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Review

Vitreous Substitutes as Drug Release Systems

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Vitreous substitutes are traditionally used to stabilize the retina after vitrectomy. In recent years, various approaches have been developed for using the vitreous substitute not only as a tamponade but also as a drug release system to tackle ocular diseases. This review provides an overview of the requirements for vitreous substitutes and discusses the current clinically applied as well as novel polymer-based vitreous substitutes as drug delivery systems, including their release mechanisms, efficiencies, challenges, and future perspectives.

Introduction

Traditional drug delivery routes include topical administration, subretinal injections, intravitreal injections, and oral medications, all of which result in poor bioavailability of the drug reaching the retinal layers.[1] The vitreous is isolated by the blood–retinal and blood–water barriers, which complicates drug delivery by topical or systemic application.[2] Topically administered drugs either pass immediately into the systemic circulation or are absorbed through the cornea into the anterior chamber, where they are excreted by the trabecular meshwork. Systemic (oral or intravenous) drug administration can overcome some of these barriers, particularly for lyophilic drugs that can bypass the blood–retinal barrier. However, the need for high systemic concentrations leads to systemic side effects.[3,4]

In contrast to topical and systemic administrations, intravitreal injections are able to achieve high drug concentrations in the vitreous and potentially high bioavailability to posterior tissues such as the retina. Intravitreal injection is performed by direct injection of the drug into the vitreous cavity. Intravitreal administration, although invasive, can be safely performed by ophthalmologists using a 27- or 30-gauge needle and is now a routine procedure in clinical settings. The injection volume in humans is usually 50 to 100 µL or less in order to limit the transient increase in intraocular pressure that results from intravitreal injection.[5] The complication profile of intravitreal injections is low. Endophthalmitis (0.018%), retinal detachment (0.013%), and lens damage (0.006%) occur very rarely.[6] However, many disease treatments require repeated injections owing to the short half-life of the agents, which increases the risk of complications; examples of this include anti–vascular endothelial growth factor antibodies and bevacizumab to suppress neovascularization in diabetic retinopathy and age-related macular degeneration. In addition to short half-lives, intravitreal administration of drugs is limited owing to rapid excretion of the drugs. Here, intravitreally delivered drugs are excreted into the systemic circulation either via the anterior route through the trabecular meshwork or the posterior route through the blood–retinal barrier.[3,7] This results in the need to inject therapeutic formulations into the vitreous every 4 to 6 weeks to ensure high efficacy.

The need for multiple intravitreal injections could be reduced or eliminated by using a suitable vitreous substitute that delivers the drug over a long term, consequently promoting patient adherence and comfort.[8,9] Vitreous substitutes are traditionally used to stabilize the retina after vitrectomy. In this review, our focus is on vitreous substitutes designed not only as a tamponade but also as a drug release system to tackle ocular diseases. Therefore, we outline the requirements for vitreous substitutes and discuss both the current clinical standard as well as novel polymer-based vitreous substitutes as drug delivery systems in terms of their release mechanisms, efficiencies, challenges, and future potential.

Vitreous Body and Its Function

The native vitreous is a soft and transparent hydrogel composed of collagen fibers and hyaluronic acid; located between the lens and retina, it occupies 80% of the volume of the eye.[10] The most important functions of the vitreous include mechanical and molecular homeostasis in the eye. Owing to its soft and viscoelastic nature, the vitreous holds the lens and retina in place and protects the eye from physical influences ranging from internal low-frequency mechanical vibrations to external mechanical trauma.[10] In addition, the vitreous plays a role in molecular exchanges with surrounding structures that are necessary for its metabolism and integrity. Examples include establishing and maintaining an oxygen gradient between the lens and retina to protect against oxidative intraocular damage and acting as a natural porous barrier in mass transfer.[11,12] The original native vitreous forms during embryonic eye development, grows with the eye from infancy through adolescence,[13] and liquefies with age.[14] Traditionally, it has been assumed that the vitreous cannot regenerate in vivo after formation during early development. However, preliminary evidence suggests that hydrogel-based vitreous substitutes can be used to promote vitreous reformation.[15]

Vitreous Replacement

Rationale

Replacement of the natural vitreous is generally necessary in the event of two incidents: (1) age-related vitreous liquefaction and (2) surgical removal of the vitreous (vitrectomy) for the treatment of vitreoretinal pathologies such as retinal detachments, proliferative vitreoretinopathy, vitreous hemorrhage, endophthalmitis, or foreign body removal.

With age, human vitreous liquefies as a result of the separation of hyaluronic acid from collagen fibers, leading to the aggregation of collagen fibers and the expulsion of bound water.[16,17] Liquefaction alters the vitreous properties in terms of size, biochemistry, structure, and viscoelasticity[18–21] and is associated with a wide variety of retinal diseases such as posterior vitreous detachment, retinal detachment, and vitreoretinal interface diseases[10,22,23] (Fig. 1). Replacement of the vitreous at advanced stages of liquefaction can both counteract the onset of severe visual impairment owing to retinal detachment and promote its therapy by appropriate tamponade of the retina.

The standard treatment of complicated retinal and vitreous diseases is a vitrectomy, in which the vitreous is removed. After surgical removal, there is no regeneration of the vitreous but rather an accumulation of endogenous aqueous fluid in the vitreous cavity,[15,24,25] which lacks the mechanical and biochemical functions of the human vitreous. A vitrectomy is performed primarily in the setting of advanced proliferative diabetic retinopathy, in the treatment of retinal detachments (rhegmatogenous, exudative, and tractional), and in the event of significant vitre-

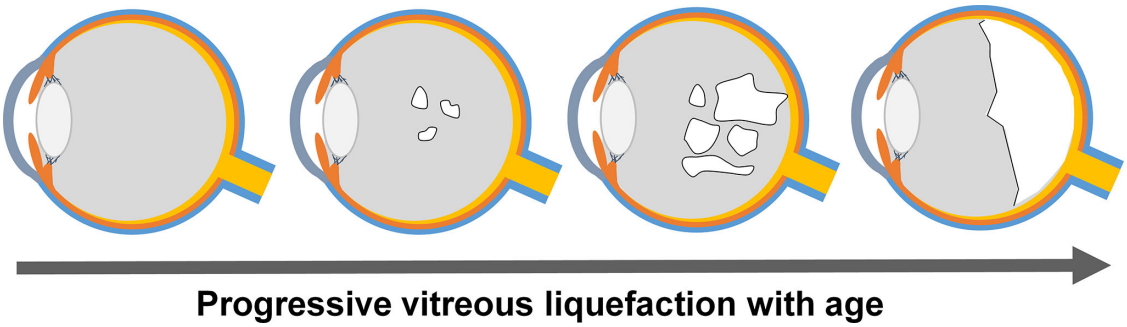

Figure 1. With age, the human vitreous liquefies and forms fluid pockets in the central vitreous, which gradually coalesce, weaken the postoral vitreoretinal adhesion, and may lead to retinal detachment.

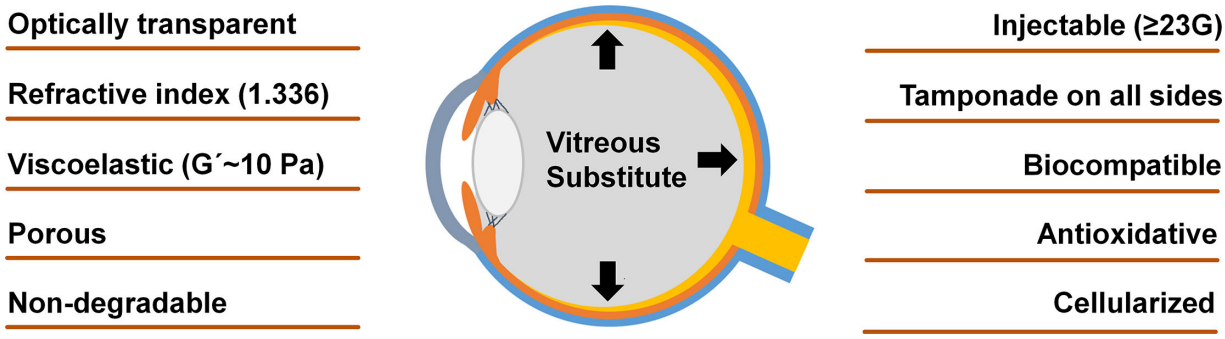

Figure 2. Requirements for ideal vitreous substitutes whose design is based largely on the nature of the juvenile, native vitreous.

ous hemorrhaging. The most common indication for vitrectomy is retinal detachments with retinal holes. Rhegmatogenous retinal detachment develops from an initial tear of the retina, through which fluid then enters the subretinal space, accumulates, and leads to detachment of the retinal pigment epithelial (RPE) layer from the retina.[16,26] Usually, rhegmatogenous retinal detachment is the result of vitreous liquefaction, in which residual vitreous adhesions exert tensile forces on the retina, causing retinal tearing.[13] In addition, high blood glucose levels in individuals with diabetes promote the diffusion of glucose from the blood into the vitreous with subsequent glycation and clumping of collagen fibers, which is accompanied by subsequent traction and tearing of the retina.[13,27] After surgical removal of the vitreous, a suitable replacement is required to ensure homeostasis of the eye. In the following sections, the necessary criteria for vitreous substitutes are provided along with descriptions of the different material systems used for this purpose.

Material Design

To ensure a compatible and functional vitreous replacement, the design of the replacement materials should be based on the properties of a healthy, juvenile vitreous (Fig. 2). The material design mainly includes (1) physicochemical material properties with optical (transparency, light refraction) and mechanical (viscoelasticity, swelling pressure, degradability, injectability) characteristics, porosity, and antioxidative activity and (2) physiological properties with high tolerability as well as the presence of biological stimuli by combining with vitreous cells.

By nature, human vitreous is a fiber-enhanced hydrogel, that is, a gel with a high water content (98–99%) and incorporated collagen fibers. Here, collagen fibers and hyaluronic acid form an inherently noncovalently bonded polymer scaffold. The optical transparency as an essential requirement for vitreous substitute materials is facilitated by the high water content. The transmission of visible light (400–700 nm) to the retina is essential for patient vision as well as for diagnostic and therapeutic purposes such as the visualization of fundus details or laser photocoagulation. At the same time, as in human vitreous, the absorption of low-wavelength radiation is beneficial to protect the retina from toxic UV radiation. A high water content further allows for a similar refractive index (i.e., close to 1.336) and density of natural vitreous bodies. Deviating refractive properties result in a decrease in the patient's visual acuity and may require additional treatment. Consequently, immobilization or intravitreal injection of drugs into vitreous substitutes must ensure preservation of optical properties to avoid limiting the patient's vision.

