Pharmaceutical, Biomedical and Ophthalmic Applications of Biodegradable Polymers (BDPs): Literature and Patent Review

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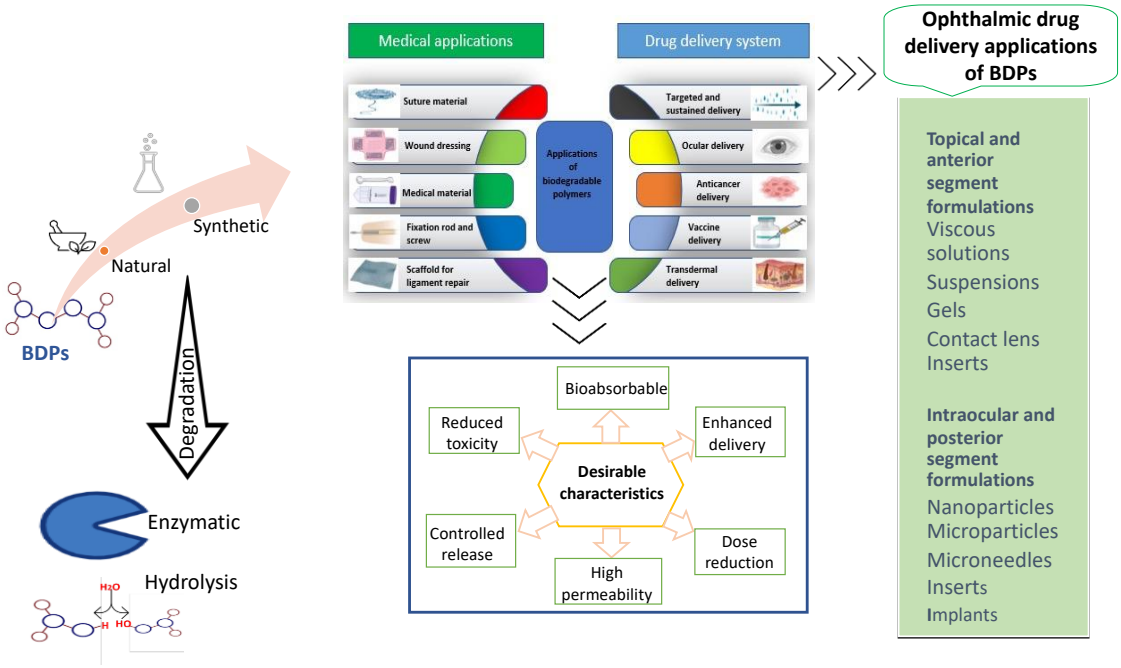
Abstract

In the last few decades, the interest in biodegradable materials for biomedical applications has increased significantly. Both natural and synthetic biodegradable polymers (BDPs) have been broadly explored for various biomedical applications. These include sutures and wound dressings, screws for bone fracture, scaffolds in tissue engineering, implants, and other carriers for targeted and sustained release drug delivery. Owing to their unique characteristics, including their surface charge variable copolymer block and composition and film-forming properties, BDPs have been widely used as favourable materials for ophthalmic drug delivery. Mucoadhesive BDPs have been used in ophthalmic formulations to prolong drug retention time and improve bioavailability, allowing ophthalmic controlled release systems to design. Furthermore, BDPs-based implants, microneedles, and injectable nano- and micro-particles enabled ocular posterior segment targeting and, most importantly, circumvented the need for removing the delivery systems after application. This review outlines the major advances of BDPs and highlights the latest progress of employing natural and synthetic BDPs for various biomedical applications, emphasising the treatment and management of ophthalmic conditions.

Keywords: Biodegradable polymers (BDPs); Natural and synthetic BDPs; Ophthalmic application; Hydrogel; Implant; Ocular patents.



Graphical abstract

Introduction

Polymeric materials have a long history in medical applications. The uses of polymeric-based materials range for traditional devices, such as catheters and syringes, to sophisticated carriers for drug delivery purposes and scaffolds for tissue engineering. According to their degradability in aqueous biological environments, polymers can be classified as biodegradable or non-biodegradable polymers (Glaser 2019).

Biodegradable vs non-biodegradable polymers: formulations and drug delivery advantages

Biodegradable polymers (BDPs) are simply, a class of polymeric materials that possesses the ability to decompose into small units, without causing harm to the body (Tamariz and Rios-Ramrez 2013). The biodegradation process occurs through the breakdown of the polymeric chains by either enzymatic or nonenzymatic mechanisms. In the enzymatic degradation, the process is carried out by special enzymes (Lin and Anseth 2013). Natural polymers are usually more susceptible to enzymatic degradation. However, synthetic polymers can undergo enzymatic degradation. For instance, proteinase K and lipases enzymes biodegrade poly(l-lactide) and poly(ε-caprolactone) respectively (Niemelä and Kellomäki 2011). In the case of nonenzymatic degradation, the backbone of the polymer

cleaves in the presence of water, where water molecules permeate the bulk of the polymer and randomly breaks down the chemical bonds, leading to a reduction in the polymer molecular (Lin and Anseth 2013). In contrast to BDPs, non-BDPs consist of long hydrocarbon chains involving chemical bonds that cannot be broken down by biological processes (Imazato et al. 2017). An obvious advantage of using BDPs is that no surgical removal is needed after the clinical application. Indeed, BDPs can safely be metabolised and eliminated from the human body through normal metabolic pathways which is not the case of non-BDPs that could potentially accumulate in different body tissues where they may induce toxicity.

BDPs are available in natural and synthetic forms. Both forms are widely used in tissue engineering (Song et al. 2018), biomedical and drug delivery applications (figure 1). Based on their chemical structure and properties, natural BDPs can be categorised as protein-based polymers, such as gelatine, albumin, collagen, and polysaccharides such as cellulose derivatives, chitosan, hyaluronic acid, alginate and cyclodextrins (George et al. 2019). In addition to their biodegradability and biocompatibility, natural polymers can be modified to improve their chemical characteristics (Doppalapudi et al. 2014). For example, the chemical modification of chitosan with thiol group is widely used to advance the bulk polymer properties and enhance its mucoadhesion capacity (Esquivel et al. 2015). On the other hand, synthetic BDPs have been more useful in the fields of medical implants (Nickel et al. 2012), controlled drug delivery (Wolinsky et al. 2012) and tissue engineering (Gunatillake et al. 2003). This is mainly due to their highly desirable properties such as mechanical strength, flexibility, resistivity, chemical inertness, and purity (Manavitehrani et al. 2016). Often studied synthetic polymers for tissue engineering applications include polyphosphazenes (Deng et al. 2010). polyphosphoesters (Manavitehrani et al. 2016; Tang et al. 2014; Deng et al. 2010), and polycarbonate (Welle et al. 2007). Similarly, polyhydroxyalkanoates have been used for various medical applications, as suture in surgeries, bone fracture fixation devices and other orthopaedic uses (Akaraonye et al. 2010). Aliphatic polyesters have been widely investigated for their use in drug delivery and controlled release for chemotherapy (Akaraonye et al. 2010; Fonseca et al. 2015) and as a carrier for antibiotics (Han et al. 2017; Kim et al. 2020), antioxidants (Gu et al. 2019) and therapeutic proteins and peptides (Landsman et al. 2011).

