



Advances in ophthalmic drug delivery

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Advances in Ophthalmic Drug Delivery

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Abstract:

Various strategies for ocular drug delivery are considered; from basic formulation techniques for improving availability of drugs; viscosity enhancers and mucoadhesives aid drug retention and penetration enhancers promote drug transport into the eye. The use of drug loaded contact lenses and ocular inserts allows drugs to be better placed where they are needed for more direct delivery. Developments in ocular implants gives a means to overcome the physical barriers that traditionally prevented effective treatment. Implant technologies are under development allowing long term drug delivery from a single procedure, these devices allow posterior chamber diseases to be effectively treated. Future developments could bring artificial corneas to eliminate the need for donor tissue and one-off implantable drug depots lasting the patient's lifetime.

Key Terms

Bandage contact lens: Device designed to fit directly onto the front of the eye to offer protection during the healing process, for example, after corneal surgery.

Container molecule: Molecular structures with cavities that can accommodate another molecule via guest – host complexation.

20 **Hydrotrope:** Water-soluble compound that improves the aqueous solubility of hydrophobic or
21 poorly water-soluble compounds.

22 ***In situ* gelling system:** Liquid formulations that turn in to gel upon dosage form administration.
23 These phase transitions can typically be triggered by changes in temperature, pH or electrolyte
24 interaction.

25 **Mucoadhesive:** Defined as a compound, usually a polymer, with the ability to adhere to mucosal
26 tissue.

27 **Ocular insert:** A drug-loaded device designed to reside within the ocular cul-de-sac, attach to
28 the conjunctiva or directly onto the cornea.

29 **Ocular implant:** Dosage forms implanted directly into the ocular globe; these can be devices
30 that bring 'quality of life benefit' such as intraocular lenses used for crystalline lens replacement.
31 Implantable devices are also used for sustained and controlled drug delivery to the posterior
32 segment.

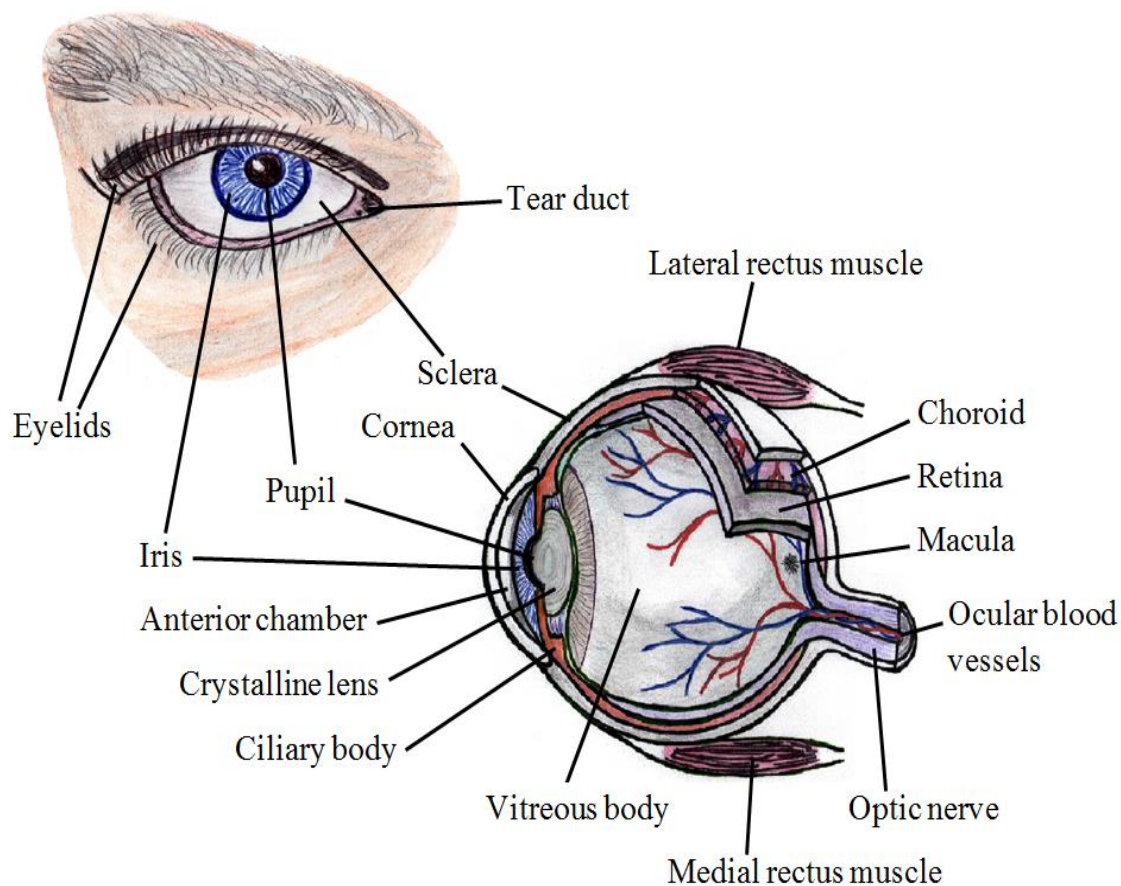
33 **'Smart' DDS:** Responsive drug delivery systems where a favourable change takes place in
34 response to some form of stimulus, for example, change in temperature, pH, ionic interactions or
35 stimulation from a light source.

36 **Introduction**

37 Ocular drug delivery is hampered by the physiological barriers presented by the eyes. These
38 include, blinking and wash out by tears, nasolacrimal drainage, non-productive losses and
39 impermeability of the cornea. [1,2]

40 Some of the various structures of the eye are detailed in **Figure 1**, highlighting the intricate
41 complexity of this organ. The conjunctiva (not shown for clarity) is the mucosa lining the inside
42 surface of the eyelids and the external surface of the front of the eye up to the limbus, the edge of
43 the cornea.

44



45

46 **Figure 1.** A sketch showing some of the key features of the human eye.

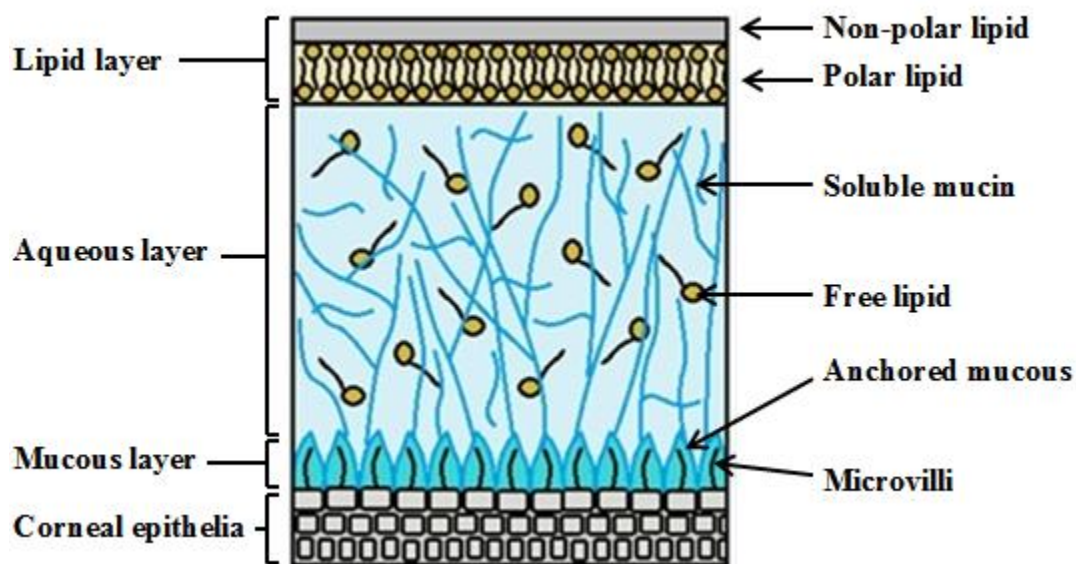
47 Despite the easy accessibility of the eye for administering medication, in many ways it is an
48 isolated organ with several barriers imposing challenges to drug delivery, tear mechanisms, the
49 physical barriers of its membranes, blood-aqueous and blood-retinal barriers.[3]

50 Topical, systemic and intraocular are the three main routes for administering ophthalmic
51 medication; each has their own advantages and disadvantages. Topical drug delivery is the most
52 accepted route accounting for ~90% aqueous ophthalmic formulations. Advantages are their
53 relative simplicity to formulate, minimal storage limitations and ease of drug instillation by most
54 patients. Disadvantages include limited drug concentration for lipophilic agents, pre-corneal
55 losses and the barrier function of the cornea.[4,5] For effective systemic delivery a relatively
56 high drug concentration needs to be circulating in the blood plasma in order to achieve a
57 therapeutically effective dose within the eye. Sustained release oral drugs can be suitable for
58 glaucoma patients, allowing for continuous and effective treatment, however this method
59 exposes the whole body to the drug often giving rise to undesired side effects.[6] Intraocular
60 drug delivery by intravitreal injection is an invasive procedure carrying a degree of risk such as
61 retinal hemorrhage or detachment, especially if the technique needs to be repeated when treating
62 chronic disorders. However, it is very effective at getting drugs to the posterior segment.[3]

