Expert Opinion

Drug delivery from ocular implants

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Developing an intraocular drug delivery system (DDS) is urgently needed because most vitreoretinal diseases are refractory to conventional pharmacological approaches; eye drops and systemically administered drugs cannot deliver therapeutic drug concentrations into vitreoretinal tissue. Intraocular DDSs address this problem. Intraocular sustained-drug release via implantable devices or injectable microparticles has been investigated to treat vitreoretinal diseases. A nonbiodegradable implant was first used in 1996 for cytomegalovirus retinitis secondary to the acquired immunodeficiency syndrome. Biodegradable implants, composed of hydrophilic or hydrophobic polymers, in the shape of rods, plugs, discs or sheets have been investigated. An injectable rod is presently being assessed in a Phase III trial to treat macular oedema secondary to diabetic retinopathy or branch-retinal vein occlusion. Intraocular DDSs using a biodegradable implant may soon be successfully used to treat serious intraocular disorders.

Keywords: controlled release, drug delivery system, implants, sustained release, vitreoretinal diseases

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1. Introduction

The eye has a very specific environment that ensures visual function. First, transparency of the inner media (i.e., the cornea, the anterior chamber, the lens and the vitreous cavity) allows direct observation of the retina, vitreous surgery using a microscope as well as the assessment of experiments and treatments. Ironically, the transparency of the ocular media makes designing a potential treatment difficult because these must preserve or allow recovery of clear media. Second, the eye involves the neurosensory retina and, therefore, treatments should not impair the physiological functions of the retina and the optic nerve, or the mechanical structure. Third, critical barriers that limit the ability of drugs to reach the vitreoretinal tissue include: the cornea; the sclera; the blood–aqueous barrier that is composed of ciliary nonpigmented epithelium and iridal vascular endothelium; the outer and inner blood–retinal barriers that are formed by the retinal pigment epithelium and retinal vascular endothelium, respectively; and the internal limiting membrane on the vitreoretinal interface (Figure 1) [1-3].

Eye drops and ointments can be applied easily to treat ocular diseases; however, drug absorption is inhibited by the cornea and the sclera, uveal blood flow to recover the extravascular fluid, and the continuous turnover of tears [4]. Consequently, eye drops must be instilled frequently or at high concentrations to achieve therapeutic concentrations, even in the anterior segment. It is much harder to deliver drugs to the posterior segment because of the longer diffusional distance and counterdirectional, intraocular convection from the ciliary body to the Schlemm's canal. Systemic administration is the ideal treatment modality; however, most vitreoretinal diseases are refractory to systemic treatment due to the blood–aqueous and blood–retinal barriers. Therefore, high drug dosages that are used to achieve efficacy unfortunately frequently cause side effects in other tissues.

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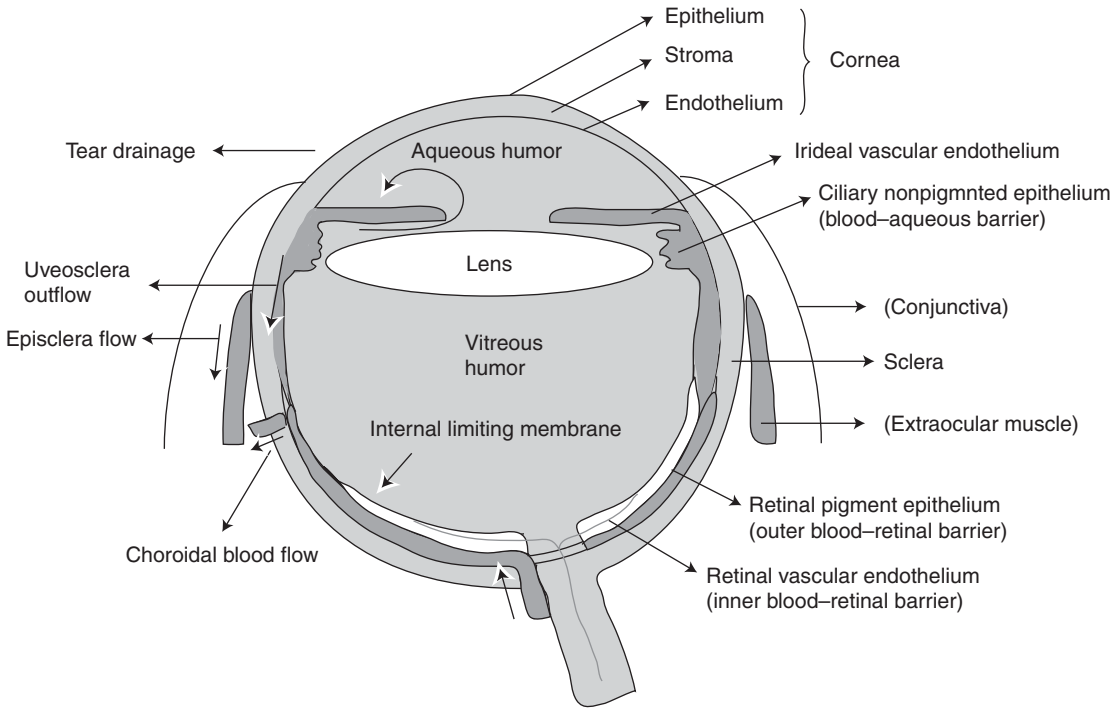

Figure 1. Barriers to intraocular drug delivery. The cornea, tear drainage, episcleral blood flow and intraocular convection limit the influx of locally administered drugs into the posterior segment of the eye. Macromolecules as large as antibodies are unlikely to penetrate the internal limiting membrane. A systemic approach should overcome the problem of the blood–retinal barriers.

Considering these problems, most recent therapies have been administered by periocular or intraocular injection in order to treat, for example, choroidal neovascularisation (CNV). In the vitreous cavity, however, the half-lifes of most drugs with a low molecular weight are as short as several hours [5]. Therefore, repeated intravitreal injections may be required, often with complications such as the development of cataracts, vitreous haemorrhage, endophthalmitis and retinal detachment [6-9]. A controlled-release system or enhanced drug penetration through the ocular barriers may overcome the problems associated with topical administration. This review will focus on controlled-release systems in ocular implants.