The viscoelasticity of the vitreous protects the eye from physical influences such as internal low-frequency mechanical vibrations to external mechanical trauma. The viscoelastic properties are generated by the polymeric network structure of the vitreous body consisting of collagen and hyaluronic acid and change with age owing to structural alterations.[21,28] Therefore, an ideal vitreous replacement should be based on the viscoelastic properties of the juvenile and healthy human vitreous (≈10 Pa). Stiffnesses that are orders of magnitude higher than those of the natural vitreous body have been shown to cause mechanical damage to surrounding tissue structures and should thus be avoided.[29]

In addition, the porosity, which arises from the polymeric network structure of collagen and hyaluronic acid in the vitreous body and is relevant for mass transport in the eye, should be mimicked by a suitable vitreous body substitute. In addition to biotransport, the porous nature is also crucial for the release profile of therapeutic agents and should be adapted to the specific application. At the same time, drug release is also influenced by the degradation of the material system. By varying the biodegradation

and resorbability of materials, short-term to long-term vitreous replacement can be realized. Depending on the severity of the retinal detachment, several days to weeks of retention of the replacement material are sufficient for reattachment. After resorption, biodegradation, or surgical removal, the endotamponade is replaced by (endogenous) fluid, which is unable to fully perform the functions of the human vitreous owing to a lack of viscoelasticity and porosity, among other reasons. Based on these factors, an ideal vitreous substitute provides permanent mechanical support and protection of surrounding ocular tissues. For reattachment of the retina, especially for multiple-hole scenarios, tamponading on all sides is desirable. Hydrophobic material systems only possess a tamponade vector in one direction, such as heavy silicone oils (downward) or gases (upward), and form an interface with the hydrophilic vitreous cavity, where growth factors can accumulate and promote proinflammatory processes such as proliferative vitreoretinopathy.[30] In this vein, the mimicry of the natural vitreous can lead to successful vitreous substitutes, which completely fill the cavity as a hydrophilic matrix (hydrogel) and uniformly tamponade all retinal areas via viscosity and swelling pressure.

When used during vitreoretinal surgery, the vitreous substitute material should be easily injectable through a needle ($\geq$23 gauge) without the loss of physical properties to ensure both treatment with minimally invasive methods and functional preservation of the tamponade.

In addition to mimicking the optical and mechanical properties, vitreous substitutes ideally mimic the biochemical functions of the vitreous as well. This includes establishing an oxygen gradient between the retina (high oxygen concentration) and the lens (low oxygen concentration) by integrating antioxidants such as glutathione. Surgical removal of the native vitreous for the treatment of vitreoretinal disease disrupts oxygen homeostasis in the eye, which can result in oxidative damage to the lens, leading to the formation of a cataract. In the future, the additional incorporation of antioxidants such as ascorbic acid and glutathione into vitreous substitutes has the potential to reduce oxidative damage following vitrectomies.

For functional, complete vitreous replacement, it is also essential to extend the material-based state-of-the-art vitreous substitutes to the tissue engineering level by incorporating cells. The integration of vitreous cells is of immense importance, especially for advancing the understanding and therapy of vitreoretinal diseases. To date, vitreal cells have been attributed with a variety of functions, including synthesis of extracellular matrix components, modulation of the immune response in the vitreous, and involvement in various stages of inflammatory processes[31] that may promote long-term vitreous replacement in the future.

Finally, the compatibility of the entire system and of all system components (also in the event of degradation) is an essential requirement for suitable vitreous substitutes. In the case of the induction or promotion of, for example, an undesired immune response, inflammation or cell death of the surrounding ocular tissues must be excluded before drugs are administered to vitreous substitutes.

Aqueous Vitreous Substitutes

During vitrectomy, an aqueous infusion is delivered that might remain in the vitreous cavity after completion of surgery. Isotonic saline, Ringer's solutions, and balanced salt solution (BSS), sometimes supplemented with various additives (BSS Plus), are aqueous substances that have found clinical use as vitreous substitutes.[10] The use of isotonic saline solutions is limited mainly by their tendency to cause corneal edema. In contrast, the use of Ringer's solution slows the onset of corneal edema by providing potassium, calcium, and lactates, but this solution is limited in its effectiveness owing to its deviating osmolarity (279 mOsmol) and pH (5–7.4). Since its introduction in the 1960s, BSS (305 mOsmol, pH = 7.4) has been the most widely accepted intraoperative irrigation solution and aqueous vitreous substitute, mainly because BSS results in less corneal edema and endothelial cell loss after vitrectomy.[32,33] Although aqueous solutions have optical properties (transparency, refractive index), density, and hydrophilicity comparable to the native vitreous, they lack surface tension, viscoelasticity, and porosity, which are necessary for mechanical and biochemical homeostasis in the eye. Moreover, the relatively rapid resorption of aqueous solutions results in short residence times in the vitreous cavity and consequently short-term and insufficient vitreous replacement.

Gases

For more than a century, intraocular gases have been used in vitreoretinal surgery[10,34] and are now an integral part of retinal surgery with vitrectomies. Nowadays, air, sulfur hexafluorides (SF_6), perfluoroethanes (C_2F_6), and perfluoropropanes (C_3F_8) are mainly used in pure form or as mixtures with air. These gases are colorless, odorless, inert, and nontoxic. Pure SF_6, C_2F_6, and C_3F_8 expand within the eye owing to their lower water solubility than nitrogen. The high surface tension and diffusion of other gases from the

Table 1. Expansion Characteristics of Clinically Used Gas Tamponades

Gas	Expansion (Times Original Size)	Time to Maximum Expansion, d	Retention Time, wk	Nonexpansible Concentration, %
Air	1.0	—	1	—
Sulfur hexafluoride (SF_6)	2.0	1–2	1–2	18–20
Perfluoroethane (C_2F_6)	3.3	1.5–2.5	4–5	15–16
Perfluoropropane (C_3F_8)	4.0	3–4	6–8	12–14

bloodstream into these gases allow them to expand and maintain a transient tamponade effect.[8,35,36] However, the buoyancy of the gases enables only unilateral tamponade and results in inconvenient positioning of the patient in a face-down position for several days until the inferior retinal breaks close and the gas has been adsorbed.[37,38] Here, the residence time or resorption of the gas varies according to the specific gas used (Table 1).

As the gas is adsorbed into the bloodstream and is simultaneously exchanged by aqueous humor, it loses its tamponade effect and can only be used in short-term applications. Intraocular gases are further limited by their low densities (SF_6: 0.00617 g/mL; C_3F_8: 0.00817 g/mL[39]), viscoelasticities, porosities, and refractive indices ($\eta \approx 1.00$ for air, SF_6, C_2F_6, and C_3F_8).[40] The latter differ from the refractive properties of the native vitreous (1.336), resulting in reduced visual acuity immediately after surgery until the gas is adsorbed. The complete light reflection of the gases sometimes prevents the physician from examining the back of the eye, preventing postoperative treatment until the gas is absorbed by the body.[39] Additionally, the increase in intraocular pressure during surgery and a few days after injection, gas-induced cataract formation, and corneal endothelial changes have been observed as serious side effects accompanying the use of intraocular gases.[41,42] It is also recommended to avoid air travel and high-altitude locations for several weeks after surgery to prevent the expansion of these gases.[43]

Silicon Oils

Silicone oils belong to the class of polydimethylsiloxanes and have been used as vitreous substitutes since the 1960s. They were approved by the US Food and Drug Administration in 1994. The use of silicone oil as a short- or long-term vitreous substitute is recommended primarily for complex retinal detachments such as tractional retinal detachment, rhegmatogenous retinal detachment, giant retinal tears, and retinal detachment owing to proliferative diabetic retinopathy.[44–46] Silicone oil has been shown to be clinically safe even when left in the intraocular cavity for a period of approximately 6 months.[47] Owing to its high surface tension of 40 mN/m, silicone oil can tamponade the retina and seal retinal tears.[48] However, with a density (0.97 g/mL) lower than water and lower buoyancy relative to gases, inferior retinas are difficult to treat. Silicone oils are transparent, chemically inert, marginally toxic, and available in different viscosities (e.g., 100 and 5000 centistokes). The slightly increased refractive index compared to native vitreous results in poor visual acuity (hyperopia shift of 4–6 diopters)[49] immediately after surgery. As hydrophobic substances, silicone oils cannot completely fill the hydrophilic vitreous cavity.[50] A small amount of fluid at the opposite pole of the buoyancy vector always remains, in which growth factors accumulate and promote proinflammatory processes such as proliferative vitreoretinopathy.[30] The nonmiscibility with water can lead to emulsification, which can cause proliferative vitreoretinopathy, failed retinal detachment, inflammation, secondary glaucoma, and keratopathy.[50,51] Silicone oils are usually removed after 3 to 6 months, once the retina has attached and there is no longer retinal traction,[10] as longer retention times in the eye may be associated with a higher risk of developing cataracts, glaucoma, and corneal decompensation.[46,52,53] Macular edema[54] and increased intraocular pressures (IOPs)[51] are also part of the complication profile of silicone oils. Even the removal of silicone oils is associated with risks such as hypotony and/or the retention of diffuse small emulsion particles on the retina, which can cause chronic inflammation.[55] The combination of silicone oil and partially fluorinated octane results in so-called heavy silicone oils (e.g., Oxane HD, Densiron, and HWS 46-3000), which are heavier than water and can serve as long-term endotamponades for complex retinal detachments with inferior proliferative vitreoretinopathy.[56,57] Heavy silicone oils are less prone to emulsification owing to increased viscosity but can cause cataract formation, intraocular inflammation, and increased IOPs, among other issues.[10,56,58,59]

Perfluorocarbon Liquid

Perfluorocarbon liquids (PFCLs) are synthetic fluorinated hydrocarbons containing carbon–fluorine bonds, originally developed as blood substitutes[60,61] and later investigated as endotamponades in vitreoretinal surgery.[62,63] Since PFCLs, namely perfluoroethers, were first studied as vitreous replacements in rabbit eyes in 1984 by Miyamoto et al.,[64] a wide variety of PFCLs have become established for this purpose, such as perfluorododecalin, perfluoro-tetradecahydrophenantrene, perfluorohexyloctane, and perfluoro-n-octane (C_8F_{18}).[65] PFCLs are used intraoperatively to temporarily flatten the retina during the repair of complex retinal detachments and are substituted for silicone oil or long-term substitutes.[45] Advantageously, PFCLs are colorless, odorless, stable at elevated temperatures, denser than water (ρ = 1.76–2.03 g/mL), and immiscible with water or silicone oil; do not adsorb laser light; and, owing their high interfacial tension, have a reduced risk of permeating under the retina through retinal breaks. However, the high density and hydrophobicity (displacing aqueous components) lead to mechanical damage and nutrient deficiencies of the retina, respectively, and consequently to long-term toxicities.[66] In addition to irreversible retinal cell damage, emulsification at 6 days after surgery has been reported in rabbit experiments.[67] Intraocular inflammatory reactions inducing epiretinal membrane formation and destruction of the intraretinal layer are also part of the complication profile of PFCLs, if they remain in the eye.[67,68] Furthermore, the low viscosity with no elastic components, the lack of porosity, and the refractive index (C_8F_{18}: 1.28), which differs from that of the native vitreous, limit PFCLs to intraoperative application.

