Biomaterials for Dry Eye Diseases Treatment

Subjects: Cell & Tissue Engineering

Contributor: Basanta Bhujel, Se-Heon Oh, Chang-Min Kim, Ye-Ji Yoon, Ho-Seok Chung, Eun-Ah Ye, Hun Lee, Jae-Yong Kim

Dry eye disease (DED) is an emerging health issue affecting millions of individuals annually. Ocular surface disorders, such as DED, are characterized by inflammation triggered by various factors. This condition can lead to tear deficiencies, resulting in the desiccation of the ocular surface, corneal ulceration/perforation, increased susceptibility to infections, and a higher risk of severe visual impairment and blindness. The history of ophthalmic biomaterials is relatively short. The primary objective of advancing successive generations of biomaterials is to address the shortcomings of previous versions and enhance safety, effectiveness, and comfort. Innovations have been made to elevate quality standards and production efficiency, ultimately reducing costs. Market demands to enhance competitiveness and accessibility have further intensified the pressure to cut expenses. Ophthalmic biomaterials have evolved into highly sophisticated devices, significantly increasing their utility in recent years. These materials must fulfill several crucial requirements, such as delivering oxygen to tissues, managing refractive changes, safeguarding tissues during surgery, facilitating tissue integration, and modulating the healing process. The recent advancements in biomaterials for treating DED include scaffolds, nanosystems, hydrogels, and drug-eluting contact lenses.

Keywords: dry eye ; dry eye diseases ; regenerative medicine ; biomaterials

1. Scaffolds

Scaffolds have a crucial function in ex vivo tissue engineering methods for various organs, offering numerous advantages in the creation and transplantation of organs. First, they enable a greater quantity of viable cells to be transplanted, which is vital for fully restoring organ function. Scaffolds offer an ideal framework for diverse cells to coalesce and thrive within a controlled microenvironment. Second, scaffolds aid the process by offering surfaces where different cell types can flourish, directing their growth to precise locations for functional outcomes. Additionally, the meticulously selected physical and chemical attributes of biomaterials, including factors like strength and degradation rates, can be customized to boost specific functions of the emerging tissues, such as in the context of the lacrimal gland.

The introduction of organ-on-a-chip technology brought about the use of three-dimensional (3D) methods, incorporating microfluidics and bioengineering, to replicate in vivo conditions [1]. An instance of this technology in the field of ophthalmology is the creation of a human blinking eye-on-a-chip [2]. In this model, 3D shell scaffolds are utilized to create corneal curvatures. These scaffolds are infused with primary human keratocytes and placed between a microfluid channel and a circular chamber. Epithelial cells are then strategically positioned on the scaffold using a color-coded method, employing green fluorescence in the center and red fluorescence along the periphery of the scaffold surface. Additionally, 3D-printed eyelids, designed to simulate natural blinking, are mechanically activated, enabling the replication of tear-film spreading and hydration of the ocular surface.

The creation of scaffolds through different methods, the use of appropriate biomaterials, and thorough biological evaluations of relevant parameters are viable options. Both 2D and 3D culturing techniques continue to be valuable for assessing various in vitro and in vivo cultures, considering functional parameters. This approach can lead to the development of an effective ex vivo manufacturing process and enable post-implantation assessments, potentially eliminating ocular surface disorders associated with DES [3].

2. Nanosystems

Nanosystems have been extensively studied in medicine, including their use in treating eye conditions [4]. Their complex, nanoscale structure shows significant promise in improving ocular drug delivery through the controlled release of different bioactive substances. Furthermore, these nanosystems have an enhanced ability to infiltrate and pass through ocular tissues, simultaneously protecting bioactive molecules from degradation [5]. A key benefit of employing nanosystems in delivering drugs to the eyes lies in their mucoadhesive properties. This characteristic boosts their ability to stick to the ocular surface, preventing the drugs from being washed away by the eye’s natural defense mechanisms [6].

