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# Recent Advances in Nanotechnology Based Ocular Drug Delivery

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**ABSTRACT**
According to the World Health Organization, globally, at least 2.2 billion people suffer from visual impairment, the leading causes being refractive errors, cataract and glaucoma. The increasing incidence of ophthalmic and ocular conditions, such as risk of cataract, diabetic retinopathy, diabetic papillopathy, glaucoma and ocular surface diseases among diabetic patients and the high prevalence of ocular morbidities among children aged between 5-15 years due to deficient Vitamin A supplementation and overexposure to smartphones, has made ocular drug delivery the most challenging field of research and development in pharmaceutical sciences. The main approaches in the development of an efficient ocular drug delivery system focus on bioavailability improvement and controlled drug release. Pharmacotherapeutic approaches aims at achieving effective drug concentration at the intended site of action, for a desired period of time in order to avoid any potential risks to the eye. Considering the factors such as increased drug permeation across the cornea, localized pharmacodynamic action on the eye, prolonged duration of action, reduction in the frequency of administration and minimization of side effects, advanced nanotechnology based ocular drug delivery systems have gained limelight in recent years. This review article aims to focus on the recent advancements in nanotechnology bases ocular drug delivery systems.
**KEYWORDS:**ocular drug delivery, nanomedicine, keratitis, glaucoma, polymeric nanoparticles

## I. INTRODUCTION

Out of around 1.4 million blind children worldwide, 270,000 are estimated to be in India.(1) However, more than 80% of the visual impairments are curable or preventable, thus increasing the demand for effective ophthalmic drugs in the management of diseases. A significant challenge in the development of ocular delivery systems is the circumvention of the protective barriers of the eye, without causing permanent tissue damage. Rapid and extensive elimination of conventional eye drops from the eye, via lachrymal drainage or drug dilution by tears reduces the ocular bioavailability and leads to undesirable side effects and toxicity. The conventional dosage forms such as eye drops and ointments possess several limitations like requirement of frequent administration, rapid pre-corneal elimination, unpredictable doses, eye-irritation and poor patient compliance. Only 5-10% of the totally administered drug penetrates the corneal layer and reaches the internal tissue. Hence, the intraocular bioavailability of topically applied drugs is extremely poor. Characteristics required for optimization of ocular drug delivery are good corneal penetration, easiness in installation and removal, good rheological properties, non-irritation and a continued contact time with corneal tissue.(2)

## BARRIERS TO OCULAR DRUG DELIVERY

The anterior and posterior segments of the eye are protected from xenobiotics by various biological barriers, which make conventional ocular drug delivery less efficient. The human cornea contains five layers namely epithelium, Bowman's membrane, stroma, Descemet's membrane and endothelium. The corneal epithelium composed of 5-6 layers of cells, is interconnected by tight junctions.(3) This serves as a major barrier for drug absorption, especially hydrophilic, from the lacrimal fluid into the anterior segment of the eye.(4) Due to the alternating polarity of the various layers of cornea, absorption of both hydrophilic and lipophilic drugs is limited. (5)

The Blood- retinal barrier located in the posterior segment of the eye is divided into two portions- the retinal pigment epithelium and the retinal endothelium. These contain tight intercellular junctions which impairs the penetration of molecules into the intraocular environment. Enzymes like dopa decarboxylase, monoaminoxidases present selectively in the retinal endothelial and epithelial cells form a metabolic barrier, which further contributes to the protective function of the blood-retinal barrier.(6)

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Entry of topically administered drugs is limited by various clearance mechanisms like lacrimation, tear turnover, solution drainage which washes away the drug from the instillation site in few seconds, resulting in lower bioavailability of the drug.(7) The protective role of tear film covering the surface of the eye is attributed to the presence of hydrophilic glycoproteins – the mucins. The mucins form a hydrophilic cover which moves over the glycocalyx of the ocular surface resulting in the clearance of pathogens, foreign substances and acts as a barrier for drug delivery.(8)

**LIMITATIONS OF CONVENTIONAL DOSAGE FORMS:**

On topical administration, absorption of drug from the site of application can be either through the corneal route or non-corneal route. The non-corneal route involves penetration of drug into the intraocular tissues through the conjunctiva and sclera. However, this is ineffective as the drug is removed by the capillary beds into the systemic circulation.(9) The corneal barriers restrict the entry of drugs into the aqueous humor. Only about 5% of the totally administered drug, enters the eye. The resulting low ocular bioavailability necessitates the need for frequent administration to attain therapeutic efficacy.

Intravitreal administration for the treatment of posterior-segment ocular diseases such as age-related macular degeneration and diabetic retinopathy is highly invasive, resulting in discomfort and non-compliance. The spaces in between the network of collagen fibers of vitreous humor are filled with negatively charged hyaluronic acid. Electrostatic interaction between the cationic drug molecules and hyaluronic acid acts as a static barrier for permeation.(10) Drug distribution pattern is not uniform throughout the vitreous body and largely depends on the molecular weight of the drug. Small molecules easily permeate through the vitreous body, whereas linear molecules over 40kDa and globular molecules larger than 70kDa exhibit a longer retention time in the vitreous body.(11)

Periocular routes of administration comprises of the retrobulbar, peribulbar, sub-tenon, sub-conjuctival and posterior juxta-scleral mode of injections. Drugs administered through these routes show promising results by attaining sustained therapeutic concentrations in the posterior segment of the eye. (12) However, the complications include subconjuctival hemorrhage, globe perforation, retrobulbar hemorrhage and respiratory arrest when used for anesthesia. Safety concerns and the requirement of specialized equipment with skilled operator is likely to affect patient compliance.(13)

**TYPES OF NANOSYSTEMS EMPLOYED FOR OPTHALMIC DRUG DELIVERY**

1. POLYMERIC NANOPARTICLES:The use of polymeric nanoparticles as drug carriers has paved way for the development of many different colloidal delivery systems. Drug loaded polymeric nanoparticles (DNPs) form a versatile drug-delivery system owing to its colloidal characteristics. Discomfort associated with conventional dosage forms like blurring of vision, stickiness and viscosity can be overcome by the dispersion of DNPs in a suitable ophthalmic vehicle.(14) DNPs possess properties such as biodegradability, nontoxicity, biocompatibility and mucoadhesiveness. Nanoparticles have large surface area and possess multi-functional groups on the surface that aids the drug in reaching the targeted site. Polymeric nanoparticles get entrapped in the ocular mucus layer to form bio adhesive polymer chains which intimately interact with the extra ocular tissues to prolong the residence time of the drug loaded in the nanoparticle. Thus, drug drainage is reduced and the bioavailability of the drug at extra ocular tissues is improved. Encapsulated nanoparticles have the ability to penetrate through the ocular tissues to deliver the drug at the intraocular site achieving improved bioavailability. The penetration of drug mainly depends on the size, charge, architecture, surface chemistry and hydrophillicity/hydrophobicity of the nanoparticulate systems.(15) Both synthetic and natural biodegradable polymers are used in nano-based drug delivery.

