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A Novel Ocular Drug Delivery System of Dexamethasone Sodium Phosphate for Noninfectious Uveitis Treatment

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Abstract

Treatment of anterior uveitis commonly requires 6–8 times daily administration of eye drops, which often leads to poor patient compliance. The treatment of intermediate and posterior uveitis is restricted to either oral medications with significant systemic side effects or local invasive methods, which are more expensive and associated with the development of ocular complications. There is an unmet need for a new drug delivery system that addresses these challenges. DSP-Visulex is a non-invasive drug delivery system that administers dexamethasone sodium phosphate by passive diffusion through the limbal sclera into the interior of the eye utilizing the transscleral pathway. Once-a-week administration of DSP-Visulex treatment regimens (i.e., 1–5 doses per month) has shown to be safe and efficacious for noninfectious uveitis in animal models including anterior uveitis, posterior uveitis, and/or panuveitis. In a clinical study of anterior uveitis, the DSP-Visulex treatments also have been shown to be safe and well tolerated and their efficacy (administered on days 1, 3, 8, and 15 with an optional treatment on Day 22) was comparable to that of the daily prednisolone acetate drops.

Keywords: noninvasive, ocular drug delivery, dexamethasone, safety and efficacy, topical treatment, uveitis

1. Introduction

Uveitis represents a group of intraocular inflammatory disorders which may result in significant visual loss and is responsible for approximately 10–15% of blindness in the USA [1–4]. The annual prevalence of uveitis ranges from 58 to 115 cases per 100,000 persons [4–6]. Anterior uveitis is the most common anatomic location representing approximately 70% of all the uveitis cases in the USA [4–6]. Although posterior and panuveitis are far less common, they owe a greater consequence in blindness [7].

Dexamethasone sodium phosphate (DSP) is a highly water-soluble form of dexamethasone. DSP undergoes rapid hydrolysis to form dexamethasone (DEX) in plasma [8] and ocular tissues [9]. Both DEX and DSP have been used for the treatment of a wide variety of ocular inflammation conditions such as keratitis, blepharitis, iritis,

conjunctivitis, uveitis, macular edema, and post-operative eye surgery [10]. There are a number of dosage forms of DEX and DSP for ocular treatments including eye drops, ointments, oral tablets, intraocular injections, and intravitreal implants. Current topical methods, however, cannot deliver drugs to the posterior segment of the eye effectively and their practice has been limited to treating anterior eye conditions [11–13]. Eye drops often yield poor patient compliance due to the required adherence to frequent administration [14]. The posterior segment of the eye can be treated systemically but significant whole-body adverse effects are major concerns [12]. Invasive methods, such as periocular injections, intravitreal injections, or intravitreal implants (e.g., Ozurdex®, Retisert®, Iluvien®, etc.), are effective but the cost of administration is high. They also involve a number of potential serious risks including retinal detachment, endophthalmitis, increased intraocular pressure (IOP), and cataractogenesis [15–18]. There is an unmet need for a new drug delivery system that can address such challenges.

Recent publications suggest that treating back-of-the-eye diseases using topical administration is feasible [19–24]. For topically administered drugs, the trans-scleral pathway can be a route for a drug molecule to reach posterior eye tissues [25–31]. A fluorophotometry study in live rabbits suggests that once drug is placed intrasclerally, there is an active, convective flow carrying drug molecules through the suprachoroidal space to the retina-choroid region at the back of the eye [32]. To administer drug through this pathway effectively, a high drug concentration on the sclera is an ideal prerequisite. This is because drug diffuses across eye tissues by concentration gradients as described by Fick's first law of diffusion: $\text{Flux} = PA(C_1 - C_2)$. Flux is the amount of drug that passes through a membrane per period of time (mg/sec). P is the permeability coefficient of the permeant (cm/sec), A is the surface area (cm²) over which diffusion is taking place, and $(C_1 - C_2)$ is the difference in concentration (mg/mL) of the permeant across the membrane for the direction of flow from C_1 to C_2 . Thus, a high concentration in the applicator (C_1) may significantly increase flux. However, the current topical ophthalmic products have failed to utilize this pathway effectively because of the short retention time at the site of application and the low drug concentration used in its formulation.

2. Visulex-P, a novel ocular drug delivery system

Visulex-P is a noninvasive ocular drug delivery system that can be used to administer drug topically through the limbal sclera into the interior of the eye utilizing the transscleral pathway [33, 34]. It is a passive diffusion-base technology developed by Aciont Inc. designed to facilitate the drug molecule entering primarily through the conjunctiva-scleral surface and minimize the drug clearance from tearing and drainage into the nasolacrimal duct. In addition, Visulex-P enables an ophthalmic application of a high drug concentration, which may expedite the passive drug diffusion through the transscleral pathway without significant ocular toxicity [34]. DSP is suitable for Visulex-P because of its high water solubility, enabling a high drug-driving force, and its high potency with respect to prednisolone acetate on a molar basis. In this chapter, the combination of this high DSP-concentration solution instilled into the Visulex-P applicator is referred to as DSP-Visulex.

3. DSP-Visulex administration

DSP-Visulex may be administered to a patient in a general clinical setting by a physician, nurse, or trained technician, and in some cases, it may be

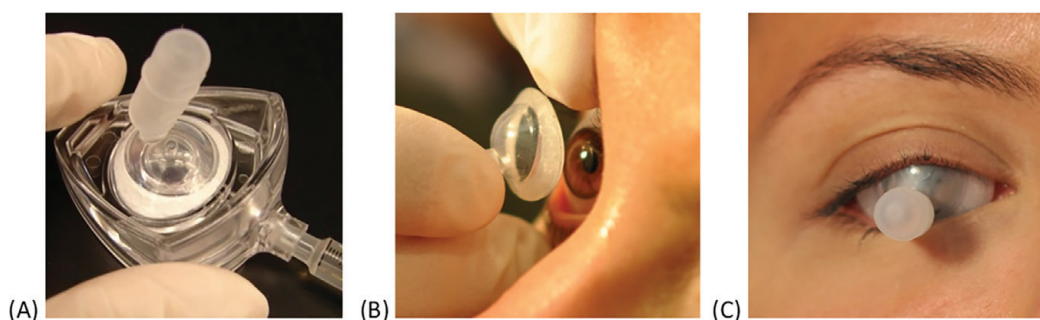


Figure 1.
 (A) Dexamethasone sodium phosphate (DSP) solution is being loaded into Visulex applicator through a drug loader. (B) DSP-Visulex is being applied onto the eye. (C) DSP-Visulex is on the eye where the sponge is in contact with the eye on the sclera and the surface area of the sponge is approximately 150 mm².

self-administered at home. The Visulex applicator resembles the handling and feel of a scleral lens which is a type of contact lens worn throughout the day by the patient who is suffering from corneal shape disorders or injuries to the eye. The details and video of DSP-Visulex administration follow:

There are a few steps in DSP-Visulex administration (**Figure 1**). Proparacaine (0.5%), a topical anesthetic agent, is first applied to the patient's eye(s). The DSP solution (250 µL) is loaded into the Visulex-P applicator with the drug loader just prior to application. The drug-loaded applicator (DSP-Visulex) is removed carefully from the loader. The DSP-Visulex is then gently placed directly onto the sclera while the care giver holds the patient's upper and lower eyelids open. The Visulex applicator is checked to ensure that it remains centered on the eye and does not make contact with the cornea throughout the treatment duration. After the treatment duration (e.g., 5 minutes), the Visulex applicator is carefully removed by squeezing the entire bulb to release the vacuum while lifting the applicator up from the eye. The DSP-Visulex is discarded after this single administration and is not reused. The DSP-Visulex administration for animal studies was similar to that in the clinical study except each animal was placed in a restrainer to limit movement during the DSP-Visulex administration.