Different types of nanosystems, including nanoparticles (NPs), nanoemulsions, lipid nanocapsules, and nanoemulsions, have been investigated for transporting drugs such as epigallocatechin gallate (EGCG), cyclosporine, dexamethasone, amfenac, and cyporin-N to the eye's surface [7]. EGCG, an anti-inflammatory substance, was integrated into gelatin nanoparticles that are biocompatible and biodegradable, and these were further coated with HA [8]. The EGCG nanoparticle formulation exhibited enhanced penetration into human corneal epithelial cell cultures. When administered twice daily over a two-week period, these nanoparticle eye drops not only reinstated tear production but also repaired the impaired corneal epithelium in a rabbit model of DED. These effects surpassed those observed with standard EGCG eye drops. Additionally, a multifunctional therapeutic gold nanoparticle was developed, featuring a substantial surface area and combining anti-inflammatory (amfenac) and antioxidant (catechin) agents to address DED [9]. Poly(catechin) capped gold nanoparticles were designed to include the anti-inflammatory drug amfenac, effectively suppressing both DED-related inflammation and reactive oxygen species (ROS)-mediated processes within four days in the rabbit DED model induced by BAC. These nanoparticles have a loose polymeric matrix containing the drug, which is uniformly confined on the gold nanoparticles' surface. This outperformed the effects of commercial cyclosporine eye drops.

In 2016, Liu and his team investigated an innovative mucoadhesive nanoparticle system. This system involved poly(D,L-lactide)-b-dextran (PLA-b-Dex) particles coated with phenylboronic acid (PBA) to prolong the retention of eye drops. This system was investigated with the inclusion of cyclosporine. Lipid nanocapsules (LNCs) are utilized for lipophilic drugs, with the lipid core providing enhanced nano-encapsulation of the drug. LNC eye drops containing CsA demonstrated quicker and more effective therapeutic outcomes in a rat model of DED, with improved TBUT (>8 s), a decreased corneal fluorescein score, and low expression of inflammatory cytokines, surpassing the effects of the commercial CsA emulsion (Restasis) [10]. Nanowafer (NW) is a drug delivery nanosystem consisting of small drug-containing nanoreservoirs arranged on a circular transparent disc [11].

Restasis, a 0.05% CsA emulsion, was the first CsA formulation approved by the Food and Drug Administration (FDA) for the treatment of DED in 2003 [12]. Safety assessments in Phase III trials revealed that Restasis was associated with sensations of burning, foreign body presence, and stinging in 25% of patients. These effects were attributed to the use of a high total drug dosage [13]. In 2003, TJ Cyporin, a 0.05% cyclosporine A nanoemulsion, received approval for treating DED in South Korea. A study conducted by Kang and colleagues compared its effectiveness with Restasis in patients with primary Sjögren syndrome. Cyporin-N exhibited a significant improvement in TBUT after 12 weeks, while Restasis did not show the same improvement. Both treatments effectively reduced inflammation in Sjögren's syndrome patients, with no notable difference in the reduction of inflammatory cytokines between the two groups. Additionally, in 2018, the US FDA approved Cequa® (manufactured by Sun Pharma, Mumbai, India), a preservative-free 0.09% nanomicellar formulation of cyclosporine A, for the treatment of DED in adult patients [14]. Nanosized hydrogels, known as nanogels, have been widely utilized in ophthalmic applications, mainly due to their prolonged ocular retention and low viscosity [15]. In a rabbit model of DED, administering nanogel eye drops twice daily provided faster and more efficient relief for dry eyes compared to the commercially available highly viscous Vidisic gel containing 0.2% poly(acrylic) acid. Dendrimers, a unique category of nanosystems, are complex, branched molecules with diverse functional groups and intricate polymeric structures. Catechins are known for their anti-inflammatory, antibacterial, and anticancer properties. A nanocomplex consisting of PEG and catechin significantly increased tear production in a mouse model of DED while also reducing fluorescein and corneal irregularity scores [16]. **Table 1** summarizes the outcomes from various studies exploring nanosystems for treating DED.

Table 1. Different Nano-systems for Treating DED.

Nano-Systems	Method of Inducing DED	Animals	Treatment Period	Outcomes	References
Gelatin nanoparticle	**0.1% BAC**	**Rabbits**	**21 days (twice daily)**	- Downregulation of TNF-α, IL-8, and IL-6 - Decrease in fluorescein score - Increase in tear secretion	**[8]**

Nano-Systems	Method of Inducing DED	Animals	Treatment Period	Outcomes	References
Gold/poly(catechin) core-shell nanoparticle	**0.15% BAC**	**Rabbits**	**4 days**	- Decrease in fluorescein score - Decrease in ROS - Decrease in inflammation	[9]
Glycol chitosan nanoparticle	**Subcutaneous injection of scopolamine hydrobromide in mice**	**Mice**	**7 days**	- Decrease in ROS - Increase in tear production - Promotion of corneal and conjuctival cell growth and integrity	[17]
Cationized gelatin and chondroitin sulfate nanoparticles	**Subcutaneous injection of scopolamine + desiccating stress**	**Mice**	**5 days**	- Increase in tear production - Upregulation of goblet cells - Reduction in the CD4+ T-cells infiltration in the conjuctiva	[18]

