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Nanoformulations and Highlights of Clinical Studies for Ocular Drug Delivery Systems: An Overview

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ABSTRACT: Several ocular drug delivery (ODD) systems, like hydrogels, microparticles, nano-emulsions, micro-emulsions, and liposomes have been researched, which can govern the drug release and sustain therapeutic levels for a delayed period in the eye. While new drugs targeting methods to the eye are possible by various nanoparticles. Presently in the market, there are fewer choices and need for novel nano-ocular delivery systems as well as therapies for prolonged delivery to the anterior and posterior eye segments. The primary objective of this article is to summarize current discoveries and proven activities of different nano- and microsystems in ODD. This article also depicts some regulatory updates along with the patents granted to the inventor for their work on ODD. Overall, a thought of how the different forthcoming of nanotechnologies like nanoparticles and nanomedicine can be used to investigate the frontiers of ODD and treatment can be withdrawn by this article.

KEY WORDS: nano-ocular drugs, ophthalmic, formulation, patents

I. INTRODUCTION

For the treatment of eye diseases and to the posterior segment, several of the novel nano-delivery systems are useful. Ocular drug delivery (ODD) to the eye has been widely investigated to treat eye diseases such as macular edema, diabetic retinopathy, and age-related macular degeneration. The World Health Organization (WHO) showed the report that approximately 2.2 billion people face a problem of blindness or vision impairment, in which 1 billion face vision impairment problem that may be treated at an early phase or can find out in early stage. WHO also listed some causes for the same as uncorrected refractive errors, cataract, age-related macular degeneration, glaucoma, diabetic retinopathy, corneal opacity, and trachoma.[1,2] The eye is a complex organ and well protected from the surroundings by various barriers and defense mechanisms with unique anatomy and physiology, hence, ODD, particularly in the retina, is a difficult challenge.[3,4] The barriers like tears, cornea, conjunctiva, sclera, choroid/Bruch's membrane, retina, blood-retinal barrier, etc., limit the ODD, drug loss and ultimately it demands the novel formulations.[5–8] Since years many drug-delivery systems (DDS) have been formulated to target drugs at the site of the ocular surface.[9,10] Drug delivery at site

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targeted tissues of ocular is restricted due to many barriers like dynamic, precorneal and static ocular. Due to these barriers, the required quantity of drugs does not reach a specific site for a longer period. From the last two decades, ocular delivery of drugs has been accelerated for the advancements in developing a safe, novel and as per patients need and various methods developed for delivery of the drug, which leads to surpass these barriers and maintain the effective drug quantity at the site targeted.[11] Several nano-formulations that have been developed and tested for ODD over the years are depicted in Fig. 1. Many research studies especially on nano-sized drug carriers have been conducted in the field of ophthalmology.[12,13] Nanoparticles (NPs), as the name implies are particles which have different size and it depends upon the target-use, which may or may not have drug molecule. The drug may be dissolved or combined with the NP matrix or it is encapsulated giving rise to various forms of NPs, nanospheres, or nano-capsules. Every one of these terms implies their characteristics, for example, they are nanosized particles. The most adaptable DDS is drug-loaded NPs, as they conquer physiological obstructions and ties the drug to intracellular compartments by ligand-mediated targeting mechanisms.[14–16]

For the advancement in ODD and to enhance the greater efficiency, the various conventional systems now can modify to the novel DDS like micro-emulsions (MEs), liposomes, NPs, and dendrimers for ocular diseases. A novel ODD system (ODDS) should have some unique features like broad application range, enhanced solubility[18,19] non-irritant and improved shelf-life like some novel ocular DDS NP, liposomes, nano-emulsions (NEs) and solid lipid NPs[20–25] are proven to improved retention and uptake into cornea; and reduced drug toxicity. This article provides an overview of various novel ocular DDS designed for the effective treatment of ocular diseases with regulatory approvals and patents granted to the various scientist for their novel work.

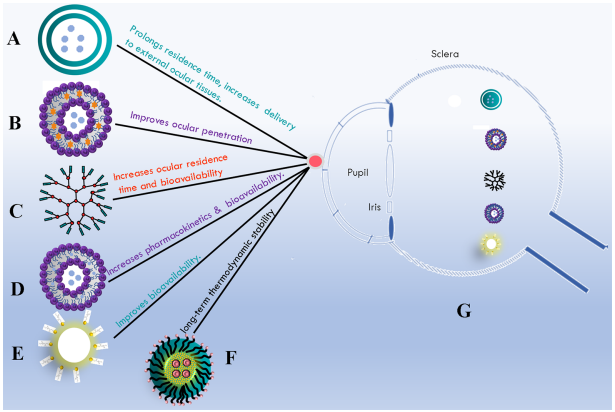

FIG. 1: Ocular nano-delivery systems. (A) Nanospheres, (B) liposomes, (C) dendrimers, (D) niosomes, (E) microemulsions, (F) nano-emulsions, (G) eye diagram (based on Battaglia et al.[17]).

II. VARIOUS NANO-SYSTEMS DESIGNED FOR ODD

Various conventional ocular DDS are employed for the treatment of eye like topical liquid/solution eye drops, emulsion, suspension, ointments, etc. This conventional formulation is with lots of limitations and produces adverse reactions upon systemic absorption.[26–28] Many DDS, like micro/NEs or nano-particles, hydrogels and liposomes are proven to enhance ODD across the biological barrier and ocular environment and reduced toxicity.[29–32] Hence, to reduce product-based side effects and to target an accurate amount of the drug in ocular tissues, current research is now being focused on evolving other new methods of ODD. In the below part, an effort has been taken to discuss the recent advances made in nanotechnology in the past decade to improve ODD and summarizes the proven nano-DDS used in ocular research.

A. NPs

NPs are a category of materials that can merge particulate substances having minimum any one measurement below 100 nm. They are nano-size particles ranging from 10 nm to 500 nm, manufactured of modified or semisynthetic polymers that are biodegradable. NPs can be of different structures such as nanospheres, nano-capsules (Fig. 2), and nanocrystals.[33] They can serve a couple of favorable benefits for ODD like they are affable to functionalization and can be tweaked to achieve explicit targets. Additionally, these could exhibit amazingly supportive for the effective transport of OD as they can accomplish drug loading and efficient mucoadhesion. They can intently interact with the mucin layer of the ocular surface to retain the drug in the cornea.[34–36]

NP formulations have additionally been accounted for to minimize the incidence of ocular irritation and toxicity because of their littler molecule size.[37,38] De Campos et al. found prolonged retention of chitosan NPs at the ocular mucosa after effective dosing in animals. This colloidal carrier stayed appended to the cornea and conjunctiva for 24 h. The advantages of such a system in ODD incorporate their ability to contact intimately with the corneal and conjunctival surfaces, in this manner improving delivery to outer ocular cells without trading off internal ocular structures and systemic medication introduction, and to give these target tissues long haul medication levels. It can prompt