Semifluorinated Alkanes

First studied in the early 2000s, semifluorinated alkanes (SFAs) are also known as partially fluorinated alkanes or fluorinated alkanes and consist of short alkyl chains linked at one or both ends with a perfluorocarbon chain. They possess suitable refractive properties and are colorless, inert, and immiscible with water but soluble in PFCLs and silicone oils.[69–71] Therefore, SFAs were initially used as solvents for silicone oils and later as temporary endotamponades for complicated retinal detachments.[72] However, SFAs are currently rarely used clinically because they are prone to causing cataract formation, emulsification, and epiretinal membrane formation as well as toxic and inflammatory reactions if allowed to remain in the eye for extended periods.[69,70] Moreover, like all liquids (and gases), SFAs lack the viscoelastic and porous characteristics of a native vitreous body.

Although effective in promoting retinal reattachment, current clinically used endotamponades radically deviate from human vitreous and consequently lead to a considerable range of complications (Table 2).

Polymer-Based Vitreous Substitutes

In recent years, a paradigm shift has taken place in light of the existing limitations of clinically used tamponades. Instead of hydrophobic materials, hydrogel-based vitreous substitutes have been developed that mimic the natural properties of a healthy human vitreous. Here, hydrogel-based vitreous substitutes have advantages such as high water content, optical transparency, suitable refractive indices and densities, adjustable rheological and porous properties, injectability, biocompatibility, and the capability to tamponade the retina on all sides via viscosity and swelling pressure. In addition to synthetic polymers, biopolymers such as hyaluronic acid,[29,73–78] collagen,[77,79] gellan,[80,81] chitosan,[78,82,83] and alginate[73,83] have been investigated for the preparation of hydrophilic retinal tamponades. However, previous concepts have been limited mainly by intransparency, deviating refractive indices, degradation, or insufficient biocompatibility, especially owing to low substance purity or toxic crosslinking agents, which have collectively hindered the translation of current systems to clinical evaluation.

Non-crosslinked polymer solutions generally lack viscoelasticity and porosity and are mainly limited by degradation, short residence times, and a lack of tamponing effects. As a result, a variety of different crosslinked hydrogel systems, which can be either pregelled or used as in situ gelling matrices, have been investigated using chemical or physical processes. The advantage of pregelled crosslinked hydrogels compared to in situ gelling systems is their ability to remove potentially toxic non-crosslinked monomers and crosslinkers by dialysis prior to intravitreal injection. However, pregelled hydrogels are thought to lose rheological properties owing to injection-induced fragmentation. Physically crosslinked alginate hydrogels, however, recently demonstrated that the required viscoelasticity persisted after the preformed gels were fragmented into a tangle of coiled bead strands through injection with a 23-gauge needle.[73] In situ gelation of uncrosslinked polymers after injection counteracts the issue of shear stress–induced gel fragmentation. However, the major drawbacks of chemically crosslinked in situ hydrogels are the toxic-

Table 2. Advantages and Limitations of Vitreous Substitutes in Clinical Use

Substance	Advantages	Limitations
Physiologic solutions	•Transparent •Desired refractive index •Desired density •Hydrophilic •Resorption/no need for removal	•Lacking viscoelasticity •Lacking porosity •Lacking surface tension •Short residence time •Corneal edema •Endothelial cell loss
Gases	•Colorless •Odorless •Inert •Nontoxic •Expansile •Resorption/no need for removal	•Low refractive index •Lacking viscoelasticity •Lacking porosity •Hydrophobic •Short residence time •Light reflection •Increased intraocular pressure •Cataracts •Corneal endothelial changes •Awkward face-down position after surgery
Silicon oils	•Transparent •Inert •High surface tension •Residence time of up to 6 months	•High refractive index •Lacking viscoelasticity •Lacking porosity •Low density •No tamponade in retinal breaks in inferior part of the eye •Hydrophobic •Emulsification •Incomplete filling •Proliferative vitreoretinopathy •Macular edema •Inflammation •Increased intraocular pressure •Cataracts •Glaucoma •Corneal toxicity •Revision surgery for removal
Perfluorocarbon liquids	•Colorless •Odorless •Moderate surface tension •No adsorption of laser light •Stabilization of the retina during vitrectomy	•Low refractive index •Lacking viscoelasticity •Lacking porosity •High density •Hydrophobic •Emulsification •Retinal cell damage •Inflammation •Long-term toxicity •Limited to intraoperative use
Semifluorinated alkanes	•Colorless •Inert •Desired refractive index •Soluble in silicone oils and perfluorocarbon liquids	•Lacking viscoelasticity •Lacking porosity •Low density •Emulsification •Cataract •Epiretinal membrane formation •Inflammation •Long-term toxicity

Table 3. Promising Polymer-Based Vitreous Substitutes Having the Potential to Enter the Clinical Phase Soon

Polymer	Crosslinking	Preclinical Performance	References
Glycidylmetacrylated hyaluronic acid	•Chemically crosslinked with *N*-vinylpyrrolidone using UV irradiation •Pregelled system	•Transparent, appropriate refractive index (1.3365) and viscoelastiy ($G' = 10–100$ Pa), injectable, porous, degradable •In vitro: biocompatible (using human fibroblastic, RPE, and photoreceptor cell lines, as well as human fetal RPE cells) •In vivo: biocompatible and stable for 12 months in rabbit eyes; no cataract formation	73, 74
Polyvinyl alcohol (modified)	•Crosslinked using modified poly(ethylene glycol) •In situ gelling system	•Transparent, appropriate refractive index (1.3385), relatively stiff ($G' = 1000$ Pa), injectable, porous, and biodegrade within 2 weeks •Non(cyto)toxic, nonirritant, nonpyrogenic, nonmutagenic •In vitro: biocompatible (using mouse fibroblastic and lymphoma cell lines) •In vivo: biocompatible in rabbits, minipigs, and mice for 1 month	141
Poly(ethylene glycol), poly(propylene glycol), and poly(ε-caprolactone)	•Physically crosslinked owing to dehydration of the poly(propylene glycol) components aggregating spontaneously via hydrophobic interactions with increasing temperature (thermogelling) •In situ gelling system	•Transparent, appropriate refractive index (1.339–1.344), relatively stiff ($G' \sim 450$ Pa), injectable, porous, and biodegrade within 3 months •In vivo: biocompatible and functional in rabbits and nonhuman primates for 6 months	15, 135, 142

ity of the monomers and/or crosslinkers remaining in the eye as well as the lack of precise control of the injection time. In contrast, toxic monomers and crosslinking agents can be largely eliminated by using physically crosslinked hydrogels. Physically crosslinked hydrogels can be formed by physical or supramolecular interactions such as hydrogen bonding, hydrophobic associations, and electrostatic (ionic) interactions. The gelation of physically crosslinked hydrogels is generally triggered by relatively mild stimuli such as temperature changes, slight pH changes, shear stress, or the presence of ionic components.[84] Most physically crosslinked systems are designed to be thermoresponsive and gel in situ at a body temperature of 37°C. However, in general, a major disadvantage of physically crosslinked hydrogels is their relatively rapid degradation, as they do not exhibit permanent crosslinking. However, physically crosslinked alginate-based hydrogels have recently been described as having the potential to provide permanent mechanical support and protection to surrounding ocular tissues, as alginates are not naturally degradable in mammals.[73]

A variety of polymeric hydrogels are currently under extensive evaluation in preclinical studies with regard to their optical and mechanical properties as well as their biocompatibility and functionality in vitro and in animal models.[39,85,86] Table 3 lists a selection of promising candidates that have the potential to enter

the clinical phase soon and thus fundamentally revolutionize ablation surgery.

Ocular Drug Delivery Using Vitreous Substitutes

Release Strategies

Traditional drug delivery routes include topical administration, subretinal injections, intravitreal injections, and oral medications, all of which result in poor bioavailability of the drug reaching the retinal layers.[1] In contrast to topical and systemic administrations, intravitreal injections can achieve high drug concentrations in the vitreous and potentially high bioavailability to posterior tissues such as the retina. However, intravitreal injections into the vitreous have limited practical use owing to rapid excretion of the therapeutic agents,[3,7] necessitating injection of the therapeutic formulations every 4 to 6 weeks to ensure high efficacy.

The need for multiple intravitreal injections could be reduced or eliminated by using a suitable vitreous substitute that delivers the drug over the long term, consequently promoting patient adherence and comfort.[8,9] Here, there are requirements for both the delivery system and the drug. Intravitreal drug delivery systems should allow for high drug loading, drug stability, and slowed releases from the matrix to achieve both long-term release and effective doses. The ideal intravitreal drug should (1) have a long half-life in order to reduce the time between administrations and the risk of complications, (2) exhibit no effect on the transparency of the ocular media to avoid impairing vision, and (3) be administered at a therapeutic dose that does not cause toxicity.[7]

In general, solutions, aerosols, or crosslinked polymer systems (hydrogels) are the most commonly investigated release systems for therapeutic agents. While releases from aqueous solutions and aerosols typically occur within hours to days, silicone oils can release drugs for up to several weeks. Typical hydrogels have polymer networks whose mesh sizes are orders of magnitude too large to prevent relatively rapid diffusion-induced efflux of entrapped drugs within a few days. While the rapid efflux of drugs may be acceptable for some applications, many require a much longer duration of release to meet therapeutic requirements. To counteract rapid efflux and allow sustained release, strategies to slow diffusion by physical or chemical means; physically entrap drugs, mainly in micro- or nanoparticles; and transiently or permanently binding therapeutics to the release system have been investigated (Fig. 3).