2. Ocular implants

So far, the ocular controlled-release systems that are commercially available include Ocusert® Pilo (controlled-release pilocarpine; Allergan), Prosert® (IOL Tech), Lacrisert® (hydroxypropyl cellulose-ocular system; Merck), Vitrasert® (sterile intravitreal implant with ganciclovir; Bausch & Lomb), and Retisert® (fluocinolone-intravitreal implant; Bausch & Lomb) (Figure 2). Ocusert Pilo inserts, which became commercially available in 1974, contain a core reservoir consisting of pilocarpine and alginic acid. The core is surrounded by a hydrophobic ethylene vinyl acetate (EVA)-copolymer membrane that controls diffusion of pilocarpine from the Ocusert Pilo insert into the eye. Pilocarpine can decrease the intraocular pressure in patients with glaucoma. Although commonly used eye drops should be administered four times/day, the insert releases pilocarpine for one week after it is placed in contact with the conjunctival surfaces. This type of insert could be easily removed if adverse effects develop. For intraocular controlled-release systems, the implants should be placed into the sub-Tenon's intrascleral, or intravitreal space. In this case, the mechanical effect of the remaining matrix and the pharmacological effect of the drug should be considered.

Intraocular controlled (sustained)-release systems have been studied enthusiastically to treat cytomegalovirus (CMV) retinitis, which affects 15 – 40% of patients with AIDS. CMV retinitis rapidly progresses and destroys the retinal tissue, which can lead to retinal detachment (occurring in 15 – 29% of patients with AIDS-related CMV retinitis), as well as permanent loss of vision. Intravenous administration of ganciclovir or foscarnet initially effectively delayed the progression of this serious ocular disease. However, ganciclovir often causes myelosuppression, and foscarnet can cause kidney dysfunction, which may result in the discontinuation of treatment [10-12]. When intravitreal

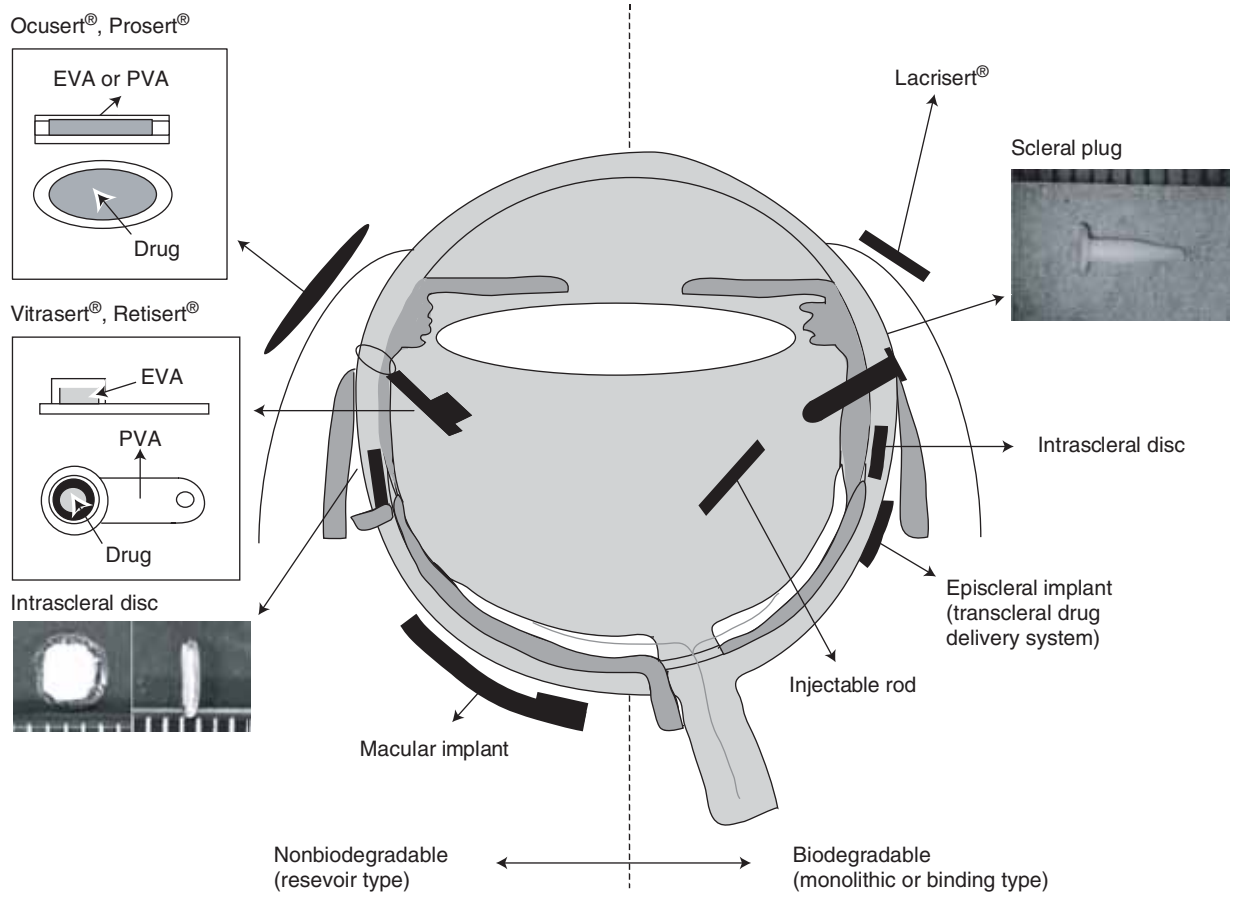

Figure 2. Controlled-release systems. Ocusert®, Prosert®, Vitrasert® and Retisert® are clinically available, nonbiodegradable (reservoir-type) devices. Lacrisert® is a biodegradable insert. Ocusert, Prosert and Lacrisert are inserted into the conjunctival sac. Vitrasert and Retisert are implanted transclerally, suspended at the pars plana. Implants can be implanted into the episcleral or intrascleral space, at the sclera, or into the vitreous cavity in various shapes, such as a disc, a sheet, a plug, a rod and a pellet.
EVA: Ethylene vinyl acetate; PVA: Poly(vinyl alcohol).

injections of ganciclovir proved to be effective [9], many researchers began to develop new intraocular controlled-release systems to improve drug compliance. Thus, liposomal formulations containing drugs [13], microspheres composed of biodegradable polymers [14], and implants made of nonbiodegradable [15] or biodegradable [16,17] polymers have been developed. Among those, a nonbiodegradable device was first introduced commercially in 1996 because of the stable, safe drug-release profile and the biocompatibility of the device [18]. The Vitrasert implant contains a ganciclovir tablet coated with polyvinyl alcohol (PVA) and EVA polymers. Research is continuing on biodegradable implants to determine their clinical application.

The structures of polymeric devices for controlled, sustained release (as shown in Figure 2) are classified into:

- the monolithic type, which is comprised of a homogeneous mixture of drugs and polymers,
- the binding type, in which a polymer hydrogel binds drugs through chemical or ionic bonds,
- the reservoir type, in which drugs are stored within an outer shell of polymers.