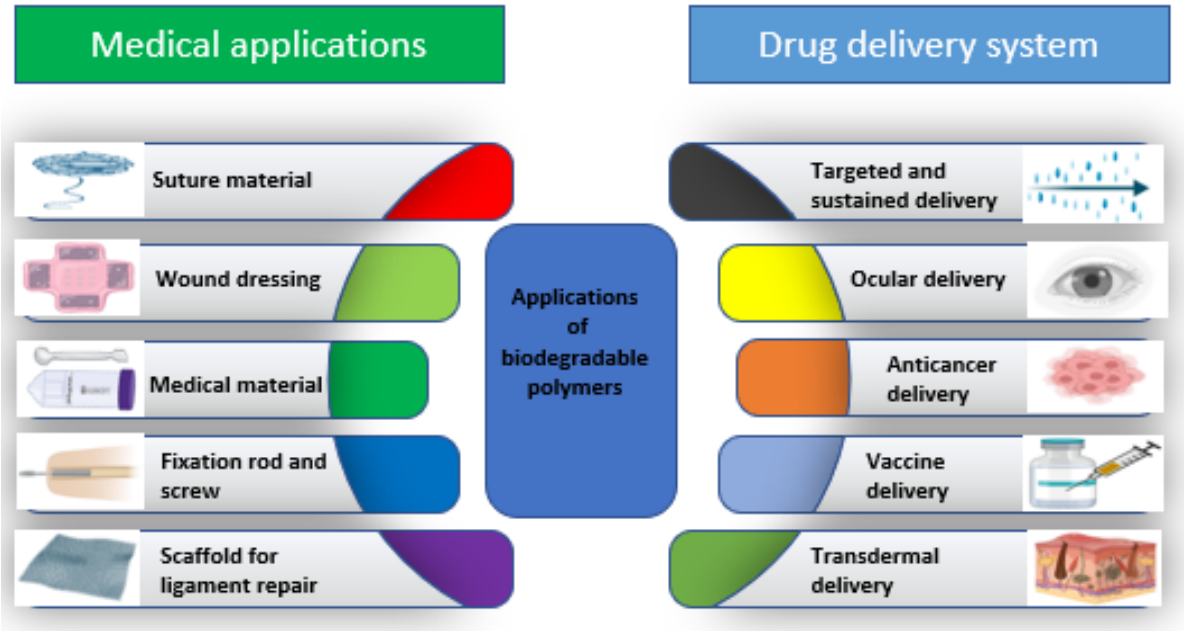


Figure 1Medical applications and various drug delivery systems of biodegradable polymers

Natural and semi-synthetic BDPs used in commercial biomedical products

Naturally occurring polymeric materials are abundant and versatile, including collagen, hyaluronic acid (HA), fibrin, chitosan, cellulosic derivatives, etc. Natural polymers possess several inherent advantages such as biocompatibility (de Moraes Porto 2012), the ability to present ligands that can bind cell receptors, and low toxicity (Deshayes and Kasko 2013). These polymers were the first biodegradable biomaterials used in clinics (Zhang et al. 2013). However, natural polymers do have shortcomings, including the strong immunogenic response associated with most of them and the need for multi-step purification processes(Dmour and Taha 2018).

Collagen

Collagen is a protein made from amino acids, specifically glycine, proline, hydroxyproline, and arginine and it is a major structural component of many human's tissues, including skin, tendon, cornea and basement membranes (Dmour and Taha 2018). It is one of the most abundant proteins in mammals, constituting around 30% of total body proteins (Sibilla et al. 2015). Owing to its biocompatibility, enzymatic degradability, and high tensile strength, collagen has been widely investigated for various biomedical applications (Gu et al. 2019). Collagen-based materials have been successfully used for skin repair. TheraSkin™, Apligraf ™ and Dermagraft™ are FDA approved products for the treatment of venous leg ulcers and diabetic foot. (Lee et al.

2016; Dmour and Taha 2018). Furthermore, collagen has also been widely used as hemostatic agents due to its high thrombogenic properties (Lee et al. 2019). Several collagen-based hemostats are currently in use for a variety of surgical indications; these include FloSeal™ (Baxter Healthcare, the USA), SurgiFlo™ (Ethicon Inc., the USA) and CollaStat™ (Dalim Tissen Co. Ltd., Korea) (Lee et al. 2019).The fact that collagen is non-toxic, can be easily cross-linked and chemically modified promoted the use of this polymer for drug delivery applications. Chlorhexidine chip made of bovine gelatine has shown beneficial effects in the management of Chronic Periodontitis (John et al. 2015). GARAMYCIN™ (Innocoll Pharmaceuticals Ltd) is a collagen-based gentamicin-delivery implant that permits the localised and sustained delivery of gentamycin with limited systemic exposure (Mishra et al. 2014).

Dextran

Dextran is a linear polysaccharide consisting of-1,6 linked D-glucopyranose residues with a few percent of -1,2, -1,3, or-1,4-linked side chains, originally it derived from wine (Khoder et al. 2018). Dextran exhibits several favourable biological properties, such as biocompatibility, biodegradability, and non- toxicity (Ali and Ahmed 2018) . In addition, it is very stable under mild acidic and basic conditions and highly water-soluble substance. For decades, this glucose- based polymer has been used clinically as a plasma volume expander (Irimia, Ghica, et al. 2018), peripheral flow enhancer (Li et al. 2018), antithrombotic agent (Mello et al. 2006). Furthermore, in ophthalmic application dextran is often used as the active ingredient in eye drops due to its lubricating nature or as artificial tears (Garg et al. 2019) such as GenTeal® Lubricant Eye Drops, Tears Naturale® eye drops (Alcon Eye Care UK Limited).

Hyaluronic acid

Hyaluronic acid (HA) is a non-toxic, non-immunogenic and non-inflammatory linear polysaccharide, consisting of alternated units of N-acetyl-β-D-glucosamine and β-D-glucuronic acid (Dicker et al. 2014). HA has been widely used in many medical applications, including wound healing, ocular surgery, and tissue engineering (Jin et al. 2010). Furthermore, HA is one of the key players in the tissue regeneration process as it promotes epithelial and mesenchymal cell migration and differentiation (Prestwich 2011). (Anika Therapeutics, Inc.) is a nonwoven 3D HA-based scaffold used as a carrier for stem cells in the treatment of the osteochondral lesion. Interestingly, HYALOFAST

pad can be cut and shaped to fit into both regular and irregular lesions (Zhong et al. 2018). Additionally, HA-based products are covering a broad range of cosmetic applications. Cross-linked HA is used as soft tissue fillers to reduce the wrinkles and improve the shape of the skin. For example, Hylan B®, Bellotero® and Aliaxin® are commercially available HA-based cosmetic products (Highley et al. 2016). HA has been formulated as eye drops, such as Hylo-Vision® HD and Hylo-Vision® plus, for the treatment of dry eye. Furthermore, viscous solutions made of high molecular-weight HA (AMVISC® and AMVISC® PLUS, Bausch & Lomb) are utilised as protection for sensitive eye tissue during glaucoma and cataract surgery (Zhu et al. 2015).

Fibrin

Fibrin is a protein-based substance that is assembled in long fibrous chains. As a fibrinogen-derivative biopolymer produced by thrombi-medicated cleavage, fibrin plays an important role in many physiological processes such as hemostasis (Litvinov and Weisel 2016). The fibrin clot adheres to the native tissue, preventing the leakage of body fluid and enhancing cell proliferation (Kattula et al. 2017). Fibrin gel has been widely used to make drug carriers (Litvinov and Weisel 2016) and scaffolds for tissue engineering (Spicer and Mikos 2010; Rubalskii et al. 2019). Fibrin gel for tissue engineering applications has two functions: delivery vehicle and scaffolding matrix (Li et al. 2015; Zadeh et al. 2019). In addition, fibrin glue is used as a hemostatic agent and sealant in surgeries. Fibrin sealant is commercially available under different brand names such as Evarrest® Fibrin Sealant Patch (Ethicon US, LLC, Somerville, NJ, USA), VISTASEAL™ Fibrin Sealant (Human) Ethicon, Tisseel (Baxter Inc., Denmark), Crosseal (OMRIX Biopharmaceuticals Ltd. Israel), and Hemaseel (Heamacure Corp., Canada) (Duarte et al. 2012).