1.1 Synthetic polymers:

1.1.1 Poly (D, L lactide-co-glycolide):

Poly D, L lactide-co-glycolide (PLGA), a co-polymer of poly lactic acid and poly glycolic acid is an FDA approved biodegradable polymer most extensively used for controlled release delivery systems. Ozurdex, a biodegradable implant of dexamethasone is an example of a FDA approved ophthalmic product containing PLGA as excipient.(16)

The rate of drug release from the biodegradable polymeric matrices depends on the

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physical properties of PLGA such as molecular weight, ratio of lactide to glycolide, exposure to water and storage temperature. Lactide rich PLGA degrade more slowly, owing to less hydrophillicity. This is due to the presence of methyl side groups in poly lactic acid that makes it more hydrophobic in nature.(17) Molecular weight of the polymer used is inversely proportional to the encapsulation efficiency. Low molecular weight polymers reduce the drug encapsulation efficiency. Increase in concentration of the polymer, increases the encapsulation efficiency and size of the nanoparticles. The use of copolymers such as polyethylene glycol with PLGA enhances entrapment efficiency and other characteristics for controlled drug release.(18)

1.1.2 Poly (ε-caprolactone):

Poly (ε-caprolactone) is a biodegradable and highly biocompatible polymeric drug carrier. It is a slowly degradable polymer, ideally suitable for long-term drug delivery extending over a period of four months or more. Implantable poly (ε-caprolactone) nanocapsules loaded with an anti-glaucoma drug (pilocarpine), have been synthesized by the emulsion-solvent evaporation method. On injection to the anterior chamber of the eye, sustained drug release over 42 days was achieved, inhibiting the progression of glaucoma.(19)

Poly (ε-caprolactone) nanocapsules loaded with the anti-glaucoma drug carteolol produced a marked decrease in intraocular pressure when compared to the conventional carteolol eye drops. In comparison to conventional eye drops, the incidence of cardiovascular side effects also declined with the use of carteolol incorporated nanocapsules, indicating the reduction in non-corneal absorption.(20)

1.1.3 Polyethylene glycol:

Polyethylene glycol, a hydrophilic polymer employed in the development of ocular drug delivery, enhances the mucoadhesiveness and permeation of the drug. An example of a nanosystem composed of methoxy poly (ethylene glycol)-polycaprolactone and chitosan, containing the drug diclofenac showed improved pre-corneal retention and enhanced penetration across the epithelial membrane. PEG enhances the stability of the formulation by preventing aggregation of nanoparticles.(21)

1.2 Natural polymers:

1.2.1 Chitosan:

Chitosan is a natural polymer obtained by the alkaline deacetylation of chitin, a major component present in fungal cell wall, exoskeleton of marine organisms, insect cuticle and other organisms such as algae and fungi. Chitosan is commonly used in ophthalmic drug delivery due to its biocompatibility, biodegradability, non-toxicity, mucoadhesive character, anti-bacterial and anti-fungal effects.(22)Mucoadhesive character is due to the ability of cationic chitosan to combine with negatively charged sialic acid present in the mucus that result in enhanced ocular retention time. Chitosan induced increase in keratocyte migration rate results in the formation of collagen, which is responsible for corneal wound healing.(23)

In a randomized trial conducted on 20 white rabbits, chitosan-N-acetyl cysteine showed an increase in the rate of corneal wound healing. (24) Chitosan enhances permeability by opening the tight junctions between epithelial cells of the cornea, thus enabling the drug to traverse the cornea. Chitosan nanoparticles can be produced by various approaches like ionotropic gelation, spray drying, water-in-oil emulsion cross-linking, reverse micelle formation, emulsion-droplet coalescence and nanoprecipitation.(25) A major limitation of chitosan is its solubility in acidic solutions only, which causes severe irritation of the eye on application. This can be overcome by using galactosylated derivatives of chitosan which are water soluble at neutral pH.(26)

1.2.2 Hyaluronic acid:

Hyaluronic acid is an anionic polymer used widely in ocular research, as it is also a component of the vitreous body and aqueous humor of the eye. The viscoelastic and mucoadhesive property improves the bioavailability of the drug by decreasing drainage and enhancing the ocular contact time.(27) In gene therapy for ocular diseases, nanoparticles composed of two biocompatible polymers, hyaluronic acid and chitosan have been used as a carrier for gene delivery to the conjunctiva and cornea. These nanoparticles obtained by ionotropic gelation method, exhibited low cytotoxicity and high transfection levels without affecting the cell viability.(28)Hyaluronan, the sodium salt of hyaluronic acid is used as a bioavailability enhancer and is found to prolong the precorneal residence time of tropicamide, gentamycin, arecoline, tobramycin, pilocarpine and

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timolol.Hyaluronic acid protects the corneal epithelium against dehydration. Hence, it is used in ophthalmology as a main component of artificial tear substitutes prescribed for the treatment of dry eye diseases.(29)

1.2.3 Sodium Alginate:

Alginates are anionic polysaccharides derived from the cell walls of brown algae namely Macrocystispyrifera, Laminaria hyperborean and Ascophyllumnodosum.(30)

Sodium alginate alters the viscosity of a formulation and is mucoadhesive making it suitable for sustained release. Chitosan-coated alginate nanoparticle formulation of daptomycin showed a better sustained release drug profile when compared to nanoparticles coated with chitosan only.(31)