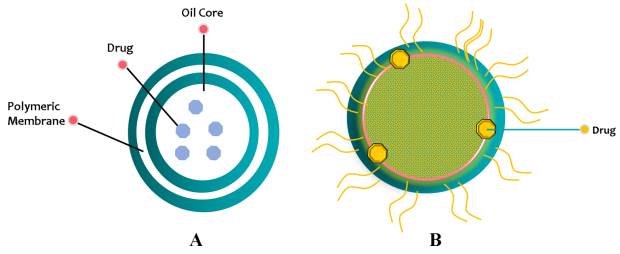

FIG. 2: Basic structure of nanospheres (A) and nano-capsules (B)

tolerating that NPs have potential as DDS to the ocular mucosa.[39] One investigation indicated that NPs made up of albumin might be a successful DDS for ocular issues, similar to CMV retinitis, because it was biodegradable, non-poisonous and have the nonantigenic characteristic. They have a high substance of charged amino acids; these NPs permit the adsorption of decidedly charged GCV or negatively charged particles like oligonucleotides.[40]

Irache et al. carried out a study using polymeric NPs having Eudragit® RL100 and formulated using the nanoprecipitation technique for ocular delivery of Amphotericin B towards Fusarium solani. The particles were having a size range of 130 to 300 nm, 60% to 80% encapsulation efficiency, and a +ve zeta potential. They do not show any signs of eye irritation and showed the stability at temperature +4°C and also at room temperature for two months.[41] Das S. colleagues solved the problem of drug drained out through the nasolachrymal drainage system, they developed levofloxacin which encapsulated by poly(lactic-co-glycolic acid) NPs and its parameters were examined like zeta potential, *in vitro* release of the drug, particle size, and also parameter like *ex vivo* trans-corneal permeability. The precorneal residence time was done on albino rabbits using scintigraphy after carrying out the radiolabeling of levofloxacin at Tc-99m. The evaluation was undergone for ocular tolerance by using hen's egg chorioallantoic membrane (HET-CAM) test. The NPs formulated in spherical shape have a mean particle size of about 190 to 195 and –25 mV zeta potential. The drug bounded with polymers was found to be 85%. The release of drugs *in vitro* shows similar results as it was shown before but it helps in the extended-release of drugs for about 24 h. The microbiological assay shows similar results of inhibition as compared with the marketed formulation. The formulated nanosuspension was retained for a prolonged duration in the eye and also it does not drain out quickly from the marketed preparation.[42] Similarly, a study on ocular disposition using poly-hexyl-2-cyanoacrylate NPs in aqueous humor, in tears, conjunctiva and cornea of albino rabbits was designed by Gupta et al. using radiotracer techniques. This study predicted that most of the NPs easily drained out and only a small amount adheres to conjunctival and corneal surfaces.[43] De Campos et al. developed chitosan (CS) NPs for ODD by identifying its interaction *in vivo* with the ocular mucosa and also its toxicity identification in conjunctival cell cultures. In which NPs of fluorescent (CS-fl) was formulated by a method using ionotropic gelation. The *in vivo* CS-fl NPs interaction in the rabbit conjunctiva and cornea was identified using the confocal microscopy and spectrofluorometry. Its toxicity was analyzed in a human conjunctival cell line by knowing viability and cell survival. It was seen that for CS-fl NPs deposition of CS-fl in conjunctiva and cornea is more for CS-fl NPs with the solution of CS-fl, the deposited amount in the eye is constant for about 24 h. Confocal studies show that NPs can easily penetrate in conjunctival and corneal epithelia. Cell survival after 24 h by incubation with CS NPs was more and the cells which are recovered its viability were obtained about 100%. This study gives justification that CS NPs are effective as vehicles in ODD.[44] Giannavola et al. evaluated nanosphere colloidal suspensions containing acyclovir as potential ophthalmic DDS. They prepared nanospheres of poly-D,L-lactic acid (PLA). Experiments were done by *in vivo* study on male rabbits of New Zealand. For

PLA nanospheres ocular tolerability was checked using a modified Draize test. It shows that PLA nanospheres which are coated by PEG give a potential ophthalmic delivery system and are used for treatment in ocular viral infections.[45] Recently a new ocular DDS was designed using biodegradable nanospheres composed of poly-ε-caprolactone (PCL) which is coated by hyaluronic acid (HA), bio-adhesive polymer, which may lead for a longer duration of action and also with the effective application. A radioimmunoassay method was mainly applied in the identification of the amount of HA present in serum but was carried out in the identification of HA on nanospheres. The results of it showed that HA is strongly bonded by nanospheres which is positively charged using the cationic surfactant. This is a stable method and is not enhanced with any dilution. They proposed a very easy method for the formulation, which leads to forming a stable HA and bonded by HA-coated nanospheres.[46] The formulation of nanospheres using flurbiprofen which is incorporated formulated by solvent displacement technique for identification of release of flurbiprofen by polymer matrix, drug-polymer physicochemical interactions, and permeation of drug in the eye which is formulated using colloidal system. The nanospheres which are formulated have about average size of 200–300 nm and having a negative charge (ξ-potential around −25 mV). The *ex vivo* study of corneal permeation showed that nanospheres which are loaded by flurbiprofen increases twice the penetration of the drug as compared with marketed eye drops having poly (vinyl alcohol) and four times increase in penetration by flurbiprofen at pH 7.4 of phosphate buffer. For each cornea, the hydration level of it was carried out for knowing the chances of damage to the cornea.[47] Khattab et al. detected the increase in the oral bioavailability of drug Olmesartan Medoxomil (OM) which is poorly water-soluble because it is prepared using lyophilization technique of oily-core nanocapsules. A comparative study of pharmacokinetic was carried out in rats for polymeric oily-core nanocapsules after the preparation and lyophilization which is compared by marketed preparation of tablets which gives the enhancement of OM in oral absorption. The study concluded that the preparation using lyophilized oily-core nanocapsules for the drug OM gives effective results for its oral bioavailability and also its therapeutic effect and also compliance of patients.[48] NPs incorporating Cyclosporin-A with chitosan were tested on were male albino rabbits, and had an average size of about 293 nm, and zeta potential about +37 mV and colloidal carrier remained for 24 h attached to conjunctiva and cornea. The outcome of the study suggested prolonged residence time, enhanced towards tissues of external ocular delivery without the barrier of the structure of inner ocular and exposure of drug systemically and tissues targeted by levels of prolonged time of the drug.[49]

B. Niosomes

Niosomes composed of lamellar structures formed by a non-ionic surfactant (Fig. 3), formulated by the thin-film hydration method. The non-ionic surfactants can be easily combined by alkyl or dialkyl polyglycerol ether group, lipids and cholesterol.[50] They are biocompatible surfactants, non-immunogenic and biodegradable having size ranging from 10 nm to 1 μm.[51] They additionally show fusion, accumulation, the release of drug

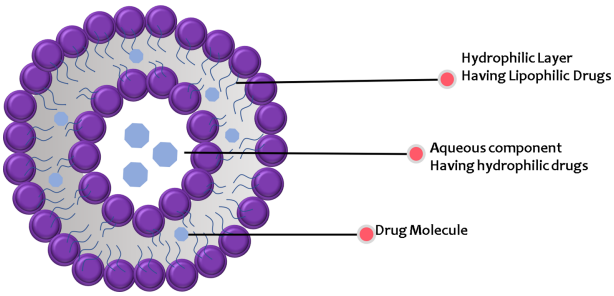

FIG. 3: Basic structure of niosomes

which is entrapped, fluid suspensions experience hydrolysis due to encapsulation, and need specific machines for obtaining multilamellar vesicles which lead to an increase in cost.[52] Niosomes also display for hydrophilic drugs greater ocular bioavailability when they are compared by liposomes. This is due to surfactants that show the increase in penetration and eliminate mucus membrane and it leads to degrading the in-between complexes.[53]

