Sustained Mechanical Release of Dexamethasone Sodium Phosphate from a Foldable Capsular Vitreous Body

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Purpose. Since 300-nm-mili apertures were present in the capsule of the foldable capsular vitreous body (FCVB), the authors tested whether the FCVB could mechanically release dexamethasone sodium phosphate (DexP) from its capsule.

Methods. In the in vitro study, DexP at concentrations of 0.25, 0.5, 1, 2, and 4 mg/mL in a balanced salt solution were injected into the capsules, which were immersed in cups of modified Franz diffusion cells. Two hundred microliters of liquid was aspirated at time intervals of 10, 20, 40, 60, 120, 180, 240, 300, and 360 minutes. In the in vivo study, the capsule was folded and implanted into the vitreous cavities of five rabbits. Approximately 0.6 mL DexP (2 mg/mL) was then injected into the capsule. An intravitreal injection with DexP was performed on another five rabbits as the control group. Aqueous humor was aspirated on days 1, 3, 7, 14, 28, and 42 after implantation. The DexP contents in the cups and aqueous humor were detected by HPLC-MS/MS.

Results. FCVB released DexP in a time-dependent and dose-dependent manner in vitro with five dosages from 10 to 360 minutes. Especially in the 0.25 mg/mL DexP group, the content (y) had good linear relationships with time (x), as shown by $y = 0.7635x + 10.205$. The DexP contents in the aqueous humor were detected until day 28 and were undetectable on day 42. However, the DexP contents were detected only before day 3 in the controls.

Conclusions. FCVB can sustainably and mechanically release DexP by capsule apertures in a time-dependent and dose-dependent manner in addition to serving as a vitreous substitute. (*Invest Ophthalmol Vis Sci.* 2010;51:1636–1642) DOI:10.1167/iovs.09-4134

Pharmaceutical treatment and pars plana vitrectomy (PPV) are the main approaches for severe vitreoretinal diseases such as diabetic retinopathy, proliferative vitreoretinopathy (PVR), traumatic retinopathy, and age-related macular degeneration.[1–3] Because of the blood-ocular barrier, it is difficult to deliver drugs for these vitreoretinal diseases into target tissues by systemic and local administration. Therefore, intravitreal injections can deliver drugs to the retina without the side effects associated with systemic administration. However, intravitreal injection does not maintain an effective concentration of the drug for a long period and can increase the risk for ocular toxicity, hemorrhage, and endophthalmitis.[4–6] Therefore, it is increasingly important to develop drug delivery systems (DDS) in the treatment of vitreoretinal diseases not only to enhance drug efficacy but also to reduce side effects.[7–11] The current intraocular DDS are mainly classified as liposome, biodegradable microspheres and nanospheres, high molecular polymers, and mechanical pumps. The few available drugs and the complex fabrication of drugs and carriers significantly decrease the popularity of DDS.

PPV can remove and replace the diseased vitreous body and provide more space for these drugs. A number of artificial vitreous substitutes are implanted to refill the vitreous cavity, including silicone oil, heavy silicone oil, and polymeric gels. Although these materials have saved numerous patients from blindness, these substitutes may lead to undesirable side effects and even severe complications, such as cataract, glaucoma, and retinal redetachment.[12–19]

The natural vitreous has a thin, membrane-like structure that continues from the ora serrata to the posterior pole, corresponding to the vitreous cortex. Therefore, in our previous studies,[20,21] we proposed a new strategy to fabricate a vitreous substitute by a novel foldable capsular vitreous body (FCVB), instead of the previous liquid or gelatinoid injectable materials. The FCVB consists of a thin (30-μm) vitreous-like capsule finely mimicked by computer with a tube-valve system. After foldable installation into the eye, a balanced salt solution can be injected into the capsule and the capsule can be inflated to support the retina. Control of the intraocular pressure can be obtained through the tube-valve system.[20] In addition, the FCVB changes the refraction very little compared with silicone oil and heavy silicone oil based on Gullstrand-Emsley and Liou-Brennan schematic eyes.[21] Interestingly, numerous 300-nm-mili apertures were observed in the capsule of the FCVB (Fig. 1). We wondered whether it could sustainably, mechanically release some ophthalmic drugs such as dexamethasone sodium phosphate (DexP) from the capsule in addition to serving as a vitreous substitute.

