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Review on Ocular Drug Delivery Systems: Advances, Challenges and Novel Approaches for Targeted and Sustained Drug Delivery

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ABSTRACT

Despite the unique anatomical and physiological defence mechanisms of the eye, ocular drug delivery is still one of the most challenging areas in pharmaceutical science. The ocular bioavailability of conventional topical formulations, for example, eye drops, is extremely low (typically <5%) because of rapid turnover of the tears, nasolacrimal drainage, and formidable barriers of the corneal epithelium and blood-ocular barriers. This means that the drug has to be administered repeatedly, which leads to poor patient compliance and a high risk of systemic side effects. More recent developments have focused on new and sustained methods of drug delivery in order to increase the time that the drug stays in the precorneal area, to improve targeted delivery and to achieve controlled release for both anterior and posterior segment diseases. In order to overcome these limitations, this comprehensive review will examine the physiological barriers of the eye, the current classification of ocular drug delivery systems, the advantages and disadvantages of both conventional and novel approaches, the therapeutic components involved and the rigorous evaluation methods, all with the aim of providing a thorough understanding of the future of ophthalmic therapeutics.

The human eye is a highly intricate and delicate organ that has elaborate mechanisms to protect the inner structures of the eye from xenobiotics, toxins, and foreign substances. But these very mechanisms make it extremely hard to treat using pharmacological methods. The anterior region of the eye comprises the cornea, conjunctiva, iris, ciliary body, and lens; the diseases that affect this part of the eye include glaucoma, dry eye syndrome, allergic conjunctivitis, and anterior uveitis. On the other hand, the posterior segment of the eye diseases like age-related macular degeneration, diabetic retinopathy, and CMV retinitis are some of the causes of blindness in the world.

Keywords: Ocular drug delivery systems; Precorneal residence time; Ocular barriers; Nanotechnology; Sustained release; Targeted delivery; In situ hydrogels; Intravitreal implants.

INTRODUCTION

Traditional topical ophthalmic dosage forms, most often eye drops in liquid form, are used in over 90% of all available ophthalmic drugs due to their simplicity and convenience [14]. Although possessing all these advantages, they are notoriously ineffective [15]. The excess volume of the solution instilled in the precorneal pocket (which usually exceeds the tear volume of 7 microliters) is immediately cleared away by overflowing, drainage and blinking in just minutes [16]. In addition to that, tight junctions of the corneal epithelium hinder paracellular delivery and tear proteins break down the API through enzymatic degradation [17]. To obtain therapeutic drug concentration, repeated application is inevitable and it often leads to local irritation, nasolacrimal toxicity and serious non-compliance [18].

In an effort to overcome the obstacles that are faced by the drugs, recent pharmaceutical science has been geared towards developing novel ODDS [19]. These innovative systems which include in-situ gel systems, mucoadhesive polymers, contact lenses, colloidal nano carriers such as liposomes, niosomes, solid lipid nanoparticles, dendrimers, implantable and micro-invasive systems have been designed to circumvent ocular barriers, extend the duration of stay, and ensure sustained release kinetics of the drugs [20, 21].

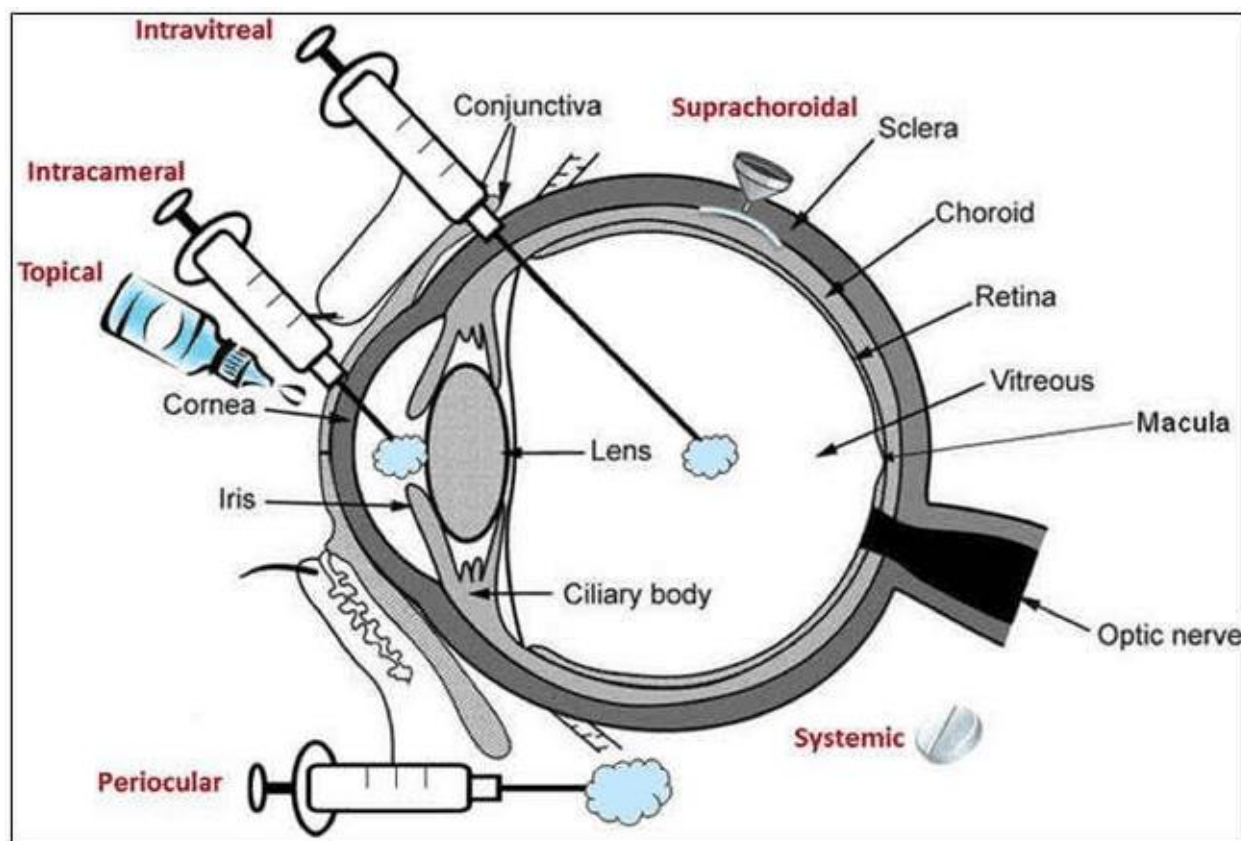


Fig No. 1 Routes of Administration

DEFINITION

A definition of Ocular Drug Delivery System (ODDS) could be described as a special pharmaceutical preparation or device designed to provide efficient and controlled delivery of drugs to targeted ocular tissues of either the anterior or posterior portion of the eye [22]. The main purpose of a modern ODDS is to improve bioavailability of the drugs within the eye, to prolong precorneal retention time, reduce dosage and minimize undesirable systemic effect of drugs [23, 24].