The research shows that acetazolamide-niosomes which is coated by Carbopol® (bioadhesive effect) for the treatment of glaucoma. The drug has less permeability co-efficient and low solubility (0.7 mg/mL) hence it needs to administer frequently. The group of scientists carried out a study by comparing niosomes coated by an aqueous suspension having a dispersing agent like 1% w/v of Tween® 80. They concluded that the concentration of acetazolamide in aqueous medium (applying microdialysis method) is twice with niosomes by comparing it using aqueous suspension and it gives prolong effect; showing the outcome as 6 h with niosomes and 3 h with the aqueous suspension.[54] Gentamicin is an antibiotic which is water-soluble that studied in niosomal system by using dicetylphosphate, Brij 35, Tween® (60 or 80), and CH. When the drug is released *in vitro*, the study shows that the drug concentration is more in vesicles and has a slow release of drug as compared by aqueous solution. The study predicted that vesicle size is according to the quantity of cholesterol and type of surfactant. The molar ratio of 1:1:0.1 (Tween® 60:CH:dicetylphosphate) has the capacity higher for drug entrapment (92%) and a higher rate of drug release about 8 h after administration (66%) and it also does not show any irritation in the eye.[55] Currently, niosomes (using Span 60) formulation reported by naltrexone hydrochloride (NTX) for ocular delivery, Niosomes were examined as having additives of bilayer membrane and it is formulated using four different techniques. In this research, 5 times enhancement shows in NTX entrapment efficiency (EE%) which was gained by using 2%–5% mol/mol additives. When it was analyzed using differential scanning calorimetry, its thermogram shows that the additives used in the formulation it completely dissolves the gel/liquid and the bilayer membranes may have used up by the additives. The formulated niosomes were when used on the 10 days old hen's chorioallantoic membrane the results showed that it was non-irritant.[56] Durak et al. stated that many nanostructures were used as ODD formulations, and niosomes

showed very high chemical stability and it easily spread on the eye surface and hence it ultimately gives more bioavailability. Niosomes also leads to higher penetration as compared by other formulations. As liposomes and niosomes are the same by their structure but used excipients for niosomes formulation are more stable than liposomes.[57] A team of the scientist investigated the benefits of using non-ionic surfactant vesicles (niosomes) as carriers and used as excipients in ophthalmic controlled delivery using the local antibiotic which is water-soluble, i.e., gentamicin sulfate. Niosomes are formulated by various surfactants (Tween 80, Tween 60, or Brij 35), by using cholesterol and increasing of negative charge using dicetyl phosphate (DCP) in different molar ratios by application of thin-film hydration method. The results obtained give a major change in the release rate of therapeutic drug and also % EE of gentamicin sulphate by the niosomal formulations because of surfactant used, in presence of cholesterol and the presence or absence of DCP. *In vitro* release of the drug proved enhancement in the retention of gentamicin sulphate in the vesicles as compared by the drug solution, it shows the release of drug *in vitro* very slowly.[58] A researcher tested Tacrolimus niosomes of particle size 1.59 ± 0.24 µm, zeta potential 28.03 ± 0.36 mV, rabbits were employed for the finding. Outcomes revealed increased aqueous humor pharmacokinetics, and bioavailability.[59]

C. Liposomes

Liposomes are vesicular systems having cholesterol and natural phospholipids comprising size ranging from 30 nm to some more micrometers. They are biodegradable, biocompatible and having less toxicity and it can entrap both drugs of hydrophilic and lipophilic (Fig. 4). They are easily combined with ligand conjugation leading to an increase in site-specific delivery of drugs.

Ideally, liposomal preparations are used to deposit in the cornea and it accumulates in the eye and it helps in the sustained delivery of drugs and for a longer period.[60,61] A study predicted the influence of using various concentrations of chitosan and different molecular weights for the coating of liposomes having ciprofloxacin. Although liposomes have very little capacity of encapsulation of the coating of drugs it enhances the ocular

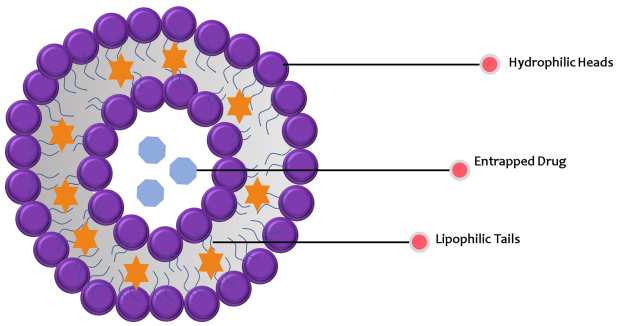

FIG. 4: Basic structure of liposomes

penetration and also gives compatible results of ciprofloxacin antimicrobial activity. An *in vitro* study showed that formulation decreases the growth of *Pseudomanas aeruginosa* for about 24 h in the rabbit's eye. As the chitosan have higher molecular weight and also, its higher concentration enhances the liposomal mucoadhesive property.[62] A study is intended for the formulation of liposomes by coating with a novel excipient having an adhesive property using silk fibroin (SF), for use in topical ODD. The formulation was evaluated for various parameters like the efficiency of drug encapsulation, morphology, permeation *in vitro* into corneal and efficiency of drug encapsulation by SF-coated liposomes (SLs) by comparing it with conventional liposome. Assay of cytotoxicity and cellular adhesion using SLs and SF were examined using human corneal epithelial cells. SLs showed *in vitro* corneal permeation and prolong drug release of ibuprofen as compared by drug solution and the marketed preparation of liposome. The outcome by application of SF-coated liposomes made them as promising ocular DDS.[63,64] A researcher formulated chitosan-coated liposomes (LCHL) for ocular delivery of drugs; he studied the coating mechanism also *in vitro* and *in vivo* properties along with cell internalization of FITC-BSA labeled LCHL and its cytotoxicity in the cell line of rabbit conjunctival epithelium (RCE). In this research, Cyclosporine-A (CsA) was used for encapsulation as a novel drug and examined for various parameters like *in vivo* adsorption of drug and drug release *in vitro*. LCHL shows that to the cells of RCE it gives less toxicity. *In vitro* release of drug calculated gives that LCHL shows delayed in drug release as compared by liposomes which is not coated. In rabbits, the study showed that *in vivo* concentrations of CsA in conjunctiva, cornea and sclera were enhanced due to LCHL. After the result, he concluded that LCHL gives compatible results for a carrier in ODD also it gives results like biocompatibility, longer duration of drug retention and increases in drug permeation.[65] A similar kind of work was done by Li N and co-workers; they prepared liposome loaded with diclofenac sodium. They were coated with LCH that leads to alter the charge on liposomes surface and also enhances is particle size. Due to this, the liposome gives better results in a longer duration for the release of the drug. Liposomes formulated with LCH coating also increases its physiochemical stability at temperature 25°C for 30 days. The property of ocular bio adhesion was examined in rabbit *in vivo* for precorneal retention activity then the results obtained was its increase in retention when compared by liposomes formulated by uncoated and with the drug solution. The outcome suggested that liposomes formulated by LCH gave great results and it enhances the higher efficiency for ODD.[66] Recently, Ciprofloxacin loaded liposomes were evaluated on the rabbit, these spherical particles that had single-walled bilayer and drug entrapment properties ranged by 49.93% to 69.82%. *In vitro* studies suggested the formulation helped in a decrease of *P. aeruginosa* growth for 24 h in the eyes of the rabbit. The penetration of ODD is enhanced and its activity of antimicrobial of ciprofloxacin.[67]

