The Subconjunctival Space of the Eye

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The subconjunctival space is the hydrophilic, fluid-filled space between the conjunctiva and the sclera. Additionally, the subconjunctival space has access to all the blood vessels found in the conjunctiva, which can help to further distribute substances throughout the whole eye. The subconjunctival space is located superior to the cornea and optimally located to distribute drugs to several different parts of the eye through minimally invasive means while limiting the development of scar tissue.

Keywords: anatomy ; subconjunctival space ; drug delivery

1. Anatomy and Key Cells

The subconjunctival space is the hydrophilic, fluid-filled space between the conjunctiva and the sclera. Additionally, the subconjunctival space has access to all the blood vessels found in the conjunctiva, which can help to further distribute substances throughout the whole eye. The subconjunctival space is located superior to the cornea and optimally located to distribute drugs to several different parts of the eye through minimally invasive means while limiting the development of scar tissue [1][2].

2. Interface

When considering periocular drug delivery via the subconjunctival space, it is critical that the agents and delivery systems do not react with the subconjunctival fluid, causing irreversible damage to the eye. This subconjunctival fluid-like gel is, like the vitreous humor, predominantly composed of water with a small percentage of hyaluronic acid, glucose, ions, and collagen [3][4]. The subconjunctival space is pressure-sensitive due to its flexibility and resistance to fluid dissipation, making it essential that pressure be monitored when administering drugs or drug delivery systems to this region [5]. Additionally, conjunctival and choroidal circulation potentially reduce the ocular bioavailability of drugs permeating from this region [1]. The retinal pigment epithelium, chemosis, and risk of subconjunctival hemorrhage pose additional challenges to this delivery route [1].

2.1. Drug Delivery

The subconjunctival route is appropriate for drug delivery to both the anterior and posterior segments of the eye [1]. Drugs administered through the subconjunctival space circumvent the cornea, conjunctiva, and the conjunctival–epithelial barrier, passing directly through the sclera into the posterior segment [1][6][7]. Studies suggest that when drugs are administered into the subconjunctival space in a free, unencapsulated form, they may be delivered at a relatively low concentration due to the ease of travel to adjacent locations. Weijtens et al. (1999) demonstrated that a subconjunctival injection of only 2.5 mg of dexamethasone disodium phosphate in humans resulted in a mean vitreous dexamethasone peak concentration that was 3 and 12 times higher than that after 5 mg and 7.5 mg doses administered by peribulbar and oral administration routes, respectively [7]. However, researchers also suggest that following subconjunctival administration, colloidal dosage forms (up to 20 nm in size) and released drug molecules are rapidly cleared by the conjunctival, choroidal, and lymphatic circulations, thereby limiting ocular bioavailability [1][7][8][9]. Additionally, free-form drug injections must be rate-limiting to avoid overdose [1]. Currently, the main types of drugs administrated through the subconjunctival space are carboplatin, topotecan, insulin, and other drugs with similar chemistries [1].

2.1.1. Drug Delivery Systems

Along with predominantly free drug injection, there have been some preliminary trials involving sustained-release drug delivery systems. These systems are generally microparticles, nanoparticles, and collagen matrices which have been found to be too large to fit between pores into the retina and do not easily break down [1]. The motivation behind developing these systems is to house and deliver drugs that would have long-lasting effects; therefore, each of the

systems releases at a different rate and appropriately administers the drug in question. Unfortunately, due to the slow rate of degradation and poor clearance of the housing material after drug delivery is complete, there have been several logistical challenges with implementing these systems. *Liu* et al. found success with biodegradable poly(lactide-co-ε-caprolactone) microfilms loaded with prednisolone and implanted in the subconjunctival space of a rat model, showing these systems to deliver the drug for 3 months at a rate of 0.002 mg/day [10]; several similar systems are under development.

A promising approach to drug delivery systems designed for the subconjunctival space is through liposomes [11][12], polymeric thermoresponsive hydrogels [13][14][15], and polymeric controlled-release systems [16][17] that would release drugs and subsequently degrade. These drug delivery systems limit the amount of drug lost compared to a free drug injection, but also break down into small enough particles that they can travel through the small pores. They can also last longer since the capsule units will degrade at varying rates. Drug delivery systems for the subconjunctival space are taken advantage of to improve the patient experience.