CLASSIFICATION

The classification of ODDS can be done according to the route of administration, physical form, complexity of the formula, and the targeted area, whether anterior or posterior ocular segment [25]. The detailed classification system allows the formulator and physician to choose the right carrier system that can overcome the natural barriers of the eye, prolong precorneal residence time, and maximize the effectiveness of the therapy for the particular ocular disorder [102].

1. Traditional Ocular Delivery Methods

Traditional dosage forms form the standard of ocular therapy, and they make up a large part of the commercially produced eye drops and ointments [14]. Solution dosage forms are liquid formulations wherein the active ingredient of the drug is dissolved. It has good patient compliance since the active ingredients are readily absorbed by the body but suffers from rapid elimination because of the tear wash out [26]. Suspension is made up of finely ground insoluble drug particles suspended in an aqueous base. The main advantage of suspension over solution is the slightly extended dissolution dependent delivery system [27]. Ointment and Cream use semisolid dosage forms using hydrocarbon or petrolatum bases that become liquid at the physiological temperature of the eyes [28].

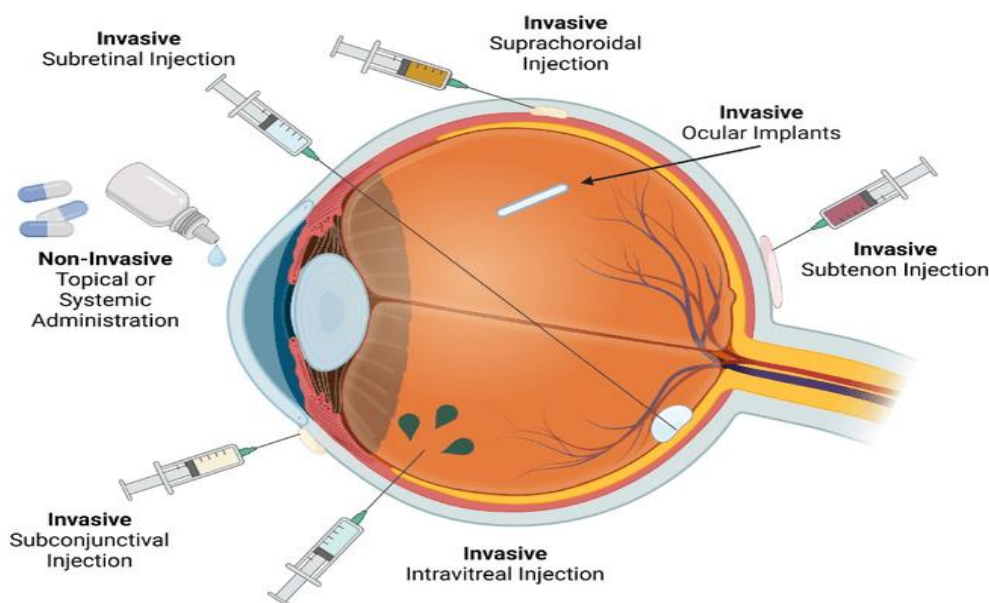


Fig No. 2 Traditional Ocular Delivery Methods

2. Advanced Precorneal and Topical Systems

In order to overcome serious limitations of traditional liquids, advanced topical systems have been developed in order to actively interact with the microenvironment of the eye [19]. In-Situ Gelling Systems are liquid preparations which undergo sol-gel transformation upon contact with environmental cues (such as temperature (e.g., Pluronic F127), pH (e.g., cellulose acetate phthalate), and ionic strength (e.g., gellan gum)) [29, 103]. Ocular inserts are solid or semi-solid preparations that can be classified as either soluble, insoluble, or bioerodible matrices that are placed within the lower cul-de-sac of the conjunctiva to allow for prolonged and controlled release of drugs from the matrix at a pre-defined zero-order or first-order rate [30]. Therapeutic Contact Lenses make use of hydrophilic hydrogels or silicone-hydrogels impregnated with drug solutions or molecularly imprinted polymers and nanoparticles [31].

