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Contact lenses in ocular therapeutics

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Drug delivery is a difficult task in the field of ocular therapeutics. Owing to the physiological and anatomical constraints of the eye, it is difficult to obtain the correct therapeutic concentration of a drug at the required site of action. This has led to clinicians recommending frequent dosing, which has resulted in noncompliance by patients and decreased cost effectiveness. To overcome these barriers, scientists have explored novel ocular delivery systems, such as *in situ* gels, ocuserts, nanoparticles and liposomes. A particularly novel form of such a delivery system are contact lenses, which are thin, curved plastic disks that are designed to cover the cornea and which cling to the surface of the eye owing to surface tension. In this article, we describe the introductory literature on ocular delivery using contact lenses, their classification and manufacturing process, and recent advances on drug delivery techniques using such lenses.

Successful drug delivery in ocular therapeutics is a challenging issue and, therefore, is a subject of interest to scientists working in multidisciplinary areas, such as the chemical, biochemical, pharmaceutical, medical, clinical and toxicological sciences. The main problem encountered when attempting to deliver drugs into an eye is attaining the optimal drug concentration at the required site of action [1] (Fig. 1). The poor ocular bioavailability of drugs is mainly the result of pre-corneal loss factors, which include tear dynamics, non-productive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the corneal epithelial membrane. As a consequence of these physiological and anatomical constraints, only a small fraction of an administered dose (1% or less) is ocularly absorbed [2]. This requires the clinician to recommend frequent dosing at a high concentration, which can result in adverse effects of the drug. To overcome this problem, novel delivery systems are being explored [3] that can achieve therapeutic action of a drug with a smaller dose and with fewer systemic and ocular adverse effects [4].

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Novel drug delivery systems

The current focus of ophthalmic research scientists is to develop drug delivery systems that not only prolong the ocular contact time of the drug, but also simultaneously reduce its elimination from the eye. To achieve these goals, novel drug delivery systems have been explored. Such systems include ocuserts [5,6], collagen shields [7,8], nanoparticles and microspheres [9,10], penetration enhancers [11,12], colloidal delivery systems [13,14] and implantable systems [15,16]. These drug delivery systems achieve high success rates, as demonstrated by Patel *et al.* [13]. These authors formulated ocular inserts of gatifloxacin sesquehydrate and moxifloxacin hydrochloride [14] that provided a good *in vitro–in vivo* correlation and remained stable for up to 2 years. In addition, Bhagav *et al.* [15] formulated ocular inserts that showed sustained release of brimonidine tartrate with no ocular irritation and improved intraocular pressure (IOP) lowering ability compared with eye drops. Colloidal drug delivery systems have also been explored for the ocular delivery of drugs because they have fast uptake with a long residence time. The latter can be attributed to the mucoadhesive nature of the polymers or lipids used in the preparation of nanoparticles [17]. Compared with a conventional solution, tobramycin-loaded solid lipid nanoparticles (SLNs) showed a longer retention time on the corneal surface and

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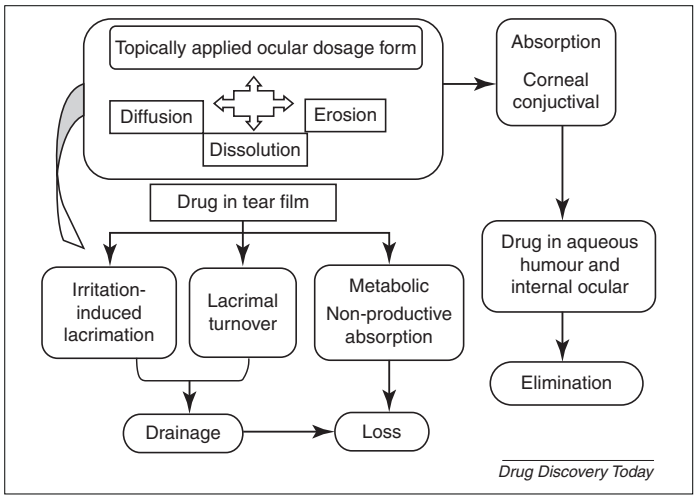

FIGURE 1

Schematic diagram of the dispersion of topically applied ocular formulations.

