Artificial Organs

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Technical Standards of a Foldable Capsular Vitreous Body in Terms of Mechanical, Optical, and Biocompatible Properties

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Abstract: We previously proposed a new strategy to fabricate a novel foldable capsular vitreous body (FCVB) as a vitreous substitute and found that the FCVB was a very good replacement for closely mimicking the morphology and restoring the physiologic function of the rabbit vitreous body. The aim of this article was to assess the mechanical, optical, and biocompatible properties of a FCVB made from liquid silicone rubber. The mechanical properties show that the shore hardness is 37.80 degrees, the tear strength is 47.14 N/mm, the tensile strength is more than 7.28 MPa, and the elongation ratio is more than 1200%; in addition, the FCVB has 300 nm mili apertures in the capsule. The optical properties reveal that transmittances are 92%, hazes are 5.74%, and spectral transmittance is 97%. The transmittance mission is 2.3% and can sustain a 1500 mW, 0.2 s, 532 nm green laser. The biocompatible properties are shown in the stable extracts experiment, no significant fever, good genetic safety, and no structural abnormality or apoptosis in the cornea, ciliary body, and retina over a 6-month observation period. These results indicate that the FCVB has good mechanical, optical, and biocompatible properties, and the assessment results can be recommended as the FCVB technical standards for industrial manufacturing and inspection. **Key Words:** Liquid silicone rubber—Capsule—Artificial vitreous body.

Since the 1970s, pars plana vitrectomy (PPV) has been one of the most important ophthalmic surgeries for treating a number of blinding diseases by removing and replacing the diseased vitreous body (1–4). Successful PPV surgery has enabled ophthalmologists to restore vision in a number of patients who would previously have been regarded as incurable (5–7). Because the vitreous body cannot regenerate, the posterior void resulting from PPV must be filled with suitable artificial materials. These artificial materials can then keep the retina in place and prevent it from detaching.

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A number of artificial vitreous substitutes, for example, silicone oil, heavy silicone oil, hydrogels, perfluorocarbons, and semifluorinated alkanes have been adopted (8–19). However, these materials cannot meet the structural and physiologic performance of the natural vitreous. For example, the fluidity cannot maintain a rigid vitreous core, and consequently causes concomitant complications, for example, intraocular toxicity, retinal cell proliferation, leakage into the anterior chamber, and difficulty in postsurgical removal. Moreover, low-density silicone oil cannot support the inferior retina and induces a hyperopic shift in the optic system. Severe post-PPV complications, such as glaucoma, cataract, corneal degeneration, and emulsification could lead to complete blindness. In spite of a half century of effort to replace the vitreous body of the eye, an ideal and permanent vitreous body has yet to be found (20,21).

The natural vitreous has a thin, membrane-like structure that continues from the ora serrata to the posterior pole that corresponds to the vitreous cortex (22). Therefore, in our previous studies (23–25), we proposed a new strategy for fabricating a novel foldable capsular vitreous body (FCVB) as a vitreous substitute, instead of the previous liquid or gelatinoid injectable vitreous material (8–19). The FCVB consisted of a thin (30 μm) vitreous-like capsule finely mimicked by computer with a tube–valve system. After a foldable installation into the eye, a balanced salt solution (BSS) could then be injected into the capsule and inflated to support the retina and control the intraocular pressure through the tube–valve system (23). In the rabbit model of proliferative vitreoretinopathy, we found that the FCVB was a very good replacement that closely mimicked the morphology and restored physiologic functions such as support, refraction, and cellular barriers during a 3-month observation period, without the obvious complications commonly induced with traditional silicone oil (Q. Gao et al., unpublished data). The FCVB changes the refraction very little when compared with silicone oil and heavy silicone oil, based on the Gullstrand-Emsley and Liou-Brennan schematic eyes (24). Moreover, the FCVB can sustainably, mechanically release dexamethasone sodium phosphate (DexP, Baiyunshan Tianxin Pharmaceutical Co., Ltd., Guangzhou, China) and be used as an intravitreal drug delivery system (DDS) in addition to serving as a vitreous substitute (25).

We are currently carrying out a multiple-center clinical trial of the FCVB in China. The purpose of this article was to evaluate the FCVB material in terms of its mechanical, optical, and biocompatible properties, and to provide uniform FCVB technical standards for industrial production and inspection.

MATERIALS AND METHODS

Basic materials and fabrication of FCVB

The FCVB is made of tailor-made modified liquid silicone rubber. The basic material, Dow Corning Class VI elastomers, was purchased from Dow Corning Company (Midland, MI, USA). The liquid silicone rubber is supplied as a two-part kit. Part A and Part B are a series of two-part platinum-catalyzed silicone elastomers and must be thoroughly mixed in equal portions, by weight, before use. When blended and cured as indicated, the resulting elastomer consists of cross-linked dimethyl and methylvinyl siloxane copolymers and reinforcing silica.

