

# A Novel Artificial Vitreous Substitute – Foldable Capsular Vitreous Body

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## 1. Introduction

The natural vitreous is a transparent, gelatinoid structure occupying four-fifths of the volume of the eye. It has a thin, membrane-like structure corresponding to the vitreous cortex that extends from the ora serrata to the posterior pole.<sup>1</sup> It is somewhat spherical but slightly flattened meridionally, and it has a cup-shaped depression in its anterior side. It consists of about 99% water by weight, collagen fibers (types II, V/XI, VI, and IX), hyaluronic acid, opticin, fibrillin, and hyaluronan, which can maintain a certain spatial relationship with dipolar water molecules.<sup>1,2</sup> However, very few cells are found in the vitreous body. These cells are mostly phagocytes that clear useless cellular debris and hyalocytes mainly found at the periphery and that produce hyaluronic acid and collagen. In human adults, the vitreous body has an approximate weight of 4 g, a density of 1.0053–1.0089g cm<sup>-3</sup>, a refractive index of 1.3345–1.3348, and a PH range of 7.0–7.4.<sup>3-5</sup>

The physiological function of the vitreous body involves supporting adjacent posterior segment structures, providing an ocular refractive medium, and acting as a cell barrier to inhibit cell migration from the retina to the vitreous cavity.<sup>6</sup> With age, the natural vitreous body gradually shrinks and collapses during the course of syneresis. This phenomenon may eventually lead to posterior vitreous detachment and can play a crucial role in the formation of retinal breaks which result in rhegmatogenous retinal detachment if untreated.<sup>7,8</sup>

The removal of diseased vitreous bodies using pars plana vitrectomy combined with artificial vitreous substitutes can restore vision in many patients. These individuals include those affected by proliferative diabetic retinopathy, proliferative vitreoretinopathy, and endophthalmitis or patients otherwise regarded as hopeless.<sup>9-11</sup>

The vitreous body cannot regenerate, so the vitreous cavity must be filled with suitable artificial vitreous substitutes that will keep the retina in place and prevent phthisis bulbi. Artificial vitreous substitutes are one of the most interesting and challenging topics of research in ophthalmology.<sup>2</sup> A number of artificial vitreous substitutes, such as gas, silicone oil, heavy silicone oil, and hydrogels, have been used.<sup>2,12</sup>

There are three major categories of currently available gas vitreous substitutes: air substitutes, expansile gas substitutes, and Xenon. Gases are used for pneumatic retinopathy

and post-operative endotamponade. However, they are suitable only as short-term vitreous substitutes (Table 1).<sup>13</sup>

G	Molecular Weight	Purity (mol%)	Expansion Coefficient	Duration* (day)	Expansion Concentration (%)
Air	29	--	0	5-7	-
Xenon	131	99.995	0	1	-
SF6	146	99.9	1.9-2.0	10-14	18
C2F6	88	99.7	1.9	10-14	-
C4F8	138	99.9	3.3	30-35	16+
C3F8	188	99.7	4	55-65	14

Table 1. Physical characteristics of gases as vitreous substitutes

In 1969, Norton et al. highlighted the advantages of clinical management with intravitreal air for the treatment of giant retinal tears.<sup>14</sup> However, the intravitreal longevity of air is only a few days<sup>15</sup> due to diffusion across the retina. The refractive index of the air (1.0008) is also incompatible with optically important tissues. Therefore, these issues limit the use of air. To date, air is mainly used in liquid-air exchanges during vitrectomy procedures.<sup>16</sup>