**2. Nanoliposomes:**

Liposome nanoparticles are the most popular vehicles for drug delivery composed of a phospholipid bilayer structure which is used to carry hydrophilic or lipophilic drugs.(32)

Liposomal nanocarriers hold a promising role for ocular drug delivery based on various advantages, such as an increased residence time for drug absorption, prolonged half-life in vitreous bodies and low toxicity. The lipid vesicles enclosing an aqueous core are biodegradable and can encapsulate a variety of drugs. They also provide a sustainable release from their inert depot without changing the intrinsic properties of the molecule administered.(33)

In a study, the therapeutic effect of cyclosporine A – encapsulated liposomes on dry eye syndrome was compared with a commercially available non-liposome formulation. Topical application of cyclosporine A-encapsulated liposomes in dry eye syndrome induced male albino rabbits, resulted in lower ocular irritation and better therapeutic efficacy with higher tear amount compared to the non-liposome group.(34)

A liposomal voriconazole formulation, showed the most promising results in the treatment of fungal keratitis. With an entrapment efficiency of over 80%, the liposome was able to deliver about 47.85 ± 5.72 g/cm$^2$ of voriconazole into porcine cornea, after 30 min of permeation test.Such drug levels are found to be higher than the minimum inhibitory concentrations of several fungal species isolated from clinical cases of corneal keratitis. The developed formulation was found to be 'non-irritant', according to HET-CAM's irritability study.(35)

A study was conducted to evaluate the effects of intravitreal injection of liposomes encapsulating tacrolimus (FK506), on experimental autoimmune uveoretinitis (EAU) in Lewis rats. The result shows that intravitreal injection of liposomal tacrolimus was highly effective in suppressing the intraocular inflammation and development of EAU without any side effects on retinal function.(36)

Nanoliposomes have shown to slow down the rate of drug clearance from the site of application. Hence, they have been studied for drug delivery to both the anterior and posterior segments of the eye. Nanoliposomes are being formulated as a homogenous formulation to prevent the formation of agglomerates which could cloud the vitreous body. The liposomal vesicles have varying sizes ranging from 10 nm to 1 μm or greater. On the basis of size and number of layers, liposomes are categorized as unilamellar vesicles (ULVs) and multilamellar vesicles (MLVs). ULVs are further classified into small unilamellar vesicles (SUVs), giant unilamellar vesicles (GUVs), and large unilamellar vesicles (LUVs) depending on their sizes. In ULVs, the vesicles have a single lipid bilayer composed of lecithin or phosphatidylglycerol which are enclosed by an aqueous core. Multilamellar vesicles consist of more than one lipid bilayer, separated by an aqueous compartment which together comprises a shape of an onion.(37)

Liposomes can be used for both topical and intraocular administration. Topical administration mainly aims on prolonging the residence time at the ocular surface, by the addition of stearylamine or other cationic substances in the phospholipid layer. The resulting cationic liposomes interact with the negatively charged mucus layer at the ocular surface and facilitate gradual release of the drug. Thus, therapeutic concentration of the drug is achieved for a longer period of time. Intraocular administration of liposomes possesses various advantages:

1. Decrease in the number of injections required due to prolonged drug release.
2. Targeted drug delivery, for e.g. to the retina or vitreous.
3. Prevention of drug degradation by enzymes such as nucleases.(38)

The membrane lipid bilayers of liposomes are mainly composed of phospholipids and cholesterol. Phospholipids are amphiphilic in nature, i.e. they have a hydrophilic head and a

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lipophilic tail. In aqueous solution they are arranged as bilayers, which form closed vesicles. In the bilayer, the fatty acid tails, being non-polar, are located in the membrane's interior, and the polar head points outward. Cholesterol molecules orient themselves in the bilayer with their hydroxyl group close to the phospholipid molecule. Cholesterol enhances mechanical stability and flexibility of the bilayer.

Some of the commonly used phospholipids are natural phospholipids such as phosphatidylcholine (lecithin), phosphatidylethanolamine, phosphatidylserine and synthetic phospholipids such as distearoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine etc.

Due to the biphasic nature of liposomes (lipid and water) both lipophilic and hydrophilic ingredients can be accommodated depending on their solubility in the liposome components; consequently, almost any type of drug can be encapsulated. (39)

There are hundreds of new methods available for preparation of liposomes according to recent articles and technologies. The most commonly used method is the solvent evaporation method. The lipids and lipophilic drugs are dissolved in an organic solvent, which is later removed under vacuum by rotary evaporation. The lipid residue forms a film on the walls of the container. Aqueous solution containing electrolytes and water soluble components is added to the film. Large MLVs are produced by this method which is further reduced in size to form SUVs by sonication .The MLVs can be sonicated by either bath or probe sonicator.(40)

The other methods employed are membrane extrusion methods where vesicles are passed through filters with decreasing pore size. Solvent dispersion methods are suitable for preparing SUVs or LUVs. In this method, lipids are first dissolved in an organic phase (ethanol or ether) and directly injected to aqueous phase containing water soluble components.

Another technique used to prepare unilamellar vesicles is called the detergent dialysis method. In this lipid and lipophilic components come in contact to the detergent and based upon the concentration of detergents, there will be formation of micelles which in turn helps in the formation of vesicles. Other available methods for preparation of liposomes such as french pressure cells or high shear force homogenization (micro fluidization) is commonly used for large scale production of liposomes.(41)

**3. Nanogels:**

Nanogels are the nanosized particles ranging from 20-200nm, that is composed of cross-linked polymer networks with solvent penetration power. Hydrogels are composed of hydrophilic polymers cross-linked by physical or chemical bonds with tremendous capacity to uptake water. Nanogels are biodegradable and biocompatible in nature. Nontoxic, stable and hydrophilic polymers such as ethyl cellulose, methyl cellulose and polysaccharides like dextran, pullulan are mainly used in the synthesis of nanogels.(42)

Nanogels possess swelling property in aqueous media, which influences the mechanism of action of this drug delivery system. The swelling/ deswellling of nanogels depend on chemical nature of the polymer, degree of cross linking and charge density in the case of polyelectrolyte gels. Environmental factors such as pH, ionic strength and temperature also affect swelling. The mucoadhesive property of gels is widely studied in the field of ophthalmology due to their ability to prolong contact time with the cornea.(43)Nanogels possess a higher drug loading capacity when compared to conventional dosage forms. Loading of drug can be done by three methods namely physical entrapment, covalent attachment of bio-molecules and controlled self-assembly. Colloidal stability of nanogels is achieved by incorporation of surface modifiers like polyethylene glycol, that produce steric effects to achieve stability or by increasing the zeta potential which results in repulsive forces between the particles that electrostatically stabilize them. Based on the type of functional group present in the polymer chain, the density and type of cross-linking agent, both hydrophilic and lipophilic drugs can be administered by nanogels.