63 The cornea is the main route for topically applied drugs to gain access into the eye and the
64 conjunctival/scleral route can also be efficient. [7,8] Drops are the most accepted means to apply
65 medication to this organ;[9] they are easy to apply by most patients and they are convenient.
66 However, regardless of the ease of access to the eye for topical application of medication,
67 efficient ocular drug delivery is hampered by a series of clearance mechanisms that protect the
68 ocular structures from foreign matter. Upon administration of traditional eye drops they are
69 immediately diluted in the tear film followed by very quick elimination by action of blinking,
70 wash out by tears, and nasolacrimal drainage. [10,11] After instilling eye drops, there remains a
71 very short time where any residual medication is in contact with the cornea during which time
72 there is opportunity for the drug to penetrate into the eye; however, due to poor corneal

73 permeability only a very small portion of active pharmaceutical ingredient will be capable of
74 crossing the cornea. Of the applied dose, only 1% or less will successfully reach the intended
75 target in most cases, the rest will be systemically absorbed via the conjunctiva or nasolacrimal
76 mucosa to be eliminated by metabolic processes.[5] The tear film comprises of several
77 compartments, **Figure 2** shows the 3 layer tear film model comprising of a coating of mucous
78 anchored to the epithelium via microvilli, an aqueous compartment containing soluble mucin and
79 free lipid and a thin lipid layer [11-14].

80



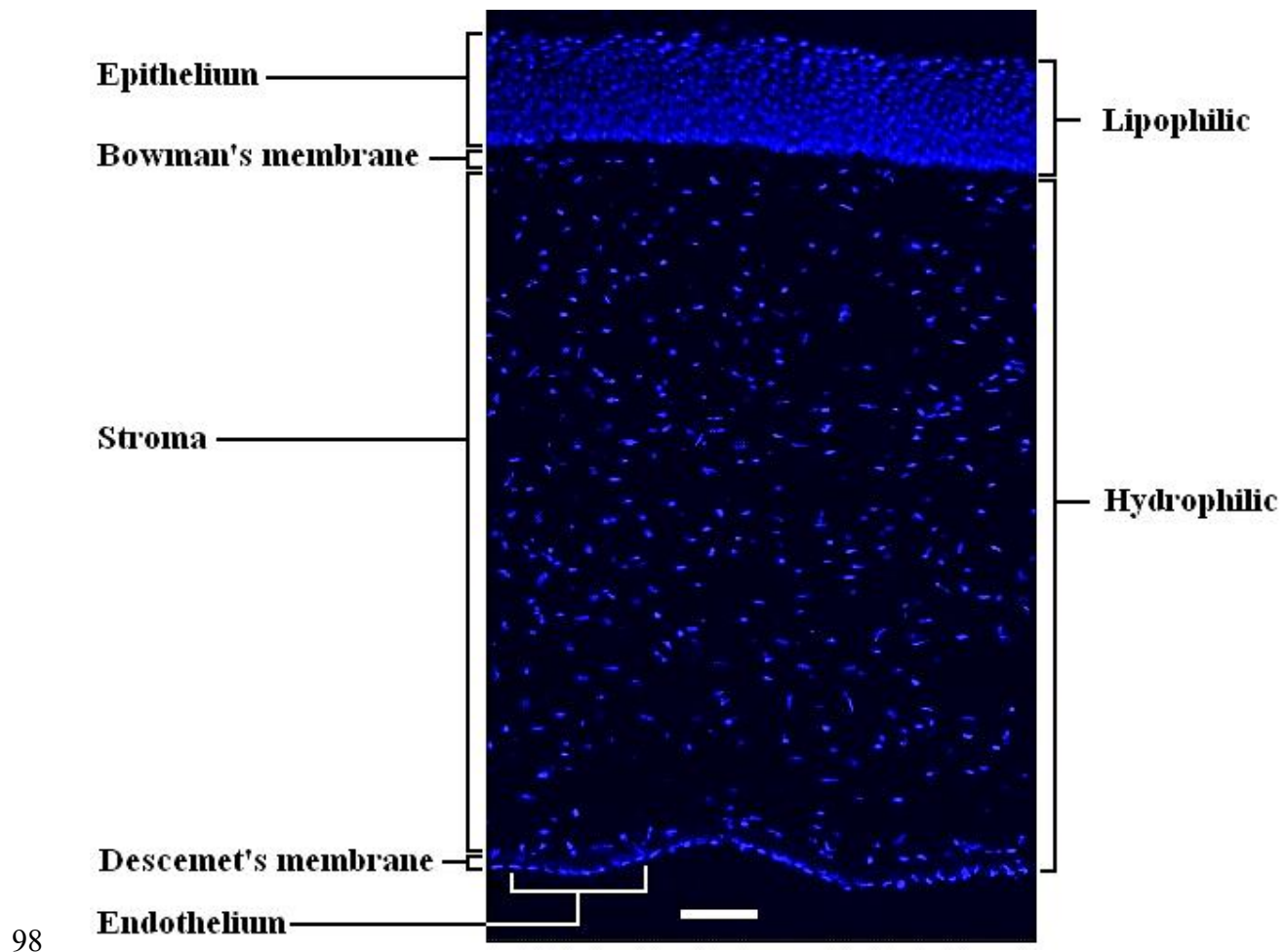
81

82 **Figure 2.** The 3 layer tear film model.

83 The tear film and ocular mucosa are the first external barriers to overcome, after which the
84 multilayered structure of the cornea (**Figure 3**) offers the next challenge; this structure has both
85 lipophilic and hydrophilic properties and there are 5 distinct layers: Epithelium, Bowman's
86 membrane, stroma, Descemet's membrane and endothelium.[6,15] The first corneal layer is the
87 epithelium which is ~50 μm at its center increasing to ~100 μm at the limbus; this layer is

88 lipophilic, offering ~90% resistance to hydrophilic drugs and ~10% to hydrophobic preparations.
89 Immediately underneath the epithelium is the Bowman's membrane, a transitional acellular
90 structure ~8-14 μm in thickness. Next we find the hydrophilic stroma; this is a gel-like structure
91 with around 80 % water, consisting of collagen, mucopolysaccharides and proteins and it forms
92 the main bulk of the cornea, some 90 % of its total thickness. Next there is the Descemet's
93 membrane, a tough membrane of around 6 μm thickness supporting the endothelium, a single
94 layer of loose, epithelia-like cells important in regulating stromal hydration, and this layer is
95 deposited by endothelial cells. The correct level of hydration is important for the cornea to
96 remain clear and transparent.[6,15,16]

97



98

99 **Figure 3.** Micrograph of a section of bovine cornea showing the multi-layered structure typical
 100 of mammalian corneas. Scale bar = 100 μm .

101 The corneal epithelial barrier also has different zones; the basement layer consists of newly
 102 formed cells firmly attached to the Bowman's layer, here they are columnar in shape. As new
 103 cells are formed the preceding basement cells are pushed forwards, becoming polyhedral in
 104 shape, eventually as they are moved towards the corneal surface where they become polygonal
 105 squamous cells. These superficial epithelial cells have Ca^{2+} dependent membrane adherent
 106 regions; zonula occludens, zonula adherens and desmosomes forming tight junctions.[17]
 107 Taken together, these tightly bound cell membrane regions and the lipophilic nature of the

108 epithelium make the structure an extremely efficient barrier that resists intrusion of foreign
109 material including potentially therapeutic compounds; this creates a major challenge for ocular
110 drug delivery.[6,11,18]

111 **Strategies for enhancing ocular drug delivery**

112 Despite traditional eye drops being convenient and simple to use, they are not very efficient and
113 only a small amount of the dose is effectively delivered to its intended target, most is lost due to
114 clearance mechanisms. There are however certain strategies that can be employed to improve the
115 bioavailability of drugs. First, solubility enhancers can be used, to improve drug concentrations
116 within the formulation; more medication in the dosage form can mean increased bioavailability.
117 This strategy could allow a smaller droplet to be applied, which would be less susceptible to loss
118 by drainage due to induced reflex tearing and blinking.[6] Second, the formulation can be
119 designed in a form that resists clearance; these dosage forms are retained for a longer period,
120 therefore they have more time to interact with ocular tissue. Next, drug penetration enhancers
121 can be incorporated into the formulation to assist their transit across the cornea.[19] Ocular
122 inserts are another area of active research and development. With this method a drug-loaded
123 device resides in the cul-de-sac under the eyelids or fits directly on the cornea like a contact lens;
124 these devices are often designed with controlled release in mind.[20,21] Drug delivery into the
125 cornea and anterior chamber is difficult enough; delivering an effective therapeutic dose to the
126 posterior segment is a major challenge, in many cases it is not possible to deliver sufficient
127 medication to the posterior structures via the topical route.[22] For diseases of the retina, such as
128 age-related macular degeneration (AMD), diabetic retinopathy, and retinitis pigmentosa and
129 related ocular neovascular disease there is often a need to resort to invasive methods for drug
130 delivery. Angiogenesis inhibitor medication via intravitreal injection is an option for getting

131 drugs to the posterior segment but these are often effective for the short term and need repeat
132 injections, which carries risks such as hemorrhage, endophthalmitis, ocular hypertension and
133 retinal detachment.[22-26] Ocular implants are devices that penetrate the sclera or reside within
134 the deeper ocular structures to deliver drugs for an extended period, sometimes many years,
135 minimising the need for repeat injections.[23] Implantable devices that are not designed to
136 deliver drugs are also employed to improve the 'quality of life' for patients with certain
137 conditions, for example, intraocular lenses. However, drugs to counter postoperative bacterial
138 infection are often included in these devices for short term protection.[27,28] These various
139 strategies will be discussed in more detail in the following sections.