Albumin

Albumin is another natural transport protein with a long plasma half-life of around 20 days. Albumin displays several ligand binding sites and interacts with cellular receptors (Gp60, Gp30 and Gp18) (Chien et al. 2012; Duarte et al. 2012). Due to its physiological transport mechanisms and high charge and solubility, albumin has been investigated for controlled release drug delivery systems (Khoder et al. 2019), both drugs half-life extension and targeted intracellular delivery applications (Larsen et al. 2016; Khoder et al. 2018). Albumin-binding domain antibodies (AlbudAbs™) provide a valuable method

for increasing the efficacy of drugs by extending the time for which therapeutic levels of the drug are presented. Victoza® (glucagon-like peptide) was approved by the FDA in 2010 for the treatment of type 2 diabetes. NeoMend ProGEL™ Pleural Air Leak Sealant is a single-use medical device that is formed by mixing two components: (1) a solution of human serum albumin (HSA) and (2) a synthetic cross-linking component of polyethylene glycol (PEG) that is functionalised with succinate groups (Matica et al. 2017).

Chitosan

Chitosan is a natural positively charged, linear polymer obtained by deacetylation of chitin (Matica et al. 2017). Chitosan displays many important properties such as mucoadhesiveness (Matica et al. 2017; Trujillo-de Santiago et al. 2019), hemostatic and antibacterial activity (Martins et al. 2014). The biodegradation of chitosan occurs enzymatically by several enzymes, such as lysozymes that disrupt the linkage between acetylated units (Matica et al. 2017). Currently, there are several chitosan-based wound dressings available in the market. HemCon® hemostatic bandages were widely used in treating external haemorrhage in military operations (Blackbourne and Butler 2016). Others chitosan-based dressings with antibacterial properties are commercially available including; GuardaCare®, ChitoFlex® and ChitoGauze. For medical applications, chitosan and its derivatives can be easily processed into various forms such as solutions (Ali and Ahmed 2018), gels/hydrogels (Irimia, Dinu-Pîrvu, et al. 2018), microparticles/nanoparticles (Al-Kinani et al. 2015; Li et al. 2018) ,membranes, and films (Mello et al. 2006). Thus, they may be used in oral, ocular, nasal administration (Garg et al. 2019) such as chitosan capsules for weight loss and cholesterol lowering, ChiSys® as a Chitosan-Based Delivery Platform for Nasal Vaccination and Chitosan-N-Acetylcysteine (Lacrimera®) eye drops for treatment of dry eye disease.

Cellulose and its derivatives

Cellulose and cellulose derivatives are the most abundant biodegradable materials that have been widely used for medical applications, such as wound dressing (Martins et al. 2014), tissue engineering (Hickey and Pelling 2019), controllable drug delivery systems (Sezer et al. 2019). Ethyl cellulose (EC) is used as a release modifier in oral solid dosage forms (Wasilewska and Winnicka 2019). DiffCORE™ (Lamictal® XR) is a cellulosic

system which delivers the drug from a tablet core through one or several apertures made in an impermeable EC coating layer. Trokendi XR™ (topiramate, Catalent Pharma Solutions), for antiepileptic therapy, is another example of the commercially available oral solid dosage form with EC as release modifier.

Cellulose derivatives are amongst the most widely used components in ophthalmic products. Eye solutions such as Rohto hydro (hydroxypropyl methylcellulose (HPMC) 0.5%), Genteal (methylcellulose (MC) 0.1-0.6%) Murcicell (MC 0,05-0.5%), CELLUVISC® 1.0% and Eco Tears 0.5% Carboxymethylcellulose sodium are commercially available as ophthalmic lubricants for the treatment of dry eye disease. In addition, microcrystalline cellulose is utilised as a release modifier in RETISERT™ formulation (fluocinolone acetonide intravitreal implant) for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

Synthetic BDPs used in commercial biomedical products

Poly (α-hydroxy acids)

Synthetic BDPs have been extensively investigated and used for various biomedical applications thanks to their good biocompatibility and controlled biodegradability properties. These applications include implants, scaffolds for tissue engineering, carriers in drug delivery, and sutures and wound healing (C and T 2015). Poly (α-hydroxy acids) are among the most extensively investigated BDPs for medicinal applications (Niemelä and Kellomäki 2011). They can easily be synthesised either by condensation or via ring-opening polymerisation (Lipsa et al. 2010). Bulk erosion usually takes place during the process of degradation of Poly (alpha-hydroxy acids) (Ginjupalli et al. 2017) .The most common polymers in this category include Poly lactic Acid (PLA), Poly glycolic acid (PGA) and their copolymers Polylactic-co-glycolic acid (PLGA). Among those, PGA was the first biomaterial utilised for offering resorbable sutures under name DexonR™. However, the hydrophilicity nature of PGA limits its applications where its high degradation rate increases the acidity of the surrounding tissues which, in turn, causes local inflammation (Stewart et al. 2018).

PLA is more hydrophobic than PGA due to presence methyl group in its structure (Gorth and Webster 2010). As a chiral molecule, PLA comes in four forms: poly (L-lactic acid) (PLLA), poly (D-lactic acid) (PDLA), poly (D, L-Lactic acid) (PDLLA), and meso-poly

(lactic acid) (Gorth and Webster 2010). PLLA and PDLLA have shown interesting applications in biomedical research. For instance, Atrisorb®, a PDLLA-based membrane, was introduced by Atrix laboratories for dentistry tissue regeneration (Annunziata et al. 2017). Similarly, PLLA has been used for a range of biomedical applications such as tissue engineering of scaffolds (Chang and Gupta 2010). PLLA bioabsorbable screws (Bio interference ScrewR™) have been used to fix bones (Sprowson et al. 2012). PLGA, synthesised by the copolymerisation of PLA and PGA, was developed to improve the degradation rate and release profiles (Makadia and Siegel 2011) . PLGA is the most studied biodegradable polymer for biomedical applications. (Bret D Ulery et al. 2011). Vicryl Rapide (VicrylR©) is an example of PLGA-based marketed absorbable sutures (Chu 2013). The favourable degradation characteristics of PLGA copolymer make it suitable for drug delivery (Makadia and Siegel 2011). Recently, a list of medicinal products based on PLGA microparticles was approved by the FDA and are currently in clinical use. (Blasi 2019). Signifor™ LAR by Novartis (Pasireotide injectable suspension) was approved by the FDA in 2014 for the treatment of patients with acromegaly. Zilretta™ by Flexion Therapeutics (triamcinolone acetonide extended-release injectable suspension) was approved by FDA in 2017 for the treatment of osteoarthritis Knee. Likewise, Perseris™ by Indivior Inc. (risperidone extended-release injectable suspension) gained the FDA approval in November 2018 for Schizophrenia treatment. Also, Arbor Pharmaceuticals produced Triptodur™ (triptorelin extended injectable release suspension) for the Treatment of Central Precocious Puberty (Makadia and Siegel 2011; Bret D. Ulery et al. 2011; Chu 2013; Blasi 2019) (Table 1).

Polycaprolactone (PCL) is a semi-crystalline polymer synthesised from ε-caprolactone monomers by ring-opening polymerisation (Cameron and Kamvari-Moghaddam 2012). Degradation of PCL occurs by hydrolysis of the ester linkages (Jain et al. 2016) . PCL has a slower degradation rate (2 to 4 years) in comparison to other polymers such as PLA and PLGA (Arakawa and DeForest 2017), making it more popular for long term therapeutic applications. for instance, Capronor® is a subdermal contraceptive device that releases levonorgestrel over a 12-to-18-month period. However, its low degradation rates can be enhanced by blending or copolymerisation with other polymers such as PLGA, PLLA (Schoubben et al. 2019), PLA (Woodruff and Hutmacher 2010) and polyethylene glycol (PEG) (Figueiredo et al. 2019). Furthermore, PCL is used for the fabrication of tissue repair patches (i.e., Ethicon Inc., Edinburgh, United Kingdom), as a filling agent

for bone regeneration (Xu et al. 2015) and as artificial nerve graft for the repair of peripheral nerve defects (Bliley and Marra 2015). Additionally, Carboplatin-PCL nanoparticles were explored for targeted brain delivery via nasal route (Malikmammadov et al. 2018), and doxycycline-loaded poly(epsilon-caprolactone) microspheres were also developed as a controlled-release drug therapy (Raval et al. 2014).