The presence of functional groups facilitates targeted drug delivery with high selectivity and also reduces the accumulation of drug in non-target tissues.(44)

3.1 DRUG RELEASE MECHANISM OF NANOGELS:

Drug release from nanogels depends on the environmental signals such as changes in pH, which facilitates targeted release of drug at a specific site with appropriate pH. For e.g. Drugs loaded into nanogels containing acid functional groups through hydrophobic and hydrogen bonding

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showed higher drug release at a higher pH. At a higher pH, deprotonation of acids on the nanogels increases the osmotic pressure and swelling of the nanogels. This, in turn will promote the release of drug through an increase in porosity.(45)

3.2 PREPARATION OF NANOGELS:

3.2.1 Cross-linking polymerization:

Ionic or neutral monomers are mixed with cross-linking agents and polymerization is initiated thermally, by UV light or by redox initiators. Temperature sensitive hydrogels containing N-isopropyl acrylamide as the monomer and pH-sensitive hydrogels containing methaacrylic acid as the monomer have been prepared by this technique. (47)Nanogel preparation by physical cross-linking involves the controlled self-aggregation of a hydrophilic polymer that is capable of cross linking via hydrophobic interactions, hydrogen bonding or van der Waals interactions. Nanogel preparation by free-radical polymerization which involves the use of bifunctional cross-linking reagents such as divinyl benzene, methylene-bis-acrylamide, is a predominantly used technique because of its ease of manipulation, efficiency and adaptability. (48)Photocrosslinked biodegradable photo luminescent polymer (PBPLPs) nanogels were prepared by free-radical cross linking of a vinyl-containing florescent polymer which led to new development of nanobiomaterials in theranosticnanomedicine for drug delivery and cell imaging.(49)

3.2.2. Photolithographic technique:

A Photolithographic technique, known as PRINT (particle replication in nonwetting templates), is widely explored for the preparation of 3-dimensional hydrogels. A nonwetting and elastomeric mold of perfluoropolyether which possesses a low surface energy is used in this technique. Dimethaacrylate functionalized perfluoropolyether oligomers are poured onto silica templates. The mold is pressed onto the silica template and on UV exposure, photochemical cross-linking of the oligomers occur which results in the desired shape-specific nanoparticles. Usually, a thin residual interconnecting film is formed between particles which have to be removed by oxidation.(50) However, in the PRINT technique, the nonwetting molds eliminate the formation of a residual interconnecting film between the molded nanoparticles. The fabricated nanoparticles can be directly collected.(51)

3.3 Ophthalmic formulations :

Hyaluronic-acid based hydrogels loaded with the antibody infliximab demonstrated a sustained release of the drug in a two-compartment in-vitro outflow model of the human eye, indicating a high potential for the development of nanogel formulations to prolong the intraocular release of proteins.(52) pH-sensitive polyvinylpyrrolidone-poly (acrylic acid) nanogels loaded with the drug pilocarpine were synthesized by gamma-radiation induced polymerization of acrylic acid in an aqueous solution of polyvinylpyrrolidone as template polymer. An in-vitro release study conducted in simulated tear-fluid, showed sustained release of pilocarpine from the nanogels when compared to the release of pilocarpine from solution.(53)

**4. Nanomicelles:**

Nanomicelles are the nanotechnology based ocular delivery systems composed of amphiphilic molecules, which are able to self-assemble into micelles ranging from 20–200 nm. Nanonization strategies have emerged as a new platform for delivery of poorly water-soluble drugs. These nanoplatforms include nanoemulsions and polymeric micelles. A common feature of these nanoplatforms is the ability to solubilize poorly water-soluble drugs in a hydrophobic reservoir or core. Among these nanoplatforms, polymeric micelles have gained large attention because of the following properties. They are formed as a result of self-aggregation of amphiphilic polymers with the hydrophobic part of the polymer on the inside (core) and hydrophilic part on the outside (shell). So, the hydrophobic core serves as a solubilisation depot for drugs with poor aqueous solubility and the hydrophilic shell provides some protection in limiting opsonin adsorption, which contributes towards a longer blood circulation time or better blood stability.(54)

The self-assembly of amphiphilic molecules occurs only above a certain concentration which is known as critical micelle concentration (CMC). Micelles can be formed when the amphiphilic polymer reaches CMC.(56)Nanomicelles investigated for ocular drug delivery can be divided into three categories i.e., polymeric micelles, surfactants and polyionic complex (PIC) micelles. Micellar aggregates formed by low molecular weight surfactants are weak and susceptible to physical instability upon dilution, because low molecular weight surfactants exhibit higher CMC and thus physical instability. On the other hand polymeric micelles formed by surfactants which exhibit low CMC impart physical stability to the solution. Hydrophobic interactions

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between the core and the drugs help in encapsulation of hydrophobic drugs in the core. Other forces such as van der Waals' interactions and hydrogen bonding may also contribute to the encapsulation in micelle core. Poly ionic micelle consists of a water soluble polymer with a charged core forming blocks. The electrostatic interaction between charged core blocks and oppositely charged API helps in formation of micelle. So, formation of polyionic micelles is dependent on the physicochemical properties of drug molecule, drug: polymer or drug: surfactant interactions, site of action, rate of drug release, biocompatibility and physical stability. Polyionic micelle as nanocarriers finds its application in gene and antisense oligonucleotide ocular delivery.(57) The basic principle in the formation of polymeric micelles mainly depends on the self-aggregation of polymers which is favored by thermodynamic stability. The CMC is an important parameter used to characterize the thermodynamic stability of micelles. It is related to thermal energy, $k_BT$, and the effective interaction energy between polymers and the bulk solution, $\varepsilon_h$.