140 **Solubility enhancers:**

141 Discovery of potentially therapeutic compounds is accelerating through developments in
142 genomics, combinatorial chemistry and the ability to use high throughput screening. High
143 proportions of newly screened compounds prove to be hydrophobic and are poorly water-
144 soluble.[29] For efficacious performance in the physiological environment drug candidates need
145 to interact within an aqueous media, the interstitial fluids within tissues.

146 Drugs used for treatment of ocular disorders often have low aqueous solubility and eye drops are
147 only in contact with ocular tissue for a short time. Formulations that are developed to increase
148 the amount of available drug in solution could improve its bioavailability, therefore solubility
149 enhancement is an important strategy to use when developing ocular medication. Solubility
150 enhancement can be achieved by employing hydrotropic compounds. Evstigneev *et al.*[30] and
151 Coffman and Kildsig [31,32] reported the effectiveness of caffeine, urea and nicotinamide and its
152 derivatives as efficient hydrotropes for enhancing the solubility of riboflavin, a vitamin with poor

153 aqueous solubility of less than 0.1 mg mL^{-1} which is used as a photosensitive drug for the
154 treatment of keratoconus. Cyclodextrins are a class of cyclic supramolecular compounds that
155 have been well studied for dissolution enhancement of low solubility drugs; Loftsson and
156 Stefansson discussed the use of cyclodextrins for complexation with steroids, carbonic anhydrase
157 inhibitors, pilocarpine and cyclosporins in eye drop formulations which are well tolerated.[33]
158 Morrison *et al.*[34] investigated cyclodextrins for their hydrotropic properties and were able to
159 show that β -cyclodextrin achieved solubility enhancement of more than 140% for riboflavin.
160 Whilst the above mentioned studies achieved modest solubility enhancements, research by Kim
161 *et al.* [29] investigating the performance of two hydrotropes; N,N-diethylnicotinamide (DENA)
162 and N,N-dimethylbenzamide (DMBA) with 13 poorly water-soluble drugs and these compounds
163 were shown to have superior hydrotropic action between 1000- to 10000- fold.
164 Supramolecular structures are sub-micron sized molecules within the realm of nanotechnology
165 and many of these assemblies have solubility enhancement properties. This technology is
166 becoming an important tool within the pharmaceutical industry with substantial investment
167 within the global market. Dendrimers, microemulsions, nanoparticles, nanosuspensions and
168 liposomes belong to this class of compound and are proving to be useful structures to improve
169 bioavailability, all of which are at the forefront of research in ocular drug delivery.[1,2,35-41]
170 Micelles are aggregates of amphiphilic molecules forming self-assembled spheres in aqueous
171 media. They have a monolayer 'shell' of polar groups with their associated fatty acid 'tails'
172 forming the core. These are useful carriers of hydrophobic drugs within the core albeit with
173 limited efficiency due to a high amphiphile / drug ratio.[42] The work of Qu *et al.*[43] involved
174 chemical modification of chitosan by increasing their hydrophobicity and this allowed them to
175 produce 100 – 300 nm sized micellar clusters which could achieve up to an order of magnitude

176 enhancement in hydrophobic drug bioavailability compared to micelles produced using triblock
177 copolymers. In ocular drug formulations they were able to show an initial prednisolone
178 concentration in the aqueous humor equivalent to that found when using a 10-fold dose of
179 prednisolone suspension.

180 An approach taken by Kulkarni *et al.* [44] was to take the poorly soluble drug, indomethacin, and
181 using simple chemistry, convert this drug into its sodium salt. They found that this improved its
182 aqueous solubility and the drug was stable at physiological pH and compatible with excipients
183 used for ocular drug formulation.

184 **Penetration enhancement:**

185 Materials that modify the corneal epithelia can allow enhancement of drug permeation and this
186 can be achieved using various strategies. Benzalkonium chloride (BAC) is commonly used as a
187 preservative in ocular drug formulations, this together with other compounds; cetylpyridinium
188 chloride (CPC), ethylenediaminetetraacetic acid (EDTA), polyoxyethylene stearyl ether (PSE)
189 and polyethoxylated castor oil (PCO) are compounds with penetration enhancing properties.
190 Their mode of action is due to destabilisation of the tear film and the protection given by its
191 mucus component (for BAC), and ultrastructural alterations [17] and solubilisation of cellular
192 membranes for the other enhancers. Useful as they are for penetration enhancement they can also
193 induce irritation and damage to ocular epithelium even at low concentrations. Chung *et al.* [45]
194 and Burgalassi *et al.* [46] investigated these materials confirming their irritation and cytotoxicity
195 effects. Liu *et al.* [47] state that penetration enhancers should be:

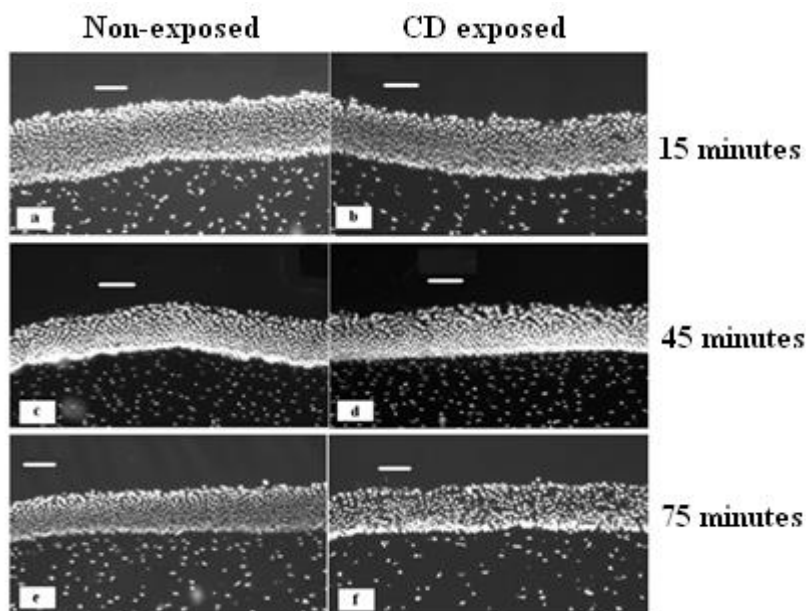
- 196 • Non-toxic;
- 197 • Non-irritant to the eye;

- 198 • Inert and compatible to other excipients within the formulation;
- 199 • Fast acting and reversible action;
- 200 • Effective at low concentration.

201 In their report they discuss the use of several penetration enhancers for ocular drugs; BAC,
202 EDTA, surfactants, heteroglycosides, bile salts, polycarbophil-cysteine conjugates and boric
203 acid, all of which have been used in ophthalmic formulations despite the fact that even at low
204 concentrations they can cause ocular irritation.[47] Morrison *et al.* [17] investigated drug
205 penetration enhancement using EDTA and two analogues EGTA and EDDS and they found that
206 this was achieved by sequestering Ca^{2+} and therefore loosen tight junctions which depend on the
207 availability of these ions.

