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Review

Towards an ideal biomaterial for vitreous replacement: Historical overview and future trends ☆

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ABSTRACT

Removal of the natural vitreous body from the eye and its substitution with a tamponade agent may be necessary in cases of complicated retinal detachment. Many materials have been variously proposed and tested over the years in an attempt to find an ideal vitreous substitute. This review highlights the evolution of research in the field of vitreous replacement and chronicles the main advances that have been made in such a context. The suitability and limitations of vitreous tamponade agents and substitutes in current clinical use are examined, and the future promise of experimentally tested biomaterials are described and discussed. Future trends in research are also considered and, specifically, the great potential of polymeric hydrogels is emphasized, as they seem to be very effective in closely mimicking the features of the natural vitreous and they could successfully act as long-term vitreous substitutes without inducing clinical complications in the patient's eye.

1. Introduction

Substitution of the vitreous body is one of the most interesting and challenging fields of research in ophthalmology. The surgical treatment of complicated cases of retinal detachment (RD) typically requires the availability of a vitreous tamponade agent able to restore the volume and internal pressure of the ocular globe and to approximate the detached neurosensory retina to the retinal pigment epithelium (RPE). Although over the years a great deal of clinical and experimental work has been performed in order to find an appropriate vitreous substitute, at present a truly functional candidate for long-term use does not yet exist. The various disadvantages of the vitreous tamponade agents clinically used today (sulphur hexafluoride, perfluorocarbon gases, perfluorocarbon liquids, silicone-based oils) has led to the investigation of several alternative materials, ranging from donor vitreous to synthetic polymers, in the search for an ideal biomaterial that may be left safely in the vitreous cavity as a long-term tamponade.

This article, after giving an overview of the anatomy and physiology of the vitreous body, as well as of the surgical procedures adopted for its substitution, focuses on the materials that are currently employed in clinical practice or experimentally tested for vitreous replacement. Their suitability, advantages and drawbacks are outlined and extensively discussed. Particular emphasis is laid on polymeric insoluble gels, the most promising candidates for long-term vitreous replacement. Finally, some methodological remarks about the need to elaborate standard guidelines to select potential vitreous substitutes are presented at the end of the work.

Table 1 provides a short glossary of the medical terms that are not explained directly in the text or that may be unclear or unknown to non-specialist readers.

2. The vitreous body: a short overview

The key ocular components are shown in Fig. 1, which gives an overview of the anatomy of the eye. The vitreous body (corpus vitreus), often termed the vitreous humour or simply vitreous, is a clear, transparent gel filling the posterior cavity of the eye and occupying more than two-thirds of the ocular volume [1–3].

2.1. Vitreous embryogenesis

From a developmental viewpoint it is common practice to distinguish between "primary" and "secondary" vitreous [4]. The term primary vitreous refers to a particular stage of embryonic development, starting in the third gestational week, in which the hyaloid artery grows into the vitreous cavity from the optic nerve head towards the crystalline lens. This vascular system ramifies and fans out to occupy almost the whole vitreous cavity. Development of

☆ This article is one of a series of contributions written as a festschrift in honour of Prof. Giuseppe Heer to celebrate his 60 years of clinical activity (and on the occasion of his 85th birthday). Prof. Heer, Head Emeritus of the Ophthalmology Ward at "Maria Vittoria", Turin Hospital (Italy) and President of the Italian Foundation against Retinopathies of Prematurity, was a pioneer of vitreo-retinal surgery.

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Table 1
Medical glossary (terms listed alphabetically).

Term	Explanation
Age-related macular degeneration (AMD)	Pathology usually affecting older adults and resulting in a loss of vision in the centre of the visual field. AMD "dry" form results from atrophy of the retinal pigment epithelial; AMD "wet" form causes vision loss due to abnormal blood vessel growth below the macula
Cataract	Clouding that develops in the crystalline lens or in its envelop, varying in degree from slight to complete opacity. It prevents clear vision and may require surgical removal of the lens
Diabetic retinopathy	Retinopathy caused by complications of diabetes mellitus. It progresses from mild non-proliferative abnormalities, characterized by increased vascular permeability, to proliferative diabetic retinopathy, with growth of new blood vessels on the retina and posterior surface of the vitreous. Macular edema can develop at all stages of this retinopathy
Epiretinal membranes	Scar tissue-like membranes that form over the macula, which may be involved in retinal detachment and other vitreo-retinal diseases
Fibroblasts	Cells located in the vitreous humour, involved in the synthesis of the constituents (collagens, glycosaminoglycans, glycoprotein and others) of the extracellular matrix
Fovea	A small pit, located in the centre of the macula, containing the highest concentration of cone cells in the retina, responsible for central vision and visual acuity
Glaucoma	Group of ocular diseases associated with increased intraocular pressure, involving damage to the optic nerve. Glaucoma has been appropriately defined as the "silent thief of sight", as the loss of vision normally occurs gradually over a long period of time and is often recognized only when the disease is quite advanced
Hyalocytes	The main cells in the vitreous humour. Their role is not clear; they exhibit functional characteristics similar to those of macrophages and are involved in maintaining a transparent and avascular vitreous
Intra-ocular pressure (IOP)	A measure of the fluid pressure inside the eye (mean value in normal population ~15.5 mm Hg). An IOP above 21 mm Hg indicates ocular hypertension, which may develop into glaucoma
Macula	Oval shaped (~5 mm) highly pigmented yellow region near the centre of the retina in human eyes
Outer plexiform layer	Retinal layer containing the axons of photoreceptors, together with horizontal cell dendrites and bipolar dendrites
Photoreceptors	Sensing elements of the retina. They are divided in cones and rods, which are sensitive to different visual conditions as they contain different light-sensitive proteins in their outer segment
Proliferative vitreoretinopathy (PVR)	Involving the formation of scar tissue in the vitreous cavity; the so-formed vitreoretinal membranes are a risk factor for tractional retinal detachment
Retinal pigment epithelium (RPE)	The retinal layer firmly attached to the underlying choroid, which plays a key role in retinal physiology by forming the outer blood–retinal barrier and by supporting the function of the photoreceptors (cones and rods)
Rhegmatogenous retinal detachment (RRD)	Retinal detachment in which fluid from the vitreous cavity enters the sub-retinal space through a full-thickness retinal break
Tractional retinal detachment (TRD)	Retina detachment in which the retina is mechanically lifted up as a result of vitreo-retinal traction

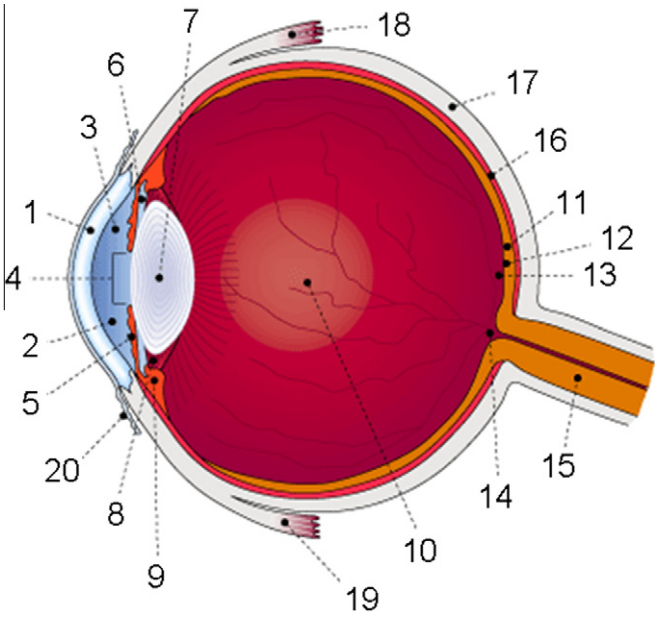

Fig. 1. The structure of the eye with its essential elements: 1, cornea; 2, anterior chamber; 3, aqueous humour; 4, pupil; 5, iris; 6, posterior chamber; 7, crystalline lens; 8, zonule; 9, ciliary body; 10, vitreous body; 11, retina; 12, macula; 13, fovea; 14, head of the optic nerve; 15, optic nerve; 16, choroid; 17, sclera; 18, lateral rectus muscle; 19, medial rectus muscle; 20, conjunctiva.

the secondary vitreous (avascular vitreous) begins at the end of the sixth gestational week. Traditional theories argued that the primary vitreous is compressed by newly formed tissue originating near the retina and expanding towards the centre of the vitreous cavity. This tissue, i.e. the secondary vitreous, forms the definitive vitreous and remains in the eye after birth [4]. Usually the hyaloid artery and its branches disappear almost completely before birth, leaving a clear central zone in the vitreous, termed Cloquet's canal, representing the area of contact between the primary and secondary vitreous. Occasionally, the artery may not fully regress (a condition termed "persistent hyaloid artery"); more commonly, small remnants of the artery may remain and sometimes be seen as floaters by the patient.

Modern theories, which were recently presented in detail by Ponsioen et al. [5], have introduced the concept of interactive remodeling of the vitreous. During embryonic development the human vitreous body is a highly dynamic matrix in which the primary vitreous is gradually replaced by the secondary vitreous. This hypothesis rejects the concept of a strict spatial separation between the two.

