Recent Patents on Drug Delivery & Formulation, 2019, *13*, 246-254

REVIEW ARTICLE

Nano-Based Drug Delivery System: Recent Strategies for the Treatment of Ocular Disease and Future Perspective

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ARTICLE HISTORY

Received: August 26, 2019
Revised: October 21, 2019
Accepted: October 29, 2019

DOI:
10.2174/1872211314666191224115211

Abstract: The structure of the eye is very complex in nature which makes it a challenging task for pharmaceutical researchers to deliver the drug at the desired sites via different routes of administration. The development of the nano-based system helped in delivering the drug in the desired concentration. Improvement in penetration property, bioavailability, and residence time has all been achieved by encapsulating drugs into liposomes, dendrimers, solid lipid nanoparticle, nanostructured lipid carrier, nanoemulsion, and nanosuspension. This review puts emphasis on the need for nanomedicine for ocular drug delivery and recent developments in the field of nanomedicine along with recent patents published in the past few years.

Keywords: Ocular drug delivery system, nanomedicine, hydrogels, solid lipid nanocarriers, nanostructured lipid carriers, nanoemulsion, inorganic nanoparticles, patents.

1. INTRODUCTION

The most thought-provoking system to deliver drugs at the target site in a therapeutic dose is the ocular drug delivery system. The complexity in the structure of the eye inhibits the deep penetration of the drug. Tear dilution, tear turnover, and lacrimation are considered as other major obstacles resulting in decreased residence time of the drug. Few conventional drug delivery systems like suspensions, eye drops, and ointments cannot be considered as very effective dosage forms in the treatment of various ocular diseases [1]. Many delivery systems have been discovered in the past few years to overcome the major challenges associated with ocular drug delivery to produce a safe and effective system and to deliver the drug at the desired location. Development of various nanotechnology-based nanomedicines and different novel systems, such as liposomes [2] Solid Lipid Nanoparticles (SLN) [3], Nanostructured Lipid Carriers (NLC) [4], dendrimers [5], polymeric nanoparticles (NPs) [6], inorganic nanoparticles, microemulsion, nanosuspension, nanoemulsion, noisome, resulted in increasing retention time, solubility of hydrophobic drug in aqueous solution, bioavailability, enhancing drug penetration across barriers present in eyes, and targeting specific cells and tissue. Encapsulation of the desired drug in nanoparticle also helps in protecting the drug from getting degraded. This review article is about the recent development in nanomedicine for the treatment of various diseases related to eye [7] and also about recent patents published related to ocular drug delivery (Table **1**).

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2. NEED FOR NANOMEDICINE FOR OCULAR DRUG DELIVERY

Transferring medication through the ocular route is a problematic task due to underlying factors such as accelerated removal of eye-drops from the ocular surface due to rapid nasolacrimal drainage, transportation of drugs across the blood-ocular barrier, and the cornea. Also, drug penetration to the posterior surface of the eye due to cornea, conjunctiva, sclera, and vitreous barriers is inadequate [7]. The permeation of the therapeutic agents through ocular tissue is facilitated by nanomedicines. Current studies in nanomedicines as a therapeutic approach assisted in addressing the principal reason for blindness-related to cataract and diabetic retinopathy by reducing intraocular pressure as the nanomedicines enhanced and improved the drug-release profile and therapeutic profile by reducing the side-effects of drugs. Several approaches like the use of liposomes, SLN, NLC, hydrogel, nanoemulsion, nanosuspension, noisome, polymeric micelles, and inorganic nanoparticles emphasized the need for nanomedicines for targeting ocular diseases [12].

2.1. Liposomes

Liposomes are vesicles that have one or more layers of phospholipid that enclose aqueous phase. The composition

2212-4039/19 $58.00+.00

Table 1. Recent patents of nanomedicine used in ocular drug delivery.