D. Dendrimers

Dendrimers are characterized by three-dimensional nano-size structures like a branch of a tree (Fig. 5). Broad stretching prompts various inside layers having similar units inside

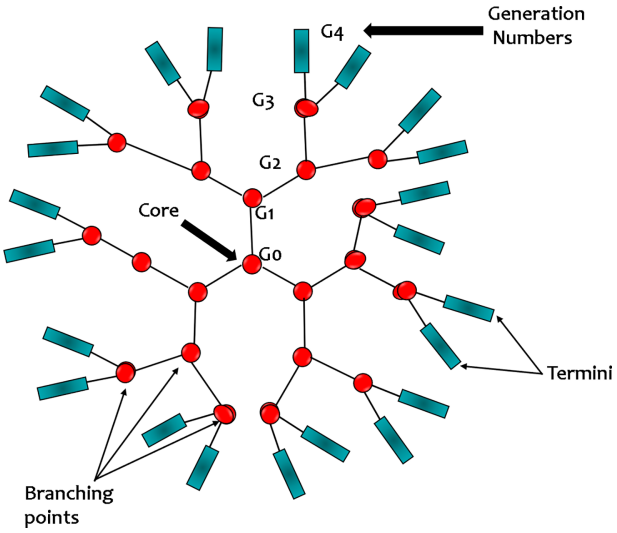

FIG. 5: Basic structure of dendrimers

the central core. Inside the empty spaces of the dendrimer, the spaces are like building squares and have spaces in which the drug molecule are easily entrapped or encapsulated.[68,69] Dendrimers are very feasible ODD because of their size range in nanometer, simple method of preparing its application and due to its property for showing many copies of their surface so that it helps in easy identification of its purpose and use.[70,71]

Dendrimers may alter the drug release pattern depending on the dosage of formulation, as per patient need, disease condition, mainly at site of delivery and intra-ODD mostly used and due to this, it helps in maintaining the dose at the site and also decreases toxicity.[72] The most common dendrimer used in ODD is poly(amidoamine) (PAMAM).[73] Vandamme et al.[74] established utilization of PAMAM dendrimers as ocular vehicles used for the delivery of drugs like tropicamide and pilocarpibe nitrate for activities like miotic and mydriatic. In this study, time for calculating mean ocular residence using fluorescein in saline and solutions of PAMAM was seen in the eye of a rabbit. Fluorescein is used in 0.2% w/v solution of Carbopol as a bio-adhesive polymer. When the outcome of results was compared using polymers, it shows that 0.2% w/v Carbopol and PAMAM solutions give effective results for mean ocular residence time as compared by saline solution. Hence, applications of dendrimers gave better results in enhancing the time for ocular residence, its treatment efficiency, and increase bioavailability. PAMAM dendrimers, when administered by tropicamide and Pilocarpine nitrate, showed an increase in the activity of miotic and mydriatic in albino rats.[74] Recently dendrimers that have phosphorous groups and contains at core one quaternary ammonium salt and have carboxylic acid at the terminal group are prepared by Spataro et al. The formulation was done by using generation 0 (3 carboxylic acid terminal groups) to generation 2 (12 carboxylic acid terminal groups). These

dendrimers easily react by carteolol which is in the neutral form (an antihypertensive drug used in glaucoma treatment) by ionic pair (saline) species. The aqueous solubility of these dendrimers composed of ionic charge is mainly because of the application of generation: generation 0 (3 carteolol) soluble easily, other generations like generation 1 (6 carteolol) and generation 2 (12 carteolol) not easily soluble. By the application of these as a vehicle in formulation for ocular delivery of drugs of carteolol they are examined *in vivo* in rabbits.[75,76] An examination was carried out for knowing the topical property of acetazolamide with poly(propylene imine) dendrimer nanoarchitectures are examined for the pressure of intraocular and its lowering potential. The dendrimers having 5.0 G PPI were formulated by ethylenediamine as the core of a dendrimer by using the divergent method and identified and by using acetazolamide. The formed dendrimer was examined for hemolytic toxicity, decrease in intra ocular pressure and ocular irritation index in normotensive albino rabbits of New Zealand in adult males as a model for *in vivo* evaluation. The study depicted that when applied in less concentration of the dendrimer preparation by aqueous solutions results in some irritation in the eye. The intraocular pressure which is prolonged and sustained shows due to the drug which is incorporated in dendrimer helps in longer retention time in the ocular cul-de sac. Later, the dendrimer by PPI formulation enhances the residence time in the eye and also gives better intraocular pressure by decreasing the effect in glaucoma treatment, which shows by various methods *in vivo* and also *in vitro*.[77]

E. MEs

MEs have the colloidal dispersions consisting of different phases at some specific ratios like an aqueous phase, oily phase, co-surfactant and surfactant. MEs consist of liquids which are transparent due to the size of droplets of dispersed phase having size smaller, mainly below 150 nm.[78,79] A basic structure of the ME oil phase and the aqueous phase are shown in (Fig. 6) below.

These systems increase the penetration of the drug which helps in corneal drug delivery.[80] Kesavan et al. investigated mucoadhesive formulated by chitosan-coated cationic ME (CH-MEs) of Dexamethasone applied for ophthalmic delivery for treating uveitis. Dexamethasone is effectively having the property of anti-inflammatory for

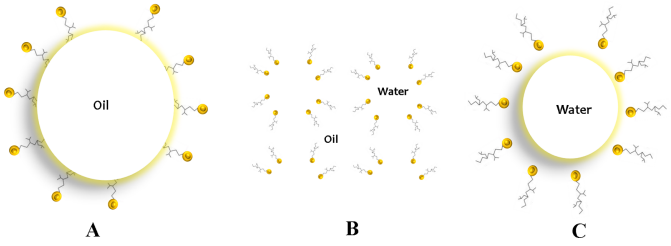

FIG. 6: Basic structure of MEs: (A) Oil phase, (B) water and oil phases, (C) water phase