Materials and Methods

Basic Material and Fabrication of the FCVB

The FCVB consisted of tailor-made modified liquid silicone rubber. The basic components were obtained from a 1:1 ratio mix of material A and

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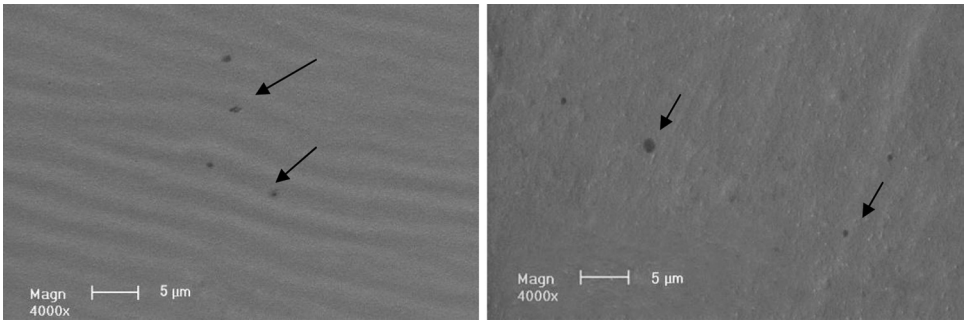

FIGURE 1. Scanning electron microscope images of the capsule of the FCVB. Before implantation (**A**) and at the end of the observation time (**B**) 300-nm-mili apertures in the capsule were observed (*arrows*).

material B purchased from American Dow Corning Company. The liquid silicone rubber was gelatinous at room temperature and became semisolid elastic rubber after it was vulcanized at 160°C for 200 seconds.

FCVB was fabricated by an injection-forming technology in a specially designed mirror steel mold. The mold mainly includes the upper composite die, lower composite die, and inner core. The core can mimic the shape by precise computer controls according to the vitreous cavity parameters of rabbits or humans. The gaps between the dies and the core control the thickness of the capsular film as thin as 30 μm.

Scanning Electron Microscopy of the FCVB

The capsule of the FCVB was cut into the appropriate size, and then the sample was cleaned, coated with gold, and fixed on a specimen stub; an image of the specimen surface was captured on a scanning electron microscope.

In Vitro Drug Sustained-Release Studies

DexP at concentrations of 0.25, 0.5, 1, 2, and 4 mg/mL in balanced salt solution was injected into the capsules of the FCVB, and then the capsules were immersed in cups of modified Franz diffusion cells as shown in Figure 2. Two hundred microliters of liquid in the cup was aspirated for measurement at 10, 20, 40, 60, 120, 180, 240, 300, and 360 minutes. The DexP content in the liquid was then detected by a sensitive liquid chromatographic-tandem mass spectrometry (LC-MS/MS) method (Thermo-Finnigan, San Jose, CA).

In Vivo Drug Sustained-Release Studies

The FCVB was implanted into rabbit eyes using PPV to evaluate the FCVB drug sustained-release property in vivo. All experimental procedures adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Before all surgical procedures, 10 New Zealand albino rabbits weighing 2.0 to 2.5 kg were anesthetized by intramuscular injection of ketamine hydrochloride (30 mg/kg) and chlorpromazine hydrochloride (15 mg/kg). Pupils were dilated with 0.5% tropicamide (Xingqi, Shenyang, China). PPV was performed, and the FCVB was implanted in the right eyes of five rabbits.[20] Standard three-port PPV was performed on the right eye of each rabbit using a Geuder (Heidelberg, Germany) vitrectomy machine. After vitrectomy, the capsule was folded and implanted into the vitreous cavity following fluid-air exchange. Approximately 0.6 mL DexP (2 mg/mL) was then injected into the capsule through a silicone tube-valve system; thus, the capsule was inflated to support the retina. The tube was subsequently fixed under the conjunctiva (Fig. 3). PPV and intravitreal injection with DexP (2 mg/mL) were performed on another five rabbits as the control group. Sclerotomies were closed with 10–0 Vicryl sutures. The operation was concluded by subconjunctival injection of gentamicin and dexamethasone and by application of compound tobramycin and atropine (1%) ointment.

On days 1, 3, 7, 14, 28, and 42 after implantation, the animals were anesthetized, and 0.1 to 0.2 mL aqueous humor was aspirated from both eyes of each rabbit. The aqueous humors were examined by the sensitive HPLC-MS/MS method.

