Past, Present and Future Perspectives in Ocular Drug Delivery and Emerging Therapeutics

Conventional Approaches in Topical Ocular Drug Delivery and Developments in the use of Contact Lenses as Drug Delivery Devices

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Abstract

Drug delivery approaches have diversified over the last two decades with the emergence of nanotechnologies, smart polymeric systems and multi-modal functionalities. The intended target for specific treatment of disease is the key defining developing parameter. One such area which has undergone significant advancements relates to ocular delivery. This has been expedited by the development of material advancement, mechanistic concepts and through the deployment of advanced process technologies. This review will focus on the developments within lens-based drug delivery whilst touching on conventional and current methods of ocular drug delivery. A summary table will also provide quick reference to note the key findings in this area. In addition, the review also elucidates current theranostic and diagnostic approaches based on ocular lenses.

Keywords: ocular drug delivery, emulsions, contact lenses, hydrogel, drug loading, nanotechnology, matrix Composition.

Introduction:

Despite being an easy accessible organ, the physiology and anatomy of the eye poses demanding challenges with regards to ocular drug delivery (ODD). Anatomical and physiological (and to a certain degree biochemical) barriers provide extensive protection from foreign matter[1,2]. Due to this, effective delivery devices must be designed and developed in order to target specific ophthalmic tissues and to help control ocular disease progression. The arena of ODD is constantly evolving with potential to exploit the emerging recognition of nano-engineering and polymer science. Over recent years, there has been emphasis on novel, non-evasive delivery devices for not only controlled and sustained ODD but also with applications extended to systemic delivery and theranostics[3-7], all showing promising results with the potential development of new ocular products in the near future.

This review will touch upon conventional approaches for ocular drug delivery and focus in on the use of contact lenses as drug delivery devices for topical drug delivery. The review also provides tabulated details for easy reference on the developments in this area. In addition, future perspectives for drug delivery are provided.

Eye Structure:

The eye is a spherical organ consisting of two “spheres”; anterior and posterior chambers. It is made up of several structures; all with specific functions with regards to the physiology of the eye.

The anterior segment makes up the front of the eye whilst the posterior segment makes up 2/3 of the organ. The outermost structure, the cornea, is one of the most important structures of the eye with respect to ODD. It works predominantly to protect the front of the eye and focus light into the eye[8]. Moreover, it is the barrier that pharmaceutical formulations/actives would pass through in order to enter the eye and have therapeutic effect. It is made up of 5 layers, each varying in thickness (500µm thick in total)[8]. Another vital part of the eye for ODD is the ciliary body which is located between the lens and choroid (part of the posterior segment). It produces the aqueous humour (AH); a transparent gel which occupies the space between the lens and the cornea (aka the posterior chamber), which believed to has immunological function to defend against pathogens. Also, it provides nutrients (i.e. amino acids and glucose) to the cornea and the lens[9]. The AH passes through the posterior chamber and move through the pupil into the anterior chamber. The

production and drainage of the AH via the Trabecular meshwork maintains the correct intraocular pressure (IOP); 12-22 mmHg[10]. If this pressure is compromised, then the consequence can be severe, as with glaucoma. The trabecular meshwork is located where the cornea meets the iris and allows the AH to drain into a set of tubes called the Canal of Schlemm to systemic blood flow.

Other structures that make up the anterior segment of the eye include the iris, sclera, lens, pupil and conjunctiva. The posterior segment houses the retina, macula, fovea and optic nerve.

Routes of Administration in Ocular Drug Delivery

There are 3 main routes for drug delivery to the targeting region of the eye; topical, systemic and intraocular. The topical route (corneal absorption) is the primary chose due to high patient compliance and ease of administration. Regardless of being a non-invasive method; physiological hurdles such as high teat turnover rate (16% per minute) and tear dilution reduces the bioavailability of the drug with less than 5% of the drug penetrating the cornea. Nasolacrimal drainage due to excess product on the corneal tear film can also occur. The precorneal film destabilises upon administration causing blinking, resulting in the drug being pumped into the systemic circulation.

Systemic administration of ocular drugs (e.g. via tablets) is often discarded due to the very small ratio of the eye to the entire body. Many ocular drugs also have dual functions e.g. timolol is an antiglaucoma drug but also acts as a non-selective beta-adrenergic blocking agent with action on the sympathetic nervous system which can cause a decrease in blood pressure and slows cardiac activity and lung function[11].

The anatomical barriers of the various structures that make up the eye and the physiology of these structures make it challenging to achieve precise drug delivery.

Intraocular approaches are utilised to delivery drugs directly to the posterior segment of the eye. Due to structural barriers of the cornea and conjunctiva, injections via the intravitreal route or periocular route can be practical and more effective. Despite low patient compliance, these injections are capable of delivering therapeutic agents directly to the target tissue; bypassing the anatomical barriers of the eye. Using a very fine needle (30-G), the drug solution is injected directly to the vitreous and retina. Regardless of delivery of drug at high concentrations directly to the targeted region, drug distribution is not homogenous. Another challenge this is met with intravitreal injections concerns the clearance of the drug. Direct delivery to the

vitreous means the drug clearance occurs either via the anterior pathway or posterior pathway. The aqueous clearance pathway consists of the drug diffusing through the AH and is subsequently drained whilst the posterior pathway involves drug management across the blood retinal barrier; requiring active transport[12]. Due to this, hydrophilic solutes with high molecular weight remain in the vitreous humour for extended period of time. This, alongside repetitive perforation of the eye tissue can lead to the development of conditions such as endophthalmitis and cataracts.

Conventional Ocular Delivery Methods

The following section will look into conventional and current approaches to topical ocular drug delivery **(Figure 1).**

Eye Drops

Eye drops make up approximately 90% of all topical ocular formulations; in the form of solutions, suspensions and emulsions[13]. Due to the nature of the targeting tissue and the mode of application, extreme care is needed for such formulations to be isotonic (same osmotic concentration/pressure as the targeted tissue), non-invasive and sterile. Ease of formulation and patient compliance make eye drops favourable to both manufactures and patients alike. Despite this, there are some drawbacks as less than 5% of the drug from a typical eye drop (50µL) actually permeates the cornea[14]. This is due to anatomical, physiological, metabolic and biochemical properties and barriers of the eye; resulting in drug loss via nasolacrimal drainage[14]. Consequently, frequent administration of drug is needed in order to achieve the therapeutic drug levels in the eye[15].

In a bid to improve the residence time of the drug in the eye, additives such as viscosity enhancers (e.g. Hydroxypropyl methylcellulose, polyethylene glycol), permeability enhancers (e.g. benzalkonium chloride, ethylenediaminetetraacetic acid (EDTA)) and cyclodextrins (e.g. Brij® 78) have been incorporated into formulations. Cyclodextrins increase the water solubility of lipophilic drugs (and aqueous stability) therefore increase drug bioavailability and absorption. Aceclofenac (a topical non-steroidal anti-inflammatory drug (NSAIDs)) used to treat anterior chamber inflammation along with pain and inflammation associated with post-operative treatment. Preservatives such as methyl paraben (MP), propyl paraben (PP), benzalkonium chloride (BAC) and viscosity enhancer (Hydroxypropyl methylcellulose

(HPMC)) were added to decrease the permeability coefficient of aceclofenac. Moreover, the apparent permeability coefficient was also reduced by increasing the solution pH value from 6.0 to 8.0[16]. The combination of MP, PP and BAC enabled an increase in the transcorneal permeation of this active drug whilst pharmacodynamics in vivo studies showed this novel formulation was effective that it is commercially available (Voltaren® ophthalmic drops 0.1% (diclofenac sodium)).

Some actives (e.g. dexamethasone[17]) and metabolites (e.g. prednisolone[18]) are poorly-soluble or insoluble in aqueous media. To improve their solubility, these materials can be complexed with cyclodextrins (CDs) to form water soluble inclusion complexes. CDs are amphiphilic (has hydrophobic and hydrophilic regions) cyclic oligosaccharides extensively used to improve the solubility and stability of some ocular drugs such as dexamethasone[17], dorzolamide[19,20], ciprofloxacin[21] and cyclosporine A[22]. Nijhawan and Agarwal, have developed an ophthalmic preparation containing ciprofloxacin by inclusion complexes of ciprofloxacin hydrochloride with hydroxypropyl-β-CDs using freeze drying method. The complexes exhibited increased water solubility of the drug, stability, biological activity and ocular tolerance when compared to a commercially available ocular formulation[21]. Dimethyl-β-CDs is another type of CDs was used for ocular delivery of prednisolone with the addition of HPMC. Prednisolone (water insoluble corticosteroid) manipulates the body's immune system response conditions such as arthritis, cancers and eye conditions (e.g. keratitis). Couto et al exploited the amphiphilic nature of dimethyl-β-CDs to form complex with prednisolone and HPMC. Dimethyl-β-CDs increased drug water solubility and maintained pseudoplastic behaviour in the suspension that presented a d90 lower than 90 µm (particle size)[18].