Overall, synthetic BDPs can be fabricated in desired shapes and their surface characteristics (Navaei et al. 2018) and degradation rate (Zhang et al. 2013) can be modified to suit different applications. Both synthetic and natural polymers have several useful properties on their own. However, combining them can form a new class of materials with improved mechanical and biological properties compared with those of single components (Zhang et al. 2013). For instance, chitosan was blended with (PLA /PLGA) (Caires et al. 2016) (PCL) (Raval et al. 2014; Navaei et al. 2018)to improve their cell interaction behaviour in tissue regeneration applications (Caires et al. 2016). Likewise, PCL was blended with collagen (Zhang et al. 2013; Caires et al. 2016) and alginate (Kim and Kim 2014) to enhance its cell-binding ability. Table 1 provides a list of some of the marketed biomedical products based on natural and synthetic BDPs.

Table1. Marketed biomedical products based on natural and synthetic BDPs

Product/ Company/FDA approval year	Polymer	Active ingredient	Formulation/ Device	Clinical indications
Natural/Semisynthetic polymers				
OSSIX® VOLUMAX Datum Dental Ltd. 2016	Collagen	Collagen	Scaffold	Multipurpose collagen membrane is used for restoring lost volume in guided bone and tissue regeneration procedures.
JUVÉDERM VOLBELLA® XC, 2016	Hyaluronic acid	Hyaluronic acid	Gel	Injection into the lips for lip augmentation and correction of perioral rhytids in adults
Restylane® Silk, Galderma Laboratories. 2017	Hyaluronic acid	Hyaluronic acid	Gel	The injectable gel is used for correction in the lines from the nose to the corners of the mouth.
Belotero Lips, Merz Pharmaceuticals. 2017	Hyaluronic acid	Hyaluronic acid	Gel	Dermal filler is used for the treatment of perioral lines and lip enhancement.
JUVÉDERM VOLUMA® XC, Allergan. 2019	Hyaluronic acid	Hyaluronic acid	Injectable gel	Dermal filler is used for cheek augmentation to correct age-related volume definition in the mid-face in adults
VISTASEAL™ Ethicon. 2019	Fibrinogen	Fibrinogen, thrombin	Spray	Surgical bleed-

				in management
Albuminex, Bio Products Laboratory, USA. 2018	Albumin	Human albumin	solution for infusion	Hypovolemia, ascites and hypoalbuminemia
Progel® (Neomend, Inc., Irvine, CA). 2010	Albumin	Albumin, polyethylene glycol (PEG).	Hydrogel	Sealant for intraoperative use during pulmonary resection.
Plenity™ Gelesis, Boston, Massachusetts, USA. 2019	Cellulose	Modified cellulose cross-linked with citric acid.	Hydrogel capsule	Obesity treatment (weight loss)
Natural/Semisynthetic polymers				
Bydureon® AstraZeneca AB. 2012	PLGA	Exenatide synthetic	liposome injectable suspension	Type 2 diabetes
Signifor Lar® Novartis. 2014	PLGA	Pasireotide (Somatostatin analogue)	Liposome injectable suspension	Acromegaly (endocrine disorders)
Sublocade® Indivior. 2017	PLGA	Buprenorphine	Nanoparticle injectable suspension	Moderate to severe opioid use disorder
Bydureon Bcise® AstraZeneca AB. 2017	PLGA	Exenatide	Microsphere injectable suspension	Type 2 diabetes

Zilretta™ Flexion Therapeutics. 2017	PLGA	Triamcinolone acetonide	Microsphere injectable suspension	To manage osteoarthritis knee pain.
TriptodurKit® ARBOR PHARMS LLC. 2017	PLGA	Triptorelin pamoate	Liposome injectable suspension	Central precocious puberty
Perseris™ Indivio Inc.2018	PLGA	Risperidone	Microsphere injectable suspension	antipsychotic medication
Sustol® /Heron. 2012	Ortho-ester	Granisetron (Biochronomer™)	Nanoparticle injectable suspension	Nausea and vomiting
ActivHeal® PHMB Foam. Advanced Medical Solutions Ltd. 2017	Polyurethane	Antimicrobial substance polyhexamethylene biguanide (PHMB, Polyhexanide)	Foam dressing	Product is indicated for moderate to heavily exuding chronic and acute wounds that are infected or are at risk of infection

Ophthalmic applications of BDPs

Ocular drug delivery is challenging due to the complex nature of the eye. Anatomical and physiological barriers of the eye prevent drug molecules from reaching the desired area (Duan et al. 2010; Sousa et al. 2013). For instance, only about 5% of the topically applied dose can reach the target tissues of the eye (Al-Kinani et al. 2012; Agrahari et al. 2016). Maintaining the therapeutic drug concentration at the target tissue is a significant factor for the successful treatment. Therefore, the bioavailability of the active drug molecule is often the foremost obstacle to circumvent (Varela-Fernández et al. 2020).

Depending on the area to be treated and the route of administration, ocular drug delivery systems are classified as topical, local, and systemic systems (Jin and Hwang 2017). Topical administration (i.e., applying medication on the eye's surface) is the most preferred method to treat the diseases affecting the ocular surface and anterior segment of the eye. However, the bioavailability of drugs applied topically is low due to their rapid elimination from the precorneal area (Alghamdi et al. 2020). Besides, the cornea, prevents drug molecules from penetrating deeper into the ocular tissue. The lipophilic properties of the corneal epithelium limit the penetration of hydrophilic drug molecules, whereas the hydrophilicity of the stroma acts as a rate-limiting membrane for lipophilic molecules (Sousa et al. 2013; Agrahari et al. 2016; Varela-Fernández et al. 2020). The sclera-conjunctival route of drug absorption has its own limitations and is usually restricted to small and hydrophilic drug molecules Using viscosity enhancers can overcome these barriers by prolonging the residence time of the drug on the surface of the eye (Jin and Hwang 2017; Alghamdi et al. 2020).

For treatment of posterior segment disorders, either systemic or local route of administration could be used. (Souto et al. 2019). However, the systemic administration (oral or intravenous) requires higher dosage and frequent administration to achieve a therapeutic concentration, causing undesirable side effects and patient discomfort (Rupenthal and Alany 2007; Gaudana et al. 2010; Huang et al. 2019). Local ocular route is more invasive than topical and systematic ones since medicine is directly injected into the target area of the eye. Intravitreal/subconjunctival injections are an alternative strategy to deliver drugs and biologics to the posterior segment of the eye (http://fyra.io). Accordingly, the drug can be delivered directly into the target site (vitreous, mainly to

reach the retina) thus allowing to bypass anatomical and physiological barriers encountered with topical and systemic administrations. However, repeated injections may be necessary to maintain a therapeutic level of the agent, which might cause haemorrhage, trauma, endophthalmitis and retinal detachment (Cañadas et al. 2016).