DexP Sample Assay In Vitro

The LC-MS/MS system consisted of a pump (Surveyor MS; ThermoFinnigan), an autosampler (Surveyor; ThermoFinnigan), and a triple quadrupole mass spectrometer (TSQ Quantum; ThermoFinnigan) equipped with an ESI source. A reverse-phase column (50 × 2.1 mm, 3 μm; Thermo-Hypersil-BDS-C18; Elite, Dalian, China) was used for all chromatographic separations at room temperature (20°C). The mobile phase (1% formic acid in water and acetonitrile (70:30, vol/vol) was pumped at a flow rate of 0.3 mL/min. The mass spectrometer was operated in the positive electrospray ionization mode. Quantification was performed using selected reaction monitoring (SRM) in the positive mode. The ion transition of the mass-to-charge ratio (m/z) 517.2 → 499.2 for DexP was monitored, with a collision-induced energy of 27 eV.

The reference formulation of DexP (lot number 100016–200011A) was obtained from the National Institute for the Control of Pharmaceutical and Biological Products. Methanol of HPLC grade was purchased from Tedia (Fairfield, OH). Ammonium acetate and formic acid

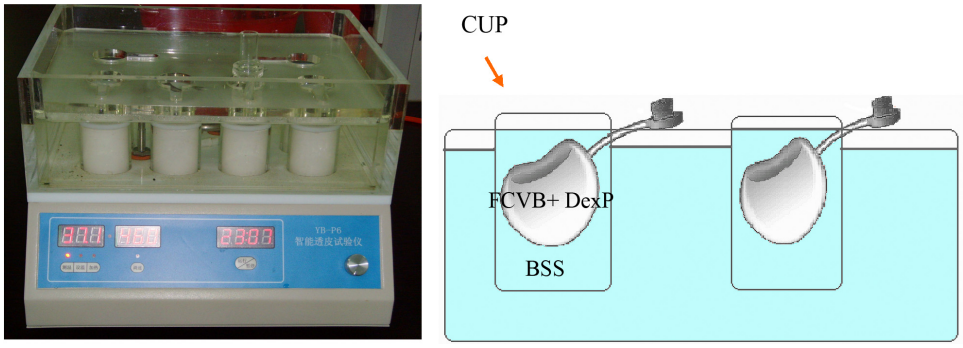

FIGURE 2. DexP sustained-release studies in vitro. DexP at concentrations of 0.25, 0.5, 1, 2, and 4 mg/mL in balanced salt solution (BSS) were injected into the capsules of the FCVB, and then the capsules were immersed in cups of modified Franz diffusion cells; 200 μL liquid in the cups was aspirated at time intervals of 10, 20, 40, 60, 120, 180, 240, 300, and 360 minutes.

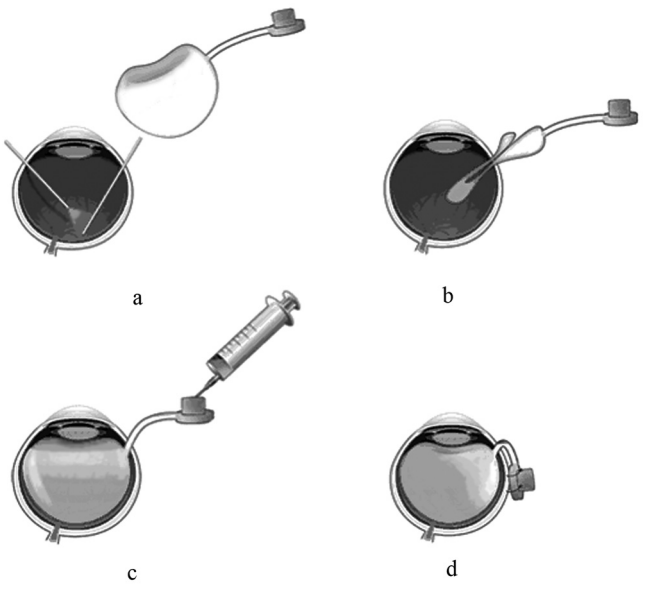

FIGURE 3. Illustration of DexP sustained-release studies in vivo from the capsule of FCVB (**a**–**d**). The capsule was folded and implanted in the vitreous cavity after fluid-air exchange. Approximately 0.6 mL DexP (2 mg/mL) in balanced salt solution in syringe was then injected into the capsule through a silicone tube-valve system, and the capsule was inflated to support the retina. The tube was subsequently fixed under the conjunctiva.

of HPLC grade were purchased from MERCK (State Food and Drug Administration of China).

Stock solutions were prepared in methanol at a concentration of 10 μg/mL in 100-mL glass vials and were serially diluted with PBS to prepare standard working solutions at the desired concentrations: 10, 20, 50, 100, 200, 400, 1000, and 2000 ng/mL. Fifty microliters of samples were transferred into 2.0-ml Eppendorf tubes. After an addition of 0.1 mL methanol, the mixture was vortexed for 1 minute and centrifuged at 13,000 rpm for 10 minutes. Approximately 0.1 mL supernatant was transferred to autosampler vials, and 20 μL was injected into the HPLC column. Data acquisition was performed (Xcalibur 1.3 software; ThermoFinnigan), as were peak integration and calibration (LCQuan software; ThermoFinnigan).

