
64. Cohen AE, Assang C, Patane MA, From S, Korenfeld M, Avion Study Investigators. Evaluation of dexamethasone phosphate delivered by ocular iontophoresis for treating noninfectious anterior uveitis. Ophthalmology. 2012 Jan;119(1):66-73. doi: 10.1016/j.ophtha.2011.07.006. PMID 22115712.
65. Patane MA, Cohen A, From S, Torkildsen G, Welch D, Ousler GW 3rd. Ocular iontophoresis of EGP-437 (dexamethasone phosphate) in dry eye patients: results of a randomized clinical trial. Clin Ophthalmol. 2011;5:633-43. doi: 10.2147/OPTH.S19349. PMID 21629568.
66. Mehrandish S, Mirzaeei S. A review on ocular novel drug delivery systems of antifungal drugs: functional evaluation and comparison of conventional and novel dosage forms. Adv Pharm Bull. 2021 Jan;11(1):28-38. doi: 10.34172/apb.2021.003, PMID 33747850.
67. Hoare TR, Kohane DS. Hydrogels in drug delivery: progress and challenges. Polymer. 2008;49(8):1993-2007. doi: 10.1016/j.polymer.2008.01.027.
68. Maharjan P, Cho KH, Maharjan A, Shin MC, Moon C, Min KA. Pharmaceutical challenges and perspectives in developing ophthalmic drug formulations. J Pharm Investig. 2019;49(2):215-28. doi: 10.1007/s40005-018-0404-6.
69. Tyagi P, Barros M, Stansbury JW, Kompella UB. Light-activated, in situ forming gel for sustained suprachoroidal delivery of bevacizumab. Mol Pharm. 2013 Aug 5;10(8):2858-67. doi: 10.1021/mp300716t, PMID 23734705.
70. Sasaki H, Yamamura K, Nishida K, Nakamura J, Ichikawa M. Delivery of drugs to the eye by topical application. Prog Retin Eye Res. 1996;15(2):583-620. doi: 10.1016/1350-9462(96)00014-6.
71. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. Adv Drug Deliv Rev. 2005 Nov 3;57(11):1595-639. doi: 10.1016/j.addr.2005.07.005. PMID 16198021.
72. Robinson JR, Mlynek GM. Bioadhesive and phase-change polymers for ocular drug delivery. Adv Drug Deliv Rev. 1995;16(1):45-50. doi: 10.1016/0169-409X(95)00013-W.
73. Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: an overview. World J Pharmacol. 2013;2(2):47-64. doi: 10.5497/wjp.v2.i2.47. PMID 25590022.
74. Sheshala R, Kok YY, Ng JM, Thakur RR, Dua K. In situ gelling ophthalmic drug delivery system: an overview and its applications. Recent Pat Drug Deliv Formul. 2015;9(3):237-48. doi: 10.2174/1872211309666150724101227, PMID 26205681.
75. El-Kamel AH. *In vitro* and *in vivo* evaluation of pluronic F127-based ocular delivery system for timolol maleate. Int J Pharm. 2002 Jul 8;241(1):47-55. doi: 10.1016/s0378-5173(02)00234-x, PMID 12086720.
76. Ma WD, Xu H, Wang C, Nie SF, Pan WS. Pluronic F127-g-poly(acrylic acid) copolymers as in situ gelling vehicle for ophthalmic drug delivery system. Int J Pharm. 2008 Feb 28;350(1-2):247-56. doi: 10.1016/j.ijpharm.2007.09.005. PMID 17961940.
77. Agrawal AK, Das M, Jain S. In situ gel systems as 'smart' carriers for sustained ocular drug delivery. Expert Opin Drug Deliv. 2012 Apr;9(4):383-402. doi: 10.1517/17425247.2012.665367, PMID 22432690.
78. Rahic O, Tucak A, Omerovic N, Sirbubalo M, Hindija L, Hadziabdic J, Vranic E. Novel drug delivery systems fighting glaucoma: formulation obstacles and solutions. Pharmaceutics. 2020 Dec 26;13(1):28. doi: 10.3390/pharmaceutics13010028, PMID 33375224.