4. Two main factors of DSP-Visulex affecting the amount of drug in the rabbit eye

Both the DSP concentration and the treatment duration of DSP-Visulex correlate with the total amount of drug in the eye [35]. After single applications of DSP-Visulex for 5, 10, or 20 minutes and for all DSP concentrations, significant amounts (i.e., 56–760 µg) of DSP were found in the eye (**Figure 2**). When qualitatively comparing both factors with respect to the whole eye, it appears that the relative increase in DSP-Visulex concentration affected the ocular tissue concentrations more than the treatment duration.

For instance, in **Figure 2** at the 5-minute application time, when the DSP concentration is increased from 4 to 15%, which is about a factor of 4, the total amount of the drug in the eye increased by about fivefold from 56 µg to 288 µg, but when the application time is increased from 5 to 20 minutes, which is also a factor of 4, the total amount of the drug in the eye increased by only twofold from 56 µg to 104 µg. This relationship appears to hold for sclera, conjunctiva, cornea, and anterior chamber (AC), but is more subtle for vitreous, retina-choroid, and lens (discussed in a later section).

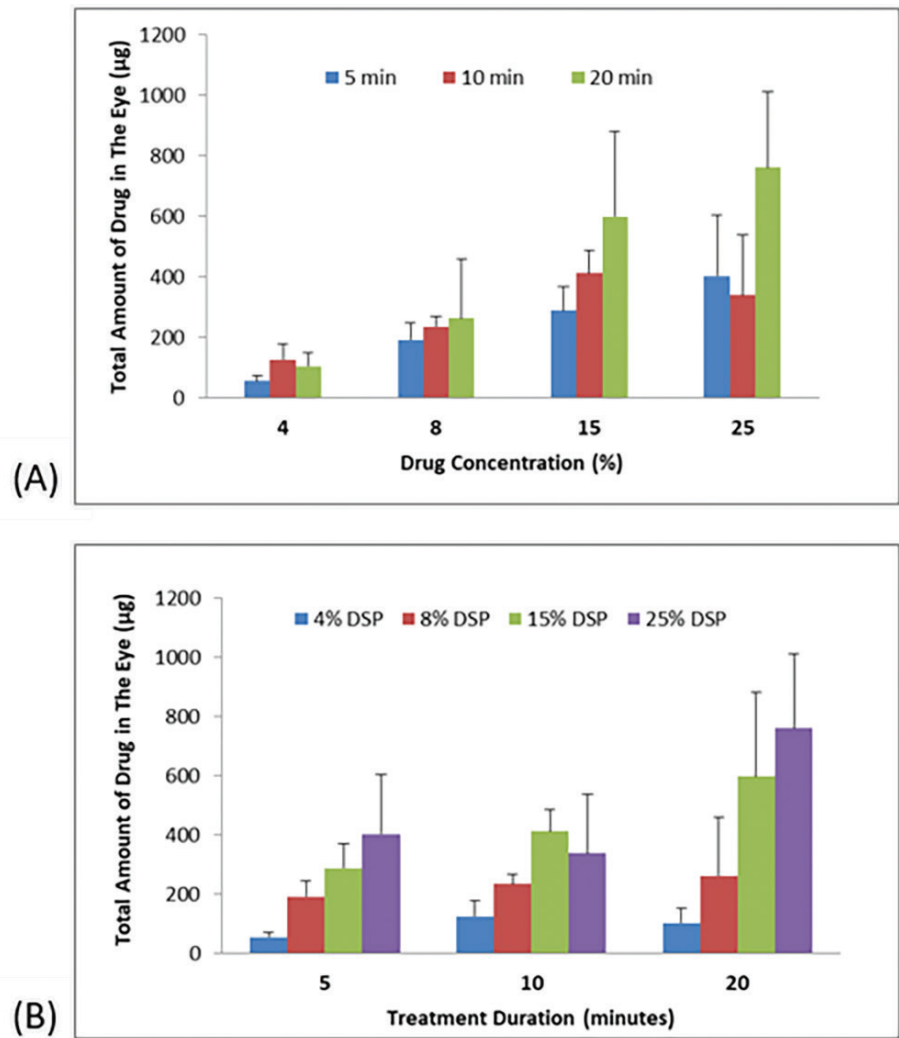


Figure 2.
(A) Effect of drug concentration on total amount of drug in the eye. (B) Effect of drug concentration on total amount of drug in the eye.

5. Drug distribution in the eye after DSP-Visulex application

The ocular drug distribution study of DSP-Visulex in rabbit illustrates the potential for the noninvasive delivery of DSP into the eye tissues from anterior to posterior section [35]. After single applications of DSP-Visulex for 5, 10, or 20 minutes and for all DSP concentrations, significant amounts of DSP and some DEX were found in all eye tissues. A typical rank order of DSP amounts in the eye tissues is sclera, conjunctiva, cornea, retina-choroid, anterior chamber, vitreous, and lens. The total amount of drugs in each tissue except vitreous and lens appears to be correlated well with the DSP concentration and application time of DSP-Visulex.

In **Table 1**, the concentration of DSP in each tissue is calculated in µg/g and summarized for potential efficacy evaluation of DSP-Visulex and the concentration of 1 µg/g or higher in the tissue is considered a potential therapeutic level [35]. After a single administration of DSP-Visulex, with exception of the lens, DSP found in most of the ocular tissues including cornea, sclera, conjunctiva, retina-choroid, and anterior chamber was significantly higher than the target level of 1 µg/g in all of the DSP-Visulex regimens tested in the study. DSP concentrations in the vitreous were around or slightly above 1 µg/g in most cases except for the 5-minute 4% DSP application. The typical order of concentration of DSP in ocular tissues, from high to low, was: cornea > sclera >