3. Hydrogels

Hydrogels, made of absorbent hydrophilic polymers, maintain their 3D structure while absorbing water. They are formed from natural, semisynthetic, or synthetic polymers like HA and poly (acrylic acid). Hydrogels offer controlled drug release, biocompatibility, and the ability to carry diverse drugs, making them promising for ocular surface disease treatment [19].

Several hydrogel products for DED treatment are available in the market, such as Hylo®gel (URSAPHARM, Saarbrücken, Germany), Vidisic® gel (Bausch and Lomb, Rochester, NY, USA), GelTears® (Bausch and Lomb, Rochester), Viscotears® (Novartis, Basel, Switzerland), and Clinitas gel® (Altacor, Reading, UK). Some products are in clinical trials, including VisuXL® gel (VISUfarmaSpA, Rome, Italy), and bovine basic fibroblast growth factor (bFGF) gel (Zhuhai Yisheng Biological Pharmaceutical Co., Ltd., Zhuhai, China). Recent patents for DED treatment involve innovative hydrogel formulations like multi-arm PEG insert with CsA/Dex, PNIPAAm and butyl acrylate plug, guar gum, PVA, and boric acid drop containing diquafosol sodium [20][21][22].

Hydrogels containing HA have been explored in a few rabbit DED models. Soft hydrogels are well-tolerated on the ocular surfaces of rats, rabbits, and dogs [19]. In a clinical trial, canines suffering from DED and previously treated with artificial tears and cyclosporine exhibited alleviated clinical symptoms in more than 65% of instances, even if they had not responded to cyclosporine treatment initially. Thermo-responsive hydrogels have attracted considerable attention in the realm of hydrogel-based drug delivery systems due to their ability to change their physical form in response to external factors such as temperature, pH, and ionic strength [23]. Another study utilized crosslinked modified HA to create a hydrogel with higher viscosity and elastic modulus compared to non-crosslinked HA solutions. This hydrogel improved TBUT in rabbits and was found to alleviate dry eye symptoms in dogs in a preliminary clinical study, outperforming commercial HA tears in terms of symptom relief [24].

Researchers have studied hydrogels as plugs for the lacrimal drainage system in models of DED. In a rabbit DED model, a thermosensitive hydroxybutyl chitosan (HBC) hydrogel plug demonstrated notable enhancements in tear volume and decreased outflow [25]. This gel was safe and well-tolerated in both animal and human evaluations. Additionally, a novel

mini eye patch containing palladium-coated gold nanorod hydrogel was developed to stimulate lacrimal tear secretion using visible light energy. The eye patch was proven safe and effective in improving tear-related parameters in healthy volunteers [26]. However, its impact on DED patients remains to be explored. **Table 2** summarizes the outcomes from different studies exploring hydrogels for treating DED.

Table 2. Different Hydrogels for treating DED.

Hydrogel	Method of Inducing DED	Animals	Treatment Period	Results	References
Crosslinked thiolated carboxymethyl HA	**Diagnosed with DED**	**Dogs**	**2 times each day for 2 weeks**	- Decreased DED symptoms in dogs - Improvement in ocular irritation, conjunctival hyperemia, and ocular discharge	[27]
Crosslinked thiolated carboxymethyl HA	**Diagnosed with DED**	**Dogs**	**3 weeks 3 times daily**	- Decreased DED symptoms in dogs - Significantly improved ocular surface health (ocular iritation, and ocular discharge)	[24]
Gelatin, poly(N-isopropylacrylamide), lectin helix pomatia agglutinin and EGCG drug	**0.1% BAC twice daily for 14 days in rabbits**	**Rabbits**	**One-time adminis-tration**	- Decreased ROS level - Decreased MCP-1 levels - Downregulation of inflammation	[28]
FK506 loadedMPEP hydrogel	**Scopolamine mice model**	**Mice**	**5 days, twice daily**	- Decreased in MMP-13 levels - Decreased inflammation - Increased goblet cells - Increased tear production	[29]
Hydroxybutyl chitosan as intracanalicular injection	**0.1% BAC for 5 weeks in rabbits**	**Rabbits**	**One-time intracan-alicular injection**	- Increased tear production - Decreased inflammation	[25]