Emulsions

Addition of additives is one approach to improve liquid formulations for topical drug delivery to the eye. Modifying the physical properties (e.g. membrane permeability, cellular uptake) of the ocular cells, in an attempt to increase drug penetration and drug presence at site of action is another approach. Emulsions are often used to improve the solubility of poorly soluble drugs. They are heterogeneous dispersions of oil in water (o/w) or water in oil (w/o), usually with the addition of surfactants or co-surfactants[23]. Emulsions are considered to be advantageous to topical ODD due to their ability to increase membrane permeability and cellular uptake due to the surfactants[24]. The underlying theory for this revolves around the fact that surfactants

interact with the lipid bilayer around ocular cells modifying their physiochemical properties. Surfactant saturation in the lipid bilayer consequently leads to the formation of micelles which act to remove lipids from the cell membrane by solubilisation that in turn increase the membrane permeability. This fundamental principle has led to numerous studies that have yielded promising results; increased drug concentration in vital structures of the eye[25,26]. There are various ways of categorising emulsions; the most common is via droplet size. Nano-(submicron) emulsions usually contain droplets 100-1000nm in diameter whilst droplets in micro-emulsions range from 10nm to 100nm. Whilst both demonstrate more stability than simple emulsions and are low in viscosity; there are some crucial differences between the types of emulsions which ultimately affect the final purpose of the emulsion. Micro-emulsions spontaneously form via self-assembly whilst nano-emulsions are formed intentionally via mechanical shearing. The stability of these emulsions is a critical attribute; nano-emulsions are kinetically stable unlike micro-emulsions which are thermodynamically stable.

The use of emulsions in topical ODD was first investigated in 1989, for the treatment of glaucoma. Incorporation of surfactant lecithin to an o/w micro-emulsion increased the bioavailability of timolol in the aqueous humour, when administered to the conjunctival sac of rabbits. When compared to a formulation without lecithin, there was 3.5 times much drug present in the aqueous humour[24]. Lidocaine, (a hydrophobic drug), has been entrapped in various oil-in-water micro-emulsions (~10-20nm particle size) before dispersion through pHEMA lenses[27]. Gulsen et al found that these particles gave a burst release at first (35% of drug) followed by 80% and 95% of the drug being released within 4 days and 9 days, respectively.

More recently, topical ODD with respect to emulsions have turned to nano-emulsions (NE); o/w or w/o. The dispersed phase is in the form of nanodroplets 50-200nm in diameter heterogeneously dispersed within the external immiscible phase. These formulations are useful for the delivery of both hydrophilic and lipophilic drugs[28], however they are still subject to emulsion instabilities; coalescence, flocculation and Otswald ripening. Nano-emulsions have been investigated for the delivery of wide range of bioactive molecules like antibacterial agents (e.g. cetalkonium chloride[29]) and anti-glaucoma drugs (e.g. dorzolamide hydrochloride[30]). The anti-glaucoma drug (delta-8-tetrahydrocannabinol) was one of first drugs to be successfully

encapsulated into NE for topical ODD. Delta-8-tetrahydrocannibinol (antiglaucoma lipophilic drug) was incorporated into the oil phase of a submicron emulsion (mean droplet size: 130±41nm) and showed an intense and long lasting reduction effect for the intraocular pressure. This formulation remains stable after steam autoclaving and after storage for 9 months[31]. These promising results sparked a search for more biocompatible actives for extended action in the eye.

Incorporation of surfactants ultimately affect the charge of formulation; due to this, cationic surfactants have been found to increase bioavailability of drugs due to electrostatic interactions between cornea and membrane protein (mucin), hence increasing drug residence time in the cornea[32,33]. However, their toxicity is a disadvantage that needs to be overcome; very few have been approved for ocular use.

Novagali, a French pharmaceutical company, has developed a cationic NE that improves drug delivery by exploiting the negative charge of ophthalmic cells at physiological pH. The use of positively charged formulations can increase the electrostatic interactions, consequently increase the residence time. This innovative technology has already been used to deliver cyclosporin A (Cyclokat® and Vekacia®)[34] with several more applications in the pipeline including latanoprost delivery for glaucoma treatment[35].

More recently, emulsion cross-linking and formulation optimisation via factorial design was utilised to improve precorneal residence time and drug penetration of the hydrophilic antibiotic doxycycline hydrochloride (DOX HC). The nanoparticles (331-850 nm size range) encapsulated around 45-80% of DOX HC. This formulation showed sustained release kinetic of DOX HC with significant antibacterial effect on strains of *Staphylococcus aureus* and *Escherichia coli* ($p<0.011$) as compared to DOX HC aqueous solution[3].

Viscoelastic gels

Viscoelastic gels are hydrophilic polymeric matrices capable of swelling after water uptake, allowing drug diffusion in and out of the system. Once swollen, the polymeric matrix is approximately 60-90% water[36]. These gels can form before administration or in situ; however, more emphasis has been placed on the latter due to ease of administration and precision of gels compared to solutions [37]. Phase transition on the ocular surface increases formulation residence time, and hence increases drug exposure. Both natural polymers (e.g. gelatin[38], dextran[39], alginate[40],

chitosan[38,41], polysaccharides[42]) and synthetic polymers (e.g. poly -hydroxyethyl methacrylate[43,44], glycolic acid[45,46] have been used as swellable matrices. It is important to note that selection of polymer is crucial due to the effect on the final gel properties. Due to different polymers having different advantageous properties, it is common to blend two or more polymers to obtain optimised gel systems. For example, chitosan has been blended with gelatin and glycerol phosphate to develop a thermoresponsive gel which enhanced in vitro and in vivo compatibility for the delivery of latanoprost[41]. In vivo release studies in rabbit models demonstrated steady drug concentration in the aqueous humour without burst release. This sustained release system continued for 8 days; with IOP being restored within this time period and maintained for further 31 days[41].

Chitosan has also been combined with poly (N-isopropylacrylamide) (PNIPAM) to exploit the thermosensitive nature of PNIPAM to develop an in situ thermoresponsive HG for the delivery of antiglaucoma drug timolol maleate (TM)[47]. In vivo studies showed increased drug permeation in rabbit cornea in the absence of any cytotoxicity. Compared to conventional TM eye drops, although the onset of action was observed at t=0.5 h, the HG demonstrated stronger IOP reduction, highlighting the potential of chitosan-PNIPAM blend of improving efficacy of TM[47].

Temperature is not the only stimulus that has been employed to trigger the swelling of gel matrices; pH triggered systems (e.g. Poly acrylic acid (PAA)[48,49]), ionic strength (e.g. sodium alginate[4,50,51]) and enzyme substrate systems have also been evaluated. PAA is a polymer which has a large array of applications, including thickening agent, suspending agent and emulsifying agent. At physiological conditions and aqueous environment, PAA is an anionic polymer and is commonly combined with hydroxypropyl methylcellulose (HPMC) to increase the viscosity of the formulation, ultimately increasing drug residence time[48].

Dubey et al studied the in vivo IOP lowering activity of PAA (carbopol C 934p)-HPMC stimuli sensitive gelling system[48]. Once administered to the eye, the pH changed accordingly causing the gel to increase in viscosity, providing sustained release of drug. In vitro release studies demonstrated zero order release; 90% of drug (TM, brimonidine tartrate (BT)) was released within 8 hours; exhibiting sustained release. The ability of the novel stimuli-sensitive TM and BT loaded HG to lower IOP was compared to a marketed formulation. The marketed formulation lowered IOP but failed to maintain this. The gelling system with a combination of

both drugs achieved greater IOP reduction which was maintained for a longer time than the marketed formulation[48].

Sodium alginate (SA) is a viscosity enhancer often used in drug delivery due to its ability to undergo gelation as a result of changes in ionic strength[52]. SA is susceptible to phase change when exposed to divalent ions such as magnesium and calcium; an ion which is abundant in tear fluid[52,53]. This property of SA has been exploited to increase drug residence time. For instance, SA along with methyl cellulose was successfully used to formulate a novel in situ gelling matrix for therapeutically efficacious sustained release and stable ophthalmic drug delivery of moxifloxacin hydrochloride[50]. There are already some marketed formulations for topical ocular delivery of timolol maleate. Timoptic-XE® is based on anionic heteropolysaccharide derived from gellan gum. In this product, an aqueous solution of gellan gum, in the presence of a cation (in precorneal tear fluid), has the ability to gel enabling prolonged exposure to the product, increasing drug release.