208 Gelucires are glycerides composed of mono-, di- and triglycerides with mono- and diesters of
209 polyethylene glycol. They are amphiphilic with surface active properties.[48] Gelucire 44/14 has
210 a melting temperature of 44°C and a hydrophilic – lipophilic balance of 14, hence its name. It is
211 a compound known for its permeation enhancing properties and is ‘generally regarded as safe’
212 (GRAS). Liu *et al.* [47] investigated Gelucire 44/14 for its permeability enhancing performance
213 *in vitro* and *in vivo* for various ophthalmic drugs and demonstrated that it enhanced transcorneal
214 permeability of drugs with a range of hydrophilicity / lipophilicity whilst remaining non-
215 irritating. Loftsson and Stefansson [33] reviewed cyclodextrins for enhanced topical delivery of
216 steroids for ophthalmic formulation and the cyclodextrin-drug complexes were found to be well
217 tolerated in eye drop formulations. Cyclodextrins and their drug complexes are too large to
218 partition into the cornea and until recently it was generally thought that they kept the drug in
219 solution at the eye surface where the drug was able to diffuse into the tissue,[47,49] or by

220 modulation of the aqueous diffusion layer on the corneal surface.[50] Morrison *et al.* [34]
221 investigated the use of cyclodextrins as ocular drug delivery excipients for permeability
222 enhancement of riboflavin for the treatment of keratoconus. They have shown that cyclodextrin
223 forms complexes with riboflavin and release their drug payload by preferential take up of
224 cholesterol from corneal epithelial cell membranes. The removal of cholesterol renders the
225 epithelium permeable, allowing enhanced drug penetration. **Figure 4** shows β -cyclodextrin
226 induced histological changes to the epithelium of bovine corneas (b,d,f), compared to those
227 without cyclodextrin exposure (a,c,e). β -Cyclodextrin induced loosening of the epithelium
228 appears to increase with exposure time of 15, 45 and 75 minutes (b,d,f respectively), and this
229 correlates with increased riboflavin penetration without complete destruction of this barrier.



230
231 **Figure 4.** Micrographs of bovine cornea cross-sections showing differences between areas that
232 were exposed to β -cyclodextrin (b,d,f) or not (a,c,e), at 15, 45 and 75 minutes. Scale bar = 100
233 μm . Adapted with permission from: Morrison *et al.*[34] Cyclodextrin-mediated enhancement of
234 riboflavin solubility and corneal permeability. *Molecular Pharmaceutics*. 10, 756-762 (2013).

235 **Retention strategies:**

236 Pre-corneal losses have a major impact on ocular drug delivery; it follows that if the drug
237 formulation stays in contact with the intended tissue for longer it is more likely to penetrate the
238 target site to afford its desired action. Adopting an approach for formulation retention is one
239 way to minimize this problem and this can be achieved by several means. Various retention
240 approaches will be discussed in the following section:

241 **Viscosity enhancing polymers;**

242 Natural and synthetic polymers prove useful for their viscosity enhancing properties in ocular
243 drug formulations for improving residence time. These materials absorb water to form
244 viscoelastic gels which prove to be suitable vehicles for drug delivery, and they include
245 derivatives of cellulose, poly(vinyl alcohol), poly(vinyl pyrrolidone), carbomers (weakly
246 crosslinked poly(acrylic acids)), and the natural mucopolysaccharide; hyaluronic acid, a
247 component of the vitreous humour.[51,52] Mechanisms for release of incorporated drugs are
248 determined by their chemical structure, network arrangement and swelling properties.[53]
249 Ocular drug delivery formulations incorporating viscosity enhancing polymers resist lacrimal
250 drainage when residing in the lower conjunctival cul-de-sac. However, disadvantages with this
251 approach are an initial blurring of vision due to changes in refractive index at the corneal surface,
252 and difficulty instilling a precise dose.[24,54,71]

253 **In situ gelling systems;**

254 'In situ' gelling systems undergo phase transition from liquid to gel under physiological
255 conditions and this technique has advantage over the simpler viscosity enhancing systems. Phase
256 transition can be mediated by physiological temperature, pH or electrolyte composition at the
257 cornea surface.

258 Thermogelling systems include polaxomers,[55,56] pluronics and tetronics,[57]. Ur-Rehman *et*
259 *al.* [58] investigated combined formulations of polaxamer 407 with chitosan as thermogelling
260 delivery systems for ocular, vaginal, orthodontal and parenteral drug administration; this process
261 allowed site specific tunable drug delivery with enhanced gel strength and mucoadhesive
262 properties. Gratieri *et al.* [59,60] also worked with polaxamer/chitosan gel forming systems, their
263 aim was to develop phase transition gels with improved mechanical and mucoadhesive
264 properties. They investigated poly(ethylene oxide) – poly(propylene oxide) - poly(ethylene
265 oxide) triblock polymers (PEO-PPO-PEO) with chitosan of various polymer ratios and found
266 that the polymer/chitosan ratio of 16:1 w/w offered optimum gelation temperature of 32°C,
267 good resistance to shearing forces at 35°C and good retention due to mucoadhesion. Poly(N-
268 isopropylacrylamide) is a well-researched thermogelling polymer with a lower critical solution
269 temperature (LCST) of 32°C, an ideal temperature for thermosensitive applications for ocular
270 drug delivery, although the polymer precipitates above the LCST forming a stiff gel which can
271 be uncomfortable for ocular drug delivery applications.[61] It also shows reduced transparency
272 above LCST,[62] which would be undesirable for eye-drop formulations. Cao *et al.*[61]
273 investigated thermogelling poly(N-isopropylacrylamide)-chitosan formulation and found it to be
274 a suitable system for ocular delivery of water-soluble drugs, but it is not clear whether they have
275 solved the ‘reduced transparency’ issue with their development. Mayol *et al.* [56] investigated
276 thermogelling polaxamers (F127 and F68) and found that on their own their gelling properties
277 were not ideal but could be optimized by addition of the naturally occurring mucoadhesive
278 polysaccharide, hyaluronic acid. They consider that this approach can be exploited for a range of
279 sustained drug delivery scenarios and they are especially suited for ocular drug delivery. PH-
280 mediated systems include Carbopol®,[63] and cellulose acetate phthalate. [64] Electrolyte

281 triggered gelling systems make the transition from liquid to gel by induction of crosslinking in
282 the gelling system mediated by cations present in the tear fluid, and these include gellan gum
283 (Gelrite®), carrageenan,[65-67] and sodium alginate.[68]

284 **Mucoadhesives;**

285 Mucoadhesion is the interaction between a compound, usually a polymer, natural or synthetic,
286 with mucosa or associated mucus.[53,69] Mucoadhesive drug delivery depends on the interplay
287 between the dosage form and mucus covered mucosal epithelial membranes, residence time
288 increases due to this interaction, allowing more time for the drug to penetrate its intended site of
289 action.[69,70] Mucosal adhesion of dosage forms can be explained using a combination of
290 theories:[71,72]

291 • *Electronic theory*, where interaction is due to electron transfer between the dosage form
292 and mucosal surface.

293 • *Adsorption theory*, attraction mechanisms are via electrostatic effects, hydrogen bonds
294 and Van der Waals forces. Hydrophobic effects are also implicated, more so when the
295 mucoadhesive polymers are amphiphilic. Covalent bonding can also come into effect
296 between some specific polymers and mucins.

297 • *Wetting theory*, mostly applies to liquid mucoadhesives where there are structural
298 similarities between the polymer and mucin, these effects reduce surface tension and
299 allow the mucoadhesive polymer to spread on the mucosal surface.

300 • *Diffusion theory*, considers the interpenetration of polymer into the mucus and diffusion
301 of soluble mucins into the mucoadhesive.

302 Neither of the above mentioned theories can be used to explain mucoadhesion on their own,
303 more, they each play a part to varying degrees within any given scenario.[71-74] In considering
304 a typical series of events involving a mucoadhesive – mucosa interaction; first of all the *wetting*
305 *theory* comes into play with wetting and associated swelling of the dosage form; next physical
306 interactions involving *electronic and adsorption theories* take place forming non-covalent bonds
307 between the system components; *diffusion theory* then comes into play when further non-
308 covalent bonds during interpenetration of polymer-protein chains during which physical and
309 covalent (chemical) bonds form again involving *electronic and adsorption theories*. [71,72]

310 With traditional ocular drug delivery systems residence time is determined by tear turnover, but
311 for mucoadhesive systems this becomes governed by mucus turnover, hence drug retention and
312 bioavailability is substantially increased.[51] Mucoadhesive polymer films could potentially
313 provide a suitable platform to deliver ocular drugs, Khutoryanskaya *et al.*[75] investigated the
314 use of complexes and blends of poly(acrylic acid) (PAA) and methylcellulose (MC) to produce
315 polymeric films as vehicles for ocular drug delivery. PAA has excellent mucoadhesive properties
316 due to an ability to form hydrogen bonds with mucin, although it has limited application for
317 transmucosal drug delivery due to being very hydrophilic, thus quick dissolving; it also has poor
318 mechanical properties and can cause irritation to delicate mucosa. MC has favourable properties
319 that are applied in transmucosal delivery systems; it has excellent biocompatibility profiles but
320 has poor mucoadhesive properties. The researchers used a polymer blend approach with different
321 combinations of PAA / MC under a range of pH and optimized a formulation bringing together
322 the favourable properties of both polymers. *In vitro* studies of drug-loaded polymer films
323 determined their release profiles and they found that films enriched in MC had significantly
324 slower drug release profiles than films enriched in PAA. This could allow a tunable drug