Polymers available as a matrix are either biodegradable or nonbiodegradable, and hydrophobic or hydrophilic. Biodegradable polymers gradually change into a soluble form through enzymatic or nonenzymatic reactions in the body, whereas nonbiodegradable polymers are not metabolised and are not eroded in the body. Both materials can assume various forms: i) injectable solutions, sol that can gel, or a suspension of micelles, lipid emulsions (microspheres), liposomes, micro(nano)spheres, or micro(nano)capsules; or ii) an implantable device in the form of a sheet, pellet, disc, rod, or plug (Figure 2).

Since the late 1990s, intravitreal injection of solid triamcinolone acetonide enables sustained drug release, reduces postoperative complications in eyes with proliferative vitreoretinopathy (PVR), and effectively treats macular oedema. Temporal impairment of the clear-ocular media resulting from

the intravitreal injection was not serious. This introduced a new concept in the field of drug delivery systems (DDSs) that hydrophobic drugs with no severe local toxicity involving corticosteroids do not need a polymer matrix to achieve controlled release [19]. Nevertheless, it would be advantageous to be able to control the release rate and duration of drug, and remove ocular implants easily when needed; whereas it would be difficult to collect all of a drug that had been injected into a suspension or as microparticles. In addition, evidence that large molecules could penetrate the sclera led to the concept of the transcleral DDS. Thus, devices can be implanted into the peribulbar and intrascleral spaces, in the vitreous cavity, and at the pars plana (Figure 2). To determine the optimal route and method for a patient, many factors should be considered, including drug water solubility, physicochemical properties, efficacy and toxicity, the half-life, required duration of release and concentrations, and the anatomy and the pathology of the targeted tissues.

3. Nonbiodegradable implants

Most of the clinically available ocular implants are reservoir-type devices comprised of the drug and coated with nonbiodegradable polymers of EVA, PVA, or both, as exemplified by Vitrasert and Retisert (Figure 2) [15-18]. PVA, a permeable polymer, not only acts as the framework of the device but also regulates the rate of ganciclovir permeation. EVA or silicone laminate, an impermeable polymer, limits the practical surface area of the device through which the drug can be released. A structure designed using both polymers enables well-controlled (zero-ordered) sustained drug release, dependent on the nature and thickness of the polymer membrane surrounding a drug core. The nonbiodegradable polymer device has no initial adverse burst of the drug, which is superior to that of the biodegradable polymer (Figure 3A). Vitrasert, however, is relatively large and requires the creation of a 4- to 5-mm sclerotomy at the pars plana for implantation. In addition, because the device is nonbiodegradable, the empty device must be removed within 5 – 8 months to implant another or in complicated cases (e.g., severe inflammation or retinal detachment related to the implant). The complications related to the implantation of this device, which occurred in 13 of 110 (12%) eyes after implantation, are vitreous haemorrhage, rhegmatogenous retinal detachment, endophthalmitis, and cystoid macular oedema with epiretinal membrane [20]. These problems must be overcome because postoperative complications may cause visual acuity loss despite treatment. Okabe and colleagues developed an intrascleral implant composed of PVA and EVA containing betamethasone in a disc (4 mg in weight, 1 mm thick, 4 mm in diameter; Figure 2) [21]. The disc released betamethasone at a therapeutic level over 4 weeks without adverse drug bursts (Figure 3A). Because intrascleral implantation does not require perforation of the eye wall, this implant may reduce complications after implantation. In addition, Kato and colleagues showed the feasibility of a macular implant of PVA and EVA for the transcleral DDS to target the macula [22]. This implant has a similar shape to a macular-buckling device used to treat retinal detachment secondary to macular hole.

The treatment of CMV retinitis extended knowledge on the biocompatibility of intraocular implants. Currently, the same type of implant containing dexamethasone, fluocinolone acetonide, or ciclosporin is being tested to treat severe uveitis [23-26]. Retisert containing fluocinolone was approved by the FDA in April 2005 for the treatment of chronic noninfectious uveitis. A total of 36 eyes with noninfectious posterior uveitis, which had had an average of 2.5 episodes of recurrence annually before implantation, had no recurrences for the first 2 years after implantation of a fluocinolone acetonide implant. In addition, the sustained release of triamcinolone and 5-fluorouracil (5-FU) proved to be feasible to treat experimental PVR [27]. However, the sustained release of steroids, such as fluocinolone acetonide and triamcinolone acetonide often causes secondary glaucoma and cataract [26], partly because steroids may have a variety of biological effects on any types of cells, and the effective doses may be at, or close to, the thresholds that cause side effects.

4. Biodegradable implants

Biodegradable implants are generally categorised in the monolithic or binding type. Formulation of these types of implants makes it more difficult to achieve optimal drug release than the reservoir type of nonbiodegradable implants. However, biodegradable implants do not need to be removed. Many synthesised polymers are hydrophobic, whereas biopolymers such as gelatin, chitosan and hyaluronic acid are often hydrophilic. The monolithic type of implant is made by solidifying a homogeneous mixture of hydrophobic polymers and drugs. The implant can achieve a zero-ordered release of drug, accompanying bulk or surface erosion of polymers. The procedure to produce the implant involves a heating and drying process. Therefore, drugs that easily degrade during these steps, such as biologically active proteins, are unsuitable for inclusion in such implants. However, the binding type of implant is suitable for delivering biologically active proteins, and consists of crosslinked-hydrophilic polymers that release drugs bound through a chemical bond or a polyion complex, following enzymatic hydrolysis of the inter- and intramolecular bonding of polymers.

4.1. Hydrophobic polymers

Biocompatible synthetic polymers (e.g., absorbable surgical sutures and silicon sponges for retinal-detachment surgery) are available for biomaterials. Representative biodegradable polymers are poly(lactic acid) (PLA), poly(glycolic acid), and their copolymers, poly(lactic-co-glycolic acid) (PLGA). Polymeric chains in these molecules are cleaved by enzymatic or nonenzymatic hydrolysis throughout the matrix. This type of erosion is referred to as bulk erosion, compared with the surface erosion