By reducing the mesh size of the hydrogel, the release could be slowed to 2 months in vitro using bovine serum albumin.[87] As the hydrogel mesh degraded hydrolytically over time, the mesh size increased and the protein could slowly efflux. Furthermore, by introducing charged groups, electrostatic interactions were harnessed to slow the diffusion of drugs from the release system.[88] However, the most promising approach is the entrapment of active agents in microparticles or nanoparticles immobilized in the polymer network of the hydrogel. In doing so,

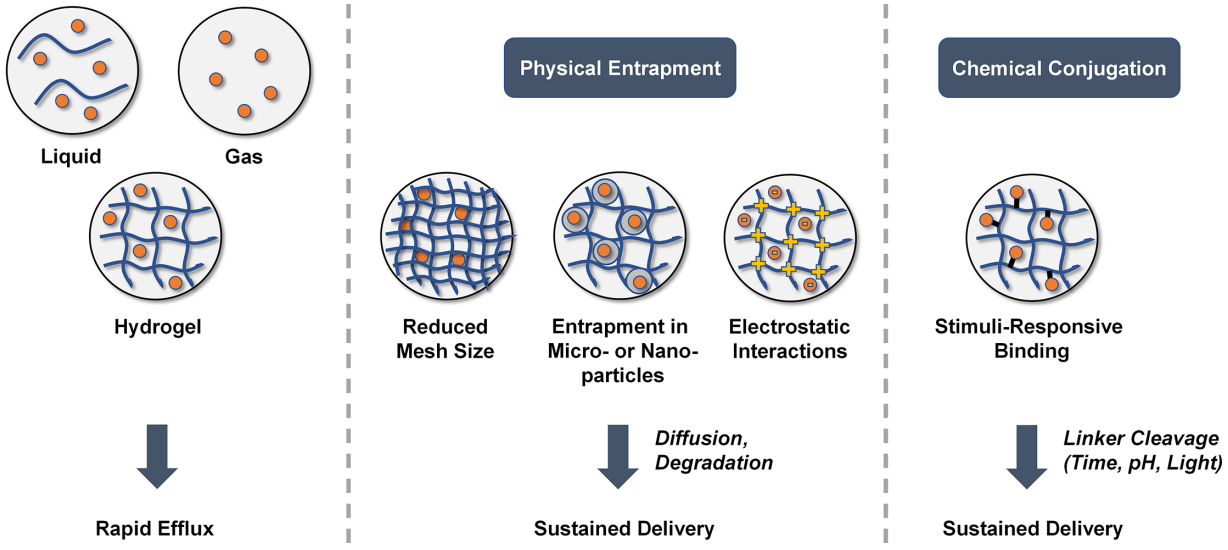

Figure 3. The use of liquids, gases, and hydrogels results in rapid, diffusion-based efflux of the immobilized drugs. Physical entrapment or chemical conjugation of drugs to the polymer network of the hydrogel allows sustained drug release.

the release of the active compound can be tuned depending on the degradability of the particles and/or hydrogel. However, in order to preserve the biological availability and activity of the included drugs, it is important that the immobilization chemistry does not interact with the therapeutic agent. To decouple the release kinetics from the mesh size, swelling, or degradation of the material, reversible chemical conjugations of drugs to the hydrogel backbone have been investigated.[89,90] Specific physiologic stimuli such as pH or temperature are thought to responsively cleave the drug–material bonds. Such stimuli-responsive coupling processes are usually drug specific and must be designed in such a way that the action of the therapeutic agent is not affected.

In the following, different vitreous substitutes will be reviewed in detail as release systems for drugs (Table 4).

Drug Release from BSS and Gases

Aqueous solutions (like BSS) and gases have been investigated for their ability to act as drug carriers and release systems. These studies are limited in scope, and are few owing to the comparatively short residence time of the substances in the vitreous cavity (several days to weeks).

BSS has been used as a drug carrier for homeostasis, pupil dilation, and anti-inflammatory effects,[91] as well as for fluorouracil (5-FU) and low-molecular-weight heparin for the prevention of proliferative vitreoretinopathy (PVR).[92,93] Here, BSS was either given as an intravitreal irrigation solution during vitrectomy or left in the eye as a vitreous substitute at the end of surgery. An advantage is that BSS dissolves hydrophilic drugs well and makes them readily available. However, due to the rapid release of drugs and resorption of aqueous solutions, only treatment scenarios requiring short-term drug administration in the range of hours to several days are feasible. The limited mechanical support also has made aqueous solutions less relevant as endotamponades for complicated retinal detachments.

Aerosolization of drugs or nanoparticles allows the administration of pharmacologically active substances in the vitreous cavity after vitrectomy in the form of drug-loaded gases. Using loaded gas endotamponades, the administration of antimetabolites for the modulation of proliferative vitreoretinopathy, antimicrobial agents for endophthalmitis, antiangiogenic compounds for vasoproliferative disorders, and corticosteroids has been targeted.[94] Zhang et al.[94] pioneered the use of aerosolized sodium fluorescein particles (407 nm) as a model intraocular drug at a concentration of 12 ng/mL administered intravitreally in pigs. Aerosol can be delivered either by continuous flow with entry through the primary sclerotomy and exit through the secondary sclerotomy or by simply filling the vitreous cavity.[94,95] Drug release from the gas occurs primarily via diffusion for smaller particles and sedimentation for larger particles.[95] In general, aerosol particle size, delivery mode, and exposure time are important parameters for drug release from gases. In addition, it should be considered that the loading capacity of gases is physically limited by colloid dispersion (50 ng total dose in 5-mL gas bubble).[96] Also, the drug delivery is limited in time (a few weeks) owing to the rapid resorption of the gases by surrounding tissues. The deposition of aerosolized particles on surrounding tissue structures could potentially lead to cell damage, depending on the quantity and nature of drug delivered. Care must also be taken when using aerosols intravitreally to avoid introducing cloudy matrices that could affect the optical properties (transparency and refractive index) and thus the patients' vision. Nevertheless, after appropriate adaptation, gas-based drug delivery systems may represent interesting options for the management of ocular pathologies that require only short-term administration of therapeutic agents.

Drug Release from Silicon Oils

In contrast to BSS and gases, silicone oils could allow a sustained release of active ingredients for up to 3 to 6 months owing to their prolonged residence time in the eye. The therapeutic substances are either applied by intravitreal injection into silicone-filled eyes or mixed or dissolved into the silicone oil prior to the application of the silicone tamponade. Owing to its hydrophobic and lipophilic properties, silicone oil has no affinity for most pharmaceuticals that are readily soluble and bioavailable in the aqueous milieu. When using hydrophilic drugs in silicone-filled eyes, it should be noted that toxic accumulation of the drug in the residual aqueous fluid level may occur. Therefore, a high lipophilicity of the active ingredients is necessary for the effective loading of drugs in silicone oils. Even relatively lipophilic agents such as triamcinolone acetonide and dexamethasone showed relatively low saturation concentrations in silicone oil.[97] Total drug loading in silicone oils can take days to weeks, requires specialized equipment owing to the high viscosity of silicone oil, and is challenging to quantify.[98] In addition, it is critical to note that highly hydrophobic toxins such as hexachlorohexane, polybiphenyls, and dichlorodiphenyl trichloroethane accumulate excessively in silicone oil during long-term tamponade and are detectable for many years.[99] Nevertheless, studies have reported reasonably safe and successful drug delivery in silicone-filled eyes.[100,101] Most

Table 4. Overview of Drug Delivery Systems for the Release of Drugs From Vitreous Substitutes

Material	Formulation	Drug	Usage	Species	Concentration	Release Mechanism	Duration	References
BSS	Intravitreal infusion during vitreous surgery, aqueous vitreous substitute	Thrombin	Intraocular bleeding	Rabbit	100 U/mL	Diffusion	NA	91
	Intravitreal infusion during vitreous surgery	5-FU	Antiproliferative; PVR	Human	200 µg/mL	Diffusion	1 hour	92
	Intravitreal infusion during vitreous surgery	Methotrexate	Antiproliferative; PVR	Human	80 µg/mL	Diffusion	NA	93
Gas/air	Aerosol	Sodium fluorescein	Model substance for antimetabolites (PVR), antimicrobial agents (endophthalmitis), antiangiogenic compounds (vasoproliferative disorder), and corticosteroids	Pig	12 ng/mL	Diffusion	1 hour	94
Silicone oil	Reservoir for intravitreal injections	Triamcinolone	Antiproliferative; PVR; anti-inflammatory; resolve macular edema	In vitro, ex vivo (pig), human	0.08–40 mg/mL	Diffusion	1–4 months	102–106
	Drug-loaded suspension	Retinoic acid	Anti-inflammatory and antiproliferative; PVR	In vitro, rabbit	9-412.5 µg/mL	Diffusion, cleavage of hydrogen bonds	16–72 days	98, 107–110
	Drug-loaded suspension	Acetylsalicylic acid	Antiproliferative; PVR	Rabbit, Human	0.2–1.67 mg/mL	Diffusion	5 days	111, 112
	Drug-loaded suspension	Dexamethasone	Anti-inflammatory and antiproliferative, immunosuppressive; PVR	In vitro, human	175 µg/mL	Diffusion	6–12 months	100, 113
	Drug-loaded suspension	5-FU	Antiproliferative; PVR	Pig	260–330 µg/mL	Diffusion	5 days	114
	Drug-loaded suspension	Ibuprofen	Anti-inflammatory and antiproliferative	In vitro	1 mg/mL	Diffusion, cleavage of hydrogen bonds	3–9 days	109
	Reservoir for intravitreal injections	Ganciclovir, foscarnet	Antiviral; viral retinitis	Human	40 mg/mL, 24 mg/mL	Diffusion	6–8 weeks	115
Hyaluronic acid	Hydrogel	Dexamethasone	Anti-inflammatory and antiproliferative, immunosuppressive; PVR	In vitro	4–20 mg/mL	Diffusion	44 h	130
PVA/chitosan	Hydrogel with drug-loaded PLGA microspheres	5-FU	Antiproliferative; PVR	In vitro, rabbit	NA	Diffusion, degradation of microspheres	15 days (24 weeks)	131
PEGMA/PEGDA	Hydrogel	Ascorbic acid	Antioxidative; prevent oxidative damage, establishing a vitreal oxygen gradient	In vitro	2.2 mM	Diffusion	7 days	132
PEGMA/PEGDA	Hydrogel	Ascorbic acid, glutathione	Anti-oxidative; preventing oxidative damage, establishing a vitreal oxygen gradient	In vitro	0.1–10 mM	Diffusion	75 days	133
Silk/hyaluronic acid	Hydrogel	Bevacizumab	AMD, PDR	Rabbit	25–100 mg/mL	Diffusion, degradation	3 months	134, 136
PEG/PPG/PCL	Hydrogel	Bevacizumab, aflibercept	AMD, PDR	In vitro, rabbit	10 mg/mL	Diffusion, degradation	40 days	15, 135

AMD, age-related macular degeneration; NA, not available; PCL, polycaprolactone; PDR, proliferative diabetic retinopathy; PEG, polyethylene glycol; PEGDA, polyethylene glycol diacrylate; PEGMA, polyethylene glycol monomethacrylate; PLGA, poly(lactic-co-glycolic acid); PPG, polypropylene glycol; PVA, polyvinyl alcohol.

notably, triamcinolone acetonide,[100,102–106] retinoic acid,[98,107–110] acetylsalicylic acid,[111,112] dexamethasone,[100,113] 5-fluorouracil,[114] ibuprofin,[109] and antiviral agents[115] have been studied as agents for intravitreal release from silicone oils.