Dose	Tissue (mean \pm SD, $\mu\text{g/g}$)						
	Cornea	Anterior chamber	Lens	Vitreous	Retina-choroid	Sclera	Conjunctiva
4% DSP, 5 min	108 \pm 74	14 \pm 4	0 \pm 0	0 \pm 1	18 \pm 16	59 \pm 25	33 \pm 29
4% DSP, 10min	216 \pm 86	11 \pm 8	2 \pm 0	2 \pm 1	59 \pm 86	131 \pm 52	56 \pm 14
4% DSP, 20min	147 \pm 75	12 \pm 4	3 \pm 1	1 \pm 1	24 \pm 7	154 \pm 49	49 \pm 26
8% DSP, 5 min	288 \pm 73	23 \pm 3	13 \pm 0	5 \pm 1	74 \pm 23	233 \pm 53	84 \pm 36
8% DSP, 10 min	459 \pm 148	23 \pm 9	0 \pm 0	2 \pm 1	63 \pm 61	314 \pm 74	104 \pm 33
8% DSP, 20 min	567 \pm 397	56 \pm 54	14 \pm 24	6 \pm 8	54 \pm 38	306 \pm 207	113 \pm 58
15% DSP, 5 min	367 \pm 118	18 \pm 3	5 \pm 0	5 \pm 3	182 \pm 176	328 \pm 60	150 \pm 26
15% DSP, 10 min	467 \pm 173	43 \pm 11	17 \pm 1	7 \pm 1	113 \pm 32	512 \pm 54	222 \pm 45
15% DSP, 20 min	1128 \pm 521	89 \pm 42	13 \pm 3	12 \pm 3	351 \pm 275	615 \pm 336	287 \pm 94
25% DSP, 5 min	714 \pm 252	39 \pm 17	6 \pm 1	6 \pm 3	114 \pm 82	452 \pm 214	221 \pm 126
25% DSP, 10 min	512 \pm 327	35 \pm 32	1 \pm 1	4 \pm 4	60 \pm 77	429 \pm 231	184 \pm 109
25% DSP, 20 min	2225 \pm 886	169 \pm 67	13 \pm 4	9 \pm 4	207 \pm 101	731 \pm 189	347 \pm 107

Table 1.
Dexamethasone sodium phosphate-equivalent concentrations in ocular tissues.

conjunctiva > retina-choroid > anterior chamber > lens > vitreous. The drug concentration in the ocular tissues (except lens and vitreous) correlated well with both increasing DSP concentration in the Visulex system and treatment duration.

Although the dynamics of aqueous flow and clearance in the eye are complex, the ocular drug distribution results are in line with an anticipated concentration gradient pattern arising from the outer eye tissues like sclera and conjunctiva, which were adjacent to the DSP drug reservoir and received the most drug, to the innermost tissues like the vitreous humor and lens that received much lesser amounts. Additionally, it should be noted this study was limited only to one time point, which was immediately after the DSP-Visulex application. More study time points should yield further understanding of the pharmacokinetic profiles of DSP administered by the DSP-Visulex including drug distribution, onset, duration of action, and half-life of the drug in the eye tissues.

Comparing the DSP-Visulex in rabbit to periocular injections and oral administration in human [36], the DSP concentration in rabbit retina-choroid after a single administration of DSP-Visulex ranged from 18 to 351 $\mu\text{g/g}$ whereas the estimated maximum DEX concentration in the subretinal fluid in patients after an oral dose of DEX (7.5 mg), a peribulbar injection (5 mg), and a subconjunctival injection (2.5 mg) was 12, 82, and 359 ng/mL, respectively [36]. When qualitatively comparing DSP-Visulex application in rabbit to the topical DSP eye drop (i.e., 1 drop of 0.1% DSP every 1.5 hours for a total of 10 or 11 drops) in human [37], the concentration of DSP in the vitreous of rabbit from DSP-Visulex is much higher: the C_{max} in human vitreous from the DSP eye drop was 1 ng/mL while most DSP-Visulex regimens yield $\sim 1 \mu\text{g/mL}$ or more in the vitreous of rabbit. While such indirect comparisons of the DSP-Visulex data in rabbit with the pharmacokinetic studies in human may be unavailing, these at least illustrate the potential significance of the DSP-Visulex approach.

6. Systemic exposure after single application of DSP-Visulex

A toxicokinetic study in rabbit suggests that DSP was rapidly absorbed into the systemic circulation after the DSP-Visulex application [35]. The plasma concentrations of DSP and DEX after single applications of DSP-Visulex are shown in **Figure 3**. T_{max} of DSP was reached at the first blood draw (5 minutes after DSP-Visulex application), whereas T_{max} of DEX was reached later at 30 minutes. The maximum plasma concentration (C_{max}) of both DSP and DEX increased with increasing DSP concentration and with longer application time. Within 24 hours, the drug plasma concentrations of all groups were approaching or under the lowest detection limit of 1 ng/mL.

For the purpose of assessing the systemic exposure of total corticosteroid after DSP-Visulex application, the DSP and DEX plasma concentrations were combined and calculated as DSP equivalent. The DSP equivalent is defined as the sum of DSP and DEX in gram equivalents, with 392.5 g of DEX equivalent to 516.4 g of DSP. The key toxicokinetic parameters are presented in **Table 2**. The systemic half-life of the drug in the rabbit is approximately 2–3 hours. C_{max} and AUC increased with increased concentration of DSP and increased application time. Similar to the eye results, the concentration seems to have more effect on the systemic exposure than application duration. For example, when the DSP concentration was increased from 4 to 15%, which is about a factor of 4, the C_{max} increased about eightfold from 148 μg to 1188 μg , but when the application time increased from 5 to 20 minutes, which is also a factor of 4, the total amount of the drug in the eye increased only fourfold from 148 μg to 795 μg . This was also the case with AUC. The increase in concentration from 4 to 15% increased the AUC by a factor of 4, whereas the increase in the application time from 5 to 20 minutes increased the AUC only by a factor of 2.

To express the results of systemic DSP exposure in rabbit in human perspective, C_{max} values of DSP in human were estimated and are presented in **Table 2**. The estimations were based on C_{max} data from intravenous (IV) injections in both rabbit [38] and human [39]: An IV injection of 1 mg DSP yields a C_{max} of 786 ng/mL in rabbit and 10.5 ng/mL in human. Accordingly, these results suggest that at a given dose of DSP,

