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A NEW VISION TO EYE: NOVEL OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

The review article is about the present trends and approaches used in the expansion of ocular drug release systems. The article begins with a concise sketch of the common anatomy of eye. Further, the approaches used in the development of ocular formulations are discussed. Approaches such as mucoadhesion, in-situ gels, colloidal carriers like nanoparticles, liposomes, niosomes, microemulsions, and microparticles are broadly reviewed. The challenges in ocular drug delivery are due to exceptional anatomy and physiology of eye. The usual dosage forms suffer from a range of drawback like quick precorneal removal, deficient of sustained and controlled drug release system, drainage of drug by gravity. To get the capable ocular delivery, an adequate quantity of active ingredient must be distributed in the eye. The improvement of controlled and sustained drug delivery system, prodrug formulation and diverse penetration enhancers increase the possibility of booming treatment of a range of ocular ailment.

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Introduction

One of the major troubles in ophthalmic drug delivery, the rapid elimination of usual liquid eye drop from the eye, still remains unsolved. An amount of factors, namely fast tear turnover and the consequential precorneal loss, stimulation of tear flow due to annoyance cause with the drug preparation, with the fairly huge quantity of the administer eye drop, lead to an elevated rate of lachrymal drainage. Due to the ensuing removal rate the precorneal half-life of drugs applied by these pharmaceutical formulations is measured to be sandwiched between 1-3 min. As a result, only the extremely slight amount of about l-3% of the dosage really penetrates throughout the cornea and is capable to get into intraocular tissues. [1] A variety of methods have been prepared to get better the bioavailability, drug discharge and absorbing speed from formulations or dosage form. Engineered nanodevices and nanostructures function individual biological system at the single-unit and molecular level. [2] External barriers obstruct direct and complete drug entrance to the correct site of action. Drug laden with micro particles exhibit good biological property contain prolonging the dwelling time of eye drops and diminishing toxicity and elevated capability of drug access into the deeper layers of the ocular arrangement and the aqueous humor minimizing precorneal drug loss by the speedy tear fluid turnover. Such microparticle can be used to treat a variety of optical diseases for example glaucoma, corneal diseases, retinal diseases. [2]

Formulation Approaches to Improve Ocular Bioavailability

Mucoadhesive polymers

To advance the optical bioavailability of drugs, various natural and synthetic viscosifying agents were supplemented to the medium in order to enlarge the viscosity of the preparation, to decrease the drainage rate and consequently progress the therapeutic value [3, 4]. Polymer associated factors influence mucoadhesion, hydration or amount of swelling, molecular weight, functional groups, molecular conformation or chain flexibility, mobility and concentration. [5, 6]

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Charged polymers both anionic and cationic exhibit an enhanced mucoadhesive capacity in contrast to non-ionic cellulose-ethers or polyvinyl alcohol. Mucoadhesive polymers are generally classified in to three categories:
Anionic: Poly (acrylic acid), Carbomer (neutralized), Hyaluronan, sodium carboxy methyl cellulose, Poly (galacturonic acid), sodium alginate, Pectin, Xanthan gum, Xyloglucan gum

Cationic: Chitosan

***In-Situ* Gels**

In-situ forming polymeric preparations are drug delivery systems that are in sol form previous to administration in the body, but once administered, go through gelation *in situ*, to form a gel. The formation of gels depends on factors related to temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets out in a constant and controlled mode. A variety of polymers that are used for the formulation of *in situ* gels including gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DL-lactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone. The selection of solvents resembling water, dimethylsulphoxide, N-methyl pyrrolidone, triacetin and 2-pyrrolidone for these formulations depends on the solubility of polymer used. Generally, *in situ* gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. The *in situ* gel forming polymeric formulations suggest several advantages similar to sustained and extended action in contrast to usual drug delivery systems. [6]

Table 1: Ophthalmic *In-situ* gels [7]

Model drugs	Polymers
Brinzolamide	Poloxamer F127 and carbopol 934P
Ketorolac tromethamine	Pluronic F-127, HPMC K4M
Diclofenac sodium	Pluronic F127
Methazolamide	Poloxamer 407 and poloxamer P188
Lomefloxacin	Pluronic F127, Pluronic F68 and sodium alginate