The FCVB was fabricated by injection-forming technology in a specially designed mirror steel mold. The mold mainly includes the upper composite die, the lower composite die, and the inner core. The core can mimic the vitreous shape via the computer according to the vitreous parameters for rabbits or humans. The gaps between the dies and the core can control the thickness of the capsular film to as thin as 30 μm. The standard weight of the FCVB for humans was 0.33 ± 0.005 g, and for rabbits was 0.21 ± 0.005 g. The standard thickness of the FCVB for humans and rabbits is 30 μm. More fabrication details were found as previously described (Q. Gao et al., unpublished).

The mechanical, optical, and biocompatible properties of the FCVB were assessed according to the International Standardization Organization (ISO) guidelines, as well as under a re-check by the State Food and Drug Administration in China (No. G20080656).

Mechanical properties

Shore hardness test

The test was evaluated following the ISO 7619-1-2004 guidelines (26). The gelatinous silicone was vulcanized to obtain three sheets of $180 \times 130 \times 2$ mm semi-solid rubber specimens. The sheets were composed together to obtain a 6-mm thick test piece. A Type A Durometer (Liuling Instrument Factory, Shanghai, China) was used to test the shore hardness; seven measurements were performed to determine the median value.

Tear strength test

The test was carried out according to ISO 34-1-2004 guidelines (27). Unnicked angle test pieces $100 \times 19 \times 2$ mm were obtained by standard dies, and fixed symmetrically in the Electromechanical Universal Tensile Testers (5560 series, Instron Corporation, Canton, MA, USA) at rates of traverse of 500 mm/min. Seven test pieces were performed to determine the median value. The tear strength is given by the formula:

$$Ts = \frac{F}{t}$$

where Ts = tear resistance (N/mm), F = maximum force to tear specimen in Newtons (N), and t = thickness of specimen (mm).

Tensile strain and stress test

The test was conducted following the ISO 37-2005 guidelines (28). Dumbbell test pieces $115 \times 25 \times 2$ mm were obtained by Type 1 standard dies, and fixed symmetrically in the Electromechanical Univer-

sal Tensile Testers (5560 series, Instron Corporation) at rates of traverse of 500 mm/min. Five test pieces were performed to determine the median value.

Porosity and permeability

Porosity

The capsule of the FCVB was cut into a 1-cm diameter disc and then the sample was cleaned, coated with gold, and fixed on a specimen stub. The image of the specimen surface was captured with a scanning electron microscope (XL 30 ESEM FEG, FEI-Philips, Eindhoven, The Netherlands).

DexP permeability

About 5 mg/mL of DexP was injected into the FCVB to achieve an inner pressure of 1.60 kPa, and the inner liquid volume was recorded. After being immersed totally in normal saline solution (NS) for 30 days, the inner liquid of the FCVB was sucked out with an injector. The changed DexP volume was measured.

Optical properties

Transmittance and haze tests

The tests were carried out according to ISO 13468-2-1999 and ISO 14782 Technical Corrigendum 1-2005 (29,30). Transmittance is the ratio of the transmitted luminous flux to the incident luminous flux when a parallel beam of light passes through a specimen. Haze is the percentage of transmitted light passing through a specimen, which deviates from the incident light by no more than 0.044 rad (2.5°) by forward scattering. Liquid silicone oil was pumped into a vacuum and was pressed and flattened between two smooth boards. The board is made up of smooth film and thick glass. Three membrane samples, measuring $50 \times 50 \times 1$ mm, were vulcanized and tested on a Hazemeter (WGT-S, Precision Instrument Co. Ltd., Shanghai, China).

Spectral transmittance

The tests were carried out according to ISO 11979-2-1999 (31). Spectral transmittance is the ratio of the transmitted radiant flux (regular and diffuse) to the incident radiant flux when a parallel beam of monochromatic radiation of a given wavelength passes through a specimen. Transmittance mission is the deviation between the maximum and minimum transmittances of a given wavelength passing through a specimen. The optic part of the capsule was taken as a specimen, and the sheets were cleaned and fixed vertically on a spectrophotometer (UV-3101 PC, Shimadzu, Nakagyo-ku, Japan) with a test wavelength of 440–800 nm. With the different refractive index, the result in air ($n = 1$) was then transformed into spectral transmittance in NS ($n = 1.336$).