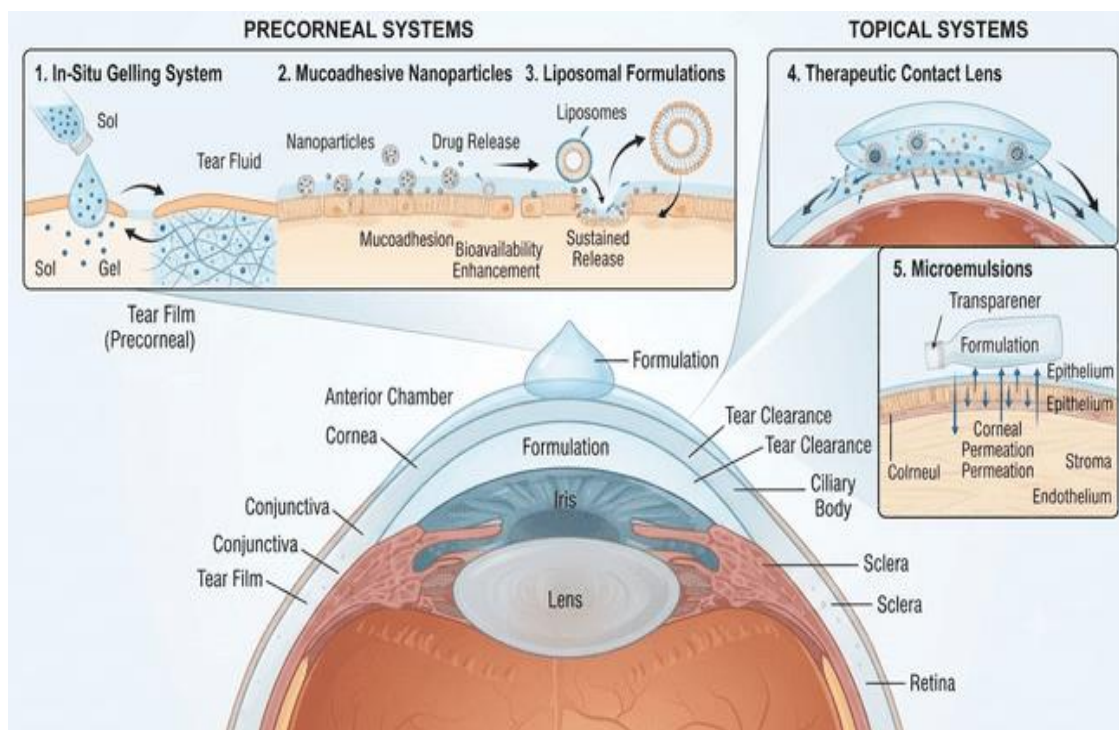


Fig No. 3 Advanced Precorneal and Topical Systems

3. Colloidal and Nanocarrier Delivery Systems

Nanocarrier delivery systems have brought about a paradigm shift in current ocular drug delivery through protection of the delicate biological molecules and increased tissue permeability [6]. Liposomes and Niosomes are vesicular carrier systems comprising phospholipids or non-ionic surfactant bilayer

vesicles for carrying hydrophilic and lipophilic drugs, increasing cellular uptake and membrane fusion [32, 33]. Polymer based Nanoparticles and Solid Lipid Nanoparticles (SLNs) are submicron particle carriers offering protection against enzymatic degradation and allowing sustained trans-corneal and trans-scleral transport [34, 35]. Dendrimers and Polymer based Micelles are highly branched nanostructures and self assembling amphiphilic aggregates which significantly increase the aqueous solubility and bioavailability of water insoluble drugs [36, 37]. Nanoemulsions and Microemulsions are thermodynamically or kinetically stable isotropic systems consisting of oil, water, surfactant and cosurfactant that increases corneal permeability using oil in water or water in oil droplets [104, 105].

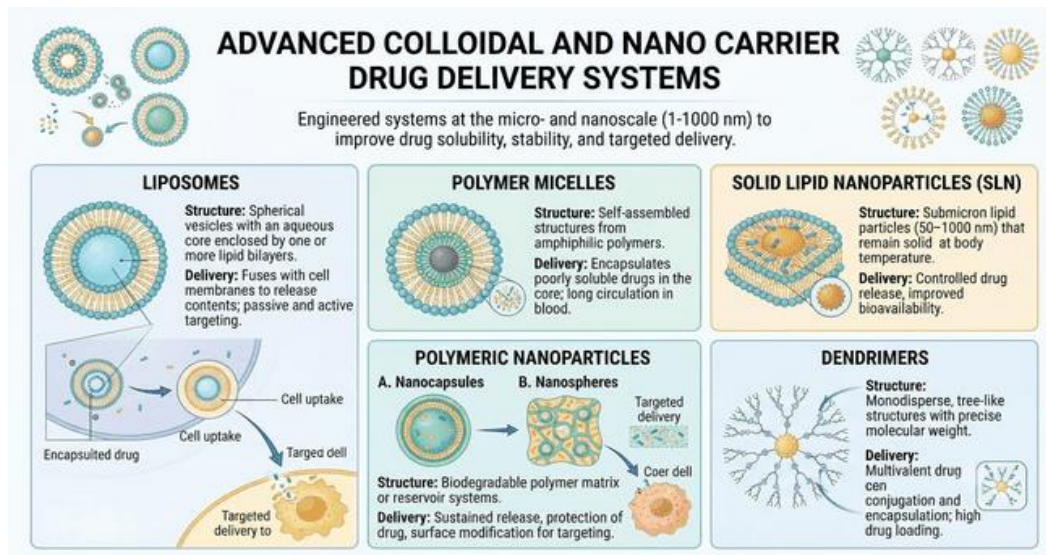


Fig No. 4 Colloidal and Nanocarrier Delivery Systems

4. Intraocular and Periocular Implants

In the case of chronic, serious diseases affecting the posterior part of the eye, such as age-related macular degeneration and diabetic retinopathy, surgical and periocular implants deliver sustained therapeutic doses without requiring frequent interventions [13, 39]. Non-biodegradable Implants (silicone matrix reservoirs and polymer-coated implants) have the ability to give a sustained drug delivery from months to years; however, their withdrawal through surgery or refilling after depletion is necessary [38]. On the other hand, Biodegradable Implants employ biocompatible and bioerodible polymers (poly(lactic-co-glycolic acid) [PLGA], polyorthoesters) that slowly degrade and liberate the loaded drugs, thus not requiring surgery for their extraction [40, 106]. Periocular and Subconjunctival Implants are implanted into episcleral or subconjunctival spaces to allow drug diffusion through the sclera to reach the choroid and retina [21].

