Drug Delivery

http://informahealthcare.com/drd
ISSN: 1071-7544 (print), 1521-0464 (electronic)

Drug Deliv, Early Online: 1–9
 DOI: 10.3109/10717544.2014.919543

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RESEARCH ARTICLE

A study of the dexamethasone sodium phosphate release properties from a periocular capsular drug delivery system

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Abstract

The aim of this study was to investigate whether a periocular capsular drug delivery system (DDS) can release dexamethasone sodium phosphate (DEXP) *in vitro* and *in vivo* to the posterior segment of rabbit's eye. *In vitro*, the periocular capsular DDS containing 2 mg/ml or 5 mg/ml DEXP was immersed in modified Franz diffusion cell. Four-hundred microliters of liquid was aspirated at 0.5, 1, 2, 4, 8, 24 and 48 h for determination. *In vivo*, the DEXP-filled periocular capsular DDS was implanted into the sub-Tenon's sac of the New Zealand rabbit. DEXP concentration at the serum aqueous humor, cornea, iris, lens, ciliary body, vitreous, retina, choroids and sclera was quantified at 1, 3, 7, 14, 28 and 56 d after implantation. The DEXP concentration was determined by ultra-performance liquid chromatography-tandem mass spectrometry. *In vitro*, the periocular capsular DDS released the DEXP in time-dependent manner from 1/2 to 48 h. *In vivo*, the concentrations of the DEXP at the retina, choroids, ciliary body and iris were 123.11 (91.23, 732.61) ng/g, 362.46 ± 330.46 ng/g, 71.64 (71.35, 180.21) ng/g and 192.50 ± 42.66 ng/g, respectively, at 56 d after implantation. Minimal DEXP was found in the aqueous, serum and vitreous. Our results demonstrated that DEXP could be sustained released from the periocular capsular DDS, which indicated that the periocular capsular DDS might be a potential candidate of transscleral drug delivery for the management of posterior segment diseases.

Keywords

Drug delivery, drug distribution, eye, rabbit, ultra-performance liquid chromatography-tandem mass spectrometry

History

Received 2 March 2014
Revised 24 April 2014
Accepted 26 April 2014

Introduction

Eye diseases, such as uveitis, age-related macular degeneration and diabetic retinopathy involved the posterior segment (retina, choroids and vitreous) can lead to irreversible visual impairments (Congdon et al., 2004; Durrani et al., 2004; Jackson & Barber, 2010). These diseases have a chronic nature and need long-time therapy. Due to the anatomic barriers of posterior segments (blood–retinal barrier, uvea and sclera) and short duration of the treatment agents, drug delivery to the posterior segments is of great concern but also challenging (Edelhauser et al., 2010).

At present, drugs are clinically administrated to the posterior segments of the eye mainly by three routes: systemic, intravitreal and periocular (Kuppermann & Loewenstein, 2010). Systemic route shows low bioavailability due to the requirement of large dosage for the effective therapeutic concentration in the eye and the consequent systemic complications (Hughes et al., 2005). Intravitreal route seems the most effective way, but also the most invasive, for the perforation of the eyeball and the undesirable complications such as the raised intraocular pressure (IOP), floaters, vitreous hemorrhage, retinal detachment and endophthalmitis (Jager et al., 2004). The periocular route can be an alternative choice for it deposits the agent adjacent to the target tissues, such as the choroids and retina, and is less invasive than the intravitreal route. But it is also restricted for the short during of most of the drugs currently used. Therefore, periocular drug delivery system (DDS) is a better choice for the ophthalmologists not only for the greater bioavailability but also the higher processing safety (Ambati & Adamis, 2002). Among the subconjunctival, retrobulbar, peribulbar and Tenon's routes of periocular drug delivery avenues, the Tenon's route is regarded as the most effective one for it can lay the agents proximal the sclera (Thrimawithana et al., 2011).

We previously fabricate a new vitreous substitute, foldable capsular vitreous body, which consists of a thin vitreous-like capsule with a tube-valve system. It has successfully released dexamethasone sodium phosphate (DEXP), siRNA-PKCα, 5-fluorouracil and levofloxacin through the 300-nm-mini

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apertures in the surface sustainedly (Liu et al., 2010; Chen et al., 2011; Lin et al., 2011; Zheng et al., 2012). In order to avoid vitrectomy accompanied by foldable capsular vitreous body and to reduce the direct disturbance of the intraocular environment of the eye, we develop a periocular capsular DDS, which can be implanted to the posterior Tenon's sac adjacent to the sclera by means of the same craft technique. The aim of this study was to investigate whether the periocular capsular DDS can release drugs such as the DEXP through the 300-nm-mini apertures, a long-acting corticosteroid, *in vitro* and *in vivo* to the posterior segment of the eye, and evaluate its release properties.

Materials and methods

Fabrication and pore-forming of the periocular capsular DDS

The periocular capsular DDS, consisting of a V-shape capsular body, a tube and valve (shown in Figure 1), was fabricated with liquid silicone rubber (NUSIL, Bakersfield, California). The silicone rubber, gelatinous at room temperature, vulcanized at 160 °C, heating for 200 s, became semisolid elastic rubber in a specially shaped mirror steel mould *via* injection-forming technology.