conjunctival sac. During *in vivo* evaluation, nanoparticles showed release over a period of 6 h compared with eye drops [18]. In similar studies, mucoadhesive chitosan-sodium alginate nanoparticles [19] or chitosan particles [16] showed sustained release of up to 24 h with a reduced dosing frequency and fewer adverse effects. Vesicular drug delivery systems, such as ganciclovir-loaded liposomal formulation, showed good transcorneal permeability compared with ganciclovir solution [20]. Compared with vasoactive intestinal peptide (VIP) solution, VIP liposomal formulation showed a 15-fold greater concentration in ocular fluid [21]. Intraocular implants also extend the length of time of drug release in ocular fluids, particularly in the posterior segment of the eye. Two monomers of polylactic acid (PLA) with different molecular weights showed a minimum burst release with pseudo zero-order kinetics [22]. In addition, many intrascleral and intravitreal drug implants have been developed for ocular therapy.

Despite these apparent successes, all novel ocular drug delivery systems have limitations. Collagen shields are not fitted individually to each patient (as soft contact lenses are); in addition, these shields are not fully transparent and thus reduce visual acuity. For colloidal drug delivery systems, nanoparticles composed of poly(-alkyl cyanoacrylate) damage the corneal epithelium by disrupting the cell membrane, whereas liposomes suffer instability problems owing to the hydrolysis of the phospholipids normally used in their preparation. Implantable systems, such as ocular inserts, have poor patient compliance and the need for surgery.

Contact lenses

Contact lenses are thin, curved plastic disks that are designed to cover the cornea. Owing to the surface tension, the contact lens clings to the film of tears over the cornea. Contact lenses are used to correct eye problems such as myopia, hypermetropia, astigmatism and presbyopia. They are also used as a cosmetic aid to change eye color through tinted lenses. Contact lenses also provide a safe and effective way to correct vision [23]. The number of people who wear contact lenses is increasing exponentially and it is expected that, over next decade, the number of contact-lens wearers will surpass the number of people who regularly wear glasses (Vision Council of America; http://www.thevisioncouncil.org/). Here, we provide a historical perspective of contact lenses (Table 1), their classification system (Fig. 2) and the processes involved in their manufacture (Fig. 3).

TABLE 1

Historical milestones of contact lens invention

Year	Historical perspectives
16th century	First contact lens invented by Leonardo da Vinci
1887	First modern contact lens made by Adolf Fick
1912	Carl Zeiss developed a glass corneal lens
1938	Obrig and Muller introduced a plastic scleral lens
1948	First plastic corneal lens made by Kevin Touhy
1971	In the USA, Bausch & Lomb introduced the first commercially available soft contact lens
1978	First toric soft contact lens introduced in the USA for the correction of astigmatism
1979	First rigid gas permeable (RGP) hard contact lens introduced
1981	Extended-wear soft contact lenses introduced
1982	Bifocal daily wear soft contact lenses became available for commercial distribution
1983	First tinted RGP lenses became available for commercial distribution
1987	Disposable soft contact lenses, soft contact lenses to change eye color, first multipurpose lens care products and a new formulation of fluorosilicone acrylate material for RGP lenses all became available for commercial distribution
1991	Frequent-replacement soft contact lenses introduced
1992	Tinted disposable soft contact lenses introduced
1995	One-day disposable soft contact lenses introduced
1996	First disposable lenses using ultra-violet absorber became available in the USA
1999	Disposable bifocal soft contact lenses introduced
21st century	Glass adapted to the eye for both surface protection and correction of ametropia