Anti-inflammatory, poorly water-soluble triamcinolone acetonide, used clinically to resolve macular edema, is typically injected intravitreally into the silicone tamponade, which forms a suspension with the silicone oil within minutes to months depending on the concentration and then precipitates at the oil–water interface, remaining visible in the oil for months.[105,106] Although triamcinolone is not toxic as a solubilized drug, sedimented crystals cause rapid

apoptotic cell death of retinal ganglion cells upon direct contact with the retinal surface.[116] Additional side effects include increased intraocular pressure and the progression of cataracts. Clinical trials with low-dose triamcinolone acetonide also showed no statistically relevant therapeutic success.[100,102–104] Therefore, triamcinolone acetonide injection into silicone-filled eyes should be avoided.

In contrast, loading silicone oil with anti-inflammatory retinoic acid (9–15 µg/mL) showed a reduction in PVR in animal experiments.[108,110,114] However, the therapeutic width was very low and the release time of retinoic acid, 7 days, was too short. Additives (modified oligo(ethylene glycol) chains) soluble in silicone oil offered hydrogen bonding sites for interaction with retinoic acid, consequently increasing both the drug loading and release period to 7 weeks in vitro,[98,109] a duration relevant to the pharmacologic treatment of PVR.[117]

Kralinger et al. investigated the pharmacokinetics and biocompatibility of acetylsalicylic acid,[111,112] which in principle is also suitable for mixing with silicone oil owing to its amphiphilic character. In rabbits, a relatively high loading of 1.67 mg/mL acetylsalicylic acid in silicone oil (5000 mPa) demonstrated biocompatibility and release up to 5 days after implantation.[111] The required filtering of acetylsalicylic acid–loaded silicone oil resulted in significantly lower concentrations (0.2 mg/mL) owing to the removal of undissolved drug crystals, which were described as safe yet ineffective in clinical studies.[112]

Thus, the use of drug-loaded silicone oils is restricted not only by the characteristics of the silicone oil itself but also by the complicated loading of the oil with the active ingredients and a relatively rapid release. Recent computational modeling studies investigated the distribution of drugs in silicone oils, thus further contributing to the understanding and optimization of drug releases from silicone oils.[118–120]

Drug Release from Polymer-Based Vitreous Substitutes

In contrast to liquids (BSS and silicone oil) and gases, the use of hydrogels allows both rapid and sustained release of a wide variety of therapeutics. Drugs can be immobilized into the porous polymer network by physical entrapment or chemical conjugation (Fig. 3). Here, inclusion in the porous structures of the hydrogel enables higher doses of the drug to be entrapped than would otherwise be tolerated in free form. Owing to the high water content of hydrogel systems, gels can be easily loaded with hydrophilic therapeutics. In contrast, hydrophobic drugs are poorly soluble in gel matrices. Here, the introduction of hydrophobic domains or cyclodextrins can improve the loading of hydrophobic drugs into the gels. The use of hydrogels as polymer-based vitreous substitutes enables a drug formulation and delivery that can be performed under mild temperatures and pH conditions and without organic solvents.[121] In addition to diffusion, the sustained release of immobilized therapeutics mainly occurs through the successive degradation of the polymer network, which is adjustable up to several months.

A variety of hydrogel-based drug delivery systems described in the past[122–126] can be applied to the vitreous cavity primarily via intravitreal injection. In contrast to vitreous substitutes, hydrogel-based drug delivery systems usually occupy only a small portion of the vitreous cavity (50–200 µL) and are typically not transparent, and their degradability is often desirable. Additionally, many therapeutic formulations using nanobiomaterials can support intraocular drug delivery.[127–129] However, these systems were not designed to replace the vitreous body—they rarely meet the multiple requirements of a vitreous body substitute—and are therefore not discussed in the present review.

In recent years, polymer-based vitreous substitutes have been investigated as drug delivery systems and have addressed the delivery of anti-inflammatory agents,[130] cytostatics,[131] antioxidants,[132,133] and proteins.[134,135]

Spitzer et al.[130] studied the in vitro release of dexamethasone from hyaluronic acid–based vitreous substitutes and found that dexamethasone accumulated in hyaluronic acid in concentrations reaching 20 mg/mL. The diffusion-controlled release proceeded over 44 hours, and the proliferation of human tenon fibroblasts and human retinal pigment epithelial cells (ARPE-19) was inhibited without causing cytotoxic effects. Both the diffusion-based kinetics and the use of uncrosslinked hyaluronic acid (Healon and Healon 5), which is enzymatically degraded in the vitreous cavity within a few weeks, limit the system to short-term vitreous replacement.

For the therapy of PVR, Yu et al.[131] recently reported an in situ physically crosslinked hydrogel based on polyvinyl alcohol and chitosan as a vitreous substitute, which was crosslinked in the presence of calcium chloride via hydrogen bonds when heated to body temperature and loaded with poly(lactic-*co*-glycolic acid) microspheres containing 5-FU as the therapeutic agent. In a PVR rabbit model, the vitreous substitute remained physically present after being placed in the eye for 24 weeks, released 5-FU slowly and effectively over several weeks, and decreased the recurrence rate of PVR. Despite the promising results,

the current approach is limited by the nontransparency of the substitute, which can lead to visual impairment, transient high intraocular pressure, and complicated cataracts occurring in some rabbit eyes.

Tram et al.[132,133] studied the uptake and release of antioxidants from vitreous substitutes to address the biochemical functions of the vitreous (oxygen homeostasis). Here, ascorbic acid was incorporated into an in situ physically crosslinked hydrogel based on poly(ethylene glycol) methacrylate and poly(ethylene glycol) diacrylate, which exhibited suitable optical and mechanical properties as well as in vitro biocompatibility. The ascorbic acid was released in vitro from the hydrogel system after a rapid efflux within 12 hours over a period of 7 days.[132] The simultaneous inclusion of glutathione significantly increased the stability of ascorbic acid and prolonged its antioxidant effect in vitro.[133] Besides establishing a vitreal oxygen gradient, the administration of antioxidant-loaded vitreous substitutes also has the potential to prevent oxidative damage to intraocular tissue after vitrectomy.

In addition, the release of anti-VEGF therapeutics from polymer-based vitreous substitutes was investigated to address vascular diseases such as age-related macular degeneration and diabetic retinopathy.[134,135] Silk hydrogels[132] formulated with bevacizumab for ocular drug delivery have been proposed as vitreous substitutes and demonstrated sustained release over 3 months in a rabbit model,[134] a prolonged administration compared to the clinical standard of every 6 weeks. Furthermore, a thermogelling in situ physically crosslinked hydrogel system based on poly(ethylene glycol), poly(propylene glycol), and poly(e-caprolactone) was preclinically investigated as a vitreous substitute.[15] The encapsulated anti-VEGFs (bevacizumab, aflibercept) were released in a relatively linear manner from the thermogel for up to 40 days in vitro. They demonstrated antiangiogenic bioactivity by inhibiting vessel outgrowth in rat ex vivo choroidal explants and reduced vascular leakage in a VEGF-driven neovascularization rabbit model.[135]

To ensure successful translation of the proposed polymer-based vitreous substitutes to the clinic, the existing aforementioned limitations must be overcome. Prior to the application of polymer-based vitreous substitutes, an appropriate purification process must be performed to completely remove toxic reagents. Purification processes such as dialysis can cause undesired leaching of portions of the drug from the hydrogel. Additionally, hydrogels are generally difficult to sterilize. A large number of polymers degrade by heat sterilization or undergo changes in their gel properties when subjected to irradiation processes or chemical sterilization. Furthermore, the activity and efficacy of entrapped proteins, cells, or biopharmaceuticals can also be affected by sterilization processes. Chemical crosslinking can also potentially alter the stability and availability of the drugs to be entrapped. In contrast, physical crosslinking through physical or supramolecular interactions such as hydrogen bonding, hydrophobic association, or electrostatic (ionic) interactions is more likely to ensure drug stability, but physically crosslinked polymer systems offer less control over gel degradation and therapeutic release. Therefore, in order to enhance the efficacy of drugs administered intravitreally, it is important to understand their distribution patterns. In this vein, modeling drug migration and release has been integral to improving the performance of drug-releasing hydrogels, especially in recent years.[136–140]

Conclusions and Future Perspectives

Current clinically used endotamponades (aqueous solutions, gases, and silicon oils) are effective in promoting retinal reattachment but radically deviate from the characteristics of the human vitreous, leading to a considerable range of complications and an inability to meet the requirements of vitreous substitutes, particularly the sustained release of drugs. In contrast, recent preclinical studies confirm the potential of polymeric hydrogels to act as vitreous substitutes and allow both rapid and sustained release of a wide variety of therapeutics. However, to ensure successful translation of the proposed polymer-based vitreous substitutes to the clinic, the aforementioned limitations must be addressed, and the systems' long-term safety and effectiveness must be examined.

Comparing the current approaches, mainly antiproliferative and anti-inflammatory agents have been investigated for the treatment of PVR as a target disease in drug-eluting vitreous substitutes. In particular, the focus was on 5-FU, triamcinolone, retinoic acid, and dexamethasone. Further, the hydrophilicity of hydrogels allowed studies on incorporated anti-VEGFs (bevacizumab and aflibercept) for the treatment of age-related macular degeneration and proliferative diabetic retinopathy. Mainly approaches based on current clinically used endotamponades (BSS and silicone oil) have already been investigated in humans, whereas novel hydrogel-based vitreous substitutes have only been evaluated in preclinical studies in vitro and in rabbits. This is due to the fact that hydrogel-based vitreous substitutes have not yet been translated into the clinic. The paradigm shift from hydrophobic to hydrophilic vitreous substitutes and the accompany-

ing strong research effort suggests that the translation of hydrogel-based vitreous substitutes into the clinic will occur within the next years. To date, drug-eluting vitreous substitutes have generally followed diffusion-based drug release. In some cases, diffusion was regulated by physical entrapment (in microspheres) or by chemical conjugation to the vitreous substitute. Using the example of 5-FU as a cytostatic drug for the treatment of PVR, the advantage of crosslinked polymer systems (hydrogels) compared to the liquid matrices BSS and silicone oil becomes apparent. While in BSS and silicone oil, 5-FU was released over a period of 1 hour and 5 days, respectively, the release of 5-FU from loaded microspheres was sustained over a clinically relevant period of several weeks and effectively reduced the recurrence rate of PVR.