During the fourth gestational month the zonular system or "tertiary" vitreous is produced at the level of the developing ciliary body. The zonules are the ligaments holding the crystalline lens in place and enabling it to change shape for near or distant vision (visual accommodation). The tertiary vitreous is not a subsequent developmental stage of the secondary vitreous; the term was coined due to the intimate association between the zonular system (Fig. 1) and the vitreous body.

2.2. Features and functions of the vitreous

In human adults the vitreous weighs approximately 4 g, has a density of 1.0053–1.0089 g cm^{-3}, a refractive index (RI) of 1.3345–1.3348 and a pH range of 7.0–7.4 [1–3]. The vitreous is a composite gel mainly composed of water (98–99 wt.%), collagen fibres (types II, V/XI, VI and IX), glycosaminoglycans (primarily hyaluronic acid) and other non-collagenous structural proteins (opticin and fibrillin), together with hyalocytes (90%) and fibroblasts (10%)

near the vitreous cortex. Hyaluronan molecules are not uniformly distributed within the vitreous, with the highest concentration found in the posterior vitreous cortex [6]. Furthermore, hyaluronic acid is present as polydisperse populations consisting of molecules of varying hydrodynamic size, which may account for its viscoelastic properties [7].

From a structural viewpoint, the vitreous is a fascinating result of natural evolution as the collagen fibres provide a rigid scaffold while the hyaluronan macromolecules impart shock-absorbing properties to the whole system. Comprehensive pictures of the supramolecular organization of the vitreous gel have been provided elsewhere [2,3,5,8] and a detailed overview of vitreous remodeling and its relation to collagen turnover was recently presented by Ponsioen et al. [5]. Details on the viscoelastic and mechanical properties of the human vitreous were reported by Zimmermann [9] and Lee et al. [10], while the rheological properties of porcine and bovine vitreous were carefully assessed by Nickerson et al. [11].

From an anatomical viewpoint, to the best of the author's knowledge the most appropriate and fascinating description of the vitreous body was given by Worst and co-workers, who developed the fascinating concept of a "cisternal anatomy" of the vitreous [4,12].

From a functional viewpoint the vitreous protects the surrounding structures and tissues from mechanical trauma, allows the circulation of metabolic solutes and nutrients throughout the eye, regulates the oxygen tension within the eye, contributes to maintain the shape of the ocular globe and keeps the crystalline lens and the retina in place.

2.3. Ageing of the vitreous

With age the vitreous mass gradually shrinks and collapses during the course of a phenomenon called syneresis, which may eventually lead to posterior vitreous detachment (PVD) [13,14]. PVD is a degenerative process in which the vitreous cortex detaches from the retina. The collagen fibres in the vitreous are held apart by electrical charges, but with ageing these repulsive charges tend to reduce. Then the fibres clump together and the hyaluronan molecules, previously located around the collagen fibres, become dissociated and form adjacent liquid lacunae. Vitreous liquefaction can be considered a physiological process. In fact, some post-mortem studies have recently demonstrated that about 50% of the vitreous gel is liquefied in people over 80 [15,16].

PVD may also occur earlier than normal in myopic people, as well as in patients who have experienced cataract surgery.

Recent research has provided new insights into the onset, progression and traction effects of PVD [17]. It was observed that PVD begins in the perifoveal macula and that the early chronic stage persists and progress slowly over months to years. Vitreous traction forces resulting from perifoveal PVD with vitreofoveolar adhesion may cause localized cystoid foveal thickening, which may eventually involve the formation of a macular hole. Epiretinal membranes develop from the cortical vitreous remnants left on the retinal surface after PVD and play a crucial role in, for instance, promoting RD. In general, PVD may cause problems in the retinal areas where attachment to the vitreous is tight, since small, often horseshoe-shaped breaks in the retina can result from persistent tugging and tearing by the vitreous [18–20]. If a retinal hole is not repaired the vitreous fluid can flow into the sub-retinal space, thereby causing RD.

3. The need, search and surgical procedures for vitreous substitution

Vitreous replacement is necessary if the vitreous body itself becomes dysfunctional, due to various pathological conditions or in the case of surgical treatment of complicated RDs.

The vitreous may become dysfunctional due to opacification, liquefaction or physical collapse. These pathological conditions may be caused by developmental abnormalities, various inflammatory diseases related to infections or retinal diseases, vitreous haemorrhage, tumours, diabetes or degenerative processes [20–22]. Age-related PVD may be accompanied by vitreous bleeding and can predispose to RD due to the traction forces developing at the points of tight vitreo-retinal adhesion [18–20]. Vitreous damage can be also caused by trauma or the presence of intra-ocular foreign bodies. All these conditions may result in poor vision or even blindness.

It is necessary to further stress that an intact vitreous is essential to a healthy human eye. In fact, as recently highlighted by Holekamp [23], age-related vitreous alterations, such as its liquefaction, often accompany several ocular diseases. The vitreous gel is known to play a key role in regulating oxygen distribution within the eye and as the gel undergoes age-related liquefaction this function is impaired and the resultant elevated intra-ocular oxygen tension may lead to oxidative stress within the eye, contributing to disease states such as nuclear cataract and primary open angle glaucoma.

However, the treatment of pathological conditions affecting the vitreous is not the most common reason for which vitreous substitution is necessary, it is the treatment of complicated RD cases that primarily requires vitrectomy procedures, i.e. full or partial replacement of the vitreous body (Fig. 2). Par plana vitrectomy was introduced by Machemer in the early 1970s [24]. It is generally necessary if the surgeon's view of a retinal break(s) is hindered by vitreous bleeding and it is recommended in severe cases of RD, such as tractional RD (TRD) or RD associated with proliferative vitreoretinopathy (PVR). This surgical technique can also be combined with scleral buckling procedures. The retinal holes are sealed by laser photocoagulation or cryotherapy. The vitreous substitute, injected into the vitreous cavity during the surgical procedure, should act as a tamponade pressing the neurosensory retina against the RPE and prevent the formation of new vitreo-retinal traction damage, which might induce retinal redetachment. In

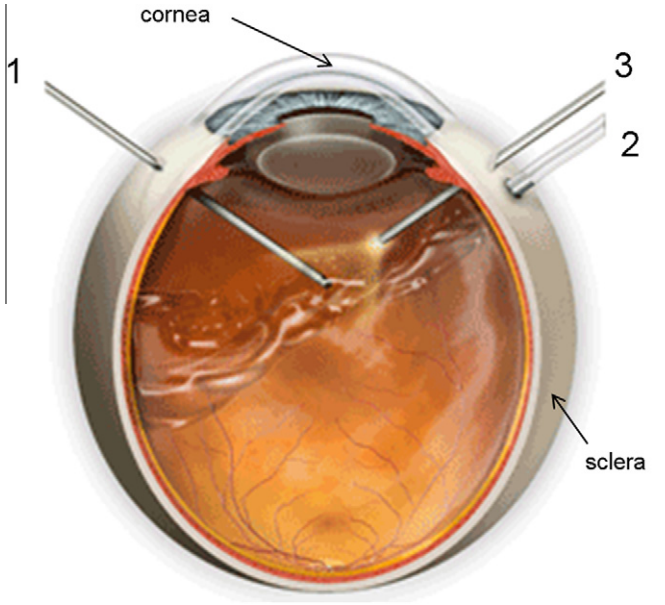

Fig. 2. Typical three-port pars plana vitrectomy procedure: the aspiration pipe (the so-called "vitrector") (1) allows slow removal of the natural vitreous; the infusion pipe (2) is used to replace the vitreous with an appropriate substitute; the light pipe (3) is useful to the surgeon for exploring the vitreous cavity and for examining the retina.

current clinical practice surgeons often inject a gas tamponade agent into the vitreous cavity. Post-operatively the gas is gradually replaced by the eye fluid, which can be considered the ideal, physiological vitreous substitute. In cases of RD associated with severe vitreo-retinal diseases (such as PVR), however, the use of a vitreous substitute with appropriate features for prolonged postoperative tamponade is required.

In uncomplicated cases of rhegmatogenous RD (RRD), pneumatic retinopexy may also be used (Fig. 3). This technique, introduced in 1986 by Hilton and Grizzard [25], is less complex than vitrectomy as it does not require vitreous removal and can be performed under local anaesthesia. Pneumatic retinopexy involves the injection of an expansive gas into the vitreous cavity to flatten the retina, allowing the sub-retinal fluid to be pumped out from beneath it. The patient's head is so positioned that the gas bubble is located exactly above the detached area and presses against it. Cryopexy or laser photocoagulation are used to seal the retinal tear. The gas bubble is gradually absorbed by the eye while scar tissue forms around the retinal hole, thereby sealing it securely. The successful retinal reattachment rate associated with pneumatic retinopexy is over 90%, but this procedure can be performed only in selected cases and often repeated operations are necessary, as has been stressed in the literature [26].