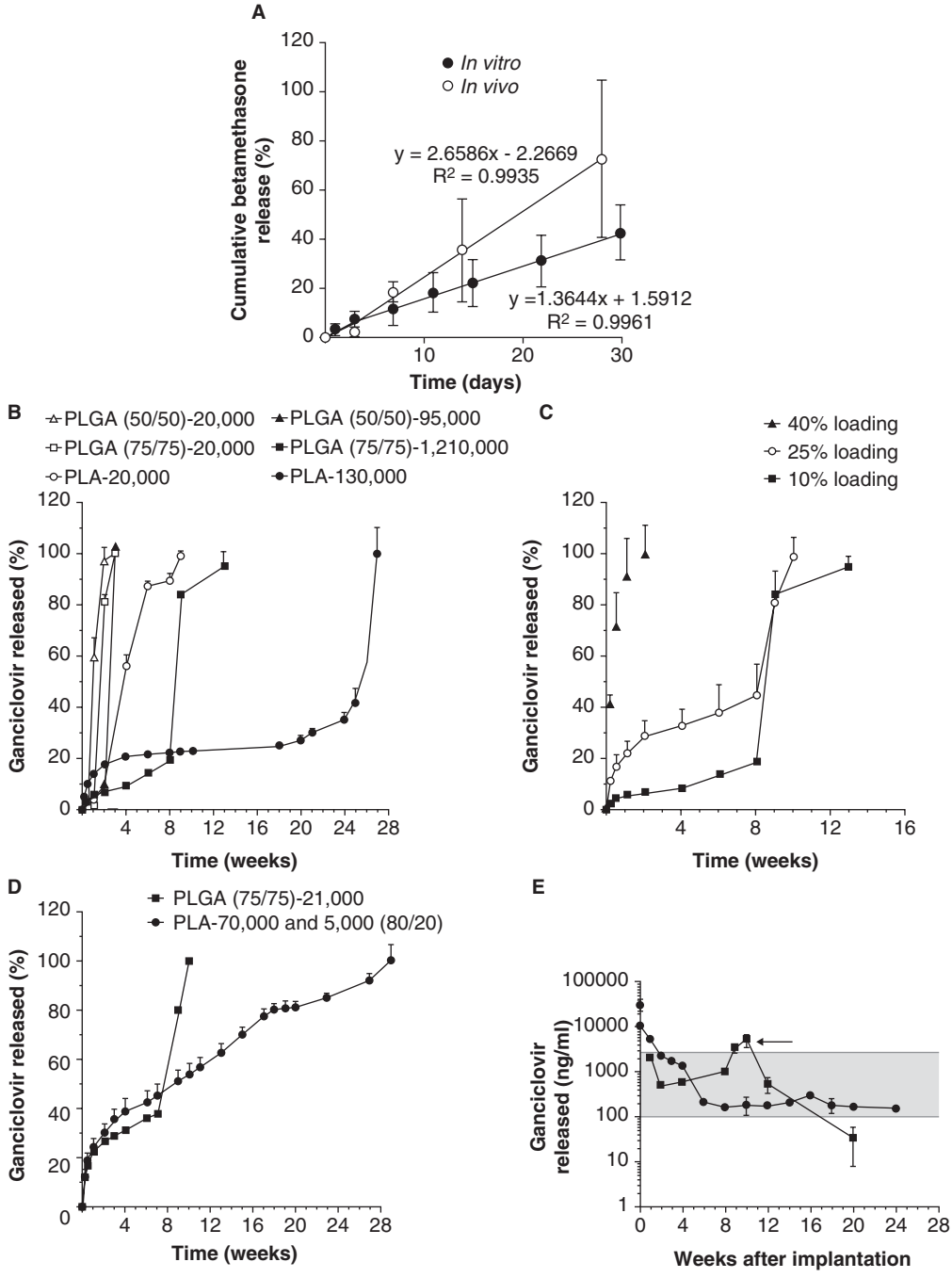

Figure 3. Drug release from nonbiodegradable (A) and biodegradable (B – E) implants. A) *In vivo* and *in vitro* release of betamethasone from a nonbiodegradable disc that can be implanted into the intrascleral pocket. The drug is released in a stable, linear pattern. *In vivo* release tends to be faster than that *in vitro* [21]. **B)** Effects of molecular weight and ratio of LA to GA on drug release (*in vitro*) from PLA or PLGA implants (scleral plugs) with 10% loading of ganciclovir. PLGA(X/Y)-M indicates a PLGA implant with an X/Y ratio of LA/GA and M molecular weight. Drug release has a triphasic pattern. An implant with a larger amount of ganciclovir and/or lower molecular weight tends to degrade and release drugs faster [31]. **C)** Effects of the drug (ganciclovir) content on drug release (*in vitro*) from PLGA (75/25)-121,000 implants (scleral plugs). Overloading of drug causes loss of most of the drug in the initial burst, as the 40% loading implant shows [31]. **D)** Improved release profile of the drug (ganciclovir; *in vitro*) from an implant (scleral plug) composed of a blend of 70- and 5-kDa PLAs in a ratio of 80/20. Compared with the previous implant (composed of PLGA [75/25]-121,000), the modified implant not only increases the release rate, but also prolongs the duration in the diffusive phase without the final burst [37]. **E)** Drug concentrations in the vitreous. The shaded area indicates a 50% effective dose of ganciclovir to inhibit human cytomegalovirus replication. Only the previous implant has the final burst (arrow) [37].
GA: Glycolic acid; LA: Lactic acid; PLA: Poly(lactic acid); PLGA: Poly(lactic-co-glycolic acid).

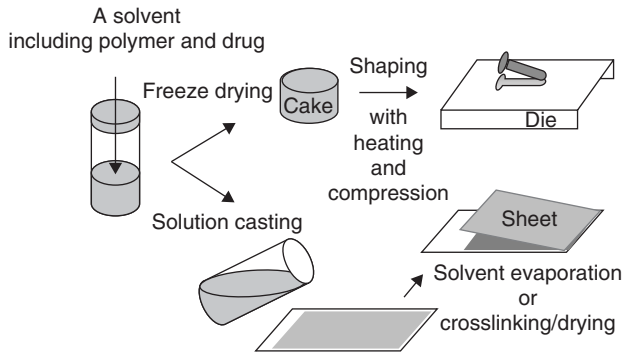

Figure 4. Procedures to process biodegradable implants into various shapes.

in other polymers in which erosion is limited to the matrix surface [28]. The subsequent products lactic and glycolic acids, are finally metabolised through the Krebs cycle to carbon dioxide and water. For controlled release, these polymers are suitable for implantable devices or injectable micro(nano)spheres [29].

Biodegradable polymers can be formed relatively easily into various shapes, including rods, plugs, pellets, discs and sheets (Figure 2). These can be implanted into the anterior chamber, the peribulbar or intrascleral space, the vitreous cavity or through the pars plana. The procedures for making implants involve compression moulding, extrusion, or solution casting (Figure 4) [28]. During moulding, the polymers are heated and compressed into a closed container to form the desired shape. During extrusion, polymers are propelled continuously under pressure along a screw through heated regions, where they are melted, compacted, and finally forced through a die into the final shape. Polymer films can be processed by melt pressing or solution casting. In solution casting, the polymers, with or without drugs, are dissolved in an adequate solvent. The resulting viscous solution is spread on a flat, nonadhesive surface, followed by evaporation of the solvent. The dried film is peeled from the surface. Thus, because procedures often include heating and drying processes, drugs that may degrade during heating and drying, such as biologically active proteins, may be unsuitable.