S. No.	Patent Number	Patent Title	Drug	Mode of Administration	Application	Summary of the Invention	References
1.	US9956195B2	Stable Liposomal Formulations for Ocular Drug Delivery	Prostaglandin	Subconjunctival Injection	Used for treatment of intraocular pressure and glaucoma	This formulation helped in releasing prostaglandin $F_{2\alpha}$ for a longer duration that resulted in decreasing IOP for about 4-6 months.	[8]
2	US10272040B2	Liposomal formulation for ocular drug delivery	Latanoprost	Subconjunctival Injection	Used for treatment of Intraocular pressure and glaucoma	The encapsulated drug was released for almost 10 days at a concentration of about 60%.	[9]
3	US20190133931 A1	Subconjunctival depot forming formulation for ocular drug delivery	Latanoprost	Subconjunctival Injection	Used in the treatment of uveitis, cataract, glaucoma, retinopathy, age-related degeneration	Different formulations of liposomes were prepared that help in the treatment of anterior and posterior segments of diseases.	[10]
4	US20180049992 A1	Glycosaminoglycan- coated metallic nanoparticles and uses thereof	Sodium hyaluronan, sodium hydroxide solution, sodium citrate	Topical	Used as a remedy to treat dry eye condition, dry skin, and wrinkled skin	Inorganic nanoparticles such as silver and gold of size 100nm, 250nm which were linked to antibodies, aggrecan, HALPN1. Later, the formulation was applied topically for the treatment of dry eye condition.	[11]

of liposome includes phospholipids, lipid conjugated polymers, and cholesterol. The classification of liposome is mainly based upon the presence of a number of phospholipid layers and size which includes small unilamellar vesicles of size ranging between 10 and 100 nm, large unilamellar vesicles ranging between 100 and 300 nm, and multilamellar vesicles comprising more than a single phospholipid bilayer [13]. The uniqueness in the structure of liposome helps them to deliver hydrophilic and hydrophobic drugs at the site of action. Liposomes are biodegradable in nature due to the presence of a lipid layer on the outer core. The presence of charged particles on the surface of liposome depends on the lipid used in the formulation of liposomes [14].

Integrating penetration enhancing polymers and bioadhesives in liposomal formulations for topical delivery results in enhancing corneal adhesion and penetration of the drug [15]. The liposomal formulation helps in minimizing various effects such as endophthalmitis, vitreous hemorrhage, and retinal detachment which are associated with intravitreal instillation of drugs due to their unique structure framework which entraps both lipophilic and hydrophilic drugs and exerts targeted delivery at the site of action. The low bioavailability of drug associated with topical instillation due to deprived precorneal residence time that is related to rapid nasolacrimal drainage and tear turnover, which majorly causes less absorption via the conjunctiva. Certainly, around l-10% or less of the dose is able to spread across the anterior segment tissues of the eye due to which, only a small portion of the absorbed drug is able to reach the posterior tissue [16]. The fluidity of lipid bilayers, charge on the surface, size, and surface hydration are some properties of liposomes that make them more acceptable for ocular drug delivery and provide them stability. The presence of charge (positive, negative, or neutral) on the surface of liposome determines the interaction of liposome with the ocular surface. High corneal permeation is mostly seen in a positively charged liposome as compared to the negatively charged liposome or with no charge (neutral) liposome [15].

Huang *et al*. (2017) prepared a formulation for the treatment of glaucoma. The liposomal formulation consisted of Betaxolol Hydrochloride (BH) along with Montmorillonite (Mt) to form (Mt-BH-LP) in order to overcome poor ocular bioavailability. From this study, it was concluded that the developed and optimized Mt-BH-LP was effective in decreasing Intraocular Pressure (IOP) and maintaining higher ocular bioavailability [17].

Vallejo JC along with his co-workers developed a topical formulation prepared by loading liposomes with triamcinolone acetonide which was used to deliver triamcinolone acetonide into vitreous cavity and retina of the rabbit. Different formulations were generated and labeled as (TA-LF1 to TA-LF4) out of which the toxicity and tolerability of TA-LF2 were evaluated by cell viability assay and by examining

the eye of rabbit and it was observed that there was no increase in the intraocular pressure and no alteration in the eye of rabbits [18].