In 1973, Norton first experimented with sulphur hexafluoride (SF6) and found that the persistence of the gas and its expansile characteristics are superior to air. SF6 expands to twice its volume by dissolving nitrogen, oxygen, and carbon dioxide from the blood. It also stays in the vitreous cavity for about two weeks.<sup>17</sup> In 1980, Lincoff et al. proposed the use of perfluorocarbon gases<sup>18</sup>. These gases expand after intravitreal injection because of the diffusion of other gases from the blood stream. Perfluoropropane expands to four times its original volume by the fourth day after injection. It is also absorbed at a much slower rate than air or sulphur hexafluoride. To date, C3F8 is the agent of choice. Expansile gases last longer in the vitreous chamber than air, but they are spontaneously absorbed in 6 to 80 days and replaced by aqueous humor. Therefore, postsurgical removal is avoided if they cause certain concomitant complications.<sup>19</sup> However, they may induce lens opacification and usually result in a high intraocular pressure (IOP).<sup>20,21</sup> As with air, the refractive indices of gases are also lower (w1.17).<sup>22</sup>

Xenon was tested in rabbit eyes to evaluate its longevity in the vitreous cavity.<sup>23</sup> It is considered as the most promising gas with successful retinal reattachment in all cases. However, the major drawback is its rapid disappearance; almost 90% of Xenon disappears 3 h after introduction.<sup>24</sup>

Silicone oil is hydrophobic, viscous, transparent, and stable. It has a specific gravity of 0.97 g/mL and a refractive index of 1.4. Its viscosity is measured in centistokes and linearly varies with chain lengths and molecular weight. The 1,000 and 5,000 centistoke varieties are commonly used in clinics. The surface tension is approximately 40 mN/m. Introduced by Cibis in 1962,<sup>25</sup> silicone oil has been the most important adjunct for internal tamponade in the treatment of complicated retinal or choroidal detachment for the past five decades. It is

commonly applied for the treatment of superior retinal detachment through buoyancy force and high interfacial tension. It is the only substance currently accepted as a long-term vitreous substitute and is the preferred choice in complex retinal detachments, such as long-standing rhegmatogenous retinal detachment, traction retinal detachment, giant retinal tears, proliferative diabetic retinopathy, and severe endophthalmitis involving the posterior segment.

However, the use of silicone oil has not always been successful. An anatomic success rate of around 70% has been reported,<sup>19</sup> with complications including cataract, keratopathy, anterior chamber oil emulsification, and glaucoma.<sup>26</sup> Several reports have demonstrated the migration of silicone oil droplets into the retina and the optic nerve. Others have shown the widespread loss of myelinated optic nerve fibers due to the oil's free-fluid characteristics within the eye.<sup>27, 28</sup>

Heavy oil, a solution of perfluorohexyloctane and silicone oil prepared as internal tamponade, has recently been used in retinal detachment surgery. However, it causes complications, such as emulsification and inflammatory reaction.<sup>29</sup> Some very recent results are encouraging,<sup>30</sup> but most clinicians are awaiting results from ongoing heavy silicone oil trials.<sup>12</sup>

Hydrogels and smart hydrogels seem to remain as the best candidates as long-term vitreous substitutes because they show excellent transparency and good biocompatibility. They can act as viscoelastic shock-absorbing materials, thereby closely mimicking the behavior of natural vitreous bodies. Hydrogels are networks of polymer chains that can contain over 99.9% water so they are hydrophilic and not flowable. Currently, a number of cross-linked polymeric hydrogels have been proposed, such as poly (vinyl alcohol) (PVA), poly poly (1-vinyl-2-pyrrolidone), poly (acrylamide) (PAA), and poly (ethylene glycol) (PEG).<sup>2,12,31-34</sup> Among these, the PVA and PAA hydrogels are the most promising candidates for long-term vitreous body replacement and are highly recommended for use. They show excellent biocompatibility, are biodegradable, and can closely mimic the physico-mechanical properties of natural vitreous bodies.<sup>2</sup> PEG is a synthetic water-soluble polymer that has been approved by the Food and Drug Administration (FDA) for use in a wide range of biomedical applications, including injectable hydrogels.<sup>35</sup> However, issues such as retinal toxicity, increased IOP, and formation of opacities still need to be addressed.<sup>36</sup> Fragmentation and changes in viscoelastic properties and resiliency after injection through a small-gauge needle have also been found in some types of hydrogels.<sup>36, 37</sup>