In vitro release of DEXP from periocular capsular DDS

DEXP, dissolved in balanced salt solution (ALCON, Fort Worth, TX), at dosages of 0.5 ml (2 mg/ml or 5 mg/ml), were injected into the periocular capsular DDS through the tube and valve, separately; then, the periocular capsular DDS was immersed in modified Franz diffusion cell. Four-hundred microliter liquid in each cup was aspirated at 0.5, 1, 2, 4, 8, 24 and 48 h for determination. The concentration was determined by ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS), according to the Liu et al. (2010).

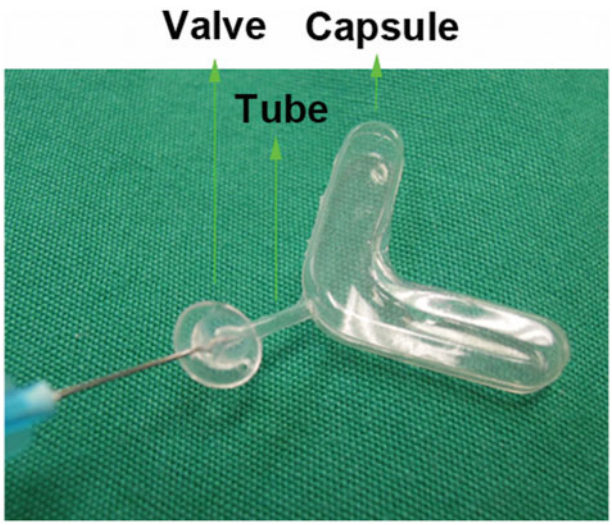

Figure 1. Dexamethasone sodium phosphate (DEXP) sustained-release studies *in vitro*. (A) The periocular capsular drug delivery system (DDS) consisted of a capsule, a tube and a valve. (B) DEXP at concentrations of 2 mg/ml and 5 mg/ml was injected into the periocular capsular DDS, which were immersed in balanced salt solution (BSS) in modified Franz diffusion cells. *Four-hundred microliter* liquid was aspirated at 0.5, 1, 2, 4, 8, 24 and 48 h.

In vivo release of DEXP from periocular capsular DDS

This study was carried out in accordance with the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Ophthalmic and Vision Research. The protocol was approved by the Committee on the Ethics of Animal Experiments of Zhongshan Ophthalmic Centre, Sun Yat-sen University (permit number: 2012-051). Thirty-four New Zealand albino rabbits weighing 2.0–3.0 kg were used for the *in vivo* study. Two groups were set: periocular capsular DDS implantation group (28 rabbits) – the periocular capsular DDS filled with 0.5 ml DEXP (5 mg/ml) was implanted in the Tenon's sac of rabbit's eye; control group (six rabbits) – 0.5 ml DEXP (5mg/ml) was subconjunctival injected to the rabbit's eyes. All surgery was performed under general anesthesia through an intramuscular injection of ketamine hydrochloride (30 mg/kg) and chlorpromazine hydrochloride (15 mg/kg), and all efforts were made to minimize suffering.

In the periocular capsular DDS implantation group, the periocular capsular DDS were washed three times with double-distilled water and then sterilized by ethylene oxide vapor prior to the surgery. After exposure of the Tenon's sac, the periocular capsular DDS was implanted to the sub-Tenon's sac with the valve and tube tightly sutured to the sclera. Then, 0.5 ml DEXP (5 mg/mL) was injected to the periocular capsular DDS through the valve and tube. The surgery procedures are shown in Figure 2. Finally, the conjunctiva was stitched up with 8–0 Vicryl sutures. At 3, 7, 14, 28 and 56 d after implantation, slip lamp photography, fundus photography and tonometry were carried out to check the biocompatibility of the periocular capsular DDS. At 1, 3, 7, 14, 28 and 56 d after surgery, rabbits in groups of 4–6 were enucleated after euthanatized with overdose of ketamine and chlorpromazine. Serum, aqueous humor, cornea, iris, lens, ciliary body, vitreous, retina, choroids and sclera were collected to determine the DEXP concentration by UPLC-MS/MS.

In the control group, the rabbits received unilateral subconjunctival injection of 0.5 ml DEXP (5 mg/ml). At one and three days after treatment, rabbits in groups of three were enucleated after euthanatized with overdose of ketamine and chlorpromazine. Different parts of the eyeball were segregated to determine the DEXP concentration by UPLC-MS/MS.

Samples were stored at −80 °C until determination. Before analysis, tissues were sonicated at 0.5 Hz for 40 s.

DEXP sample assay

Sample analysis was determined by UPLC-MS/MS in the School of Pharmaceutical Sciences of Sun Yat-sen University, Guangzhou, China.

Chromatographic separation was achieved on a Waters Acquity UPLC® BEH C18 column (2.1 × 50 mm ID, 1.7 µm; Waters, Wexford, Ireland). The elution *in vitro* consisted of mobile phase A (acetonitrile) plus mobile phase B (distilled water containing 0.05% ammonia and 5 mM ammonium acetate, HPLC grade, MERCK, Darmstadt, Germany) (A:B, 30:70, v/v) was pumped at 300 µl/min. The elution *in vivo* consisted of mobile phase A (methanol) and mobile phase B (distilled water containing 0.05% ammonia