treating various eye diseases like acute and chronic diseases in uveitis. Also, due to its less solubility in water, it confined the clinical benefits. The *in vivo* effectiveness of the preparations and the formulation from marketed preparation was examined by administering topically in the rabbit model having endotoxin-induced uveitis. *In vivo* studies carried out in the rabbit's eye gives considerable results of anti-inflammatory property of mucoadhesive CH-ME-treated eye as compared by the formulation marketed suspension in the rabbit eye model which is induced with uveitis.[81] *In vivo* studies in rabbits displayed a prolonged effect of the drugs which is incorporated in ME, which results in increases its bioavailability. The reason and mechanism for prolonged drug action are due to the absorption on the cornea of the eye of the drugs nanodroplets, which is not eliminated by lachrymal drainage and it helps as a drug reservoir.[82] Zheng et al. studied ME composed of 0.3% chloramphenicol for the treatment of trachoma and keratitis. The organic phase consists of butanol, isopropyl palmitate and isopropyl myristate and used water as the aqueous phase. He carried out a study and concluded that the drug is having stability for about three months by comparing it by standard eye drops having chloramphenicol. The drug having hydrophilic is incorporated in shells by drops of ME.[83] The stability enhancement was carried out by another researcher in which the study was carried out for ocular delivery of the drug by using ME with moxifloxacin for bacterial keratitis treatment. The size of droplets is below 40 nm and gives the results of sustained drug release. The study gives the results that, *in vivo*, it enhanced the microbial activity on the treatment of bacterial keratitis in the rabbit's eye compared to the results with marketed eye drop preparation.[84] Bharti S.K et al carried out a study of ME in phase transition systems for ocular delivery of drug pilocarpine hydrochloride (ideal for hydrophilic drugs). The study consist of five various formulations having aqueous phase at 5% (w/w) (ME is 5%), 10% (w/w) (ME is 10%), 26% (w/w) (LC), 85% (w/w) (O/W EM) and 100% (solution) with the ideal drug at 1% (w/w). The addition of drug pilocarpine hydrochloride does not show any effect on the results of its phases. Initially, its viscosity was enhanced using dilution by ME 5% to ME 10% then LC, showing the structure of the system, before quantity was decreased in the formulation of EM. Drug release was seen according to the viscosity of formulations, as higher the viscosity the release rate of the drug is also decreased. The response of miotic and duration of action was seen greater in formulations having ME and LC by giving higher bioavailability in the eye. He shows that phase transition by ME having greater results in ODD as it gives the fluidity due to viscosity, as its viscosity enhances the retention time in the eye and ultimately it gives better therapeutic results.[85] In another research study by Chan J and group, Water-in-oil ME (w/o ME) were prepared a formulation with Crill 1, Crodamol EO, Crillet 4 an alkanediol or an alkanol as water and cosurfactant. This system of ME was having a property to convert in phase transition with lamellar liquid crystals (LC) or with bio continuous ME with aqueous dilution. Hypothetically it was stated that phase-transition of ME to LC may be due to tearing and it helps in a longer duration of precorneal and it was examined. The potential of ocular irritation of formulations and its excipients was examined by modified hen's egg choriallantoic membrane test (HET-CAM) and retention of preocular was some preparations were carried out in rabbit's eye

by gamma scintigrahy. The outcome was such that it was non-irritant by using Crodamol EO, Crillet 4 and Crill 1. The co-surfactants which were examined gave the results as an irritant in the eyes and the irritation in the eye is due to the presence of length of the carbon chain. Formulation having w/o in absence of co-surfactant shows the protective effect rather than using in the aqueous phase which is a strong irritant (0.1 M NaOH). Precorneal clearance studies showed that retention in the eye of colloidal system and coarse dispersed is more as compared by aqueous solution, by resulting in no change in between the ME systems (with 5% and 10% water) and by o/w emulsion having water about 85%. On the other hand, LC system was prepared without co-surfactant which gives comparably greater results with other preparations.[86] Recently, Pilocarpine loaded ME shows improved bioavailability in rabbits. M.E has the size of particles (100–150 nm) Drug concentration was 1.70% w/w and retention of 20.8% of the total pilocarpine.[87]

F. Nano-Emulsions

Nano-emulsions (NEs) are biphasic dispersion of two immiscible liquids: either water in oil (W/O) or oil in water (O/W) (Fig. 7) droplets or formulations are combined using an amphiphilic surfactant.[88] The word nanoemulsion usually can be interchangeable as it is used for mini emulsion or with submicron emulsion; also with ME formulations, it should not be confused. NEs as having a similar size of the droplet with ME, have various other differences like prolonging thermodynamic stability and structural behaviour.[89] They are having the property of thermodynamically stable or optically isotropic due to the size of the diameter of a droplet mostly between 10 and 100 nm. Basically, on the relative distribution and its constituents of dispersed phase/phases internally and mostly due to continuous phase, NEs are said as biphasic formulations (W/O or O/W) or multiple NEs (W/O/W).[90]

Their surface tensions are very low, and their droplet size is small which makes them highly absorbable and permeable. Because, NEs have different structure and due to its properties, they are mainly considered as ideal formulations in ocular delivery for most of the drugs. NEs are mostly formulated easily and sterilized, easily incorporate molecules both lipophilic and hydrophilic and are mostly stable.[91] NEs mostly have 5–20% oil/lipid droplets in the formulation of O/W emulsion, in some instances, it may

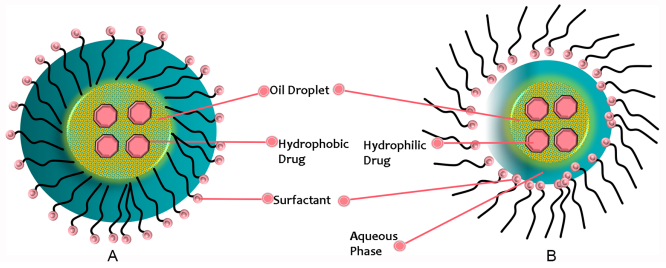

FIG. 7: Nano-emulsions: (A) O/W nano-emulsion, (B) W/O nano-emulsion

be more (about 70%). Lipids/oils used in the formulation of NEs must be such that, it must have drug solubility. From soybean oil extracted re-esterified oil.[92–94] The prolong the duration of its stability is due to the small size of droplets, which gives the conventional phenomenon of its destabilization like sedimentation, creaming and coalescence. Mostly Brownian motion is sufficient for gravity or viscosity as it enhances its kinetic stability. In the parenteral dosage form, NEs were mostly capable of solubilizing and it also not let the drug degrade in various environmental conditions (pH, oxidation, hydrolysis) and it helps in target organs so that it can give increase the effect of retention time and also increase its permeability.[95,96] Drug release by NEs can be done by partitioning with oil and into the surfactant layer and then in a layer of the aqueous phase. The drug which is solubilized diffuses out by oil and it comes in water contact and it leads to nanoprecipitation. This helps in enhancing the surface area of the drug slowly and leads to dissolution according to the Noye-Whitney's equation. The drug release patterns may be enhanced at every single step and hence it leads to varying the drug release of NE and gives the sustained and controlled release system.[97] Salimi designed a novel NE system of drug celecoxib (CXB) as on ocular delivery of drug system to know the physicochemical characteristics and also permeability in the rabbit's cornea to increase in drug penetration. The drug permeation percentage by rabbit cornea was seen in NE component NEC-1 is (6.1%) and (NEC)-5 is (15.73%) and respectively. All NE preparations having varying compositions and their properties give enhancement of partitioning, permeability coefficient and flux in the rabbit's cornea. The study shows that a small change in composition and quantity of NEs may lead to a change in physicochemical properties and parameters of permeability when the drug is diffuse by NE formulations. This is due to a change in the corneal structure and also in presence of NECs.[98] Nowadays Celecoxib NEs are formulated by examination of its solubility in various parameters like in surfactants, cosurfactants and oils. It helps in identifying the pseudo-ternary phase diagram, the optimum ratios used and applied full factorial design using 3 variables at levels 2 and it gives eight formulations. The formulated NEs were examined for pH, particle size, viscosity, stability, *in vitro* drug release, and corneal rabbit permeability. The results gave the mean size range of droplet of NE formulations was in 6.96–26.65 nm size range and pH 6.5–6.9. The viscosity was in the range of 118–245 cps, drug release was showed that 82.6 % and within 24 h of the experiment. The drug percentage shows minimum and maximum by the rabbit's cornea was shown in NE component NEC-1 is (6.1%) and (NEC)-5 (15.73%). This study gives that small change in quantity and NEs composition leads to a change in physicochemical properties and also in permeation of drugs from the NE formulations.[99] A group of researchers formulated NE system having triacetin, isopropyl myristate, ethyl alcohol and Tween 80 to enhance its permeability of lutein and also its solubility and also gives medication effectively in macular degeneration. The pseudo-ternary phase diagram was done to know the region of self-emulsification. Eight formulations were chosen to know the properties of each formulation. They show and evaluated for various parameters like stability, drug solubility and turbidity. The NEs loaded with lutein gave an increase in the release of lutein and sustained release. Also, when the lutein