BDPs offer several benefits to improve drug administration into the eye and optimise therapeutic outcomes of ophthalmic formulations (Tsai et al. 2018). The main advantage of using BDPs resides in their ability to degrade inside the eye into non-toxic natural by-products which can be eliminated by the eye without the need for surgical intervention (Alghamdi et al. 2020) . A further advantage of many BDPs is their viscosity modifying and mucoadhesive properties, that could prolong residence time, enhance membrane permeability, and improve bioavailability (Kamaly et al. 2016). BDPs have been widely used in ocular controlled-release systems. Controlling drug release minimise fluctuation of drug concentration, allowing reduced dosing frequency and improved patient adherence (Jafariazar et al. 2015). For example, Ozudex (Allergan, CA) is a PLGA-based intravitreal implant that can control the release of dexamethasone over six months for the treatment of diabetic macular oedema. Thus, reducing the need for the daily use of multiple eye drops.

Applications of BDPs for ocular surface and anterior segment drug delivery

One of the strategies to increase the drug duration of action and the bioavailability at the surface of the eye is to use viscosity and penetration enhancers (Moiseev et al. 2019). This helps maximise the drug ocular absorption and minimise the precorneal loss (Duan et al. 2010; Tsai et al. 2018). Natural BDPs such as chitosan and gelatine have been successfully employed as viscosity enhancer in ocular formulations. Silva et al. investigated the interaction between mucin and antibiotic (ceftazidime)-loaded nanoparticles made of chitosan and sodium tripolyphosphate-hyaluronic. The authors highlighted the mucoadhesive properties of the NPs formulation and its ability to interact with the ocular surface (Silva et al. 2017). Another recent study revealed that chitosan-colloidal nanoparticle systems facilitated the penetration of the drug via the cornea by opening the tight junctions in the epithelial tissue (Lynch et al. 2019). Also, gelatine was extensively employed for the fabrication of ocular devices such as nanoparticles, (Kaur and Smitha 2002; Jafariazar et al. 2015) microspheres and hydrogels (Gu et al. 2019). Song et al. prepared chitosan-gelatine hydrogel loaded with an anti-glaucoma drug

(timolol maleate) for topical ophthalmic applications. The *in vivo* animal studies showed a long-lasting and effective intraocular pressure lowering efficacy of hydrogels for up to 24 h compared with the conventional eye drops (Y et al. 2018).

Polymer hydrogels

Polymeric gels, based on natural or synthetic polymers, have been employed to increase the viscosity of instilled ocular solutions (Irimia, Ghica, et al. 2018) .Polymeric gels can be divided into two categories: preformed hydrogels and *in-situ* gelling (gel-forming) systems. Polymers in bio-adhesive preformed hydrogels can form strong noncovalent bonds with membrane-associated mucins present on the surface of the epithelium (Almeida et al. 2013). Polymers such as polyvinyl alcohol (PVA), chitosan and polyacrylic acid (PAA) are the most utilised bioadhesive polymers in ophthalmic formulations.

Polyvinyl Alcohol (PVA) is a synthetic, biodegradable, biocompatible and non-toxic polymer that has been widely used in ophthalmic drug delivery system (Jiang et al. 2011). PVA has excellent film-forming and mucoadhesive properties. PVA hydrogels can be made of PVA, or of blends of PVA with other polymers like gelatine (Santos et al. 2019). Gelatine is a natural polymer that is well-tolerated on ocular administration and has good mucoadhesive properties (Rashid et al. 2019). However, its unfavourable mechanical properties limit its potential application as a biomaterial. To overcome this limitation and improve the functional properties of gelatine, it is essential to modify it through physical or chemical methods, such as blending, cross-linking, and grafting (Rashid et al. 2019). Taking this into an advantage, Jain et al. formulated biosynthetic PVA–gelatine ocular inserts loaded with ciprofloxacin. Compared with eyedrops, the inserts showed superior mechanical, mucoadhesive and biocompatible properties, suggesting the PVA–gelatine polymeric blends as a promising material for antibiotic prolonged-release ocular inserts (D. Jain et al. 2011). Additionally, Terreni and co-workers were used PVA in combination with other mucoadhesive polymers to prepare hybrid nanomicelle-polymer inserts for improved delivery of cyclosporine A to the surface of the eye. The results were promising as the system demonstrated prolonged precorneal residence compared with eyedrops Ikervis® with no ocular adverse effects when tested in the rabbit eye(Terreni et al. 2021).

In situ hydrogels (gel forming systems)

Ocular *in situ* gelling systems are polymeric formulations in forms of viscous solutions that undergo a phase change of ‘’sol to gel’’ upon exposing to external stimuli (Rupenthal et al. 2011; Wu et al. 2019; Santos et al. 2019; Abdelkader et al. 2020). The main types of stimuli-responsive polymers used in ocular formulations are thermo-responsive, pH-responsive, and ion-activated polymers (Wu et al. 2019). *In situ* gelling systems prolong the residence time of the drug on the corneal and/or conjunctival epithelium via enhanced viscosity and mucoadhesive characteristics, hence improve the overall ocular bioavailability of ophthalmic application (Silva et al. 2017).

Thermo-responsive gels

Thermo-responsive polymers change their consistency in response to temperature (Irimia, Ghica, et al. 2018). Thermo-responsive gels for ocular application are liquid at room temperature (20-25°C), however they undergo a phase change to form a gel once in contact with the ocular surface (Kushwaha et al. 2012). For the phase transition to happen and produce the hydrogel form, the thermo-responsive polymer found in solution must become insoluble above or below a certain temperature, known as the lower and upper critical solution temperature (LCST or UCST, respectively) (Kumar et al. 2013; Wu et al. 2019). Polymers exhibiting LCST are dissolved in an aqueous system and miscible at temperatures below the critical value. Once LCST is reached, individual polymer chains in the system collapse followed by aggregation, increasing scattering of light in the solution, causing cloudiness. As a result, two phases occur: gel-phase and water phase (Kushwaha et al. 2012; Al Khateb et al. 2016) . The most common biodegradable polymers used i*n-situ* gel thermosensitive systems are poloxamers (polyoxypropylene-polyoxyethylen copolymers), poly (N-isopropyl acrylamide) and cellulose derivatives. Pluronic® F-127 is a thermo-responsive poloxamer which is widely used in the ophthalmic formulations. PF-127 turns into a transparent gel by changing its microstructural properties in response to temperature change (Kushwaha et al. 2012; Silva et al. 2017). Al khatib et al. evaluated the use of Pluronic F127 (20% w/w) in *in-situ* gelling for ocular drug delivery and compared it with other pluronics. In this study, the thermal transitions of F127, F68 and their binary mixtures in aqueous solutions were investigated. Pluronic F127 was more effective as a transparent gel was observed under

physiological conditions when 20% w/w PF-127 solutions were used (Al Khateb et al. 2016).

Poly (N-isopropyl acrylamide) is a water-soluble polymer at its low LCST (32°C), above which a phase change occurs transforming the water-soluble liquid to a hydrophobic gel (Wu et al. 2019). Lai et al. developed a thermo-responsive system based on gelatin/poly (N-isopropyl acrylamide) for the intracameral administration of pilocarpine in the treatment of glaucoma (Vigani et al. 2020). Methylcellulose (MC), is a water-soluble natural polymer, derived from cellulose. At low concentrations (1-10% w/w), the liquid form of MC transfers into the gel phase when slightly high temperature (40-50 °C) is applied (Bennett 2016). Interestingly, the transition temperature of the MC can be reduced to the eye temperature by adding salts. The sol-gel transition temperature of MC depends on the MC concentration (Almeida et al. 2014; Vigani et al. 2020) and salt type. While, the salt-out salts, such as NaCl, Na_2SO_4, assist in the sol-gel transition, salt-in ones like KI and NaSCN tend to suppress the formation of the gel (Bromberg and Ron 1998; Xu et al. 2004; Al Khateb et al. 2016).