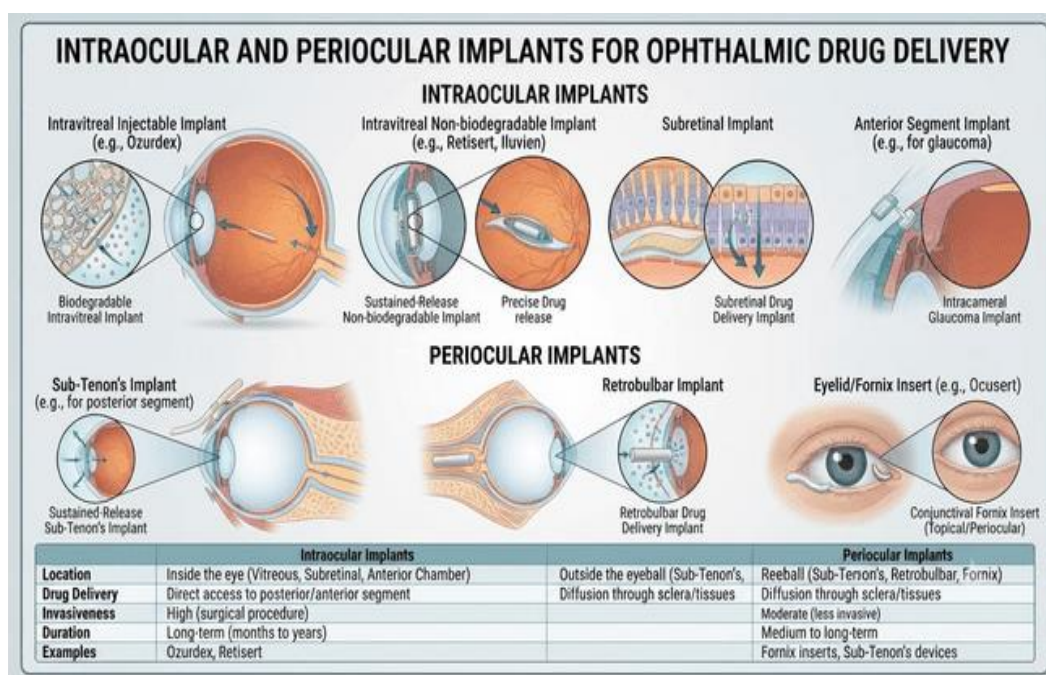


Fig No. 5 Intraocular and Periocular Implants

ADVANTAGES

Increased Ocular Bioavailability:

New carriers enhance penetration into the cornea and conjunctiva, providing higher concentration of drugs in intraocular tissues than conventional eye drops [41].

Increased Precorneal Retention:

The mucoadhesion and increased viscosity of the excipients prevent tear washout and blinking clearance [42].

Decreased Dosing Frequency:

Through sustained release technology, therapeutic windows can be achieved for days, weeks, or months, hence, reducing the frequency of drug administration [43].

Limited Systemic Toxicity:

As delivery is localized and targeted, there is limited drainage of the drug into the nasolacrimal duct and therefore limited systemic toxicity [44].

Protecting Fragile Drugs:

Proteins, peptides, and genetic materials can be protected through encapsulation in nanoparticles, liposomes, or polymer matrices [45].

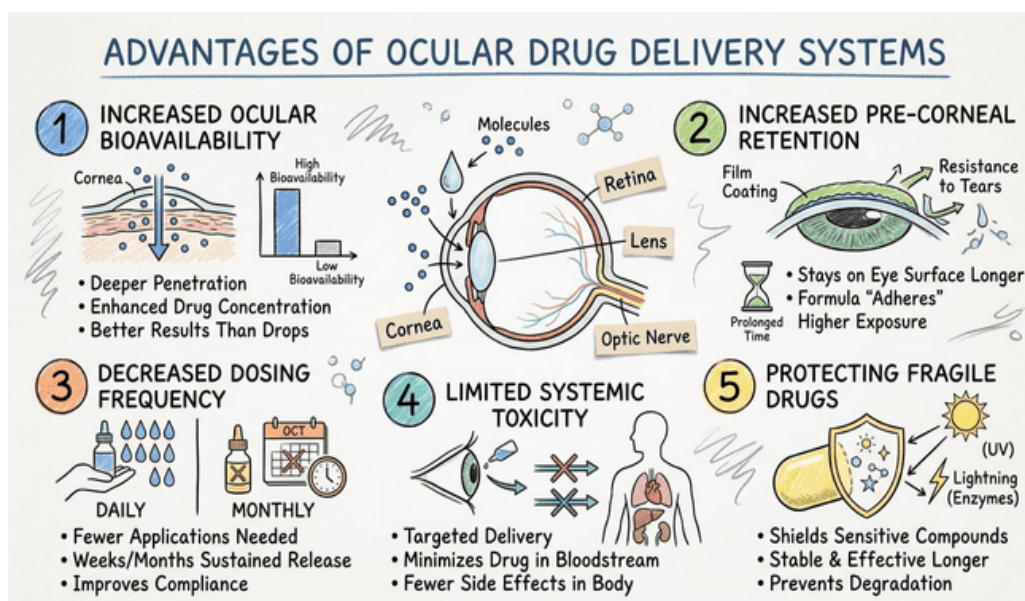


Fig No. 6 Advantages of Ocular Drug Delivery System

DISADVANTAGES

Complex Manufacturing and Higher Costs:

The manufacture of advanced nanocarriers and implants demands complicated fabrication technology and high costs [46].

Ocular Irritation and Possible Toxicity:

Some polymers used in nanocarriers or inserts, together with some organic solvents that might not be fully removed from the system, may lead to local irritation or hypersensitivities [47].

Temporary Visual Impairment:

Thick ointments, gels, and some inserts may cause temporary visual impairment and irritation [48].

Invasive Procedures:

Intraocular implants and intravitreal injections are procedures with a built-in danger of developing endophthalmitis, retinal detachment, bleeding, and anxiety [49].

Sterilization Issues:

The problem is how to achieve sterilization of heat-labile biological nanocarriers or complicated implantable devices without affecting the stability of drugs [50].