325 delivery system depending on whether rapid or sustained release is required. They further
326 investigated *in vivo* retention of the polymer films using rabbits and found that 100% MC films
327 were retained for up to 50 minutes but successful application was hampered by poor
328 mucoadhesive properties. 100% PAA films were strongly mucoadhesive but retention was poor
329 due to quick dissolution. They concluded that polymer blends had good bioadhesive qualities and
330 showed better retention of 30-60 minutes compared to the films composed of individual
331 polymers. [75]

332 **Nanoparticles;**

333 Nanoparticle drug delivery systems are more generally described as submicron sized structures;
334 these systems were described by Nagarwal *et al.*[19] as 10 to 1000 nm particles in which drugs
335 could be loaded by attachment to the matrix or dissolved within, encapsulated or entrapped
336 within the structure giving a versatile drug delivery system. Hans and Lowman [76] discuss
337 biodegradable polymeric nanoparticles for drug delivery, they suggest that surface modified
338 biodegradable solid nanoparticles have an advantage regarding controlled release, principally for
339 targeted drug delivery for the treatment of specific organs, in particular for extended drug
340 delivery to the cornea and conjunctiva.[76] Ibrahim *et al.*[77] describe a mucoadhesive
341 nanoparticle system as a carrier for gatafloxacin/prednisolone biotherapy for treatment of
342 bacterial keratitis, a serious corneal condition which could lead to blindness without rapid and
343 appropriate intervention. The drug loaded nanoparticle systems they describe were produced
344 from Eudragit® RS 100 and RL 100 and were coated with the bioadhesive polymer hyaluronic
345 acid. Nanoparticles within the suspensions produced using these systems were in the range of
346 315 nm to 973 nm. For ocular drug delivery, supramolecular structures, complexes and
347 composites belong to nanoparticulate systems and these can include microemulsions, liposomes,

348 niosomes, dendrimers and cyclodextrins.[1,2,36-41] Kassam *et al.*[78] investigated the use of
349 nanosuspensions for ophthalmic delivery of three virtually insoluble glucocorticoid drugs in
350 aqueous media; hydrocortisone, prednisolone and dexamethasone. Their findings show an
351 enhancement to the rate and extent of ophthalmic drug absorption together with improved drug
352 performance compared with aqueous solutions and microcrystalline suspensions. De Campos *et*
353 *al.*[79] investigated the interaction of poly(ethylene glycol)- or chitosan- coated colloidal
354 nanocapsules with ocular mucosa; they conclude from *ex vivo* studies that the systems they
355 developed enhanced permeation of dye through the cornea. Evidence from confocal microscopy
356 shows their systems penetrated the epithelium of rabbit cornea via the transcellular pathway and
357 they found that PEG-coated colloids had an enhanced rate of transport across the whole
358 epithelium; whilst chitosan-coated nanocapsules were retained in the superficial epithelial layers.
359 They suggest these systems could be designed as colloidal drug carriers targeting a specific
360 purpose, that is, to attach to the cornea or penetrate into or through it. This implies these systems
361 should prove useful of treating conditions of the cornea and deeper structures within the eye.

362 Diseases of the posterior section of the eye include macular degeneration, diabetic retinopathy,
363 retinitis pigmentosa and related ocular neovascular disease. Topical delivery of drugs to the
364 posterior section of the eye is particularly challenging due not least to ocular barrier function and
365 internal clearance mechanisms within the anterior chamber. Recent developments in the field of
366 nanoparticles involve submicron-sized liposomes (ssLips) and these are proving useful for
367 topical drug delivery systems in the form of eye drops for the treatment of posterior segment
368 diseases. Studies by Hironaka *et al.* and Inikuchi *et al.* [80,81] show successful delivery of
369 coumarin-6 to the retina via non-corneal and non-systemic pathways using eye drops. *The*

370 *assumption can be made that posterior section delivery is via penetration through the sclera*
371 *using ssLips [8,41] (emphasis highlights conclusion of the authors of this review).*

372 **Ocular inserts:**

373 Ocular inserts are drug loaded devices placed in the upper or lower cul-de-sac and in some cases,
374 directly on the cornea; their purpose is to act as a controlled release drug reservoir. These
375 systems can be insoluble devices that need to be removed after a given period of time or they can
376 be designed to dissolve, erode or biodegrade at the ocular surface. Early forms of ocular inserts
377 have been used since the middle ages and were given the arabic term *al-kohl*. By the nineteenth
378 century, paper patches soaked with drug solutions were used and in the early twentieth century
379 glycerinated gelatin systems were in use.[82] It is not clear how effective these early devices
380 were, however, drug delivery by this means has developed and devices can be of soluble
381 ophthalmic drug inserts (SODI) or insoluble polymers, mucoadhesives or soluble natural
382 materials such as collagen (e.g. from porcine sclera).[4] Ideally these devices could be applied
383 and left in place with no further intervention thereafter. Ocular inserts need to be discreet and
384 comfortable to gain patient acceptance. Sustained release ophthalmic inserts are defined as
385 sterile devices which can be drug impregnated thin, single or multi-layered films, solid or
386 semisolid materials. The objective being to extend ocular contact time thus improving
387 bioavailability. Development of ocular inserts that bring reliable controlled release drug delivery
388 and patient comfort offers a considerable challenge. The main classes of devices are insoluble,
389 soluble and biodegradable inserts.[83] Ocusert® was the first relatively successful product for
390 delivery of pilocarpine for the treatment of ocular hypertension and has been commercialised
391 since 1974. Ocusert® consists of a pilocarpine-alginate reservoir sandwiched between thin
392 ethylene-vinyl acetate films, the devices are designed to deliver pilocarpine at either 20µg per

393 hour or 40 µg per hour. Some disadvantages of this system were unreliable control of intraocular
394 pressure, leakage, folding, difficulty inserting the devices and ejection or irritation.[82,84]
395 OcuFit SR® are sustained release rod shaped devices made from silicone elastomer, designed to
396 reside in the lower conjunctival fornix; these devices are well tolerated and expulsion is
397 significantly less than with oval or flat inserts. Minidisc ocular therapeutic system (OTS) by
398 Bausch & Lomb are drug-loaded polymer discs with similar shape as contact lenses but are
399 smaller (4-5 mm); they were designed to reside on the sclera in the upper or lower fornix and
400 deliver the antibiotics gentamicin or sulfisoxazole between 3-14 days depending on the system.
401 The company produces non-erodible hydrophobic and hydrophilic systems and erodible devices
402 based on hydroxypropyl cellulose. The inserts are comfortable and easy to use for most patients.
403 Smith & Nephew Pharmaceutical Ltd patented what they term 'new ophthalmic delivery system'
404 (NODS®); these devices offer precision pilocarpine delivery for glaucoma patients from
405 poly(vinyl alcohol) (PVA) film flags. These devices attach to the mucosal surface of the lower
406 conjunctival sac where it takes up fluid from the tears, swells and delivers its drug payload at a
407 pre-determined rate into the lacrimal fluid as it slowly dissolves.[82] Mydriaserit® are insoluble
408 devices marketed by IOLTech for the delivery of phenylephrine and tropicamide to induce
409 sustained mydriasis during surgery or for examination of the fundus (interior ocular surface).[3]

410 Human amniotic membrane has been used for corneal transplant to treat corneal disorders and
411 ulcerative ocular conditions. Resch *et al.* [85,86] investigated its use as drug loaded ocular
412 devices to deliver ofloxacin *in vitro* and they concluded that single layer human amniotic
413 membrane had a significant reservoir capacity capable of delivering the drug for up to 7 hours *in*
414 *vitro*. They propose that drug pretreatment of amniotic membrane could be beneficial when using

415 this tissue for ocular transplant when treating infectious keratitis.[85,86] **Table 1** lists some
416 advantages and disadvantages for using ocular inserts. [20,82,87]

Advantages	Disadvantages
<ul style="list-style-type: none">• Increased residence time / bioavailability• Precision dosing with controlled release, avoids pulsate drug delivery• Minimal systemic absorption• Administration frequency reduced• Conjunctival / scleral route to internal target• Better shelf life and no preservatives• Combinational therapeutic approaches	<ul style="list-style-type: none">• Physical and psychological obstacles of placing solid objects on the eye, foreign body sensation• Movement around the eye could interfere with vision• Potential accidental loss• Some devices difficult to insert or remove• Potential burst release upon insertion prior to controlled delivery