pH-responsive

pH-responsive polymers possess polyelectrolyte properties that are mainly attributed to their acidic or basic functional groups (Kocak et al. 2017). Interestingly, pH-responsive polymers can change their physicochemical properties, including chain configuration and solubility, in response to environmental pH changes (Mutalabisin et al. 2018). PAA and chitosan are amongst the most used pH-sensitive polymers for ophthalmic applications. PAA and its derivates (Carbopol® or carbomer®) contain ionisable pH-responsive functional groups. The ionisation of these groups results in acquiring or donating protons at low and high pH value, respectively. Sol-gel phase transition in aqueous solution takes place when pH value exceeds 5.5. At this pH range, electrostatic repulsion between negatively charged anionic groups (carboxyl groups) causes polymer swelling. Subsequently, gelation occurs in response to pH changes in the surrounding environment (You et al. 2010). Furthermore, Carbopols widely used for its aqueous solubility, biodegradability, and bioadhesive properties that increase the precorneal residence time of the drug (Shaikh et al. 2011). However, the acidic nature of Carbopol gel has been associated with local irritation and ocular tissues damages (Wu et al. 2019). The combination of Carbopol with other polymers, such as Methylcellulose (MC), chitosan, and hydroxypropyl methylcellulose (HPMC) was explored as a strategy to enhance the

Carbopol gelling properties and overcome the acidity related issue. Khutoryanskaya et al. prepared a polymeric film comprising PAA/MC as a carrier for ophthalmic drug delivery. The PAA/MC film was optimised to bring together the favourable properties of both polymers (Khutoryanskaya et al. 2014). A slow-release profile of the drug was observed *in-vitro*. The *In-vivo* studies revealed that the PAA/MC polymeric films extended the ocular retention time by 30–60 minutes more than films made of individual polymers. Wu et al. evaluated Carbopol/HPMC gel as an ocular carrier for sustained release of Baicalin. Rheological studies demonstrated an improvement in the gel strength under physiological conditions. Additionally, the formulation displayed a constant release of the Baicalin over 8 hours. *In vivo*, ocular pharmacokinetics study showed that the maximum concentration of the drug in the aqueous humour of rabbit eye was 3.6 times higher than the control solution (Wu et al. 2011).

Ion-responsive hydrogels

Ion-activated polymers cross-link in the presence of the electrolytes (Ca^{2+}, $Mg^{2+}$and Na^{+}), leading to sol-gel transition (ID et al. 2011) . Examples of ion- activated polymers used in ophthalmic formulations include alginate, hyaluronic acid, and gellan gum. Alginate is an anionic, biodegradable, mucoadhesive co-polysaccharides that consists of residues of β-Dmannuronic acid and α-L-guluronic acid joined with alpha 1,4 bonds (Aramwit 2016). The interaction between Ca^{2+} ions present in the tear film and guluronic acid residues increases alginate viscosity, hence the residence time of the drug formulation on the surface of the eye (Makwana et al. 2016). Alginate gel properties depend on the ratio of its constituents. Increasing the ratio of guluronic acid exhibits better gelling properties (Laddha and Mahajan 2017). The combinations of alginate with chitosan have been used to enhance the flexibility of gel formulation (El Maghraby and Arafa 2019). Ionic interaction between the carboxyl groups of alginate and positive amine groups of chitosan leads to a stable polymeric structure (Kulig et al. 2016). Gupta et al. developed an *in-situ* gelling formulation based on sodium alginate and chitosan containing levofloxacin. The authors concluded that the *in-situ* gel provided a prolonged retention time on the corneal surface compared with eye drops (Gupta et al. 2015).

Colloidal nano-carriers

Colloidal Drug Delivery system including liposomes, niosmoses, microemulsions, nanoemulsions and nanoparticles plays an important role in the effective transportation

of loaded drug to the target site. Liposomes are lipid-based bilayer vesicles in which an aqueous volume is surrounded by lipid bilayers membrane (mainly phospholipids and cholesterol) of natural and synthetic origin (Abdelkader et al. 2014). liposomes offer several advantages including biocompatibility, capacity for self-assembly. Liposomes have been investigated for the delivery of vaccine (Wang et al. 2019), gene (Balazs and Godbey 2011), anticancer (Olusanya et al. 2018), and anti-HIV drugs (Chopra et al. 2013). For ophthalmic drug delivery system liposomes have been used as a drug carrier for posterior segment (Garg et al. 2019) and anterior segment (Agarwal et al. 2016) of the eye. In addition, it has been reported that liposomal formulations enhance the therapeutic efficiency of certain antibiotics and peptide in ocular delivery (Rupenthal and Alany 2007**) .** As an alternative controlled drug delivery system to liposomes, niosomes are developed to overcome the challenges associated with sterilization, size production and stability. Niosomes are a hydrated mixture of cholesterol and non-ionic surfactants (Ge et al. 2019). Over the last few decades, niosomes have received much attention as potential drug delivery systems. Niosomal carriers are suitable for the delivery of various pharmacological agents, including antioxidants, anticancer and anti-inflammatory (Gharbavi et al. 2018). In ocular drug delivery system, niosomes have been employed as a carrier for the delivery of wide range of drugs including anti-glaucoma (Gooch et al. 2012; El Hoffy et al. 2021), antibiotics (Allam et al. 2019).

Nanoemulsions have attracted increasing interest as a vehicle for topical ocular drug delivery through prolonging precorneal retention, increasing corneal permeability and their ability to Increase the solubilization of lipophilic drugs (Shakeel and Faisal 2010). The solubility of the ketorolac tromethamine was enhanced using nanoemulsion (Smail et al. 2021). Microemulsions are another colloid system with significant thermodynamic stability and low surface tension and small drop size. Microemulsions as topical ocular drug carriers can lead to great ocular drug adsorption due to their enhanced retention time. T.R. Thrimawithana et al developed a hydrogel based on Methylcellulose and iota carrageenan for transscleral drug delivery of macromolecules. The hydrogel was loaded with antisense oligonucleotides against a junction protein (Cx43). Study results demonstrated a significant increase in the bioavailability in the sclera and choroid when compared with an injection of an oligonucleotide solution (Thrimawithana et al. 2011).

For ophthalmic applications, colloidal dosage forms such as nanoparticulate systems have been used widely for the drug delivery to the anterior segment of the eye. Using biodegradable polymeric for NPs preparation has many advantages such as reducing the

risk of irritation, improving the intracellular penetration due to small size, reducing the dosing frequency by providing sustained drug release, and causing fewer side effects by providing tissue targeted drug delivery. Furthermore, nanoparticles can be coated with mucoadhesive polymers such as PEG, chitosan, and HA (G.K. Jain et al. 2011). Similarly, NPs can be dispersed in stimuli-responsive solution that form *in-situ* gelation. Consequently, nanoparticles can be used to improve the bioavailability of the loaded therapeutic agents by prolonging its precorneal residence time (H.S. Boddu 2012). Synthetic biodegradable polymers such as PLA, PLGA and PCL, have been used to fabricate a range of nano and micro-particulate carriers (Song et al. 2018). These polymers have been evaluated for sustained release and reduction of topical administration frequency for various eye diseases such as glaucoma and eye infection (Liu et al. 2013). Ibrahim et al. developed typical ophthalmic formulations of an anti-glaucoma agent (brimonidine) loaded into nanoparticles prepared from different biodegradable polymers PLA, PLGA, PCL. *In vitro*, data showed that all formulations provided drug sustained release compared to the commercial Alphagan® eye drop solution (Ibrahim et al. 2013). Cañadas et al. developed PLGA-NPs loaded with anti-inflammatory drug pranoprofen. The developed nanoparticles were tested *in-vitro* for cytotoxicity, *ex-vivo* for corneal permeation and *in-vivo* for ocular tolerance and anti-inflammatory efficacy. Results revealed that obtained NPs exhibited a high concentration of pranoprofen in the cornea. The rapid onset of anti-inflammatory action has significantly reduced the ocular edema compared to the eye drops and free drug solution. Additionally, pranoprofen formulated in PLGA NPs showed optimal ocular tolerance (Cañadas et al. 2016).