4. Drug-Eluting Contact Lenses

Delivering drugs using contact lenses (CL) has numerous benefits, including prolonged drug release, enhanced drug absorption, improved patient adherence, and greater comfort [30]. Advancements in CL materials and better patient education have resolved initial concerns, making CL more comfortable and increasing global adoption in the past decade [31]. Soft CL for delivering drugs to the eyes was first introduced in the 1960s. However, notable advancements in biomaterials from the 2000s onward have sparked increased research into CL drug delivery. Hydrogels and silicone hydrogels are the main materials employed in creating these lenses. Drug-releasing CL releases drugs that fall into two

categories: lubricants and anti-inflammatory drugs. Various techniques, such as soaking, molecular imprinting, ring implantation, and incorporating nanocarriers and functional molecules, are used to load these drugs into the lenses.

Researchers have investigated the use of CL as a delivery method for lubricants and anti-inflammatory drugs. Studies have successfully achieved sustained drug release over extended periods, ranging from 48 h to 15 days, in an in vitro experiment. Maulvi and colleagues (2015) investigated two methods of loading HA into hydrogel CL: soaking and direct entrapment during polymerization. Soaking allowed HA release for up to 48 h, while the entrapment method achieved a prolonged release lasting up to 264 h at therapeutic levels in vitro. These hydrogels were non-toxic and, with the direct entrapment method, demonstrated prolonged HA release for 15 days in the precorneal area of rabbits. Additionally, ring implants not only prolonged the presence of HA and maintained its continuous release onto the eye surface but also decreased corneal epithelial damage and reinstated tear volume in a BAC-DED rabbit model when compared to untreated eyes [32]. To enhance the sustained release, chitosan nanoparticles loaded with HA were integrated into ring-shaped poly(vinyl) alcohol hydrogels that were implanted in CL and that were able to release HA for 14 days [33].

In a recent study, a porous carrier loaded with CsA was created utilizing a supercritical fluid method and incorporated into a hydroxyethyl methacrylate (HEMA) hydrogel CL. This resulted in an initial rise in CsA concentration, followed by sustained release lasting 48 h. Its application resulted in elevated tear volume and extended TBUT, along with decreased corneal staining scores in the rabbit DED model in contrast to 0.05% CsA eye drops, balanced salt solution (BSS), and soft contact lenses. Additionally, CsA-CL significantly lowered pro-inflammatory cytokine IL-1β levels compared to BSS-soft CL groups [34]. The inclusion of vitamin E in CL prolonged the dexamethasone release significantly [35]. When loaded with 30% vitamin E, the release time was extended to 7–9 days. For p-HEMA hydrogel lenses, CsA was released for one day, while for silicone hydrogel lenses, the release continued for two weeks. [36]. **Table 3** summarizes the results from different studies using various drug-eluting contact lenses for treating DED, and **Table 4** summarizes the pros and cons of the most commonly used contact lenses for treating DED.

Table 3. Different drug-eluting contact lenses for treating DED.

Contact Lens Material	Drug/Molecule	Method of Drug Loading	Animals	Treatment Period	Outcomes	References
HEMA hydrogel	**HA**	- Soaking and direct entrapment	**Rabbits**	**15 days**	- Transmittance at 95% with soaked HA CL - Decrease in transmittance with HA entrapped CL - Increase in HA mean residence time and area in pharmacokinetics studies in rabbit tear fluid	**[32]**
HEMA hydrogel	**HA**	- Ring implant and soaking	**Rabbits**	**15 days**	- Decreased contact angle with increase in HA loading - Increment of residence time of HA - Faster and complete healing of DES	**[37]**

Contact Lens Material	Drug/Molecule	Method of Drug Loading	Animals	Treatment Period	Outcomes	References
HEMA hydrogel	**PVP-K90**	- Soaking - Direct entrapment	**Rabbits**	**-**	- Downregulating corneal epithelium damage - Upregulation of tear volume - Transmittance more than 95%	[38]
Silicone hydrogel	**Flurbiprofen sodium diclofenac sodium ketorolactromethamine**	- Vitamin E loading + cationic surfactants	**-**	**-**	- Enhanced both the loading and prolonged release of medications within the therapeutic period	[39]
Silicone hydrogel	**Pirfenidone**	- 20% vitamin E loading	**Rabbits**	**3 h**	- Drug presence in the aqueous humor for 3 h - Decrease in expression of TNF-α, IL-1β, and TGF-β1	[40]