Table 2: Marketed Products of ophthalmic *In-situ* gels [8]

Product Name	Drug Used	Mfg. Company
Timoptic-XE	Timolol maleate	Merck and Co.Inc
Cytoryn	Interleukin-2(IL-2)	Macromed
Azasite	Azithromycin	InSite Vision
AktenTM	Lidocaine hydrochloride	Akten
Virgan	Ganciclovir	Spectrum Thea Pharmaceuticals

Aqueous gels formulated by means of hydrophilic polymers (hydrogels) along with those based on stimuli responsive polymers permit the incorporation of a diversity of ophthalmic pharmaceuticals to attain beneficial levels of drugs and bioactive at target ocular sites. [9]

Colloidal Drug Delivery System

Colloidal system work as carrier for drug delivery. They offer sustain and extended release of drug, it excretes the recurrent dosing of the medicament. They can also target the medicament to particular site. The nature of the carrier should be non-irritant, biocompatible, and biodegradable. [10]

Liposome

They are ended up of phospholipids and cholesterol and other minute molecules having diameter range of 80–100 nm. They can liberate both types of drug, i.e., Hydrophilic and lipophilic (−). The assimilation of the drug can be improved by liposomes. They improve the close contact with conjunctival and corneal surface. The earlier research indicates that liposome, when connected with idoxuridine, is quality to the solution form of the drug to cure herpes simplex keratitis in rabbits. [11] In a recent study, for delivery of latanoprost to anterior part of ocular tissues, liposomal formulation was developed by Natarajan et al. The solo subconjunctival injection of latanoprost/liposomal formulation in rabbit eye produced sustained IOP lowering effect over a stage of 50 d with IOP decrease equivalent to daily eye drop administration. [12] Gel-core liposomes are advanced systems offering benefits making it a high-quality tool for enhanced ocular drug delivery and dwelling time. Fluconazole (FLZ) was chosen as a challenging significant ocular antifungal suffering from poor corneal permeation and short residence time. [13]

Niosomes

Liposome has a number of drawbacks such as cost, degradation of phospholipids, and chemical instability; this problem can be sorted out by the development of niosomes having comparatively stable and osmotically active. Niosomes have been reported as an improved ophthalmic carrier. [14]

Nanoparticles

The ground of ‘nanomedicine’ uses nanoscale technologies (≤100 nm, typically) for the analysis, cure and/or avoidance of diseases, plus to achieve a perceptive of the pathophysiology of a variety of diseases, with a final object of improving worth of life. Nanomedicine offers various rewards compared to treatment with drugs alone. These comprise continuous release of

remedial agents, targeted delivery of drugs to particular cells or tissue, better delivery together with water-insoluble drugs and big bimolecular drugs, and reduced side effects. [15]

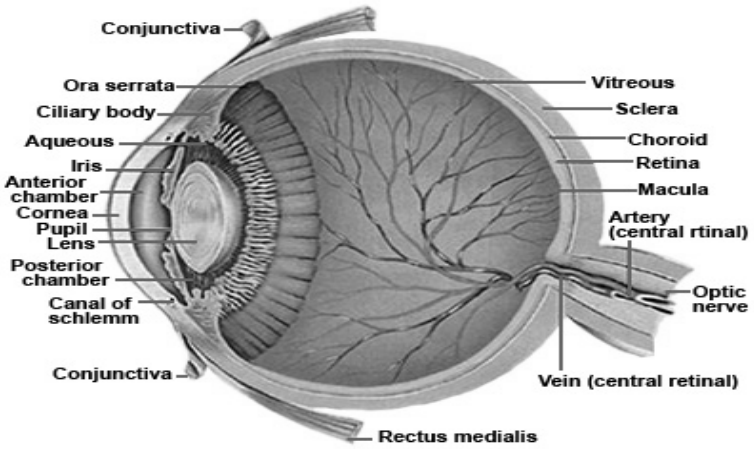

Figure 1: Structure of Eye [2]