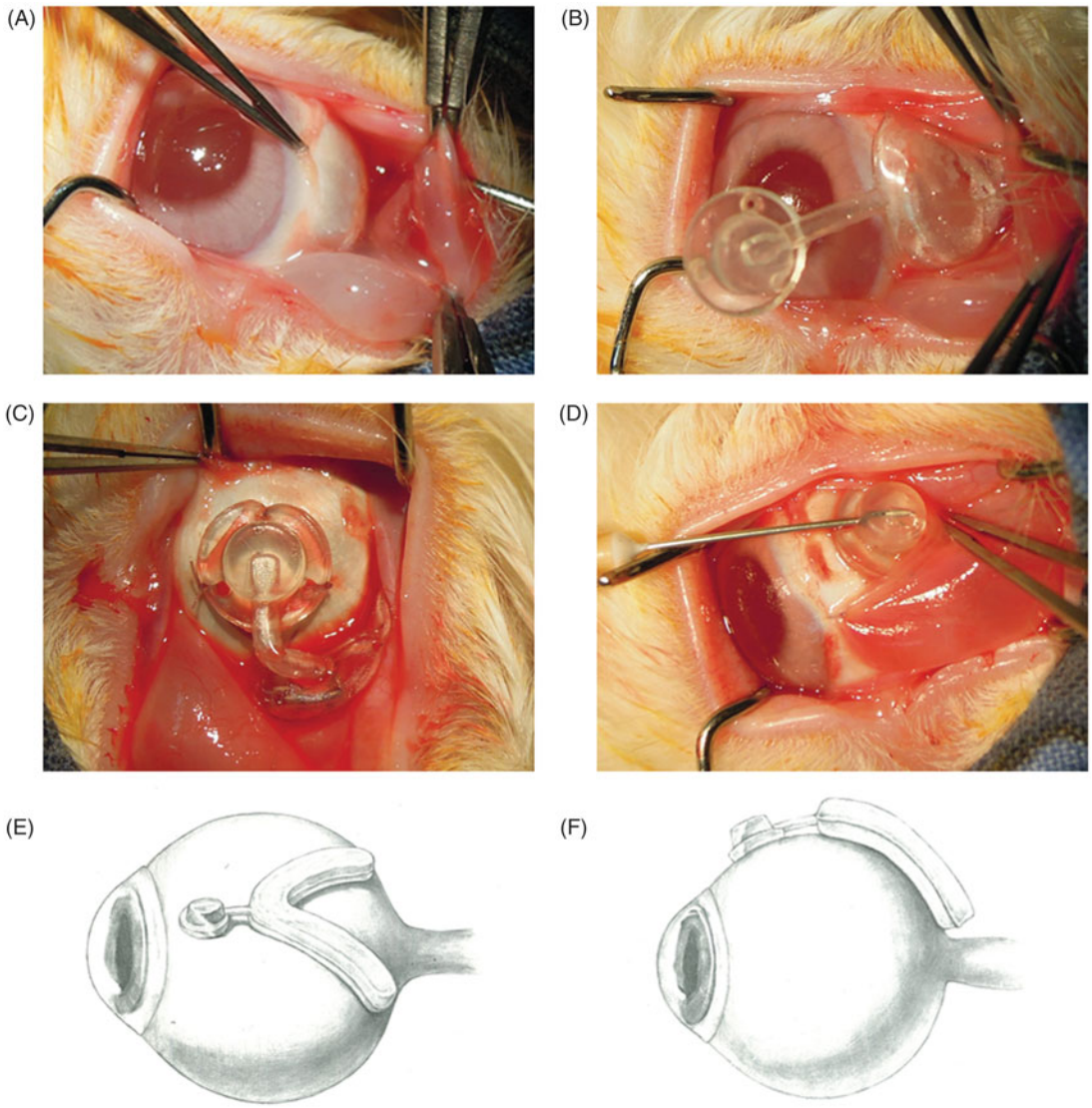

Figure 2. Periocular capsular drug delivery system (DDS) was implanted to the sub-Tenon's sac of rabbit eye. (A) The sub-Tenon's sac was exposed, (B) the periocular capsular DDS was laid in the sub-Tenon's sac, (C) the periocular capsular DDS was fixed on the episclera, (D) the dexamethasone sodium phosphate (DEXP) was injected through the valve and tube to the capsule of the periocular capsular DDS, (E) the schematic diagram of the periocular capsular DDS implanted to sub-Tenon's sac of the upper view and (F) the schematic diagram of the periocular capsular DDS implanted to sub-Tenon's sac of the lateral view.

and ammonium acetate) (A:B, 70:30, v/v) was pumped at 250 µl/min. A typical injection volume was 10 µl.

A tandem quadrupole mass spectrometer (Waters Quattro Premier XE™, Micromass MS Technologies, Manchester, UK), operated in ESI mode, was used for the detection of DEXP. Multiple-reaction monitoring mode was selected for quantification. The mass spectrometer was operated in the negative electrospray ionization mode. The ion transition of the mass-to-charge ratio (m/z) 471.3 → 78.6 for DEXP was monitored with collision energy of 29 EV, a capillary voltage of 2.0 KV, a source temperature of 120 °C, a desolvation temperature of 350 °C, respectively. Ultra-high pure nitrogen and argon were used as desolvation gas (650 µl/h) and collision gas (210 µl/min), respectively.