5. Contact Lens-Based Drug Delivery for DED

The objective of managing dry eye is to alleviate symptoms, enhance the eye's surface, enhance vision, and tackle root causes. Various therapies, including drug delivery through contact lenses, have been proposed to manage the complex nature of DED. CsA can be incorporated into contact lenses for treating dry eyes. Compared to corticosteroids, CsA offers advantages such as reversible effects, minimal systemic absorption, and no notable side effects. These pharmacokinetic benefits are crucial for the prolonged treatment of chronic conditions like dry eye [41].

In a study conducted by Mun and colleagues in 2019, they showed that the liberation of CsA from CL significantly enhanced the treatment of DED in rabbit eyes. To induce DED, they administered 3-concanavalin A injections to rabbits and discovered that the contact lens facilitated consistent CsA release for a duration of 7 days. The effectiveness of the treatment was confirmed through corneal immunofluorescence staining, focusing on MMP9, a marker for DED [42]. In a study conducted by Desai and colleagues in 2022, they observed a decrease in MMP9 intensity in the right eyes treated with CsA/C-HA micelle contact lenses and eye drops compared to the control group in the left eyes. Moreover, rabbits exhibited swift recovery from DED when using a graphene contact lens loaded with CsA, ensuring a continuous high concentration of CsA in the corneal fluid [43].

6. Biosensors Integrated Contact Lenses

A biosensor is a diagnostic tool that utilizes a biological element and a physicochemical indicator to detect a specific chemical substance [44][45]. It employs biological components like enzymes, antibodies, cell receptors, etc. to interact with the target analyte. The biosensor works through various mechanisms, such as piezoelectric, electrochemiluminescence, optical, and electrochemical, to measure and quantify the analyte. The results are displayed simply through a connected reader [46]. The human eye holds essential chemical, physical, and biological information relevant to human health. This aspect has become a focal point for the advancement of soft electronic systems employed in diagnosing different eye ailments and other organ-related disorders. Wearable and pliable medical devices such as CL can take on pivotal tasks in the diagnosis and management of ocular diseases [47].

Table 4. Advantages and disadvantages of most commonly used contact lens biomaterials.

Contact Lens Biomaterials	Pros	Cons	References
Poly (vinyl alcohol) (PVA)	- Cost effective - Biocompatible - Effortless manufacturing	- Less permeability to oxygen - Fixed water contact	[48]
Silicon hydrogel	- High permeability to oxygen - High strength and longevity	- Costly - Aggressive conduct	[49]
HEMA hydrogel	- Cost effective - Biocompatible - Various copolymer options	- Low permeability to oxygen - Protein deposition issues	[50][51]
Polymethyl methacrylate (PMMA)	- Low cost - Extensively studied polymer	- Impermeable to oxygen - Rigid in eyes - Hostile conduct	[50][52]