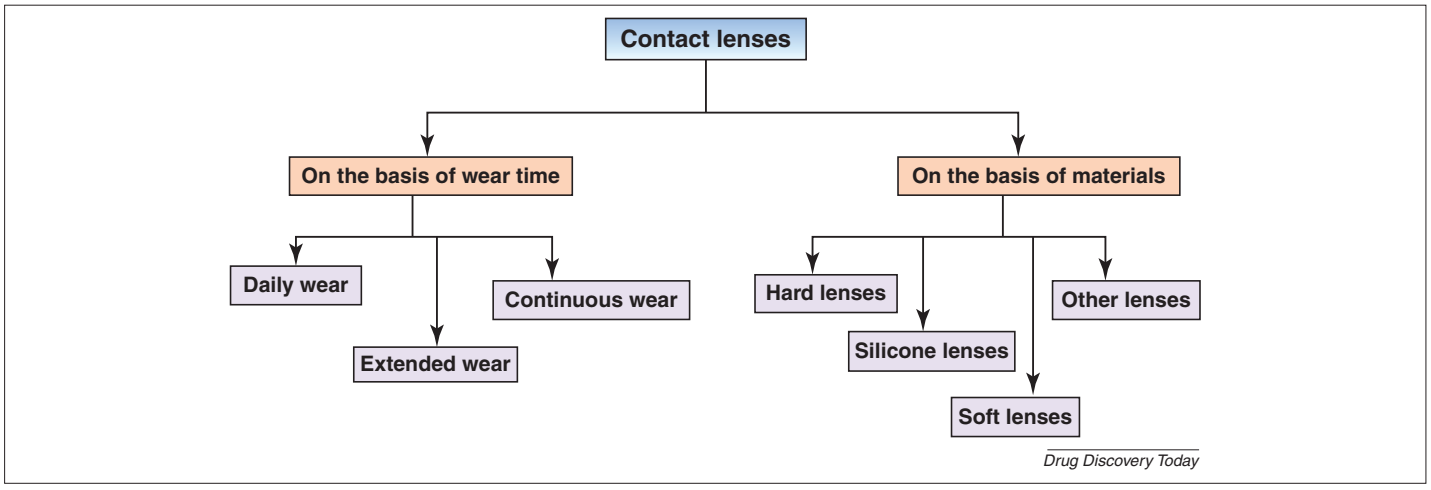

FIGURE 2

Classification of contact lenses on the basis of wear time and material used.