Manufacture of the standard curve: DEXP (LOT 100016-201015, purity 99.8%, National Institute for the Control of Pharmaceutical and Biological Products), dissolved in methanol (Tedia, Fairfield, OH) to 1 mg/ml, was kept as stock solution at −20 °C. Standard working solutions were prepared by diluting the stock solution with BBS (*in vitro*) or blank tissue (*in vivo*) to the desired concentrations: 2, 4, 10, 20, 50, 100, 500 and 2000 ng/ml (*in vitro*); 5, 10, 20, 100 and 500 ng/ml (*in vivo*). After addition of 100 µl acetonitrile to 100 µl sample, the mixture was whirled for one minute and centrifuged at 16 000 rpm for 15 min. Approximately 100 µl supernatant was transferred to auto-sampler vial, and 10 µl was injected into the UPLC column. One-hundred microliter distilled water was add to the tissue sample, and the mixture tissue homogenate was homogenized by a homogenizer. After centrifugation at 16 000 rpm for 15 min of the homogenate, supernatant was collected. Then, the supernatant will be treated as the stock solution. Masslynx™ 4.1 software (Waters Corporation, Massachusetts, USA) was used to collect and process data.

Data analysis

Statistical analyses were performed by SPSS 13.0 (SPSS Inc. Chicago, USA). Data were assessed for normality by the

Shapiro–Wilk W test and parametric or nonparametric tests were used as appropriate. If the data followed a normal distribution, they were expressed as mean ± standard deviation. If the data did not follow a normal distribution, they were expressed as median (P25 and P75).

Simple linear regression analysis was used to assess whether the released time distributed to the cumulative concentration of DEXP *in vitro*. One-way ANOVA was used to assess the IOP after surgery. The values of $p \leq 0.05$ were considered as statistically significant.

Results

DEXP sample assay

To increase the selectivity and sensitivity of the liquid–liquid extraction procedure, the mass spectrometry and the chromatography conditions were optimized (Figure 3). After electrospray ionization, the ion transition of mass-to-charge ratio (m/z) 471.3 → 78.6 was chosen as the production for monitoring DEXP. The representative UPLC-MS/MS chromatograms of DEXP and accuracy and precision of the quality control samples are shown in Figure 4 and Table 1, respectively.

In vitro release of DEXP from periocular capsular DDS

The cumulative released concentration of DEXP from periocular capsular DDS is shown in Figure 5. DEXP released from the capsular increased with time in a 48-h experimental time period in the 2 mg/ml and 5 mg/ml groups, separately. Through great standard deviation, however, the cumulative concentration of DEXP (y) had a definite linear relationship with released time (x) in the 2 mg/ml group ($y = 5.690x + 45.959$, $p < 0.0001$, $R^2 = 0.586$) and 5 mg/ml group ($y = 20.973x + 50.200$, $p < 0.0001$, $R^2 = 0.274$), indicating that the DEXP from the periocular capsular DDS can be released stably in time-dependent pattern.

In vivo release of DEXP from periocular capsular DDS

After implantation of the periocular capsular DDS in the rabbit Tenon's sac, slight inflammation was found in the first two weeks (Figure 6A). One rabbit suffered from slight posterior subcapsular opacification at 56 d after implantation, except that, there was nothing abnormal with the anterior chamber of the rabbit eyes. No obvious change of the fundus was found after the implantation (Figure 6B). There was also no significant change of IOP found after implantation ($p > 0.05$) (Figure 6C).

Table 2 lists the distribution of DEXP in the serum and rabbit eyes in serum, aqueous humor, cornea, iris, lens, ciliary body, vitreous, retina, choroids and sclera, and 1, 3, 7, 14, 28 and 56 d after periocular capsular, DDS was implanted in the Tenon's sac of the rabbit eyes. In the periocular capsular DDS implantation group, the choroids showed the highest concentration of DEXP while the retina showed the second highest. There was also a certain amount of DEXP in the ciliary body and iris. Low level of DEXP was found in the lens and sclera. Meanwhile, the serum, aqueous humor, cornea and vitreous were almost under the detection limit.

In the control group, there was certain amount of DEXP found in cornea, lens, iris, ciliary body, retina, choroids and sclera. However, there was no DEXP found in the serum and the tissues of eyes three days after subconjunctival injection of DEXP.

Discussion

In this study, the periocular capsular DDS was fabricated by the same material and craft technique of the foldable capsular vitreous body, of which biocompatibility has been demonstrated in rabbits (Wang et al., 2012) and human through the exploratory clinical trials (government number, NCT 00910702) (Lin et al., 2011) and now are under multi-center-clinical trial in China (VES-CTR-001). Through the slit lamp photography, fundus photography and tonometry after the implantation surgery, there was nothing abnormal found in the rabbit eyes except the inflammation response of the first two weeks to repair the surgical wound. It can be concluded that the periocular capsular DDS has good biocompatibility. What's more, it was found that the periocular drug DDS could release DEXP *in vitro* in time-dependent pattern and to the retina and choroids successfully for 56 d.