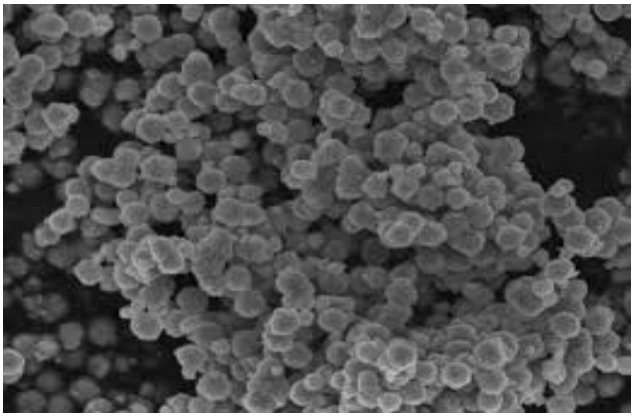

Figure 2: Nanoparticles [15]

Nanoparticles improves corneal residence time, yet eye drops are the mainly conventional formulation for optical drug delivery, they usually offer small bioavailability (less than 5%) due to reduced pre-corneal retention and diffusion. The causes affecting pre-corneal retention comprise fast tear turnover, flashing and solution drainage, which affect the loss of drug following topical administration. Consequently, regular instillations are necessary to preserve the beneficial level of drug. [16] The original nanoparticulate delivery system studied was Piloplex, consisting of pilocarpine ionically bound to poly (methyl) methacrylate – acrylic acid copolymer nanoparticles. The mainly used biodegradable polymers in the preparation of nanoparticulate system for optical drug delivery are poly – alkyl cyano acrylates, poly - ε – caprolactone and polylactic - co - glycolic acid copolymers. [17]

Table 3: Nanoparticles for Ocular Delivery [18-24]

Eye Diseases	**Drug Nanoparticles**
Corneal inflammation	Gatifloxacin
Glaucoma	Dorzolamide
	Brimonidine Tartrate and Timolol Maleate
Dry Eye	Cyclosporine A
Viral keratitis	Acyclovir
Retinal Disease	Fluocinolone Acetonide
Post Cataract Treatment	Dexamethasone Sodium phosphate

Nowadays, single-chain polymer nanoparticles (SCNPs) immediately entered the field of (biomedical) applications, with fresh advances in polymer science enabling the arrangement of bio-inspired nanosized architectures. [25] Exclusive intramolecular fall down of individual polymer chains consequences in individual nanoparticles with sizes an order of

magnitude lesser than conventional polymer nanoparticles, SCNPs are in the size regime of many proteins and viruses (1–20 nm). [25] Ziyi Wen studied the pharmacokinetics, biodistribution and metabolism of phospho-sulindac (PS), a novel agent efficacious in the management of dry eye, formulated in nanoparticles (PS-NPs) following its topical administration to the eye of New Zealand White rabbits. [26]

Nanomicelles

Nanomicelles are nano-sized carrier systems prepared from ampiphilic monomer units. They can be surfactant or polymer based and encapsulate hydrophobic drugs. Nanomicellar formulation have gained wonderful attention because of ease of preparation, high drug payload, enhanced bioavailability of therapeutic moieties. [27]

Patrizia Chetoni determine whether tobramycin as ion-pair incorporated in mucoadhesive Solid Lipid Nanoparticles (SLN) reaches the inner parts of the eye favoring drug activity. After technological characterization of the tobramycin entrapped SLN formulation (Tobra-SLN), a pharmacokinetic research in rabbits after topical instillation and intravenous administration of the formulation has been performed. Moreover, the intracellular activity of Tobra-SLN formulation against phagocytosed *Pseudomonas aeruginosa* was evaluated. [28]

Nanosuspensions

Ophthalmic nanosuspension (ONS) can be defined as colloidal dispersions on nanosized drug particles that are formed by an appropriate process and stabilized by an appropriate stabilizer; these can be a benefit for drugs that reveal poor solubility in lachrymal fluids. [29] Nanosuspensions, by their inborn capability to improve the saturation solubility of the drug, characterize an ultimate approach for optical delivery of hydrophobic drugs and nanoparticulate character of the drug allow its delayed dwelling in the cul-de sac, giving sustained release of the drug. [30] Khan MS. *et al* formulate pilocarpine nitrate nanosuspensions from inert polymer resin (Eudragit RL 100) with changeable drug to polymer ratio using Lutrol F68 solution in different concentration. Nanosuspensions were fruitfully prepared by solvent displacement method. [30]