Macular Edema (ME), is a disorder related to impairment in retinal capillary permeability [19]. In order to treat this disorder, Li *et al.* prepared a liposome formulation loaded with Triamcinolone Acetonide (TA) drug by using calcium acetate gradient method, and later coated it with chitosan (TA-CHL) to increase the effectiveness of TA. The prepared formulation of TA was found to be safe for ocular delivery. The study was concluded by mentioning that TH-CHL was a more effective novel delivery system, due to its physical stability, high Entrapment Efficiency (EE), sustainable release of the drug, and less toxicity when applied as an eye drop [20].

The uniqueness in the structure and protection mechanism of the eye does not allow the drug to retain for a longer duration of time. Therefore, to enhance the duration of drug release in the eye, Dong *et al*. investigated the liposomal formulation loaded with ibuprofen for topical delivery of the drug by using Silk Fibroin (SF) as mucoadhesive material. A comparative study was performed between SF-coated Liposomes (SLs) and conventional liposomes and the prepared liposomes were evaluated for drug encapsulation efficiency, *in vitro* release, and *in vitro* corneal permeation. The human corneal epithelial cell was used to carry out cytotoxicity studies of the formulation (SLs) and no toxicity was reported in the corneal cell. The study concluded that the SF-coated liposome was more promising in delivering the drug at the ocular site [21].

de Sá et al. with his co-worker prepared topical liposomal formulation integrating voriconazole (VOR) for treating fungal keratitis. Drug entrapment efficiency, average diameter, drug recovery, and Poly-Dispersity Index (PDI) were evaluated as the characterization property of the formulation. Various parameters were also assessed such as *in vitro* mucosal interaction, irritancy levels, and *ex vivo* permeation studies. The EE was found to be 80% and the formulation was termed as 'non-irritant' on performing HET-CAM's test (hen's egg-chorioallantoic membrane test). The study concluded that VOR liposomes had great potential for treating fungal keratitis [22].

2.2. Niosomes

Niosomes are primary vesicles that are bilayered and are composed of non-ionic surfactants which have a unique ability to grasp both hydrophilic (in vesicular bilayer membranes) and lipophilic compounds (in aqueous compartments) [23]. The size of the niosomes prevails between 10 nm to 01 μm. The preparation and modification of niosomes are easy because of the functional group present on their hydrophilic heads. Niosomes are biodegradable and non-immunogenic. They are preferred over liposomes because of various reasons like they are economical and have long storage time (shelf-life) with no special conditions required for handling as well as storage as compared to liposomes. As niosomes can reduce side effects associated with the drug by reducing their systemic absorption and also enhanced the therapeutic effectiveness of the drug, that's why it is preferred drug carrier for ocular delivery of the drug [20].

Niosomes are skilled at providing drug supply in a targeted manner in the ocular cavity. Vesicles in the niosomes act as a storehouse which assists in discharging the drug in a prolonged and sustained manner to the site of action. Niosomes can be instilled into eyes in the form of drops that in-turn enhances the preocular retention on the surface of the eye due to the presence of cholesterol that improves the firmness of the membrane's bilayer of niosomes, thereby reducing the systemic drainage and enhancing precorneal retention on eye's surface. As compared to the stability in conventional dosage forms, the *in vitro* stability profile of niosomes is preferably higher. Niosomes are lipid vesicles that enhanced the rate and extent of drug absorption by the mechanism of loading and passage of the drug via an ocular barrier, thereby modifying the permeability of the conjunctival and scleral membranes of the ophthalmic region thereby enhancing the absorption of the drug. By inhibition of ocular metabolism in the lachrymal fluid, niosomes offer an extended duration of action. Niosomes are highly beneficial in the treatment of ocular hypertension, dry eyes, glaucoma, and eye infection [24].