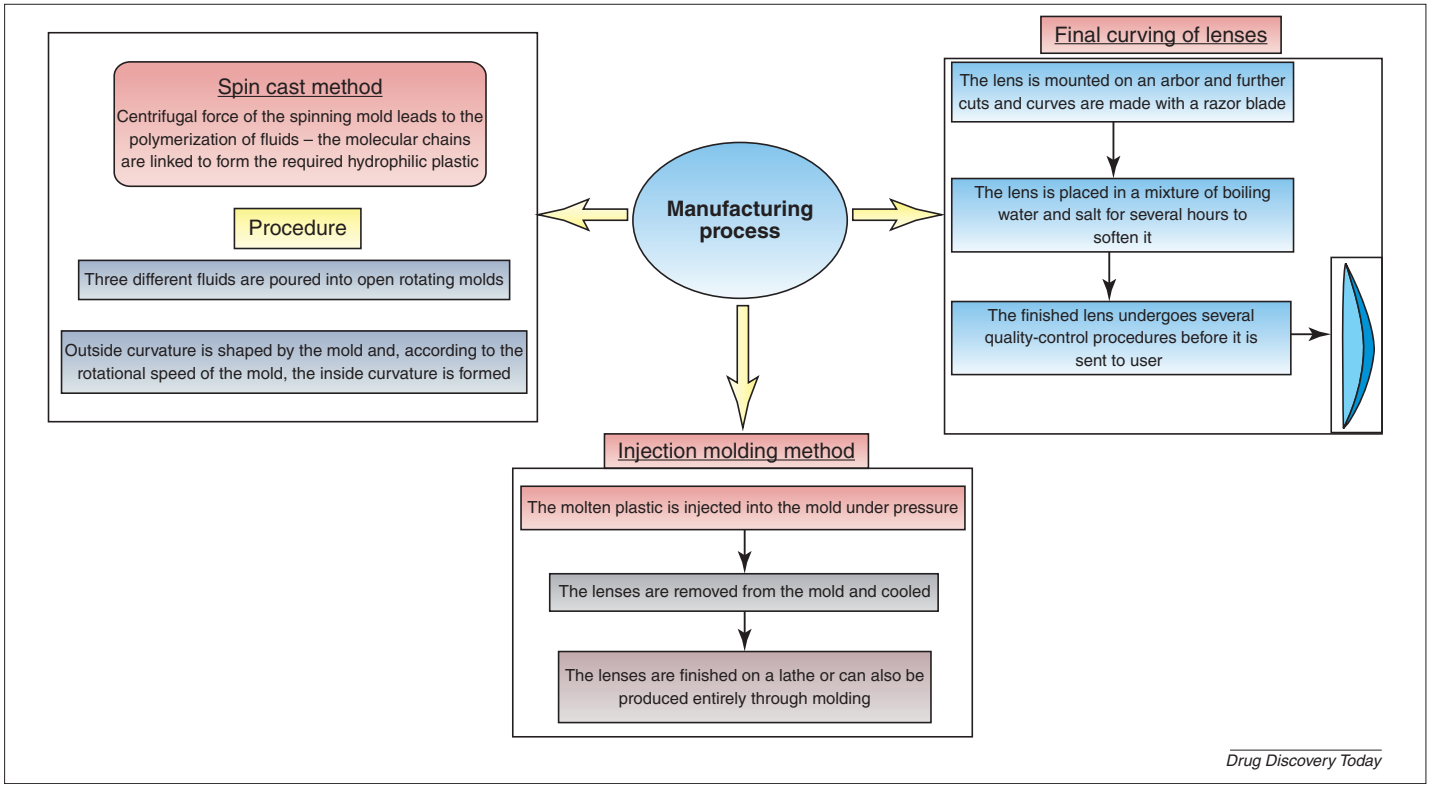

FIGURE 3

The various processes of manufacturing contact lenses.

Techniques used for drug delivery through contact lenses

Soaking

Owing to the hydrophilic nature of contact lens material, a drug solution can be soaked in the contact lens for delivery to the eye [24,25]. This technique can be used by two ways, either as pre-soaked or post-soaked technique. Using the pre-soaked technique, marketed contact lenses can be soaked for hours in a drug solution and then applied to the eye. Using the post-soaked mechanism, the contact lens is placed on the cornea and eye drops are then administered or applied to the lens to release a drug over a prolonged period of time. Other approaches include placing the ophthalmic solution in the concavity of the contact lens and then placing the lens onto the eye.

In 2006, Li and Chauhan [26] investigated drug release from contact lenses into the pre- and post-lens tear films (PLTF) with the subsequent uptake of the drug by the cornea. Their results showed that the dispersion coefficient of the drug in the post-lens tear film was unaffected by the release of the drug from the lens. Furthermore, simulation results showed that drug delivery from a contact lens was more efficient than drug delivery by drops. In 2007, the same authors combined *in vitro* experiments with modeling to

investigate the delivery of timolol maleate. *In vitro* experiments were conducted to create a transport model for releasing the drug from poly(2-hydroxyethyl methacrylate) (pHEMA) lenses. The transport model included drug adsorption on the polymer and drug diffusion in the bulk water. Results showed that at least 20% of the drug (timolol) that was entrapped in the lens entered the cornea, which is larger than the fractional uptake recorded from using eye drops [27]. As pHEMA is mostly used in the manufacture of contact lens, some researchers tried different combination of monomers to test their efficacy in drug delivery. Andrade-Vivero *et al.* incorporated 4-vinyl-pyridine (VP) and *N*-(3-aminopropyl) methacrylamide (APMA) in the contact lens structure (25–150 mM) to test the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac and ibuprofen. The incorporated monomers did not change the viscoelastic properties or the state of the bulk water, but did increase the amount of ibuprofen (up to tenfold) and diclofenac (up to 20-fold) that was loaded on the lens [28]. Mullarneya *et al.* used hydrophobically modified hydrogels for pheniramine maleate release. Co-polymers of *N*,*N*-dimethyl acrylamide (DMA) and 2-(*N*-ethyl-perfluorooctanesulfonamido) ethyl acrylate (FOSA) were prepared by free-radical polymerization. The power law exponent ($n \approx 0.5$) and the swelling interface number ($Sw \gg 1$) suggested that the drug release mechanism from these developed hydrogels was Fickian and not swelling controlled [29]. Dracopoulos *et al.* analyzed the interactions of benzalkonium chloride (BAK) which is used as preservative in eye drops, with silicone-containing (lotrafilcon A and galyfilcon A) and pHEMA-containing (etafilcon A and vifilcon A) hydrogel contact lenses. Four soft contact lens types [Focus Monthly® (vifilcon A), Focus Night & Day® (lotrafilcon A), Acuvue® Advance with Hydraclear (galyfilcon A), and SUREVUE® (etafilcon A)] were soaked for 24 h in various concentrations of BAK (1%, 0.1%, 0.01% and 0.001%) in 20-mL glass vials. Lens extracts showed increased levels of the back vertex distance variability of the cultured bovine lens, indicating that unknown chemical agents might be leached from contact lens polymers [30]. Winterton *et al.* presented a new system by photo-crosslinking a macromer species in lieu of monomeric polymerization. The system comprised high molecular weight non-functionalized polyvinyl alcohol (PVA), which was added to the lens matrix for later release into the tears. *In vitro* drug release showed release over a 20-h period [31]. Kim and Chauhan explored the much higher bioavailability of dexamethasone (DX) via pHEMA contact lenses compared with eye drops. Three derivatives of dexamethasone [dexamethasone 21-disodium phosphate (DXP), DX and dexamethasone 21-acetate (DXA)] were loaded onto lenses by soaking the lenses in either aqueous or ethanol solutions. The authors utilized their previous transport model to predict the bioavailability of these three compounds. The transport of each drug was diffusion limited, with diffusivities of 1.08×10^{-11} and 1.16×10^{-11} m^2/s for DX and DXA, respectively. The diffusivity of DXP was much smaller than that for either DX or DXP [32].