Innovative Systems

Implants

Ocular implants are effective drug delivery devices which are able to sustain drug delivery over months and even years. These devices are loaded with therapeutic agents and are surgically inserted to the eye at the target site. The main advantage of these systems is they serve dual purpose; the implants can act as controlled delivery systems but also help maintain therapeutic concentrations in the eye. Thee material from which these implants are made can differ between non-biodegradable (e.g. polyvinyl alcohol (PVA), silicon) and biodegradable (PLGA, Polylactic acid) (PLA)). PVA and ethylene vinyl acetate have been utilised in a commercial ocular implant to achieve the sustained delivery of antiviral drug ganciclovir. The Vitrasert® Implant (containing a ganciclovir tablet) is surgically inserted and can be removed and replaced following exhaustion of drug; often after 5 to 8 months. The PVA provides a semi-permeable matrix allowing drug diffusion whilst ethylene vinyl acetate is an impervious layer; providing the sustained release of ganciclovir.

Renexus® is a non-vitreous implant used in the treatment of retinitis pigmentosa and age-related macular degeneration. The non-biodegradable implant is transfected with a plasmid encoding ciliary neurotrophic factors loaded into human cells. These

encapsulated cells releases the factors in the posterior segment of the eye for the treatment of posterior conditions.

Biodegradable implants are preferred due to their ability to degrade in the body (into water and carbon dioxide) after depletion of drug. Polymers PLA, PLG and PLGA are frequently researched and used as a result of their biocompatibility and long shelf life with respect degradation. Ozurdex® has been approved by the FDA for the treatment of diabetic macular edema. This biodegradable rod-shaped implant contains dexamethasone which delivers drug delivery to the posterior segment[54].

Natu et al have developed dorzolamide-loaded device which can be surgically introduced into the eye. *In vivo* testing demonstrated more efficient lowering of IOP in rabbit eyes compared to topical delivery of dorzolamide.

Iontophoresis

Ocular iontophoresis utilises a low electrical current to drive ionised drugs into ocular cells or tissue. Anodes are used to drive positively charged drugs through tissue and cathodes for negatively charged molecules. Iontophoresis is a painless, fast, non-invasive drug delivery method and is capable of delivering therapeutic concentrations of drug to the targeted tissue; increasing drug bioavailability and decreasing the frequency of dosing. The first study to apply this theory was reported in 1943 for transcleral delivery[55]. Due to constant evolution in the pharmaceutical industry and ocular field has developed a novel system in which iontophoresis is used to delivery therapeutic concentrations of drug to both anterior and posterior segment. The Eyegate II delivery System by EyeGate Pharmaceutical Inc employs an inert electrode to ionise water to produce hydroxide or hydronium ions required to drive charge drug molecules. This system has been used to delivery dexamethasone phosphate solution for the treatment of dry eye and is currently in phase 3 clinical trials[56].

Microneedles

Microneedles (MNs) are drug delivery devices which have rapidly developed in the last decade. These devices consist of very small needles capable of piercing tissue,

creating micropaths through which drug molecules can permeate through[57-59]. The rapid development of these devices has shown the potential in enhanced intraocular drug delivery. Solid MNs (500-700µm) were coated with pilocarpine and showed rapid dissolution of drug within scleral tissue within 30 seconds of insertion. *In vitro* analysis proved the mechanical strength of the MNs whilst showing lack of complications that are usually associated with intraocular injections and systemic administration[60]. More recently, stainless steel MNs were used to study the delivery of bevacizumab for treatment of corneal neovascularisation[61]. MNs 400µm in height were coated in drug and inserted into New Zealand white rabbits. Rabbit eyes treated with eye drops showed a 6% reduction of neovascularisation after 18 days whilst eyes treated with MNs showed a 44% reduction compared to untreated eyes.

Thakur et al have developed rapidly dissolving MNs for delivery via intrastromal or intrascleral route[62]. High molecular weight PVP arrays 800µm in height showed to withstand higher forces than low molecular weight arrays. MNs using high molecular weight PVP showed complete dissolution in 180 seconds compared to the 10 seconds of low molecular weight PVP. The use of MN in corneal and scleral tissues showed the enhancement of macromolecules delivery following puncturing by MNs; with drug molecules forming depots in the tissue; enhancing sustained drug delivery.

Contact lenses

Despite the efforts to improve conventional methods to achieve extended drug exposure time to ophthalmic tissue, these methods are no longer adequate for treating ocular conditions. Regardless of patient compliance, ease of administration and formulation, there are some fundamental drawbacks with respect to the formulation itself (e.g. eye-drops, *in situ* gels). The extended residence time, blurred vision and poor availability (due to nasolacrimal drainage) can limit the application/administration of such formulations to specific times (e.g. night)[63]. Many systems (e.g. microneedles) also have low patient compliance, which can alter drug administration and reduce drug bioavailability. Appreciating these limitations has shifted focus onto developing various ocular devices. The most common device to emerge from this research is contact lens (CL). Soft contact lenses are polymeric/hydrogel discs which are inserted into the eye and come into contact with

the cornea; held to the corneal tear film by surface tension[64]. The main use of CLs is for vision correction (e.g. conditions such as astigmatism and myopia)[65] but uses have also been exploited in cosmetics/aesthetics as well as therapeutics and theranostics[66-69].

The idea of CLs was first conceptualised by Sir John Herschel in 1832; with the first glass CL being developed in 1887. Principle breakthrough for soft contact lenses came in the 1960's where Wichterle and Lim experimented with soft, water-absorbent materials for biological use[70]. Advances in material development led to a breakthrough in the topical ocular drug delivery arena. The crosslinking of 2-hydroxyehtyl methacrylate with ethylene glycol dimethylacrylate yielded a polymer (poly (hydroxyethyl methacrylate) (pHEMA)) capable of forming flexible hydrophilic HG's[65]. The ability of pHEMA to retain up to 38% water to form flexible matrices overcame the vital disadvantages met with earlier proposed rigid materials for contact lenses such as period of usage. Due to CO_2 retention when eyes are closed, there is a prerequisite for CLs to have increased gaseous permeability.

In 1999, material development led to monomers (e.g. tris(trimethylsiloxy) silane) being used to fabricate silicone hydrogels[71]. These lenses possessed increased oxygen permeability, unlike conventional pHEMA lenses and therefore could be worn for prolonged periods of time. Silicone lenses have more rigid structure, accordingly development and manufacture was much easier. Only in the last two decades, CLs have been considered as useful devices suitable for drug delivery for such drugs like antibiotics, NSAIDs and anti-glaucoma drugs. As a result, many concepts (conventional and novel) to alter HG lenses have been introduced to achieve sustained/extended ocular drug delivery. Timolol has been incorporated into contact lenses which exhibited a 12 hr of sustained release[72] while lidocaine-loaded contact lenses demonstrated a sustained released over 8 days[73]. Table 1 summarises some of the research carried out based on the use of contact lenses as drug delivery devices.

Mechanisms of drug loading

Soak and release

One of the first attempts to develop drug loaded CLs involved soaking pre-prepared lenses in an aqueous drug solution, allowing drug to be taken into the hydrophilic matrix of the lens. This conventional method was first proposed over 40 years ago[74]

and is now commonly used for delivery of anti-glaucoma drugs[75-78], antihistamines[79,80] and antibiotics[66]. Upon insertion in the eye, initial burst release of active is achieved followed by sustained release via diffusion. The drug solution can alternatively be topically applied to the eye with the lens in situ.

Hillman et al were one of the first to utilise this method, using cholinergic anti-glaucoma drug pilocarpine hydrochloride. A blend of vinyl pyrollidone/acrylic monomers were used as CL material. The resulting hydrophilic lens were soaked in a 1% drug solution and inserted into the eyes of patients with acute closed angle glaucoma. An average of 54.8% IOP reduction was observed within 2 h treatment; notably comparable to the 49.7% IOP reduction seen with intensive pilocarpine treatment (1-2 drops every minute for 5 min, every 5 min for 30 min)[75].

More recently, the potential delivery of hyaluronic acid from CLs was assessed for the treatment of dry eye syndrome. The HG CLs loaded with HA exhibited release for up to 48 h; whilst maintaining the physical properties of the lens. In vivo release pharmacokinetics in rabbit tear fluid demonstrated effective increase in HA residence time in comparison to HA eye drops[81].

In an attempt to retard the diffusion of hydrophilic drugs from CLs for sustained release, vitamin E (VE) has been incorporated into lens matrices to provide a hydrophobic barrier[66,77,82-85]. Soaking of lens in VE:ethanol solution prior to drug loading poses a barrier to the drug molecules when diffusing out of the matrix presenting the potential for sustained drug delivery; advantageous for conditions where frequent doses are essential.

Cystinosis is a rare genetic condition which mostly affects children in which the amino acid ‘cysteine’ accumulates in vital organs (eye, kidney, pancreas and brain). Hsu et al developed lenses loaded with cysteamine with incorporation of VE to achieve sustained drug release[83]. Addition of VE increased drug duration from 10 minutes to 3 h in solution. The lenses exhibited therapeutic concentration of the drug within 2 h of the lenses being worn; mimicking the action of hourly eye drops. Hsu et al also demonstrated that 20-30% of VE increased the release of moisturising agent dexpanthenol and osmoprotectant (compatible solutes that restore cell volume, stabilise proteins and protect cells from hyperosmolarity stress[86]) betaine from silicone lenses to 10 h; 60 times longer than unmodified lenses[84]. Topical anaesthetics such as lidocaine, bupivacaine and tetracaine (all hydrophilic at

physiological pH) were loaded into VE soaked lenses[82]. These lenses continually released drug for 1-7 days, beneficial for post-operative pain of corneal surgery.