Smart hydrogels are a relatively new class of stimuli-sensitive hydrogels. They possess the common properties of conventional hydrogels, and they can respond to a variety of signals, including PH, temperature, light, pressure, electric fields, or chemicals.<sup>38</sup> Temperature-sensitive hydrogels, such as poly(N-isopropylacrylamide), the most extensively studied one, undergo sharp hydrophilic-hydrophobic transition in aqueous media at a lower critical solution temperature of 32 °C, which is close to the body temperature.<sup>39</sup> Generally, smart hydrogels appear promising, but they are still at an early experimental stage, and their long-term toxicity is unknown.<sup>12</sup> Therefore, despite half a century of research efforts to replace the vitreous body of the eye, an ideal and permanent vitreous body replacement has yet to be found.<sup>40,41</sup>

Current research on artificial vitreous bodies aims to determine ideal materials that are nontoxic and inert, thin and transparent, and have good water and oxygen permeability, high compatibility, and good elasticity<sup>46</sup> in order to mimic the natural vitreous perfectly. The materials must be hydrophilic and can form a gel within the vitreous cavity.<sup>35</sup> However, directly injected vitreous substitutes, like silicon oil and heavy silicon oil, often result in severe complications, such as intraocular toxicity, retinal cell proliferation, leakage into the anterior chamber, and difficulty of complete removal if emulsified with time, among others.

Inspired by the structure of the natural vitreous, we postulated a novel foldable capsular vitreous body (FCVB) to restore the shape and function of the natural vitreous body. The FCVB consisted of a capsule, drain tube, and valve. The capsule exactly mimicked the vitreous body using a computer. The intra-capsule pressure can be adjusted from the valve with a syringe, and there is a slice of anti-penetrating metal in the valve. Figure 1 and Table 2 show the images and parameters of the FCVB, respectively.<sup>50</sup> Silicone rubber elastomer has been used for tissue augmentation for many years,<sup>43-45</sup> so it was utilized to manufacture the capsule of FCVB. It showed good oxygen permeability, good mechanical and optical properties (Shore A hardness: 37.4, tensile intensity: >5.86 MPa, elongation ratio: >1200%, tear intensity: 34KN/m, transmittance: 93%, Hazes<1%),<sup>46</sup> and good biocompatibility as shown in stable extracts experiment (no significant fever, good genetic safety, and no structural abnormality or apoptosis in the cornea, ciliary body, and retina over a six-month observation period).<sup>50</sup> After pars plana vitrectomy, the seamlessly connected FCVB was triple-folded and inserted into the vitreous cavity through a 3 mm × 1 mm scleral incision without air fluid exchange. Then an injectable medium, such as balanced salt solution (BSS) or silicone oil, can be injected into the capsule and inflated to support the retina. Through the tube–valve system, IOP can be adjusted by the volume of the injected medium. Similar to the glaucoma valve, the valve can be fixed onto the sclera surface.<sup>46</sup>

Component parts		Dimension (mm)	Permissible deviation (mm)
Capsule	Diameter	20.00	±2.00
	Rise of arch	2.00	±0.20
	Radius of curvature of fovea lentis	6.00	±0.50
	Chord length of fovea lentis	9.50	±0.50
	Optic part thickness	0.06	±0.02
Drain tube	Outside diameter	1.50	±0.20
	Inner diameter	1.20	±0.20
	Tube length	4.00	±0.50
	Vertical distance from the open end to the principal axis	7.99	±0.20
Drain valve	Top diameter	4.00	±0.20
	Bottom diameter	6.00	±0.20
	Total thickness	3.50	±0.20
	Puncture part thickness	2.00	±0.20
	Location hole diameter	0.50	±0.05

FCVB, foldable capsular vitreous body; BSS, balanced salt solution.