532 nm laser irradiation stability

The FCVB with a BSS encapsulated alone and ink smeared on the surface additionally were irradiated by a 532 nm laser of varied output powers. The diameter was 50 μm, the output power rose from 50 mW to 1500 mW, and the exposure time increased from 0.1 s to 0.2 s. Five irradiations per power were performed on the capsule to determine the conventional power laser irradiation stability and the maximum power that perforated the capsule. In addition, both the test material and the extracts were evaluated to determine whether there was any cytotoxicity.

Biocompatibility tests

Extracts experiment

A total of 200 mg samples of FCVB were immersed in 55°C NS for 15 days; this would equal to 60 days' immersion in 37°C NS. Then the change in mass of the FCVB was measured.

Rabbit pyrogen test

This test evaluated the material-mediated pyrogenicity (fever) of the test material and/or extracts (32). A pyrogenicity test was carried out on six New Zealand albino rabbits by intravenously injecting rubber saline extracts in a dose of 1 mL per kg of body weight. Rectal temperatures were measured with indwelling rectal thermistors and recorded for 5 h after administration.

Genetic toxicology test

The test was evaluated following the ISO 10993-3:2003 guideline (33). Extracts of the FCVB were used as samples, and the Ames test and mouse lymphoma assay test were performed according to Option 2.

Intravitreal implantation

FCVB were implanted in six New Zealand albino rabbits' right eyes, and the left eyes were left as the controls. After 6 months' follow-up, the rabbits were sacrificed with an overdose of sodium pentobarbital, the whole eyes were enucleated, and the anterior chambers, lenses, and vitreous substitutes were removed. Then, some of the remaining eyecups were fixed in 4% paraformaldehyde and were processed for routine paraffin embedding. Ten consecutive 6-mm thick sections of each sample were made and stained with hematoxylin-eosin (HE). The paraffin