Along with impeding drug diffusion, VE aggregates can provide UV protection to the cornea without altering lens transparency. Operating at a wave length smaller than that of visible light ensures there is no obstruction with respect to vision[87]. Although the method of soak and release has been met with various successes, the main challenge is to achieve and maintain the controlled release kinetic.

Molecular Imprinting

Molecular Imprinting (MI) is a novel technique which involves creating template nano-cavities within the lens matrix, which are subsequently used in molecular recognition. Incorporation of functional monomers (e.g. methacrylic Acid (MAA)) on polymer backbone advances drug affinity to the lens by providing sufficient binding sites for drugs[88]. Selection of functional monomer is crucial; they must be compatible with respect to lens material whilst having high affinity to the active. The process of MI is based on arranging the functional monomer around the drug molecules during polymerisation, creating a fixed, rigid structure due to the cross-linking stage in polymerisation[88]. The drug and any unreacted monomers are extracted leaving behind nano-cavities that only have molecular recognition for that particular drug. The lens can then be loaded by soaking in drug solution. MI is also a sought out technique as it enhances the spatial arrangement of the lens matrices, ensuring maximum drug loading.

Timolol has been used with MAA acting as the functional monomer and ethylene glycol dimethacrylate (EDGMA) as cross-linker due to its ionic interaction with timolol[6,72,89,90]. Hiratani et al were among the first to evaluate the in vivo potential of MI N-N-diethylacrylamide lenses[72,91]. Using different concentrations of the cross linker EGDMA, Hiratani et al utilised the MI method to increase timolol loading capacity. Imprinted contact lenses increased hydrogels affinity for timolol with prolonged drug release in the tear fluid of rabbits. Timolol from MI lenses was detected for 180 minutes; 2 fold longer than that found by non-imprinted lenses and 3 times longer than the 60 minutes observed with 0.25% aqueous eye drops[72]. The same team also prepared imprinted HGs that increased the uptake of broad-spectrum antibiotic norfloxacin (300 fold) using acrylic acid as the monomer[92].

Other therapeutic agents have also benefitted from MI; including NSAIDs (where a 10 fold increase ibuprofen and diclofenac loading capacity with sustained release for up to a week was observed[93]) and antibiotics (e.g. polymyxin B and vancomycin[94], ciprofloxacin[95,96]).

Hui et al developed imprinted lenses with acetic and acrylic acid (the functional monomer) that extended the release duration of ciprofloxacin to 3-14 days[95]. Using various ratios of acetic acid to ciprofloxacin solution, Hui et al also developed MI silicone lenses[96]. Compared to non-imprinted lenses, the modified lens matrices released ciproflaxcin for a considerably longer time ($P<0.05$). The MI lenses were evaluated for the ability to inhibit gram negative bacterium *Pseudomonas aeruginosa.* Lenses loaded with 0.3% ciprofloxacin demonstrated complete bacteria inhibition for initial 2 days; showing inhibitory concentrations of drug were being reached/release from the lenses. However, after day 3, an increase in the bacterial concentration was observed; this was thought to be due to the reduction of ciprofloxacin concentration after being released from the lenses. Although differences in bacteria population was observed when comparing both non-imprinted lenses and MI lenses; they were not statistically significant ($P>0.05$)[96].

Modifying Lens Matrix Composition/ionic interactions

The permeability of ocular therapeutic agents can be affected by their charge under physiological conditions. Modifying the lens composition and exploiting the ionic interactions of functional monomers can potentially aid in achieving sustained or controlled drug release[97]. A common approach in this respect is to incorporate monomers based on hydrophilicity and ionic nature. Variations in these side groups ultimately affect the final properties of the HG lenses; subsequently the monomer used and its ratios can be altered to achieve specific criteria/use. Incorporating cationic or anionic functional monomers (also known as ligands), can increase the weak interactions (e.g. hydrogen bonding, electrostatic forces), allowing the HG matrices to store charged drugs on the basis of ion exchange reactions. Ergo, the percentage of HG matrix that is made up of ligands will be directly proportional to the drug loading efficiency[97].

MAA is the most common ligand used to increase the ionic interactions in lenses; most prominent in pHEMA lenses. It is highly hydrophilic and anionic. Release kinetics of various ophthalmic drugs from MAA-loaded lenses has been studied

numerous times; all yielding promising results[98-100]. Uchida et al have developed contact lenses using hydrogels with cationic functional group on the side chain (using methacrylamidopropyltrimethylammonium chloride (MAPTAC) and 2-hydroxyethyl methacylate to obtain the cationic group)[98]. Hydrogels were capable of storing azulene (anionic drug), by the effect of ion exchange reaction, and releasing the drug under physiological conditions. There was a problem related to the size change of the hydrogel pre- and post- drug release; changes which were prevented by adding anionic monomers MAA and 2-methacryloyloxyethyl phosphate (MOEP) to the matrix[98]. MAA and MOEP were also added to pHEMA lenses resulted in extended release of naphazoline (a cationic vasoconstrictor). About 85% of the drug was released for 14 h, with the uptake of drug increasing by increasing the amount of anionic ligands within the matrix[99].

Modifying pHEMA soft lenses with functional monomers (different concentrations of MAA or N-vinyl-2-pyrrolidone (NVP)) was used to assess the in vitro release kinetics of corticosteroid triamcinolone acetonide[100]. The modified lenses with MAA exhibited similar swelling behaviour in physiological conditions; however, MAA-containing lenses demonstrated higher degree of swelling with the change in pH. This is a result of repulsive forces contained by the hydrogel generated by ionisation of carboxyl groups of MAA residues. Moreover, MAA lenses showed the best drug loading and the fastest drug release when compared with NVP hydrogels.

On basis of the ion-ligand mechanism, the in vitro uptake of antibiotic agents' gatifloxacin (GFL) and moxifloxacin (MFL) was assessed[101]. The drug uptake seemed to increase as percentage weight of anionic MAA increased. Initial burst release kinetics was observed from the modified lenses. In vivo studies exhibited greater drug concentration in cornea (GFL: 0.89µg/mL, MFL: 2.22µg/mL) and aqueous humour (GFL: 4.1µg/mL, MFL: 9.35µg/mL) after 24 hours when compared to antibacterial eye drops with the same antibacterial agents, which indicate an improvement in penetration into the eye.

Whilst the previous studies focussed on incorporating the ligands via copolymerisation, another novel concept was proposed in order to improve the release of ionic drug for more than 2 hours by using surfactants. Generally, this can be done by creating a high surface charged lens by adsorbing an ionic surfactant on the hydrogel matrix increasing the sustained release for an extended time. For instance, pHEMA CLs were developed for the controlled release of anionic drug

dexamethasone 21-disodium phosphate using the cationic surfactant cetalkonium chloride. The drug release time was significantly improved from 2 h to 50 h[102].

Altering the composition of the matrix can also solve the issue of low oxygen permeability. Ocular hypotensive (timolol) and steriod (dexamethasone) have been released at a sustained rate from lenses when silicone polymers have been used to replace conventional lens material (pHEMA)[76]. Silicone polymers are highly advantageous with regards to O_2 permeability but can encounter problems with lack of patient compliance as a result of decreased water content leading to stiffness of the lens[103].

Colloidal Carriers and Nanocarriers

The arena of nanotechnology has already been successfully exploited in drug delivery for an array of therapeutic applications e.g. transdermal[104], nasal[105] and ocular[5]. The concept has extended to ocular drug delivery via contact lenses in the form of nanoparticles (NPs), surfactants, liposomes and cyclodextrins. The nature of these nano-carriers can protect sensitive materials from harsh external environments and can prevent drug degradation; the active can exist in an environment they would otherwise be unstable in. The sizes of these colloidal carriers also prove advantageous; patients' vision is not compromised upon administration. The most common types of NPs are either lipid-based or polymeric-based.

Liposomes:

Liposomes are amphiphilic, closed bilayer phospholipid vesicles. They consist of a hydrophilic core and surface within internal hydrophobic ring. Their amphiphilic nature enables to encapsulate both hydrophilic and lipophilic drugs whilst their high thermodynamic stability can achieve high drug loading capacity with subsequent extended drug release[106]. Liposomes also have the ability to change their size (20nm to few µm), zeta potential as well as their surface charge; allowing these carriers to be customised for specific applications. They are usually incorporated into the pre lens or post lens region of the eye; retarding diffusion in both directions i.e. extended/sustained release[65]. The interaction between liposomes and cornea was first investigated by Schaeffer and Krohn in 1982[107]. They found that corneal liposome uptake was greatest with positively charged liposomes, suggesting preliminary interaction is electrostatic adsorption; the uptake of water soluble penicillin G was increased 4 fold using positively charged unilamellar liposomes[107].