In perspective, the approach of using vitreous substitutes as drug delivery systems will benefit from:

- Adapting the various existing hydrogel-based delivery systems, which are primarily delivered to the vitreous cavity by intravitreal injection, to the requirements of vitreous substitutes
- Ensuring that immobilization or intravitreal injection of drugs does not affect optical properties (transparency and refractive index) to avoid limiting the patient´s vision
- Matching the stiffnesses/viscoelasticities of the drug release system to the native characteristics of the juvenile and healthy human vitreous to avoid mechanical damage to surrounding tissue structures
- Fine-tuning the degradation/release profile to match the treatment periods of the specific ocular diseases
- Avoiding hydrophobic vitreous substitutes to reduce or eliminate emulsions, unilateral tamponading, the formation of interfaces, and the insolubility of hydrophilic drugs
- More effective and simpler drug loading, especially for silicon oils and gases
- Simultaneous administration of adjuvants to increase the stability and efficacy of the therapeutic agents to be released
- Applying intravitreal injections of therapeutic agents into implanted polymer-based vitreous substitutes
- Increased incorporations of degradable nanoparticles or microparticles to promote the sustained release of drugs from polymer-based vitreous substitutes
- Immobilizing cells into polymer-based vitreous substitutes for the secretion of therapeutic proteins

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References

1. Tsai C-H, Wang P-Y, Lin I, Huang H, Liu G-S, Tseng C-L. Ocular drug delivery: role of degradable polymeric nanocarriers for ophthalmic application. *Int J Mol Sci*. 2018;19:2830.
2. Cunha-Vaz JG. The blood-ocular barriers: past, present, and future. *Documenta Ophthalmol*. 1997;93:149–157.
3. Del Amo EM, Urtti A. Current and future ophthalmic drug delivery systems: a shift to the posterior segment. *Drug Discov Today*. 2008;13:135–143.
4. Gaudana R, Jwala J, Boddu SHS, Mitra AK. Recent perspectives in ocular drug delivery. *Pharm Res*. 2009;26:1197–2216.
5. Tabandeh H, Thomas G, Boyer D, et al. Intraocular pressure following intravitreal injection. *Invest Ophthalmol Vis Sci*. 2007;48:3374.
6. Meyer CH, Krohne TU, Issa PC, Liu Z, Holz FG. Routes for drug delivery to the eye and retina: intravitreal injections. *Retinal Pharmacother*. 2016;55:63–70.
7. Maurice D. Practical issues in intravitreal drug delivery. *J Ocular Pharmacol Ther*. 2001;17:393–401.
8. Colthurst MJ, Williams RL, Hiscott PS, Grierson I. Biomaterials used in the posterior segment of the eye. *Biomaterials*. 2000;21:649–665.
9. Yu L, Ding J. Injectable hydrogels as unique biomedical materials. *Chem Soc Rev*. 2008; 37:1473–1481.
10. Kleinberg TT, Tzekov RT, Stein L, Ravi N, Kaushal S. Vitreous substitutes: a comprehensive review. *Surv Ophthalmol*. 2011;56:300–323.
11. Filas BA, Shui Y-B, Beebe DC. Computational model for oxygen transport and consumption in human vitreous. *Invest Ophthalmol Vis Sci*. 2013;54:6549–6559.
12. Siegfried CJ, Shui Y-B, Holekamp NM, Bai F, Beebe DC. Oxygen distribution in the human eye: relevance to the etiology of open-angle glaucoma after vitrectomy. *Invest Ophthalmol Vis Sci*. 2010;51:5731–5738.
13. Sebag J. *The Vitreous: Structure, Function, and Pathobiology*. New York: Springer Science & Business Media; 2012.

14. Sebag J. Ageing of the vitreous. *Eye*. 1987;1:254–262.
15. Liu Z, Liow SS, Lai SL, et al. Retinal-detachment repair and vitreous-like-body reformation via a thermogelling polymer endotamponade. *Nat Biomed Eng*. 2019;3:598–610.
16. Bracha P, Giuliari GP, Ciulla TA. Vitreous pathology. In: Guidoboni G, Harris A, Sacco R, eds. *Ocular Fluid Dynamics*. Cham (Switzerland): Springer; 2019:277–287.
17. Sebag J. Posterior vitreous detachment. *Ophthalmology*. 2018;125:1384–1385.
18. Itakura H, Kishi S, Kotajima N, Murakami M. Decreased vitreal hyaluronan levels with aging. *Ophthalmologica*. 2009;223:32–35.
19. Berman ER, Michaelson IC. The chemical composition of the human vitreous body as related to age and myopia. *Exp Eye Res*. 1964;3:9–15.
20. Sebag J. Age-related changes in human vitreous structure. *Graefes Arch Clin Exp Ophthalmol*. 1987;225:89–93.
21. Schulz A, Wahl S, Rickmann A, et al. Age-related loss of human vitreal viscoelasticity. *Transl Vis Sci Technol*. 2019;8:56.
22. Foos RY, Wheeler NC. Vitreoretinal juncture: synchysis senilis and posterior vitreous detachment. *Ophthalmology*. 1982;89:1502–1512.
23. Sebag J. Anatomy and pathology of the vitreoretinal interface. *Eye*. 1992;6:541–552.
24. Donati S, Caprani SM, Airaghi G, et al. Vitreous substitutes: the present and the future. *BioMed Res Int*. 2014;2014:1–12.
25. Gao Q-Y, Fu Y, Hui Y-N. Vitreous substitutes: challenges and directions. *Int J Ophthalmol*. 2015;8:437.
26. Michel R, Wilkinson C, Rice T. *Retinal Detachment*. St Louis, MO: CV Mosby; 1990.
27. Stitt AW, Moore JE, Sharkey JA, et al. Advanced glycation end products in vitreous: structural and functional implications for diabetic vitreopathy. *Invest Ophthalmol Vis Sci*. 1998;39:2517–2523.
28. Tram NK, Swindle-Reilly KE. Rheological properties and age-related changes of the human vitreous humor. *Front Bioeng Biotechnol*. 2018;6:199.
29. Schnichels S, Schneider N, Hohenadl C, et al. Efficacy of two different thiol-modified crosslinked hyaluronate formulations as vitreous replacement compared to silicone oil in a model of retinal detachment. *PLoS One*. 2017;12:e0172895.
30. Scholda C, Egger S, Lakits A, Walch K, von Eckardstein E, Biowski R. Retinal detachment after silicone oil removal. *Acta Ophthalmol Scand*. 2000;78:182–186.
31. Sakamoto T, Ishibashi T. Hyalocytes: essential cells of the vitreous cavity in vitreoretinal pathophysiology? *Retina*. 2011;31:222–228.
32. Benson WE, Diamond JG, Tasman W. Intraocular irrigating solutions for pars plana vitrectomy: a prospective, randomized, double-blind study. *Arch Ophthalmol*. 1981;99:1013–1015.
33. Matsuda M, Tano Y, Edelhauser HF. Comparison of intraocular irrigating solutions used for pars plana vitrectomy and prevention of endothelial cell loss. *Jpn J Ophthalmol*. 1984;28:230–238.
34. Chirila TV, Tahija S, Hong Y, Vijayasekaran S, Constable IJ. Synthetic polymers as materials for artificial vitreous body: review and recent advances. *J Biomater Appl*. 1994;9:121–137.
35. de Juan E, Jr., McCuen B, Tiedeman J. Intraocular tamponade and surface tension. *Surv Ophthalmol*. 1985;30:47–51.
36. Kim SS, Smiddy WE, Feuer WJ, Shi W. Outcomes of sulfur hexafluoride (SF6) versus perfluoropropane (C3F8) gas tamponade for macular hole surgery. *Retina*. 2008;28:1408–1415.
37. Chang TS, Pelzek CD, Nguyen RL, Purohit SS, Scott GR, Hay D. Inverted pneumatic retinopexy: a method of treating retinal detachments associated with inferior retinal breaks. *Ophthalmology*. 2003;110:589–594.
38. Mansour AM. Pneumatic retinopexy for inferior retinal breaks. *Ophthalmology*. 2005;112:1771–1776.
39. Su X, Tan MJ, Li Z, et al. Recent progress in using biomaterials as vitreous substitutes. *Biomacromolecules*. 2015;16:3093–3102.
40. Shepherd JE. Optical effects of intraocular gas tamponade. 2019;1–17.
41. Vaziri K, Schwartz SG, Kishor KS, Flynn HW, Jr. Tamponade in the surgical management of retinal detachment. *Clin Ophthalmol (Auckland, NZ)*. 2016;10:471.
42. Lee DA, Wilson MR, Yoshizumi MO, Hall M. The ocular effects of gases when injected into the anterior chamber of rabbit eyes. *Arch Ophthalmol*. 1991;109:571–575.
43. Scott IU, Murray TG, Flynn HW, Jr, Feuer WJ, Schiffman JC; Perfluoron Study Group. Outcomes and complications associated with giant retinal tear management using perfluoro-n-octane. *Ophthalmology*. 2002;109:1828–1833.
44. Sokol JT, Schechet SA, Rosen DT, Ferenchak K, Dawood S, Skondra D. Outcomes of vitrectomy for diabetic tractional retinal detachment in Chicago's county health system. *PLoS One*. 2019;14:e0220726.