DexP Sample Assay In Vivo

The HPLC-MS/MS system includes a liquid chromatography model (LC-20A; Shimadzu, Kyoto, Japan), an autosampler (SIL-20AC; Shimadzu), and a mass spectrometer (API 4000 Q Trap; ABI/MDS-Sciex, Applied Biosystems, Foster City, CA). The mass spectrometer, which was equipped with an electrospray ionization (ESI) source, was operated in a positive electrospray ionization mode. The analytes were separated on an ultimate C18 (2.1 $\times$ 150 mm, 3 μm; Dikma Technologies, Dalian, China) column. Quantification was performed using SRM in the positive mode. The ion transitions of the mass-to-charge ratio (m/z) 473→435 for DexP were monitored, with a cleavage energy of 15 eV.

The reference formulation of DexP (purity >99.8%) was obtained from the National Institute for the Control of Pharmaceutical and Biological Products. Methanol of HPLC grade was purchased from Tedia. Ammonium acetate and formic acid of HPLC grade were purchased from Merck (State Food and Drug Administration of China).

Stock solutions were prepared in methanol at a concentration of 1.0 mg/mL in 20-mL glass vials and were kept refrigerated (4°C). The stock solutions were then serially diluted with methanol to prepare standard working solutions at the desired concentrations of 10, 30, 40, 200, and 400 ng/mL. Fifty microliters of aqueous humor samples were similarly transferred. The mixture was vortexed for 1 minute and centrifuged at 10,000 rpm for 10 minutes, and 20 μL was injected into the HPLC column. Data were processed with LC/MS control software (ABI/MDS-Sciex Analyst 1.4.2; Applied Biosystems).

RESULTS

The standard weight of an FCVB for humans and rabbits was 0.33 $\pm$ 0.005 g and 0.21 $\pm$ 0.005 g, respectively. As shown in

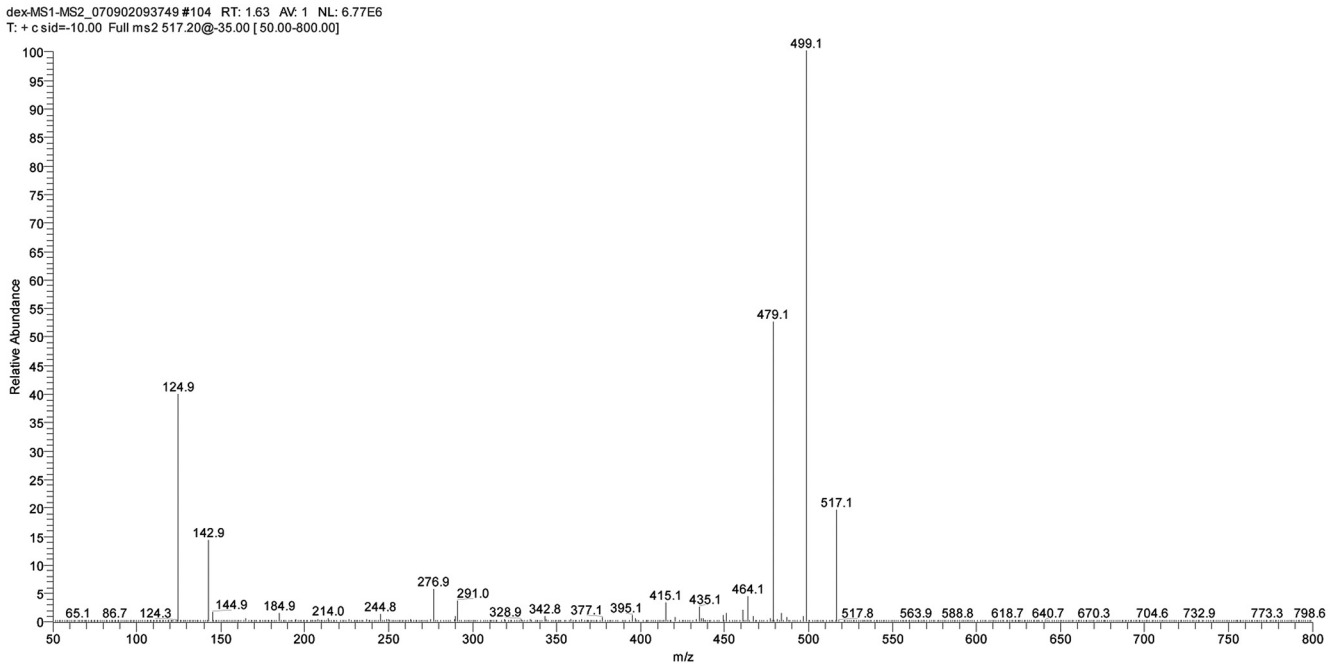

FIGURE 4. The production mass spectra of [M+H]+ for DexP. The fragment ions of m/z 499.2 were chosen as the production for monitoring DexP.