Particle-laden contact lenses

The method of using colloidal particles (nanoparticles, liposomes, etc.) incorporated into the matrix of contact lenses for sustained delivery is called 'particle-laden contact lens drug delivery'. Liposomes in particular have been used for drug delivery and targeting. When the liposomes are confined to a solid support, such as silica beads, the process is known as immobilization. Danion *et al.* immobilized intact liposomes onto soft contact lenses and X-ray photoelectron spectroscopy (XPS) clearly revealed that the different layers on the soft contact lenses were properly immobilized. Polyethylenimine was covalently bounded onto the hydroxyl groups available, and NHS-PEG-biotin molecules were then bonded onto the surface amine groups by carbodiimide chemistry. NeutrAvidin protein was then bonded onto the PEG-biotin layer. Liposomes containing PEG-biotinylated lipids were docked onto the surface-immobilized NeutrAvidin. Consecutive addition of further NeutrAvidin and liposome layers enabled multi-layers to be formed. By blocking with excess biotin surface-immobilized NeutrAvidin on contact lenses with PEG-biotin layers, ELISA showed that the docking of NeutrAvidin was dependent on biotin–NeutrAvidin affinity binding. However, it was not possible to differentiate the specific versus nonspecific binding of NeutrAvidin attached to PEG-biotin layers via grafting. Atomic force microscopy (AFM) imaging revealed liposome sizes of 106 and 155 nm for layers of liposomes produced by (i) the consecutive addition of further NeutrAvidin and liposomes; and (ii) the exposure of NeutrAvidin-coated contact lenses to liposome aggregates, respectively. The release kinetics of a fluorescent dye demonstrated that intact liposomes had been immobilized onto the surface of the contact lenses [33]. Danion *et al.* validated the biocompatibility and transmittance properties of liposomes in contact lenses. Biocompatibility of soft contact lens was evaluated through direct and indirect *in vitro* cyto-compatibility assays. Assay was carried out on human corneal epithelial cells, reconstructed human corneas and on *ex vivo* rabbit corneas. Contact lenses bearing layers of stable liposomes did not induce any significant changes in cell viability or cell growth. Elution assays revealed that no cytotoxic compound leaked from the lenses. Histological analyses of reconstructed human corneas and rabbit corneas revealed that there is no alteration in the corneal cell and tissue structures. Liposomal contact lenses are biocompatible and their transmittance properties are not affected in the visible light range [34].

Molecularly imprinting

Molecular imprinting is a technique used to generate template-shaped cavities in polymer matrices. The basis of this technique is the 'lock and key' model that is used by enzymes for substrate recognition. Alvarez-Lorenzo *et al.* developed imprinted pHEMA lenses using spatially ordered functional monomers, which had the ability to load norfloxacin (NRF) to control its release. Isothermal titration calorimetry (ITC) studies revealed that the maximum binding interaction between NRF and acrylic acid (AA) occurred at a ratio of 1:1, and that the process saturates at a molar ratio of 1:4. All hydrogels showed a similar degree of swelling (55%) and, once hydrated, they had adequate optical and viscoelastic properties. After immersion in 0.025, 0.050 and 0.10 mM drug solutions, imprinted hydrogels loaded greater amounts of NRF compared with non-imprinted ones [35]. Rebeiro *et al.* have designed hydrogels that have high affinity for carbonic anhydrase (CA) inhibitor drugs. Their objective was for these hydrogels to mimic the active site of the physiological metallo-enzyme receptor. Zinc methacrylate, 1- or 4-vinylimidazole (1VI or 4VI), and *N*-hydroxyethyl acrylamide (HEAA) were combined to reproduce in the hydrogels (which

resembles the cone-shaped cavity of the CA), which contain a Zn^{2+} ion coordinated to three histidine residues. The function of 4VI is more similar to that of histidine than is that of 1VI and, consequently, pHEMA-ZnMA2 hydrogels bearing 4VI moieties had the greatest ability to host other carbonic anhydrase drugs, such as acetazolamide or ethoxzolamide. Therefore, more drugs can be loaded onto biomimetic networks, which can control drug release better than can conventionally synthesized pHEMA hydrogels [36].