45. Kim RW, Baumal C. Anterior segment complications related to vitreous substitutes. *Ophthalmol Clin North Am*. 2004;17:569–576.
46. Azen SP, Scott IU, Flynn HW, Jr, et al. Silicone oil in the repair of complex retinal detachments: a prospective observational multicenter study. *Ophthalmology*. 1998;105:1587–1597.
47. Scheerlinck LM, Schellekens PA, Liem AT, Steijns D, van Leeuwen R. Retinal sensitivity following intraocular silicone oil and gas tamponade for rhegmatogenous retinal detachment. *Acta Ophthalmol*. 2018;96:641–647.
48. Friehmann A, Eng UZ, Rubowitz A. Fluid viscosity but not surface tension, determines the tamponade effect of intravitreal fluids in a novel in vitro eye model of retinal detachment. *J Mechanical Behav Biomed Mater*. 2020;101:103452.
49. Hotta K, Sugitani A. Refractive changes in silicone oil–filled pseudophakic eyes. *Retina*. 2005;25:167–170.
50. Kawaguchi M. Silicone oil emulsions stabilized by polymers and solid particles. *Adv Colloid Interface Science*. 2016;233:186–199.
51. Barca F, Caporossi T, Rizzo S. Silicone oil: different physical proprieties and clinical applications. *BioMed Res Int*. 2014;2014:1–7.
52. Federman JL, Schubert HD. Complications associated with the use of silicone oil in 150 eyes after retina-vitreous surgery. *Ophthalmology*. 1988;95:870–876.
53. Ichhpujani P, Jindal A, Jay Katz L. Silicone oil induced glaucoma: a review. *Graefes Arch Clin Exp Ophthalmol*. 2009;247:1585–1593.
54. Issa R, Xia T, Zarbin MA, Bhagat N. Silicone oil removal: post-operative complications. *Eye*. 2020;34:537–543.
55. Inoue M, Iriyama A, Kadonosono K, Tamaki Y, Yanagi Y. Effects of perfluorocarbon liquids and silicone oil on human retinal pigment epithelial cells and retinal ganglion cells. *Retina*. 2009;29:677–681.
56. Li W, Zheng J, Zheng Q, Wu R, Wang X, Xu M. Clinical complications of Densiron 68 intraocular tamponade for complicated retinal detachment. *Eye*. 2010;24:21–28.
57. Lim BL, Vote B. Densiron intraocular tamponade: a case series. *Clin Exp Ophthalmol*. 2008;36:261–264.
58. Morescalchi F, Costagliola C, Duse S, et al. Heavy silicone oil and intraocular inflammation. *BioMed Res Int*. 2014;2014:1–16.
59. Lai WW, Wong D, Li KK, Leow P-L. Emulsification and inverted hypopyon formation of oxane HD in the anterior chamber. *Graefes Arch Clin Exp Ophthalmol*. 2008;246:1633–1635.
60. Geyer RP. Fluorocarbon-polyol artificial blood substitutes. *N Engl J Med*. 1973;289:1077–1082.
61. Clark LC, Jr, Gollan F. Survival of mammals breathing organic liquids equilibrated with oxygen at atmospheric pressure. *Science*. 1966;152:1755–1756.
62. Chang S. Low viscosity liquid fluorochemicals in vitreous surgery. *Am J Ophthalmol*. 1987;103:38–43.
63. Chang S, Ozmert E, Zimmerman NJ. Intraoperative perfluorocarbon liquids in the management of proliferative vitreoretinopathy. *Am J Ophthalmol*. 1988;106:668–674.
64. Miyamoto K, Refojo MF, Tolentino FI, Fournier GA, Albert DM. Perfluoroether liquid as a long-term vitreous substitute: an experimental study. *Retina*. 1984;4:264–268.
65. Mackiewicz J, Maaijwee K, Lüke C, et al. Effect of gravity in long-term vitreous tamponade: in vivo investigation using perfluorocarbon liquids and semi-fluorinated alkanes. *Graefes Arch Clin Exp Ophthalmol*. 2007;245:665–675.
66. Malchiodi-Albedi F, Morgillo A, Formisano G, et al. Biocompatibility assessment of silicone oil and perfluorocarbon liquids used in retinal reattachment surgery in rat retinal cultures. *J Biomed Mater Res*. 2002;60:548–555.
67. Migliavacca L, Bottoni F, Miglior S. Experimental short-term tolerance to perfluorodecalin in the rabbit eye: a histopathological study. *Curr Eye Res*. 1998;17:828–835.
68. Mertens S, Bednarz J, Engelmann K. Evidence of toxic side effects of perfluorohexyloctane after vitreoretinal surgery as well as in previously established in vitro models with ocular cell types. *Graefes Arch Clin Exp Ophthalmol*. 2002;240:989–995.
69. Roider J, Hoerauf H, Kobuch K, Gabel V-P. Clinical findings on the use of long-term heavy tamponades (semifluorinated alkanes and their oligomers) in complicated retinal detachment surgery. *Graefes Arch Clin Exp Ophthalmol*. 2002;240:965–971.
70. Kirchhof B, Wong D, van Meurs J, et al. Use of perfluorohexyloctane as a long-term internal tamponade agent in complicated retinal detachment surgery. *Am J Ophthalmol*. 2002;133:95–101.
71. Heimann H, Stappler T, Wong D. Heavy tamponade 1: a review of indications, use, and complications. *Eye*. 2008;22:1342–1359.
72. Stefaniotou MI, Aspiotis MV, Kitsos GD, Kalogeropoulos CDR, IC Asproudis, Psilas KG. Our experience with perfluorohexyloctane

(F6H8) as a temporary endotamponade in vitreoretinal surgery. *Eur J Ophthalmol*. 2002;12:518–522.
73. Schulz A, Rickmann A, Wahl S, et al. Alginate- and hyaluronic acid–based hydrogels as vitreous substitutes: an in vitro evaluation. *Transl Vis Sci Technol*. 2020;9:34.
74. Schramm C, Spitzer MS, Henke-Fahle S, et al. The cross-linked biopolymer hyaluronic acid as an artificial vitreous substitute. *Invest Ophthalmol Vis Sci*. 2012;53:613–621.
75. Barth H, Crafoord S, Andréasson S, Ghosh F. A cross-linked hyaluronic acid hydrogel (Healaflow) as a novel vitreous substitute. *Graefes Arch Clin Exp Ophthalmol*. 2016;254:697–703.
76. Su W-Y, Chen K-H, Chen Y-C, Lee Y-H, Tseng C-L, Lin F-H. An injectable oxidated hyaluronic acid/adipic acid dihydrazide hydrogel as a vitreous substitute. *J Biomater Sci*. 2011;22:1777–1797.
77. Nakagawa M, Tanaka M, Miyata T. Evaluation of collagen gel and hyaluronic acid as vitreous substitutes. *Ophthalmic Res*. 1997;29:409–420.
78. Wang S, Chi J, Jiang Z, et al. A self-healing and injectable hydrogel based on water-soluble chitosan and hyaluronic acid for vitreous substitute. *Carbohydrate Polymers*. 2021;256:117519.
79. Yadav I, Purohit SD, Singh H, Das N, Roy P, Mishra NC. A highly transparent tri-polymer complex in situ hydrogel of HA, collagen and four-arm-PEG as potential vitreous substitute. *Biomed Mater*. 2021;16:65018.
80. Santhanam S, Liang J, Struckhoff J, Hamilton PD, Ravi N. Biomimetic hydrogel with tunable mechanical properties for vitreous substitutes. *Acta Biomater*. 2016;43:327–337.
81. Suri S, Banerjee R. In vitro evaluation of in situ gels as short term vitreous substitutes. *J Biomed Mater Res Pt A*. 2006;79:650–664.
82. Yang H, Wang R, Gu Q, Zhang X. Feasibility study of chitosan as intravitreous tamponade material. *Graefes Arch Clin Exp Ophthalmol*. 2008;246:1097–1105.
83. Jiang X, Peng Y, Yang C, Liu W, Han B. The feasibility study of an in situ marine polysaccharide-based hydrogel as the vitreous substitute. *J Biomed Mater Res Pt A*. 2018;106:1997–2006.
84. Nguyen DD, Lai J-Y. Advancing the stimuli response of polymer-based drug delivery systems for ocular disease treatment. *Polymer Chem*. 2020;11:6988–7008.
85. Swindle KE, Ravi N. Recent advances in polymeric vitreous substitutes. *Expert Rev Ophthalmol*. 2007;2:255–265.
86. Lin Q, Lim JYC, Xue K, Su X, Loh XJ. Polymeric hydrogels as a vitreous replacement strategy in the eye. *Biomaterials*. 2021;268:120547.
87. Tong X, Lee S, Bararpour L, Yang F. Long-term controlled protein release from poly (ethylene glycol) hydrogels by modulating mesh size and degradation. *Macromol Biosci*. 2015;15:1679–1686.
88. Purcell BP, Kim IL, Chuo V, Guenin T, Dorsey SM, Burdick JA. Incorporation of sulfated hyaluronic acid macromers into degradable hydrogel scaffolds for sustained molecule delivery. *Biomater Sci*. 2014;2:693–702.
89. Santi DV, Schneider EL, Reid R, Robinson L, Ashley GW. Predictable and tunable half-life extension of therapeutic agents by controlled chemical release from macromolecular conjugates. *Proc Natl Acad Sci USA*. 2012;109:6211–6216.
90. Ashley GW, Henise J, Reid R, Santi DV. Hydrogel drug delivery system with predictable and tunable drug release and degradation rates. *Proc Natl Acad Sci U S A*. 2013;110:2318–2323.
91. de Bustros S, Glaser BM, Johnson MA. Thrombin infusion for the control of intraocular bleeding during vitreous surgery. *Arch Ophthalmol*. 1985;103:837–839.
92. Asaria RHY, Kon CH, Bunce C, et al. Adjuvant 5-fluorouracil and heparin prevents proliferative vitreoretinopathy: results from a randomized, double-blind, controlled clinical trial. *Ophthalmology*. 2001;108:1179–1183.
93. Sadaka A, Sisk RA, Osher JM, Toygar O, Duncan MK, Riemann CD. Intravitreal methotrexate infusion for proliferative vitreoretinopathy. *Clin Ophthalmol (Auckland, NZ)*. 2016;10:1811.
94. Zhang G, Feng X, Wabner K, et al. Intraocular nanoparticle drug delivery: a pilot study using an aerosol during pars plana vitrectomy. *Invest Ophthalmol Vis Sci*. 2007;48:5243–5249.
95. Yamada N, Olsen TW. Routes for drug delivery to the retina: topical, transscleral, suprachoroidal and intravitreal gas phase delivery. *Retin Pharmacother*. 2016;55:71–83.
96. Szurman P, Frank C, Kaczmarek RT, Spitzer MS. Vitreous substitutes as drug release systems. *Klin Monatsbl Augenheilkd*. 2009;226:718–724.
97. Pastor JC, Del Nozal MJ, Zamarron E, Garcia M. Solubility of triamcinolone acetonide and other anti-inflammatory drugs in silicone oil: implications for therapeutic efficacy. *Retina*. 2008;28:1247–1250.