formulated by using starch and oil had restricted releasing of the drug below 5%. The formulated NE by lutein is an alternative for the delivery system of lutein.[100] In summary, the increasing influence of NEs in every aspect of drug delivery NEs is expected to be the novel delivery system in research and development. Also, many difficulties still need to be considered to enhance the market of pharmaceuticals so that it can go-ahead from the laboratory to the patient bedside.

III. CLINICAL STUDIES ON NOVEL ODD SYSTEMS

Human trials always provided a piece of evidence for the efficacy and safety of a drug when conducted ethically for the betterment of society, some recent clinical studies performed worldwide on novel ODDS are summarized below:

A. Study Title: Comparison of Tear Evaporation Rate with Systane Complete in Dry Eye and Non-Dry Eye (BULLDOG) (NCT04091581)

The purpose of this clinical intervention was to compare the tear evaporation rate, calculated by an ideal evaporimeter, before and after an hour of application of eye drop having nano-sized droplets which is introduced. This research work is sponsored by the University of Waterloo-Canada, Ontario, where 36 participants both male and female 18 years and older were enrolled. The study is going on in Canada, Ontario. Inclusion criteria were kept flexible for all the volunteers. The drug and intervention used were Systane, which was introduced and the rate of evaporation was assessed. It is a Phase 4 study where primary outcome measurement was an alteration in the rate of tear evaporation at the following time duration: baseline (before instillation); 10, 30, and 60 minutes after installation. The Principal Investigator for the current study is Lyndon Jones, PhD, FCOptom Centre for Ocular Research & Education. Since the study is currently going on no results are posted yet.[101]

B. Study Title: Study of Efficacy and Tolerability of SYSTANE Complete in Patients with Dry Eye Disease (NCT03492541)

The study aims to examine the tolerability and clinical use of SYSTANE® totally in adult patients having dry eye disease. Fluorescein-stained tear film break-up time (TFBUT) was examined. In this study, 134 volunteers both male and female above 18 years of age participated. This research was a multi-centric study carried out in various locations within the United States, including Missouri and Virginia and also in Spain and the United Kingdom. The inclusion criteria kept for the research was that the participant should have TFBUT = 5 seconds in at least one of the eyes at the screening visit. Also, should be present best-corrected visual acuity (BCVA) = 20/80 or = 0.6 early treatment diabetic retinopathy study (ETDRS) = 55 letters score, the log of the minimum angle of resolution (LogMAR) value during screening visit in both eyes. The intervention of drug was nano-emulsion ocular lubricant having other name: SYSTANE® Complete and

Propylene glycol-based eye drops where patients were instructed to carry out 4 visits which are scheduled: Screening Visit i.e. (Day-7 to Day 0), Baseline Visit/Visit1, Visit 2 (Day 14) and Visit 3 (Day 28). Study Director: Alcon Pharmaceuticals Alcon Research is the investigator for this study. Since the study is currently going on no results are posted yet.[102]

C. Study Title: Topical Dexamethasone - Cyclodextrin Microparticle Eye Drops for Diabetic Macular Edema (DECEDE) (NCT01523314)

A group of investigators designed a novel ODD method of cyclodextrin NPs. The indication plan of this work is to treat diabetic macular edema (DME). A significant stage in the research usually was the innovation of cyclodextrin NPs, which is currently, granted a US patent. The pre-clinical work and clinical work of the study have confirmed the investigator's suspension of eye drop having NPs of cyclodextrin shows effective outcome compared by marketed eye drops. They show the absorption of drugs effectively in the eye and decrease supply in the systematic circulation of the drug, decreasing its adverse effects. Eye drops having Cyclodextrin NP deliver the drugs into the eye in its posterior segment, therefore resolving the issue in ocular pharmacology. This was a randomized study performed on 40 participants, both male and female with the age range 20 to 70 years at Riyadh, Saudi Arabia, under the investigation of Marwan A. Abouammoh, MD. It was a Phase 2 and Phase 3 study in which the drug used was dexamethasone - Cyclodextrin eye drops and intravitreal Avastin injection +/– macular laser for both the phases respectively. The method and procedure kept in were the volunteer eye will be given eye drop having dexamethasone NP for 3 times a day for 3 months. The subject is given an eye drop IP bottle for every visit which is monthly and advice for self-administration of the eye drop. When the eye drop is open by the subject, should be marked and advised to discard after a week (if it does not have a preservative in it). Primary outcome measurements were best-corrected visual acuity on ETDRS chart and intraocular pressure (IOP). Patients having Type 2 diabetes were also admitted to the research. Dexamethasone-cyclodextrin eye drops used topically have properties of tolerability, inhibit the central macular thickness, and enhance visual activity in DME. The results help in carrying out comparative studies of dexamethasone cyclodextrin with microparticles of eye drops with other DME having treatments.[103]

D. Study Title: Efficacy and Safety Study of TJCS for Treatment of Moderate to Severe Dry Eye Syndromes (NCT02461719)

The arms of the clinical trial were Restasis Eye Drops 0.05% (Cyclosporine ocular suspension) and TJCS Eye Drops 0.05% [cyclosporine ocular nano-emulsion (NE)] group after giving 12 weeks of its treatment, each group which is on treatment is evaluated for safety and efficacy in subjects having moderate to severe dry eye disease. Interventions applied were Cyporin N Eye Drops 0.05% (TJCS eyedrop) 1 drop twice/day for 12

weeks in both eyes, having other names Cyclosporine Eye Drops (CYPORIN N). The primary and secondary outcome measurements were the corneal staining test and conjunctival staining. The inclusion criteria listed were male or female, with age 20 or above, and patients with moderate to severe dry eye. This phase 3 study was performed in Korea, Catholic University of Korea, Seoul St. Mary's Hospital with a total of 158 participants treated randomly. Sponsored by Taejoon Pharmaceutical Co. Ltd., Korea, the collected data submitted to ClinicalTrials.gov by the investigator or by the sponsor, but is not available for the public or for common people even though not posted on site of on ClinicalTrials.gov.[104]