References

1. Zhang, B.; Radisic, M. Organ-on-a-chip devices advance to market. Lab Chip 2017, 17, 2395–2420.
2. Seo, J.; Byun, W.Y.; Frank, A.; Massaro-Giordano, M.; Lee, V.; Bunya, V.Y.; Huh, D. Human blinking ‘eye-on-a-chip’. Investig. Ophthalmol. Vis. Sci. 2016, 57, 3872.
3. Heidari, M.; Noorizadeh, F.; Wu, K.; Inomata, T.; Mashaghi, A. Dry eye disease: Emerging approaches to disease analysis and therapy. J. Clin. Med. 2019, 8, 1439.
4. Khiev, D.; Mohamed, Z.A.; Vichare, R.; Paulson, R.; Bhatia, S.; Mohapatra, S.; Lobo, G.P.; Valapala, M.; Kerur, N.; Passaglia, C.L. Emerging nano-formulations and nanomedicines applications for ocular drug delivery. Nanomaterials 2021, 11, 173.
5. Mirza, A.Z.; Siddiqui, F.A. Nanomedicine and drug delivery: A mini review. Int. Nano Lett. 2014, 4, 1–7.
6. Lynch, C.; Kondiah, P.P.; Choonara, Y.E.; du Toit, L.C.; Ally, N.; Pillay, V. Advances in biodegradable nano-sized polymer-based ocular drug delivery. Polymers 2019, 11, 1371.
7. Thacker, M.; Singh, V.; Basu, S.; Singh, S. Biomaterials for dry eye disease treatment: Current overview and future perspectives. Exp. Eye Res. 2023, 226, 109339.
8. Huang, H.-Y.; Wang, M.-C.; Chen, Z.-Y.; Chiu, W.-Y.; Chen, K.-H.; Lin, I.-C.; Yang, W.-C.V.; Wu, C.-C.; Tseng, C.-L. Gelatin–epigallocatechin gallate nanoparticles with hyaluronic acid decoration as eye drops can treat rabbit dry-eye syndrome effectively via inflammatory relief. Int. J. Nanomed. 2018, 13, 7251–7273.
9. Li, Y.-J.; Luo, L.-J.; Harroun, S.G.; Wei, S.-C.; Unnikrishnan, B.; Chang, H.-T.; Huang, Y.-F.; Lai, J.-Y.; Huang, C.-C. Synergistically dual-functional nano eye-drops for simultaneous anti-inflammatory and anti-oxidative treatment of dry eye disease. Nanoscale 2019, 11, 5580–5594.
10. Zhang, A.; Sun, R.; Ran, M.; Deng, Y.; Ge, Y.; Zhu, Y.; Tao, X.; Shang, L.; Gou, J.; He, H. A novel eyes topical drug delivery system: CsA-LNC for the treatment of DED. Pharm. Res. 2020, 37, 146.
11. Yuan, X.; Marcano, D.C.; Shin, C.S.; Hua, X.; Isenhart, L.C.; Pflugfelder, S.C.; Acharya, G. Ocular drug delivery nanowafer with enhanced therapeutic efficacy. ACS Nano 2015, 9, 1749–1758.
12. Agarwal, P.; Craig, J.P.; Rupenthal, I.D. Formulation considerations for the management of dry eye disease. Pharmaceutics 2021, 13, 207.