*Note:* The FCVB consisted of capsule, drain tube, and valve. The capsule was mimicking the vitreous body exactly by computer, and BSS was injected through the tube-valve system to inflate the capsule.

Table 2. Standard dimensions of the components of the human FCVB

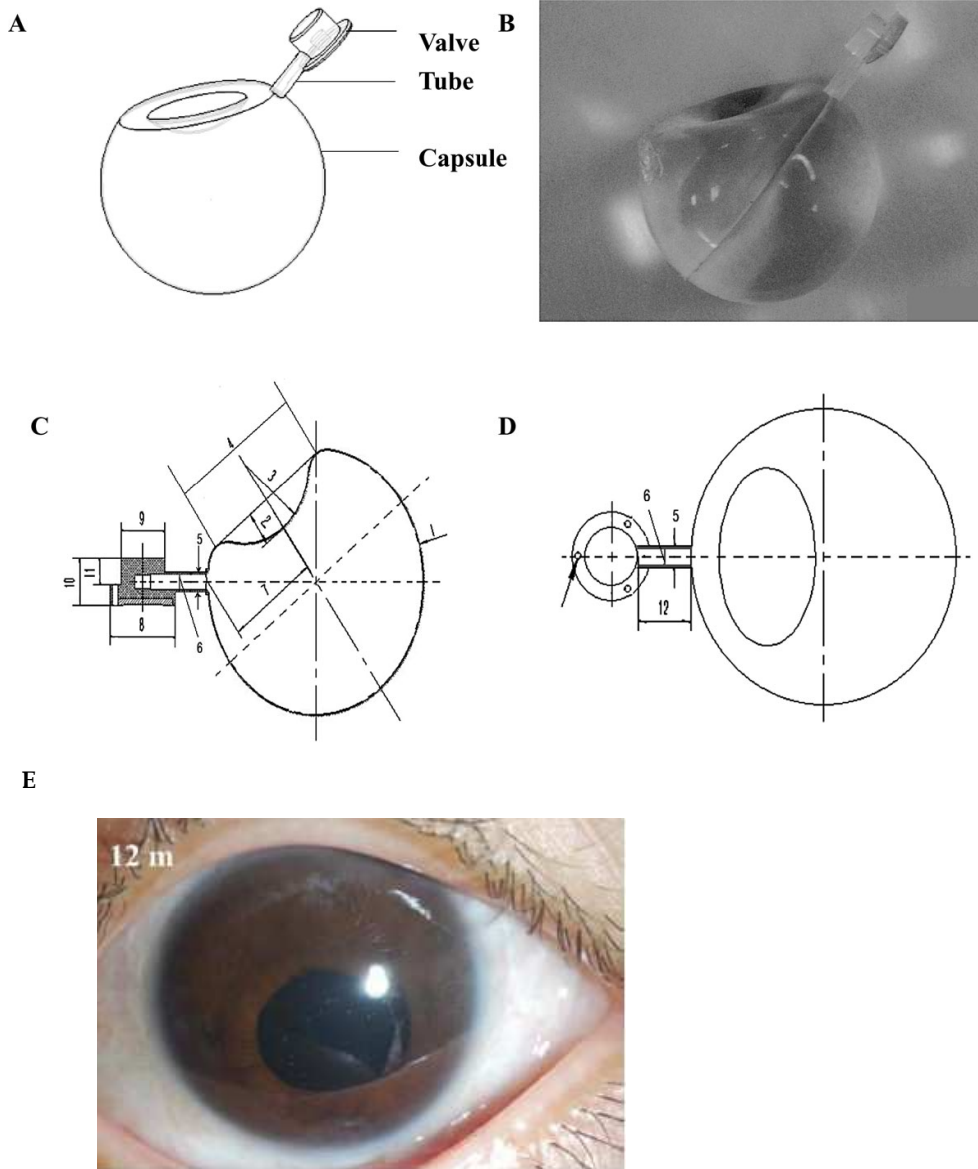


Fig. 1. The human foldable capsular vitreous body (FCVB) consists of vitreous-shape high molecular capsule, tube, and valve. The intra-capsule pressure can be adjusted from the valve with a syringe and there is a slice of anti-penetrating metal in the valve; the designed parameters finely mimic the vitreous shape of a human. (A) Illustration of FCVB. (B) Final sample of the FCVB (Outside the eye). (C) Side view of varied parameters. (D) Vertical view of varied parameters. (E) FCVB inside the eye (Twelve months after implantation).