417

418 **Recent developments in ocular insert drug delivery systems:**

419 Colo *et al.* [88] investigated the effect of adding chitosan hydrochloride (CH-HCl) to
420 mucoadhesive erodible ocular inserts produced from poly(ethylene oxide) (PEO) of various
421 molecular weight for delivery of ofloxacin. They added 10, 20 and 30 % medicated CH-HCl
422 microparticles to PEO formulations made from 900 kDa or 2000 kDa. Erosion of the devices
423 was accelerated proportional to CH-HCl content. The lower molecular weight PEO proved more
424 suitable for prolonged drug release. They conclude that inclusion of CH-HCl in the devices aids
425 erosion and enhances corneal permeability of ofloxacin when compared to devices not
426 containing CH-HCl. Hornof *et al.* [89] developed mucoadhesive devices based on thiolated
427 poly(acrylic acid) (PAA) and these were evaluated in human in vivo studies. Their aim was to

428 develop mucoadhesive ocular inserts for controlled delivery of ophthalmic drugs using
429 fluorescein as a fluorescent tracer to determine release rates from the devices in humans. They
430 compared mean fluorescein concentrations in the tear film and cornea as a function of time after
431 instillation of eye drops and inserts composed of thiolated and unmodified PAA. The thiolated
432 polymer inserts formed a soft, insoluble hydrogel and were well tolerated by volunteers. Their
433 findings show this material offers a promising platform for ocular drug delivery for a prolonged
434 duration. Mishra and Gilhotra [63] designed and characterized a bioadhesive in-situ gelling
435 ocular insert for the delivery of gatifloxacin using a mixture of sodium alginate with chitosan,
436 which was plasticized with glycerin. They combined sodium alginate for its gelling properties,
437 with chitosan for its bioadhesive qualities, formulations of various proportions were prepared
438 and films were produced using the solvent casting technique as described by Pandit *et al.* [90]
439 Using this system they found an accumulative drug release of 95-99% during 8-12 hours and the
440 formulation consisting of 2% alginate with 1% chitosan had the most sustained release of 12
441 hours. They conclude that this system allowed production of uniform in situ gelling polymer
442 films suitable for controlled release of gatifloxacin for the treatment of bacterial keratitis and
443 conjunctivitis.[63] Natamycin is a polyene antibiotic used for the treatment of fungal blepharitis,
444 bacterial keratitis and conjunctivitis and it has the ability to reduce intraocular pressure.
445 Rajasekaran *et al.*[91] compared the controlled release performance of natamycin from ocular
446 inserts they designed from a variety of polymeric materials; Eudragit® L-100, S-100, RL-100,
447 hydroxypropyl methyl cellulose phthalate (HMCP) and cellulose acetate phthalate (CAP) in
448 different proportions with poly(ethylene glycol-400) (PEG-400) as a plasticizer. Their aim was
449 to develop devices for in situ sustained drug delivery and their approach was to prepare
450 polymeric films using the solvent casting method. 1 cm discs were cut from the films to be used

451 as inserts; these were evaluated for their physicochemical properties such as drug concentration,
452 weight, folding durability, thickness, moisture absorption and vapour transmission rate. FTIR
453 studies established that there was no chemical interaction between the drug and polymers used.
454 *In vitro* studies were conducted to determine their drug release kinetics; devices made from CAP,
455 HPMCP and Eudragit® S-100 released all of their drug payload within 10-15 hours, whilst
456 inserts made from increased concentrations of Eudragit® RL-100 continued release for 18-23
457 hours; best performance was shown for formulations consisting of 3% Eudragit® RL-100 and
458 1% Eudragit® L-100. They conclude that nataycin loaded ocular inserts produced from 3%
459 Eudragit® RL-100 and 1% Eudragit® L-100 plasticised with 33% PEG-400 are capable of
460 controlled drug delivery up to 23 hours.

461 **Contact lenses for drug delivery**

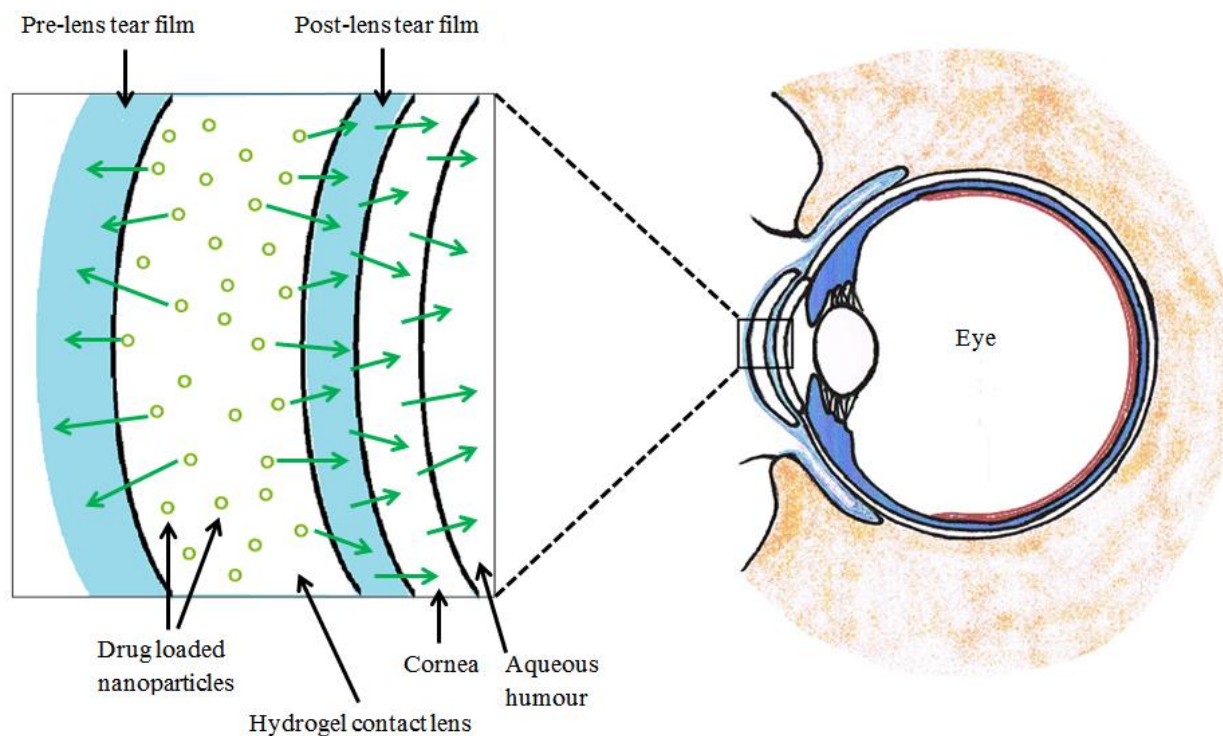
462 Contact lenses are hard or soft polymeric devices designed to fit directly onto the cornea to
463 correct refractive abnormalities; they can be produced from hydrophilic or hydrophobic
464 polymers. Hydrogel contact lenses are realistic products to act as ocular drug delivery systems;
465 they are able to imbibe a large volume of aqueous solution relative to their anhydrous form. If
466 the aqueous solution that hydrates the contact lens contains sufficient pharmaceutically active
467 material this will be able to diffuse from the polymer matrix into the tear film bathing the eye
468 and subsequently interact with the ocular tissue. However, there still remains a need to retain the
469 drug within the devices sufficiently to provide sustained release.

470 The idea of using hydrogel contact lenses as drug delivery devices was first suggested by
471 Wichterle *et al.* [29,92] in their 1965 patent, in which they suggest the inclusion of medication
472 upon lens hydration to offer extended drug availability during wear. Contact lens design
473 determines how they are to be used; daily, weekly and monthly disposable options are

474 available.[92] Early approaches to contact lens aided drug delivery relied on absorbance of drug
475 loaded solution during pre-wear soaking. Conventional contact lenses have limited drug loading
476 potential and drug delivery using this method proves unreliable, giving an initial ‘burst release’
477 followed by rapid decline over a relatively short period.[20,93] Other methodologies include
478 molecular imprinting technology, drug loaded coating or addition of a sandwich layer of drug-
479 loaded polymer, inclusion of drug-loaded nanoparticles and cyclodextrin grafting.[28]
480 Molecular imprinting technology is a technique whereby the polymer formulation is modified to
481 give it a higher affinity towards drug molecules, thus increasing their drug loading potential and
482 prolonging delivery [94-96]. Hiratani *et al.* [93] took this approach in developing a system
483 employing methacrylic acid, *N,N*-diethylacrylamide and the drug timolol; from this system they
484 were able to achieve sustained timolol release for almost 48 hours *in vitro*. Alvarez-Lorenzo *et*
485 *al.* [97] applied the same strategy to produce norfloxacin-loaded poly(hydroxyethyl
486 methacrylate) contact lenses and they report that reservoir capacity was enhanced by up to 300
487 fold compared with pHEMA lenses without molecular imprinting technology. Hyatt *et al.*[98]
488 investigated the release profiles of gentamicin and vancomycin from fibrin coated and fibrin
489 sandwiched contact lenses *in vitro*; their aim was to develop a system that could offer controlled
490 and sustained drug delivery for a minimum period of 8 hours. They conclude that the fibrin
491 gel/lens systems performed better for extended delivery of gentamicin compared to normal
492 lenses soaked with the antibiotic solution, however, their performance for delivering vancomycin
493 was poor compared to soaked lenses. Lenses incorporating fibrin showed potential for treating
494 microbial keratitis. Ciolino *et al.*[99,100] investigated poly(lactic-co-glycolic acid) (PLGA)
495 coatings and sandwiched films with contact lenses as potential drug delivery devices. They found
496 that contact lenses incorporating PLGA film retained antifungal properties up to 3 weeks *in vitro*,