One of the first attempts to use liposomes for ocular topical drug delivery was for the treatment of acute and chronic herpetic keratitis; where Smolin et al found the delivery of idoxuridine was more effective with liposomes than without[108,109].

Liposomes were first used in conjunction with soft CLs by Gulsen et al[73]. Lidocaine was entrapped in the lipid bilayer of dimyristoyl-phosphatidylcholine liposomes; subsequently loaded into pHEMA lenses. The lenses remained transparent and exhibited initial burst release (due to free drug) followed by sustained release from entrapped drug for up to 8 days[73].

A group in Canada demonstrated sustained release of levofloxacin (6 days) by incorporating the drug into liposomes which were immobilized on to the surfaces of soft CLs[110]. The same research team immobilized intact liposomes onto multi-layered CLs[111]. Polyethylenmine was first covalently bound to Hioxifilcon B lenses (via hydroxyl groups). NHS-PEG-biotin molecules were attached to the amide surface groups onto which protein Neutr-Avidin was bound. The intact liposomes (loaded with PEG-biothylated lipids were docked onto surface immobilized Neutr-Avidin; further exposure to Neutr-Avidin and liposomes yielded multi-layered soft CLs[111].

Niosomes

Niosomes are highly stable, biodegradable, bi-layered vesicles. They possess a bilayer structure and assemble due to non-ionic surfactant and cholesterol interaction in the aqueous phase. In recent years, the use of niosomes as carriers to achieve sustained ocular drug release has increased. Li et al from China utilised niosomes for the delivery of Tacrolimus (FK506)[112]. Poloxamer 188 and lecithin were employed as surfactants and cholesterol as the stabiliser. The FK506 loaded niosomes showed no irritation and exhibited significantly increased drug retention time compared to 0.1% FK506 commercial ointment.

Spherical cationic niosomes (200nm) loaded with PCMSEGFP plasmids successfully transfected HEK-293 and ARPE-19 cells without affecting the viability of said cells following intravitreal and subretinal injections[113]. This plasmid has also been incorporated into niosome/DNA vectors loaded with protamine[114]. These niosomes were 150nm (average) in size and spherical in shape. Upon administration in the eye, the EGFP expression was detected in different retinal cell layers with lack of toxicity. Intravitreal administration of niosomes demonstrated more uniform

distribution of protein expression through inner retina which was exhibited for at least one month.

More recently, cationic lipids were used to evaluate the use of niosomes on transfection efficiency in rat retina and brain[115]. Formulations containing lipids with a dimethylamine ethyl pendent showed greater transfection efficiency in ARPE-19 cells and PECC cells than lipids containing primary amine group or triglycine group. In vivo studies involving subretinal and intravitreal injection demonstrated promising transfection efficiencies.

Polymeric Micelles

Surfactants are amphiphilic entities which have the ability to solubilise aqueous and lipophilic drugs/material. During polymerisation of matrix for CLs, the incorporated surfactants come together forming spherical micelles with a hydrophobic core and a hydrophilic shell. Hydrophobic molecules occupy the space within these micelles during polymerisation, enabling the drug to remain in an environment in which it would otherwise be unstable. Entrapment of drug using this method retards drug diffusion; providing sustained release[116]. Surfactant molecules consist of a hydrophilic head connected to a hydrophobic tail; which interacts with the CL matrix, creating lenses with charged surfaces. This can help enhance drug loading; charged drugs can adsorb onto these charged surfaces hence extended drug release[117].

A HG containing silica shell cross-linked methoxy micelles (SSCM) were developed in which polycaprolactone formed the core and silica constructed the shell of the micelles[118]. The SSCMs were loaded with dexamethasone acetate (hydrophobic nature) before they were incorporated into HGs. The release rate of the drug from the HGs was observed for up to 30 days. About 97% of the drug was released within 10 hours with 60% being released within 8 hours via burst release. The same research group used Cyclosporine A to study the potential development of pHEMA lenses for the controlled release using various Brij surfactants[22,119]. Focussing on how chain length of surfactant affects the HG, Brig 78 exhibited the longest release rate (70% after 50 days) compared to pure pHEMA (90% in less than 10 days)[119]. Cyclosporine A was also used as a model ophthalmic drug to develop surfactant-laden lenses where the effect of thickness of the lens on drug release was also assessed[22]. 100µm thick lenses indicated extended release of 7-8 days (2% Brij 78)

and 16 days (8% Brij 78) whilst with 200µm thick lenses, the release rate was extended to 16-17 days and 40 days for 2% and 8% surfactant, respectively[22].

Nanoparticles

Nanoparticles are colloidal carriers on the nanoscale. Trapping API's within NPs before dispersion through the hydrogel matrix provides a degree of protection to the drug from interaction with the hydrogel itself during polymerisation. Gulsen et al developed lidocaine-loaded NPs using hexadecane microemulsions (stabilised with silica shell). These NPs enabled the initial burst release of lidocaine where 50% of drug was released within the first few hours. This was followed by 80% of drug being released after 5 days [120].

More recently, silicone hydrogels have been loaded with propoxylated glyceryl triacrylate (PGT) NPs containing timolol, a beta-blocker used in the treatment of glaucoma. It was observed that a HG with 5% drug loading was able to delivery timolol at the therapeutic concentration for 1 month at room temperature, preliminarily[121]. In vivo testing in glaucomatous beagle dogs demonstrate a reduction in IOP but release was much faster at higher temperatures (>40°C), releasing almost 100% within 3-4 days. This is thought to be due to the ester links between the timolol and PGT[121].

Nanocrystals (100nm) of bovine serum albumin coated meloxicam (NSAID) were prepared and dispersed in pHEMA HG for the treatment of post cataract endophthalmitis. The gel released the meloxicam-nanoaggregates for approximately 5 days in which the thickness of the lens and degree of cross-linking were the dependent variables of drug release and by altering these; the drug release rate could be optimised[122].

Silver NPs have also been embedded into lenses to enhance the antimicrobial properties of lenses. In vitro testing using *Pseudomonas aeruginosa* and *Staphylococcus aureus* demonstrated great antimicrobial effects against *P. aeruginosa* but only lenses with increased concentration of silver NPs were effective against *S. aureus* at 48 and 72 h[123].

More recently, anti-fungal agent voriconazole was loaded into lipid-based NPs[124]. The resulting NPs were 182.0±4.1nm in size. The poorly water soluble active was readily released from the nanocarrier and inhibited the reproduction of fungus.

Lipid NPs were also utilised to encapsulate indomethacin for delivery to anterior and posterior segment ocular tissues[125]. The resulting particles (266±5nm) achieved encapsulation efficiency of 81.0±0.9%. Modifying the lipid NPs with chitosan hydrochloride increased the ocular penetration of indomethacin; showing these nanocarriers as potential vehicles in ocular drug delivery.

Cyclodextrins

Cyclodextrins (CDs) are oligosaccharides made up of glucose units linked via α 1,4 – glycosidic bonds. These cyclic structures are categorised based on the number of glucopyranose units they possess; α-CDs, β-CDs or γ-CDs. Their cyclic structure enables the entrapment of hydrophobic drugs (e.g. puerarin[126] and ethoxzolamide [127,128]) resulting in increased drug bioavailability, stability along with reducing potentials of undesirable side effects. Ribeiro et al exploited the ability for natural β-CDs and γ-CDs to form inclusion complexes with carbonic anhydrase inhibitors acetazolamide and ethoxzolamide in aqueous solution and developed N-N-dimethylacrylate-co-N-vinylpyrrolidone lenses with these pendant CDs[128]. Incorporation of CDs had no lasting effect on optical transparency of the lenses or on the cytocompatiblity of the lenses. Acetazolamide-loaded HG sustained release for 3-6 h whilst ethoxzolamide HGs sustained release for over a week[128]. Ethoxzolamide was also loaded into poly-CDs which notably enhanced drug solubility and provided much more delayed drug release rate compared to free CDs[127]. The poly-CDs also enhanced drug loading; resulting in sustained release for several weeks.

Puerarin β-CD complexes were successfully loaded into pHEMA lenses where in vitro and in vivo studies showed drug- β-CD complexes were 7.2 times and 4 times as effective as eye drops and isolated lenses, respectively (concentration of drug in vitreous humour was around 46.55μg/mL)[126]. Drug loading was found to be depended on the β-CD content; as was the in vitro release of puerarin. In vivo analysis showed that drug retention in precorneal region was enhanced with greater bioavailability using β-CD loaded pHEMA lenses[126]. Puerarin was also used to synthesise cyclodextrin-containing hydrogels for ophthalmic drug delivery. The amount of puerarin loaded into HG matrix using a crosslinkable chitosan derivative containing β-CD was greatly increased and the release was much more controlled with the addition of the CD[129].