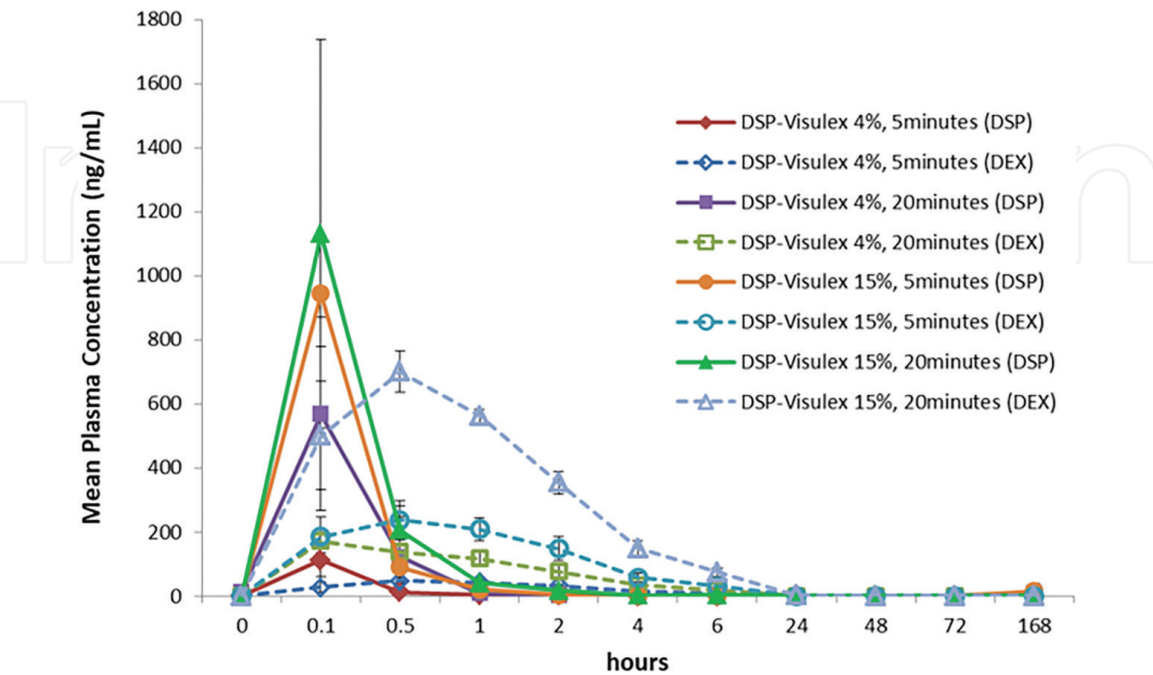


Figure 3. Mean plasma concentration of DSP (solid line) and DEX (dot line) following single administration of DSP-Visulex at predose, 5, 30, 60, 120, 240, and 360 minutes, and 24, 48, 72, and 168 hours. To reveal all pharmacokinetic data, all the graphs were not plotted in a linear time scale on the x-axis.

Dose	C _{max} (ng/mL)	t _{1/2} (h)	AUC (ng*h/mL)	Estimated C _{max} in Human (ng/mL)
4% DSP, 5 min	148 ± 71	3.1 ± 2.2	418 ± 93	2 ± 1
4% DSP, 20 min	795 ± 344	2.3 ± 0.6	996 ± 144	11 ± 5
15% DSP, 5 min	1188 ± 306	1.7 ± 0.9	1595 ± 418	16 ± 4
15% DSP, 20 min	1844 ± 664	2.7 ± 0.3	3779 ± 472	25 ± 9

Table 2.
Dexamethasone sodium phosphate-equivalent concentrations in plasma.

the C_{max} of DSP for rabbit is approximately 75 times higher than that for human. The estimated C_{max} values in human of the lowest dose (4% DSP, 5 minutes) and the highest dose of DSP-Visulex (15% DSP, 20 minutes) are 2 and 25 ng/mL, respectively. In addition, the estimated C_{max} values in human in the range of 2–25 ng/mL may be supported by an ocular iontophoretic delivery of dexamethasone phosphate (4%w/v) in uveitis patients, which showed the plasma C_{max} of dexamethasone in the range of 2–10 ng/mL [40]. This is because the ocular iontophoresis delivered approximately the same order of magnitude of dexamethasone phosphate to the rabbit ocular tissues as DSP-Visulex [35], it is reasonable to speculate that the systemic drug exposure in human of DSP-Visulex would be in the same order of magnitude as the ocular iontophoresis.

When compared to the plasma C_{max} from a single application of DSP-Visulex to the literature C_{max} from a single IVT injection, a single topical eye drop, an oral tablet, a single peribulbar injection, and a single subconjunctival injection [41], it suggests that DSP-Visulex may have a higher systemic exposure than eye drops and IVT injections but less than oral and periocular injections (i.e., peribulbar injection and subconjunctival injection).

7. Ocular toxicity of DSP-Visulex in animal

A 12-week toxicity study of DSP-Visulex at 4, 8, 15, and 25% suggests that multiple treatments of DSP-Visulex are well tolerated [35]. The ocular findings observed in treated eyes from the study (i.e., 20-minute treatment duration of DSP-Visulex) were conjunctival injection, chemosis discharge, and corneal haze. These ocular findings were transient and mild in nature. No abnormalities or signs of ocular toxicity were observed in untreated eyes. The only frequent ocular adverse event was conjunctival injection, which appeared to resolve within a week. This sign of irritation correlates with increasing DSP concentration. Some accumulations of conjunctival injection were observed in the high concentration formulations (i.e., 15 and 25% DSP) after 2 months into the weekly treatment regimen. The tonicity of the DSP formulation may have played a role in the conjunctival irritation. The persistence and severity of the conjunctival irritation were found to be much lower in the 4 and 8% DSP formulations (i.e., isotonic formulation) compared to the 15 and 25% formulation (i.e., hypertonic formulation). It may be noted that conjunctival injection, which is also known as conjunctival hyperemia or conjunctival erythema, is a common side effect found among FDA-approved corticosteroid ophthalmic solutions including prednisolone, dexamethasone, and difluprednate. A temporary corneal haze was found in one rabbit when the placement of DSP-Visulex is placed

off center. This is an adverse effect that can be avoided by checking whether the DSP reservoir has any direct contact with the cornea while in position during treatment.

As for the histopathology after multiple treatments of DSP-Visulex for 12 weeks, all eyes were considered to be morphologically normal, except one treated eye in the 8% DSP group showed mild chronic inflammation at the limbus of the cornea. Besides this one eye, there were no significant findings with any ocular tissue examined: no edema or congestion of conjunctiva, ciliary body, or cornea was observed in any group; no neovascularization on the cornea was found; and no inflammation in conjunctiva, cornea, anterior chamber, trabecular meshwork, iris, ciliary body, vitreous, choroid, and retina tissues and no test article changes were identified.

There were no significant weight changes in the 4 or 8% DSP-treated rabbits. However, the animals in the 15 and 25% DSP groups showed trends of decreasing body weight. Although only the 25% DSP group showed statistically significant reduction in body weight, the consistent decline in body weights of the animals in these two groups indicate that long-term exposure at these levels of DSP-Visulex dosing (i.e., 15 and 25% DSP for 20 minutes) may have significant systemic side effects on rabbit. Since all animals exhibited systemic exposure of both DSP and DEX after single administration of the DSP-Visulex (discussed above), this is an expected outcome after multiple treatments of DSP-Visulex for 3 months [42, 43]. It should be noted that the 20-minute treatment duration and 25% DSP tested in this study were an exaggerated wearing time and concentration to find the adverse effect (if any). The intended clinical use in the patient population would be 10 minutes or less and the DSP concentration would be 15% or less.