Table 4: Current marketed formulations using nanosuspension technology [31]

Drug	Use	Company/ Individual	Preparation technology
Sirolimus (RAPAMUNE)	Immunosuppressant	Wyeth	Elan Drug Delivery Nanocrystals
Aprepitant (EMEND)	Antiemetic	Merck	Elan Drug Delivery Nanocrystals
Fenofibrate (TriCor)	Treatment of hypercholesterolemia	Abbott	Elan Drug Delivery Nanocrystals
Megestrol Acetate (MEGACE ES)	Appetite stimulant	PAR Pharmaceutical	Elan Drug Delivery Nanocrystals
Fenofibrate (Triglide)	Treatment of Hypercholesterolemia	First Horizon Pharmaceutical	SkyePharma IDD

Dendrimers

Dendrimers are monodispersing macromolecules with numerous reactive end groups that encase a small molecule and form an internal hollow space. Their tree-like divided architecture displaying a diversity of prohibited terminal group is very capable for biomedical applications. [32]

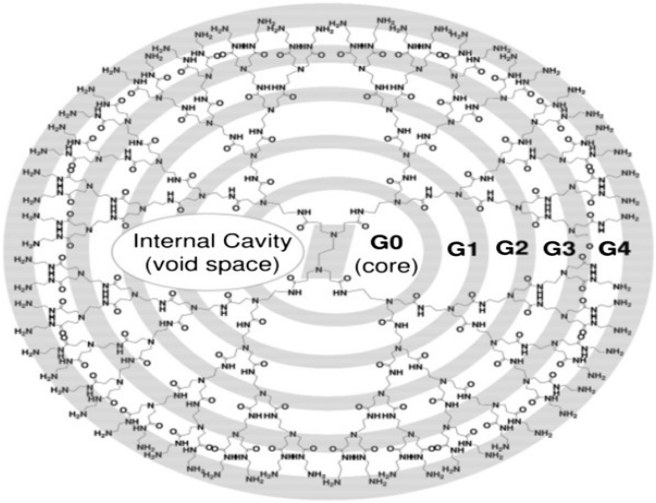

Figure 3: Dendrimer [32]

Dendrimers (from the Greek Dendron meaning tree), are separate nanoparticles with “onion skin-like” split layers. Dendrimers are defined as synthetic macromolecules characterized by a huge amount of branching points, a three-dimensional round shape, monodispersity, and nanometric size range. Their three-dimensional arrangement has an important

impact on their physical and chemical properties. Above all, their round shape and capacity to penetrate cell walls with no trouble, due to their size and lipophilicity, render them perfect as drug delivery systems and are in general more preferable for these applications than the typical linear polymers. [33]

Table 5: Ocular applications of dendrimers and dendrimeric delivery systems [34-38]

Drug	Dendrimer type	Administration	Treatment
Piocarpine nitrate and tropicamide	PAMAM G1.5-4	Topical	Myosis and mydriasis
Carteolol	Phosphorus containing dendrimers	Topical	Glaucoma
Gatifloxacin	Dendrimeric polyguanidilyated translocators	Topical	Conjunctivitis and intraocular infections
Glucosamine and glucosamine 6-sulfate	PAMAM G3.5-COOH	Subconjunctival injection	Antiangiogenic in glaucoma surgery
Carboplatin	PAMAM G3.5-COOH (dendrimeric nanoparticles)	Subconjunctival injection	Retinoblastoma

Microemulsions

Microemulsions are dispersions of water and oil facilitated by a fusion of surfactant and co-surfactant in a way to decrease interfacial tension. These systems are usually characterized by elevated thermodynamic stability, minute drop size (~100 nm) and clear appearance. [39] An analysis on application of microemulsions in ocular drug delivery by Vandamme *et al*., deals scientifically with the variety of developments and challenges happening in the ground. Collection of aqueous phase, organic phase and surfactant/co-surfactant systems are serious parameter which can influence strength of the system. Optimization of these components results in major improvement in solubility of the drug molecule e.g. indomethacin, chloramphenicol. [40]

Micropartciles

Microspheres are minute globular particles, with diameters in the micrometer range (typically 1 μm to 1000 μm (1 mm). Microspheres are occasionally referred to as microparticles.