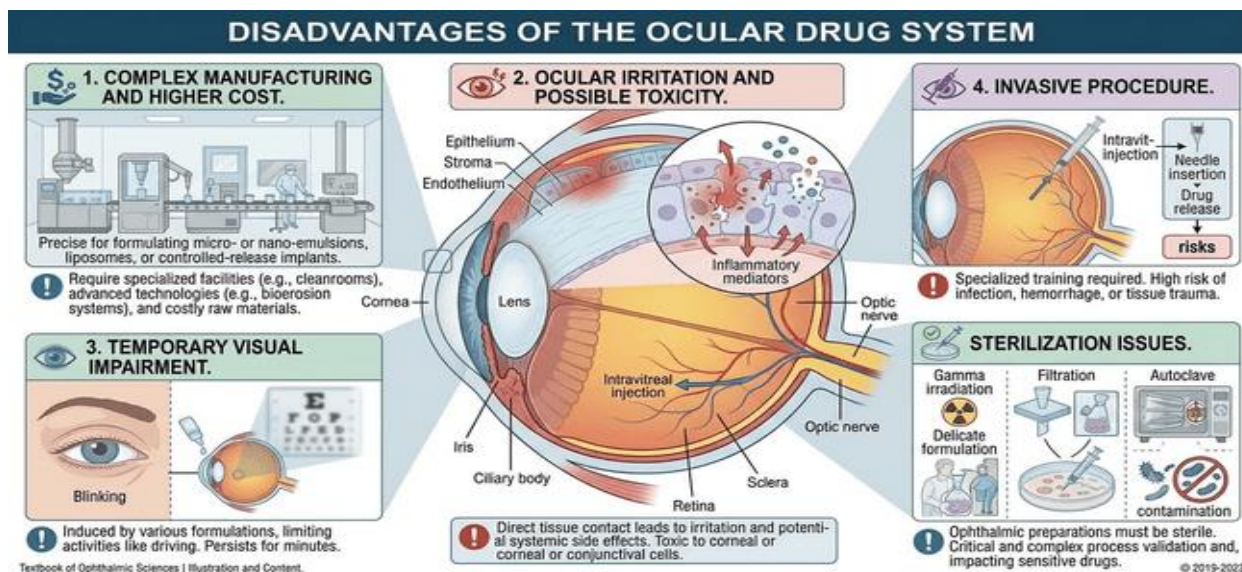


Fig No. 7 Disadvantages of Ocular Drug Delivery System

COMPONENTS & THERAPEUTIC VALUE

Inclusion of the active components in the preparation of ocular drug delivery system entails the following components aimed at enhancing their therapeutic function [51]:

Active Pharmaceutical Ingredients (APIs):

Consists of anti-glaucomas (timolol, latanoprost), anti-inflammatory (corticosteroids, NSAIDs), anti-infectives (antibiotics, antivirals, antifungals), anti-VEGF (ranibizumab, aflibercept for wet AMD), and immunosuppressants [52, 53].

Polymers & Gelling Agents:

Consists of natural and synthetic polymers (chitosan, hyaluronic acid, sodium alginate, carbopol, Pluronic F127) used for viscosity modification, mucoadhesive nature and stimulus-responsive gelling [54, 55].

Surfactants & Emulsifiers:

Non-ionic surfactants (Polysorbate 80, Cremophor) act as stabilizers for colloidal dispersion systems, increase wettability and enhance drug solubility [56].

Permeation Enhancers:

Comprise of EDTA, bile salts, and cyclodextrins which are used to transiently disrupt tight junctions between epithelial cells in order to increase corneal penetration [57, 58].

Buffers & Tonicity Modifiers:

Physiologically important compounds such as phosphate buffered saline, boric acid, sodium chloride that maintain physiological pH (7.4) and isotonicity to avoid ocular irritation [59].

EVALUATION, TESTING and METHODS

Intensive physicochemical, biopharmaceutical and toxicological evaluations are a must to confirm the safety, effectiveness and quality of ocular delivery systems [60]:

Physicochemical Characterization:

Assessment of particle size, polydispersity index (PDI), zeta potential, surface morphology with the help of scanning electron microscopy (SEM) or transmission electron microscopy (TEM), entrapment efficiency and chemical stability via FTIR and DSC [61, 62].