Advance in drug delivery to the posterior segment is a very important part for the treatment of retinal and choroidal diseases (Edelhauser et al., 2010). Periocular drug delivery deposited the therapeutic agents against the external surface of the sclera, which can avoid the risk of the intraocular drug delivery such as the vitreous hemorrhage and endophthalmitis and make it safe and efficient to deliver the agents to posterior segment (Shah et al., 2010). The efficacy of periocular drug delivery is mainly determined by the static anatomic barriers

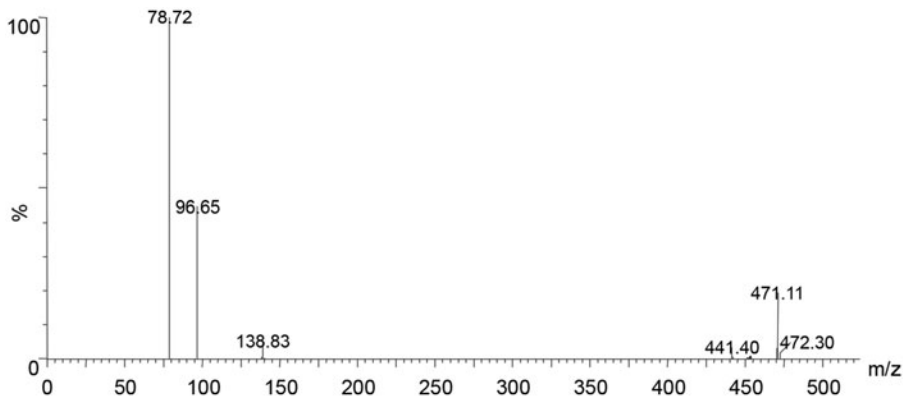

Figure 3. The production mass spectra of dexamethasone sodium phosphate (DEXP). The ion transition of mass-to-charge ratio (m/z) 471.3 → 78.6 was chosen as the production for monitoring DEXP.

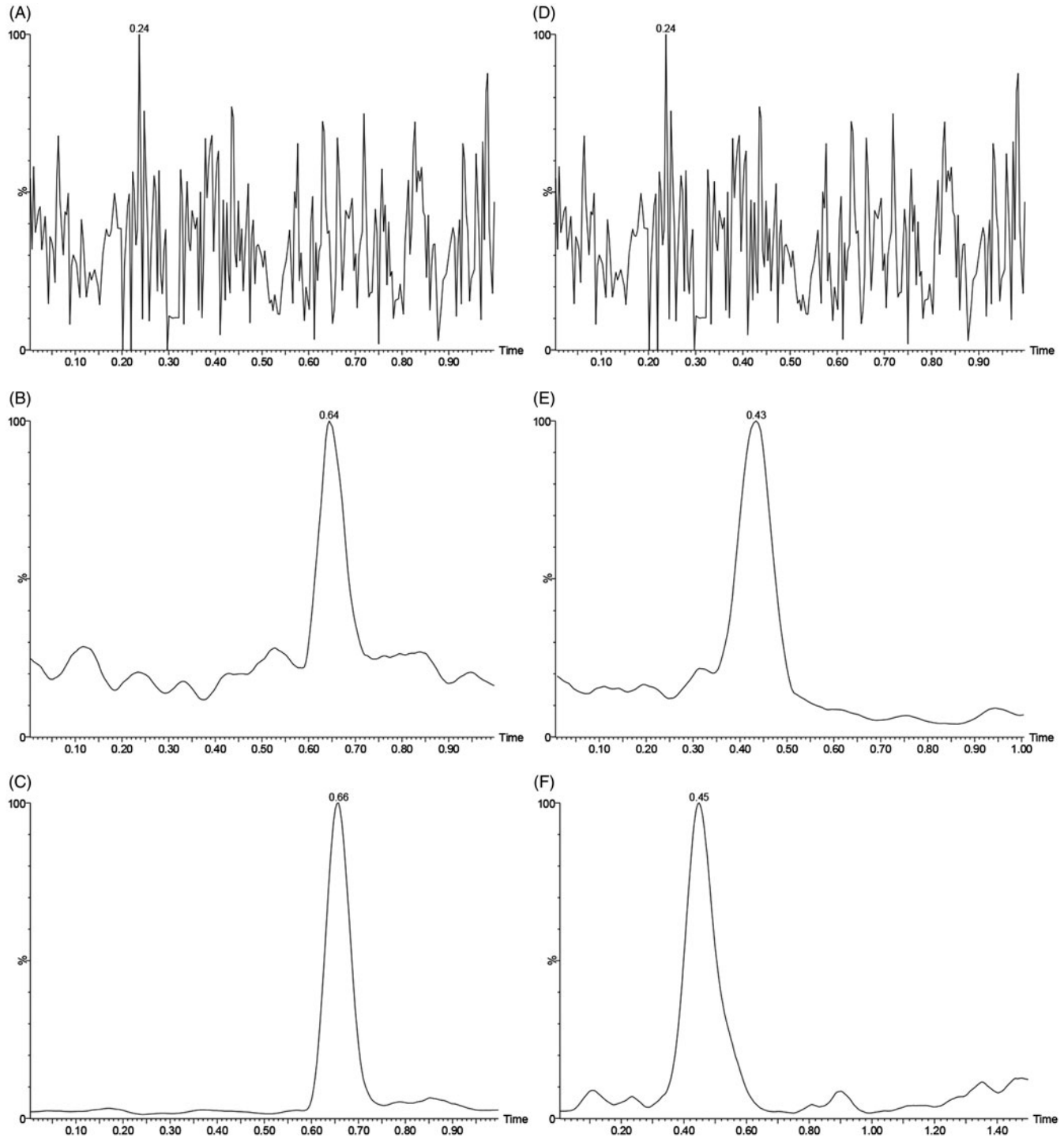

Figure 4. Representative ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) chromatograms of dexamethasone sodium phosphate (DEXP). (A) Balanced salt solution (BSS) *in vitro*, (B) blank BSS with standard DEXP *in vitro*, (C) samples *in vitro*, (D) blank tissue sample *in vivo*, (E) standard DEXP in blank tissue *in vivo and* (F) tissue samples *in vivo*.