In summary, repeated 20-minute weekly treatments of 4 and 8% DSP-Visulex are well tolerated over 3 months, whereas, respective 15 and 25% DSP-Visulex treatments potentially are limited to shorter periods of time, perhaps between 4 and 8 weeks. The safety of DSP-Visulex with a shorter application time (i.e., 8 and 15% DSP for 5 minutes) was evaluated in phase I/II clinical trial for the treatment of noninfectious anterior uveitis discussed in a later section.

8. Efficacy of DSP-Visulex on an experimental uveitis rabbit model

Experimental uveitis, also known as experimental autoimmune uveitis (EAU), has been a method for evaluation of various therapeutic agents as well as new drug delivery systems for intermediate, posterior, and panuveitis [44–50]. By preimmunization and challenge of Mycobacterium tuberculosis H37Ra antigen, this induction causes a severe panuveitis in rabbit that lasts for more than 4 weeks [44–51].

Single application and multiple applications of DSP-Visulex (i.e., 8 and 15%) have been shown to be effective in treating the experimental uveitis over the course of a 29-day study [34]. In the study, rabbits were randomly assigned into six groups after uveitis induction. Rabbit eyes were examined by indirect ophthalmoscopy. A modified McDonald-Shadduck scale [52] was used for scoring inflammation. An average of all scores over the course of study is calculated for comparison. The eyes were collected at the end of the study on Day 29 for histopathology evaluation.

All induced eyes showed signs of inflammation within a day after the uveitic induction. Overall, inflammation occurred more significantly in the posterior chamber than in the anterior chamber (**Tables 3 and 4**). The most apparent finding from the eye examination in assessing the severity of uveitis is inflammation in vitreous (**Figure 4 and Table 3**). All animals in the control group (untreated) reached a severe vitritis, which remained on average above a score of 3 through the end of study. The average inflammation score of vitreous for the control group was significantly higher than all the DSP-Visulex treatment groups. The resolution speed of inflammation in the vitreous appears

Treatment Regimen	Inflammation Score		
	Conjunctival injection	Anterior Chamber	Vitreous
Group 1: Control (No treatment)	0.9 ± 0.8	0.5 ± 0.5	3.3 ± 1.1
Group 2: 15% DSP (15min, 4 doses)	0.5 ± 0.4**	0.1 ± 0.2***	0.4 ± 1.0***
Group 3: 15% DSP (10min, 1 dose)	0.3 ± 0.4***	0.1 ± 0.2***	0.6 ± 1.2***
Group 4: 8% DSP (10min, 1 dose)	0.5 ± 0.5**	0.3 ± 0.4**	0.4 ± 0.8***
Group 5: 8% DSP (5 min, 4 doses)	0.9 ± 0.8	0.5 ± 0.5	1.4 ± 1.7***
Group 6: 4% DSP (10min, 2 doses)	0.5 ± 0.5*	0.4 ± 0.6	1.4 ± 1.6***

*P < .05, **P < .01, and ***P < .001.

Table 3.
Inflammation scores from observations using indirect ophthalmoscope.

to correlate with both the DSP concentration and frequency of DSP-Visulex treatment. The same correlation also corresponds to the inflammation score observed by histopathology (**Table 4**). A complete resolution of the highest dosing regimen was observed at Day 10 and the lowest dosing regimen was observed at Day 22.

Statistical differences in the average scores observed between the control group and each DSP-Visulex treatment group were assessed by the Wilcoxon rank-sum test with *P < .05, **P < .01, and ***P < .001.

The signs of inflammation in the anterior section including the anterior chamber (AC) and conjunctiva were mild even with the control group. This made it difficult to see significant differences between the control and the low dosing regimens through the observations using indirect ophthalmoscope. The efficacy of the low dosing regimens for the anterior section was mainly supported by histopathology evaluation (**Table 4**).

For histopathology evaluation, the average inflammation scores for both anterior and posterior sections are presented in **Table 4**. The total inflammatory scores of anterior section were high for the untreated eye; whereas for the DSP-Visulex treatment groups, they were significantly lower. The efficacy of DSP-Visulex treatment in the anterior section appears to be related to DSP concentrations. The

Treatment Regimen	Total Inflammatory Score of Anterior Section	Inflammatory Cell Infiltration Score	
		Anterior Section	Posterior Section
Group 1: Control (No treatment)	4.4 ± 2.6	0.7 ± 1.0	2.9 ± 1.2
Group 2: 15% DSP (15min, 4 doses)	0.2 ± 0.4***	0.0 ± 0.2***	0.1 ± 0.3***
Group 3: 15% DSP (10min, 1 dose)	1.0 ± 1.1**	0.2 ± 0.4**	1.8 ± 1.5**
Group 4: 8% DSP (10min, 1 dose)	1.8 ± 0.7**	0.3 ± 0.7**	1.2 ± 0.9***
Group 5: 8% DSP (5 min, 4 doses)	1.4 ± 1.7**	0.2 ± 0.8***	1.9 ± 1.6**
Group 6: 4% DSP (10min, 2 doses)	1.9 ± 1.1*	0.3 ± 0.7**	2.9 ± 1.0

*P < .05, **P < .01, and ***P < .001.

Table 4.
Inflammation scores and inflammatory cell infiltration score from histopathology examination.

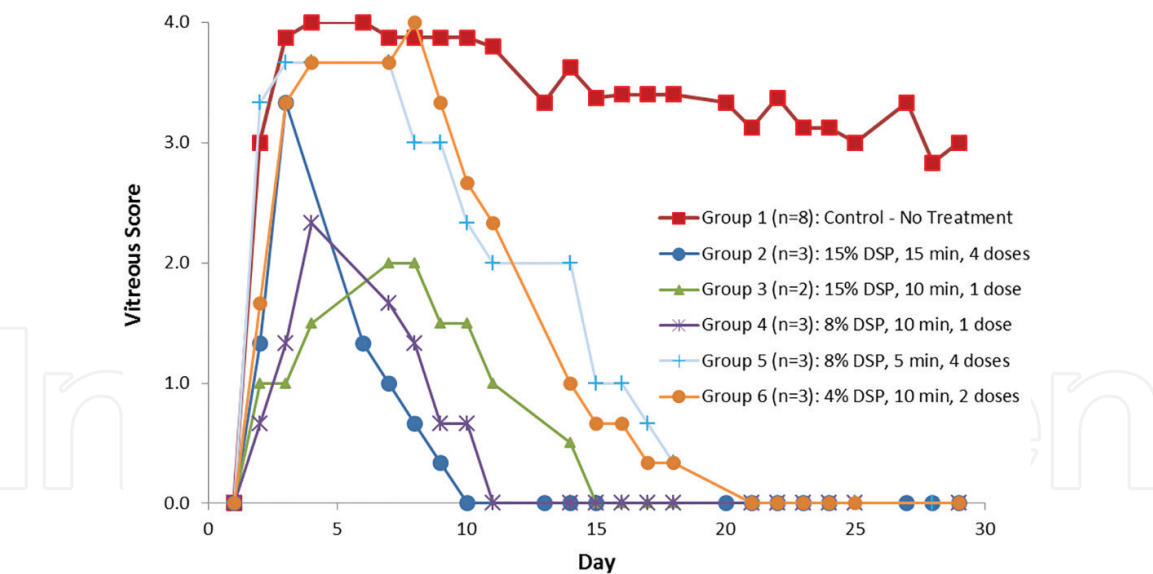


Figure 4.
Vitreous scores of various treatment groups tested in the experimental uveitis rabbit model.

intermediate and posterior uveitis was persistent in the control group for 29 days, consistent with the ophthalmoscopic observations. The eyes from the highest dose regimen had almost no pathological signs of uveitis present and their posterior tissues appeared to be healthy with minimal inflammation while the untreated eyes appeared to be completely impaired (**Figure 5**). The overall inflammation scores of the posterior section suggest that all DSP-Visulex treatment regimens, except the lowest dosing regimen, were less inflamed in the posterior section than the controls.