Allam and co-workers prepared a niosomal formulation to enhance the therapeutic activity of vancomycin which was further loaded into a polymeric solution that changed into a gel (vancomycin niosomal gel) when administered into the eye, that helped in increasing the residence time at the ocular site. Since vancomycin is very effective in eliminating Methicillin-Resistant *Staphylococcus Aureus* (MRSA) infections, therefore, *in vitro* and *in vivo* studies were performed to assess its activity. It was found that the developed formulation enhanced the antibacterial activity up to 180 folds in MRSA- infected rabbits when compared with vancomycin free drug solution which produced its anti-bacterial activity only up to 2.5 folds [25].

Nabarawi and his co-workers developed natamycin (NAT) loaded niosomes in Ketorolac Tromethamine (KT) gels topically which increased penetration rate thereby enhancing the effectiveness of natamycin via corneal tissue by reducing the infection which was associated with Fungal Keratitis (FK). It was found that prepared formulation showed hindrance up to 57.32% when compared with marketed preparation during the *in vitro* study. The formulation also showed promising results in the treatment of candida keratitis as compared to other formulations along with combined marketed formulations (Natacyn and Ketoroline). This showed superlative results of the niosomal formulation in all *in vitro*, *in vivo* experimental, and histopathological studies [26].

2.3. Solid Lipid Nanoparticle (SLN)

SLN is defined as colloidal nanoparticles having a size ranging from 10 nm to 01 μm. The nanoparticle is prepared using synthetic or natural lipids and is suitable for enhancing the delivery of drugs and reduce the toxicity [27]. These are dispersed colloidal systems which have various constituents like steroid, triglycerides, and fatty acids [28]. The solid lipid used in SLN helps in releasing the drug at a controlled rate, by hindering the mobility of the drug in the solid state in comparison to the liquid state [29]. These nanoparticles offer many advantages as compared to other carriers, as they are able to encapsulate hydrophilic and lipophilic compounds.

The problem of toxicity is less due to biocompatibility entrapping the drugs in the carrier [30].

Because of their nano size, SLN crosses barriers of eye such as epithelial barrier, blood–aqueous barrier, and blood–retinal barrier and has been found to be effective for ocular drug delivery as they help in increasing the corneal absorption, thus elevating bioavailability and retention time at the ocular site which facilitates sustained release of the drug [31, 32]. Numerous benefits are associated with SLN such as they help in targeting the drug, provide for high drug loading capacity for either hydrophilic or hydrophobic drugs, having long term stability, and are easy to produce at large scale. Due to their lipophilic nature, penetration of the drug through the corneal site is easy which enhances the uptake by ocular tissue [33, 34].

Eid and co-workers prepared an SLN formulation loaded with ofloxacin, for the treatment of local eye infection by coating it with Polyethylene Glycol (PEG) and chitosan to study the change in trans corneal permeation, retention time, and bioavailability at the cornea. The addition of chitosan provided mucoadhesive strength but the addition of PEG brought a slight change in mucoadhesive strength along with enhancement in the trans corneal permeation. It was concluded from the study that the developed and optimized OFLOX-CTS-PEG-SLN increased the drug released two-three times higher as compared to conventional formulation [35].

Singh and co-workers prepared a formulation by loading highly potent anti-tubercular drug Isoniazid (INH) in SLN using a micro-emulsification technique for the treatment of ocular TB. The toxicity and tolerability of the formulation were determined. Different particulate nature helped INH-SLN in exhibiting high corneal permeation and retention. The prepared formulation showed high aqueous humor concentration, long half-life, and mean residence time supporting the advantageous effect of this formulation. The C_{max} of INH-SLN formulation was found to be 1.5 times higher than the INH-SOL and the AUC was found to be 427.6% [36].