More recently, conventional and silicone lenses (synthesized with methacrylated β-CD and methacrylated 2-hydroxypropyl-β CD) were loaded with natamycin and its release was assessed. These lenses improved drug release up to a threshold despite not extending the drug release duration[130].

Engineering Methods to Coat Lenses

Rather than incorporation of drug into the lens matrix, there have been attempts to coat the surface of lenses in a bid to revolutionise ocular topical drug delivery. This approach has been met with promising results[5,131-134]. For instance, rapamycin is an immunosuppressant agent used for prevention of organs transplant rejection. It was incorporated into a poly (lactic-glycolic acid) (PLGA)-chloroform solution, which was subsequently sprayed on the edge of poly-(methyl methacrylate) (PMMA) lens in an attempt to prevent formation and development of posterior capsular opacification (PCO). Unmodified lenses (group A) and PLGA lenses (group B) served as controls and group C was the rapamycin-sprayed lenses. After 7 days, the mean concentration of rapamycin in aqueous humour reached 1.10±0.30μ/mL after peaking to 14.57±0.99μg/mL after 24 h after administration to albino rabbits. In vivo analysis showed that the initial detection of PCO in rabbits in group C was much later than in groups A and demonstrating effective prevention of PCO formation and development[131].

HEMA lenses have been exposed to octadecyl isocyanate (OI) solution where it was established that the polyurethane bonds between the hydroxyl groups on the HEMA lenses and the isocyanate groups retarded norfloxacin release. Immersion of lenses in OI solution for 60 minutes led to more than 90% of the drug being released within 2 h; although this is rapid, it is slower than non-coated lenses[133]. Coating of PMMA lenses (with amino groups) with poly (sodium 4-styrene sulfonate) and ampicillin enhanced drug release with a 6-layer coating provided sustained release for 7 days (105μg of ampicillin)[134].

Electrohydrodynamic atomisation (EHDA) is a novel technique was utilised to develop multi-functional ocular lenses. It employs electrical forces to atomise liquid to produce nano- and micro-metre structures. This is such a technique which the maturing area of nanotechnology has already exploited and benefitted from[135,136]. EHDA was used to produce poly-(vinyl pyrrolidone) (PVP) NPs (50-130nm) and PVP fibres (130-250nm) to coat both sides of the contact lens. As PVP is a rapidly

dissolving polymer, the release was over 80% within 2 minutes with fibres demonstrating slightly longer sustained release due to lower surface area[5].

Contact Lenses as theranostic devices

The use of contact lenses has been exploited further than just vision correction and therapeutic applications. Recent research has extended to using contact lenses for the purpose of diagnostics and monitoring various chemical components present in the eye[7,137,138] **(Table 3)**. In the early 21st century, Miller and Wilson developed a novel, non-invasive technique for intraocular drug detection[139]. Commercial lenses were optimised to direct light across the anterior chamber of the eye of rabbits. The eye effectively acted as a cuvette enabling optical absorbance to be measured, giving an indication to the drug concentration in the eye[139].

Various attempts have been made to monitor glucose levels in situ using contact lenses. A team in USA designed contact lenses with integrated glucose sensor by creating cavities on the polymeric substrates which were then shaped into contact lenses. These devices exhibited quick responses, high sensitivity and good reproducibility[140]. Kudo et al reviewed the development of soft contact lens biosensor which consisted of film electrodes on the surface of poly dimethyl siloxane (PDMS) lens with glucose oxidase being immobilised around the electrodes, monitoring tear glucose when inserted in the eye[141]. Biocompatible lenses with PDMS as the glucose sensor have been fabricated and assessed on rabbits where a basal glucose level of 0.11mM was observed[142]. An oral glucose test was conducted to demonstrate the accuracy of the device which showed an elevation in glucose level with a delay of 10 mins.

More recently, the arena of theranostics has exploited the nanotechnology platform. Gold nano-antennas were coated with boronic acid HG (which swells in the presence of glucose). The high sensitivity to low glucose of this formulation is highly advantageous; the functionalised HG was highly specific to glucose (due to the boronic acid) hence the presence of other molecules (e.g. protein, salts) was irrelevant in detection of glucose. This novel approach highlights the potential of plasmonic nano-structures as biosensors for glucose detection in tear fluid[137].

A research team in Sweden developed dual-functional hybrid surface to modulate and detect a pathogenic attack. Mak et al employed a facile layer-by-layer surface engineering technique which enabled the device to capture inflammatory cytokines

(e.g. interleukin 1-α) specifically for non-invasive diagnostics. The lenses showed effective anti-HSV-1 activity and good analytical performance for interleukin 1-α detection[138].

Conclusion:

This review has scrutinized the key systems and methods utilised for ocular drug delivery, with greater emphasis on drug delivery via contact lenses. The potential and drawbacks of more conventional methods (eye drops, emulsions, and gels) were also discussed. Constant evolution in material knowledge encourages the advancing therapeutic approaches in ocular drug delivery, forging novel pioneering ways to improve drug bioavailability and overcome the physiological and anatomical barriers of the eye. Current advancements in the ocular drug delivery remit show great potential and constant development of materials, equipment and processes in the pharmaceutical industry can aid the innovations in ocular drug delivery; resulting in promising potential products.

Executive Summary:

- **Eye structure**
  - *This section is a brief explanation of the complexity of eye structure*
- **Routes of Administration in Ocular Drug Delivery**
  - *The three main routes of for drug delivery are clarified and summarised; with advantages and disadvantages of each route.*
- **Conventional Methods**
  - *This section has summarised existing methods currently used to topically treat ocular conditions with some examples currently being researched.*
    - *Eye Drops*
    - *Emulsions*
    - *Viscoelastic Gels*
    - *Innovative Systems*
      - *Implants*

        - *Iontophoresis*
        - *Microneedles*
- **Contact lenses:**
    - *This section focuses is on contact lenses; composition, contact lenses as drug delivery systems, different drug loading mechanisms alongside utilising contact lenses in theranostics.*

Reference Annotations

- **Reference 5** Mehta P, Justo L, Walsh S, et al. New platforms for multi-functional ocular lenses: Engineering double-sided functionalized nano-coatings. *J Drug Target.* 23(4), 305-310 (2015).**
    - Combining 2 processes and materials (EHDA, Contact Lenses) to develop a novel, innovative drug delivery device
- **Reference 34** Lallemand F, Daull P, Benita S, Buggage R, Garrigue J. Successfully improving ocular drug delivery using the cationic nanoemulsion, novasorb. *J Drug Deliv.* 2012604204 (2012).**
    - Commercial products show the potential of emulsions for improved drug delivery in practise.
- **Reference 60* Jiang J, Gill HS, Ghate D, et al. Coated microneedles for drug delivery to the eye. *Invest.Ophthalmol.Vis.Sci.* 48(9), 4038-4053 (2007).**
  Reference 61* Kim YC, Grossniklaus HE, Edelhauser HF, Prausnitz MR. Intrastromal delivery of bevacizumab using microneedles to treat corneal neovascularization. *Invest Ophthalmol Vis Sci.* 55(11), 7376-7386 (2014).
    - These two papers combine 2 relatively novel methods to produce a whole new delivery system with promising results.
- **Reference 70** Wheeler J, Woods J, Cox M, Cantrell R, Watkins F, Edlich R. Evolution of hydrogel polymers as contact lenses, surface coatings, dressings, and drug delivery systems.**
  Reference 71 Vanderlaan DG, Nunez IM, Hargiss M, Alton ML, Willams S, inventorsSoft Contact Lenses. patent US 5998498 A. 07/12/1999, 1999**
    - These papers document the first look at the potential of hydrogels as contacts lenses and drug delivery systems
- **Reference 139* Miller J, Wilson CG, Uttamchandani D. Minimally invasive spectroscopic system for intraocular drug detection. *J Biomed Opt.* 7(1), 27-33 (2002).**
  Reference 142* Chu MX, Miyajima K, Takahashi D, et al. Soft contact lens biosensor for in situ monitoring of tear glucose as non-invasive blood sugar assessment. *Talanta.* 83(3), 960-965 (2011).