79. Kumar D, Jain N, Gulati N, Nagaich U. Nanoparticles laden in situ gelling system for ocular drug targeting. J Adv Pharm Technol Res. 2013 Jan;4(1):9-17. doi: 10.4103/2231-4040.107495, PMID 23662277.
80. Wu Y, Liu Y, Li X, Kebebe D, Zhang B, Ren J, Lu J, Li J, Du S, Liu Z. Research progress of in-situ gelling ophthalmic drug delivery

system. Asian J Pharm Sci. 2019 Jan;14(1):1-15. doi: 10.1016/j.ajps.2018.04.008. PMID 32104434.

81. Almeida H, Amaral MH, Lobão P, Sousa Lobo JM. Applications of poloxamers in ophthalmic pharmaceutical formulations: an overview. Expert Opin Drug Deliv. 2013 Sep;10(9):1223-37. doi: 10.1517/17425247.2013.796360, PMID 23688342.
82. Escobar Chavez JJ, Lopez Cervantes M, Naik A, Kalia YN, Quintanar Guerrero D, Ganem Quintanar A. Applications of thermo-reversible pluronic F-127 gels in pharmaceutical formulations. J Pharm Pharm Sci. 2006;9(3):339-58. PMID 17207417.
83. Desai SD, Blanchard J. *In vitro* evaluation of pluronic F127-based controlled-release ocular delivery systems for pilocarpine. J Pharm Sci. 1998 Feb;87(2):226-30. doi: 10.1021/js970090e, PMID 9519158.
84. Qian Y, Wang F, Li R, Zhang Q, Xu Q. Preparation and evaluation of in situ gelling ophthalmic drug delivery system for methazolamide. Drug Dev Ind Pharm. 2010 Nov;36(11):1340-7. doi: 10.3109/03639041003801893, PMID 20849349.
85. Nesseem DI. Ophthalmic delivery of sparfloxacin from in situ gel formulation for the treatment of experimentally induced bacterial keratitis. Drug Test Anal. 2011 Feb;3(2):106-15. doi: 10.1002/dta.170, PMID 21322120.
86. Graham S, Marina PF, Blencowe A. Thermoresponsive polysaccharides and their thermoreversible physical hydrogel networks. Carbohydr Polym. 2019 Mar 1;207:143-59. doi: 10.1016/j.carbpol.2018.11.053. PMID 30599994.
87. Mayol L, Quaglia F, Borzacchiello A, Ambrosio L, La Rotonda MI. A novel poloxamers/hyaluronic acid in situ forming hydrogel for drug delivery: rheological, mucoadhesive and *in vitro* release properties. Eur J Pharm Biopharm. 2008 Sep;70(1):199-206. doi: 10.1016/j.ejpb.2008.04.025. PMID 18644705.
88. Al Khateb K, Ozhmukhametova EK, Mussin MN, Seilkhanov SK, Rakhypbekov TK, Lau WM, Khutoryanskiy VV. In situ gelling systems based on pluronic F127/Pluronic F68 formulations for ocular drug delivery. Int J Pharm. 2016 Apr 11;502(1-2):70-9. doi: 10.1016/j.ijpharm.2016.02.027. PMID 26899977.
89. Wu Y, Liu Y, Li X, Kebebe D, Zhang B, Ren J, Lu J, Li J, Du S, Liu Z. Research progress of in-situ gelling ophthalmic drug delivery system. Asian J Pharm Sci. 2019 Jan;14(1):1-15. doi: 10.1016/j.ajps.2018.04.008. PMID 32104434.
90. Almeida H, Amaral MH, Lobao P, Lobo JM. In situ gelling systems: a strategy to improve the bioavailability of ophthalmic pharmaceutical formulations. Drug Discov Today. 2014 Apr;19(4):400-12. doi: 10.1016/j.drudis.2013.10.001. PMID 24120893.