Khames and co-workers developed a formulation through the emulsification-ultrasonication technique by loading Natamycin (NAT) in SLN used for the treatment of Fungal Keratitis (FK). The developed formulation helped to overcome the poor corneal penetration of NAT and to increase the residence time inside the eye. It was found that the antifungal activity of the drug was higher without causing any toxicity to the eye [37].

Tatke and associates used hot homogenization and ultrasonication technique to load Triamcinolone Acetonide (TA) drug in SLN (TA-SLN) and later combined it with gellan gum (TA-SLN-IG) to upsurge the penetration property through deeper ocular tissues. Trans corneal permeability and ocular distribution of the formulation were performed on animals which were grouped to receive either the prepared formulations and triamcinolone acetonide solution (TA-SOL). The result revealed that TA-SLN-IG was able to deliver maximum drug quantity in the deeper ocular tissues which resulted in higher drug concentration in tears as compared to TA-SLN and TA-SOL [38].

Ahmad and co-workers developed a formulation by loading etoposide into solid lipid nanoparticle using melt-emulsification and ultrasonication technique. The optimization of the prepared formulation was carried out using a Box-Behnken design (version 9.0.2.0, Stat Ease Inc, USA). Different parameters were used to characterize the size of a formulation, penetration ability, and entrapment efficiency. The scintigraphic analysis was performed on albino rats in order to determine the concentration at the ocular site. The results presented in the study concluded that SLN loaded with etoposide helped in maintaining dose at the desired concentration without any serious effect [39].

2.4. Nanostructured Lipid Carrier (NLC)

NLC is considered as the second generation of nano lipid carriers. They comprise a blend of biocompatible lipids, surfactants, and drugs. Due to their biocompatibility behavior and stability, NLC is a better option in comparison to SLN. NLC was introduced to tackle the problems of drug escape via matrix during storage and also to overcome lower drug loading efficiency. Various methods are used to prepare NLC for instance cold homogenization, hot-emulsification-ultrasonication, and hot homogenization [40].

For ocular administration, NLC displays the most promising results because of their better biocompatibility. They also possess modified drug release kinetics. The biocompatible nature makes it a promising approach for drug delivery. Apart from all these characteristics, NLCs also possess non-immunogenic, biologically non-toxic, and compatible nature. As the majority of the drugs are lipophilic in nature, their biocompatibility with lipids and solubility is a major aspect of the formulation as NLC [40].

Almedia and co-workers designed an eyedrop of ibuprofen in the form of dispersion that encompassed a combination of lipid nanoparticle and a thermoresponsive polymer that had a characteristic of mucomimetic properties (Pluronic F-127). The formulated dispersion was then examined for its cytotoxicity in Y-70 human retinoblastoma cells and significant cytotoxicity was observed. NLC-related cytotoxicity was later checked by Alamar Blue reduction assay, which displayed it to be nontoxic. Later, the result displayed enhanced bioavailability and therapeutic efficacy along with sustained-release drug profiles of ibuprofen [41].

2.5. Inorganic Nanoparticles

Inorganic nanoparticles (IP) are the new era in the field of nanotechnology having various desirable properties like high physical stability, large surface area, and good catalytic property. They are multifunctional in nature and hold specificity in biological functions and are more compatible as compared to organic nanoparticles in the biomedical research field. The different types of pharmaceutical inorganic nanoparticles researched extensively to deliver drugs include gold nanoparticles, silver nanoparticles, Iron oxide nanoparticles, Quantum Dots (QD's), Silica nanoparticles, fullerenes, and carbon nanotubes [42].

The inorganic nanoparticles are mostly comprised of two regions: a core comprising the inorganic constituent (such as gold, quantum dots, silica, or iron oxide) and a shell region

consisting mainly of organic polymers (or metals) that help in providing an appropriate substrate to protect the core region from unsolicited physicochemical interactions thereby, protecting the drug by providing shield and therefore preventing degradation [43]. Gold nanoparticle possesses intrinsic beneficial properties like antiangiogenic and anti-inflammatory properties that can be an added advantage when delivering drugs for ocular diseases. Besides this, these nanoparticles help in retaining the drug for several weeks at the desired level. Glaucoma, retinal diseases, AMD, corneal fibrosis, retinoblastoma (RB), ocular inflammation are some of the disorders that have been efficiently treated using inorganic nanoparticles as drug delivery systems [44].