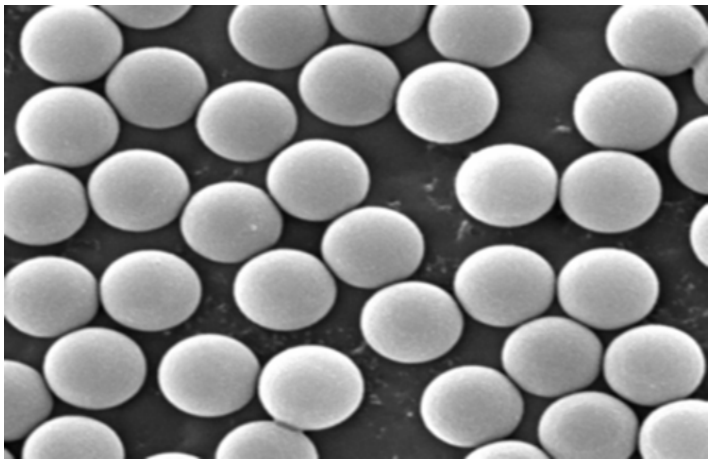

Figure 4: SEM of Microparticles [41]

Microspheres can be manufactured from different natural and synthetic resources. The particle size for ophthalmic application should not go beyond 10 mm as with larger sizes a scratching sensation may happen. Therefore, a decrease in particle size improves the patient comfort throughout administration. Frequent microsphere composition includes polystyrene (PS), poly (methyl methacrylate) (PMMA) and silica. These resources have special physical and optical properties, which may present advantages or restrictions for different applications. Polymer beads are commonly hydrophobic, and as such have elevated protein binding ability. [41, 42] Microparticle can be use in ocular drug delivery since this exhibit favorable biological behavior such as bioadhesion, permeability-enhancing properties, and attention-grabbing physico-chemical characteristics, which make it a distinctive substance for the blueprint of ocular drug delivery vehicle. Owing to their elastic property, polymer hydro gels propose improved suitability, regarding solid or semisolid formulation, for ophthalmic delivery, for example suspensions or ointments, ophthalmic chatoyant gels improve adhesion to the cumin, which coats the conjunctiva and the corneal surface of the eye, and amplify precorneal drug residence times, slowing down drug removal by the lachrymal flow. [41] Mark R. Prausnitz *et al* formulated microparticles by emulsification using poly (lactic-co-glycolic acid) (PLG) and poly (ethylene glycol) (PEG) as the center material and mucoadhesion promoter. The particle size was restricted to be below 10 μm to avoid eye annoyance and for eventual clearance through the

lachrymal canals. When an aqueous suspension of microparticles with PEG was administer topically to the rabbit eye *in vivo*, microparticles were see for up to 30 min on the optical surface in the cul-de-sac, which was a spectacular enhance in abode time as compare to usual eye drop formulations. [41] Prerana Vengurlekar *et al* developed a sustained release microspheric *in-situ* gel for bromfenac sodium (BNa) to be administered throughout ocular route. It was ready for the treatment of post-operative cataract surgery. It increases the therapeutic effectiveness, reduces dosing frequency and extended duration of action. Albumin microspheres were prepared by protein gelation method and dispersed into *in-situ* gel, which was prepared by pH triggered method. The particle size analysis exposed that all formulations gave particles size in the range of 1-10 µm which is appropriate for ocular administration of formulation. [42]

Table 6: Microparticles for Ocular Delivery [43, 44]

Eye Diseases	Drug Microparticles
Bacterial Keratitis	Sulfacetamide Sodium Moxifloxacin HCl
Ocular Surface Disease	Doxycycline
Uveitis	Dexamethasone