E. Study Title: Photo Dynamic Therapy of Subfoveal Choroidal Neovascularization of Macular Degeneration in Age-Related by Verteporfin

Details of the clinical research which supported the approval of Visudyne™ therapy for AMD may be found in various sources.[93–98] A Phase I/II non-randomized dose-escalation trial was conducted in Lausanne (Switzerland), Boston (USA), and Lubeck (Germany). This study established the treatment parameters which were used in subsequent Phase III trials. Phase I/II study also showed that whilst the CNV appeared to be completely closed in essentially every patient using the best treatment regimen, most patients showed a re-opening of the CNV during follow-up. Several additional treatments demonstrated the feasibility of closing recurrent CNV without major short-term safety concerns. On the base of Phase I/II study, the TAP study (treatment of age-related macular degeneration with photodynamic therapy) was designed as a double-blind, randomized, multi-center placebo-controlled trial to examine the value of Visudyne™ therapy in decreasing loss of vision in patients having subfoveal CNV. The study of TAP was a 2-year clinical study involving over 600 patients. Two-thirds of the patients were randomly assigned to take Visudyne™ and one third to receive a placebo. The study patients were examined every three months for about 2 years. As per protocol, the treatment is four times in a year in every 3 months, as per the assessment for visual activity and fluorescein angiography to know the leakage of CNV. The TAP trial shows clearly that therapy of Visudyne™ may decrease the rate of vision loss in maximum patients involved in the trial as compared by the AMD in wet form. The trial subjects who depicted the better results of visual activity that are undergoing Visudyne™ therapy are those who are receiving the CNV treatment. In these patients which having sub-group mostly about 40% had a vision stable or improved in the duration of 12 months, which is mostly the outcome twice of it undergoing the placebo group of patients. The trial indicated that on average, patients required 3.4 treatments in the initial 12 months and 2.4 treatments in the second 12 months. To further follow-up, there is reason to hope that the sum of treatments required will progressively decrease further. Visudyne™ therapy has been approved for the treatment of classic sub-foveal CNV after the AMD in the United States, Canada, Switzerland, Argentina, Australia, Brazil, Malta, Korea, and the European Union.[105–110]

IV. REGULATORY APPROVALS AND SAFETY STANDARDS FOR ODD

The advantages of using various nano formulations compared by the marketed formulations mostly needed the coordination between the method of formulation and methods of quality control and ensured efficacy and safety. It is the role of regulatory authorities to look after the standards and approvals. In below (Fig. 8) the approvals of ocular preparation by USFDA over the last ten years are listed. This year (2020) first the treatment carried for thyroid and eye disease. FDA approved Tepezza (teprotumumab-trbw) for the treatment in adults; this is a rare condition in which fatty tissues and muscles behind the eye.[111] Similarly, for another a rare eye disease neurotrophic keratitis which approved by FDA first drug that is Oxervate (cenegermin).[112] Another regulatory stand was made in 2016 where FDA gave revisions on product-specific guidance for Cyclosporine ocular emulsion, bacitracin ocular ointment, erythromycin ocular ointment.[113] Other approvals and stands year wise are summarized.

V. PATENTS APPROVED FOR ODD IN THE LAST 7 YEARS

Filing and approval of a patent are a final confirmation about a commercial interest of a particular product. In this regard, various patents have been granted to the researcher for their innovation in the field of novel ODD. The patents offer an owner the exclusive rights to an invention and prevent others to misuse it. Some of the patents which are granted to the researcher for their work on ODDS are discussed below in Table 1.

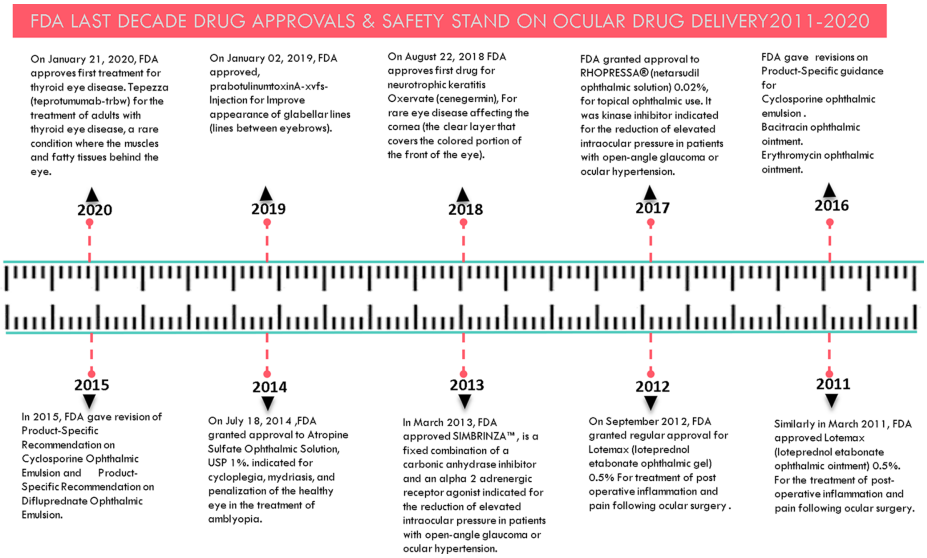

FIG. 8: Regulatory approvals from the U.S. Food & Drug Administration over the last decade ODDS

TABLE 1: Patents granted to inventors for ocular DDS

Inventors	Patent number	Summary of the invention and reference	Date of patent
Jie Fu, Peter A. Campochiaro, Justin Scot Hanes	US20190070302A1	In the area of novel ocular drug delivery, JieFuPeter and co-worker proved that the NPs, implants and microparticles are formed by the combination of polymer-drug which have the capacity of delivering drug easily of required dose and also have the ability to deliver more than one active drug for a longer time, hence he was awarded the patent. Further, they disclosed that administration in the eye of the therapeutic agent in a multiblock conjugate of copolymer-drug form of a non-linear which shows fewer side effects as compared by giving alone of the therapeutic agent. The awarded patent included the method for treatment in intraocular neovascular diseases, like wet age-related macular degeneration also the disorders and diseases of the eye which is related by inflammation like uveitis.[114]	Mar. 7, 2019
Shikha P. Barman, Moli Liu, Koushik Barman, Kevin L. Ward, Brendan Hackett	US9931306B2	Recently an approval of patent was given for a nanostructured biocompatible wafer which was used in conjuctival cul-de-sac. The used wafer has a mucoadhesive polymer and reacts by tissue and leads to the generation of a mesh of multiple fibers of hydrophobic polymer. He also patented procedure for glaucoma treatment and also for ocular surface disorder or ocular infection on the surface by application of a nanostructured wafer which is biocompatible.[115]	Apr. 3, 2018

TABLE 1: (*continued*)