Li and co-workers used a simple one-step method to develop nanoparticle to treat dry eye disease which was associated with the decrease in the production of tears and inflammation of conjunctiva and cornea. The formulation of nanoparticle consisted of gold nanoparticle capped with polycatechin later loaded with amfenac (AF) drug which is an NSAID. The formulation (Au PC-AF NP) possessed anti-inflammatory and the anti-oxidative effect that helped in treating dry eye disease. The prepared formulation was delivered as a drop at the corneal site to release the drug at the desired rate without causing any toxic effect. The anti-inflammatory effect was shown by the drug whereas the anti-oxidative effect was shown by polycatechin [45].

Cataract disorder is caused due to clouding of the eye lens thus hindering the passage of light [39]. Therefore, to treat this disorder, Wang and co-workers articulated a formulation using gold nanoparticle (Au-NP) fabricated by extract of bark *Coccinia grandis* and loaded it with N-Acetyl Carnosine (NAC) for treating cataract. The formulation was found to be spherical in shape, and even in its size. The bioavailability and biocompatibility of the drug were found to be higher when loaded in gold nanoparticle (Au-NP) at the target site with no significant cytotoxic effect. This research could further be used in the advanced treatment of cataract [46].

Maulvi and co-workers established a formulation by using gold nanoparticles loaded with timolol for the treatment of glaucoma. There were two methods used for embedding Timolol in Au-NP. One method involved formulating Au-NP-SS by soaking Au-NP in the drug solution. Another method involved combining Au-NP with contact lenses. The study examined that the properties like swelling and optical transmittance of contact lenses did not change even though they were loaded with Au-NP. *In vivo,* pharmacokinetic, and pharmacodynamic studies helped in elaborating the comparison between the prepared formulation and conventional method, in regards to the concentration of timolol. The results obtained gave knowledge that there was a considerable decrease in the IOP due to the substantial amount of drug delivered at the desired site. Later the study was concluded by depicting that the use of Au-NP improved the uptake of the drug by contact lenses without any alteration [47].

To effectively treat glaucoma, Kim and co-workers developed a formulation consisting of Amino-functionalized Mesoporous Silica (AMS) which acted as a carrier for the drug, brimonidine that helps in the treatment of glaucoma. Encapsulation of brimonidine into AMS helped in increasing the residence time of drugs at the corneal site when applied topically on the rabbit's eye. The efficacy of the prepared formulation was compared with the marketed formulation and it was found that brimonidine-AMS resulted in decreasing the intraocular pressure more than the marketed formulation and the bioavailability of drug was found to be higher in the brimonidine-AMS formulation [48, 49].

2.6. Polymeric Micelles

Polymeric micelles are nanoscopic core in a shell structure formed by amphiphilic copolymers. They have a size varying from 10 nm to 100 nm with excellent property of solubilizing poorly soluble drugs and surface modification is also possible. Being an effective drug delivery system, polymeric micelles have been verified to be effective carriers of hydrophobic drugs and have helped in protein delivery also via biological membranes. They are also responsible for enhancing the stability of unstable drugs, and to regulate the release pattern of drugs [50].

Li and co-workers along with his co-workers designed Diclofenac loaded Rb1 micelles (Rb1-Diclofenac micelles) and evaluated them for ocular permeation and anti-inflammatory effects. Rb1-Dic micelles were tested on the rabbit's eyes and were found to be non-irritant. Rb1, when compared with commercial diclofenac eye drops, proved to enhance the *in vivo* corneal permeation and anti-inflammatory effectiveness [51].