Theoretically, a new artificial vitreous has the following advantages. First, it does not flow into the anterior chamber and subretinal regions or other sites. Second, it does not emulsify or damage the media over time nor cause it to be isolated in the capsule. Third, it has the capability to support discretionary retina using a 360-degree solid arc.

Developing an irregular vitreous-shaped thin capsule and smoothly connecting it to a very thin diameter tube and a pressure-control valve are very difficult. According to this hypothesis, a mirror steel mold is specially designed to fabricate FCVB using an injection-forming technology that would make the capsule, drainage tube, and valve of the FCVB seamlessly connected. The mold consists of an upper composite die, a lower composite die, and a core.<sup>47</sup> The core shape can be manipulated using a computer to match the human vitreous parameters. The capsular film is 60  $\mu\text{m}$  thick, only one-third the thickness of the retina. In its natural shape, the human FCVB is somewhat spherical, but it is slightly flattened meridionally and has a cup-shaped depression anteriorly.

In the rabbit model of severe retinal detachment, the BSS-filled FCVB was found to mimic the morphology of the natural vitreous very closely and to restore its physiological functions, such as support, refraction, and cellular barriers, during a three-month observation period and without obvious complications. By contrast, the silicone oil control group showed obvious lens opacity, significant hyperopic shift, recurrent retinal detachment, preretinal membrane formation, and vitreoretinal traction.<sup>48</sup> The FCVB capsule can provide the detached retina with a platform to form a flat scar and a barrier to block cell migration from the retina to the vitreous cavity.

Interestingly, the BSS-filled FCVB very slightly changes the refraction compared with silicone oil and heavy silicone oil based on Gullstrand-Emsley and Liou-Brennan schematic eyes.<sup>49</sup> Reports from the State FDA in China show that FCVB has suitably mechanical, optical, and biocompatibility properties.<sup>50</sup> Its optical characteristics indicate that FCVB has high light transmission and laser irradiation stability.

In the early development of breast implants in plastic surgery, similar to current clinical vitreous substitutes, directly injectable materials were used. In fact, hydrophilic polyacrylamide gel (PAAG) was directly injected into the breast. This procedure was practiced widely in China and Eastern Europe in the 1990s. The breast implantation procedure was analogous to the use of silicone oil to replace the vitreous body. However, the injected PAAG was gradually found to induce severe complications, such as inflammation and infection, multiple indurations, hematoma, painful masses, and mastalgia. Currently, the direct injection of PAAG is prohibited, and it has been replaced with the use of capsule-like implants whose fluid substitute is contained in a thin, elastic capsule. This approach to implantation has shown clinical success.<sup>51</sup> In case of severe complications, as mentioned above, the implant can be completely removed without leaving behind residual fluid substitute. Apparently, the development of both artificial vitreous and breast substitutes shared a similar path, and both have suffered setbacks from the direct injection of the fluid substitute into the organ. Therefore, similar lessons can be learned, and the use of a capsule-type implant may be a good replacement for the use of the vitreous body.<sup>46</sup>