and the dynamic clearance mechanisms (subconjunctival–episcleral blood/lymph vessel flow for 80% and choriocapillaris blood flow for 20%) (Robinson et al., 2006). The drugs have to permeate several layers (sclera, choroids-Bruch's membrane and retinal pigment epithelium) to reach the neuroretina (Kim et al., 2007). The transscleral intraocular tissue distribution of corticosteroids was primarily driven by the drug solubility (Thakur et al., 2011). A study has demonstrated that a refillable silicone episcleral exoplant can facilitate diffusion of fluorescein through the sclera resulting in high levels in the back of the eye and low levels of systematic absorption, comparing to the periocular injection (Pontes De Carvalho et al., 2006). Lee et al. (2008) have demonstrated that Oregon Green-labeled triamcinolone acetonide is capable of diffusing across rabbit sclera into the retina/choroids *via* transscleral diffusion after a sub-Tenon's injection.

The sclera, a highly porous tissue consisting of 68% water, is permeable to a series of hydrophilic compounds with various molecular weights (Olsen et al., 1995) and high

molecular weight compounds from 4 to 150 kDa (Ambati et al., 2000). It has been reported the sclera permeability is similar to the cornea *in vitro*, so that the primary route of solute transport through the sclera passive diffusion is through an aqueous pathway (Prausnitz & Noonan, 1998). In this study, we sutured the periocular capsular DDS to the sclera to make it close proximity to the sclera. And the fact that DEXP liquid was encapsulated limited the clearance from the subconjunctival–episcleral blood/lymph vessel flow. These two factors can increase the bioavailability of the periocular capsular DDS (Geroski & Edelhauser, 2001). DEXP, a water-soluble phosphate of dexamethasone (Rohdewald et al., 1987), of which the molecular mass is 516.41 Da, can leak from out from the tiny apertures of the periocular capsular DDS and easily pass the sclera to the choroids. The formation of apertures is attributed to the fabrication of the periocular capsular DDS. During vulcanizing of the semisolid elastic rubber membrane, air traverses and forms nanometer-grade channels (Jiang et al., 2012). However, it seems opposite to the former researchers that the DEXP level at the sclera was much lower than at the choroids and retina (Thakur et al., 2011). We speculated that because in this experiment, total amount of the sclera, retina and vitreous were collected to determine the average DEXP level of different tissue, but the transscleral concentration gradient just formed at fixed region of eye where the periocular capsular DDS was implanted, and the total amount of sclera is much higher than the total amount of the choroids and retina.

The choroids, a fenestrated blood vessel network located between the sclera and the retina, form the secondary elimination pathway for molecules that diffuse through the sclera. However, compared to the conjunctival lymphatics/blood flow, choroids show much lower influence on the periocular drug delivery bioavailability of corticosteroids (Robinson et al., 2006). Bill et al. (1980) also found that the choroids permeability to low-molecular-weight substances is high. Cheruvu et al. found that the hydrophilic solutes are more easily to permeate the choroids–Bruch's membrane than the lipophilic solutes (Cheruvu & Kompella, 2006). These researches are consistent with our result that the DEXP concentration in the choroids was the highest among the eye.

However, the retina pigment epithelium is the major rate-limiting barrier in the retinal delivery of hydrophilic drugs and macromolecules through the periocular route in bovine eyes (Pitkanen et al., 2005). But surprisingly, the DEXP concentration in the retina was just second to the choroids among the eye in this experiment. The underlining reason still need further research to explain this contradiction. Meanwhile, we can just find low concentration of DEXP in the vitreous, maybe owning to the integrated internal limiting membrane, a basement membrane, which acts as a border between the vitreous humor and the neuroretina (Dalkara et al., 2009; Candiello et al., 2010). Overall, the high concentrations of the DEXP in the choroids and retina ensure that the periocular capsular DDS can act as an alternative choice to the posterior drug delivery.

In the anterior segment of the rabbit's eye, high concentration of DEXP was found at the iris and ciliary body, just second to the choroids and vitreous. We speculated that the DEXP came from the posterior to anterior transition or the DEXP permeated to the sclera then to the root of the iris. There was also low concentration of DEXP at the cornea, indicating that maybe small amount of DEXP got into the anterior segment of the eye from the cornea. Slight posterior subcapsular opacification was found in one rabbit at 56 d after implantation maybe owing to the distribution of low level DEXP in the lens (James, 2007). However, trace amount of DEXP was found in the serum, indicating that systematic absorption of the DEXP was rare and a hematogenic route for the DEXP to reach the retina and choroids is excluded from consideration. It also means that rarely systemic side effect will be brought by the implantation of periocular capsular DDS since the poor systematic absorption of the DEXP. The result was different from Bodker et al. (1993) and Weijtens et al. (1999) for they demonstrated that periocular injection of dexamethasone can achieve the choroids and retina through the hematogenic route. The divergence maybe came about as they take the dexamethasone as evaluation criterion; and in this experiment, DEXP was used as evaluation criterion.

Table 1. Summary of accuracy and precision of quaility control samples in UPLC-MS/MS detection of dexamethasone sodium phosphate (DEXP).

Added (ng/ml)	Found (ng/ml)	Standard deviation (%)	Relative standard deviation (%)	Relative error (%)
10	9.78	1.70	5.77	–6.32
200	198.22	10.12	6.23	–4.22
2000	2014.35	14.87	10.43	2.58

Linear equation: $y = 1.634x - 1.592$; correlation coefficient (r^2): 0.9974.