The equation is given as, CMC = exp $(-n\varepsilon_h/k_BT)$. Lower values indicate greater thermodynamic stability. The CMC of the samples can be determined by Dynamic Light Scattering, which provides sensitive and accurate results. The degree of self-aggregation generally depends on the polymer chain concentration, the properties of the drug or any targeting agents, and the mass and composition of the copolymer backbone .The concentration of polymer chain can be determined by aggregation number i.e. the number of polymer chains that assemble to form a micelle .The aggregation number (Nag) is given by the equation: Nag = M/M0 M is the molecular weight of one micelle and M0 is the molecular weight of the polymer backbone.(55) Depending upon the molecular weight of the block copolymers, micelles can have different shapes including spherical, cylindrical and star-shaped structures.

The most common polymeric micelles used in drug delivery are amphiphilic di-block (hydrophilic—hydrophobic) or tri-block (hydrophilic—hydrophobic—hydrophilic) polymers. The most widely studied core-forming polymers are poly (lactide), poly (propylene oxide) (PPO), poly (glycolide), poly (lactide-co-glycolide), and poly (ε-caprolactone) (PCL). Polymers used to prepare nanomicelles should be biocompatible, non -toxic and should not exert inflammatory effects on ocular tissues.(57)

Polymeric micelle can be prepared by various conventional methods such as 1.Direct dissolution method 2.Dialysis 3.Freeze-drying method 4.Co-solvent evaporation method. The direct dissolution method is the simplest technique in which co-polymer along with drugs are dissolved at or above CMC resulting in self-aggregation and the formation of micelles. Only the smallest amount of drug can be loaded by this technique which can be increased by increasing the temperature of the system before addition of polymer. Dialysis process is a technique in which the drug along with a copolymer block is dissolved in water -soluble organic solvent and the resulting solution is dialyzed against water. During dialysis process, the organic solvent is replaced by water which induces self-association of block copolymers and the entrapment of drugs. In the solvent evaporation process the drug along with copolymer is dissolved in a volatile organic solvent and upon evaporation results in thin film which is reconstituted in aqueous solution. Some of the others methods include freeze drying, co-solvent evaporation method, and oil in water emulsion method. (59) These conventional methods are used only in lab -scale, because the use of organic solvent in conventional method possesses harmful residual impurities. The recent radiation energy techniques and ionic liquids have been employed to overcome the difficulties of conventional methods.

The advantages of nanomicelles in the formulation of hydrophobic drugs have paved way to the usage of clear aqueous solutions in the conjunctival sac. Some of the nanomicellar formulations of lipophilic compounds used in ocular delivery such as indomethacin, itraconazole, curcumin and spironolactone and the properties of nanomicelles such as ability to retain the drug in ocular surface and targeted delivery have improved the scope of research and development in nanomicelles.(60)

**5. Nanotubes :**

Fullerene, graphene and carbon nanotubes are allotropes of $sp^2$-like hybridized carbon atoms that differ in shape and dimensionality. Fullerenes resemble a soccer ball structurally, whereas graphene and carbon nanotubes possess planar and cylindrical arrangement of carbon atoms, respectively. These allotropes however possess unique properties such as electrical and thermal conductivity, chemical inertness and mechanical strength that have led to its widespread application in the field of nanosciences, biomedicine and

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electronics. Carbon nanotubes are of particular interest, due to its potential in targeted drug delivery. Carbon nanotubes are cylinders formed by rolling one or multiple graphene layers, based on which they are classified as single-walled carbon nanotubes (SWCNs) and multiple-walled carbon nanotubes (MWCNs).(61)

The small size and high surface area to volume ratio of carbon nanotubes, enables efficient transportation of therapeutic agents to the desired site, without causing toxicity to healthy tissues while allowing prolonged release of the drug. Carbon nanotubes have highly hydrophobic surfaces making it insoluble in aqueous solutions. This problem can be overcome by functionalization of nanotubes, a chemical process where desired functional groups can be introduced on the walls of the nanotubes, resulting in the enhancement of solubility, encapsulation efficiency, biocompatibility and multi-model drug delivery.(62)

5.1 Preparation of carbon nanotubes:

Heating carbon black with graphite, in a controlled environment is a widely used method for preparation of nanotubes. However, nanotubes prepared by this method are irregular in shape, size, mechanical strength, quality and purity. In recent times, a number of artificially developed methods have been used for the synthesis of nanotubes.(63)

5.1.1. Chemical vapor deposition:Chemical vapor deposition is an economical technique used to synthesize carbon nanotubes at a low temperature and ambient pressure. The yield and purity of nanotubes produced by chemical vapor deposition is better when compared to those produced by arc-discharge and laser ablation techniques. The process is based on the thermal decomposition of hydrocarbons in the presence of metal catalysts. The hydrocarbon vapor is decomposed on passage through a tubular reactor containing a metal catalyst at 600-1200°C. Carbon nanotubes grow on the catalyst in the reactor, which is collected upon cooling the system to room temperature. In case of a liquid hydrocarbon, it is first heated in a flask and is purged with an inert gas, which in turn carries the hydrocarbon vapor into the reactor. If a solid hydrocarbon is used as the precursor for nanotubes, it can be placed directly in the low-temperature zone of the reaction tube. When the hydrocarbon comes in contact with the "hot" metal, it decomposes into carbon and hydrogen species; hydrogen is removed away and carbon gets dissolved into the metal. As the metal reaches the carbon-solubility limit, the dissolved carbon precipitates out and crystallizes in the form of a cylindrical network, which is energetically stable.(64)

5.1.2 Electric arc discharge:

Carbon nanotubes are prepared when a high voltage electron beam from an arc strikes the graphite electrodes, in an inert atmosphere. Helium is the most widely used inert gas due to its high ionization potential. The electric arc provides the high temperature required to vaporize carbon atoms into plasma. The yield of carbon nanotubes depends on the stability of the plasma formed between the graphite electrodes, the current density, inert gas pressure and rate of cooling of the electrodes. (65)