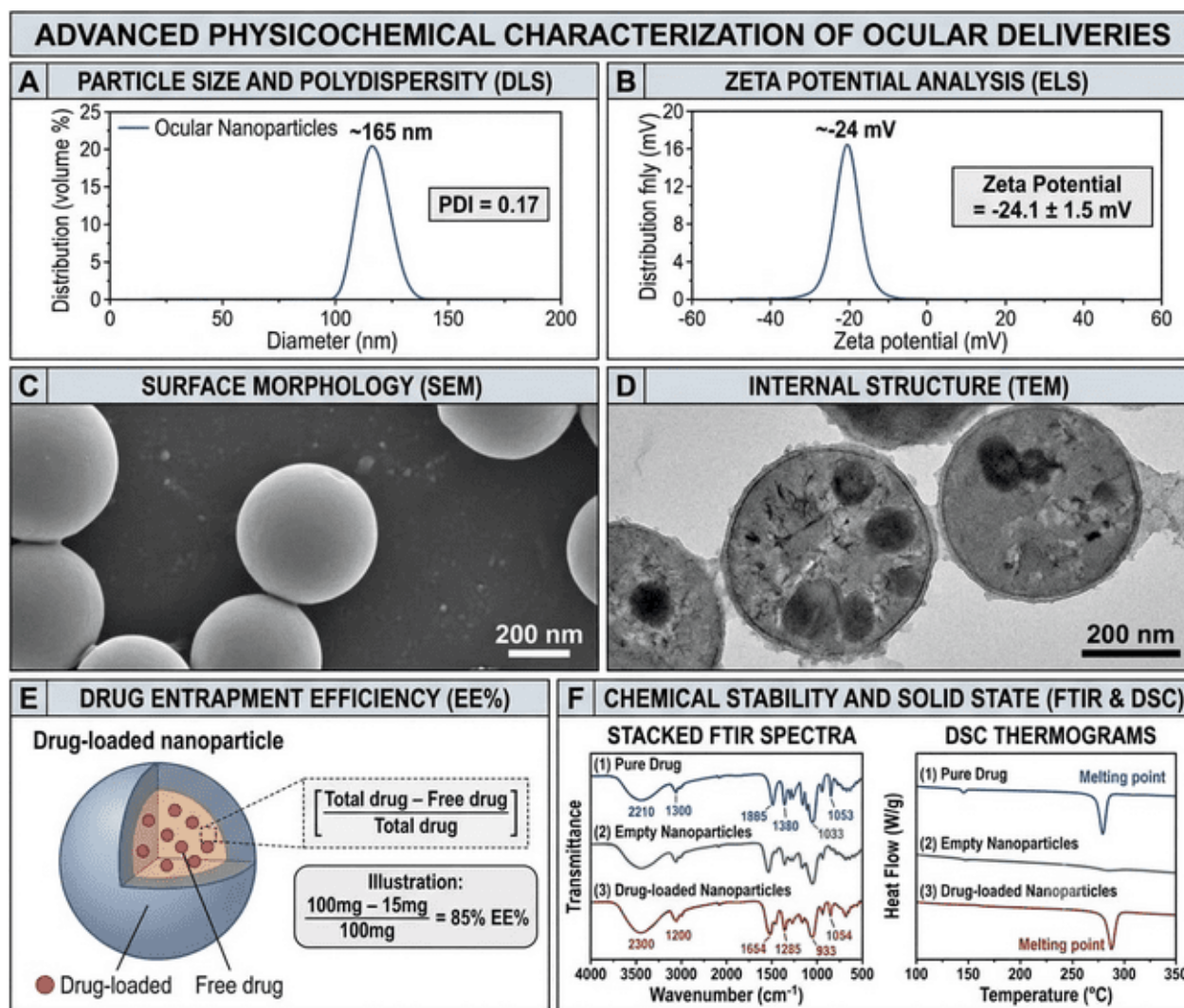


Fig No. 8 Physicochemical Characterization

Rheological and Viscosity Evaluations:

Determination of flow behaviour, viscosity profile and sol-gel transition temperatures for in-situ gelling and viscous preparations by means of rotational viscometers [63].

In-vitro Drug Release Assays:

Carrying out the kinetic analysis of release through modified Franz diffusion cells or dialysis sac method in simulated tear fluid at 34°C [64, 65].

Ex-vivo Corneal Permeation Assays:

Using the excised goat, rabbit or bovine corneas mounted in diffusion cells to evaluate the trans-corneal flux and apparent permeability coefficient [66, 67].

Ocular Irritation and Biocompatibility Testing: Conducting the standard Draize rabbit eye irritation test, Hen's Egg Chorioallantoic Membrane (HET-CAM) test and in-vitro cytotoxicity analysis, e.g. MTT assay on corneal epithelial cell lines [68, 69].

2. Physiological and Anatomical Barriers to Administration

Mechanisms of defence of the eye can be divided into static, dynamic and biochemical barriers that each contribute to the premature clearance of therapeutics.[70]

2.1 Fixed Barriers

Static barriers are the physical layers of tissue that block diffusion of molecules. [76]

The Cornea:

The major barrier to topical delivery. It has three main layers: the lipophilic epithelium, the hydrophilic stroma (which makes up about 90% of the corneal tissue and contains hydrated collagen) and the lipophilic endothelium. [89] Therefore, a drug should have a proper balance between hydrophilicity and lipophilicity to cross all these three layers effectively. [90]

The Conjunctiva and Sclera:

The sclera is about 10 times more permeable than the cornea and provides a possible transscleral route to circumvent the cornea-conjunctiva barrier for large and hydrophilic molecules. [93] However, the conjunctiva is highly vascularized, often resulting in systemic absorption and nonproductive loss of the drug. [96]

Blood-Aqueous Barrier (BAB) and Blood-Retinal Barrier (BRB):

The posterior segment is tightly regulated by the BRB. [101] The tight junctions of the retinal pigment epithelium (RPE) restrict paracellular transport, resulting in the BRB being selectively permeable to only highly hydrophobic molecules. [109]

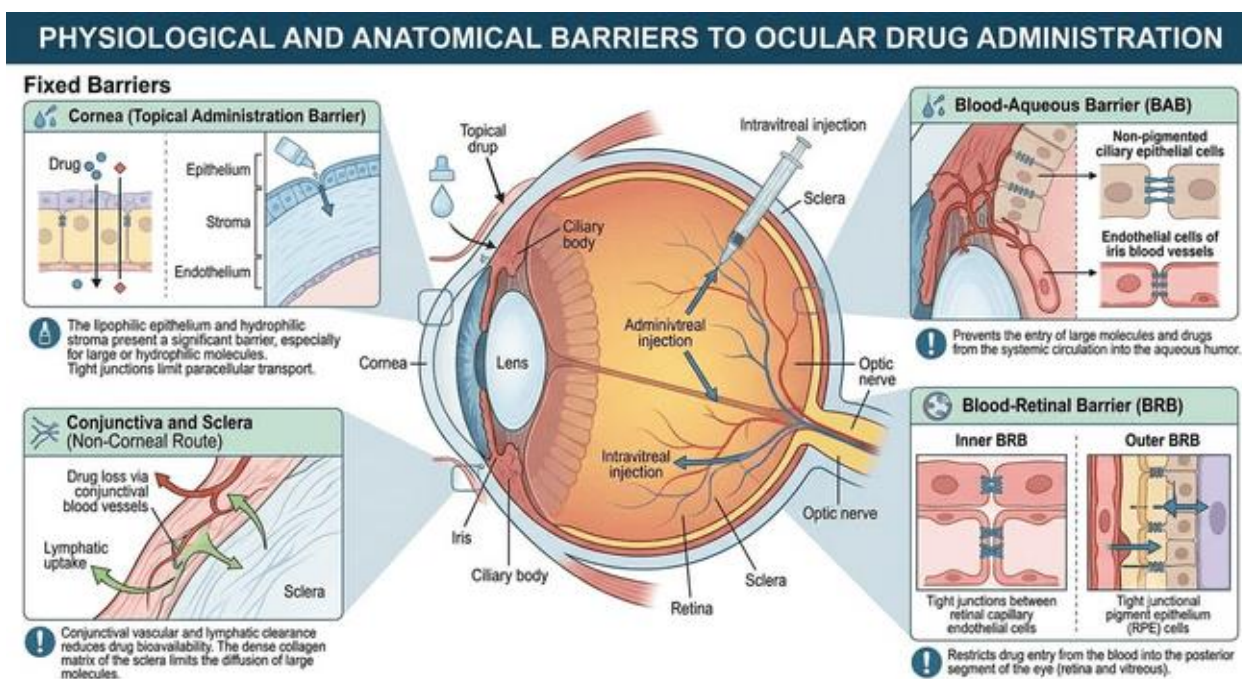


Fig No. 9 Fixed Barriers

2.2 Barriers in Motion

The dynamic barriers actively clear drugs from the ocular surface and internal chambers. [59]