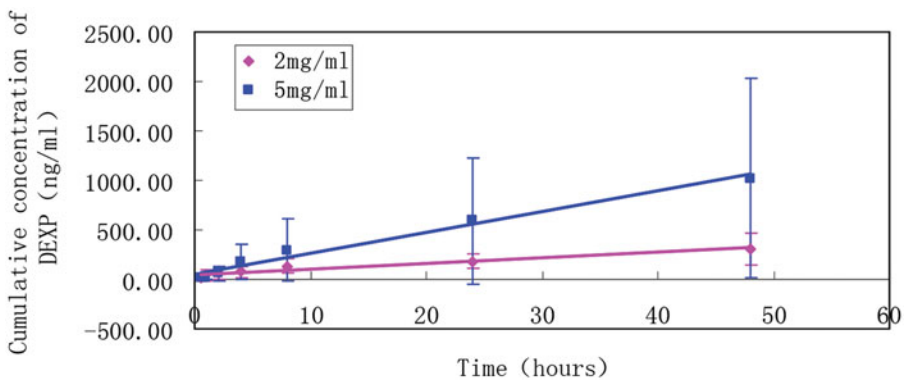

Figure 5. The cumulative release profile of dexamethasone sodium phosphate (DEXP). The periocular drug delivery system can release dexamethasone sodium phosphate in a time-dependent manner *in vitro* in the 2 mg/ml and 5 mg/ml groups *in vitro*.

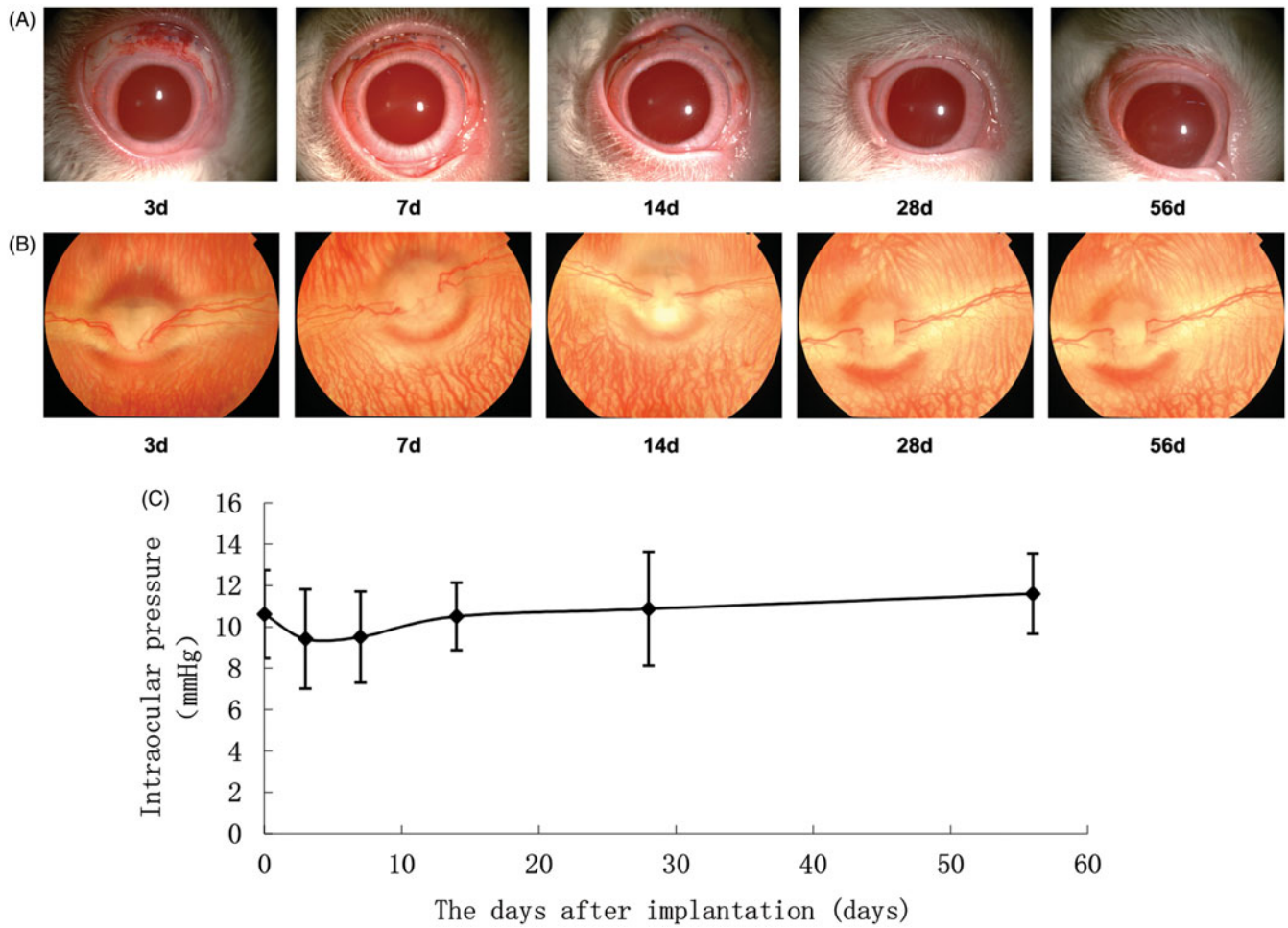

Figure 6. Clinical observations after the drug delivery system implantation in the Tenon's sac of rabbit eye. (A) Slip lamp photography, slight inflammation was found in the first two weeks after surgery after implantation; (B) Fundus photography, no obvious change of the fundus was found after implantation; and (C) no significant change of IOP found after implantation ($p > 0.05$). *d, days.