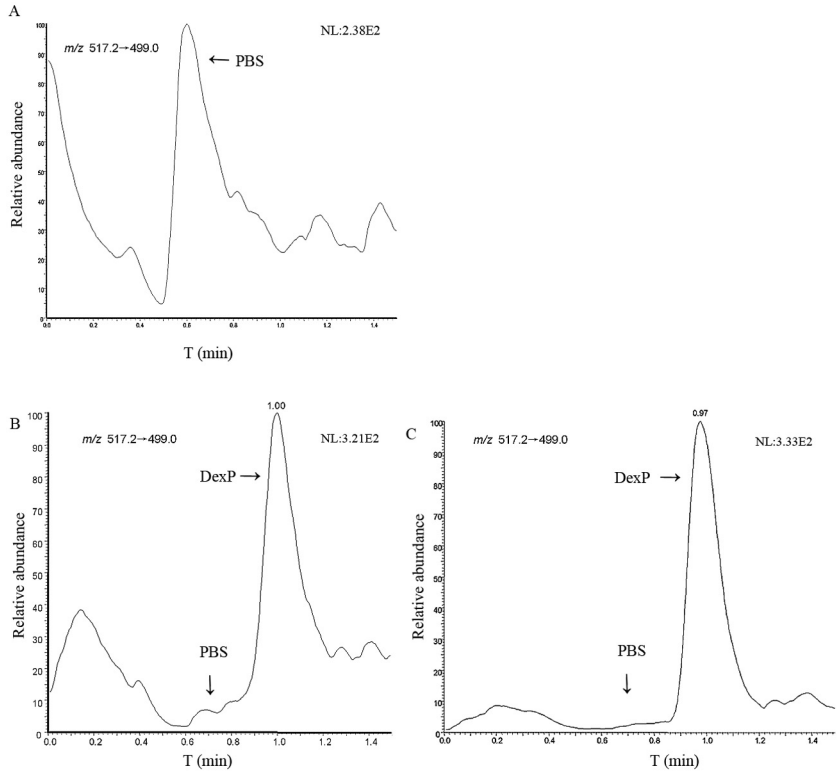

FIGURE 5. Representative LC-MS/MS chromatograms of DexP. (**A**) Blank PBS. (**B**) Blank PBS with standard working solutions of DexP (20 ng/mL). (**C**) Blank PBS with a sample of DexP.

Figure 1, numerous 300-nm-mili apertures were observed in the capsule of the FCVB.

Representative mass spectra, LC-MS/MS chromatograms, accuracy, precision of the quality control (QC) samples, FCVB sustained release of DexP in a time-dependent manner and a dose-dependent manner in vitro, and FCVB sustained release of DexP in a time-dependent manner in vivo are shown in Figures 4 and 5, Table 1, and Figures 6, 7, and 8.

LC-MS/MS parameters were optimized to produce the maximum response for DexP in the positive ion mode. Figure 4 shows the production mass spectra of $[M+H]^+$ of DexP. After electrospray ionization, positive ion fragments of m/z 517.2 were detected in the SRM mode with a triple quadrupole tandem mass spectrometer, and the fragment ions of m/z 499.2 were chosen as the production for monitoring DexP.

Representative LC-MS/MS chromatograms of DexP are shown in Figure 5. Retention times of PBS and DexP were 0.6 minute and 1.0 minute, without interferences observed between them, demonstrating that the method we selected has good selectivity and acceptability.

The accuracy (RE%) and precision (RSD%) results for the QC samples are summarized in Table 1. The results of RE $\leq \pm 15\%$ and RSD $\leq \pm 15\%$ proved the acceptable accuracy and precision of the proposed method.

TABLE 1. Summary of Accuracy and Precision of QC Samples in HPLC-MS/MS Detection

Added (ng/mL)	Found (ng/mL)	SD (%)	RSD (%)	RE (%)
50	46.27	2.00	4.33	−8.07
200	188.61	10.49	5.56	−6.04
2000	1949.02	89.42	4.59	−2.61

Linear equation: $y = -1037.97 + 139.368\,x$; correlation coefficient (r^2): 0.9913. RSD, relative standard deviation; RE, relative error.