5.1.3 Laser ablation technique: The laser ablation technique involves the vaporization of material from a solid target. Intense localized heating of the target by laser beam, results in high velocity ejection and evaporation of the impacted material. The rate of evaporation depends on the nature of the target material and the wavelength, intensity and pulse duration of the laser beam. Usage of high energy laser beam results in 'spalling' effect, in which huge amount of the target material is removed rather than a small outer surface. A sequence of two laser beams with a short time delay, results in increased ablation rate. The first beam heats the target, whereas the second laser beam interacts with the heated target surface resulting in enhanced vaporization.(66)

5.2 Ophthalmic applications:

Carbon nanotubes have gained attention recently, due to their ability to deliver drug molecules to a specific site in a controlled manner. Drugs or biomolecules can be directly attached to the walls of the carbon nanotubes or loaded inside the hollow tubes. Hydrophobic and van der Waal's forces play an important role in the insertion of drug molecules to the carbon nanotubes. The hollow monolithic structure of nanotubes with an outer and inner core, which can be modified by functionalization with desired groups, makes it a promising drug delivery system. The drug molecule is usually loaded in the inner core environment, whereas the outer surface is immobilized with suitable materials for achieving biocompatibility and biodegradation.(67)

Carbon nanotubes are used in ocular delivery of therapeutic agents, as it is found to be helpful in

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local targeting of drugs molecules to the retinal site. They have the ability to cross the blood-retinal barrier, making it possible for drugs such as mydriatics, anti-cholinergics and antibiotics to cross the tough membrane.(68)

## 6. Nanowafers:

Nanowafers are tiny, transparent circular discs that contain arrays of drug loaded reservoirs, from which drug is released in a controlled manner for few hours to days. The slow drug release from the nanowafers enhances the ocular residence time of the drug subsequently increasing its absorption into the surrounding ocular tissues. It can be applied on the ocular surface with a fingertip, and can withstand constant blinking without getting dislocated. After the stipulated period of action, the nanowafer dissolves away. (69)

### 6.1 Fabrication of nanowafers:

Nanowafers can be fabricated using various polymers such as polyvinyl alcohol, polyvinylpyrrolidone, hydroxypropyl methylcellulose and carboxymethylcellulose. The selection of suitable polymers is based on the aqueous solubility, biocompatibility, mucoadhesiveness, film-forming property and the ability to stick to the wet mucosal surface by adjusting to the curvature of the eye. The biopolymers used in the fabrication of nanowafers can be immunostimulatory, i.e., it can induce inflammation and exacerbate the existing condition resulting in delayed wound healing. Hence, efficient ocular drug delivery by nanowafers can be achieved by choosing the right polymer that enhances the tolerability, stability and therapeutic effect of the drug and is non-stimulatory to the immunological responses of the cornea.

Preparation of nanowafers involves the following steps:

a) The arrays of nanowells, 500nm in diameter and 500nm in depth are fabricated on a silica wafer by e-beam lithography followed by preparation of its poly (dimethylsiloxane) imprint.
b) A polymer solution is poured on the poly (dimethylsiloxane) template, followed by baking.
c) The polymer wafer containing the reservoir wells is peeled off and placed on the flat surface to expose the wells.
d) The wells in the polymer wafer are filled with solution of the drug.(70)

### 6.2. Ophthalmic applications:

Dexamethasone, an anti-inflammatory glucocorticoid was fabricated into a nanowafer to evaluate the suppression of inflammation in an ocular burn+ desiccating stress model. Methylcellulose polymer was used for nanowafer fabrication due to its water solubility, transparency and mucoadhesive properties.C57BL/6 mice subjected to alkali ocular burn with concomitant desiccating stress for 2-5 days were topically treated with 0.1% Dexamethasone topical eye drops, four times a day and compared with mice, treated once in a day, with Dexamethasone-nanowafers. Sustained release of dexamethasone from the nanowafer for over 24 hours reduced the expression of inflammatory cytokines with the same efficacy as topical eye drops given four times a day. (72)

Cystinosis is a rare autosomal recessive disorder, characterized by accumulation of cysteine crystals in the ocular surface due to the failure of cysteine transport out of lysosomes. Crystal accumulation in the ocular surface leads to opacity of the cornea and loss of vision. The conventional cysteamine hydrochloride eye drops possess several limitations such as poor corneal penetration, brief ocular residence time requiring the need of frequent administration of eye drops up to 12 times a day, which leads to poor patient compliance. Side effects such as ocular inflammation, eye pain and redness are frequently encountered on administration of eye drops. Scientific advancements have led to the development of cysteaminenanowafers, made of poly (vinyl alcohol) which is more effective in clearing up cysteine crystals compared to eye drops. Nanowafers also have lubricating properties on the ocular surface.(73)

## 7. Nanofibers:

Nanofibers are the polymeric fibers with diameter in the nanoscale range, i.e. less than or equal to 100nm. Natural polymers such as collagen, gelatin, cellulose, keratin and synthetic polymers such as polylactic-co-glycolic acid, polyurethane and polycaprolactone can be used to synthesize nanofibers of different diameters.