Therefore, the search for suitable substitutes that can be left safely in place after vitrectomy is a challenging and attractive field of research in ophthalmology. As outlined by Chirila et al. in two fundamental contributions to the ophthalmic literature [27,28], an ideal artificial vitreous should fulfil a complex series of requisites. Specifically, it should be (i) non-toxic and biocompatible with the ocular tissues, (ii) clear and transparent with a RI and density similar to those of natural vitreous, (iii) able to maintain its light transparency post-operatively without undergoing opacification, (iv) biologically and chemically inert, (v) appropriately rigid to act as an effective tamponade agent, (vi) able to allow the transfer of metabolites, proteins and solutes, (vii) preferably non-absorbable and non-biodegradable in order to be maintained in the vitreous cavity for a period as long as possible (ideally indefinitely), (viii) preferably hydrophilic and insoluble in water, (ix) injectable through a small gauge needle, (x) able to maintain its properties after injection, (xi) storable and sterilizable without lacking the above mentioned properties.

At present materials able to fulfil this complex set of requisites do not yet exist, although many experiments have been carried out over the years and, as stated by Sebag [29], "history has witnessed the injection of nearly ever imaginable substance into the vitreous". One of the major issue concerns the ability of the potential substitute to allow the diffusion of oxygen, nutrients and solutes within the eye. As extensively underlined by Laude et al. [30], this function becomes essential for those vitrectomized patients who need intra-vitreal drug therapy for the treatment of neovascular age-related macular degeneration (AMD).

Thus it is clear that the design and development of suitable vitreous substitutes is a complex issue, and achieving this will involve close collaboration between synthetic chemists, materials scientists, physicists, biologists and ophthalmic surgeons.

4. First attempts at vitreous replacement: vitreous transplants

Chronologically, healthy animal donor vitreous was the first material used for vitreous replacement at the beginning of the 20th century, when Deutschmann injected fresh calf and rabbit vitreous into human patient eyes [31]. Later, human donor vitreous [32,33] was also used. Such agents failed as they induced severe inflammation in the patient eyes due to an immunological response. Post-operative complications such as cataract, corneal damage, glaucoma and various retinal diseases were also reported.

5. Vitreous tamponade agents currently used in clinical practice

Over the years several materials ranging from gases to liquid agents have been found to be suitable to replace the vitreous and, therefore, used in human patients. Table 2 displays the materials in current use. They will be examined in detail in the following sections.

5.1. Gases

5.1.1. Air

Air was the first gas to be injected into the eye to reattach the neurosensory retina to the RPE. In 1911 Ohm [34] injected purified air into the vitreous cavity to treat a case of RRD. In 1938 Rosengren reattached a retina using intra-vitreal air injection combined with diathermy and drainage of the sub-retinal fluid [35]. In 1969 Norton et al. highlighted the advantages of this technique for treating giant retinal tears [36]. Although further studies demonstrated that air is not suitable as a long-lasting tamponade agent due to its short residence time (a few days), however, since the mid 1980s air has been successfully used in some pneumatic retinopexy procedures [37–39]. Air has been also tried in conjunction with other

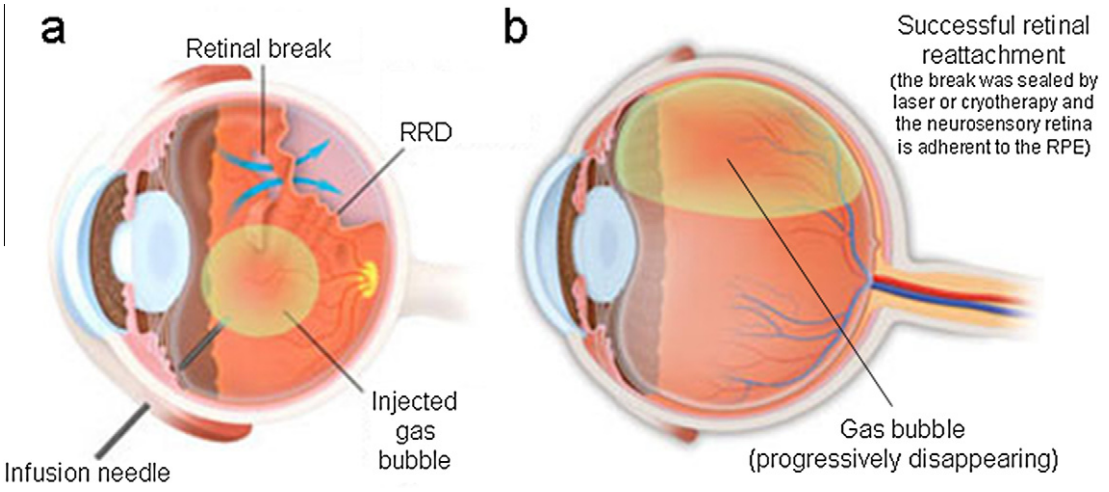

Fig. 3. Pneumatic retinopexy: (a) surgical procedures; (b) successful clinical outcomes.

Table 2
Overview of the main vitreous tamponade agents and substitutes used in clinical practice (human patients).

First use	Substance	Type[a]	Remarks	References
1911	Air	G	Short residence time (few days); suitable for air/PFCL exchange	[34–41]
1912	Water	L	Short residence time	[57,58]
1948	Saline solutions	L	Short residence time; suitable for the vitreous cavity saline/PFCL exchange and for rinsing	[59]
1962	Silicone oil	L	Long-term vitreous substitute, with problems of oil toxicity mainly due to emulsification	[21,60–92]
1973	SF_6	G	Short residence time; cataract, problems due to IOP rise	[42,46,47–49,51]
1980	C_2F_6, C_4F_8, C_3F_8	G	More prolonged tamponade than SF_6; cataract, problems due to IOP rise	[43–48,50–54]
1982	Xenon	G	Very short residence time (few hours)	[55,56]
1988	Perfluoro-*n*-octane, perfluorodecalin	L	Intraoperative use only is recommended; it is usually the agent of choice	[101–104,106–111,115,118–123]
1990	Flurosilicone oil	L	Useful in the treatment of inferior RD; drawbacks analogous to those of silicone oil	[92–97]
1992	Perfluorotetradecahydrophenantrene	L	Intraoperative use only is recommended	[103,105,112,116,117,122]
2002	Perfluorohexyloctane	L	Good clinical outcomes; cataract; removal recommended 2–3 months after operation	[124,126–130]
2003	Oxane HD®	L	Adverse affects including emulsification, cataracts, IOP rise	[137–142]
2005	Densiron-68®	L	Good clinical outcomes; possible emulsification (oil removal after 3 months is strongly recommended)	[131–135,140–142]
2007	HW 46-3000	L	Very good success rate in retinal reattachment; high rate of cataract formation; no inflammation and emulsification	[136,140]

[a] G, gas; L, liquid.

vitreous tamponade agents during vitrectomy procedures, for instance in perfluorocarbon liquid–air exchange [20,40]. Furthermore, air can be used during the so-called D-ACE procedure (drain, air, cryotherapy, explant) introduced by McLeod and coworkers in the mid 1980s [41].

5.1.2. Sulphur hexafluoride and perfluorocarbon gases

In the 1970s intra-vitreal expanding gases began to be used during pars plana vitrectomy procedures. In 1973 Norton first experimented with sulphur hexafluoride (SF_6) [42] and found it to be more persistent than air, which has an intra-vitreal residence time of only a few days. In 1980 Lincoff et al. [43] proposed the use of perfluorocarbon gases (PFCGs), consisting of a hydrocarbon molecule in which all the hydrogen atoms are replaced by fluorine atoms. Various PFCGs have been proposed over the years [43–46], but at present C_3F_8 is the agent of choice [20]. In general, their advantages with respect to SF_6 include lower required intra-vitreal injected volumes due to increased expansion and longer persistence thanks to their low solubility [45,46]. Thus, the use of PFCGs may result in a lower rise in initial intra-ocular pressure (IOP) than that evaluated with SF_6 (acute glaucoma) because of the smaller injected volume. In addition, their increased persistence (from 1 week to 2 months or more depending on the specific PFCG, versus 3–4 days for air) allows prolonged tamponade activity, thereby promoting the formation of secure chorio-retinal adhesions. The major drawbacks related to gases are the need for patient post-operative posturing to exert the maximum tamponade effect and the persistence of quite high IOP values that could result in damage to the optic nerve. Furthermore, cataract formation and possible damage to the ciliary body and retina may occur [20,47,48].

SF_6 and PFCGs have also been used in cases of RD associated to PVR [49,50], but silicone oil was found to be a more suitable tamponade agent as it led to better clinical outcomes.

SF_6/air and C_3F_8/air mixtures were also experimented with. The duration of intra-ocular gas tamponade could be controlled by varying the concentration of air and other gases. The success rate was similar to that obtained using SF_6 or PFCGs alone [51,52].

At present SF_6 and C_3F_8 are the gases of choice for use as vitreous tamponades. In addition, such gases are also successfully used in pneumatic retinopexy procedures [20,37,53]. Unfortunately, holes located in the inferior retina are not easily amenable to closure by intra-ocular gases [54].