A new development in microparticulate drug delivery system is microsponges. Microsponges are polymeric delivery system composed of spongy microspheres. They are minute sponge-like sphere-shaped particles with a huge spongy surface. Furthermore, they might improve stability, decrease side effect and vary drug discharge favorably. [44] Microsponge technology has many constructive characteristics, which formulate it a versatile drug delivery medium. Microsponge Systems are based on minute, polymer-based microspheres that can suspend or confine a broad range of substance, and can then be included into a formulated product such as a gel, cream, liquid or powder. Drug delivery systems that can specifically control the release rates or target drugs to an exact body site have had a huge impact on the healthcare system. Microsponge particles are tremendously tiny, inert, indestructible spheres that do not bypass the eye and from there it releases the drug in also sustained or controlled mode. [45]

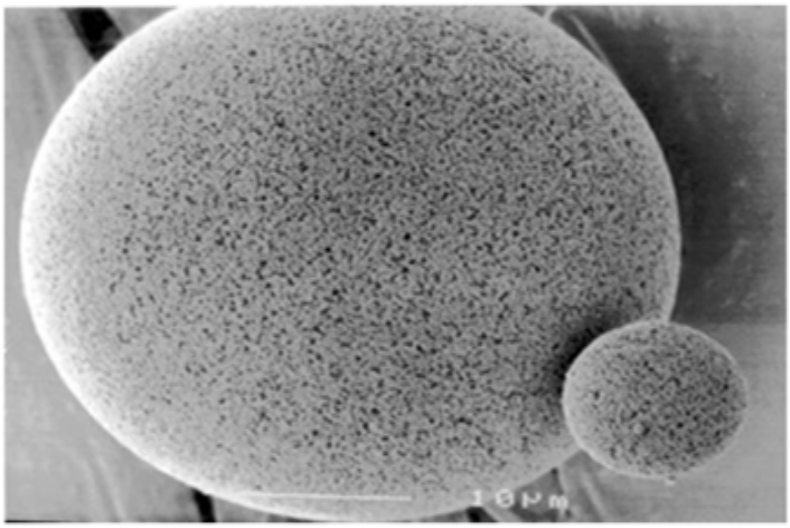

Figure 5: Structure of Microsponge [45]

The antiglaucoma drug, acetazolamide, was formulated as microsponges *in situ* gel for ocular drug delivery aiming an increased therapeutic influence and reduction in the systemic side effects of oral acetazolamide. The microsponges were prepared by the quasi emulsion solvent diffusion method and were incorporated into 25% pluronic F-127 *in situ* gel. Ethyl cellulose polymer in diverse proportions with drug was applied to prepare the microsponges. [46]

Lipid emulsion

LEs are biphasic system of immiscible liquids (either w/o or o/w types) and one connected with stability problems occurring because of aggregation and coalescence of the globules loading to phase separation. [47] LEs are thermodynamically stable and colloidal dispersion, stabilize by interfacial film of emulsifier. In ocular drug delivery, they are associated with several advantages which include sterilization, high clarity, and ease of preparation. [47]

A. Madni *et al* developed terbinafine hydrochloride (TH)-loaded micelles according to a soft non-ionic surfactant-macrogol 15 hydroxystearate (HS 15) and to explore their *in-vivo* cornea penetration. Briefly, 0.25% TH-loaded HS 15 micelles (TH-HNMs) were developed by a simple co-solvent approach. [48]

CONCLUSION

With demand for novel and extremely competent pharmaceutical as well as beauty products, the market holds considerable potential for microsponges and the flexibility they offer. As formulators think novel and innovative ways to deliver actives, they can understand the full capability of these sole material providing better safety, enhanced stability, reduced side effects from actives, better multifuntionality and enhanced ingredient compatibility. A microsponge drug delivery system can capture wide range of active ingredients and can restrict the rate of drug release. Microsponges are initially developed for topical delivery. These days it can also be used for tissue engineering, controlled oral delivery, ophthalmic and additional pharmaceutical application. Therefore, micropsonge is an extremely promising field, which is desirable to be explored.

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