In general, compressed devices that degrade during bulk erosion have three phases in their drug-release profile: the initial drug burst, the diffusive phase and the final drug burst [30-34]. One difficulty is regulating the initial and final bursts. The initial burst is derived from drugs distributed on and near the surface of the polymer matrix, and depends on the total surface area of the device, the percentage of the loaded drug, as well as the water solubility of the drug. Thus, the large total surface area (such as on microspheres rather than implantable devices), high-drug loading, and hydrophilic drug are likely to result in an intense, initial burst. This burst may be problematic, especially when potent cytotoxic agents such as antimetabolites are used. To overcome this problem, preincubation with saline for several hours before use may reduce the burst, although the implants may become more fragile. In the diffusive phase, the drug is gradually released by the outward diffusion of newly dissolved drug under osmotic pressure and surface erosion of the matrix. This phase is well regulated by the speed of polymer degradation, the total surface area of the device, the percentage of the loaded drug, and the water solubility of the drug. Polymers with a lower molecular weight tend to degrade faster, whereas the degradation speed varies among polymers. Copolymers such as PLGA, especially with a 1:1 ratio of lactic acid to glycolic acid, degrade faster than PLA or poly(glycolic acid) [35]. Bulk erosion accompanies occult hydrolysis of polymers throughout the matrix during the diffusive phase, causing the final burst. A highly compressed matrix, which may be used as an implantable device, may precipitously disintegrate and rapidly release most of the remaining drug load when the inner hydrolysis of the polymers reach a critical point. The higher the ratio of the volume to the total surface area of the matrix, the more intense the burst is. The subsequent increase in the actual area in contact with water then accelerates polymer degradation and drug release. The uncontrollable final burst is undesirable and possibly problematic. This has been the major disadvantage of a controlled-release system using biodegradable polymers compared with nonbiodegradable polymers. In addition, because the total surface area to mass ratio of the implant is much smaller than that of microspheres, devices should be made of polymers with a higher degradation speed, or loaded with more drug to achieve a rate of drug release comparable to that of microspheres. However, the devices composed of polymers with a higher degradation speed subsequently shorten the duration of the diffusive phase (Figure 3B), and the devices loaded with more drug (when overloaded with drugs), release most of the drug in the initial burst because too little polymer cannot preserve the drug in the matrix (Figure 3C) [31].

To overcome these problems, a new device with two polymers of different molecular weights has been designed that achieved an effective release rate of drugs, extended the diffusive phase and eliminated the final burst (Figure 3D and E) [36,37]. In this device, polymers with a higher molecular weight act as the framework, whereas gradual, constant hydrolysis of another lower molecular-weight polymer controls the drug release. This type of biodegradable implant could achieve sustained release comparable to that of nonbiodegradable implants. A scleral plug made of 80% 70-kDa PLA and 20% 5-kDa PLA released ganciclovir without the final burst into the vitreous cavity at concentrations sufficiently effective to treat CMV retinitis for > 200 days [36].

Effective sustained delivery has been achieved using a variety of drugs: antiviral [31,36-39], antifungal [40], antimetabolic [16,41-43], or immunosuppressive agents [44], steroids [43,45,46] or other substances [43] Intravitreal sustained delivery of ganciclovir using a biodegradable scleral plug (8.5 mg in weight, 5 mm long, and 1 mm in diameter; Figure 2) through a 1-mm sclerotomy at the pars plana was effective for treating

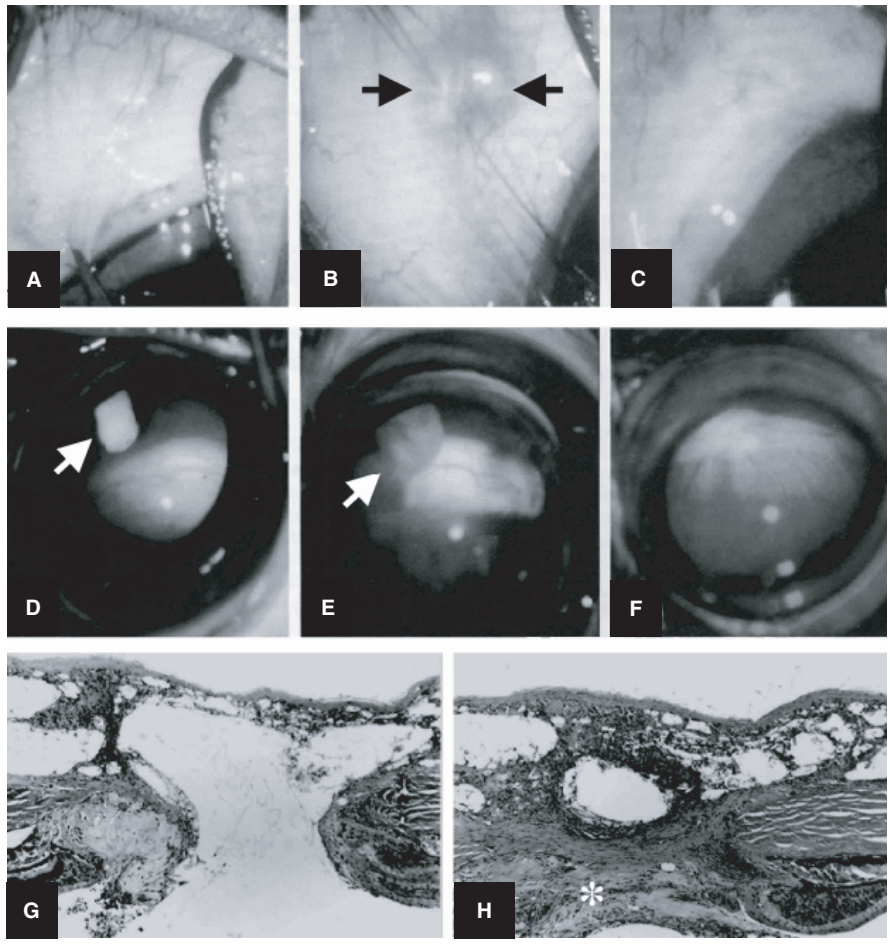

Figure 5. Macroscopic (A – F) and histological (G and H) appearance of an eye implanted with a plug-type biodegradable implant of PLGA [75/25]-121,000 with 25% loading of ganciclovir, 8 (A and D), 12 (B and E) and 20 (C and F) weeks after implantation under the conjunctiva (top) and in the vitreous cavity (bottom) in rabbits. A – F) The implantation site is watertight at all times. Slight injection observed in the conjunctiva at week 12 (arrows in **B**) improved spontaneously when the portion of the implant under the conjunctiva disappeared at week 20 (**C**). The plug in the vitreous cavity (white arrows) is swollen at week 12 (**E**) and thereafter dissolves ophthalmoscopically (**F**) [38]. **G** and **H)** Implantation site of a biodegradable plug 12 (**G**) and 24 (**H**) weeks after implantation in rabbits. **G)** The scleral plug remains. Inflammatory cells infiltrate the matrix pore. **H)** The sclerotomy site (asterisk) is closed with fibrous tissue. The residual matrix of the device is observed in the subconjunctival space [37].
PLGA: Poly(lactic-co-glycolic acid).