Venkatesh *et al.* applied this principle of biomimesis to incorporate a natural receptor-based rational design strategy in the synthesis of novel recognitive soft contact lenses. The authors demonstrated the potential of biomimetic carriers to load significant amounts of H_1-antihistamines, as well as to release a therapeutic dosage of a drug *in vitro* in a controlled fashion for 5 days, with further extension in the presence of protein [37]. Ali *et al.* experimentally demonstrated the zero-order release of ketotifen fumarate (molecular weight = 425) from molecularly imprinted hydrogels. The authors performed dynamic *in vitro* drug release studies from imprinted hydrogel contact lenses within a novel microfluidic device. They simulate the volumetric flow rates, tear volume and tear composition of the eye. Imprinted gels, with multiple functional monomers and complexation points, demonstrated a significantly delayed release of a drug compared with less functionalized systems (i.e. non-imprinted systems). Under infinite sink conditions, imprinted contact lenses demonstrated Fickian (concentration-dependent) release kinetics with diffusion coefficients ranging from 4.04×10^{-9} to 5.57×10^{-10} cm^2/s. The highest functionalized gel exhibited a diffusion coefficient averaging ten times smaller than those from less functionalized gels. The gels released the drug for 5 days with three distinct rates of release. Under physiological volumetric flow rates, the release rate was constant for a duration of 3.5 days, which delivered a therapeutically relevant dosage and was fit to a power law model indicating zero-order release characteristics with $n = 0.981 \pm 0.006$ ($r^2 = 0.997$) [38].

Ion ligands

A ligand is an ion or molecule that binds to a central metal atom to form a coordination complex. Opposite charged ions from a solution have been exchanged and exploited for drug loading. Rei *et al.* developed the epoch-making contact lens, which is equipped with a drug delivery system. The hydrogels contain a cationic functional group in their side chains. The gels were prepared with HEMA and methacrylamide propyl trimethyl ammonium chloride (MAPTAC). The hydrogel obtained is able to store anionic drugs, such as azulene, based on the ion-exchange reaction. The size of the hydrogel can change before and after drug release. It was discovered that the addition of anionic monomers, such as methacrylic acid (MAA) and 2-methacryloxyethyl acid phosphate (MOEP), to the above-mentioned composition can prevent the size change [39]. Takao *et al.* used naphazoline, a model drug with a cationic group, and incorporated it into soft contact lenses (because of its phosphate groups). It was released over a period of approximately 14 h. The naphazoline content of the contact lens was equivalent to its phosphate group content. It has been suggested that therapeutic soft contact lenses can be designed to contain the required amount of a drug through the choice of the ionic group (for the ligand). Furthermore, soft contact lenses containing amide groups and phosphate groups had high transparency and an unchanged shape. It is suggested that amide groups and phosphate groups must be introduced into the polymer in equi-molar amounts to give the necessary polymer–drug interaction [40].

Miscellaneous

Contact lenses made of microemulsion-laden gels are expected to deliver drugs at therapeutic levels for a few days. The delivery rates can be tailored by controlling the particle size and the drug loading. It might be possible to use this system for therapeutic drug delivery and the lubrication of eye to enable extended lens wear. Gulsen *et al.* encapsulated ophthalmic drug formulations in dimyristoyl phosphatidylcholine (DMPC) liposomes to disperse the drug-laden liposomes in the lens material. *In vitro* release studies proved that these gels were able to release drugs for up to a period of 8 days. The presence of a tightly packed surfactant at the oil–water interface of microemulsions might provide a barrier to drug transport, and this could be used to control the drug delivery rates [41]. Li *et al.* focused on trapping ethyl butyrate in water microemulsions, which are stabilized by pluronic F127 surfactant in HEMA gels. The results showed that microemulsion-laden gels could have higher drug loadings, particularly for drugs such as timolol base, which can either be dissolved in the oil phase or form the oil phase of the microemulsions [42].

In 2008, Kapoor and Chauhan developed nanostructured pHEMA hydrogels containing microemulsions or micelles of Brij® 97 for extended delivery of cyclosporinA (CyA). *In vitro* drug release results showed that the surfactant and microemulsion-laden gels could deliver CyA at a therapeutic dose for a period of 20 days. The results also showed that these hydrogels retain their effectiveness even after exposure to all the relevant processing conditions [43].