5.1.3. Occasionally used gases

In the early 1980s Lincoff et al. tested five gases, argon, helium, xenon, N_2O and CO_2, in rabbit eyes to evaluate their longevity in the vitreous cavity [55]. Xenon was considered the most promising and it was also used in four human patients with successful retinal reattachment in all cases [56]. The major drawback related to xenon was that it disappeared very rapidly (almost 90% disappeared by 3 h after introduction) and, therefore, it was necessary to replace the gas with an aqueous solution to ensure an adequate tamponade effect, preventing ocular hypotension.

5.2. Liquids

5.2.1. Physiological solutions

Water [57,58] and balanced salts solutions [59] were the first liquids to be injected intra-vitreally for retinal tamponade. No relevant differences in the clinical outcomes were found on using physiological solutions or donor vitreous. The low viscosity and the short residence time in the vitreous cavity of the physiological solutions prevented an adequate tamponade effect. However, saline solutions are still used after the removal of other tamponade agents such as silicone oil. Furthermore, physiological solutions are employed as intra-vitreal rinses that are necessary, for instance, to ensure complete removal of perfluorocarbon liquids from the vitreous cavity (see Section 5.2.3).

5.2.2. Silicone-based oils

Over the years different types of silicone oil and silicone oil derivatives have been proposed and investigated as vitreous substitutes. The most relevant features of these oils are summarized in Table 3.

The first use of silicone oil to treat RD in humans was attempted in 1962 by Cibis, who encountered some difficulties in managing the oil and reported several post-operative complications [21]. After the development of pars plana vitrectomy in the mid 1970s the results of the use of silicone oil improved significantly and its use as a long-term vitreous substitute became quite widespread. The features, advantages, drawbacks and indications for use of silicone-based oils for vitreo-retinal surgery have been reviewed in detail by Giordano and Refojo in a fundamental treatise of ophthalmic literature [60].

Table 3
Relevant physical properties of silicone-based oils (adapted from Giordano and Refojo [60], Versura et al. [92], and Yamamoto and Takeuchi [94]).

Oil	RI (at RT)	Density ($g\ cm^{-3}$)	Kinematic viscosity (cSt)
Silicone oil	1.404	0.97	1000–12 000
Fluorosilicone oil	1.382	1.29	1000–10 000
Silicone/fluorosilicone co-polymer oil	1.387	1.16	170–200

Formally, silicone oils for ophthalmic use are synthetic polymers belonging to the class polydimethylsiloxanes. As reported in Table 3, the viscosity of the silicone oils varies over quite a wide range, but the agent of choice is generally considered the 5000 cSt oil. In the mid 1990s it was approved by the Food and Drug Administration (FDA) for intravitreous use in the USA and since then has been marketed worldwide.

Today silicone oil is usually recommended for long-term retinal support and tamponade. In the past silicone oil was also used as an intra-operative tool to stabilize the retina [61] and unroll the flaps of retinal tears [62], but this use has been almost completely abandoned since the introduction of perfluorocarbon liquids, which exhibit a higher surface tension at the water interface, for intra-operative use in the 1980s (see Section 5.2.3). It is necessary to underline that the low density of silicone oil in comparison with water and aqueous solutions (Table 3) causes it to float upon residual vitreal fluid, which leads to a reduced or no tamponade effect in the case of inferior retinal breaks. In aphakic eyes the eye is usually filled with silicone oil up to the level of the pupil. Surgeons must be careful to avoid overfilling and ANDO iridectomy can be helpful in preventing pupillary block, migration of the oil into the anterior chamber of the eye and the development of post-operative glaucoma, keratopathy and other complications [63–65]. Many studies have suggested the use of silicone oil as the preferred choice in the case of long-standing RRD, TRD, giant retinal tears and RD caused by proliferative diabetic retinopathy (PDR) [66–81]. In addition, silicone oil is usually employed as the first surgical procedure in patients unable to position for gases, with the need to travel by air immediately after surgery [82] or suffering from AIDS and related retinal complications [83,84].

Although in most cases silicone oil is well tolerated by ocular tissues, its use in vitreo-retinal surgery has been repeatedly criticised, and the controversy about its actual suitability as a long-term vitreous substitute lingers. On the one hand, silicone oil is a very promising candidate for prolonged vitreous substitution as it can be retained indefinitely in the vitreous cavity without loosing its optical transparency and chemical inertness. In addition, it can provide an extended retinal tamponade activity and is considered to prevent post-operative iris neovascularisation [74,79,82,85,86]. On the other hand, however, there is convincing evidence that silicone oil can induce severe long-term complications in the patient's eye, such as glaucoma, cataract, corneal damage and so-called "silicone retinopathy" [60,87,88]. In these cases surgical removal of the silicone oil is necessary, but any remaining might be retained indefinitely in the eye. Retinal redetachment may also occur after the removal of silicone oil [89]. In the last two decades the incidence of various complications has been progressively reduced by improvements in oil purification technologies (the residual components of polymerization reactions were demonstrated to be toxic [90]), advances in surgical techniques and the possibility of successfully treating most of these post-operative diseases. Several lines of evidence have suggested that the main cause of the above mentioned complications is not intrinsic oil toxicity, which is a typical feature of low molecular weight monomers and polymerization residues [90], but abnormal cell behaviour caused by emulsification and dispersion of the silicone oil [91,92]. In fact, cells in contact with the oil may incorporate silicone vesicles, whose presence can interfere with the transport of metabolites. The emulsification rate, being related to fluid viscosity, can be successfully reduced by employing oils with a viscosity higher than 5000 cSt.

Therefore, although silicone oil exhibits very suitable properties for vitreous substitution, it should only be used in very critical or desperate cases, preferably for temporary vitreous replacement and, in general, only when other surgical procedures have been shown to be unsuccessful.

Besides silicone oil, two other silicone-based oils should be mentioned, poly(methyl-3,3,3-trifluoropropylsiloxane) (fluorosilicone oil) and poly(methyl-3,3,3-trifluoropropylsiloxane–co-dimethylsiloxane) (silicone/fluorosilicone co-polymer oil), often referred to as second generation silicone oils.

Fluorosilicone oil exhibits properties similar to those of silicone oil, but has a higher emulsification rate and a lower intra-ocular tolerance: in fact, complications associated with silicone oil also occur with fluorosilicone oil, but within a shorter time period [92–94]. Fluorosilicone oil, being heavier than water (Table 3), has been used to flatten the retina intra-operatively with the patient in a prone position to displace sub-retinal fluid thanks to the difference in density. In addition, fluorosilicone oil has been successfully used as an extended tamponade for inferior retinal breaks [93,94].

Silicone/fluorosilicone co-polymer oil is a polysiloxane derivative investigated especially by Refojo's group [95,96]. It has been used for intra-operative fixation of the retina, for short-term vitreous substitution and as a vehicle for the intra-vitreal release of drugs preventing PVR [95–97]. Likewise, fluorosilicone oil, silicone/fluorosilicone co-polymer oil is heavier than silicone oil (Table 3) and, therefore, can be successfully used in cases of inferiorly or posteriorly located retinal breaks. In comparison with silicone oil, silicone/fluorosilicone co-polymer oil has a lower viscosity (Table 3), which facilitates oil injection into the eye, as well as its removal. The use of silicone/fluorosilicone co-polymer oil for prolonged vitreous substitution has induced unwanted side-effects similar to or more serious than those observed in the presence of perfluorocarbon liquids (see Section 5.2.3). Doi and Refojo injected silicone/fluorosilicone co-polymer oil into rabbit eyes [96]. After 6 months of retinal tamponade they found loss of the outer plexiform layer and disorganization of the photoreceptor layer. Therefore, the authors suggested the use of silicone/fluorosilicone co-polymer oil only as an intra-operative tool or for short-term retinal tamponade (<2 months) [96].

Finally, it is interesting to mention a clever approach suggested by Dailey et al. [98], who attempted to overcome the problem of poor surface tension by using magnetic silicone-based fluid as a vitreous substitute coupled with a magnetic band (scleral buckle) around the eye. The magnetic field resulting from the scleral buckle would contribute to maintain the vitreous substitute, in which metal nanoparticles were dispersed, in contact with the retina. However, it must be noted that magnetic iron, cobalt, nickel and rare earth metals are all potentially toxic to ocular tissues. Therefore, the toxicity of the constituents and problems with possible removal of the buckle after successful retinal reattachment are crucial issues that should be taken into account in future studies.

5.2.3. Perfluorocarbon liquids

Perfluorocarbon liquids (PFCLs) are colourless and odourless. The most relevant properties of the three PFCLs marketed for vitrectomy procedures are reported in Table 4. The first use of PFCLs for vitreous substitution was reported in 1984 by Miyamoto et al., who injected perfluoroether into rabbit eyes. However, this tamponade agent was deemed unsuitable as a long-term vitreous

Table 4
Relevant physical properties of the most commonly used perfluorocarbon liquids (adapted from Versura et al. [92] and Peyman et al. [122]).