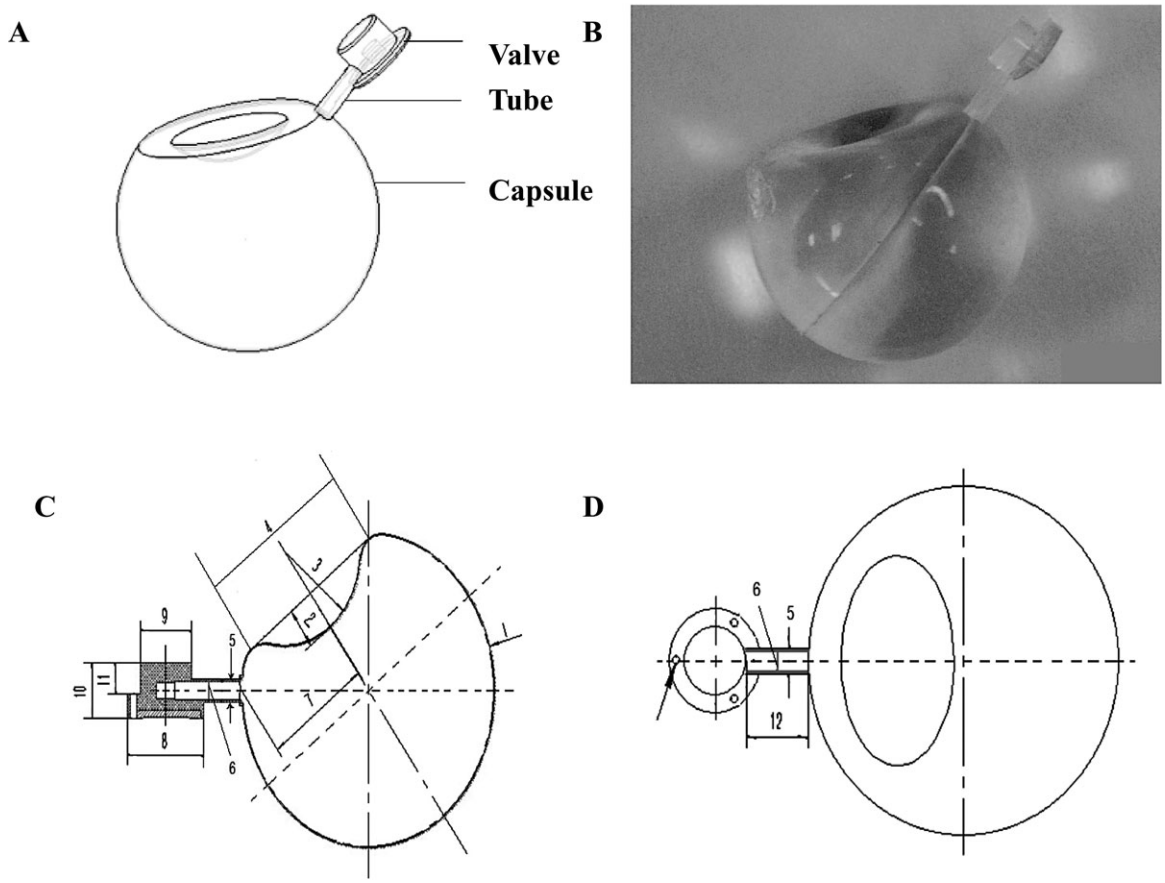

FIG. 1. The human foldable capsular vitreous body (FCVB) consists of vitreous-shape high molecular capsule, tube, and valve; the designed parameters finely mimic the vitreous shape of a human. (A) Illustration of FCVB. (B) Final sample of the FCVB. (C) Side view of varied parameters. (D) Vertical view of varied parameters.

sections were also used for TdT-mediated dUTP nick end labeling (TUNEL) assay (Keygen Biotech. Co. Ltd., Nanjing, China) to observe the apoptosis cells in both the retina and the ciliary body contacting the vitreous substitutes. Photographs were taken using a fluorescent microscope.

Statistical analysis

Data were reported as mean ± standard deviation (SD). Group differences were statistically examined using one-way analysis of variance with Tukey's honestly significant differences (HSD) post-hoc test. Statistical significance was considered at a probability of $P < 0.05$.

RESULTS

Figure 1 and Table 1 show the illustration and parameters of the FCVB. In the present study, we assessed more detailed properties such as the mechanical, optical, and biocompatible properties of the FCVB for its use as a novel vitreous substitute.

Mechanical FCVB properties

The following properties were observed: shore hardness (37.80 degrees), tear strength (47.14 N/mm), tensile strength (>7.28 MPa), and elongation ratio (>1200%). The test pieces for the different items are shown in Fig. 2, and the corresponding results for the different tests are shown in Table 2. Three hundred (300)-nm mili apertures in the capsule of the FCVB were observed, as shown in Fig. 3, and the volume of the inner DexP changed more than 10% after 30 days.

Optical FCVB properties

The following properties were observed: transmittances (92%) and hazes (5.74%). As shown in Fig. 4,

TABLE 1. *Standard dimensions of the components of the human FCVB*

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.

the spectral transmittance was 97%, and transmittance mission was 2.3%. When a BSS was encapsulated alone, a 1500 mW, 0.2 s, 532 nm green laser caused no damage to the FCVB, and with ink smeared superficially, conventional laser power formed a white patch on the FCVB, while a 1500 mW, 0.1 s laser perforated the capsule. No cytotoxicity was observed after laser irradiation.

Biocompatibility tests

The extracts experiment showed that the FCVB was stable in 55°C NS, and the change in the mass of the samples was less than ±0.9% after 15 days' immersion. The febrile responses were quantified by determining the maximum temperature rise above the respective control temperatures (ΔT, °C). As shown in Fig. 5, the extracts from the samples did not cause any significant fever with a ΔT of 0.2°C, which was obviously below the temperature rise of the pyrogenic threshold (0.6°C). Negative results were observed in the genetic toxicology tests and indicate the genetic safety of the implant in an organism. After 6 months' intravitreal implantation, HE and TUNEL staining cells in both the retina and ciliary body contacting with the vitreous substitutes are shown in Fig. 6. There was no structural abnormality or apoptosis in the cornea, ciliary body, and retina of the FCVB rabbit eyes over a 6-month observation period.

DISCUSSION

The basic material of the FCVB consists of a liquid silicone rubber that is a stable nontoxic material used commonly in medicine; the most successful example is its usage in breast implant surgery for more than 20 years. In ophthalmology, silicone rubber is used only outside the eye as an encircling scleral buckle.

TABLE 2. *Mechanical properties tests according to the ISO guidelines*

	Sample number								
	1	2	3	4	5	6	7	Mean	SD
A									
Shore hardness (degree)	38.00	37.80	38.50	40.00	39.50	39.00	40.00	37.80	0.86
B									
Maximum load (N)	99.01	95.75	92.78	97.04	91.21	92.49	91.60	94.27	3.01
Tear intensity (kN/m)	49.51	47.88	46.39	48.52	45.61	46.25	45.80	47.14	1.50
C									
Maximum load (N)	89.70	9.65	95.23	88.93	87.38	—	—	—	—
Maximum tensile stress (MPa)	7.48	7.97	7.94	7.41	7.28	—	—	—	—
Tensile strain (%)	1276.36	1309.55	1309.60	1242.58	1282.58	—	—	—	—

SD, standard deviation.
(A) Shore hardness test was evaluated following the ISO 7619-1-2004 guidelines, and resulted in 37.80 degrees hardness.
(B) Tear strength test was carried out according to ISO 34-1-2004 guidelines, and resulted in 47.14 N/mm tear strength.
(C) Tensile strain and stress test was conducted following the ISO 37-2005 guidelines, and resulted in >7.28 MPa tensile strength, >1200% elongation ratio.