2.1.2. Liposomes

Liposome drug delivery treatments for the subconjunctival space are being evaluated for how quickly the drugs can be transmitted into the subconjunctival space and subsequently diffuse into other areas of the eye while maintaining a relatively large concentration. In one study evaluating tobramycin liposomes, Assil et al. used negatively charged liposomes to deliver tobramycin to infected rabbit eyes [11]. This study found that liposomes allowed for higher, more rapid peaks of the drug compared to topical treatments. They also found that they were able to sustain drug delivery for 24 h in the cornea after the liposomes were administered to the subconjunctival space. After 24 h, the drug concentration dropped dramatically, suggesting that liposome treatments would require frequent administrations for long-term illnesses, which could have growing complications [11].

Another study used negatively charged liposomes to deliver gentamicin to infected rabbit eyes [12]. This study revealed that not all parts of the eye received the drug, and in those parts that did, the drug was unequally distributed, and gentamycin levels were higher in the sclera and cornea than when gentamycin was injected in its free form. This study also confirmed the inability of negatively charged liposomes to migrate throughout the ocular structures, partially also due to their large size. This result may differ with a positive charge [12].

From both of these experiments, it is clear that liposomes cause a rapid peak in drug concentration when first administrated, which could be useful when combating an initial infection that would require additional follow-up injections. Moreover, liposome subconjunctival drug delivery was effective at delivering drugs more posteriorly as compared to topical treatments. For targeted drug delivery, liposomes are a promising method to provide a rapid and high concentration in specifically targeted ocular regions.

2.1.3. Hydrogels

Environmentally responsive hydrogels offer another promising option for sustained-release drug delivery into the subconjunctival space owing to their ability to be injected into the space and offer slow and controlled drug release without a risk of migration. Thermoresponsive hydrogels can be injected into the space through a small gauge needle at room temperature and proceed to collapse into a more solid form upon reaching body temperature, promoting the release of encapsulated drug [14][18]. Additionally, these hydrogels can be made biodegradable, eliminating the need for a removal surgery [19]. In a 2008 study, Kang Derwent (Kang-Meiler) and Mieler demonstrated the ability of thermoresponsive PEG and poly(N-isopropylacrylamide) (NiPAAM)-based hydrogels to be manipulated to control their drug release rate, confirming the absence of an immune response. Kang-Mieler also established that while the hydrogels themselves did not migrate, the encapsulated drug was able to travel to the posterior region of the eye [15]. Dosmar et al. demonstrated the use of these hydrogels loaded with vancomycin and injected into the subconjunctival space to prevent acute endophthalmitis in the vitreous following ocular surgery in male rodents [14]. These hydrogels released detectable levels of vancomycin at a steady rate for nearly three weeks.

2.1.4. Polymeric Controlled-Release Systems

Polymeric controlled-release systems for the subconjunctival space are less common due to their larger size and the fact that they do not typically biodegradable. While more frequently used on the ocular surface, several labs have developed polymeric systems for the subconjunctival space. Cui et al. used 5-fluorouracil-loaded poly(lactic acid) discs implanted into the subconjunctival space after glaucoma filtration surgery in rabbit eyes. The discs sustained drugs throughout the critical period for 2 weeks until 1 month where they failed to administer additional drug [20]. Animals experienced some subconjunctival hemorrhage, which was attributed to the disc implantation. Different polymer mixtures resulted in toxic

effects that cause conjunctival hyperemia and corneal edema [20]. Zignani et al. experimented with two different anti-inflammatory drugs (dexamethasone sodium phosphate and 5-fluorouracil (5-FU)) to see which one would reduce the harmful effects of hydrophobic poly(ortho ester) on the subconjunctival space [21]. The study revealed the promising effects of dexamethasone to abate the toxic effects of a typically reactive polymer, making it possible for use as a long-term drug delivery system [21].

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