The successful treatment with a single-dose of DSP-Visulex was not anticipated in this uveitis model because the DSP was estimated to be cleared from the eye tissues and eventually from the body within 24 hours based on the pharmacokinetics of dexamethasone sodium phosphate [38, 39]. Although the duration of action for dexamethasone can last up to 72 hours [53], it cannot explain the long anti-inflammatory effect of the single dose of DSP-Visulex in this chronic uveitis model, unless a very high dose of DSP (similar to the 8 and 15% DSP-Visulex) can stop the inflammatory process in the uveitic eye without a repeat dose. More studies (e.g., a dose-ranging study of DSP IVT injection in experimental uveitis rabbit) need to be done to confirm this hypothesis.

The uveitis model used in this DSP-Visulex study was similar to (if not the same as) the uveitis rabbit model used in the preclinical studies of intravitreal DEX implant [44, 46]. Considering a qualitative (DEX vs. DSP) and indirect comparison

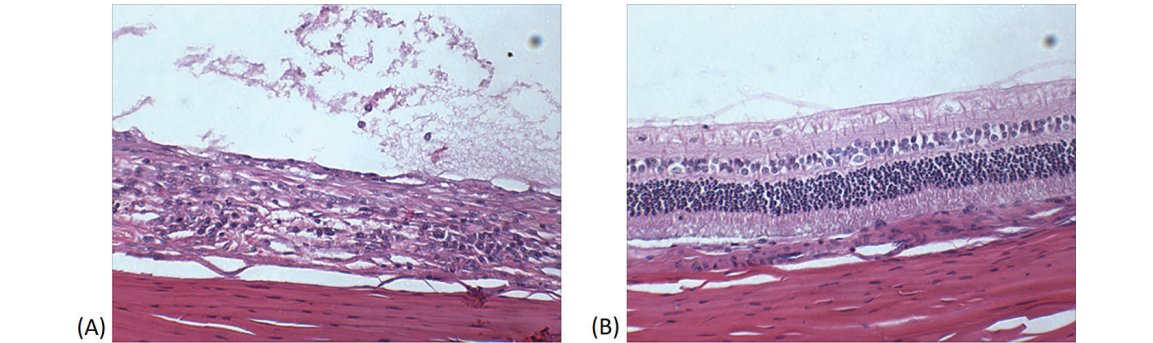


Figure 5.
Comparative histopathologic presentation of the posterior section of the eyes at the end of study (Day 29). (A) Control (untreated eye): The inflammation is severe and the photoreceptor layer is completely damaged. (B) 15% DSP (15 minutes, 4 doses): Inflammation is minimal and the tissue structure is well preserved.

(nonhuman primate vs. rabbit) to intravitreal DEX implant (Ozurdex®) from a pharmacokinetic study in nonhuman primate [41], the C_{\max} of DEX from Ozurdex® was 1.1 µg/g in the retina at Day 60 and 0.2 µg/mL in the vitreous at Day 60 whereas the concentration of DSP in the retina-choroid and vitreous from DSP-Visulex was much higher immediately after a single administration (i.e., ≥ 18 µg/g in the retina-choroid and ≥ 1 µg/mL in vitreous) [35]. This may suggest a more rapid onset of the pharmacological action with DSP-Visulex compared to Ozurdex®. However, since Ozurdex®, which is a controlled release product, provides a much longer exposure of DEX in eyes compared to DSP-Visulex, the risks and benefits of the two products in the eye diseases will need to be further evaluated, particularly in well-controlled efficacy models.

In summary, the ophthalmoscopic observations and histopathological examinations strongly indicate that the DSP-Visulex treatment was safe and well tolerated in the rabbit uveitis model. Overall, all the 8 and 15% DSP-Visulex treatment regimens in this study can be considered for the treatment of anterior, intermediate, posterior, and panuveitis. On the other hand, the 4% DSP-Visulex regimen may only be considered for the treatment of anterior and intermediate uveitis but not for posterior uveitis unless more frequent dosing is tested.

9. Safety and efficacy of DSP-Visulex for noninfectious anterior uveitis: a randomized phase I/II clinical trial

DSP-Visulex treatment regimens (two applications on the first week and then weekly after) were evaluated for safety and efficacy against daily prednisolone acetate eye drop (PA) for noninfectious anterior uveitis [54]. The study (called DSPV-201) was a phase I/II, multicenter, randomized, parallel group, double-masked, active-controlled, and dose comparison study.

A total of 44 patients were randomized in 1:1:1 ratio to the three treatment groups: 14 patients to the 8% group (8% DSP-Visulex with placebo eye drops), 15 patients to the 15% group (15% DSP-Visulex with placebo eye drops), and 15 patients to the PA group (Vehicle-Visulex with 1% PA eye drops). All patients received the Visulex treatments (either DSP-Visulex or Vehicle-Visulex) at Visit 1 (Day 1), Visit 2 (Day 3 \pm 1), Visit 3 (Day 8 \pm 1), and Visit 4 (Day 15 \pm 1) with an optional Visulex treatment at Visit 5 (Day 22 \pm 1). The optional Visulex treatment was at the investigator's discretion. Patients self-administered the study eye drops 6 times daily through Visit 4, then tapered off. Both safety and efficacy assessments were made at all visits. Efficacy parameters included anterior chamber cell (ACC) count and anterior chamber flare (ACF) grade, which were graded based on the Standardization of Uveitis Nomenclature (SUN) Working Group classification [55]. The safety parameters assessed were the incidence of treatment-emergent adverse events (AEs), best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit lamp biomicroscopy assessments, ophthalmoscopy assessments, and ocular pain.

A total of 40 patients completed the study: 12 patients in the 8% group, 14 patients in the 15% group, and 14 patients in the PA group. The patient characteristics regarding age, gender, and race were comparable among the three groups [54]. The uveitis baseline of the three treatment groups including anterior chamber cell (ACC) grade, anterior chamber flare (ACF) grade, VAS for pain, visual acuity, and IOP were similar. Moreover, the baseline characteristics were also comparable to larger phase III studies [54, 56].