In another study, Xu with his co-workers developed Nifedipine loaded in PLA-PEG micelles. This was used as eye drops which prevented cataract. This facilitated in refining anticataract activity by showing a negative calcium ion influx. It also displayed acceptable results by skillfully hindering the anticataract activity via constraining the influx of extracellular calcium ion along with pronounced biocompatibility and bioavailability [52].

Mandal along with his co-workers designed a formulation that was composed of two polymers, octoxynol 40 and polyoxyethylene hydrogenated castor oil 40. Here, proteins and peptides were loaded in a polymer which was further compressed in a core of organo-micelles, later loaded in a layer of similar polymer to form an aqueous stable nano micelles formulation. An *in vitro* study was carried out for octreotide laden multi-layered nano micelles in PBST (Phosphate Buffered Saline with Tween) and STF (Simulated Tear Fluid) which displayed that octreotide continued to release for 27 days in STF and 11 days from PBST formulation. This study explained the effective delivery of small peptide due to its biodegradable nature and high loading capacity [53].

2.7. Nanosuspension

Nanosuspension is another nano-controlled release system used in the treatment of various diseases associated with the eye. These are the colloidal discrete system which is heterogeneous in nature and are stabilized by surfactant [54]. Their size ranges between 10 to 1000nm which helps them to overcome the barriers present in ocular drug delivery [55]. Nanosuspension can be considered as a shelter for solutions that display poor dissolvability in lachrymal fluids. They can

serve as carriers for hydrophobic solutions to elevate the dissolvability of drugs [56].

Güven and co-workers developed a nanosuspension formulation of olopatadine hydrochloride loaded in polymeric Kollidon® SR nanoparticles for the treatment of allergic eye disease. The developed formulation was spherical in shape with good entrapment efficiency, drug loading percentage, and persistent drug release patterns. In comparison with other polymeric nano-formulations with variant polymer ratios such as NP-1, NP-2, NP-3, it was found NP-2 exhibited high drug loading efficiency, along with increasing drug release pattern. Later it was concluded that the formulation could deliver the drug for a longer duration of time, at a sustained rate [57].

Ahuja along with his co-workers formulated Eudragit S100 based nanosuspension encapsulated with diclofenac using the nanoprecipitation technique. The *in-vivo* studies were performed on the PGE2-induced ocular infected rabbit model showed higher inhibition of PGE2 induced polymorphonuclear leukocytes migration and lid closure score by prepared formulation on comparison with diclofenac's aqueous solution. Therefore, it was concluded that Eudragit S100 nanosuspension proves to be a potent and better anti-allergic agent for ophthalmic delivery [58].

Verma along with his co-workers designed chitosan nanosuspension encapsulated with itraconazole for ocular delivery. The above-mentioned formulation was developed by co-precipitation of itraconazole and chitosan and was then evaluated for zeta potential, particle size, solubility, and EE. The optimized nanosuspension formulation on the addition of Poloxamer-188 displayed a 12-fold increase in aqueous saturation solubility of itraconazole and resulted in an effective *in-vitro* discharge of the drug. A comparative study held between itraconazole nanosuspension and itraconazole commercial suspension performed on goat's cornea displayed a relatively greater percentage of cumulative permeation of medication as compared to that of commercial suspension of itraconazole. Thus, the study concluded that formulation of itraconazole based nanosuspension can prove to be a potent, non-inflammatory, and acceptable way of drug delivery [59].

2.8. Hydrogels

Hydrogels can be defined as cross-linked, polymeric assemblies which consist of water. Hydrogels have the unique ability to absorb water because of their hydrophilic functional group. Hydrogels can be prepared using a natural or synthetic polymer. Hydrogels are widely used for ocular tissue engineering purposes. Modification of hydrogels is commonly done for ocular drug delivery for the treatment of ocular diseases. It is said that high hydrophilicity in medicament in the hydrogel leads to faster liberation of the drug [60].