7.1 Synthesis of nanofibers:The various techniques available for the synthesis of nanofibers are electro spinning, self-assembly and phase separation. Electro spinning is the most widely used technique that yields promising results for drug delivery and tissue engineering applications. The thickness and

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composition of the nanofibers along with the porosity of the nanofiber mesh can be controlled by this technique. In this process, fibers are produced by applying an electric potential to a polymeric solution. The polymeric solution is expelled from a syringe at a uniform rate, forming a droplet at the tip. The solution is held at the tip of by virtue of its surface tension. The applied electrical potential provides a charge to the polymer solution. Mutual charge repulsion in the polymer solution induces a force that is directly opposite to the surface tension of the polymer solution. When the surface tension is overcome by the electrostatic repulsion of charges, the droplet is ejected forming a jet towards the collector. The jet gradually thins in air primarily due to elongation and solvent evaporation and eventually forms randomly oriented nanofibers that are collected on a stationary or rotating grounded metallic collector. (74)

7.2 Ophthalmic applications:Electrospun nanofibers have gained interest in the field of ocular drug delivery due to easy adaptability to the corneal and scleral surfaces and the ability to remain on the eye surface for a moderate period of time acting as sustained release platforms. Nanofibers create a stable transmembrane gradient that facilitates the diffusion of both hydrophilic and lipophilic drugs across the ocular barriers. Ophthalmic inserts composed of hyaluronan nanofibers for dual delivery of an anti-oxidant ferulic acid and an anti-microbial peptide ε-polylysine, offered an increased residence time on the ocular surface, controlled release and accurate dosing.(75)Hydrophilic chitosan-polyvinyl pyrrolidone based nanofibers were developed by electrospinning method for the delivery of triamcinolone acetonide.Uniform and bead-free nanofibers were obtained that followed zero-order kinetic profile. The ocular inserts achieved prolonged therapeutic drug concentrations in a single-dose making it a promising delivery system. Limited systemic exposure and side effects enhanced patient adherence to therapy.(76)Nanofibers made of poly (vinyl alcohol) and polycaprolactone containing a combination of timolol maleate and dorzolamide as active ingredients exhibited controlled drug delivery. The reduction in intraocular pressure was compared with traditional formulations. While the maximum reduction in intraocular pressure was achieved 4 hours after administration in traditional formulations, the time taken by nanofibrous patches was enhanced to 20 hours, depicting prolonged release of the drug.(77)

**8. Dendrimers:**

Dendrimers are one of the classes of polymeric architecture that has a promising role in ocular delivery. Mainly four types of polymeric architecture are used for drug delivery such as linear, cross -linked, branched and dendritic types. Dendrimers, (in Greek, Dendron = tree and meros = branch) are globular tree-like branched nanostructured polymers.(78) The size of dendrimers ranges from 3–20 nm. Dendrimers are discrete nanostructures/nanoparticles with 'onion skin-like' branched layers. They are comprised of a central molecule known as the "core" and side chain moieties known as "Dendrons". Thus, dendrimers consist of three distinct parts i.e. 1) an inner core 2) highly branched repeating units called layers of generation 3) peripheral multivalent functional groups. Starting from the core these nanostructures grow in concentric layers to produce stepwise increase in size, similar to globular proteins. These branched tree-like concentric layers are referred to as 'generations'. The outer generation has a precise number of functional groups at the terminal part in which the functional group can be positive or negative or neutral.(79)Early investigation based on traditional methods were merely used for pharmacokinetic and pharmacodynamic profile but recent nanoparticles may now be synthesized reproducibly in highly monodispersed forms with 'critical nanoscale design parameters' (CNDPs) such as size, surface chemistry and shapes that closely mimic important biological entities such as proteins, RNA/DNA, membrane bilayers and viruses.Dendrimers are obtained from any soft or hard atomic element found in the periodic table and has been synthesized with dozens of different elemental compositions. Dendrimers may be categorized into two types such as covalent type and supramolecular type but recent advances focus on covalent type. Different structures have been used till date for increasing residence time and systemic absorption and toxicity, among them polyamido-amine (PAMAM) dendrimers have been widely investigated. The core of PAMAM consists of linear molecule chain of primary amines .The commonly used primary amines are ethylene diamine, ammonia and cystamine. Ethylenediamine and cystamine are used for four core multiplicity, i.e. up to 4 chains whereas ammonia is used for three core multiplicity.(81)

The higher generations of PAMAM dendrimers are produced by two repetitive processes, Michael addition and amidation. The molecular weight,

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number of atoms and terminal primary amine group of PAMAM increases for each generation. For each PAMAM generation the size increases by up to 1 nm per generation and ranges from 1.1 to 12.4 nm as they proliferate from generations 1 to 10. This higher generation exhibits various properties and also shows globular-like shapes which make them more suitable for encapsulation and adsorption of biomolecules. This unique architecture of dendrimers has many advantages such as

1.Rapid cellular entry
2.Reduced macrophage uptake
3.Targetability and more facile passage across biological barriers by transcytosis.(82)

8.1. PREPARATION OF DENDRIMERS: Dendrimers are generally prepared using either a divergent method or a convergent one. In divergent method the dendrimers grow outward from the multifunctional core and each core reacts with monomer molecules containing one reactive and two dormant groups. This result in formation of first-generation dendrimer and further generations are formed on reaction with more monomers. This process is repeated for several generations and a dendrimer layer is built up. Some of the examples are 'starburst'. Some of the disadvantages are defect in structure due to side reaction and incomplete reaction of the end product and difficulty in purification of the product.In convergent method,dendrimers are formed in a stepwise manner starting from the end of the group and going inwards. When the required amount of branched polymeric groups is processed they get attached to multifunctional core molecules and the growing branched polymeric arms are called dendrons. The higher generation of dendrimers which leads to formation of 3D structure which forms an extraordinary combination of guest–host and interfacial surface functional advantages for the delivery of drugs, gene and imaging agents and tissue-targeting application.(83)

8.2. APPLICATION OF DENDRIMERS:

Dendrimers are used as topical administration for various corneal diseases because of sustained release and increased residence time. PAMAM dendrimers showed remarkable interactions with membrane associated mucin layers because of which the use of dendrimers in eye-drop formulations with drug molecules covalently conjugated to the dendrimer surface groups are widely used. pH-dependentdendrimers have stronger interactions in pathological conditions (pH 5.5 for tear fluid) compared to physiological conditions. Dendrimers are applied for the following disease condition such as

a) Corneal scarring, glaucoma infiltration and cataract surgeries
b) Corneal infections such as keratitis and conjunctivitis
c) Dendrimers are used as Ocular sealants for accelerated corneal wound healing

Dendrimers as an injection formulation have been used because they increase residence time in vitreous body. Dendrimers can be used to solubilize hydrophobic drugs and provide a sustained release depot adjacent to the sclera. Eg. Carboplatin has been delivered as a single subconjunctival injection using PAMAM aggregates and was able to produce effect for three weeks. Dendrimers have been used for intraocular posterior segments of the eye because of their fewer side effects caused by intravitreal injection. Dendrimers are used for some of the intraocular condition such as uveitis, cytomegalovirus retinitis, and endophthalmitis and intraocular tumors such as retinoblastoma and uveal melanomas.(84)