The percentages of patients with zero ACC count were comparable among all three treatment groups at the end of the study (**Figure 6A**). The profiles of ACC clearing over the course of the study are similar among the three treatment groups

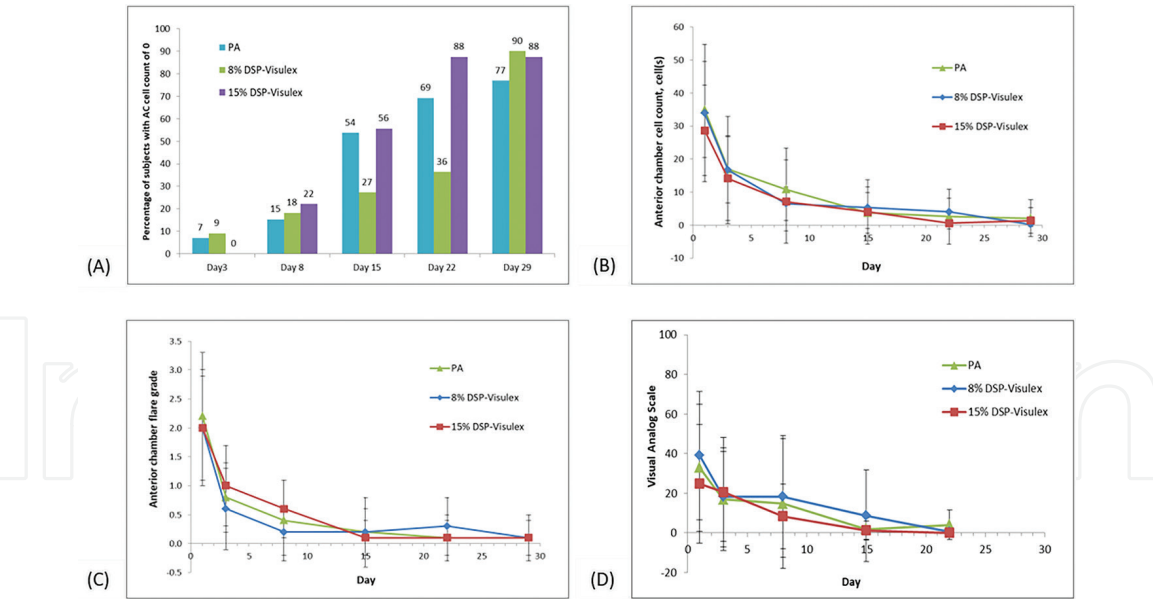


Figure 6. (A) Percentage of patients with anterior chamber cell count of 0. (B) Anterior chamber cell count. (C) Anterior chamber flare grade based on SUN classification. (D) Ocular pain measured by a visual analog scale.

(Figure 6B). All showed a rapid reduction of ACC counts to the average of 5 cells or lower within 14 days, then gradually approaching 0 cell subsequently. The same trends were also observed with respect to ACF. The 15% illustrated a trend for stronger potency compared with the 8% on the basis of the percent of patients with ACC count of 0 at Visit 5 (Day 22) and the need for an optional dose at Visit 5. Based on the criteria of the SUN working group on the short-term evaluation of a new therapy (i.e., a two-grade decrease in ACC grade or decrease to grade 0 is considered sufficient improvements) [55], weekly DSP-Visulex treatments are considered effective therapy for noninfectious anterior uveitis. Majority of patients in all groups showed similar improvement in visual acuity (i.e., the reductions of logMAR) [54].

The eye pain was measured by visual analog scale (VAS). The reduction in VAS pain scores throughout the study (Figure 6D), which coincided with the improvement of other aspects of anterior uveitis, including ACC and ACF, demonstrated that while patients had moderate pain at enrollment, the patients experienced minimal or no pain by the conclusion of the study. These observations can be attributable to either an improvement in symptoms related to a treatment effect of the anterior segment inflammation and/or acquired tolerance to the treatment modality itself over time, the differential effects being difficult to clearly delineate.

No safety concerns were identified in the study. Overall, 19 of 44 patients reported 58 AEs, of which 54 were ocular. The numbers of AE reports from each group were 10, 36, and 12 for the 8%, 15%, and PA groups, respectively. A summary of AEs is presented in Table 5. The higher ocular AEs reported with the 15% group are possibly due to the hypertonicity of the 15% DSP formulation compared with the isotonic formulations of 8% DSP and 1% prednisolone acetate, resulting in more ocular irritation. Most AEs were related to ocular surface phenomena. The most frequently reported AEs were corneal abrasion (n = 4), conjunctival staining (n = 4), and cornea staining (n = 4). These findings are consistent with preclinical studies [35] and such AEs are similar to those found with contact lens wearers [57–59]. The AEs are believed to be caused by physical/mechanical abrasion of the Visulex applicator on the corneal and conjunctival surface (i.e., epithelium). Two patients experienced a serious adverse event (SAE), including hospitalization for diabetic ketoacidosis and surgical treatment for unilateral retinal detachment. Both of these SAEs were identified as unrelated to the investigational product. Throughout the

	8%DSP-Visulex (N=14)	15%DSP-Visulex (N=15)	Prednisolone Acetate (N=15)
General			
Patients reporting Any AEs	7	9	3
- Suspected drug –related AE	2	6	2
- Not suspected drug – related AE	5	3	1
Treatment-emergent AEs			
Conjunctival haemorrhage	1	0	0
Conjunctival edema	0	0	1
Eye pain	0	1	2
Eyelid pain	0	1	0
Glaucoma	0	1	0
Keratic precipitates	0	1	0
Keratitis	0	1	0
Ocular hyperemia	0	1	0
Retinal detachment	1	0	0
Retinal haemorrhage	1	0	0
Uveitis	0	2	0
Visual acuity reduced	0	1	0
Conjunctivitis	0	1	0
Conjunctivitis viral	1	0	0
Gastroenteritis viral	0	1	0
Nasopharyngitis	1	0	0
Corneal abrasion	1	3	0
Conjunctival staining	1	2	1
Vital dye staining cornea present	1	2	1
Diabetic ketoacidosis	0	0	1
Headache	0	0	1
Granulomatous dermatitis	1	0	0

Table 5.
Adverse events.

course of this study, no apparent corticosteroid-mediated AEs were observed and only four reported AEs were even considered as systemic AEs (three were from PA group and one, which was granulomatous dermatitis, was from the 8% group). None of the systemic AEs were considered treatment-related. These findings suggest negligible systemic exposure of DSP-Visulex in human as discussed above. The safety outcomes of PA are consistent with expectations and the incidence of AEs are comparable to other clinical studies [56, 60]. This suggests that the Visulex applicator by itself contributes minimally to any adverse effects and tolerability.