DexP was released from the FCVB in a time-dependent manner in vitro in five concentrations of 0.25, 0.5, 1, 2, and 4 mg/mL, at 10, 20, 40, 60, 20, 180, 240, 300, and 360

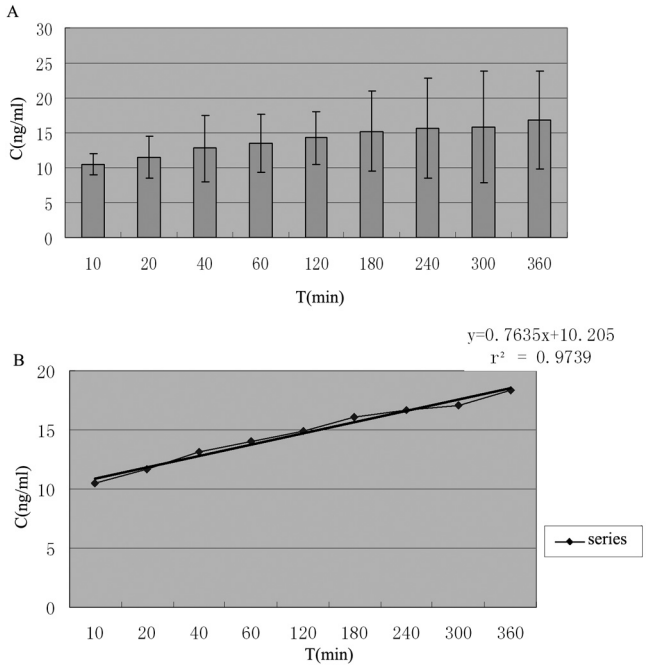

FIGURE 6. DexP was released from the capsule of FCVB at the concentration of 0.25 mg/mL in a time-dependent manner in vitro. (**A**) The DexP content (ng, y axial; minute, x axial) in the liquid was then detected by mass spectrometry. The contents at different time points are statistically different ($F = 2.554$; $P < 0.05$). (**B**) DexP was released from the capsule of the FCVB in a time-dependent manner ($y = 0.7635x + 10.205$).

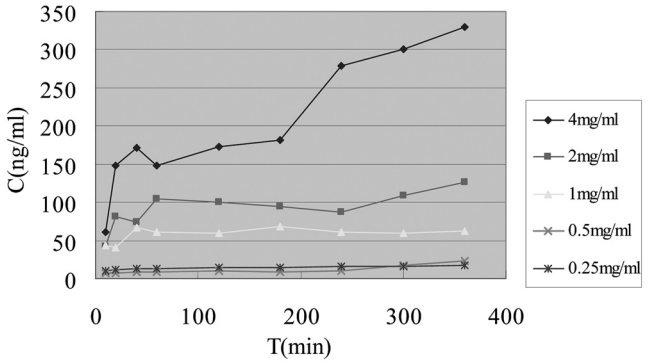

FIGURE 7. DexP was released from the capsule of the FCVB in a time-dependent and a dose-dependent manner in vitro from concentrations ranging from 0.25 to 4 mg/mL. In all five concentrations, the DexP outside the FCVB increased over time. The tendency in 4 mg/mL was more obvious than in 0.25, 0.5, 1, and 2 mg/mL.

minutes. In all five concentrations, the DexP outside the FCVB increased over time, as shown in Figures 6 and 7. The tendency in 4 mg/mL was more obvious than that in 0.25, 0.5, 1, and 2 mg/mL. (Fig. 7). Content (y) had a good linear relationship with time (x), especially in the 0.25-mg/mL DexP group, as seen by $y = 0.7635x + 10.205$ ($r^2 = 0.9739$), indicating that the FCVB released the DexP stably with 0.7635 ng/mL every minute. The contents at different time points are statistically different ($F = 2.554$; $P < 0.05$; Figure 6). According to the linear tendency, the FCVB kept releasing afterward.

DexP was released from the FCVB in a dose-dependent manner in vitro in five concentrations of 0.25, 0.5, 1, 2, and 4 mg/mL (Fig. 7). With the increased DexP concentrations in the FCVB, the outside concentration of DexP rose; this dose-dependent tendency began from the first 10 minutes, and lasted until the 6th hour.