91. Pique N, Gomez Guillen MDC, Montero MP. Xyloglucan, a plant polymer with barrier protective properties over the mucous membranes: an overview. Int J Mol Sci. 2018 Feb 27;19(3):673. doi: 10.3390/ijms19030673, PMID 29495535.
92. Miyazaki S, Suzuki S, Kawasaki N, Endo K, Takahashi A, Attwood D. In situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. Int J Pharm. 2001 Oct 23;229(1-2):29-36. doi: 10.1016/s0378-5173(01)00825-0, PMID 11604255.
93. Kumar D, Jain N, Gulati N, Nagaich U. Nanoparticles laden in situ gelling system for ocular drug targeting. J Adv Pharm Technol Res. 2013 Jan;4(1):9-17. doi: 10.4103/2231-4040.107495, PMID 23662277.
94. Majeed A, Khan NA. Ocular in situ gel: an overview. J Drug Delivery Ther. 2019;9(1):337-47. doi: 10.22270/jddt.v9i1.2231.
95. Lin HR, Sung KC. Carbopol/pluronic phase change solutions for ophthalmic drug delivery. J Control Release. 2000 Dec 3;69(3):379-88. doi: 10.1016/s0168-3659(00)00329-1, PMID 11102678.
96. Nanjawade BK, Manvi FV, Manjappa AS. In situ-forming hydrogels for sustained ophthalmic drug delivery. J Control Release. 2007 Sep 26;122(2):119-34. doi: 10.1016/j.jconrel.2007.07.009. PMID 17719120.
97. Singh K, Verma S. Novel polymeric in situ gel-forming system for ophthalmic drug delivery. Int J Drug Deliv Technol. 2017;4(1). doi: 10.25258/ijddt.v4i1.8854.
98. Gupta C, Juyal V, Nagaich U. Formulation, optimization, and evaluation of in-situ gel of moxifloxacin hydrochloride for ophthalmic drug delivery. Int J App Pharm. 2019:147-58. doi: 10.22159/ijap.2019v11i4.30388.
99. Wu H, Liu Z, Peng J, Li L, Li N, Li J, Pan H. Design and evaluation of baicalin-containing in situ pH-triggered gelling system for sustained ophthalmic drug delivery. Int J Pharm. 2011 May 30;410(1-2):31-40. doi: 10.1016/j.ijpharm.2011.03.007. PMID 21397671.
100. Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G, Jain S. Development and characterization of 99mTc-timolol maleate for evaluating efficacy of in situ ocular drug delivery system. AAPS PharmSciTech. 2009;10(2):540-6. doi: 10.1208/s12249-009-9238-x, PMID 19424806.
101. Upadhayay P, Kumar M, Pathak K. Norfloxacin loaded pH triggered nanoparticulate in-situ gel for extraocular bacterial infections: optimization, ocular irritancy and corneal toxicity. Iran J Pharm Res. 2016;15(1):3-22. PMID 27610144.
102. Makwana SB, Patel VA, Parmar SJ. Development and characterization of in-situ gel for ophthalmic formulation containing ciprofloxacin hydrochloride. Results Pharma Sci. 2016;6:1-6. doi: 10.1016/j.rinphs.2015.06.001. PMID 26949596.
103. Rupenthal ID, Green CR, Alany RG. Comparison of ion-activated in situ gelling systems for ocular drug delivery. Part 2: Precorneal retention and *in vivo* pharmacodynamic study. Int J Pharm. 2011 Jun 15;411(1-2):78-85. doi: 10.1016/j.ijpharm.2011.03.043. PMID 21453763.
104. Sultana Y, Aqil M, Ali A. Ion-activated, gelrite-based in situ ophthalmic gels of pefloxacin mesylate: comparison with conventional eye drops. Drug Deliv. 2006 May–Jun;13(3):215-9. doi: 10.1080/10717540500309164, PMID 16556574.