Table 1. List of colloidal systems loaded with different drugs for ocular delivery

Drug	Oil/ Surfactant	Formulation	Result	Ref
Dexamethasone	Oil	CS MEs	Enhance bioavailability	(Kesavan et al. 2013)
Riboflavin phosphate	Docosahexaenoic acid in triglyceride form (fatty acid)	MEs	significant relief of the dry eye condition	(Lidich et al. 2019)
Bimatoprost	Oil + Pluronic F68 and Tween 20	MEs	The *in vivo* studies in the rabbit tear fluid showed low burst release and improvement in the bimatoprost retention time with ME contact lens	(Xu et al. 2019)
α-linolenic acid	Fatty acid- Tween 80, Cremophor EL and Trascutol P	MEs	MEs exerted strong antimicrobial effects against *N. gonorrhoeae* and *S. aureus* without being irritant to the eye based on the BCOP and HET-CAM studies	(Butt et al. 2018)
Cyclosporine	Chitosan CS	NPs	Enhanced residence time at the corneal and conjunctival surfaces	(Başaran et al. 2014)
Betoxalol	Chitosan CS	NPs	Marked reduction in IOP	(Jain et al. 2013)

Dorzolamide hydrochloride or timolol maleate	sodium alginate–chitosan	NPs	Produced a marked decrease in IOP higher bioavailability as compared to the uncoated nanoparticles.	(Nagarwal et al. 2012)
Melatonin	PLGA	NPs	Produced a marked decrease in IOP	(Musumeci et al. 2013)
5-FU	Chitosan CS	NPs	Bioavailability NPs was significantly higher than 5-FU solution in aqueous humor of rabbit eye	(Nagarwal et al. 2011)
Melatonin	PLGA	NPs	Produced a marked decrease in IOP	(Musumeci et al. 2013)
Besifloxacin	Lipid	Liposomes	Enhance drug bioavailability	(dos Santos et al. 2020)
berberine hydrochloride	Polyamidoamine (PAMAM G3.0)	Liposomrs	liposomes exhibited appreciable cellular permeability in human corneal epithelial cells and enhanced bio-adhesion on rabbit corneal epithelium.	(Lai et al. 2019)
Minocycline	Lipid	Liposomes	Enhance the therapeutic efficacy in retina after a subconjunctival injection	(Kaiser et al. 2013)
Tacrolimus	Bile salts + lipid	Liposomes	3–4-fold higher cellular uptake than conventional liposomes and sustained corneal permeation	(Fujisawa et al. 2012)

Diclofenac	Lipid	Surface-modified liposomes	Increased 1.8-fold concentration in retina–choroid compared to that of the unaltered diclofenac solution	
Fluconazole	Lipid	Liposomes	Fluconazole-loaded liposomal formulation shown better action as compared to drug solution on Rabbits infected with C. albicans	(Habib et al. 2010)
Timolol maleate	Non-ionic surfactant	Niosomes	1.7 times higher peak concentration of drug in aqueous humor as compared to the pure timolol maleate solution and 2.34 times AUC higher than TMS	(Abdelkader et al. 2014)
naltrexone hydrochloride	Surfactant/ lipid	Niosome	Enhanced corneal uptake	(Abdelkader et al. 2012)
naltrexone hydrochloride	Surfactant/ lipid	Discomes	Control drug permeation and enhance its corneal permeability in ex vivo.	(Abdelkader et al. 2011)
Acetazolamide (ACZ)	Non-ionic surfactant	transgelosomes (TGS)	ACZ-loaded TGS exhibited more prolonged drug release and a significant lowering of intraocular pressure (IOP) for 24 h in rabbit eye.	(Mazyed and Abdelaziz 2020)
pilocarpine nitrate	poly(amidoamine) (PAMAM)	Dendrimer	prolonged precorneal residence of pilocarpine provided by dendrimer solutions	(Lancina and Yang 2017)
Dorzolamide	Gamma-cyclo-dextrin (γ CD)	Cyclodextrins	Dorzolamide-γCD eye drop microsuspension enhanced ocular bioavailability	(Loftsson et al. 2012)

BDPs for posterior segment targeting

Ocular drug delivery for the treatment of posterior segment diseases has enormously been advanced. However, the challenge remains to bring the therapeutic agents to the target site at safe and effective concentrations (Yadav et al. 2018). Different static and dynamic barriers have a great impact on drug transportation and, subsequently, on efficiency (Yadav et al. 2018). To overcome these barriers, surgical implantation and intravitreal injection have become the common practices for drug delivery to the posterior segment (Pearce et al. 2015) .Topical and systemic administration has also been considered with limited results. (H.S. Boddu 2012; Kim and Kim 2014) . The use of frequent intravitreal injections increases the risk of serious side effects, such as retinal detachment and endophthalmitis (Sampat et al.). Therefore, targeted and sustained-release drug carriers based on BDPs have been designed to achieve prolonged drug concentrations in ocular desired tissues.

Intravitreal injection

Intravitreal injection systems, in the form of suspensions or microspheres (Shah et al. 2010), maximise therapeutic drug levels in targeted tissue of the posterior segment and minimise systemic toxicity (Yamada and Olsen 2015). The potential of PLGA microspheres have been investigated to reduce the intravitreal administration frequency for various chronic eye diseases (Ye et al. 2015). Rodriguez et al. developed PLGA-microspheres for the extended-release of dexamethasone for the treatment of chronic diseases in the back of the eye. A small size (20-40 µm) of PLGA microparticles with high drug encapsulation efficiency (> 90%) were obtained. The release studies indicated a little burst effect (lower than 5%) during the first five hours; afterwards, drug release was sustained over 30 days. In addition, the obtained microparticles were stable under standard refrigerated storage conditions for 12 months (Rodríguez Villanueva et al. 2016). Similarly, in an animal model study, Fernández-Sánchez et al. evaluated the efficacy of intravitreal controlled delivery of the antiapoptotic agent, tauroursodeoxycholic acid, encapsulated in PLGA microspheres for retinal degenerative diseases. The *In-vitro* study showed that there was a steady and gradual release of the active ingredient from PLGA-microspheres for 28 days. ERG electroretinography recordings showed more photoreceptor rows in treated eyes than controls. Investigators found that the PLGA-based microparticulate system improved the drug concentration at

the target site by providing prolonged diffusion-controlled release (Fernández-Sánchez et al. 2017).

Intraocular implants

Intraocular sustained-drug release can be achieved by using implantable devices (Manickavasagam and Oyewumi 2013). Implants can be designed in different shapes (flat sheets, pellets, discs, rods, or plugs) (Boia et al. 2019). PCL is a synthetic, hydrophobic biodegradable polymer with a slow degradation rate in comparison to other polymers. The degradation rate of PCL can be amended by copolymerising it with other fast degrading polymers such as PLA (Tamboli et al. 2012). According to a study performed by Prata's team, dexamethasone was loaded in biodegradable implants made of (PCL/PLA). The implants were prepared by two different methods: melting casting method and solvent casting method. *In-vitro* results showed that the preparation method had a little influence on the release profiles. Dexamethasone was released from the implant in a controlled fashion over two months (Prata et al. 2018). Boia et al. developed a porous PCL implant with a fast degradation rate compared with a typical slow-degrading implant for intraocular injection. The implant was prepared by supercritical carbon dioxide foaming/mixing method. The results showed that higher porosities and surface area increased the degradation rate leading to a faster drug release. Also, *in-vitro* and animal models studies indicated that the implant was not toxic and well-tolerated by retinal neural cells (Boia et al. 2019). In another study, the release of clindamycin phosphate (anti-toxoplasmosis drug) from PLA-PLGA intraocular implant was evaluated *in-vitro*. PLA-PLGA intraocular implant allowed a sustained drug release for about five weeks. The degradation process of the implant occurs in two phases; the first phase corresponded to the burst release observed in the first 24 hrs followed by a second phase where the release rates were found to be proportional to the molecular weight and monomer ratio of copolymers and polymer-to-drug ratios (Mostafavi et al. 2015). Commercially, DURYSTA™ (Allergan, USA) is an intracameral biodegradable implant that is made of blended PLA, PLGA and polyethene glycol. The implant has a sterile rod-shape containing 10 mcg of bimatoprost (prostaglandin analogue). This controlled delivery system is designed to lower intraocular pressure over a 4-6-months. Surodex™ (Allergan, USA) is a rod-shaped implant made of PLGA-hydroxypropyl methylcellulose. It is designed for the delivery of steroids, namely dexamethasone (60 μg), into the anterior chamber of the eye. The implant provides a sustained drug release at a constant rate over