Perfluorocarbon	RI (at RT)	Density (g cm^{-3})	Kinematic viscosity (cSt)
Perfluoro-*n*-octane	1.28	1.73	0.8
Perfluorodecalin	1.31	1.93	2.7
Perfluorotetradecahydrophenantrene	1.33	2.02	8.0

substitute as it induced the formation of pre-retinal membranes, retinal disorganization and eventual RD after being in the vitreous cavity for 4–6 months [99]. Chang et al. tested perfluorotributylamine as a long-term vitreous substitute in rabbit eyes and also found unwanted side-effects, such as retinal disorganization and cell deposition in the vitreous cortex and in the posterior crystalline lens [100]. Thus, the attention of researchers was drawn to the use of PFCLs only as intra-operative tools. In 1988 PFCLs were first used in human eyes as an adjunct in the management of RD associated with PVR [101]. Since then, PFCLs have been successfully employed in the intra-operative management of RRD complicated by PVR [102–104] and giant retinal tears [105–107], and TRD in PDR [108,109]. In addition, they have also been used as short-term post-operative vitreous substitutes in particularly complicated RD cases [110,111]. PFCLs have also been successfully used in the management of suprachoroidal haemorrhage [112].

It is important to further stress that PFCLs should not be used for prolonged vitreous substitution. As already mentioned, early experimental studies in rabbits where PFCLs were used for long-term vitreous substitution showed the occurrence of severe complications [99,100]. However, if PFCLs were removed 2–4 days after introduction no significant side-effects were observed, for instance, no morphological changes in the retina were observed in animal models using pigs [113] and monkeys [114]. The use of PFCLs in human eyes, thanks to the development of appropriate surgical procedures, has generally led to few post-operative complications, however, if PFCLs are used as short-term post-operative tamponade agents a second operation for their removal is unfortunately unavoidable.

There have been some case reports in which retinal damage has been attributed to intra-vitreal [115–117] or sub-retinal retention [118–121] of PFCLs in both animal models and in humans. In fact, in spite of apparently adequate removal of PFCL at the end of the surgical procedure, PFCL bubbles may remain in the vitreous cavity post-operatively. Residual PFCL can be detected, for instance, by ophthalmic ultrasound analysis. Patients with remaining intra-vitreal PFCL must be carefully monitored to detect any sign of retinal toxicity, and an additional procedure may be required to remove residual PFCL bubbles. In the presence of RRD with severe PVR or TRD with massive proliferation, penetration of PFCL into the sub-retinal space may be an additional risk, especially for large retinotomies [121]. In that case careful PFCL–air or PFCL–physiological solution exchange must be performed, as well as drainage/active aspiration through the same retinotomy or through an additional one.

The post-operative complications related to PFCLs seem to be due to their high density (Table 4), resulting in mechanical damage to cells through compression and extensive emulsification, rather than to intrinsic toxicity of the material [122]. In addition to retinal damage, other reported complications include post-operative glaucoma due to retained intra-vitreal PFCL in human eyes [116,120] and corneal toxicity (loss of endothelial cells, stromal inflammation, neovascularisation) in aphakic rabbit eyes [115].

Weinberger et al. also reported the case of seven patients with PFCL droplets in the anterior chamber, however, after a 9 month follow-up no signs of corneal damage or intra-ocular toxicity were detected [123].

5.2.4. Semifluorinated alkanes and heavy oils

The use of semifluorinated alkanes (SFAs) in vitreo-retinal surgery is relatively new. Many lines of evidence seem to indicate that SFAs can offer the potential to act as long-term vitreous substitutes. These materials consist of short alkyl chains joined at one end or both ends to a perfluorocarbon chain, thereby corresponding to the general formulae $F(CF_2)_n(CH_2)_mH$ and $F(CF_2)_n(CH_2)_m(CF_2)_n F$ (n, m = 3–20 in both cases), respectively. SFAs are colourless (RI ≈ 1.3), immiscible with water and physically, chemically, physiologically inert [124]. Generally, SFAs are less viscous (kinematic viscosity ~2.5 cSt) than the other currently used intra-vitreal materials (Tables 3 and 4). In addition, they can be more easily handled than silicone-based oils and their density (1.1–1.7 g cm^{-3}) is lower than that of PFCLs [124–126]. SFAs are approved for clinical use in Europe and they are mainly marketed as biocompatible solvents for silicone oil. In addition, it has been demonstrated that SFAs can be successfully used as intra-operative tools to unfold and reattach the retina [127,128] and as long-term vitreous tamponade agents [129,130]. Optically clear mixtures of silicone oil and SFAs (so-called "heavy oils" or third generation silicone oils), with typical densities in the range 1.0–1.3 g cm^{-3}, have also been successfully tested in the treatment of complicated RD cases (Table 5). For instance, Densiron-68® was recently found to be safe and effective in both the treatment of primary inferior RRD cases [131] and the reoperation of persisting macular holes [132]. Long-term tamponade using this heavy oil resulted in high anatomical success and was generally accompanied by functional improvements in the patients' visual acuity [131–134] with mild post-operative complications [135]. In recent experiments HWS 46-3000 was well tolerated by the ocular tissue and its use was accompanied by a high rate of success in treating complicated RD cases [136]. In contrast, oxane HD was found to be unsuitable for clinical use due to the incidence of adverse effects, including oil emulsification, glaucoma and cataract [137–139]. A comprehensive review of the use of heavy oils in vitreo-retinal surgery was recently published by Heimann et al. [140].

Meinert and Roy underlined that SFAs have great potential for use as solvents for intra-vitreal drugs that could be released in situ post-operatively [126].

There is much reasonable evidence that both SFAs as such and, particularly, some heavy oils can be considered very promising candidates for long-term vitreous substitution thanks to their attractive characteristics, including good retinal tolerance [141] and reduced emulsification with respect to silicone oil [142]. They could successfully replace the agents currently adopted for vitreous substitution, but they are not in common use yet.

6. Towards an ideal artificial vitreous: polymers mimicking the features of natural vitreous

The drawbacks and limitations related to the currently used vitreous substitutes have led to the investigation of a wide variety of materials in the search for an ideal artificial vitreous. Table 6 lists the various candidates that have been experimentally proposed from the mid 1950s up to now. To the best of the author's knowledge none of them has been approved for clinical use.

According to the author's view, the research has essentially tried to duplicate the natural vitreous following two approaches: (i) bio-mimicry of the chemical composition of the natural vitreous, in an attempt to reproduce its structure and properties; (ii) bio-mimicry of the peculiar features of the natural vitreous, rather than its composition or structure. The final aim was to find an appropriate biomaterial to be safely and indefinitely left in situ without undergoing degradation and/or losing its physico-mechanical features. The first approach, involving the use of modified natural polymers, failed substantially. Some potential

Table 5
Relevant physical properties of the most commonly used heavy oils (adapted from Heimann et al. [140] and Mackiewicz et al. [141]).

Heavy oil	Composition	RI (at RT)	Density (g cm^{-3})	Kinematic viscosity (cSt)
Oxane HD®	5700 cSt silicone oil + RMN-3 (partially fluorinated olefin)	1.40	1.02	~3300
Densiron-68®	5000 cSt silicone oil + F_6H_8	1.387	1.06	~1500
HW 46–3000	10^5 cSt silicone oil + F_4H_6	1.369	1.105	~3100

Table 6
Experimental polymers for vitreous substitution.

First use	Polymer	Type[a]	Recipient[b]	Toxicity	Persistence[c]	Remarks	References
1954	Poly(1-vinyl-2-pyrrolidone) solutions	SP	A	No	ST		[159,160]
1961	Hyaluronic acid solutions	MNP	H	No	ST		[145,146]
1966	Polygeline	MNP	A, H	No	ST		[147,148]
1966	Hyaluronate/collagen gel	MNP	A	No	ST		[153,155]
1968	Polyacrylamide	SP	A	No	LT	Promising physico-mechanical properties; possible gel degradation during injection	[167–173]
1968	Poly(glyceryl methacrylate)	SP	A	No	LT	Traumatic implantation (dense pieces) or degradation during injection (gel)	[174,175]
1969	Collagen	MNP	A, H	Yes	ST	Unsuitable	[149–152]
1971	Poly(2-hydroxyethyl methacrylate)	SP	A	No	LT	Unsuitable (too traumatic implantation)	[176]
1984	Poly(2-hydroxyethyl acrylate)	SP	A	Yes	LT	Unsuitable	[177]
1990	Hydroxypropyl methylcellulose	SP	A	No	ST		[178,179]
1990	Pluronic F127	SP	A	Yes	ST	Unsuitable	[181]
1991	Poly(vinyl alcohol) hydrogels	SP	A	No	LT	Good maintenance of physico-mechanical properties	[182–185]
1992	Silicone gel	SP	A	No	LT	Lacking of retinal tamponade effect	[186]
1993	Hyaluronic acid hydrogel	MNP	A	No	ST/LT	Potential problems of gel coherence. Degradation time (>1 month) depends on the amount of cross-linking agent	[190,191]
1995	Poly(1-vinyl-2-pyrrolidone) hydrogels	SP	A	No	LT	Possible gel degradation during injection	[161–165]
1995	Poly(methyl 2-acrylamidoglycolate methyl ether)	SP	A	Yes	LT	Unsuitable	[187]
1997	Methylated collagen	MNP	A	No	ST		[153,154]
2000	Adcon®-L hydrogel	SP	A	Yes	ST	Unsuitable	[188]
2004	Poly(vinyl alcohol methacrylate)	SP	IV	No	LT	Significantly stiffer than natural vitreous	[189]
2006	Hyaluronic acid/gellan gum	MNP	IV	No	ST	Insufficient mechanical properties	[156]
2010	Gelatin hydrogels	MNP	A	No	ST		[192]

[a] MNP, modified natural polymers; SP, synthetic polymers.
[b] A, animal; H, human; IV, in vitro only.
[c] ST, short-term (due to resorption or degradation); LT, long-term.

substitutes for short-term use have been suggested, but the various studies have demonstrated that is impossible to duplicate Nature and to make up a "natural" vitreous artificially. Therefore, research attention has been progressively drawn to synthetic polymers that are chemically different from natural vitreous but are potentially able to mimic its physico-mechanical properties.