The results of IOP elevation in the PA arm (**Figure 7**) are consistent with a phase 3 study of PA in treating noninfectious anterior uveitis [56] and other local corticosteroid treatments including eye drops, intravitreal injection, periocular injections, and intravitreal implants [61]. With respect to the DSP-Visulex arms, no IOP elevation was observed after the first week of treatment. The IOP results from both DSP-Visulex groups are not congruent with those typically observed for topical steroid treatments. However, this outcome is consistent with the preclinical studies of DSP-Visulex in rabbits, in which IOP elevations are minimal and transient (unpublished data). We hypothesize that the length of steroid exposure to the eye, which is the main difference between the DSP-Visulex treatment and the other corticosteroid therapies,

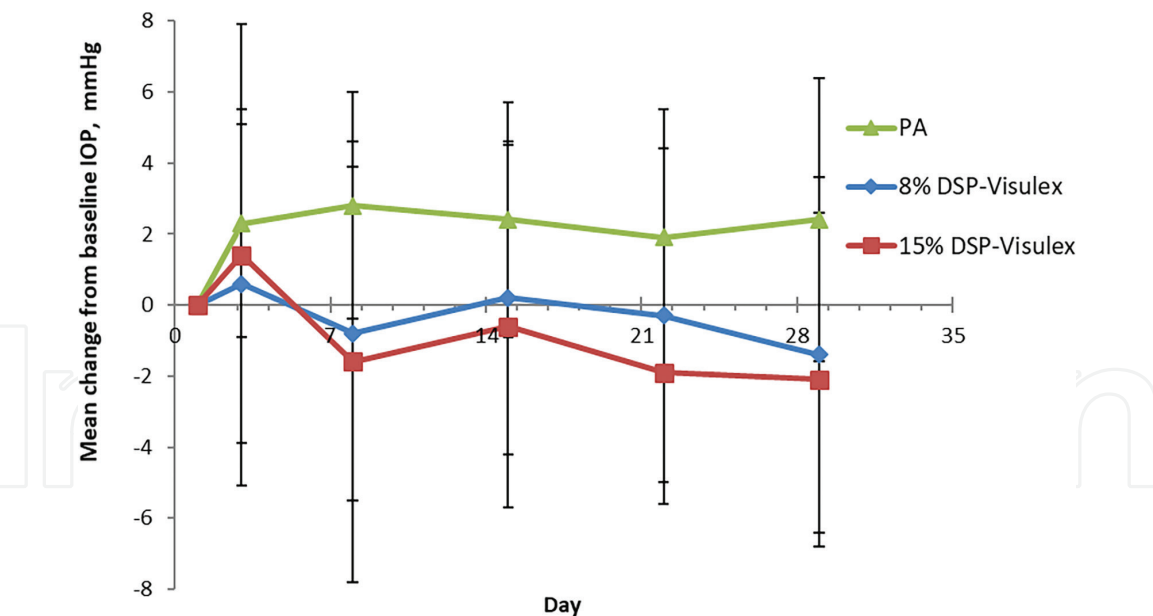


Figure 7.
Mean changes in intraocular pressure (IOP) from baseline.

affects the IOP elevation. Frequent daily eye drops, sustained release implants, and IVT injections of corticosteroid suspensions represent constant drug exposure to eye tissues including trabecular meshwork. By contrast, the steroid exposure to the eye in the case of DSP-Visulex is intermittent (i.e., twice in the first week and then once a week thereafter). We speculate that this unique pulsatile treatment of DSP-Visulex optimizes the balance between the anti-inflammatory and IOP effects of steroid therapy. Furthermore, the delivery method of steroid into the AC with DSP-Visulex may be analogous to that of a micropulse of relatively high concentration of local steroid into the eye, and that frequent micropulse of steroid may be more efficacious from inflammatory perspective and not over expose trabecular meshwork to more sustained concentrations of steroid over a long period of time. Glaucoma, diabetic, or elderly patients who are more susceptible to the IOP increases could benefit from DSP-Visulex treatments. However, this plausible benefit of IOP along with the efficacy and safety must be confirmed in a pivotal study with a larger sample size.

10. DSP-Visulex compared to an iontophoresis of dexamethasone phosphate

It is of interest to compare two novel ocular drug delivery systems of dexamethasone phosphate: one employs electrical current (also known as iontophoresis) and another is based on passive diffusion (i.e., no electrical current). On a semi-quantitative basis, the present DSP-Visulex results may be compared to the ocular iontophoresis results of 4% dexamethasone phosphate as reported by Güngör et al.[62]. The 8% DSP-Visulex (5-minute application or longer) appears to deliver DSP to retina-choroid tissues to the same extent as the iontophoresis results (5-minute application at 2, 4, and 6 mA) and the 15 and 25% DSP-Visulex appear to be somewhat better than the iontophoresis results.

An iontophoresis of dexamethasone phosphate, known as EGP-437, is also being investigated in clinical studies for noninfectious anterior uveitis. While not directly comparable, in the phase 2 clinical trial of EGP-437 for noninfectious anterior uveitis [40], the percentage of patients achieving the ACC score of zero were

48% at Day 14 and 60% at Day 28 for EGP-437, whereas, the respective percentage of DSP-Visulex patients in the present study achieving the ACC score of zero were approximately 41% at Day 15 and 89% at Day 29. In the phase 2 study of EGP-437, it appeared that the higher the electrical current used, the lesser the efficacy. While this was an unexpected outcome of the EGP-437 study, Pescina et al. [63] suggested that under certain iontophoretic conditions used in the study of EGP-437, the electroosmotic flow occurring during iontophoresis may oppose the direction of drug transport into ocular tissues resulting in an inverse relationship of electrical current and efficacy. As for safety comparisons, the number of ocular AEs produced from a single dose of EGP-437 is higher than those following multiple applications of DSP-Visulex. Although the comparative discussions of the two studies are qualitative, the results of the DSP-Visulex study may raise a question of the fundamental utility of iontophoresis in DSP administration for the treatment of noninfectious anterior uveitis.

11. Conclusion

DSP-Visulex may address problems of existing corticosteroid treatments for uveitis and other eye diseases. This includes eliminating the need for frequent dosing of eye drops (i.e., multiple drops 6–10 times/day), reducing side effects inherent with systemic drug therapies, and avoiding serious risks associated with intravitreal and periocular injections. Data suggest that DSP-Visulex has clinical potential for the noninvasive treatment of ocular diseases including uveitis, macular edema, postoperative inflammation, diabetic retinopathy, and age-related macular degeneration. In the future, many other drug molecules can be incorporated into the Visulex-P platform for various ophthalmic applications. With the positive outcomes of DSP and other in-house-tested therapeutic molecules (e.g., mycophenolic acid, rapamycin, triamcinolone acetonide phosphate, and lipoic acid), we are optimistic that Visulex-P is a new ophthalmic drug delivery system that can benefit both anterior and posterior eye diseases.

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Conflict of interest

Kongnara Papangkorn, and John Higuchi are employees of Aciont, Inc. Balbir Brar is a consultant at Aciont, Inc. William Higuchi is a founder and CTO of Aciont, Inc.

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