- These papers show how research has now gone beyond just therapeutics; combining therapeutics and diagnostics in the pharmaceutical remit; yielding a whole new application of contact lenses

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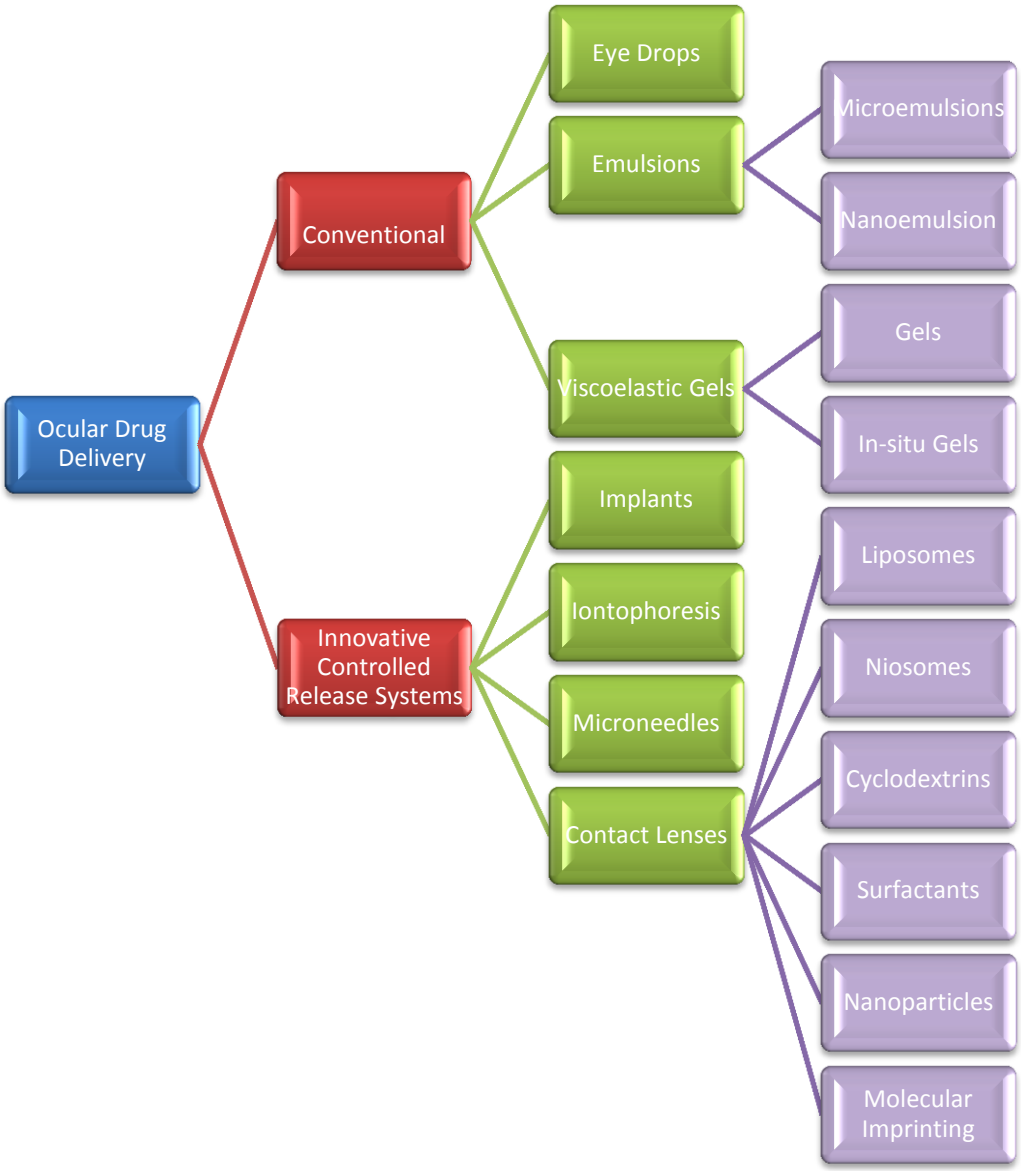

Figure 1: Systematic diagram depicting drug delivery approaches in topical ocular drug delivery.

Table 1: different loading mechanisms of different drugs.

Mechanism of Drug loading	Lens Material	Active		Reference Number
		Name	Function	
soak and release	"Sauflon" Hydrophilic lenses (vinyl pyrollidone/acrylic copolymer)	Pilocarpine	Anti-glaucoma	74
	Silicone: N,N-dimethylacrylamide, 3-methacryloxypropyltris(trimethylsiloxy)silane, bis-alpha,omega-(methacryloxypropyl) polydimethylsiloxane, 1-vinyl-2-pyrrolidone, ethylene glycol dimethacrylate	Timolol, Dexamethasone, Dexamethasone 21-acetate	Anti-glaucoma	75
	ACUVUE® TruEye™	Timolol	Anti-glaucoma	76
	NIGHT AND DAY™ Silicone Hydrogel lenses	Timolol	Anti-glaucoma	77
	Balafilcon A, Etafilcon A, Etafilcon A Daily Disposable, Nelfilcon A, comfilcon A	Ketotifen Fumarate	anti-allergy	78

	silicon lenses containing (Lotrafilcon and balafilcon) and p-HEMA-containing (etafilcon, alphafilcon, polymacon, vifilcon and omafilcon)	Cromolyn sodium, ketotifen fumarate, ketorolac tromethamine, dexamethasone sodium phosphate	NSAID, Anti-histamine, corticosteroid	79
	Lotrafilcon A, Galyfilcon A, Senofilcon A, Lotrafilcon B, Balafilcon A	Dexamethasone 21-disodium phosphate, timolol maleate, flucnazole	Corticosteroid, Anti-glaucoma, anti-fungal agent	65
	HEMA, EGDMA, MAA	Hyaluronic Acid	Dry Eye	92
	Lotrafilcon B	Lidocaine, bupivacaine, tretracaine	Anesthetic	93
	Narafilcon B (silicone), Senofilcon A (silicone), Lotrafilcon B (silicone), Balafilcon A (silicone),Etafilcon A (p-HEMA)	cysteamine hydrochloride	Cytinosis	94

	Senofilcon A (silicone), Narafilcon B	Betaine, Dexpanthenol	Ocular Dryness	83
	Senofilcon A (silicone), Lotrafilcon A (silicone), Lotrafilcon B (silicone)	Dexamethasone	NSAID	84
Molecular Imprinting	HEMA	Timolol maleate	Anti-glaucoma	71,89
	HEMA	Timolol	Anti-glaucoma	103
	poly (hydroxyethyl methacrylate)	norfloxacin	Antibiotic	90
	HEMA	polymyxin B, vancomycin	Antibiotic	92
	SCL	ciprofloxacin	Antibiotic	93
	HEMA	ciprofloxacin	Antibiotic	94
Modifying Matrix Composition	HEMA	Azulene		95
	HEMA	Naphazoline	Sedative	97
	pHEMA	Triamcinolone acetonide	corticosteroid	98
	SCL	Gatifloxacin, Moxifloxacin	Antibiotic	99

	pHEMA	Dexamethasone 21-disodium phosphate	corticosteroid	100
Liposomes	pHEMA	lidocaine	Anaesthetic	83
	Hioxifilcon B	levofloxacin	Antibiotic	108,109
Surfactants	pHEMA	Dexamethasone acetate	corticosteroid	112
	pHEMA	Cyclosporin A	immunosuppressant	113
	pHEMA	Cyclosporin A	immunosuppressant	22
Nanoparticles	pHEMA	lidocaine	Anaesthetic	114
	pHEMA	lidocaine	Anaesthetic	115
	Silicone: N, N-Dimethylacrylamide, 1-vinyl-2-pyrrolidone, 3-Methacyloxypropyl-tris (trimethylsiloxy)silane, MAA	timolol maleate	Anti-glaucoma	116
	pHEMA	Meloxicam	NSAID	114
	HEMA	Silver	Antimicrobial Agent	118
Cyclodextrins	pHEMA	Puerarin	Anti-glaucoma	119
	HEMA	ethoxzolamide	Carbonic Anhydrase Inhibitor	120
	N,N-dimethylacrylamide-co-N-vinylpyrrolidone	ethoxzolamide, acetazolamide	Carbonic Anhydrase Inhibitor	121
	HEMA	natamycin	Anti-fungal Agent	123
Engineering methods of coating lenses	PMMA	Rapamycin	immunosuppressant	124
	HEMA	norfloxacin	antibiotic	126

	PMMA	ampicillin	Antibiotic	127
	Balafilcon A	Dye	Probe	5

SCL: silicon contact lenses, **NPs**: nanoparticles, **IOP**: intraocular pressure, **HEMA**: 2-hydroxyethyl methacrylate, **pHEMA**: poly (hydroxyethyl methacrylate), **NVP**: N-vinyl-2-pyrrolidone, **MAA**: Methacrylic acid, **MOEP**: 2-methacryloxyethyl acid phosphate, **MAPTAC**: methacrylamido-propyltrimethylammonium chloride, **MPTS:** 3-Methacryloxypropyltris(trimethylsiloxy) silane, **EGDMA**: ethyleneglycole dimethacrylate, **TRIS**: 3-methacryloxypropyltris (trimethylsiloxy) silane, **DMA**: N,N-dimethylacrylamide, **HA**: hyaluronic acid, **HG**: hydrogel, **DMPC**: dimyristol-phosphatidylcholine, **CAC**: benzyldimenthylhexadecyl-ammonium chloride, **MePEG-b-PCL:** methoxy(polyethylene glycol)-block-polycaprolactone, **CD**: cyclodextrin, **β-CD**: β-cyclodextrin, **PMMA**: poly-(methyl methacrylate), **PCO**: posterior capsular opacification, **PVP**: poly-(vinyl pyrrolidone).