98. Cauldbeck H, Le Hellaye M, McDonald TO, et al. Modulated release from implantable ocular silicone oil tamponade drug reservoirs. *J Polymer Sci Pt A Polymer Chem*. 2018;56:938–946.
99. Bambas B, Eckardt C, Vowinkel E, Kruse H. Toxic substances with silicone oil after intraocular injections. *Ophthalmologe*. 1995;92:663–667.
100. Banerjee PJ, Quartilho A, Bunce C, et al. Slow-release dexamethasone in proliferative vitreoretinopathy: a prospective, randomized controlled clinical trial. *Ophthalmology*. 2017;124:757–767.
101. Iglicki M, Zur D, Fung A, et al. TRActional DIabetic reTInal detachment surgery with co-adjuvant intravitreal dexamethasONe implant: the TRADITION STUDY. *Acta Diabetol*. 2019;56:1141–1147.
102. Chen W, Chen H, Hou P, Fok A, Hu Y, Lam DSC. Midterm results of low-dose intravitreal triamcinolone as adjunctive treatment for proliferative vitreoretinopathy. *Retina*. 2011;31:1137–1142.
103. Banerjee PJ, Xing W, Bunce C, et al. Triamcinolone during pars plana vitrectomy for open globe trauma: a pilot randomised controlled clinical trial. *Br J Ophthalmol*. 2016;100:949–955.
104. Ahmadieh H, Feghhi M, Tabatabaei H, Shoeibi N, Ramezani A, Mohebbi MR. Triamcinolone acetonide in silicone-filled eyes as adjunctive treatment for proliferative vitreoretinopathy: a randomized clinical trial. *Ophthalmology*. 2008;115:1938–1943.
105. Da M, Li KKW, Chan KC, Wu EX, Wong DSH. Distribution of triamcinolone acetonide after intravitreal injection into silicone oil-filled eye. *BioMed Res Int*. 2016;2016:1–9.
106. Spitzer MS, Kaczmarek RT, Yoeruek E, et al. The distribution, release kinetics, and biocompatibility of triamcinolone injected and dispersed in silicone oil. *Invest Ophthalmol Vis Sci*. 2009;50:2337–2343.
107. Veloso Jr, Kadrmas EF, Larrosa JM, Sandberg MA, Tolentino FI, Refojo MF. 13-cis-retinoic acid in silicone-fluorosilicone copolymer oil in a rabbit model of proliferative vitreoretinopathy. *Exp Eye Res*. 1997;65:425–434.
108. Araiz JJ, Refojo MF, Arroyo MH, Leong F-L, Albert DM, Tolentino FI. Antiproliferative effect of retinoic acid in intravitreous silicone oil in an animal model of proliferative vitreoretinopathy. *Invest Ophthalmol Vis Sci*. 1993;34:522–530.
109. Cauldbeck H, Le Hellaye M, Long M, et al. Controlling drug release from non-aqueous environments: moderating delivery from ocular silicone oil drug reservoirs to combat proliferative vitreoretinopathy. *J Control Release*. 2016;244:41–51.
110. Nakagawa M, Refojo MF, Marin JF, Doi M, Tolentino FI. Retinoic acid in silicone and silicone-fluorosilicone copolymer oils in a rabbit model of proliferative vitreoretinopathy. *Invest Ophthalmol Vis Sci*. 1995;36:2388–2395.
111. Kralinger MT, Kieselbach GF, Voigt M, Parel J-M. Slow release of acetylsalicylic acid by intravitreal silicone oil. *Retina*. 2001;21:513–520.
112. Kralinger MT, Stolba U, Velikay M, et al. Safety and feasibility of a novel intravitreal tamponade using a silicone oil/acetyl-salicylic acid suspension for proliferative vitreoretinopathy: first results of the Austrian Clinical Multicenter Study. *Graefes Arch Clin Exp Ophthalmol*. 2010;248:1193–1198.
113. Flores-Villalobos EO, Ramírez-Estudillo JA, Robles-Contreras A, Oliva-Ramírez JL. Dexamethasone implant in silicone oil: in vitro behavior. *Int J Retina Vitreous*. 2018;4:1–9.
114. Schmidt Laugesen C, Steffansen B, Scherfig E, La Cour M. Pharmacokinetics of intravitreal 5-fluorouracil prodrugs in silicone oil: experimental studies in pigs. *Acta Ophthalmol Scand*. 2005;83:184–190.
115. Meshi A, Friehmann A, Sella S, et al. Intravitreal administration of antiviral agents in silicone oil–filled human eyes. *Ophthalmol Retina*. 2017;1:288–293.
116. Szurman P, Sierra A, Kaczmarek R, et al. Different biocompatibility of crystalline triamcinolone deposits on retinal cells in vitro and in vivo. *Exp Eye Res*. 2007;85:44–53.
117. Guidetti B, Azema J, Malet-Martino M, Martino R. Delivery systems for the treatment of proliferative vitreoretinopathy: materials, devices and colloidal carriers. *Curr Drug Deliv*. 2008;5:7–19.
118. Henein C, Awwad S, Ibeanu N, et al. Hydrodynamics of intravitreal injections into liquid vitreous substitutes. *Pharmaceutics*. 2019;11:371.
119. Kathawate J, Acharya S. Computational modeling of intravitreal drug delivery in the vitreous chamber with different vitreous substitutes. *Int J Heat Mass Transfer*. 2008;51:5598–5609.
120. Stein S, Bogdahn M, Weitschies W, Seidlitz A. Influence of Siluron insertion on model drug

distribution in the simulated vitreous body. *Curr Directions Biomed Eng*. 2016;2:665–668.
121. Qiu B, Stefanos S, Ma J, et al. A hydrogel prepared by in situ cross-linking of a thiol-containing poly (ethylene glycol)-based copolymer: a new biomaterial for protein drug delivery. *Biomaterials*. 2003;24:11–18.
122. Chang D, Park K, Famili A. Hydrogels for sustained delivery of biologics to the back of the eye. *Drug Discov Today*. 2019;24:1470–1482.
123. Ilochonwu BC, Urtti A, Hennink WE, Vermonden T. Intravitreal hydrogels for sustained release of therapeutic proteins. *J Control Release*. 2020;326:419–441.
124. Wang K, Han Z. Injectable hydrogels for ophthalmic applications. *J Control Release*. 2017;268:212–224.
125. Luo L-J, Nguyen DD, Lai J-Y. Benzoic acid derivative-modified chitosan-g-poly (N-isopropylacrylamide): methoxylation effects and pharmacological treatments of Glaucoma-related neurodegeneration. *J Control Release*. 2020;317:246–258.
126. Nguyen DD, Luo L-J, Lai J-Y. Dendritic effects of injectable biodegradable thermogels on pharmacotherapy of inflammatory glaucoma-associated degradation of extracellular matrix. *Adv Healthcare Mater*. 2019;8:1900702.
127. Nguyen DD, Lai J-Y. Synthesis, bioactive properties, and biomedical applications of intrinsically therapeutic nanoparticles for disease treatment. *Chem Eng J.* 2022;435(2):134970.
128. Luo L-J, Jian H-J, Harroun SG, Lai J-Y, Unnikrishnan B, Huang C-C. Targeting nanocomposites with anti-oxidative/inflammatory/angiogenic activities for synergistically alleviating macular degeneration. *Appl Mater Today*. 2021;24:101156.
129. Luo L-J, Nguyen DD, Lai J-Y. Harnessing the tunable cavity of nanoceria for enhancing Y-27632-mediated alleviation of ocular hypertension. *Theranostics*. 2021;11:5447.
130. Spitzer MS, Yoeruek E, Kaczmarek RT, et al. Sodium hyaluronate gels as a drug-release system for corticosteroids: release kinetics and antiproliferative potential for glaucoma surgery. *Acta Ophthalmol*. 2008;86:842–848.
131. Yu Z, Ma S, Wu M, et al. Self-assembling hydrogel loaded with 5-FU PLGA microspheres as a novel vitreous substitute for proliferative vitreoretinopathy. *J Biomed Mater Res Pt A*. 2020;108:2435–2446.
132. Tram NK, Jiang P, Torres-Flores TC, Jacobs KM, Chandler HL, Swindle-Reilly KE. A hydrogel vitreous substitute that releases antioxidant. *Macromol Biosci*. 2020;20:1900305.
133. Tram NK, McLean RM, Swindle-Reilly KE. Glutathione improves the antioxidant activity of vitamin C in human lens and retinal epithelial cells: implications for vitreous substitutes. *Curr Eye Res*. 2021;46:470–481.
134. Lovett ML, Wang X, Yucel T, et al. Silk hydrogels for sustained ocular delivery of anti-vascular endothelial growth factor (anti-VEGF) therapeutics. *Eur J Pharm Biopharma*. 2015;95:271–278.
135. Xue K, Zhao X, Zhang Z, et al. Sustained delivery of anti-VEGFs from thermogel depots inhibits angiogenesis without the need for multiple injections. *Biomater Sci*. 2019;7:4603–4614.
136. Thakur SS, Shenoy SK, Suk JS, Hanes JS, Rupenthal ID. Validation of hyaluronic acid-agar-based hydrogels as vitreous humor mimetics for in vitro drug and particle migration evaluations. *Eur J Pharm Biopharm*. 2020;148:118–125.
137. Auel T, Großmann L, Schulig L, Weitschies W, Seidlitz A. The EyeFlowCell: development of a 3D-printed dissolution test setup for intravitreal dosage forms. *Pharmaceutics*. 2021;13:1394.
138. Dosmar E, Vuotto G, Su X, et al. Compartmental and COMSOL multiphysics 3D modeling of drug diffusion to the vitreous following the administration of a sustained-release drug delivery system. *Pharmaceutics*. 2021;13:1862.
139. Santoveña A, Monzon C, Delgado A, Evora C, Llabrés M, Fariña JB. Development of a standard method for in vitro evaluation of triamcinolone and BMP-2 diffusion mechanism from thermosensitive and biocompatible composite hyaluronic acid-pluronic hydrogels. *J Drug Deliv Sci Technol*. 2017;42:284–291.
140. Sarkhel S, Ramsay E, Kontturi L-S, Peltoniemi J, Urtti A. High-throughput in vitro drug release and pharmacokinetic simulation as a tool for drug delivery system development: application to intravitreal ocular administration. *Int J Pharm*. 2014;477:469–475.
141. Stryjewski TP, Stefater JA, III, Roth L, et al. PYK-1105: preclinical evaluation of a novel biodegradable vitreous substitute for retinal tamponade. *J Vitreoretinal Dis*. 2021;5:32–39.
142. Xue K, Liu Z, Lin Q, et al. PCL-based thermogelling polymer: molecular weight effects on its suitability as vitreous tamponade. *ACS Appl Bio Mater*. 2020;3:9043–9053.