497 and their prototype ciprofloxacin eluting contact lens demonstrated controlled release at
498 therapeutically active concentrations for up to 4 weeks *in vitro*. Although fibrin or PLGA film
499 sandwiched and coated lenses bring sustained drug delivery benefits, the lenses are opaque;
500 therefore they require clear ‘window’ in the centre of the lens allowing the patient to see during
501 treatment.[97-100] Inclusion of drug loaded nanoparticles within the polymer matrix of contact
502 lens is an effective strategy for prolonged drug delivery. This approach can allow sustained
503 release which can be tuned towards the patient’s needs, anything between a few hours to several
504 weeks. Gulsen and Chauhan [101] conducted a pilot study to determine the effectiveness of
505 nanoparticle laden pHEMA. The nanoparticles were based on oil-in-water microemulsion
506 loaded with lidocaine, a hydrophobic drug; the droplets were then encapsulated in a silica shell
507 which stabilized the nanoparticles and these were incorporated in the hydrogel matrix during
508 polymerization. Hydrophobic lidocaine has a slight and finite solubility in water; therefore it is
509 able to slowly diffuse from the nanoparticles into the aqueous phase of the gel matrix where it
510 would then be able to further diffuse into the tear film. The nanoparticle-laden hydrogels
511 remained clear and drug release studies *in vitro* showed an initial burst release followed by slow
512 and steady release thereafter; by day 10 virtually all the drug had been released. They conclude
513 that the nanoparticle-loaded hydrogels could be suitable for controlled drug delivery for several
514 days at therapeutically effective concentrations. Gulsen and Chauhan [102] followed up their
515 previous investigation of nanoparticle-laden pHEMA by developing four more microemulsion
516 based formulations, type 1 and 2 were based on canola oil with Tween® 80 and Panadon SDK,
517 with or without a stabilizing silica shell, and type 3 and 4 were based on hexadecane with Brij®
518 97 with or without a stabilizing silica shell; they incorporated lidocaine as a model drug. Type 1
519 formulation was opaque due to the poor solubility of Tween® 80 in HEMA, type 2 formulation

520 lost some transparency but was not opaque indicating that the silica shell reduced interaction
521 between the surfactant and HEMA. Type 3 showed minimal transparency reduction but was not
522 as transparent as pHEMA, type 4 showed no observable loss of transparency due to stabilization
523 afforded by the silica shell. Release studies *in vitro* determined that formulations based on
524 hexadecane with Brij® 97 were suitable for sustained drug delivery at therapeutic rates for up to
525 8 days, Tween®80 based formulation was deemed unsuitable due to poor stability and particle
526 aggregation. Gulsen and Chauhan speculate that furthering this work to develop ‘smart’
527 particulate based systems which could respond to pH or temperature change could minimise
528 burst release and decaying release rates.[101,102] The approach followed by Jung and Chauhan
529 [103] was to develop a timolol loaded nanoparticle / HEMA based contact lens system. Their
530 aim was to produce nanoparticles without using surfactant due to opacity issues when these are
531 used with HEMA. Using thermal polymerization techniques they formed drug loaded
532 nanoparticles based on crosslinking monomers; propoxylated glycerol triacrylate (PGT) and
533 ethylene glycol dimethacrylate (EGDMA) and incorporated these in pHEMA hydrogels. Their
534 product was a transparent drug loaded hydrogel with temperature dependent release rates
535 between 2-4 weeks. They conclude their system maintains drug stability under refrigerated
536 conditions and the temperature change promotes drug release upon insertion of the lenses into
537 the eyes. **Figure 5** shows how nanoparticles could release entrapped drug molecules into the pre-
538 and post-tear films.



539

540 **Figure 5.** Drug diffusion from nanoparticles encapsulated within hydrogel contact lens. The
 541 scale used in this image has been exaggerated for clarity.

542 Drug loading capacity of hydrogel contact lenses can be enhanced by the inclusion of ‘container
 543 molecules’. Cyclodextrins, with their ‘guest-host’ properties have been investigated for this
 544 purpose. Complexation between cyclodextrins and drug molecules is a dynamic process due to
 545 the weak non-covalent interactions in play. The strategy followed by dos Santos *et al.*[104] was
 546 to synthesise methacrylated β -cyclodextrin and use it to form co-polymer with HEMA and
 547 EGDMA, the polymers formed had clear gel properties. Drug loading was achieved by soaking
 548 the anhydrous polymers in solutions of acetazolamide or hydrocortisone for 4 days. The
 549 performance of these methacrylated β -cyclodextrin hydrogels was studied *in vitro* and they were
 550 found to offer tunable drug loading/release rates with capacity for sustained drug delivery over
 551 several days. They followed up this study with development of another hydrogel formulation

552 using β -cyclodextrin grafted onto pHEMA-co-GMA (glycidyl methacrylate). This system was
553 able to enhance diclofenac loading by 1300% and could sustain drug release for 2 weeks in
554 lacrimal fluid. They conclude that these systems could have potential for pharmaceutical
555 applications in soft contact lenses and other medicated devices.[105] Xu *et al.*[106] produced
556 hydrogel films and contact lenses from HEMA, mono-methacrylated β -cyclodextrin and
557 trimethylolpropane trimethacrylate. Puerarin was incorporated as a model drug by soaking in
558 drug solution to hydrate the gel. *In vitro* studies determined loading and release rates were
559 dependent on β -cyclodextrin content. *In vivo* studies using rabbits showed the gels offered
560 sustained drug release with superior performance compared to commercial puerarin eyedrops.
561 The devices had excellent mechanical properties and the researchers propose the material is
562 suitable for drug delivery from re-usable daily wear contact lenses.

563 **Ocular implants:**

564 **Treating the posterior segment**

565 Historically, the posterior segment has been exceptionally difficult to treat due to the many
566 barriers that obstruct ingress of foreign matter into the eye. The development of ocular implants
567 have allowed these external barriers to be overcome. Modern devices allow long term treatments
568 for otherwise impossible to treat conditions, many devices provide medication for years from a
569 single procedure. [107,112]

570 **Drug eluting intraocular lenses**

571 Intraocular lens (IOL) surgery is a well-established and safe procedure routinely performed
572 worldwide; however as with any surgical technique there is always risk from infection or other

573 complications, for example, postoperative inflammation, posterior capsule opacification (PCO)
574 and secondary cataracts caused by epithelial cell adhesion and proliferation in the posterior lens
575 capsule. Introduction of preventative medication during surgery is subject to decay or
576 elimination before it can be effective. Much research is currently carried out for development of
577 drug eluting IOL's to minimise postoperative problems, and also to address concurrent
578 pathologies. IOL / drug combinations can be achieved by pre-insertion soaking in concentrated
579 drug solution (only useful for drugs with a high affinity for the polymer), coating with layers of
580 drug/polymer, chemical grafting of drugs, drug impregnation using super critical fluids and
581 attaching inserts onto the haptics (the 'arms' of the IOL).[28] A study by Kleinmann *et al.*[113]
582 determined that commercial hydrophilic acrylic lenses (C-flex, Rayner intraocular lenses) [114]
583 have affinity for fourth generation fluoroquinolones and were able to release this drug above the
584 minimum inhibitory concentration in rabbits for at least 12 hours. They conclude C-flex/drug
585 combination is safe and effective for delivery of these antibiotics. Davis *et al.*[115] investigated
586 concentrations of 4 antibiotics (moxifloxacin, gatifloxacin, linezolid and ceruroxime) in aqueous
587 and vitreous humour samples from rabbit eyes. Drug released from implanted hydrophilic IOL's
588 was analysed using HPLC to determine drug concentration in the ocular fluid samples. The
589 IOL's used were STAAR Nanoflextm Colamer®, 40% water content material comprised of a
590 collagen, pHEMA blend,[116] pre-soaked in antibiotic solution. Ocular fluid samples were
591 taken for analysis at intervals up to 24 hours. It was established that the antibiotics studied were
592 above the minimum inhibitory concentration in the aqueous humour for at least 6 hours, notably,
593 gatifloxacin concentrations remained above this level at 24 hours after implantation.[116]
594 Layer-by-layer deposition is a technique used for coating opposing charge polymers to rigid
595 hydrophobic IOL's, a drug can be incorporated during this process. Coating pHEMA based