13. Barber, L.D.; Pflugfelder, S.C.; Tauber, J.; Foulks, G.N. Phase III safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years. Ophthalmology 2005, 112, 1790–1794.
14. Goldberg, D.F.; Malhotra, R.P.; Schechter, B.A.; Justice, A.; Weiss, S.L.; Sheppard, J.D. A phase 3, randomized, double-masked study of OTX-101 ophthalmic solution 0.09% in the treatment of dry eye disease. Ophthalmology 2019, 126, 1230–1237.
15. Ilka, R.; Mohseni, M.; Kianirad, M.; Naseripour, M.; Ashtari, K.; Mehravi, B. Nanogel-based natural polymers as smart carriers for the controlled delivery of Timolol Maleate through the cornea for glaucoma. Int. J. Biol. Macromol. 2018, 109, 955–962.
16. Lee, H.; Shim, W.; Kim, C.E.; Choi, S.Y.; Lee, H.; Yang, J. Therapeutic efficacy of nanocomplex of poly (ethylene glycol) and catechin for dry eye disease in a mouse model. Investig. Ophthalmol. Vis. Sci. 2017, 58, 1682–1691.
17. Yu, F.; Zheng, M.; Zhang, A.Y.; Han, Z. A cerium oxide loaded glycol chitosan nano-system for the treatment of dry eye disease. J. Control. Release 2019, 315, 40–54.
18. Contreras-Ruiz, L.; Zorzi, G.; Hileeto, D.; Lopez-Garcia, A.; Calonge, M.; Seijo, B.; Sánchez, A.; Diebold, Y. A nanomedicine to treat ocular surface inflammation: Performance on an experimental dry eye murine model. Gene Ther. 2013, 20, 467–477.
19. Yu, Y.; Chow, D.W.Y.; Lau, C.M.L.; Zhou, G.; Back, W.; Xu, J.; Carim, S.; Chau, Y. A bioinspired synthetic soft hydrogel for the treatment of dry eye. Bioeng. Transl. Med. 2021, 6, e10227.
20. Tan, H.; DeFail, A.J.; Rubin, J.P.; Chu, C.R.; Marra, K.G. Novel multiarm PEG-based hydrogels for tissue engineering. J. Biomed. Mater. Res. Part A Off. J. Soc. Biomater. Jpn. Soc. Biomater. Aust. Soc. Biomater. Korean Soc. Biomater. 2010, 92, 979–987.
21. Ekerdt, B.L.; Fuentes, C.M.; Lei, Y.; Adil, M.M.; Ramasubramanian, A.; Segalman, R.A.; Schaffer, D.V. Thermoreversible Hyaluronic Acid-PNIPAAm Hydrogel Systems for 3D Stem Cell Culture. Adv. Healthc. Mater. 2018, 7, 1800225.
22. Ailincai, D.; Dorobanțu, A.M.; Dima, B.; Irimiciuc, Ș.A.; Lupașcu, C.; Agop, M.; Olguta, O. Poly(vinyl alcohol boric acid)-diclofenac sodium salt drug delivery systems: Experimental and theoretical studies. J. Immunol. Res. 2020, 2020, 3124304.
23. Buwalda, S.J.; Boere, K.W.; Dijkstra, P.J.; Feijen, J.; Vermonden, T.; Hennink, W.E. Hydrogels in a historical perspective: From simple networks to smart materials. J. Control. Release 2014, 190, 254–273.
24. Williams, D.L.; Mann, B.K. Efficacy of a crosslinked hyaluronic acid-based hydrogel as a tear film supplement: A masked controlled study. PLoS ONE 2014, 9, e99766.
25. Lin, H.; Liu, Y.; Kambhampati, S.P.; Hsu, C.-C.; Kannan, R.M.; Yiu, S.C. Subconjunctival dendrimer-drug therapy for the treatment of dry eye in a rabbit model of induced autoimmune dacryoadenitis. Ocul. Surf. 2018, 16, 415–423.
26. Pang, Y.; Wei, C.; Li, R.; Wu, Y.; Liu, W.; Wang, F.; Zhang, X.; Wang, X. Photothermal conversion hydrogel based mini-eye patch for relieving dry eye with long-term use of the light-emitting screen. Int. J. Nanomed. 2019, 14, 5125–5133.
27. Williams, D.L.; Mann, B.K. A crosslinked HA-based hydrogel ameliorates dry eye symptoms in dogs. Int. J. Biomater. 2013, 2013, 460437.
28. Luo, L.-J.; Nguyen, D.D.; Lai, J.-Y. Long-acting mucoadhesive thermogels for improving topical treatments of dry eye disease. Mater. Sci. Eng. C 2020, 115, 111095.
29. Han, Y.; Jiang, L.; Shi, H.; Xu, C.; Liu, M.; Li, Q.; Zheng, L.; Chi, H.; Wang, M.; Liu, Z. Effectiveness of an ocular adhesive polyhedral oligomeric silsesquioxane hybrid thermo-responsive FK506 hydrogel in a murine model of dry eye. Bioact. Mater. 2022, 9, 77–91.
30. Jones, L.; Hui, A.; Phan, C.-M.; Read, M.L.; Azar, D.; Buch, J.; Ciolino, J.B.; Naroo, S.A.; Pall, B.; Romond, K. BCLA CLEAR–Contact lens technologies of the future. Contact Lens Anterior Eye 2021, 44, 398–430.
31. Toffoletto, N.; Saramago, B.; Serro, A.P. Therapeutic ophthalmic lenses: A review. Pharmaceutics 2020, 13, 36.
32. Maulvi, F.A.; Soni, T.G.; Shah, D.O. Extended release of hyaluronic acid from hydrogel contact lenses for dry eye syndrome. J. Biomater. Sci. Polym. Ed. 2015, 26, 1035–1050.
33. Akbari, E.; Imani, R.; Shokrollahi, P.; Heidari Keshel, S. Preparation of Nanoparticle-Containing Ring-Implanted Poly(Vinyl Alcohol) Contact Lens for Sustained Release of Hyaluronic Acid. Macromol. Biosci. 2021, 21, 2100043.
34. Choi, J.H.; Li, Y.; Jin, R.; Shrestha, T.; Choi, J.S.; Lee, W.J.; Moon, M.J.; Ju, H.T.; Choi, W.; Yoon, K.C. The efficiency of cyclosporine a-eluting contact lenses for the treatment of dry eye. Curr. Eye Res. 2019, 44, 486–496.
35. Kim, J.; Peng, C.-C.; Chauhan, A. Extended release of dexamethasone from silicone-hydrogel contact lenses containing vitamin E. J. Control. Release 2010, 148, 110–116.