experimental CMV retinitis in rabbits [39]. In the treatment of experimental PVR, the PLGA rod (6 mm long, 0.9 mm in diameter) containing 5-FU decreased the incidence of retinal detachment from 89 to 11% without retinal toxicity [42]. Intravitreal 5-FU concentrations were sustained at ≥ 1 µg/ml or higher for 14 days, and then at 0.3 µg/ml for 21 days. Hashizoe *et al.* reported the efficacy of a scleral plug made of 20-kDa PLA containing doxorubicin hydrochloride in experimental PVR in rabbits, and showed that the incidence of retinal detachment decreased from 100 to 64% [41]. The toxicity and biocompatibility of implants have been evaluated by slit-lamp examination, electroretinography and light microscopy [16,17,37,38,40,41,47]. An implant containing ganciclovir gradually swelled, eroded and dissolved several months after implantation (Figure 5A – F) [38]. Slit-lamp biomicroscopy showed no ocular inflammatory reactions. Eyes implanted with a scleral plug containing ganciclovir, doxorubicin hydrochloride or fluconazole had no substantial changes on electroretinograms after the drug was released completely [16,34,38,40,46]. Histology showed no abnormalities in the rabbit-retinal tissue adjacent to the implanted site and the posterior pole [16,37,40,46] (Figure 5G and H).

More recently, these efforts led the PLGA rod with dexamethasone (6.5 mm long, 0.45 mm in diameter; dexamethasone posterior segment DDS [DEX PS DDS®], Allergan CA, USA) to a Phase III clinical trial in patients with macular oedema secondary to diabetic retinopathy and branch retinal vein occlusion. It is innovative that this device is injectable without a surgical incision by use of a special injector and does not disturb the clear media of the eye,

comparable to the case when suspension or microparticles are injected.

Delivery of multiple drugs has also been investigated. Zhou *et al.* developed a multiple drug delivery implant to treat PVR [43]. The PLGA implant (7 mm long, 0.8 mm in diameter) is composed of three cylindrical parts containing 5-fluorouridine, triamcinolone and human recombinant tissue plasminogen activator (tPA). This implant released 5-fluorouridine at the maximal rate of 1 µg/day over 4 weeks and triamcinolone at the rate of 10 – 190 µg/day over 2 weeks. The portion containing tPA was coated with PLGA so that the release of tPA started after 2 days at the rate of 0.2 – 0.5 µg/day for the subsequent 2 weeks, which may minimise the risk of postoperative bleeding. Three scleral plugs are available to close the three sclerotomy ports made during conventional vitreous surgery if implanted as a therapeutic adjunct to this surgery. The scleral plugs provide the opportunity to investigate the feasibility of codelivery of different drugs, or drugs with different release profiles. Codelivery of 5-FU and steroids significantly reduced the incidence of tractional retinal detachment in experimental PVR with a synergistic effect [34]. Yasukawa *et al.* evaluated the effect of implantation of two scleral plugs containing *cis*-hydroxyproline with different release profiles on experimental PVR in rabbits [47]. Combining two types of scleral plugs was the most effective way to inhibit tractional retinal detachment, which suggested that more intricate drug delivery at high doses for the first several days after surgery and at moderate doses for the subsequent weeks could be more effective. In the future, the optimal composition of implants should be determined to maximise the release profiles of drugs designed based on the predicted time course of each disease.

Polyanhydride and poly(ortho ester) are examples of polymers degraded by surface erosion. The commonly used polyanhydride for drug delivery is a copolymer of bis(*p*-carboxyphenoxy) propane and sebacic acid. Polyanhydride implants containing 5-FU, 5-fluorouridine, mitomycin C, toxol or etoposide have been evaluated as adjuncts in glaucoma-filtration surgery [28]. The process of surface erosion is thought to provide more controlled drug release than bulk erosion because drug release is regulated mainly by surface degradation of the polymers, rather than drug diffusion. Recent researches demonstrated that suprachoroidal and intravitreal injection of poly(ortho ester), a bioerodible semisolid polymer were well tolerated, suggesting the potential for drug delivery to the posterior segment [48,49].

Recently, transleral drug delivery has been advocated, based on evidence that drugs administered into the peribulbar space reach the chorioretinal tissue through the sclera. This may increase the availability of biodegradable implants because they may be more advantageous for peribulbar implantation, compared with nonbiodegradable implants that require removal [46]. An intrascleral implant made of 20-kDa PLA in a disc form (7 mg in weight, 0.5 mm thick, 4 mm in diameter; Figure 2) delivered betamethasone phosphate into the vitreous and the retina–choroid at concentrations that suppressed inflammatory reactions for > 8 weeks [46].

For commercial use, the sterilisation process is important. Herrero-Vanrell *et al.* demonstrated that an effective sterilising dose of 2.5 megarad did not produce significant changes on the ganciclovir release-rate behaviour from a PLGA polymer (microspheres), whereas irradiation caused a minimal temperature rise [50].

4.2 Hydrophilic polymers

Biopolymers such as proteins, polysaccharides and nucleic acids are distributed throughout the body. Hydrophilic polymers should have little immunogenicity for clinical use. Materials that are available for the binding-type device with controlled drug release include albumin, gelatin, collagen, chitosan, starch and dextran. These hydrophilic macromolecules, when crosslinked, form a three-dimensional hydrogel, which is permeable to water. The crosslinkages limit the swelling of the matrix in an aqueous environment. In these systems, erosion can occur by intra- or intermolecular hydrolysis of the crosslinked backbone. Therefore, this type of matrix can retain drugs the same as how the binding type of controlled drug release through chemical or ionic bonds. To deliver biologically active proteins, the complicated procedure of chemical binding tends to reduce drug bioactivity. When macromolecules with a number of electrically charged groups form multiple ion bonds with one another, all ion bonds are rarely released simultaneously, resulting in relatively strong binding, which is referred to as a polyion complex (Figure 6) [51,52]. Thus, biodegradable polymers with electrically charged groups can bind these biologically active proteins through a polyion complex or salt crosslinking, and release them through polymer degradation (Figure 6) [51,52]. Biopolymers with this property include albumin, gelatin, collagen, fibrin and hyaluronic acid.