The use of FCVBs in the eyes is not yet a common practice worldwide. Therefore, an exploratory study of our new treatment for severe retinal detachment was conducted. The

detachment cannot be easily reattached with silicone oil tamponade, such as posterior scleral ruptures with large disruptions of the retina or severe scleral ruptures with retinal and choroidal detachments. It may also have rigid retinal redetachments or inferior holes occurring after silicone or heavy oil tamponade had been attempted. At Zhongshan Ophthalmic Center, 11 patients were implanted with FCVBs filled with BSS,<sup>52</sup> whereas 3 patients were implanted with FCVBs filled with silicone oil.<sup>53</sup> Patients with serious eye inflammation, with only one eye remaining, with silicone oil-filled eyes, with serious heart, lung, liver, or kidney dysfunctions, or have other diseases that make them unsuitable for inclusion were excluded from the research. Retinal reattachments were found by B-scan in 8 (73%) of the 11 eyes at the end of the three-month treatment time; leakage of FCVB caused failure in three eyes. The production method of FCVB was correspondingly revised, and this addressed the problem. No obvious inflammation was observed in any eye after FCVB implantation, and UBM showed that the FCVB did not crush the ciliary body. There was no obvious difference between the FCVB's spectral transmittance before implantation and after removal.<sup>52</sup> Overall, the results showed that FCVB is an effective and safe artificial vitreous body for severe retinal detachments. It can help avoid the complications induced by silicone oil, such as glaucoma, corneal keratopathy, and silicone oil emulsification during a 12-month implantation time.<sup>53</sup>

Current data have demonstrated the theoretical advantages of using FCVBs, as mentioned above. Even if an ideal injectable material can be found, the use of FCVB is necessary to the artificial vitreous body. It acts as a transporter that can be injected with media, such as BSS, silicone oil, heavy oil, and hydrogels. In the present research, BSS was injected into the capsule of FCVB after PPV, and it was demonstrated as a flexible, effective, and safe vitreous substitute over a three-month implantation period.<sup>52</sup> Further multiple-central clinical trials are in progress in China, and the encapsulation of silicone oil, heavy oil, or hydrogels in PPV eyes will be attempted. Some common substances are active, such as collagen, hyaluronic acid, water, and the natural vitreous that consists of approximately 99% water and 1.0% inorganic salts, organic lipids, and hyaluronan<sup>1</sup>, so these are not recommended as encapsulated tamponades in PPV eyes.

In addition, tiny (300 nm) apertures (Fig.2)<sup>54</sup> exist in the capsule, so the FCVB can release dexamethasone sodium phosphate and Protein kinase C $\alpha$ . It can also be used as an intravitreal drug delivery system in addition to serving as a vitreous substitute.<sup>54,55</sup> Therefore, without the need to change its chemical properties, FCVB may provide a common vehicle for different drug releases, including antibiotics, anti-proliferative agents, and vascular endothelial growth factor antagonists.

The present exploratory clinical study was not large enough to provide a definitive conclusion. Further, the effects of FCVB on the lens should be further evaluated because 10 of 11 eyes were aphakic, and only one eye was phakic.<sup>52</sup> Based on this trial, a nine-hospital clinical trial is currently in progress in China to ascertain FCVBs' safety and efficacy as a vitreous substitute. The FCVB produced by Guangzhou Vesber Co. Ltd. is still in the stage of clinical trial, so it is not commercially available.

FCVBs have some similarities to thin elastic capsule breast implants and tissue expander systems used in plastic surgery. However, they also have differences, which are as follows.

(1) Production methods: FCVBs are formed by injection forming technology and have a US

patent, whereas capsule breast implants and tissue expander systems are made by dip forming for large balloons. (2) Sample size: Producing an irregular vitreous-shaped thin capsule and smoothly connecting it to a 1.2 mm diameter tube and a pressure-control valve are major challenges. However, capsule breast implants and tissue expander systems are large and easily made. (3) Implantation site: FCVBs are implanted into the vitreous cavity and come into contact with very tender tissues, such as the retina, ciliary body, lens, and anterior chamber. However, capsule breast implants and tissue expander systems directly come into contact with adipose tissues. Therefore, there are a number of safety issues in the use of FCVBs, which have to be addressed.