36. Peng, C.-C.; Chauhan, A. Extended cyclosporine delivery by silicone–hydrogel contact lenses. J. Control. Release 2011, 154, 267–274.
37. Maulvi, F.A.; Shaikh, A.A.; Lakdawala, D.H.; Desai, A.R.; Pandya, M.M.; Singhania, S.S.; Vaidya, R.J.; Ranch, K.M.; Vyas, B.A.; Shah, D.O. Design and optimization of a novel implantation technology in contact lenses for the treatment of dry eye syndrome: In vitro and in vivo evaluation. Acta Biomater. 2017, 53, 211–221.
38. Maulvi, F.A.; Patel, P.J.; Soni, P.D.; Desai, A.R.; Desai, D.T.; Shukla, M.R.; Ranch, K.M.; Shah, S.A.; Shah, D.O. Novel poly (vinylpyrrolidone)-coated silicone contact lenses to improve tear volume during lens wear: In vitro and in vivo studies. ACS Omega 2020, 5, 18148–18154.
39. Torres-Luna, C.; Hu, N.; Tammareddy, T.; Domszy, R.; Yang, J.; Wang, N.S.; Yang, A. Extended delivery of non-steroidal anti-inflammatory drugs through contact lenses loaded with Vitamin E and cationic surfactants. Contact Lens Anterior Eye 2019, 42, 546–552.
40. Jia, Z.; Lv, Y.; Zhang, W.; Zhang, X.; Li, F.; Lu, X.; Zhao, S. Mesenchymal stem cell derived exosomes-based immunological signature in a rat model of corneal allograft rejection therapy. Front. Biosci.-Landmark 2022, 27, 86.
41. Kymionis, G.D.; Bouzoukis, D.I.; Diakonis, V.F.; Siganos, C. Treatment of chronic dry eye: Focus on cyclosporine. Clin. Ophthalmol. 2008, 2, 829–836.
42. Mun, J.; won Mok, J.; Jeong, S.; Cho, S.; Joo, C.-K.; Hahn, S.K. Drug-eluting contact lens containing cyclosporine-loaded cholesterol-hyaluronate micelles for dry eye syndrome. RSC Adv. 2019, 9, 16578–16585.
43. Desai, D.T.; Maulvi, F.A.; Desai, A.R.; Shukla, M.R.; Desai, B.V.; Khadela, A.D.; Shetty, K.H.; Shah, D.O.; Willcox, M.D. In vitro and in vivo evaluation of cyclosporine-graphene oxide laden hydrogel contact lenses. Int. J. Pharm. 2022, 613, 121414.
44. Banica, F.-G. Chemical Sensors and Biosensors: Fundamentals and Applications; John Wiley & Sons: Hoboken, NJ, USA, 2012.
45. Khalilian, A.; Khan, M.R.R.; Kang, S.-W. Highly sensitive and wide-dynamic-range side-polished fiber-optic taste sensor. Sens. Actuators B Chem. 2017, 249, 700–707.
46. Jones, L.; Downie, L.E.; Korb, D.; Benitez-del-Castillo, J.M.; Dana, R.; Deng, S.X.; Dong, P.N.; Geerling, G.; Hida, R.Y.; Liu, Y. TFOS DEWS II management and therapy report. Ocul. Surf. 2017, 15, 575–628.
47. Ma, X.; Ahadian, S.; Liu, S.; Zhang, J.; Liu, S.; Cao, T.; Lin, W.; Wu, D.; de Barros, N.R.; Zare, M.R. Smart contact lenses for biosensing applications. Adv. Intell. Syst. 2021, 3, 2000263.
48. Ferraz, M.P. Biomaterials for Ophthalmic Applications. Appl. Sci. 2022, 12, 5886.
49. Tighe, B.J. Contact lens materials. Contact Lenses 2006, 2, 18–31.
50. Musgrave, C.S.A.; Fang, F. Contact lens materials: A materials science perspective. Materials 2019, 12, 261.
51. Rossos, A.; Banti, C.; Kalampounias, A.; Papachristodoulou, C.; Kordatos, K.; Zoumpoulakis, P.; Mavromoustakos, T.; Kourkoumelis, N.; Hadjikakou, S. pHEMA@ AGMNA-1: A novel material for the development of antibacterial contact lens. Mater. Sci. Eng. C 2020, 111, 110770.
52. Franco, P.; De Marco, I. Contact lenses as ophthalmic drug delivery systems: A review. Polymers 2021, 13, 1102.