In vivo, DexP was sustainably released from the FCVB in the aqueous humor, as shown in Figure 8. In the FCVB-treated group, DexP contents were detected by HPLC-MS/MS until day 28, ranging from 4.00 to 5.24 ng/mL, but not on day 42; however, the DexP content was detected only before day 3 in the control group. This long-lasting release showed the FCVB could be used as DDS in rabbits.

DISCUSSION

DDS is the consensus ideal method in vitreous body drug administration. The ideal intravitreal DDS is not only an intravitreal drug delivery material but also a vitreous tamponade agent.[18] Previous studies demonstrated that the FCVB was a fine vitreous substitute that closely mimics vitreous morphology and restores its physiological function, such as support, refraction, and cellular barriers, during a 3-month observation period without obvious complications commonly induced by silicone oil (data not shown). The present study has shown that the FCVB can also be used as a drug-sustained release system.

In the capsule, 300-nm-mili apertures assign the FCVB the capability of DDS. Because the molecular mass of DexP is 516.41 Da, the drug molecules diffuse freely through the apertures. As long as the FCVB with DexP is immersed in the balanced salt solution, the osmotic pressure forces the DexP molecules to move through the apertures to the circumference. Especially in vivo, as the released DexP is taken away by blood or is metabolized quickly, the osmotic pressure maintains the strain. On the other hand, the number of apertures also restricts the total flow rate and limits the rapid loss of the DexP, and then sustained drug release is achieved.

Kwak et al.[22] reported that DexP reached its highest level (8.2 ± 0.7 μg) in 1.5 hours in the aqueous with a 3.48-hour half-life but that it could not be detected in the vitreous at 72 hours after one injection of 0.1 mL intravitreal DexP at a dose of 4 mg/mL. In the present study, the DexP content in the aqueous could be detected only before day 3 in the control group. This deviation may be attributed to limited DexP detection at different HPLC, which was 5.2 ± 1.7 μg and 3 ng, respectively.

Intraocular DexP DDS has been previously described by Wadood et al.,[23] Siqueira et al.,[24] Kuppermann et al.,[25] and Williams et al.[26] An intraocular drug delivery system (Surodex; (Oculex Pharmaceuticals, Sunnyvale, CA), which can be described as a kind of anterior segment DexP DDS, appeared to be as effective as dexamethasone 0.1% eyedrops in controlling intraocular inflammation after cataract surgery by phacoemulsification, and both methods had a similar safety profile.[23] An intraocular lens containing a DexP DDS showed therapeutic concentrations of dexamethasone were detectable in the aqueous and vitreous throughout the 9-day period in rabbit eyes.[24] In persistent macular edema, a single intravitreal DexP DDS treatment produced statistically significant best-corrected visual acuity improvements 90 days after treatment and was well tolerated for 180 days. The application of 700 μg DexP DDS may have potential as a treatment for persistent macular edema.[25] Recently, in patients with persistent macular edema resulting from uveitis or Irvine-Gass syndrome, 700 μg DexP DDS was well tolerated and produced statistically significant improvements in visual acuity and fluorescein leakage.[26]

In our study, DexP was released from the capsule of the FCVB in a time-dependent and a dose-dependent manner in vitro and a time-dependent manner in vivo. DexP was detected until day 28 and vanished on day 42 in the aqueous, indicating that the FCVB can be used as DDS in addition to serving as a vitreous substitute. Clinical trials are in progress to ascertain FCVB biocompatibility and effectiveness as a silicone oil substitute in human eyes at Zhongshan Ophthalmic Center in China. The clinical trials have been approved by the Sun Yat-sen University Medical Ethics Committee (Zhongshan Ophthalmic Center Medical Ethics [2009] No. 07) and have been successfully registered with ClinicalTrials.gov (ID: NCT00910702) and in the Chinese Clinical Trial Register (ChiCTR-TNC-00000396).

The current intraocular DDS confront some major disadvantages: they are opaque, may interfere with vision, and result in a nonuniform drug distribution.[18] In contrast, FCVB has good transparency, induces few refractive shifts,[21] and permits the DexP in solution to evenly disperse in the capsule and to permeate outside uniformly. Therefore, the FCVB can sustainably and mechanically release drugs without changing the chemical property of drugs and may provide a common vehicle for different drug release.