Liu and co-workers designed a formulation of a degradable microsphere which was able to deliver aflibercept in a précised manner. They suspended the drug in poly(ethylene glycol)-co-(l-lactic acid) diacrylate/N-isopropyl acrylamide (PEG-PLLA-DA/NIPAA) hydrogel that was thermoresponsive in nature. With the help of radiolabelled aflibercept Iodine-125 (^{125}I), they characterized EE and *in vitro* drug release profiles, which further displayed the variations in dry weight that gave degradation profile of hydrogel. Finally, the cytotoxicity of the byproducts of the degraded drug delivery system (DDS) was evaluated by quantifying cell viability via the LIVE/DEAD® assay technique. Later, the study revealed that the microsphere laden hydrogel system was safe and effective for the treatment of ocular neovascularization in comparison with bolus injection loaded hydrogel [61].

Silicon-based imprinted and non-imprinted hydrogels were formulated by Silva and co-workers where they encapsulated antibiotic moxifloxacin hydrochloride (MXF) and checked its therapeutic effectiveness as Soft Contact Lenses (SCLs). It was found that no specific variations were observed in the release between TRIS + D and TRIS/AA hydrogels which is silicone (3-tris (trimethylsilyloxy) silylpropyl 2-methylprop-2-enoate). TRIS and TRIS/AA + D hydrogels displayed faster release and sustained release, respectively. Hence, this comparison proved to be useful for imprinted materials for daily therapeutic SCLs [62].

2.9. Nanoemulsion

Nanoemulsions are a nanosized novel drug delivery system found to possess kinetic stability that persists for months, stability against any change in temperature and dilution [63]. Nanoemulsion is preferred for ocular drug delivery because it provides high penetration of the drug into deeper ocular tissue through the cornea by releasing the drug at a sustained rate. Nanoemulsion requires low formulation cost and is less viscous in nature [64]. This colloidal dispersion provides an improvement in ocular residence time and enhanced corneal drug permeation. Interaction of nanoemulsion with the lipid layer of the tear film helps the drug to stay for a longer period of time in the conjunctival sac and act as a drug depot [65].

Mahboobian and co-workers prepared formulation of Brinzolamide (BZ) loaded in Nanoemulsions (NE) for the treatment of glaucoma. The optimized nanoemulsion formulation showed high corneal penetration by 2 to 3-fold higher when compared to the marketed ocular suspension (Azopt). The *ex vivo* and *in vivo* studies revealed that the prepared formulation was safe and had a high penetrating effect as compared to Azopt [66].

NE is considered to be beneficial in ocular drug delivery as they help in enhancing the bioavailability of the drug. Shah *et al*. formulated the nanoemulsion formulation of Moxifloxacin to enhance the therapeutic efficacy of the drug. This study showed that the drug concentration at the target site was higher. When the irritation study was performed, it showed good tolerance of the formulation. After noticing the beneficial effect of this delivery system, it was concluded that the drug was able to produce a therapeutic effect even at low dosing level [67].

CONCLUSION

Conclusive shreds of evidence obtained through various researches have provided for enhanced residence time, bioavailability, biodistribution, and biocompatibility of the numerous formulations of drugs. Liposomes, nanosuspen-

sions, hydrogel, NLC (nanostructured lipid carrier), SLN (solid lipid nanoparticles), and polymeric micelles are some of the several nanoformulations that have been investigated that were found to deliver the drug at therapeutic dose in sustained manner and also helped in cumulative enhancement in the bioavailability of drugs at the target site. Drugs incorporated in different nanocarriers proved to be beneficial in treating various ophthalmic disorders like ARMD (Age-Related Macular Degeneration), dry eye, uveitis, choroidal neovascularization, conjunctivitis, and glaucoma. In the era of conventional and nanomedicines drug delivery systems, different research works with promising results will continue to come.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

The supporting grant is given by the All India Council for Technical Education (AICTE, Government of India) for this work. AICTE GPAT Scholarship ID 1-4049434203.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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