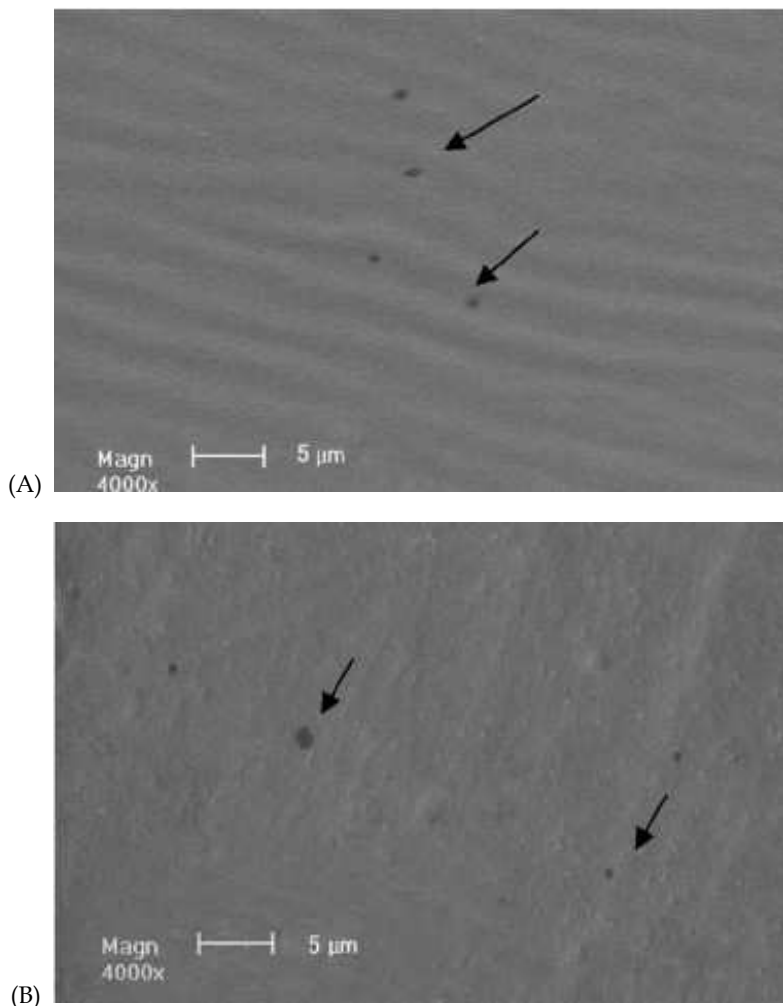


Fig. 2. Scanning electron microscope images of the capsule of the FCVB. Before implantation (A) and at the end of the observation time (B) 300-nm-mili apertures in the capsule were observed (arrows).



In conclusion, a new paradigm for the fabrication of a vitreous body substitute using FCVB was proposed in the current work. FCVB was established as an acceptable replacement as it closely mimics the morphology and restores the physiological function of the vitreous body. This idea provided us with a novel approach in researching on a new therapy strategy mimicking the natural vitreous that has been used for nearly half a century.

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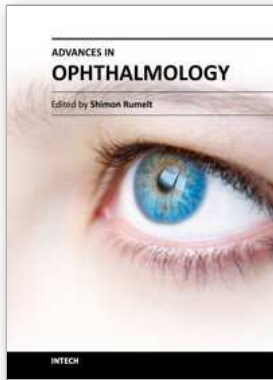
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This book focuses on the different aspects of ophthalmology - the medical science of diagnosis and treatment of eye disorders. Ophthalmology is divided into various clinical subspecialties, such as cornea, cataract, glaucoma, uveitis, retina, neuro-ophthalmology, pediatric ophthalmology, oncology, pathology, and oculoplastics. This book incorporates new developments as well as future perspectives in ophthalmology and is a balanced product between covering a wide range of diseases and expedited publication. It is intended to be the appetizer for other books to follow. Ophthalmologists, researchers, specialists, trainees, and general practitioners with an interest in ophthalmology will find this book interesting and useful.

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