Table 2. ocular drug delivery using conventional methods

Method	Active	Excipient	Target	Condition	Reference Number
Eye Drop	Aceclofenac	MP, PP, HPMC, PVA, BAC, PMN, PMA, BA, chitosan	cornea, anterior chamber	Anterior Chamber inflammation, post-surgery pain and inflammation	16
	Dexamethasone	--	Intermediate and Posterior Uveitis	Non-Infectious Uveitic macular oedema and vitritis	17
	Prednisolone	HPMC, Dimethyl-β-cyclodextrin	Cornea, posterior segment	ocular infections, post cataract surgery antibiotic	18
	Dorzolamide	Disodium edetate dehydrate, monosodium phosphate dihydrate, benzalkonium chloride, HPMC 4000, Tyloxapol	Cornea, aqueous humour	glaucoma	19
	Ciprofloxacin	--	Primarily cornea	Antibiotic	21
Emulsions	Timolol Maleate	Octanoic acid, 1-butanol, isopropyl myristate, 1-4 dioxane, egg lecithin	aqueous humour	glaucoma	24

	delta-8-Tetrahydrocannabinol	Purified soy-bean oil, crude egg yolk phospholipids, Pluronic F-68, glycerin, α-tocopherol	aqueous humour	glaucoma	30
	Cyclosporin A, latanoprost	Cationic emulsion	Primarily cornea	Dry Eye	33,34
	Doxycycline hydrochloride	Gellan Gum, Polyvinyl alcohol, dichloromethane, calcium chloride	Corn	Bacterial Infection	3
Hydrogel	gentamycin sulphate, dexamethasone	Chitosan, Gelatin, BAC, Propylene glycol, Thioglycolate medium, Soybean casein digest	Cornea, conjunctiva	Conjunctivitis	37
	Bovine Serum Albumin	Porcine type I atelocollagen, morpholinoethansulfonic acid, sodium alginate	Cornea	protein delivery	39
	latanoprost	chitosan, gelatin, glycerol phosphate	Cornea	glaucoma	40
	Avastin	Glycol Chitosan, Oxidise alginate,	cornea, posterior chamber	Age-related macular degeneration, proliferative diabetic retinopathy	41
	timolol maleate	chitosan, poly (n-isopropylacrylamide),	Cornea	Glaucoma	46
	timolol maleate, brimonidine tartrate	Poly acrylic acid, HPMC, sodium chloride, BAC	Cornea	glaucoma	47

	Ofloxacin	PAA, Noveon AA-1 USP Polycarbophil	Cornea	acute conjunctivitis, bacterial keratitis, keratoconjunctivitis	48
	sparfloxacin	sodium alginate, methylcellulose,	multiple eye tissue	bacterial infection	4
	Moxifloxacin Hydrochloride	Polyox, HPMC, Poloxamer, sodium alginate	Primarily cornea	bacterial infection	49
	Cromolyn Sodium	Pluronic F 127, HPMC, carbopol 940, xanthan gum, sodium alginate	Primarily cornea	Inflammation	50

MP: Methyl paraben, **PP**: Propyl Paraben, **HPMC**: Hydroxypropyl Methylcellulose, **BAC**: Benzalkonium Chloride, **PMN**: Phenyl mercuric nitrate, **PMA**: Phenyl mercuric acetate, **BA**: Benzyl Alcohol, **γ-CD**: gamma cyclodextrin, **β-CD**: beta cyclodextrin, **PAA**: Poly acrylic acid, **HG**: hydrogel, **NSAIDs**: non-steroidal anti-inflammatory drug, **NPs**: nanoparticles.

Table 3: Theranostics Using Contact Lenses

Method	Probe/Detection	Comments	Reference number
--	Drug	Commercial lenses were optimised to direct light to the anterior chamber of rabbit eyes; the eye acted to focus the light, allowing optical absorbance to be measured; hence obtaining drug concentration data.	132
Chip	Glucose	An electrochemical sensor was integrated into a functional contact lens which was based on the activation and deactivation of glucose oxidase. This chip was integrated into cavities in polymeric matrix; subsequently shaped into contact lenses. They exhibited quick responses and high sensitivity to tear glucose levels.	133
film	--	Film electrodes were attached to the surface of PDMS lenses. Glucose oxidase were immobilised on around the electrodes; monitoring tear glucose levels.	134
	--	Oral glucose test reiterated and confirmed the accuracy of PDMS as the glucose sensor incorporated into biocompatible lenses.	135
Antenna	--	The swelling of boronic acid hydrogels in the presence of glucose is highly advantageous due to high specificity to glucose; other materials in tear composition is irrelevant/would not compromise the data.	130
--	inflammatory cytokines	these lenses were developed specifically for non-invasive diagnostics for detection of pathogenic attack. The lenses also contained an antiviral coating to protect against disease as a first line of defence.	131

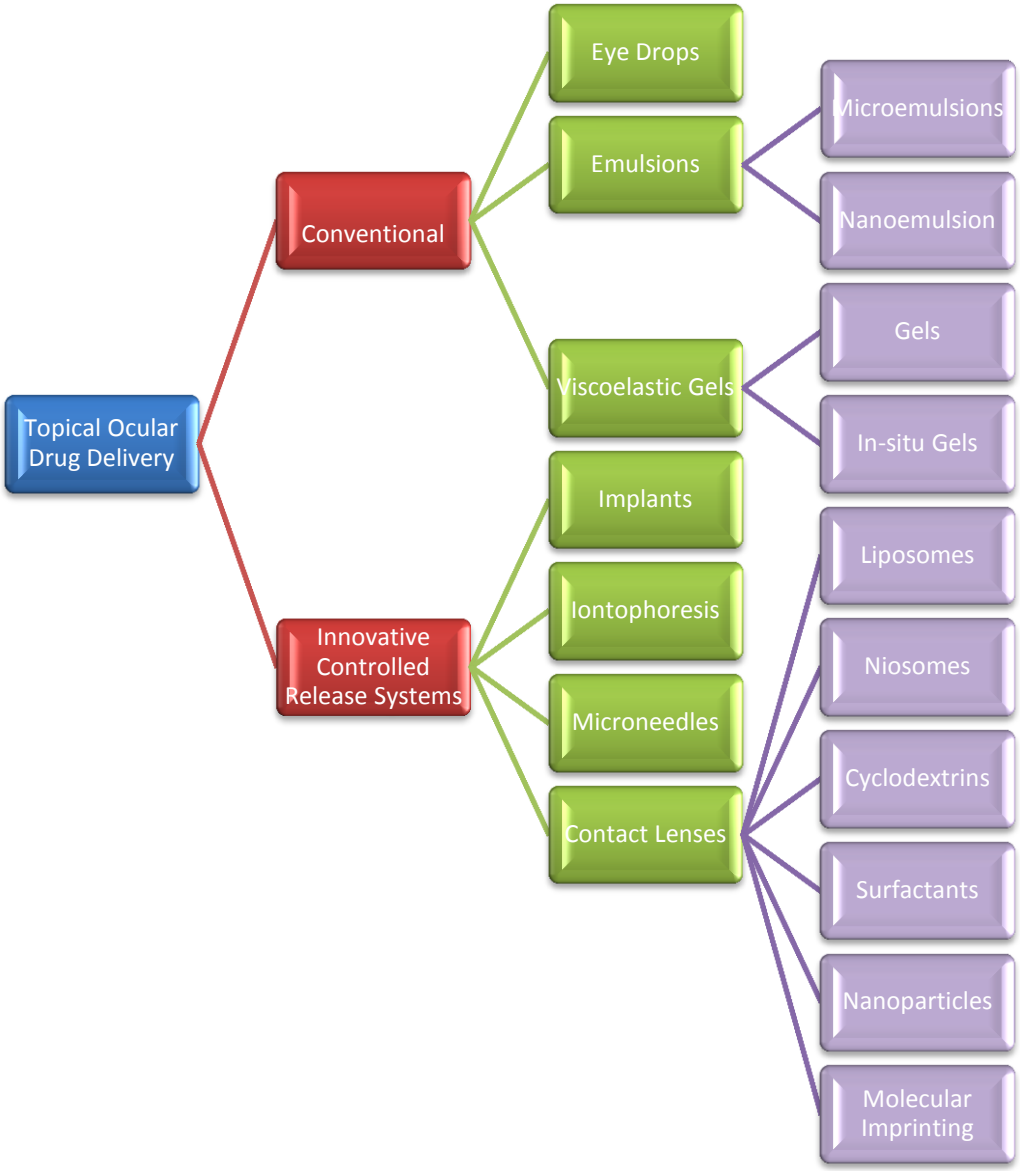

Figure 1: Systematic diagram depicting drug delivery approaches in topical ocular drug delivery.