Gelatin is generally purified from tissues with abundant collagen through alkaline or acid processes. In the alkaline process, because the medium is basic, some amide groups ($-CONH_2$) in a collagen molecule undergoing hydrolysis are subsequently transformed into carboxyl groups (-COOH). Thus, the alkaline process generates acidic gelatin with a high density of carboxyl groups. On the other hand, the acid process provides basic gelatin with the isoelectric point (pI) of ~ 9, similar to that of collagen. When the hydrogel of these gelatins is immersed in a solution of inversely charged proteins, protein molecules and the gelatin matrix form a polyion complex. Thus, biologically active proteins susceptible to degradation can be preserved in the matrix without a heating and drying process, and are released gradually, accompanying enzymatic degradation of a crosslinked gelatin hydrogel. The polyion complex may also prevent binding proteins from enzymatic metabolism because basic fibroblast growth factor (bFGF) and other growth factors are preserved and regulated in the extracellular matrix, and

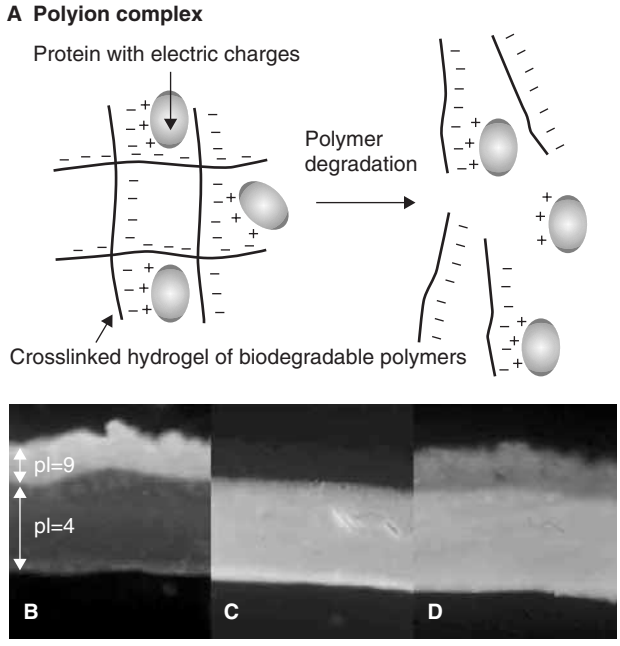

Figure 6. Polyion complex of crosslinked gelatin hydrogel matrix with biologically active proteins [51]**. A)** Biologically active proteins bound to hydrogel through the formation of a polyion complex are released according to the hydrolysis of the backbone of hydrogel. **B – D)** A gelatin hydrogel-bilayer sheet composed of acidic (pI 4.9) and basic (pI 9.0) gelatins is impregnated with the solution involving fluoresceinated acidic (**B**) or basic (**C**) gelatin, or IgG with neutral pI (**D**), which was shown to bind predominantly to the basic or acidic matrix of gelatin or to both matrices, respectively. Thus, neutral proteins are also likely to be preserved in acidic, basic, or both matrices through the formation of a polyion complex.
Ig: Immunoglobulin; pI: Isoelectric charge.

bound with acidic glycosaminoglycan, heparan sulfate, or other proteins [53]. Therefore, a gelatin matrix may be suitable for controlled release of biologically active proteins. Hydrogel can also be formed into injectable microspheres or implantable devices.

Gelatin-hydrogel sheets are fabricated by the solution-casting method (Figure 4). Briefly, immediately after the addition of glutaraldehyde (a crosslinking agent), a solution of 10% gelatin is spread onto a sheet of polypropylene to yield a thin film of gelatin hydrogel. After a crosslinking reaction at 4°C for 14 h in a humidified environment, this film is immersed in 100 mM of glycine solution at 37°C for 1 h to counteract the remaining glutaraldehyde and active intermediate products, washed twice with distilled water and freeze dried. The water content (degradation speed) of this gelatin hydrogel can be modified by adjusting the amount of glutaraldehyde that is used. The dried gelatin-hydrogel film is then dissected into small pieces of optimal size for implantation. Before use, phosphate-buffered saline solution (pH 7.4) with a biologically active protein, such as bFGF, is impregnated into this dried film and incubated for 1 h to allow the formation of a polyion complex of the gelatin hydrogel and proteins.

Intracorneal implantation of a hydrogel sheet of acidic gelatin (pI 4.9) binding bFGF induced rabbit corneal neovascularisation (Figure 7A – D) [54]. The 1 × 2 mm sheet was implanted into an intrastromal-lamellar pocket in rabbit corneas. The corneal epithelium healed within a day after implantation. New vessels continued progressing towards the implanted sheet for 14 days in eyes implanted with the sheet, whereas bFGF alone or the gelatin sheet without bFGF did not induce revascularisation. This corneal neovascularisation was reproducible, and dependent on the dose of bFGF and the amount of glutaraldehyde used for crosslinking (Figure 7E and F). The inflammatory reaction was minimal at the implantation site. Recognised as a degraded extracellular matrix by keratocytes, the implanted gelatin hydrogel may undergo enzymatic hydrolysis and subsequently release bFGF. This model could be useful to elucidate the mechanism of angiogenesis or to test new antiangiogenic compounds. This sheet may be available for intrascleral or peribulbar implantation for transcleral–intraocular delivery of biologically active proteins.

5. Target diseases

Potent target diseases are:

- diseases in which frequent local administration of the drug may be effective (e.g., CMV retinitis);
- diseases that originally required vitreoretinal surgery (e.g., PVR, diabetic retinopathy and CNV);
- chronic diseases that respond to pharmacological therapies (e.g., uveitis and CNV);
- chronic diseases with no satisfactory therapies (e.g., macular oedema, CNV, geographical atrophy in age-related macular degeneration [ARMD] and retinitis pigmentosa).

In the treatment of CNV in ARMD, many candidate drugs including anecortave acetate (steroid), pegaptanib sodium (VEGF aptamer) and ranibizumab (anti-VEGF antibody fragment) require repeated topical administration in clinical trials. To improve efficacy and decrease the incidence of complications, ocular implantation of a sustained-release system may be useful.