105. Balasubramaniam J, Kant S, Pandit JK. *In vitro* and *in vivo* evaluation of the gelrite gellan gum-based ocular delivery system for indomethacin. Acta Pharm. 2003 Dec;53(4):251-61. PMID 14769232.
106. Rupenthal ID, Alany RG, Green CR. Ion-activated in situ gelling systems for antisense oligodeoxynucleotide delivery to the ocular surface. Mol Pharm. 2011 Dec 5;8(6):2282-90. doi: 10.1021/mp200140e, PMID 21985532.
107. Cohen S, Lobel E, Trevgoda A, Peled Y. A novel in situ-forming ophthalmic drug delivery system from alginates undergoing gelation in the eye. J Control Release. 1997;44(2-3):201-8. doi: 10.1016/S0168-3659(96)01523-4.
108. Morsi N, Ibrahim M, Refai H, El Sorogy H. Nanoemulsion-based electrolyte triggered in situ gel for ocular delivery of acetazolamide. Eur J Pharm Sci. 2017 Jun 15;104:302-14. doi: 10.1016/j.ejps.2017.04.013. PMID 28433750.
109. Kim HM, Woo SJ. Ocular drug delivery to the retina: current innovations and future perspectives. Pharmaceutics. 2021 Jan 15;13(1):108. doi: 10.3390/pharmaceutics13010108, PMID 33467779.
110. Yadav HK, Almokdad AA, Shaluf SI, Debe MS. Polymer-based nanomaterials for drug-delivery carriers. Nanocarriers Drug Deliv. 2019:531-56.
111. Nasimi P, Haidari M. Medical use of nanoparticles. Int J Green Nanotechnol. 2013;1:1-5. doi: 10.1177/1943089213506978.
112. Bhagav P, Upadhyay H, Chandran S. Brimonidine tartrate-eudragit long-acting nanoparticles: formulation, optimization, *in vitro* and *in vivo* evaluation. AAPS PharmSciTech. 2011 Dec;12(4):1087-101. doi: 10.1208/s12249-011-9675-1, PMID 21879393.
113. Pignatello R, Ricupero N, Bucolo C, Maugeri F, Maltese A, Puglisi G. Preparation and characterization of eudragit retard nanosuspensions for the ocular delivery of cloricromene. AAPS PharmSciTech. 2006 Mar 24;7(1):E27. doi: 10.1208/pt070127, PMID 16584158.
114. Ibrahim HK, El-Leithy IS, Makky AA. Mucoadhesive nanoparticles as carrier systems for prolonged ocular delivery of gatifloxacin/prednisolone bitherapy. Mol Pharm. 2010 Apr 5;7(2):576-85. doi: 10.1021/mp900279c, PMID 20163167.
115. Agnihotri SM, Vavia PR. Diclofenac-loaded biopolymeric nanosuspensions for ophthalmic application. Nanomedicine. 2009 Mar;5(1):90-5. doi: 10.1016/j.nano.2008.07.003. PMID 18823824.

116. Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G. Sparfloxacin-loaded PLGA nanoparticles for sustained ocular drug delivery. Nanomedicine. 2010 Apr;6(2):324-33. doi: 10.1016/j.nano.2009.10.004. PMID 19857606.
117. Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G. Biodegradable levofloxacin nanoparticles for sustained ocular drug delivery. J Drug Target. 2011 Jul;19(6):409-17. doi: 10.3109/1061186X.2010.504268, PMID 20678034.
118. Nagarwal RC, Kumar R, Pandit JK. Chitosan coated sodium alginate-chitosan nanoparticles loaded with 5-FU for ocular delivery: *in vitro* characterization and *in vivo* study in rabbit eye. Eur J Pharm Sci. 2012 Nov 20;47(4):678-85. doi: 10.1016/j.ejps.2012.08.008. PMID 22922098.