**9. Nanosuspension:**

Nanosuspensions are made by dispersion of drugs of nanoscale range in a colloidal carrier which is stabilized using suitable stabilizers.(85)Nanosuspension is employed for poorly water insoluble drugs and cause less side effects by excipient providing a better drug delivery. It is one of the better emerging methods for ocular delivery. When compared to other methods the formulation of nanosuspension is less expensive. These are simple to prepare and more advantageous than other techniques. Recently nanosuspension has become an integral part of nano-carriers and has several advantages which are listed below , improved bioavailability, targeted drug delivery to a specific site, reduced dosing frequency, sustained and controlled release effects, high patient compliance, better stability, ease of administration through different routes (86)Nanosuspensions can be utilized for drug form crystals with high energy which are neither soluble in hydrophilic or lipophilic media. The polymeric nanosuspension utilize inert polymeric resin for preparation for drug delivery as they do not irritate cornea ,iris or conjunctiva and they act as inert carriers for ophthalmic drugs. They are also capable of prolonged drug release and increase bioavailability.(87)Nanosuspensions prepared by polymeric resin such as Eudragit RS100s and

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RL100s and loaded with flurbiprofen (FLU), were formulated to show better anti-inflammatory properties with less toxicity to ocular tissues .Nanosuspensions were prepared by a quasi-emulsion solvent diffusion method and the resulting nanoparticles showed mean sizes around 100nm and a fixed positive charge (x-potential around +40/+60 mV). Ocular trauma (paracentesis) was induced into the rabbit's eye and in vivo anti - inflammatory effect was studied. The final result obtained contained better drug levels in aqueous humor after application of the nanosuspension and did not show toxic effect in ocular tissue.(88)

9.1 PREPARATION OF NANOSUSPENSION:Nanosuspensions can be prepared by particle size reduction that is also known as top up method or by precipitation of dissolved particles into nanosized particles is also known as bottom up method. In detailed version 'The bottom-up technology' is an assembling method from molecules to nanosized particles and 'top down technology' is break down of large particle or micro -particles to nanosized particles .The basic principle of preparation come under four approaches or methods, they are: (a) Homogenization (b) Wet milling (c) Emulsification-solvent evaporation and (d) Precipitation or micro precipitation method.

Micro precipitation, micro emulsion, emulsification methods are examples of bottom up approach and high-pressure homogenization and media milling methods are some of the examples of top up approach. Emulsion as templates and microemulsion as templates are recent approaches for preparation of nanosuspension.

MEDIA MILLING:

This patent-protected technology was developed by Liversidge et al (1992) acquired by Elan Drug Delivery. In this approach, nanosuspensions are formulated using a high shear mill called pearl mill. The equipment consists of a milling chamber, a milling shaft and a recirculation chamber. The milling chamber is loaded with the milling media, water, drug and stabilizer and pearl or milling media are subjected to high shear. High energy and shear forces are obtained due to impact produced by media milling which helps in disintegration of drugs from large particles to nanosized particles and the process is done at controlled temperatures. The media is composed of glass, zirconium oxide or highly cross-linked polystyrene resin. The nanosize of less than 200 can be obtained within a time duration range of 30-60 mins.

Advantages:

- The process is easy and little batch-to-batch variation.
- By this process nanosuspension concentration can be very dilute as well as highly concentrated based on the handling 1 mg/ml to 400 mg/ml drug quantity.
- Nanosized distribution of final nanosized product is achieved.

HIGH PRESSURE HOMOGENIZATION:

High pressure homogenization is mostly used technique for preparation of nanosuspension. In this method, the suspension containing drug and surfactant is forced under pressure through a nanosized aperture valve present in the high pressure homogenizer. A high-pressure homogenizer is composed of a high-pressure plunger pump with a subsequent relief valve (homogenizing valve). The purpose of the plunger pump is to provide the energy level required for the relief. The relief valve consists of a fixed valve seat and an adjustable valve. The homogenizers are available in two forms such as continuous or discontinuous. Pre- suspension of the micro sized drug with surfactant should be made using high speed stirrers .The pressure range maintained is between 100 to 1500 bars and no .of homogenization is based upon the product. Typically 3, 5 or 10 cycles are carried out.

Advantages:

- The drug which are poorly soluble in both aqueous and organic media can be formulated by this technique
- Production of nanosuspension under aseptic condition which will be used for parenteral use.

Disadvantages:

- There is a chance of contamination of the product by metal ions coming from the walls.
- Prerequisite of suspension formation using high-speed mixers before subjecting it to homogenization

PRECIPITATION:

Precipitation is an approach to the bottom up process. In this process the drug is usually dissolved in suitable solvent and solution is mixed up with miscible antisolvent along with surfactant. The addition of drugs rapidly to antisolvent leads to super saturation of drugs which result in formation of ultrafine crystalline or amorphous drug. This process is less expensive and a simple process .The only disadvantage is that growing of crystals must

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be limited using surfactant and drug should soluble at least in one solvent. (89)

- Limitations:
- Though it has various advantages, some of the major problems of nanosuspension are sedimentation of dispersed particles during storage which leads to physical instability. Pharmaceutical nanosuspension can be subjected to wear and tear during transportation due to bulkiness so extra care should be taken during transportation.

## II. CONCLUSION:

Nanotechnology based ocular drug delivery systems play a prominent role in overcoming the ocular barriers. The growing potential of nanoformulations which enhance bioavailability and biocompatibility serves as a solution for problems in treatment and management of ocular diseases.Nanosystems have been evaluated for various applications in preclinical studies such as controlled and targeted drug delivery systems, gene therapy, nano-electromechanical devices for imaging and diagnosis and implantable nanomaterials for prolonged, local therapy. Although, preclinical nanomedicine research for ocular use has witnessed advances, only few have reached the market after being approved for human clinical use. The future aspects focus on well-established reproducible manufacturing of nanoparticles for approval by FDA and large scale GMP manufacturing.

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