Given that the dosage released from the FCVB is not high enough for clinical therapy, future research will focus on increasing the level of the released drug, such as increasing the number or size of apertures in the capsule, and on the

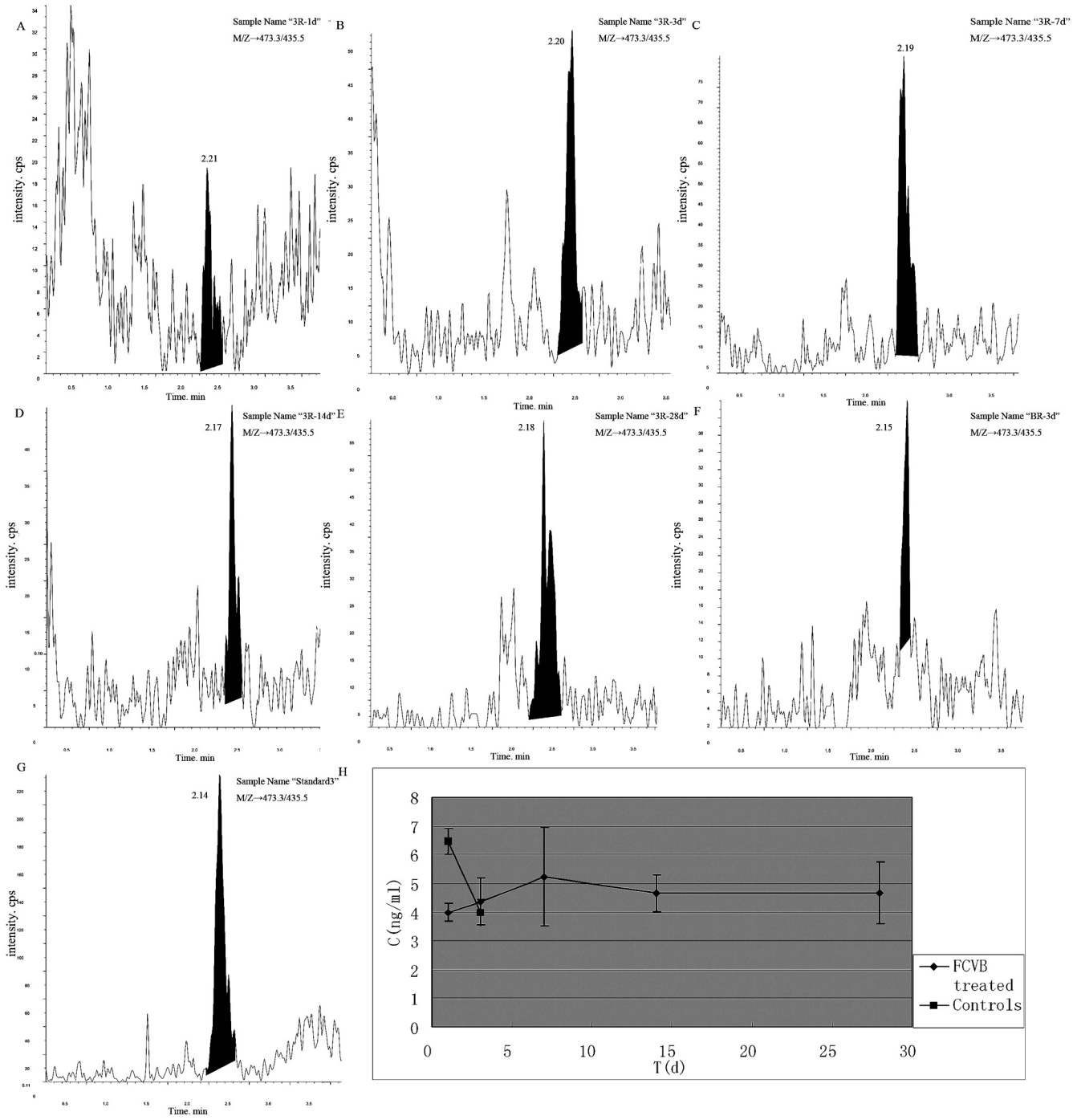

FIGURE 8. Representative HPLC-MS/MS chromatograms of aqueous humor containing DexP. (**A–E**) Aqueous samples containing DexP on days 1, 3, 7, 14, and 28 in the FCVB-treated group. (**F**) Aqueous samples containing DexP on day 3 in the control group. (**G**) A spiked blank aqueous sample containing 13.3 ng/mL DexP. (**H**) Line graph of released DexP contents. The DexP contents were detected until day 28, ranging from 4.00 to 5.24 ng/mL, but not on day 42 in the FCVB-treated group; however, the DexP was detected only before day 3 in the control group.

investigation of other drugs, including antibiotics, antiproliferation agents, and vascular endothelial growth factor antagonists.

In conclusion, the FCVB can sustainably and mechanically release DexP through the apertures of capsules in a time-dependent and a dose-dependent manner. This study provides us with a novel combined research and therapy strategy for a vitreous substitute and drug delivery system.

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