Tear Turnover and Drainage:

The normal rate of tear production (0.5–2.2 $\mu\text{L}/\text{min}$) leads to rapid washout of instilled solutions. More than 75% of an administered ophthalmic solution is lost through nasolacrimal drainage. [77]

Blood and Lymphatic Flow:

The conjunctiva and choroid are highly vascularized, offering a “sink” to rapidly clear drugs into systemic circulation prior to reaching therapeutic targets in the inner eye. [99]

2.3 Biochemical barriers

Secondary defense mechanisms include efflux pumps (e.g., P-glycoprotein) and metabolic enzymes in ocular tissues that metabolize active pharmaceutical ingredients or actively pump them out of the cells before they can achieve a therapeutic effect. [106]

3. Novel Approaches for targeted and sustained release

To overcome these barriers, researchers have developed different advanced ocular delivery systems for drugs (ODDS) capable of prolonged residence time, enhanced tissue permeation and controlled release kinetics. [101]

3.1 Nanocarriers system

Nanotechnology involves manipulating matter at a scale of 10-1000 nm. This is a size that can penetrate ocular tissues, but larger micro-particles cannot. [103]

Liposomes:

Lipid-based vesicles comprising a phospholipid bilayer enclosing an aqueous core capable of entrapping hydrophilic or hydrophobic drugs. [82] Cationic liposomes are highly effective due to their electrostatic attraction to the negatively charged mucin layer of the tear film, greatly extending the residence time. [85]

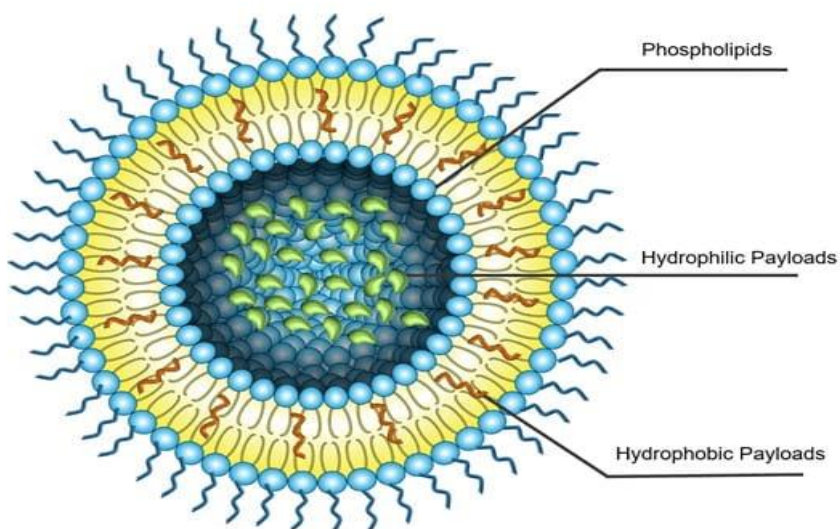


Fig No. 10 Liposomes

Polymeric Nanoparticles:

Biodegradable polymers like PLGA or chitosan are used to prepare nanoparticles that protect drugs from enzymatic degradation. They can be engineered to release drugs over weeks or months, thus creating subconjunctival or intravitreal depots. [110]

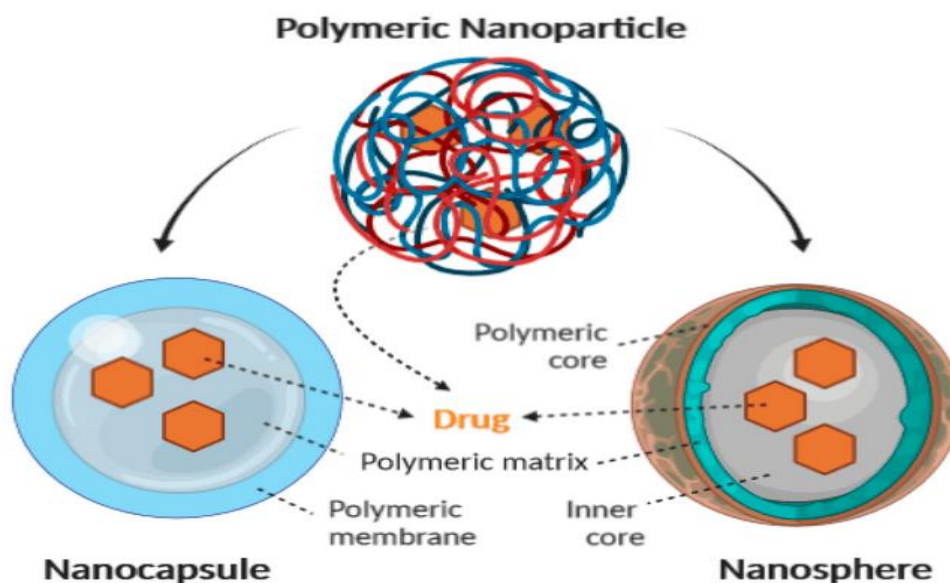


Fig No. 11 Nanoparticles

Dendrimers:

Highly branched, tree-like macromolecular architectures with enormous surface-area-to-volume ratios. Their well-defined structures permit the simultaneous conjugation of targeting ligands and drug molecules, thus providing a highly tunable delivery platform. [98]