596 hydrophilic IOL's by immersion in octadecyl isocyanate can be an effective method to give
597 controlled release from norfloxacin containing IOL's. Grafting drug molecules onto the IOL
598 surface can provide a permanently active surface to prevent cell adhesion, or allow release of
599 drugs by some external trigger, for example light irradiation. High drug concentrations within a
600 polymeric matrix can be achieved using supercritical CO₂ as a means to force drugs into the
601 polymer without the need for organic solvent.[28] Duarte *et al.*[117] employed supercritical CO₂
602 technology to impregnate p(MMA-EHA-EGDMA), a suitable polymer for IOL manufacture,
603 with flurbiprofen, an anti-inflammatory drug used for intraocular delivery. Their experiments
604 found the process allowed higher drug impregnation and release studies showed the system to be
605 effective for up to 3 months. The approach employed by Garty *et al.* [27] was to produce
606 norfloxacin loaded pHEMA cylinders in 1.0 mm diameter microglass tubes with 0.09 mm
607 stainless steel wire through the centre during room temperature polymerization. When fully
608 polymerized the hydrogel was ejected from the tube and the wire removed leaving a tubular
609 hydrogel structure, this was washed with sterilized water to remove unreacted components. The
610 gel was cut into 1.0 mm lengths and lyophilized. Next they added a hydrophobic coating using
611 octadecyl isocyanate to control drug release. The devices were used as sleeves placed over IOL
612 haptics and this assembly was used in lens replacement procedures in the rabbit model. Results
613 from *in vivo* studies showed the devices offered sustained drug delivery above the minimum
614 inhibitory concentration for over 4 weeks. They conclude that these controlled release devices
615 are effective at sustained delivery of therapeutic levels of drugs within the anterior chamber post
616 operatively. Incorporation of drugs with IOL's has predominantly aimed at postoperative
617 delivery of antibiotics and anti-inflammatory medication.

618 **Drug delivery by intravitreal injection**

619 There are many debilitating and sight threatening conditions resulting from posterior segment
620 diseases and in most cases the only way these can be treated is by invasive procedures, for
621 example ‘intravitreal injection’. In the main this still remains so, however, developments have
622 brought a diverse range of effective implantable drug delivery systems targeting posterior
623 segment disease and the various options will now be considered. [22] The most common means
624 to place drugs in the posterior chamber employs injection into the vitreous humour; this provides
625 a high concentration of drug where it is needed and minimises systemic complications. Xu *et al.*
626 investigated the diffusion of polystyrene nanoparticles of various size and surface chemistries in
627 fresh bovine vitreous and they were able to achieve tuneable drug transport within the posterior
628 chamber depending the designed properties of the nanoparticle [118]. However, many conditions
629 require repeated treatment and this can cause intraocular problems, for example, cataract, retinal
630 detachment, haemorrhage, endophthalmitis and ocular hypertension.

631 **Intraocular implants**

632 In an attempt to overcome the problem of frequent injections biodegradable and non-
633 biodegradable drug depot devices which can offer long term drug release into the posterior
634 chamber have been developed and further research in this area is ongoing. Solutions, liposomes,
635 micelles, nanoparticles and vectosomes are suitable for intravitreal injection although these
636 dosage forms only give short term drug availability, generally days to several weeks.[23,119]
637 Biodegradable and non-biodegradable drug depot devices have been developed and further
638 research in this area is ongoing. Implantable devices for long term drug delivery are on the
639 market or currently undergoing clinical trial. Vitrasert® is a drug depot device for sustained
640 delivery of ganciclovir via a rate limiting poly(vinyl acetate)/ethylene vinyl acetate (PVW/EVA)

641 membrane for up to 8 months.[22,119,120] Retisert® intraocular inserts were approved by the
642 FDA in 2005. They are inserts for delivery of the corticosteroid, fluocinolone acetonide for
643 treatment of posterior uveitis, a serious sight threatening condition. The devices are designed for
644 long term drug release up to 30 months.[121] Vitrisert® and Retisert® inserts are non-
645 degradable and require surgical implantation and removal.[22] Medidur® are implantable
646 devices for delivering fluocinolone acetonide for up to 36 months. This device consists of a
647 narrow cylindrical polyimide tube loaded with the drug and PVA-based end caps provide rate
648 limiting drug delivery. The 3.5 mm long device is inserted through a 25-g needle carried out
649 under local anaesthesia and creates a self-healing wound eliminating the need for surgery.[122]
650 Implants employing biodegradable polymers are promising systems for intraocular drug delivery.
651 Sivaprasad *et al.* [123] report the use of the Posurdex® biodegradable polymer device for
652 treatment of macula oedema using dexamethasone. This drug has a half-life of less than 24 hours
653 therefore it provides only limiting management of this condition by injecting the drug. However,
654 dexamethasone containing Posurdex® devices were shown to deliver the drug at a constant rate
655 for up to 4 months, these devices have been re-named Ozurdex® and are marketed by Allergan
656 Inc. [124] *In vivo* studies using monkeys showed the system was effective at reducing retinal
657 vasculopathy and neuropathy.[125] Surodex® is a poly(lactic-glycolic acid) device to be
658 inserted in the anterior or posterior chamber at the time of cataract surgery to deliver
659 dexamethasone for up to 10 days. Tan *et al.* [126] conducted a randomized clinical trial to
660 evaluate the effectiveness of the Surodex® insert as a safe and effective treatment of intraocular
661 inflammation in post-cataract surgery. Their study employed flare meter readings to determine
662 inflammation and this showed that measured values were lower in all readings from the
663 Surodex® group compared to those treated post operatively with dexamethasone eye drops, they

664 conclude that implantation of a single Surodex® device at the time of cataract surgery reduces
665 post-surgery inflammation [126,127].

666 **Future perspectives:**

667 In this review the various strategies for enhancing bioavailability of ophthalmic drugs have been
668 considered; how drug bioavailability can be improved using solubility, retention and
669 permeability enhancers has been explored. Drug loaded contact lenses allow localised delivery
670 directly to the cornea, where the lenses offer controlled release whilst isolating the post corneal
671 tear film from lachrymal clearance. Nanoparticle technology is allowing drug delivery to the
672 posterior chamber via topically applied formulations. Future research is likely to bring
673 discoveries of materials with superior performance compared with those in current use.

674 The use of ocular inserts for extended and intimate contact between the dose form and ocular
675 tissue proves to be a beneficial strategy and the use of ocular implants allows all external barriers
676 to be overcome, giving direct access to internal tissues whilst minimising side effects. Many of
677 these approaches have been developed in recent decades and continue to be improved upon with
678 new innovations. Looking to the future innovative advances to delay or prevent blindness could
679 be made; developments in two main areas could be speculated; the cornea and vitreous humour.
680 First, corneal disease has a major influence on visual health; corneal tissue engineered constructs
681 are being developed to test new ocular drugs. Future development of artificial corneas could
682 become a possibility to replace diseased ones without the need for donor tissue, which is a scarce
683 commodity.[127,128] Another area for advanced drug delivery is the posterior segment;
684 vitrectomy is an invasive but well-established procedure for many posterior segment disorders. A
685 synthetic material is used to replace natural vitreous humour. The possibility of developing
686 synthetic materials for whole or partial vitrectomy as a drug depot could allow long term

687 controlled release for decades. A one off procedure would be more favourable than many less
688 effective ones over the course of a lifetime.[129,130]

689 **Executive summary:**

690 Strategies to enhance the bioavailability of drugs are;

691 **Drug solubility and penetration enhancement**

- 692 • Many ocular drugs have low aqueous solubility; this can be improved using hydrotropic
693 compounds. Formulating for higher drug concentration means increased availability.
- 694 • Inclusion of penetration enhancers within a formulation improves drug partitioning into
695 tissue.

696 **Drug retention strategies**

- 697 • Viscosity enhancing polymers, in situ gels and bioadhesives allow eye drop formulation
698 to resist pre-corneal losses and they retain intimate contact with ocular tissue longer
699 giving the dose form more time to penetrate ocular membranes.
- 700 • Drug delivery from ocular inserts are a means to place the dose form in immediate
701 contact with ocular mucosa, this strategy allows controlled and sustained drug release for
702 an extended period.

703 **Ocular implants**

- 704 • Implantable devices are designed to penetrate the ocular membranes or reside entirely
705 within the eye. This strategy overcomes all external barriers and can offer short term
706 medication or deliver medication for several years when treating chronic conditions.

707 **Future perspectives**

- 708 • A speculative outlook considered the possibility of innovative technologies developing
709 synthetic tissues to enable testing new drugs and possibly even produce artificial corneas
710 for transplant. The idea of developing novel materials for vitreous humour replacement as
711 lifetime drug delivery depots could potentially become realised.

712

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