Concluding remarks

Therapeutic contact lens is an upcoming technology for ocular drug delivery. Contact lenses had already proved its worth cosmetically and now need to repeat the history in field of therapeutics. Several techniques had been discovered till now i.e. soaking, particle laden contact lenses, molecular imprinting and ion ligands etc. Though many research were carried out, this area need more efforts and techniques to make this novel concept to reach market after proper clinical trials. Patient compliance with timely delivery should be the aim in development of therapeutic contact lens.

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References

1 Lang, J.C. (1995) Ocular drug delivery conventional ocular formulations. *Adv. Drug Del. Rev.* 16, 39–43

2 Rathore, K.S. and Nema, R.K. (2009) An insight into ophthalmic drug delivery system. *Int. J. Pharm. Sci. Drug Res.* 1, 1–5

3 Gupta, H. *et al.* (2007) Sustained ocular drug delivery from a temperature and pH triggered *in situ* gel system. *Drug Deliv.* 14, 507–515
4 Gaudana, R. *et al.* (2009) Recent perspectives in ocular drug delivery. *Pharm. Res.* 26, 1197–1216
5 Hsiue, G.H. *et al.* (2001) Poly (2-hydroxyethyl methacrylate) film as a drug delivery system for pilocarpine. *Biomaterials* 13, 763–769
6 Gupta, H. *et al.* (2010) Ion- and pH-activated novel *in situ* gel system for sustained ocular drug delivery. *J. Drug Target.* 18, 499–505
7 Sawusch, M.R. *et al.* (1988) Use of collagen corneal shields in the treatment of bacterial keratitis. *Am. J. Ophthalmol.* 106, 279–281
8 Zimmer, A.K. *et al.* (1991) Studies on the transport pathway of PBCA nanoparticles in ocular tissues. *J. Microencapsul.* 8, 497–504
9 Gupta, H. *et al.* (2010) Sparfloxacin loaded PLGA nanoparticles for sustained ocular drug delivery. *Nanomedicine* 6, 324–333
10 Van der Bijl, P. *et al.* (2001) Effects of three penetration enhancers on transcorneal permeation of cyclosporine. *Cornea* 20, 505–508
11 Burgalassi, S. *et al.* (2001) Cytotoxicity of potential ocular permeation enhancers evaluated on rabbit and human corneal epithelial cell lines. *Toxicol. Lett.* 122, 1–8
12 Davies, N.M. *et al.* (1992) Evaluation of mucoadhesive polymers in ocular drug delivery: II. Polymer coated vesicles. *Pharm. Res.* 9, 1137–1144
13 Patel, U.L. *et al.* (2009) Preparation and evaluation of ocular inserts for controlled delivery of gatifloxacin sesquehydrate. *Int. J. Pharm. Sci.* 1, 342–352
14 Patel, U.L. *et al.* (2010) Design and evaluation of polymeric ocular drug delivery system for controlled delivery of moxifloxacin hydrochloride: *in vitro* and *in vivo* evaluation. *Acta Pharm. Sci.* 52, 523–535
15 Bhagav, P. *et al.* (2011) Sustained release ocular inserts of brimonidine tartrate for better treatment in open-angle glaucoma. *Drug Deliv. Translat. Res.* 1, 161–174
16 Rajendran, N.N. *et al.* (2010) Acyclovir-loaded chitosan nanoparticles for ocular delivery. *Asian J. Pharm.* 4, 220–226
17 Sahoo, S.K. *et al.* (2008) Nanotechnology in ocular delivery. *Drug Discov. Today* 13, 144–151
18 Cavalli, R. *et al.* (2002) Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin. *Int. J. Pharm.* 238, 241–245
19 Motwani, S.K. *et al.* (2008) Chitosan–sodium alginate nanoparticles as submicroscopic reservoirs for ocular delivery: formulation, optimisation and *in vitro* characterisation. *Eur. J. Pharm. Biopharm.* 68, 513–525
20 Shenand, Y. and Tu, J. (2007) Preparation and ocular pharmacokinetics of ganciclovir liposomes. *AAPS J.* 9, E371–E377
21 Lajavardi, L. *et al.* (2007) Down regulation of endotoxin-induced uveitis by intravitreal injection of vasoactive intestinal peptide encapsulated in liposomes. *Invest. Ophthalmol. Vis. Sci.* 48, 3230–3238