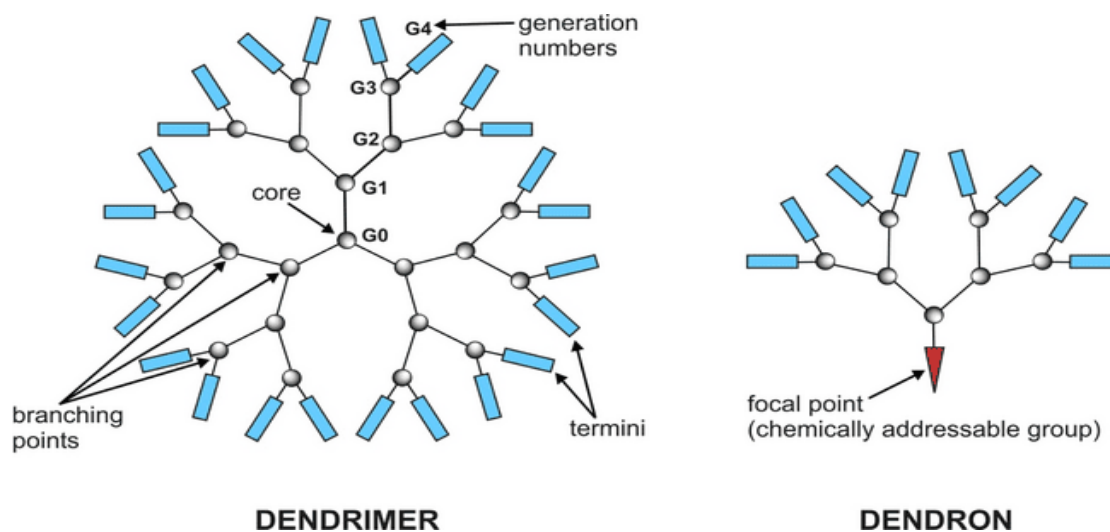


Fig No. 12 Dendrimers

3.2 In-Situ Gelling Hydrogels:

Standard hydrogels are thick and hard to instill. In-situ gels overcome this problem by being in the form of a low-viscosity solution when they are being instilled, and then undergoing a sol-gel phase change when exposed to stimuli in the eye—for example, temperature (temperature-sensitive), pH (pH-sensitive), or ion concentration (ion-sensitive). [85] This phase change results in the formation of a viscoelastic matrix in the cul-de-sac of the eye, which prevents nasolacrimal drainage and causes the drug enclosed within to be released slowly as the polymer erodes gradually. [77]

3.3 Ocular implants and Ocusersts:

In the case of chronic conditions such as glaucoma or diabetic macular edema, devices which deliver medication over periods of months or years are a major advancement. [65]

Ocusersts:

These are thin, multi-layered discs which are placed into the conjunctival cul-de-sac. They have a central drug reservoir located between two rate-controlling polymeric membranes and the drug is released by means of diffusion, osmosis or bioerosion, thus reducing the number of doses from daily applications of drops to one insertion per week. [62]

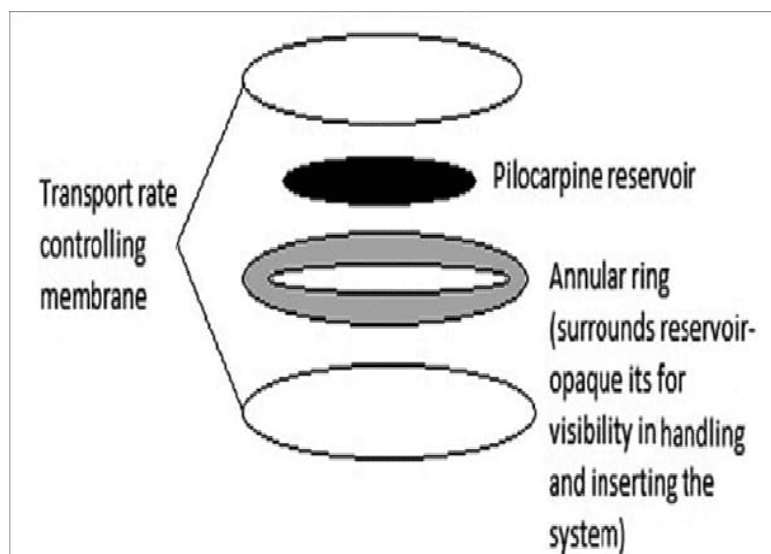


Fig No. 13 Ocusersts

Intravitreal implants:

are available in two forms, namely biodegradable ones (for example Ozurdex®) and non-biodegradable ones (such as Retisert®); they are inserted surgically or by injection into the vitreous humour in order to produce a zero-order release directly to the macula and retina for a period of up to three years. [59]

3.4 Soft contact lenses (SCLs) and Nanowafers:

Contact lenses have been put to use as devices for delivering drugs. [81] This is achieved either by soaking hydrogel lenses in a drug solution or by using advanced molecular imprinting techniques, so that scleral contact lenses can act as a continuous reservoir for the drug over the cornea. [91] The lens causes the drug molecules to stay in the tear film after the lens for a longer period of time, which in turn leads to a greater flux through the cornea and reduces systemic drainage. [94]

3.5 Microneedles:

Microneedles provide a minimally invasive way of passing through the sclera. Coated, dissolving, or hollow microneedles can penetrate only fractions of a millimetre in order to place drug depots in the suprachoroidal space. [102] This method results in high bioavailability for the posterior segment while completely avoiding the problems linked with deep intravitreal injections. [93]

4. FUTURE PERSPECTIVES:

The future of ocular pharmacotherapy will depend on the use of combined methods and "smart" drug delivery systems. Ongoing clinical trials are looking at combining nanoparticle-loaded hydrogels with drug delivery technologies powered by AI which use closed-loop feedback. [70] Moreover, prodrug strategies involving the chemical modification of molecules to boost their lipophilicity and enable specific targeting of transporters (for example, by targeting peptide influx pumps) have shown that they can greatly increase the half-lives in the vitreous and retina. [99] However, the main obstacles to regulatory approval will continue to be the large-scale production of nanoparticles and the establishment of long-term toxicological safety for use over a prolonged period. [105]

CONCLUSION

Significant progress has been made in the development of ocular delivery system since conventional, but ineffective, eye drops [76]. In spite of existing physiological challenges like fast elimination rate and strong ocular barriers, recent developments in nanotechnology, mucoadhesive polymers, stimuli-sensitive in-situ gels and bioerodible implants can provide new possibilities [71]. Interdisciplinary research in the field of pharmaceuticals, materials science and ophthalmology is going to make possible the practical implementation of the novel systems in clinics. [111]

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