The following sections give an overview of the potential vitreous substitutes tested in both approaches. In the mid 1990s Chirila et al. extensively reviewed the early attempts at vitreous replacement using hydrophilic polymers [27,28], and in 2000 Colthurst et al. [143] gave an overview of new advances. More recently, part of a review of biomaterials used in the treatment of RD was dedicated to this topic, but such work is incomplete [144]. The history and performance of experimental polymers have now been exhaustively reviewed, and advances over the last decade, as well as the promise for the future, particularly highlighted.

6.1. First approach: compositional/structural bio-mimicry

6.1.1. Hyaluronic acid

Hyaluronic acid and its derivatives, such as sodium hyaluronate, have been widely tested as vitreous substitutes in humans since the early 1960s [145]. The choice of hyaluronic acid seemed reasonable as it is one of the two major components, together with collagen, of the natural vitreous. Sodium hyaluronate is commercially available in a wide range of solutions for pharmaceutical use, and it showed excellent biocompatibility and tolerance in ocular tissues. However, these solutions were found to be unsuitable for prolonged post-operative vitreous tamponade due to their short residence time in the vitreous cavity [146].

6.1.2. Gelatin and collagen

Gelatin is a collagen derivative marketed worldwide in various forms. As for hyaluronic acid, the use of this material was suggested based on the fact that collagen is present in the natural vitreous.

In 1966 Oosterhuis et al. implanted polygeline, a polymer of urea and polypeptides derived from degraded gelatin, in rabbit eyes [147]. Further studies in humans [148] showed that the material (RI = 1.3390, M_w = 35 kDa) was well tolerated in all cases without adverse tissue reactions and immediate retinal reattachment was achieved in most patients. However, polygeline exhibited a short retention time in the vitreous cavity and a rapid decrease in viscosity. Attempts to increase the material viscosity by adding

gelatin, agar, methylcellulose or poly(ethylene glycol) caused inflammation of the ocular tissues and vitreous opacification. Therefore, polygeline was deemed suitable only as a short-term vitreous substitute. Despite good biocompatibility and optical properties, there have been no other studies on the ocular use of polygeline.

In the late 1960s a proctase-treated collagen gel was also tested for vitreous replacement in animal models. Studies in rabbits by Stenzel et al. [149] and in monkeys by Dunn et al. [150] showed that collagen did not elicit adverse effects in ocular tissues other than mild transient inflammation.

In the early 1970s Pruett et al. tested collagen gels in human patients [151,152]. Moderate inflammation of the ocular tissues was reported, together with other severe complications related to clinical outcomes. Only 19% of the cases exhibited retinal reattachment and all patients had blurred vision due to vitreous opacification. In addition, the gel underwent fragmentation during injection, decreasing its mechanical properties.

More recently, some of these drawbacks were overcome by using methylated type I/III collagen [153,154]. After material implantation in rabbit eyes no inflammation and no vitreous/lens/cornea opacification was detected, however, a poor tamponade effect due to a low surface tension made this polymer unsuitable for RD treatment.

6.1.3. Hyaluronate/collagen gel mixture

Special mention should be made of the so-called "reconstituted vitreous", a mixture of sodium hyaluronate and collagen, which are the two major structural components of the vitreous body. The basic idea, proposed in the 1960s by Balazs and Sweeney [155], was fascinating since the aim was to mimic Nature by duplicating both the composition and structure of the natural vitreous. After injection at low temperature (~10 °C) the mixture underwent gelification in situ at body temperature. However, in vivo studies revealed problems of gel hazing during post-operative follow-up and, occasionally, ocular tissue inflammation. In addition, the material was completely bioabsorbed within 5 months after implantation.

More recently, Nakagawa et al. injected different formulations of hyaluronate/collagen gels into rabbit eyes [153], however, these gels were not considered suitable for long-term vitreous substitution due to their water solubility and, therefore, their tendency to become viscous solutions rather than gels over time, resulting in a poor tamponade effect on the retina.

6.1.4. Hyaluronic acid/gellan gum gel

In 2006 Suri and Banerjee suggested the use of a mixture of hyaluronic acid and gellan gum for vitreous replacement [156]. Gellan gum formed a gel at room temperature and the gel structure was maintained at body temperature. In vitro cytotoxicity tests using mouse fibroblast cells showed excellent biocompatibility (cells viability >90%). However, the rheological and mechanical properties were found to be insufficient with respect to those of natural vitreous. An attempt to improve the mechanical properties of the gel was carried out by adding $CaCl_2$ to the gellan gum/hyaluronic acid mixture in order to obtain a highly cross-linked hydrogel, but further studies are necessary. However, the gel does not seem suitable for long-term tamponade as it degrades after 1 week of soaking in simulated body fluids.

6.1.5. Occasionally tested polysaccharides

Various solutions of different polysaccharides, e.g. dextran, dextran sulphate, sodium alginate, alginic acid and chondroitin sulphate, have occasionally been tested as vitreous substitutes in animal models and humans [157,158]. No or only mild inflammation was usually reported, but often the vitreous underwent hazing and the materials failed to produce reattachment of the retina due to their poor tamponade effect.

6.2. Second approach: functional bio-mimicry

6.2.1. Poly(1-vinyl-2-pyrrolidone)

Chronologically, poly(1-vinyl-2-pyrrolidone) (PVP) was the first synthetic polymer to be tested as a potential vitreous substitute. In 1954 Scuderi [159] injected variable amounts of PVP solutions in rabbit eyes. No adverse histological reaction was reported, but problems of opacification occurred. In 1959 Hayano and Hoshino tested PVP solutions with different dilution rates in human eyes with RRD [160]. PVP induced a lesser inflammatory reaction than physiological solutions but no data about polymer retention in the vitreous cavity were reported. No other studies on the use of PVP solutions are available in the literature.

More recently, Chirila and co-workers performed a careful selection of PVP gels on the basis of their viscoelastic properties. Eventually, 1-vinyl-2-pyrrolidone (VP) monomer was polymerized with divinyl glycol (DVG) as cross-linking agent to obtain a transparent (RI = 1.3390) hydrogel with a density and viscosity very similar to those of human vitreous [161,162]. The cross-linked PVP was implanted in rabbit eyes. No damage to the retina was detected, but vitreous opacification occurred. In addition, the polymer underwent biodegradation due to phagocytosis [163]. VP was also co-polymerized with 2-hydroxyethyl methacrylate (HEMA) using DVG or diallyl ether (DAE) as cross-linking agent and the hydrogel obtained was implanted in rabbit eyes [164]. The resulting gel was clear, transparent, insoluble in water and exhibited mechanical properties close to those of natural vitreous. From a clinical viewpoint, no adverse effects were detected after implantation, except for transient vitreous opacity. However, the process of injection via a small gauge needle caused polymer fragmentation, resulting in a decrease in the hydrogel mechanical properties. Furthermore, all eyes were characterized by the presence of inflammatory cells and vacuoles containing granular material, which indicates that the material underwent phagocytosis [163].

Dalton et al. performed a detailed study on selected cross-linked PVP-based polymers and suggested that rheological analysis can provide useful eliminatory criteria in the selection of potential vitreous substitutes [165].

6.2.2. Polyacrylamide

Although acrylamide as such is highly toxic, after complete polymerization the resulting polymer exhibits good biocompatibility. Obviously, the presence of residual monomer can have dramatic effects on patient health.

In 1968 Muller-Jensen and Kohler [166] reported several clinical trials concerning the use of polyacrylamide (PAA) as a vitreous substitute in rabbit eyes. The monomers were polymerized directly inside the vitreous cavity without using cross-linking agents. Irritation was observed in all cases in the course of the first post-operative days and the vitreous underwent opacification at high PAA concentrations, however, no histological degeneration was observed within 3 months after implantation. Cross-linked PAA was also implanted into rabbit eyes after in situ polymerization, with better clinical outcomes [167]: the material was well tolerated by the tissues and remained clear 14 months after implantation. In 1973 Refojo and Zauberman [168] reported a detailed investigation of the optical properties of cross-linked PAA.

For many years no further studies were performed on the use of PAA as a potential vitreous substitute. In the mid 2000s acrylamide and bis(acryloyl)cistamine (BAC) were co-polymerized with disulphide cross-linking agents by Ravi and co-workers [169–173]. The use of disulphide cross-linkers allowed highly purified final

polymer to be obtained by removing all the residual monomers. Two procedures are possible for implantation: the gels can be formed directly in the eye or the final polymer can be injected into the vitreous cavity without undergoing fragmentation or loss of elasticity and mechanical properties, as demonstrated by preliminary tests carried out using human eyes from cadavers or ex vivo porcine eyes as recipients [169,173]. Furthermore, in vitro tests showed that the biocompatibility of the gel can be further improved by adding N-phenylacrylamide (hydrophobic monomer) [170]. These promising results justify further investigations of the suitability of PAA as an artificial vitreous.