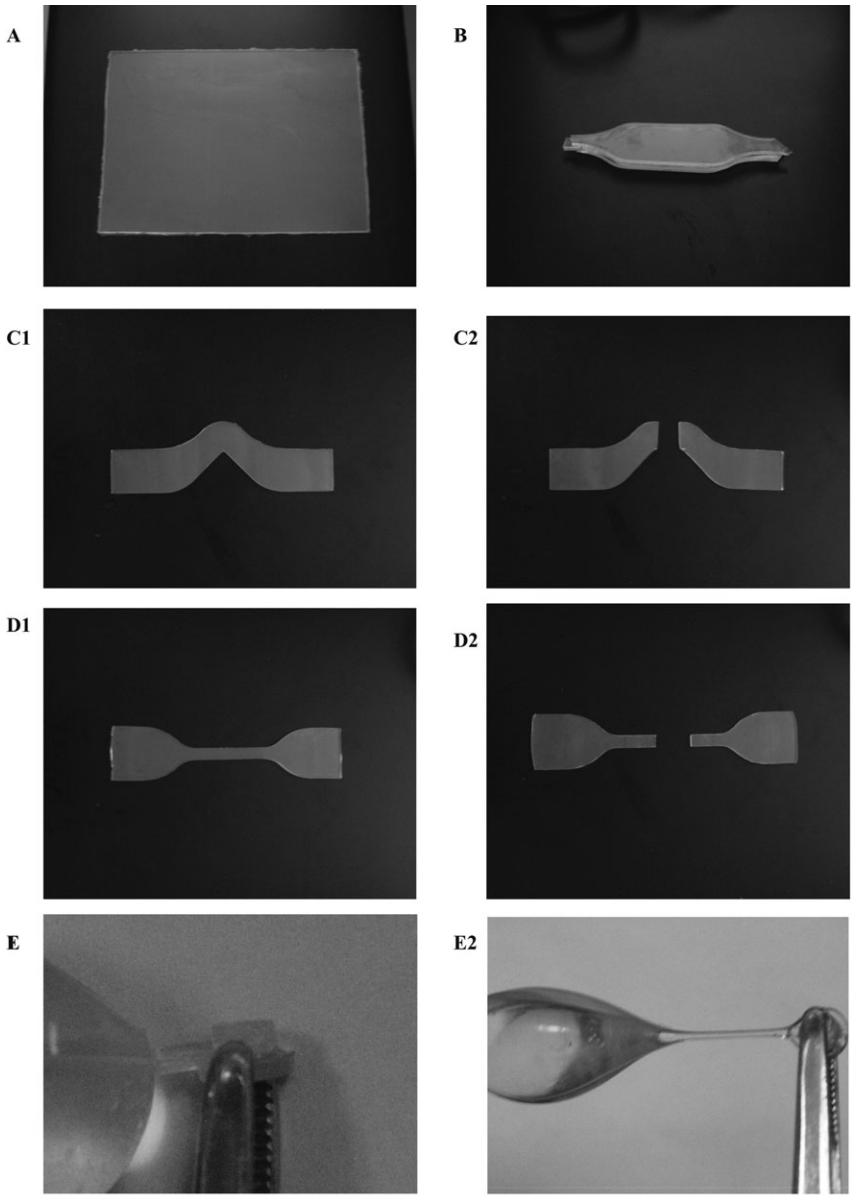

FIG. 2. Test pieces for mechanical properties according to International Organization for Standardization guidelines and sample test of foldable capsular vitreous body (FCVB). (A) Test sheets. (B) Shore hardness test pieces. (C) Tear strength test pieces. (D) Tensile strain and stress test pieces. (E) FCVB sample test.

Although the FCVB implanted into the rabbit eye could finely mimic the morphology and restore the main physiologic function of the vitreous body compared with silicone oil (Q. Gao et al., unpublished data), the detailed properties of the FCVB are essential and decisive.