119. Retraction notice to 'Enhanced antiproliferative activity of carboplatin loaded chitosan-alginate nanoparticles in retinoblastoma cell line'. Acta Biomater. 2013 Jun;9(6):7075. doi: 10.1016/j.actbio.2013.02.025, PMID 23802318.
120. Sharma UK, Verma A, Prajapati SK, Pandey H, Pandey AC. *In vitro*, *in vivo* and pharmacokinetic assessment of amikacin sulphate laden polymeric nanoparticles meant for controlled ocular drug delivery. Appl Nanosci. 2015;5(2):143-55. doi: 10.1007/s13204-014-0300-y.
121. Qiu F, Meng T, Chen Q, Zhou K, Shao Y, Matlock G, Ma X, Wu W, Du Y, Wang X, Deng G, Ma JX, Xu Q. Fenofibrate-loaded biodegradable nanoparticles for the treatment of experimental diabetic retinopathy and neovascular age-related macular degeneration. Mol Pharm. 2019 May 6;16(5):1958-70. doi: 10.1021/acs.molpharmaceut.8b01319. PMID 30912953.
122. Musumeci T, Bucolo C, Carbone C, Pignatello R, Drago F, Puglisi G. Polymeric nanoparticles augment the ocular hypotensive effect of melatonin in rabbits. Int J Pharm. 2013 Jan 20;440(2):135-40. doi: 10.1016/j.ijpharm.2012.10.014. PMID 23078856.
123. Soni V, Pandey V, Tiwari R, Asati S, Tekade RK. Design and evaluation of ophthalmic delivery formulations. Basic Fundam Drug Deliv. 2019:473-538.
124. Jacob S, Nair AB, Shah J. Emerging role of nanosuspensions in drug delivery systems. Biomater Res. 2020 Jan 15;24:3. doi: 10.1186/s40824-020-0184-8, PMID 31969986.
125. Weinreb RN, Jani R. A novel formulation of an ophthalmic beta-adrenoceptor antagonist. J Parenter Sci Technol. 1992 Mar–Apr;46(2):51-3. PMID 1588458.
126. Ramesh Y, Kothapalli CB, Reddigari JRP. A novel approaches on ocular drug delivery system. J Drug Delivery Ther. 2017;7(6). doi: 10.22270/jddt.v7i6.1512.
127. Patton TF, Robinson JR. Ocular evaluation of polyvinyl alcohol vehicle in rabbits. J Pharm Sci. 1975 Aug;64(8):1312-16. doi: 10.1002/jps.2600640811, PMID 1151703.
128. Holden CA, Tyagi P, Thakur A, Kadam R, Jadhav G, Kompella UB, Yang H. Polyamidoamine dendrimer hydrogel for enhanced delivery of antiglaucoma drugs. Nanomedicine. 2012 Jul;8(5):776-83. doi: 10.1016/j.nano.2011.08.018. PMID 21930109.
129. Bourges JL, Bloquel C, Thomas A, Froussart F, Bochot A, Azan F, Gurny R, BenEzra D, Behar Cohen F. Intraocular implants for extended drug delivery: therapeutic applications. Adv Drug Deliv Rev. 2006 Nov 15;58(11):1182-202. doi: 10.1016/j.addr.2006.07.026. PMID 17107737.
130. Del Amo EM, Urtti A. Current and future ophthalmic drug delivery systems. A shift to the posterior segment. Drug Discov Today. 2008 Feb;13(3-4):135-43. doi: 10.1016/j.drudis.2007.11.002. PMID 18275911.
131. Lee SS, Hughes P, Ross AD, Robinson MR. Biodegradable implants for sustained drug release in the eye. Pharm Res. 2010 Oct; 27(10):2043-53. doi: 10.1007/s11095-010-0159-x., PMID: 20535532.
132. Yasukawa T, Ogura Y, Kimura H, Sakurai E, Tabata Y. Drug delivery from ocular implants. Expert Opin Drug Deliv. 2006 Mar;3(2):261-73. doi: 10.1517/17425247.3.2.261., PMID: 16506952.