10 days to control postoperative inflammation after cataract surgery. Dextenza (Ocular Therapeutix, USA) is FDA-approved intracanalicular insert for the treatment of postoperative ocular pain. It is comprised of micronized dexamethasone particles suspended within a polyethylene glycol (PEG) hydrogel matrix. The designed insert provides sustained release of dexamethasone to the ocular surface for up to 30 days.

BDPS patents for ocular drug delivery

The current challenge in ophthalmic drug delivery is not simply designing an effective therapy for ocular diseases but also discovering more efficient drug delivery technologies to overcome the ocular barriers without causing any patient discomfort. During the last decade, many innovative technologies have been patented. However, a need for further research and continuous innovation is still necessary. The research studies resulted in several patent disclosures, reporting a significant increase in therapeutic efficacy for various chronic ocular disease states of both anterior segment diseases (Glaucoma, Dry Eye, Conjunctivitis, Uveitis, Choroidal Neovascularization) and posterior segment diseases (Age Related Macular Degeneration). Tablet 3 shows Some ocular patents based on biodegradable polymers published during last decade.

Table 2. Patents based on biodegradable polymers in ophthalmic drug delivery system

Patent number and inventor	Clinical indication / ophthalmic condition	Formulation type	Polymer / excipient used	Drug / biologic	Comments	Ref.
US8956655B2 Robert et al.	Glaucoma, Uveitis, Macular degeneart-ion, macular edema	Implant	PLGA/PEG, fatty-alcohols, or cholesterol	Beta-blocker, Anti-inflamm-atory, Anti-Angiogenesis, Anti-VEGF	Road-shaped implant containing a plurality of segments. Each of the segments comprises an active agent and a biodegradable polymer with different drug release characteristics (3 to 6 months post-implantation).	(Robert T. Lyons et al. 2015)
US20140035184 A1 Nivaggioli, et al.	Uveitis,	Implant	PLGA	Anti-inflammatory Anti-VEGF	The implant includes an active agent mixed with or dispersed within a range of PLGA (each polymer has different release characteristics). The implant delivers a prolonged release of an active agent at a therapeutically effective amount between 1 to 12 months.	(Thierry Nivaggioli, et al. 2014)
US20170000644 A1 Cuevas	Posterior capsular opacification (PCO)	Implant	PLA, PLGA, PCL/PLA, PLA/PEO	Antibiotic, anti-glaucoma, antiallergenic agents	The device consists of biocompatible, biodegradable material in the form of a flexible membrane containing an active agent which implanted between an intraocular lens and the surface of the posterior capsule of the eye. Thus, it inhibits movement of residual lens epithelial cells after cataract surgery by providing structural or pharmaceutical barriers to reduce PCO of the eye.	(Kevin H. Cuevas 2017)

US8715713B2 Ghebremeskel and Spada.	Glaucoma	Implant	PLGA	Latanoprost	The device is an intraocular implant shaped as disc or a rolled thin film containing latanoprost incorporated in a PLGA matrix. The rolled film unfurls into its original shape when it implants into an eye and releases latanoprost continuously for at least 30 days.	(Alazar N. Ghebremeskel, and Spada, 2014)
US20130295157 A1 Shiah et al.	uveitis, vascular occlusion, or macular edema.	Implant	PLGA	Anti-inflammatory agent	The implant is designed from a mixture of hydrophilic end and hydrophobic end PLGA. The device delivers active agents into an ocular region without a high burst release over various time periods (from less than one month to 6 months)	(Shiah et al. 2015)
US20130172268 A1 Jarrett et al.	Ocular inflammation.	Hydrogel plug	Polyethylene glycol (PEG).	Anti-inflammatory agent	Punctal plug for blocking or reducing tear flow through a punctum or canaliculus of an eye and delivering a drug to the eye. It formed of a dehydrated covalently cross-linked hydrophilic polymer that absorbs water to form a hydrolytically biodegradable hydrogel and releases the drug over at least six days.	(Jarrett; Peter et al. 2013)

US20160199297 A1 Edelman et al.	Diabetic macular edema, acute macular neuroretinopathy, Behcet's disease	Implant	PLA, PLGA, PCL	tyrosine kinase inhibitor (TKI)	The invention is a biodegradable intravitreal implant comprising a tyrosine kinase inhibitor (TKI) and a biodegradable polymer. It is capable of delivering therapeutic amounts of a TKI for 30 days to about a year.	(Edelman; Jeffrey L et al. 2016)
US20140314868 A1 Robinson et al.	Glaucoma	Implant	PLGA, PLA /PEG, hyaluronic acid	Latanoprost, Bimatoprost and Travoprost	The device is in the form of an implant, or a plurality of microspheres can release the therapeutic agent between two and six months.	(Robinson; Michael Whitcup; Scott R et al. 2014)
US20170071953 A1 Liu et al.	Glaucoma, neovas-cularization and inflammation of the eye.	Microsphere Aqueous liquid or gel	PLA, PLGA, PEG /hyaluronic acid, sodium hyaluronate, a hydroxyethyl cellulose (HEC), a ca-rboxymethylcellulo-se (CMC), a hydroxypropylmethyl cellulose (HPMC), a polyvinylproline (PVP).	Prostamide, prostaglandin, α-2 agonists, a TKI, SAIDs and NSAIDs.	Drug delivery system for sustained intraocular release comprising biodegradable microspheres sized (40- 200 μm) and carrier aqueous liquid or gel. Also, it can be used for intracameral administration. It can effectively retain in the anterior chamber of the eye for an extended period (1-12 months) without producing hyperemia.	(Liu; Hui et al. 2017)
US20190336441 A1 Whitcup et al	Dry AMD	Microsphere in a gel.	PLA, PLGA/ HA, HEC	Anti-VEGF (Bevacizumab)	The invention is a sustained release drug delivery system suitable for intraocular use, including bevacizumab-PLGA microspheres in the hyaluronic acid (cross-linked or non-crosslinked). The dug can be released into the vitreous over a 1 to 6 months period.	(Whitcup; Scott M. et al. 2019)

Conclusion

Biodegradability and biocompatibility are the main advantages of biodegradable materials over biostable polymers. Furthermore, physical, and chemical properties of these polymers are suitable for manufacturing a broad range of medical devices, including sutures, wound healing, screws, and bone fixation devices. Biodegradable polymeric materials contribute an indispensable role in a targeted and controlled drug delivery system, especially in the field of ophthalmology. Combination of these polymers leads to formulating a wide range of ocular drug delivery systems, with desired properties, including implants, nano/micro-particles, inserts, contact lenses, scaffolds, and stimuli sensitive hydrogels. All these systems are strategies to overcome the challenges faced by ocular drug delivery. However, further improvements in processing techniques are needed to achieve effective and highly patient compliant therapies, especially with computer-aided technology. For example, computer-aided design for drug delivery systems can optimise drug delivery by fabricating deferent particles, scaffolds, and medical devices with extremely complex architectures that can mimic their biological counterparts.

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