22 Kunou, N. *et al.* (2000) Long-term sustained release of ganciclovir from biodegradable scleral implant for the treatment of cytomegalovirus retinitis. *J. Control. Release* 68, 263–271
23 Gasson, A. and Morris, J. (1992) *The Contact Lens Manual: A Practical Fitting Guide*. Butterworth Heinemann
24 Peterson, R.C. *et al.* (2006) Clinical performance of daily disposable soft contact lenses using sustained release technology. *Cont. Lens Anterior Eye* 29, 127–134
25 Stefan, S. (2006) Combination of serum eye drops with hydrogels bandage contact lenses in the treatment of persistent epithelial defects. *Graefes Arch. Clin. Exp. Ophthalmol.* 244, 1345–1349
26 Li, C.C. and Chauhan, A. (2006) Modeling ophthalmic drug delivery by soaked contact lenses. *Ind. Eng. Chem. Res.* 45, 3718–3734
27 Li, C.C. and Chauhan, A. (2007) Ocular transport model for ophthalmic delivery of timolol through p-HEMA contact lenses. *J. Drug Deliv. Sci. Technol.* 17, 69–79
28 Andrade-Vivero, P. *et al.* (2006) Improving the loading and release of NSAIDs from pHEMA hydrogels by copolymerization with functionalized monomers. *J. Pharm. Sci.* 96, 802–813
29 Mullarneya, M.P. *et al.* (2006) Drug diffusion in hydrophobically modified N,N-dimethylacrylamide hydrogels. *Polymer* 47, 3845–3855
30 Dracopoulos, A. *et al.* (2007) *In vitro* assessment of medical device toxicity: interactions of benzalkonium chloride with silicone-containing and p-HEMA-containing hydrogel contact lens materials. *Eye Contact Lens* 33, 26–37
31 Winterton, L.C. *et al.* (2008) The elution of poly (vinyl alcohol) from a contact lens: the realization of a time release moisturizing agent/artificial tear. *J. Biomed. Mater. Res. B* 80, 424–432
32 Kim, J. and Chauhan, A. (2008) Dexamethasone transport and ocular delivery from poly(hydroxyethyl methacrylate) gels. *Int. J. Pharm.* 353, 205–222
33 Danion, A. *et al.* (2007) Fabrication and characterization of contact lenses bearing surface-immobilized layers of intact liposomes. *J. Biomed. Mater. Res. A* 82, 41–51
34 Danion, A. *et al.* (2007) Biocompatibility and light transmission of liposomal lenses. *Optom. Vis. Sci.* 84, 954–961
35 Alvarez-Lorenzo, C. *et al.* (2006) Imprinted soft contact lenses as norfloxacin delivery systems. *J. Control. Release* 113, 236–244
36 Rebeiro, F. *et al.* (2011) Bioinspired imprinted PHEMA-hydrogels for ocular delivery of carbonic anhydrase inhibitor drugs. *Biomacromolecules* 12, 701–709
37 Venkatesh, S. *et al.* (2007) Biomimetic hydrogels for enhanced loading and extended release of ocular therapeutics. *Biomaterials* 28, 717–724
38 Ali, M. *et al.* (2007) Zero-order therapeutic release from imprinted hydrogel contact lenses within *in vitro* physiological ocular tear flow. *J. Control. Release* 124, 154–162
39 Rei, U. *et al.* (2003) Azulene incorporation and release by hydrogels containing methacryl amide propyl trimethylammonium chloride, and its application to soft contact lens. *J. Control. Release* 92, 259–264
40 Takao, S. *et al.* (2005) Application of polymer gels containing side-chain phosphate groups to drug delivery contact lenses. *J. Appl. Polym. Sci.* 98, 731–735
41 Gulsen, D. and Chauhan, A. (2005) Dispersion of DMPC liposomes in contact lenses for ophthalmic drug delivery. *Curr. Eye Res.* 30, 1071–1080
42 Li, C.C. *et al.* (2007) Timolol transport from microemulsions trapped in HEMA gels. *J. Colloid Interface Sci.* 315, 297–306
43 Kapoor, Y. and Chauhan, A. (2008) Ophthalmic delivery of cyclosporine A from Brij-97 microemulsion and surfactant-laden p-HEMA hydrogels. *Int. J. Pharm.* 361, 222–229