The mechanical properties indicate that the liquid silicone rubber has suitable hardness and high strain capability that allow the 30-μm thin FCVB to stretch its capsule to evenly and gently support the detached retina, and performs a completely different semi-solid support, contrasting with the liquid tensile support of silicone oil. The upper detached retina will receive effective support, and patients are freed from

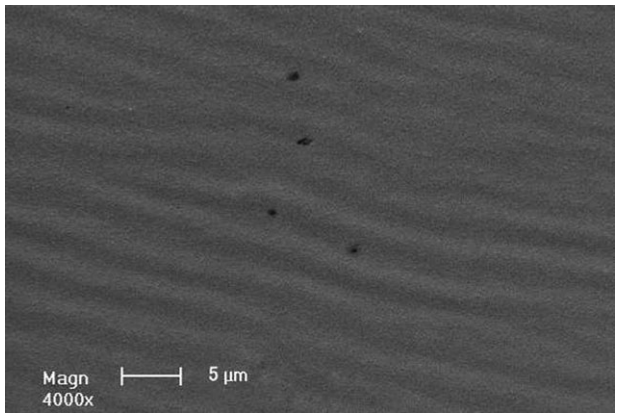

FIG. 3. Scanning electron microscope image of the capsule of the foldable capsular vitreous body. Three hundred (300)-nm mili-apertures in the capsule were found.

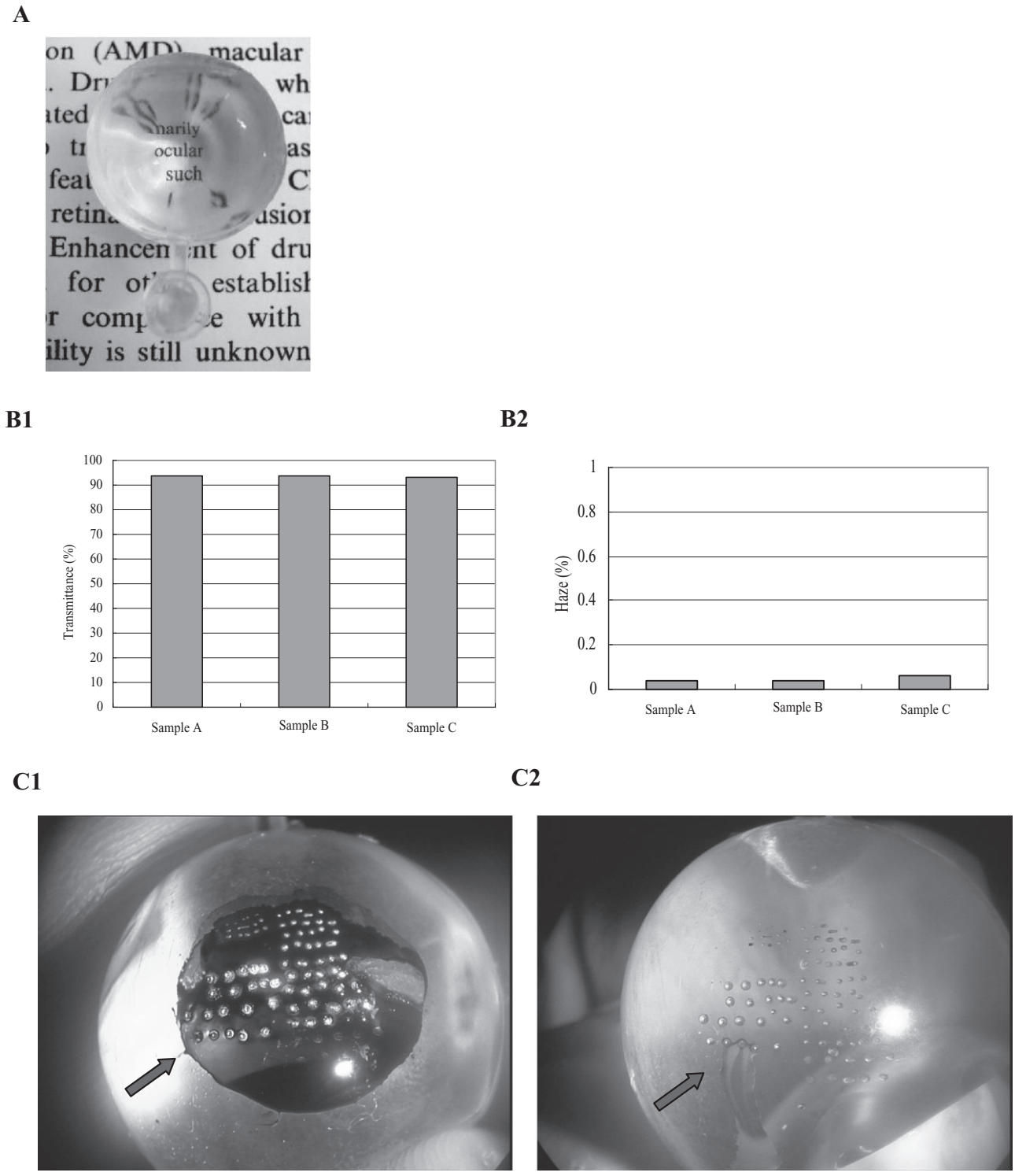

FIG. 4. Optical properties permit high light transmission and irradiation stability of the foldable capsular vitreous body. (A) High transparence when reading. (B) Histogram of high light transmission as transmittances are 92% and hazes are 5.74%. (C1) White patches on the capsule with ink smeared superficially under varied output powers of 532 nm green laser. (C2) Perforation and leakage under 1500 mW power of 532 nm green laser.