6.2.3. Poly(glyceryl methacrylate)

In 1968 Refojo and co-workers first used poly(glyceryl methacrylate) (PGMA) as a vitreous substitute [174]. Spherical pieces of dehydrated PGMA were implanted in the rabbit vitreous cavity through a small surgical incision. The implants swelled in situ after contact with vitreous fluid, reaching post-operative volumes up to 32 times greater than in the dry state. The hydrogel was found to be highly biocompatible (no inflammation or clinical complications were detected), but PGMA was eventually considered unsuitable for clinical use as its implantation was too traumatic. Furthermore, swelling was too slow, resulting in problems with immediate tamponade affects.

In 1976 Hogen-Esch et al. synthesized an injectable PGMA hydrogel using very low amounts of cross-linking agent [175]. The gel was able to absorb up to 96 wt.% saline solution, and after swelling remained soft and sufficiently transparent. Although a slight loss of light transmittance was found, the final RI (1.3364) was still very close to that of natural vitreous. After implantation in rabbit eyes good clinical outcomes without complications were observed, however, as the hydrogel underwent fragmentation upon injection no further studies were carried out on PGMA as a vitreous substitute.

6.2.4. Poly(2-hydroxyethyl methacrylate)

In the early 1970s Refojo implanted solid pieces of poly(2-hydroxyethyl methacrylate) (PHEMA) into rabbit eyes [176]. PHEMA was well tolerated by ocular tissues, did not elicit retinal damage and did not undergo bioabsorption or biodegradation. It was insoluble in water and, being solid, could maintain its position post-operatively in the vitreous cavity better than a liquid agent. However, its implantation required difficult and often too traumatic surgical procedures and, therefore, no further investigations were undertaken.

6.2.5. Poly(2-hydroxyethyl acrylate)

In the early 1980s Chan et al. tested poly(2-hydroxyethyl acrylate) (PHEA) as a potential vitreous substitute in rabbit eyes [177]. The hydrogel exhibited excellent physical properties, such as high transparency, a viscosity similar to that of natural vitreous, non-absorbability and easy injectability, which made it, theoretically as well as experimentally, an ideal artificial vitreous. However, some adverse effects have been reported. PHEA induced corneal oedema, glaucoma and damage to the lens, as well as opacification, formation of fibrous membranes in the vitreous cavity and severe retinal complications. Therefore, the material was considered unsuitable for clinical use.

6.2.6. Hydroxypropyl methylcellulose

In 1990 Fernandez-Vigo et al. injected a solution of hydroxypropyl methylcellulose (HPMC) (viscosity ~6000 cSt, M_w = 86 kDa) in rabbit eyes [178]. HPMC was completely eliminated from the vitreous cavity within 10 weeks after implantation and, therefore, HPMC solutions were deemed unsuitable both for long-term vitreous replacement and for sealing retinal holes in RRD due to the lack of a tamponade effect. However, the excellent biocompatibility of HPMC encouraged the same research group to perform another animal study in which they demonstrated that it was possible to control and tailor the residence time of HPMC in the vitreous cavity by varying its molecular weight [179]. Specifically, using a product of M_w = 120 kDa and viscosity ~6000 cSt the half-life of the substitute was 38 days. Nonetheless, such a substitute was still unsuitable for prolonged tamponade.

6.2.7. Pluronic F127

Pluronic F127 (P-F127) solutions at a concentration of 20 wt.% and above show thermoreversible gelation behaviour [180]. For instance, a 20 wt.% P-F127 solution is liquid when cold but forms a clear gel (RI = 1.032) at 21 °C as the solution is heated. In spite of the attractive physical properties, P-F127 solutions were found to be unsuitable for vitreous substitution. In 1990 Davidorf et al. [181] showed that the polymer can induce severe retinal toxicity and, therefore, it was considered unsuitable for clinical use.

6.2.8. Poly(vinyl alcohol)

In 1991 Benlian et al. first selected poly(vinyl alcohol) (PVA) as a potential vitreous substitute on the basis of its optical properties [182]. The preliminary results after implantation in rabbit eyes were promising, as no inflammation or damage to the retina was detected after 2 months follow-up.

In 1991 Yamauchi [183] also reported an extensive investigation on autoclave sterilized PVA hydrogels consisting of 99 wt.% water. The gels were produced by γ-irradiation of a 7 wt.% PVA solution and then injected into rabbit eyes. A comparison of the performance with respect to saline solution was also reported. Inflammation and long-term vitreous opacification occurred more frequently with PVA than with physiological solutions. The short-term optical properties were excellent, as the gels were indistinguishable from the host vitreous during the first post-operative weeks. A mixture of PVA/chondroitin sulphate was also studied. It displayed superior transparency to PVA and absorbed more water than PVA alone, but it was found to be less biocompatible in rabbit eyes.

In 2006 Maruoka et al. [184] prepared PVA hydrogels by treating the polymer solution in an autoclave before γ-irradiation and injected the gels thus obtained into monkey eyes. During the first post-operative weeks ocular inflammation and an increase in IOP occurred; 3 months after implantation the eyes had regained normal IOP and retinal activity.

In 2010 Leone et al. synthesized PVA hydrogels using different amounts of trisodium trimetaphosphate (TSTMP) as cross-linking agent [185]. The authors performed a very comprehensive characterization of the materials, including light transmittance, water content assessment, rheological measurements (oscillatory shear stress analysis, shear creep analysis and thixotropic properties) and in vitro cytotoxicity assays. In addition, the diffusion behaviour of the hydrogel using a model solute was assessed. All these tests seemed to show that the hydrogel with a molar ratio TSTMP:PVA of 1:8 fulfilled the requirements for a good vitreous substitute.

Due to their good optical properties, rheological features and long-term biocompatibility PVA hydrogels are promising candidates for vitreous substitution, but further studies need to be performed to collect more data on their retention time, mechanical properties and ability to reattach the retina.

6.2.9. Silicone gel

In 1992 Peyman et al. [186] injected silicone gel into monkey eyes. Specifically, two polymer formulations, clear and cloudy gels, were tested. The liquid monomers were injected into the vitreous cavity where polymerization occurred in situ. Apart from minimal inflammation lasting for 1 week post-operatively, no other adverse

effects were reported. No retinal damage was detected, and both gels maintained their cohesiveness and, specifically, the clear gel remained transparent post-operatively. However, these silicone gels were hydrophobic and, therefore, they exerted a very poor tamponade effect on the retina, remaining separated from it. Thus, silicone gels were deemed unsuitable for the treatment of RD cases.

6.2.10. Poly(methyl 2-acrylamidoglycolate methyl ether)

In 1995 Chirila et al. performed a careful selection among several polymers derived from (methyl 2-acrylamidoglycolate methyl ether) as potential vitreous substitutes [187]. Eventually, the homopolymer poly(methyl 2-acrylamidoglycolate methyl ether) (PMAGME), synthesized in 80 wt.% water and without cross-linking agents, was selected for in vivo testing in rabbits. Negligible fragmentation upon injection was observed, but severe post-operative clinical complications were reported, including RD, inflammation and damage to the optic nerve. The cause of the toxic effect remained unclear, as it could be due to the polymer itself or, maybe more reasonably, to residual toxic acrylamide. The authors first reported the results of in vitro studies using mouse fibroblasts, which revealed cytostatic and cytocidal effects of the hydrogel [187]. For the first time in vitro cytotoxicity testing was suggested as an important criterion for preliminary selection of biomaterials as potential vitreous substitutes.

6.2.11. Adcon®-L hydrogel

In 2000 De Jong et al. [188] reported a study of the use of Adcon®-L hydrogel for vitreous substitution in the right eye of five rabbits. Adcon®-L hydrogel, a polymer of proteoglycan esters in porcine gelatin, is highly biocompatible and is currently used in neurosurgery without unwanted side-effects. However, this material was found to be unsuitable as a vitreous substitute, as severe post-operative complications were reported. The results obtained suggested potential retinal toxicity of this hydrogel, as well as a significant and persistent post-operative inflammation reaction. Other reported complications were cornea opacification in two rabbits and cataract in all rabbits. In addition, biodegradation rate of the hydrogel was rather fast and it had totally disappeared from the vitreous cavity after 3 weeks.

6.2.12. Poly(vinyl alcohol methacrylate)

In 2004 Cavalieri et al. [189] carried out preliminary investigations on poly(vinyl alcohol methacrylate) (PVA-MA) to test its potential suitability as a vitreous substitute. The polymer contained a photoinitiator and the gel network could be formed by irradiation at 365 nm. The degree of cross-linking could be tailored by varying the photoinitiator concentration and the radiation exposure time. PVA-MA was able to gel in situ, but only at polymer concentrations above 4 wt.%. In vitro tests using bovine serum showed that hydrogel degradation occurred in the presence of a low degree of cross-linking. Thus, potentially suitable PVA-MA hydrogels were deemed to be those synthesized at high polymer concentrations and with a high degree of cross-linking, however, such gels were found to be significantly stiffer than natural vitreous. Further studies addressing reducing this mismatch between the mechanical properties of PVA-MA and those of natural vitreous are needed to understand whether such a material remains a valid contender for vitreous substitution.