Subramanian Venkatraman, Jayaganesh V. Natarajan, Tina Howden, Freddy Boey	US9956195B2	A researcher developed an ocular delivery of stable liposomal preparation. The preparation has liposomes that contain at least one bilayer of lipid a prostaglandin $F_{2\alpha}$ and phosphatidylcholine which is encapsulated in liposome. He researcher also patented for the method for ocular disorder treatment by the formulation stated.[116]	May 1, 2018
Ashim K. Mitra, Sidney L. Weiss	US8980839B2	A patent was granted to a researcher for ophthalmic preparation of nanomiceller which is aqueous having fatty acid, polyoxyl lipid, polyalkoxylated alcohol and cyclosporine. This patent included formulations for topical use, like ophthalmic preparations and its procedures for application of it. Also, involve procedure for treatment and decrease the conditions of diseases like ocular diseases and its conditions.[117]	Mar. 17, 2015
Michael R. Robinson, Wendy M. Blanda, Patrick M. Hughes, Guadalupe Ruiz, Werhner C. Orilla, Scott M. Whitcup, Devin F. Welty, Joan-En Lin, Lon T. Spada	US8969415B2	The patentee discovered the Biodegradable implants sized and suitable for implantation in an ocular region or site and methods for treating ocular conditions. The implants provided an extended-release of an active agent at a therapeutically effective amount for a while between 10 days and one year or longer.[118]	Mar. 3, 2015

TABLE 1: (*continued*)

Inventors	Patent number	Summary of the invention and reference	Date of patent
Ashim K. Mitra, Poonam R. Velagaleti, Ulrich M. Grau	US9017725B2	A researcher was granted a patent for his work on Nanomicelles having octoxynol-40, vitamin E TPGS and dexamethasone. This was topical DDS for ophthalmic purpose involve formulations of mixed nanomicellar and procedure for the treatment of it which affect segments of the posterior eye which is seen. In a form of aqueous ophthalmic solution which involves nanomicelles formulated in a buffer solution with 5.0–8.0 pH. Also, the concentration of corticosteroid is 0.01% w/v to 1.00% w/v was mixed by the micellar hydrophobic core having the composition of hydrophilic chains composed by corona towards the hydrophobic core.[119]	Apr. 28, 2015
Jie Fu, Justin Hanes, Donald Jeffrey Zack, Zhiyong Yang, Derek Stuart Welsbie, Cynthia Ann Berlinicke	US10525034B2	Jie Fu et al. awarded a patent for developing in enhancing the encapsulation or Sunitinib incorporation into the polymeric matrices. The outcome of results shows that controlled and sustained release of drug sunitinib or other JNK signaling inhibitors, which form a bond by DLK. Drug loading is carried out using alkaline solvent. Due to the enhancement of intraocular pressure, the change in the compositions of pharmaceuticals is carried out to decrease the neuronal death. When the formulation is administered of Sunitinib or other inhibitor diffuses slowly for the longer period and the release concentrations give required therapeutic effect, and decrease in cytotoxity for an unacceptable range of cytotoxicty and give longer release due to inhibitor without conjugate.[120]	Dec. 15, 2014

TABLE 1: (*continued*)

Glenn Noronha, Christopher John Brooks, Rafael Victor Andino, Samirkumar Patel, Daniel White	US20180042765A1	The present invention relates to devices and methods for uveitis treatment and macular edema which is due to uveitis and also macular aedema with retinal vein occlusion in humans which is needed. In many cases, devices applied as the carrier of the drug, in which the drug is entrapped, part of the distal end having therapeutic drug having coupling part which is easily removed and have and needles like device and the part of proximal end of a drug inducing part consist of the longitudinal shoulder, a flange and composed of movable piston which allows the drug to release from the container and handle which is coupled at the end part of proximal side of having a piston.[121]	June. 17, 2014
Omathanu P. Perumal, Satheesh K. Podaralla, Ranjith Kumar Averineni	US8697098B2	This patent was approved for the invention of methods of encapsulating molecules using the conjugates of the invention. Where Prolamine protein conjugated to a polymer is used to prepare micelle formulations. The research innovation has micelle assemblies its methods of formulation and its quantities used are carried out. He shows that micelle assemblies have many applications like cancer treatment, enhancement of drug efficiency which is entrapped *in vivo*, drug toxicity, target the tumor cells, increases drug solubility in water, it also gives protection against the degradation of drug.[122]	Apr. 15, 2014
Ijeoma F. Uchegbu, Andreas G. Schatzlein, Xueliang Hou	US8470371B2	Research invented that the micellar clusters may be transformed into stable NPs incorporated by therapeutic agents, mostly the drugs which do not effectively show water solubility, it, therefore, allows the water-insoluble drugs to cross the biological barriers. The researcher formulated a polymer aggregate of micelles consists of the size of particles of about 20 and 500 nm within both hydrophilic and hydrophobic polymer of carbohydrate.[123]	Jun. 25, 2013

TABLE 1: (*continued*)

Inventors	Patent number	Summary of the invention and reference	Date of patent
Luke Clauson, Tsontcho Ianchulev, Nathan White, Richard S. Lilly, Matthew Newell, Michael Schaller	US20140323995A1	This disclosure relates generally to methods and devices for use in treating eye conditions. In some embodiments, a site-specific therapeutic agent is mixed with a releasing agent with a dual syringe apparatus to achieve homogeneity. Once mixed, the site-specific therapeutic agent and releasing agent can be either dispensed directly within an area of the eye or within an implant. The implant can be at least partially filled with the site-specific therapeutic agent and releasing agent either before or after implantation into the eye. Some ratios of site-specific therapeutic agents to releasing agents are disclosed which provide various releasing profiles of the site-specific therapeutic agent within the eye.[124]	Mar. 24, 2013
Jane-Guo Shiah, Chetan Pujara	US9610246B2	Jane-Guo and his colleague invented intraocular implants that are biocompatible and which consist of biodegradable polymer and brimonidine free base which increase the brimonidine free base release into the ocular system having a matrix of polymer which increase not only twice of release time but increases its period more than that.[125]	Feb. 15, 2013

VI. CONCLUSION

To accomplish the operative drug amount at the targeted site for a prolonged time is an obligatory desire for several medicinal products. But for drugs, projected for ODD, their poor bioavailability because of pre-corneal factors, diseases of the eye are treated by typical topical drug usage in various forms like suspension, solution, and ointments. Though, these forms are not sufficient to deliver the maximum drug into the eye. Still, a major developmental issue must be resolved, including multiple dosing, stability and control of the release of the drug. Clinically valuable DDS is required for the delivery of drugs in a certain specific amount that gives therapeutic results and also for a longer period. Such results can be obtained by nanoscale and microscale DDS manufactured by nanotechnology. This article gave justification that nanomedicines may deliver the drug at the specific time in a reproducible and safe manner at site-specific targeted delivery (in the segment of an eye of posterior and also in anterior) at definite proportions. This article also discussed the latest progress and specific novel development relating to liposomes, noisome, NPs, and ME in ODD. Listed patents gave the idea that currently, very few novel ocular DDS have been commercialized. Therefore, there is more need for more work and a combination of technologies that may hold the key to achievement. This article also stated the clinical trials, and regulatory status of novel ocular DDS which may be a useful method not done before, which gives an ideal method for future aspects. These current trends in ocular therapeutics suggested that the existing therapies will be replaced by novel ocular DDS in the future.

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