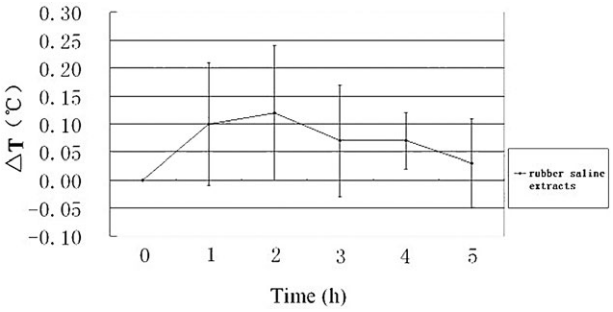

FIG. 5. Pyrogenicity of the extracts from the foldable capsular vitreous body. Rabbits were injected intravenously with 1 mL/kg of the rubber saline extracts. Rectal temperatures were measured for 5 h after the injection. Data are expressed as the mean ± SD ($n = 6$ rabbits). The rubber saline extracts did not cause any significant fever with a ΔT of 0.2°C, which was obviously below the temperature rise of the pyrogenic threshold (0.6°C). ΔT, change in temperature.

keeping a prone position during convalescence. When accommodating intra-ocular pressure with an injector through the valve, the stable durability of the drainage valve will also eliminate the worry of leakage after repeated pinhead pricks. Also, with the 300-nm mili apertures in the capsule, the FCVB performs DexP permeability and can be used as an intravitreal DDS. In a previous study, a mixture of a drug such as DexP and a BSS was injected into the capsule via the valve. It was found that the FCVB could release DexP in a time- and dose-dependent manner with 0.25, 0.5, 1, 2, and 4 mg/mL dosages from 10–360 min in vitro. Experiments in vivo showed that the DexP could be detected in the anterior chamber liquid after FCVB implantation with 2 mg/mL DexP internally over a 6-week time period (25).

The optical properties indicate that the material has high light transmission and laser irradiation stability that result in few complaints of dimmed brightness, and permit retinal photocoagulation and further laser therapy. Due to the high transparency and 160°C vulcanization of the FCVB, 1500 mW induced no damage on the capsule. Ink smeared exteriorly will greatly absorb the heat of the laser, and then the conventional power forms a white patch on the capsule, but perforation and leakage of the FCVB are observed only under the maximal 1500 mw power. Few cases will need such high output powers. Combined with the high elasticity, the rubber will shrink and seal the small pore, and the FCVB will retain integrity again. Laser irradiation stability will allow retinal photocoagulation after the FCVB has been tamponaded and after further laser therapy.

The less than 0.9% mass change in the extracts experiment, nonsignificant febrile responses, and negative genotoxicity suggest the chemical and biologic stability and safety of the material when contacting within the eyes. Furthermore, no obvious structural abnormality or tissue apoptosis was observed in the 6 months' intravitreal implantation in the rabbit eye, demonstrating that the FCVB possesses longer-term implant compatibility and would reduce the high risk of serial complications that current vitreous substitutes bring about clinically. All of these advantages underscore the concerns about biologic safety and compatibility that previously imperiled efforts of current vitreous substitutes.

Hence, the FCVB provides a potential new substitute for the silicone oil clinically used for nearly half a century, and a new vehicle for ophthalmologic DDS for more drugs such as antibiotics, antiproliferation agents, and vascular endothelial growth factor or its antagonists, such as Avastin. Therefore, the FCVB will potentially be a new approach combining vitreous function and a DDS for the future.

Most of the crucial technical difficulties in manufacturing have been resolved, and the mold for the FCVB can mimic the natural vitreous exactly. We can manufacture the FCVB industrially now, and the assessment results here could be recommended as the technical standards for industrial manufacture and inspection. Based on this study, clinical trials are in progress to ascertain FCVB biocompatibility and effectiveness as a silicone oil substitute in human eyes. The clinical trials adhere strictly to the principles of the World Medical Association Declaration of Helsinki, have been approved by the Sun Yat-sen University Medical Ethics Committee (Zhongshan Ophthalmic Center Medical Ethics [2009] No.07), and have successfully been registered in ClinicalTrials.gov (ClinicalTrials.gov ID: NCT00910702) and the Chinese Clinical Trial Register (ChiCTR-TNC-00000396). According to the ISO guidelines, we have formulated technique standards for industrial manufacturing and inspection. The FCVB could be manufactured uniformly, and then, different laboratories could share the same results with the comparability.