In this study, we set the subconjunctival injection of DEXP as control group for subconjunctival injection is the easiest and most popular method among periocular injection routes applied by the ophthalmologists (Bali et al., 2010; Dieleman et al., 2011; Manandhar, 2011). However, in this study, DEXP can just persist in the eye for no longer than three days after subconjunctival injection, as no DEXP was detected in the eye three days after subconjunctival injection. This was consistent with Weijtens et al. (1999) reports that dexamethasone can just be detected after 24 h after subconjuctival injection of DEXP, and the peak was at three hours after injection (Weijtens et al., 1999). They also reported that peribulbar injection of DEXP can just result the peak dexamethasone concentration in vitreous 6–7 h after injection (Weijtens et al., 1997). Compared to direct periocular injection, the periocular DDS has priority in the sustained released time of the DEXP for 56 d.

Compared to the most popular intravitreal dexamethasone implant (Ozurdex), which can released dexamethasone for six months (Chang-Lin et al., 2011), the periocular DDS in this study can just release in 56 d. However, the valve and tube of the periocular capsular DDS, allowing the replenishment of the drug, facilitates for the need of longer time therapy. More importantly, although the periocular DDS need surgical implantation to the sub-Tenon's sac, it does not mechanically break the normal structure of the retina and choroids and can be easily removed if severe complication occurs. While the implantation of Ozurdex needed surgical penetration of the sclera, choroids and retina, and the Ozurdex can wander in the vitreous cavity (Bansal et al., 2012) and cause vitreous traction (Bakri & Omar, 2012; Clemens et al., 2013). What's more, if severe complication occurs, removal of the Ozurdex was not so easy for the ophthalmologists. The periocular DDS can act as a drug delivery carrier to carry.

Conclusion

In conclusion, the periocular capsular DDS in this study could provide sustained release of DEXP to the posterior segment of the eye for 56 d and showed good biocompatibility. It seems that the periocular capsular DDS can act as an alternative choice for the transscleral drug delivery to the posterior segment of the eye. However, the verification of the release potency of periocular capsular DDS must be performed in experimental diseased animal models in the future. More emphasis will be put on the precisely controlled released of drugs by the periocular capsular DDS. Additional studies can be carried to for the release of the other drugs for the

Table 2. The dexamethasone sodium phosphate (DEXP) released DEXP *in vivo*.

Time (d)	Serum (ng/ml)	Aqueous (ng/ml)	Cornea (ng/g)	Lens (ng/g)	Iris (ng/g)	Ciliary body (ng/g)	Retina (ng/g)	Choroid (ng/g)	Sclera (ng/g)	Vitreous (ng/g)
Periocular capsular DDS implantation group										
1	n.d	n.d	n.d	0.00 (0.00, 1.38)	49.77 ± 46.44	8.47 ± 10.52	12.71 ± 16.79	0.00 (0.00, 20.58)	2.97 ± 4.09	n.d
3	n.d	n.d	11.00 ± 11.56	6.33 ± 7.01	200.84 ± 61.50	212.81 ± 158.80	193.12 (142.50, 193.42)	240.22 ± 229.10	8.15 ± 5.18	n.d
7	0.00 (0.00, 12.76)	0.00 (0.00, 3.01)	0.00 (0.00, 33.68)	12.02 ± 9.19	240.63 ± 172.22	208.76 ± 170.13	384.36 ± 312.77	514.43 ± 591.33	220.37 ± 133.55	6.51 ± 7.45
14	n.d	n.d	n.d	22.52 (21.36, 46.86)	227.77 ± 55.54	125.03 ± 58.95	79.47 ± 70.67	171.06 ± 91.80	1.19 ± 1.76	n.d
28	n.d	0.00 (0.00, 2.84)	n.d	9.35 ± 9.15	209.34 ± 123.81	129.55 ± 56.28	159.50 ± 164.61	370.00 ± 180.87	2.25 ± 1.58	n.d
56	n.d	0.00 (0.00, 17.64)	0.00 (0.00, 4.47)	11.09 ± 1.54	192.50 ± 42.66	71.64 (71.35,180.21)	123.11 (91.23, 732.61)	362.46 ± 330.46	3.55 ± 1.50	n.d
Control group										
1	n.d	n.d	0.00 (0.00, 7.19)	17.92 ± 21.48	256.07 ± 53.06	145.19 (142.56, 200.35)	50.72 (46.99, 223.71)	92.09 ± 33.05	10.77 (6.17, 10.92)	n.d
3	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d

n.d, none detected.

Periocular capsular DDS implantation group: the DEXP concentration in the serum and different parts of rabbit eyes 1, 3, 7, 14, 28 and 56 d after periocular capsular DDS was implanted in the Tenon's sac of the rabbit eye. Control group: the DEXP concentration after one and three days subconjunctival injected of 2.5 mg DEXP in the rabbits.

periocular DDS can carry drugs without physical modification of the drugs.

Declaration of interest

This study was supported by the 12th Five-Year Plan of Ministry of Science and Technology of the People's Republic of China (2012BAI08B02).

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