6.3. A meeting point between the two approaches: a promise for the future

As mentioned above, perhaps the major limitation of modified natural polymers is their short residence time in the vitreous cavity and a poor tamponade effect, which makes them unsuitable in the treatment of RD cases. The development of hyaluronic acid and gelatin hydrogels could provide a new class of substitutes combining a composition similar to that of the natural vitreous with appropriate physico-mechanical properties, degradation kinetics and tamponade ability.

6.3.1. Cross-linked hyaluronic acid

In the early 1990s Balazs and co-workers developed the so-called "hylan gel", obtained by cross-linking sodium hyaluronate with divinyl sulphone or formaldehyde [190]. The gel, tested in rabbits and monkeys, was water insoluble and biocompatible, however, it could enter the sub-retinal space through retinal breaks due to its insufficient coherence.

Very recently promising results were achieved by Su et al. [191], who synthesized a hydrogel formed of oxidized hyaluronic acid cross-linked with adipic acid dihydrazide (ADH). The refractive index of the final hydrogel was in the range 1.3420–1.3442, which is quite similar to that of human vitreous. In vitro degradation tests showed that the hydrogel maintained the gel matrix over 35 days, depending on the ADH concentration. Interestingly, cytotoxicity was evaluated using RPE cells and the material was found to be non-toxic. In addition, the hydrogel was injected into the vitreous cavity of rabbit eyes with no adverse reactions being detected after 3 weeks. Further tests on the mechanical properties of the gel are necessary, but these preliminary results make it an interesting candidate as a potential long-term vitreous substitute.

6.3.2. Cross-linked gelatin

In 2010 Lai investigated the ocular biocompatibility of two chemically modified gelatin hydrogels in detail [192]. These materials were proposed as aqueous humour substitutes and matrices for controlled drug delivery, as well as potential application in the context of vitreous replacement. The gelatin base was cross-linked with glutaraldheyde (GTA) or 1-ethyl-3-(3-dimethyl aminopropyl)carbodiimide (EDAC). A significant inflammatory reaction was elicited by the presence of GTA-treated material, whereas gelatin cross-linked with EDAC exhibited good biocompatibility and was well tolerated without eliciting adverse effects. These preliminary results warrant further study, particularly an assessment of the potential residence time of the gelatin hydrogel in the vitreous cavity.

7. Hydrogels: the best candidates for vitreous substitution?

The existing literature demonstrates that, ideally, optically transparent and biocompatible solutions of several polymers can be successfully used as short-term vitreous substitutes without inducing clinical post-operative complications in the patient eye. In contrast, the search for a suitable biomaterial to be used as a long-term substitute is a more complex issue. Essentially, the major problem is to find an appropriate formulation that can be left in situ indefinitely without unwanted long-term side effects requiring removal of the substitute. An ideal candidate for an artificial vitreous should closely mimic the light transmittance of the natural vitreous humour, as well as its physical and mechanical properties. Most importantly, the features should not change post-operatively. Polymeric hydrogels seem to be promising materials for long-term vitreous replacement, as they generally show excellent transparency, are highly biocompatible and can act as viscoelatic shock-absorbing materials, thereby closely mimicking the behaviour of natural vitreous. By varying the formulation and synthetic process of the hydrogel the density and rigidity of the final vitreous substitute could be tailored to match those of natural vitreous. In addition, some experimentally tested hydrogels can gel after injection into the vitreous cavity, thereby avoiding gel

fragmentation due to shear stresses during injection through small gauge needles. An interesting approach to solve this problem was recently proposed by Ravi and co-workers [169,173], who studied the in situ regelation of PAA gels. Finally, hydrogels might be used as smart matrices for controlled drug release within the vitreous cavity of patients suffering from serious intra-vitreal problems, such as PVR.

At present cross-linked PVA [184,185] and PAA [169,173] seem to be the most promising candidates as long-term vitreous substitutes and, therefore, they are undoubtedly worthy of further investigation and experimentation in the next few years.

8. Criteria and guidelines for selecting suitable vitreous substitutes

Over the years many substances have been proposed as potential candidates for vitreous substitution, but in most cases they were selected according to ambiguously defined criteria. In general, ease of injection and good optical transparency (before and after injection) have been considered the primary criteria of choice, but often no systematic investigation of the biocompatibility of the potential vitreous substitute or of injection-induced changes in its rheological properties have been carried out prior to in vivo testing.

In the mid 1990s Chirila et al. [187], in a study of PMAGME, for the first time suggested the use of in vitro cytotoxicity testing as an eliminatory criterion in the selection of polymers as potential vitreous substitutes. Such tests are also useful because they avoid unnecessary animal experiments. Another important eliminatory criterion arises from the consideration that the natural vitreous body possesses viscoelastic properties, therefore, a potential candidate for prolonged vitreous substitution should be viscoelastic and exhibit rheological properties similar to those of the natural vitreous. In this viewpoint, cross-linked gels have been shown to be very suitable for vitreous replacement. However, a serious problem has to be considered: the shear stresses produced by polymer injection into the vitreous cavity cause significant deformation of the gel, possibly resulting in physical properties different from those displayed before injection. A detailed study by Dalton et al. clearly demonstrated that careful rheological analysis plays a crucial role in the selection of hydrogels as vitreous substitutes [165]. Specifically, the effect of gel injection through small gauge needles should be investigated, since it can have detrimental consequences on the mechanical properties of the polymer.

In the next few years it would be very useful to elaborate a standard and detailed protocol for selecting and testing materials proposed as potential vitreous substitutes. Very recently Leone et al. published a comprehensive and complete research work on the suitability of different cross-linked PVA hydrogels for vitreous replacement [185]. Taking this work as a starting point and on the basis of the suggestions provided over the years by other authors [27,165], it is possible to draft an ideal testing protocol that should include the following investigations before eventual in vivo experimentation:

(i) light transmittance (for instance by UV–vis spectrophotometry);
(ii) assessment of the kinetics of hydration, water uptake and swelling (for instance by weight measurements);
(iii) rheological measurements: oscillatory shear stress analysis, shear creep analysis and thixotropic properties (using a rheometer);
(iv) assessment of the diffusion coefficient of a model solute (for instance by means of NMR spectroscopy, as done for the first time by Leone et al. in a pilot study [185]);
(v) in vitro biocompatibility, cell proliferation and cell viability tests (the appropriate ISO standard should be followed [193]; the cell type for preliminary tests could be mouse fibroblasts, as already used by Chirila and co-workers [165], Suri andBanerjee [156] and Leone et al. [185], or RPE cells as used by Su [191]);
(vi) evaluation of possible degradation of the vitreous substitute during injection, for which ex vivo animal or human cadaver eyes could be used, as was done by Ravi and co-workers [169,173].

9. Conclusions

Replacement of the vitreous body is a challenging and also complex issue of ophthalmic research. Although several and various substances have been proposed over the years as potential vitreous substitutes, at present only silicone oil is used in clinical practice for long-term vitreous substitution, although it may induce several clinical complications. Gases are used as temporary vitreous substitutes, and PFCLs are recommended for intra-operative use only during vitrectomy procedures. The future of vitreous substitutes is to find an appropriate biomaterial that can be left in situ indefinitely without long-term complications. Primarily, an ideal artificial vitreous should mimic the light transmittance and mechanical properties of the natural vitreous. Polymeric hydrogels seem to be promising materials for long-term vitreous replacement, as they exhibit excellent transparency, are highly biocompatible and can act as viscoelastic shock-absorbers, thereby closely mimicking the behaviour of the natural vitreous. By varying the formulation and synthetic process of the hydrogels the density and rigidity of the final vitreous substitute could be tailored in order to match those of the natural vitreous. Furthermore, it has been demonstrated that some hydrogels can undergo in situ gelation after injection into the vitreous cavity, thereby avoiding unwanted injection-induced changes in the final gel. Eventually, hydrogels may also be used as matrices for intra-vitreal drug release. On the basis of studies available in the literature up to now, cross-linked PVA and PAA seem to be the most promising candidates, but they were not yet approved for clinical use.

Another class of very attractive substances comprises SFAs and the so-called "heavy oils" (mixtures of silicone oil and SFAs), that in the last decade have been successfully studied for the management of primary and persistent RRD cases with very good long-term clinical outcomes. Further studies on the potential and performance of these tamponade agents are currently in progress, but they are already marketed worldwide and used by several ophthalmic surgeons in clinical practice.

The development in the next few years of a standard protocol for selecting and investigating potential vitreous substitutes would be desirable, as a useful tool for researchers working on this topic.

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Appendix A. Figures with essential colour discrimination

Certain figures in this article, particularly Figures 1–3, are difficult to interpret in black and white. The full colour images can be found in the on-line version, at doi:10.1016/j.actbio.2010.10.030.

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