CONCLUSION

The FCVB has good mechanical, optical, and biocompatible properties, and the assessment results can be recommended as the FCVB technical standard for industrial manufacture and inspection.

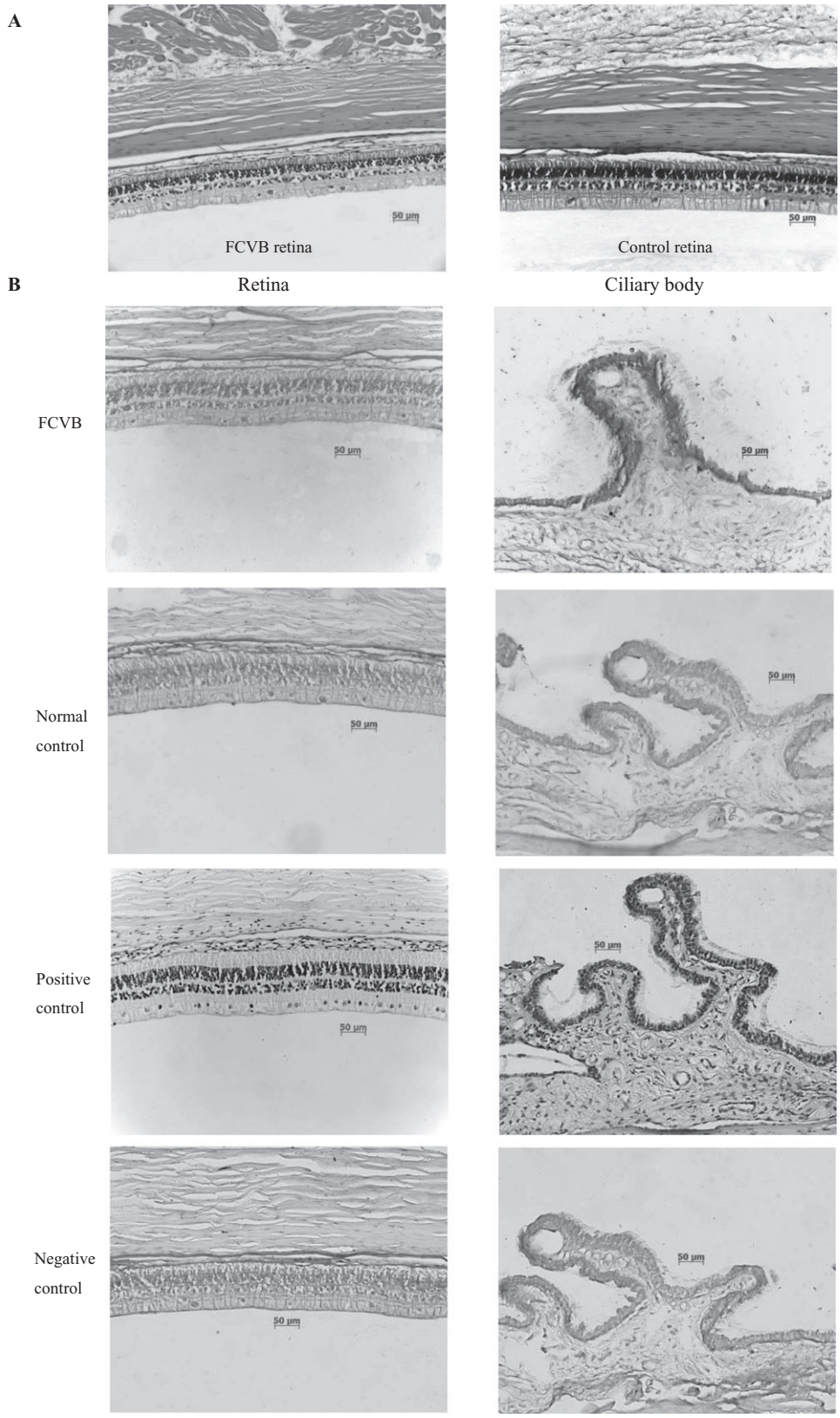

FIG. 6. Histologic studies (A) and TdT-mediated dUTP nick end labeling staining (B) showed no structural abnormality or apoptosis in the ciliary body and retina in the foldable capsular vitreous body rabbit eyes or contralateral control eyes over the 6-month observation period.

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