6. Conclusions

Although Ocusert Pilo, the first product for ocular DDS, became commercially available in 1974, it has been < 10 years since Vitrasert, the first intraocular DDS, entered the market. Many treatment modalities have been tested to treat ARMD, including surgery, laser application, radiation therapy and medications, but none has had striking efficacy. Attention is again focused on the pharmacological approach because preventing progression of neurodegenerative disorders seems to be more practical for preserving vision than treatment in the advanced stages, and the pharmacological approach may be feasible for the early stage and in multiple trials. However,

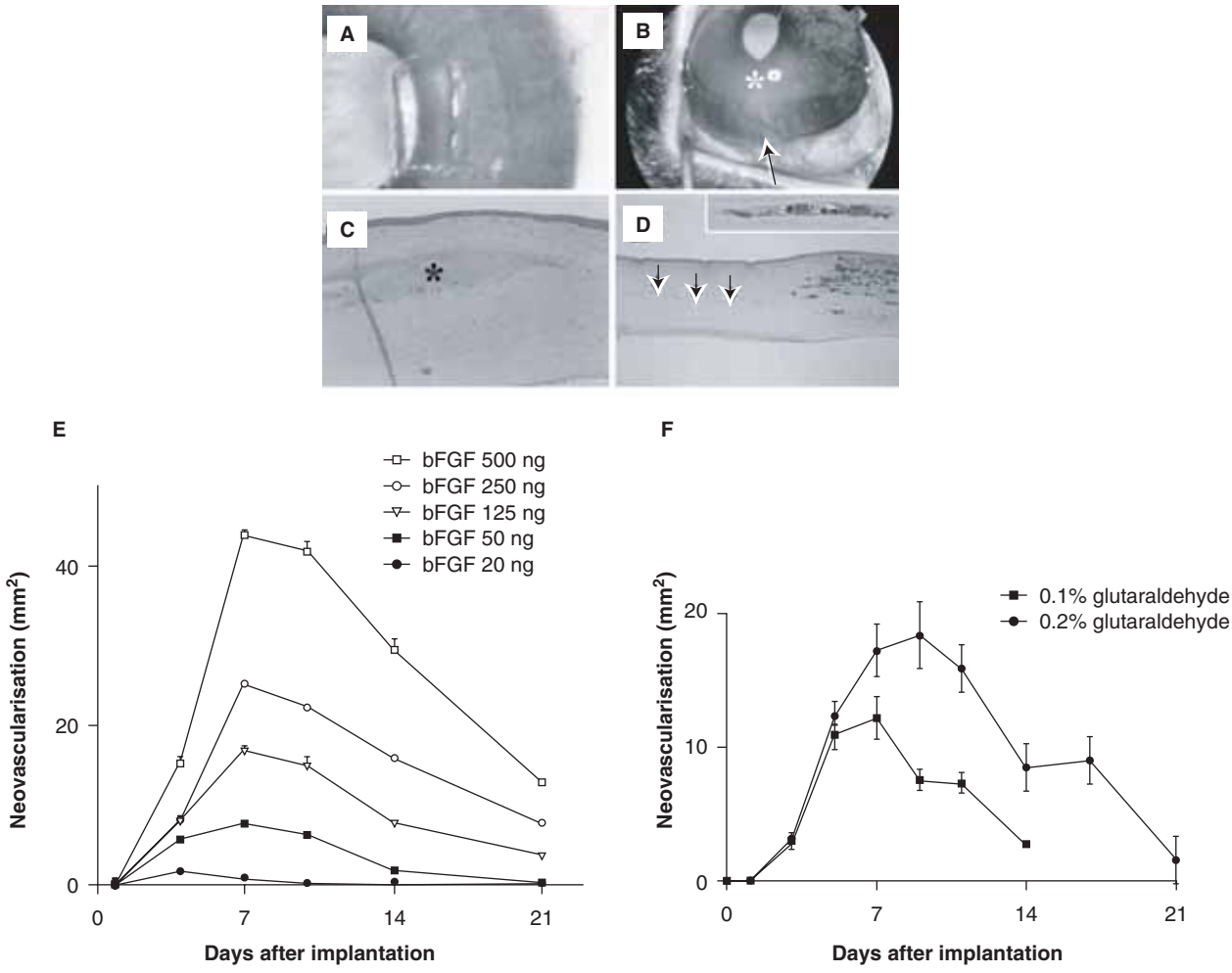

Figure 7. Macroscopic (A and B) and histological (C and D) appearance of a bFGF-impregnated gelatin hydrogel sheet (1 × 2 mm) implanted in a rabbit cornea (A and C) and induced-corneal neovascularisation (B and D). New vessels (arrow in **B**) are sprouting and extend toward the area of implantation (asterisk in **B**). The hydrogel sheet (asterisk in **C**) observed in the intracorneal space on day 1 has degraded with a minimal inflammatory reaction on day 7 (arrows in **D**). Inset in **D** shows new vessels in the cornea [54]. Effect of the dose of bFGF (**E**) and the density of crosslinks of gelatin hydrogel (**F**) on corneal neovascularisation [51]. **E)** The angiogenic response is dose dependent. **F)** Highly crosslinked hydrogel exhibits more sustained release of bFGF; the peak of the angiogenic response shifts to the right. This release profile may be affected by the kind of tissue being implanted and the volume of hydrogel.
bFGF: Basic fibroblastic growth factor.

potent agents are likely to face the same limitations. In the drug market, the concept of the DDS has been applied to some extent to ≥ 10% of commercially available drugs, and DDSs are becoming increasingly essential in the fields of genetics, photochemistry, surgical therapies, regenerative medicine and pharmaceuticals. Using a DDS may achieve a breakthrough in the development of more successful treatment modalities for ocular diseases.

7. Expert opinion

It is important to develop a new substance to treat challenging vitreoretinal diseases. Regarding CNV, many drugs have been investigated *in vitro*, *in vivo* and in clinical trials. Unfortunately, most drugs did not have striking efficacy compared with the photodynamic therapy using verteporfin, a representative non-invasive therapy. Even sub-Tenon's injection of drugs is invasive and, therefore, needs to demonstrate therapeutic efficacy that is superior to that of photodynamic therapy. Most researchers and pharmacies simply try to discover other potent compounds with a sufficient therapeutic effect. However, if there was an inevitable critical limitation to conventional topical- or systemic-drug administration, upcoming new drugs would have the same disappointing results. On the other hand, the development of DDSs may make such drugs, which have once been given up for clinical use, feasible by increasing efficacy and decreasing

side effects. Thus, research on DDSs may be as important as that done to develop a new drug. The controlled release is provided by microparticles (such as microspheres, micelles, or liposomes) and solid forms of lipophilic drugs, as well as biodegradable or nonbiodegradable implants. Implants and injectable agents can be placed in intraocular, intrascleral and sub-Tenon's space. The most efficacious combination of the optimal route, optimal dose and duration of controlled release should be considered carefully according to the pathology and time course of the targeted diseases. Nevertheless, intraocular implants are now nearly ready for clinical use. For development of a new drug, innovators should consider a DDS when seeing a new therapeutic approach in the treatment of difficult vitreoretinal diseases.

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