Thirty years ago, John Shell, PhD, wrote a classic article on drug delivery in which he defined the problem of eye drops: this delivery method is pulsatile, drugs have limited bioavailability due to the many barriers through which they must pass to reach the site of action, and the residence time of the drug on the ocular surface is short-lived. The very phrase *ophthalmic drug delivery* implies a challenge in delivering medication to the eye. Eye drops are relatively inefficient delivery systems: they use volumes (25-50 µL) larger than the available space (approximately 7 µL in the lower cul-de-sac), with relatively poor bioavailability into the target site of the anterior chamber (approximately 1%-5%). Eye drops also require reliable administration, yet in one study, only about 20% to 30% of experienced glaucoma patients were able to instill one drop in their eye without touching the tip of the bottle against the ocular surface.

Most people are able to take oral medication, and there are numerous drug delivery systems for sustained release (eg, transdermal). Some drugs can be administered by systemic routes (eg, antimetabolites for uveitis). Unfortunately, the relative safety (also known as the *therapeutic index*) of systemic therapy for purely ocular disease is not optimal. Local therapy with minimal systemic exposure is therefore needed to achieve an acceptable therapeutic index.

I summarized many of the drug development and regulatory challenges with a 21st century view of ophthalmic drug delivery systems approximately 5 years ago. I wrote on glaucoma-specific delivery systems for *Glaucoma Today* at approximately the same time. This article provides an update on drug delivery systems for glaucoma therapies.

I will use the analogy of purchasing airline tickets. A generation ago, most tickets were bought through travel agents. Today, most travelers connect to the airlines’ websites and personally make their reservations and purchase their tickets. This puts the action in the best place (ie, in the hands of the traveler who knows his or her needs and preferences best). In the same way, rather than have patients be responsible for their glaucoma pharmacotherapy, there is a movement to put the responsibility in the hands of the ophthalmologist.
SOURCES

There are relatively few full articles on ophthalmic drug delivery systems currently in clinical evaluation. Thus, for the purpose of this article, I have used a variety of publicly available sources, including not only full articles but also abstracts from scientific meetings, published patent applications and patents, clinical trial registries, and press releases.

APPROACHES

Approved

Since the 19th century, pilocarpine has been known as an effective ocular hypotensive agent, but its utility is limited by muscarinic agonist adverse events (miosis and accommodative spasm) and the drug’s short duration of action, requiring frequent instillation by the patient. The Ocusert (Alza), inserted into the lower cul-de-sac, released pilocarpine over approximately 7 days and was approved in the United States in the early 1970s (Figure 1). Unfortunately, untoward events such as “dose-dumping” and occlusion of the visual axis limited its therapeutic value.

US-marketed ocular hypotensive agents are administered by several means. A molecular, prodrug approach was used for dipivefrin (Propine [Allergan], a prodrug of epinephrine), levo-bunolol (Betagan [Allergan], itself active as well as having an active metabolite, dihydro-levo-bunolol), and latanoprost (Xalatan [Pfizer], a prodrug of the active latanoprost free acid). Other approaches in patients’ hands include eye drops with a longer presumed residence time and, therefore, longer presumed duration of action (pilocarpine [Adsorbocarpine; Alcon] and timolol maleate gel-forming solution [Timoptic-XE; Valeant Pharmaceuticals]). To my knowledge, there are no approved products using systems that are “in the hands of the doctor” such as the Ocusert.

Investigational

Several investigational products are in the hands of patients. These include lyophilization of latanoprost on Teflon strips, clonidine on plastic rods, hydrophilic contact lenses (NCT00445874; Vistakon Pharmaceuticals), and a cationic emulsion of latanoprost (Catioprost; Novagali Pharma).

As to investigational products in the hands of doctors, Mati Therapeutics has inserted latanoprost into a punctal plug (NCT02014142). Ocular Therapeutix has inserted travoprost into an erodible insert that is placed in the punctum (NCT01845038). Both of these devices are in phase 2 trials. A sub-Tenon injection of anecortave acetate has been investigated. Peregrine Ophthalmic is developing a liposomal latanoprost for subconjunctival injection; the drug lowered mean IOP from 28 to 15 mm Hg in an open-label study of six patients. Allergan is evaluating an erodible, anterior chamber implant of bimatoprost (EudraCT 2011-005091-42). BioLight Israeli Life Sciences Investments is evaluating a nonerodible, controlled-release insert containing latanoprost for subconjunctival injection (NCT02129673). Envisia Therapeutics is developing an erodible implant of travoprost intended for intracameral placement. Replenish is developing an ophthalmic “micropump” that is placed subconjunctivally and that might have applications for glaucoma therapy. Another bioerodible, sustained-release implant of latanoprost intended for the subconjunctival space is being developed by pSivida. ForSight Vision5 has completed enrollment of a study of the “Helios” insert (NCT01943721).

Ocular iontophoretic technology might be applicable to glaucoma (Aciont, EyeGate Pharma, ReAble Empi [formerly Iomed], and Buckeye Pharmaceuticals), as might an erodible intracameral implant from Icon Biosciences.

With respect to the posterior segment, no drug is approved for neuroprotection in glaucoma. Intraocular drug delivery systems are approved for other indications. In the United States, these include nonerodible intravitreal systems (ganciclovir [Vitrasert; Bausch + Lomb] and fluocinolone acetonide [Retisert; Bausch + Lomb]) and, in Europe, fluocinolone acetonide (Iluvien; Alimera Sciences). Also approved in the United States is an erodible intravitreal implant of dexamethasone (Ozurdex; Allergan).

Figure 2. Dr. Novack and a friend backpacking in the Sierras as an example of the “payload” issue.
“It will most likely be several years until a novel drug delivery system is available to patients with glaucoma.”

CHALLENGES

In the decades since the approval of Ocusert, to my knowledge, no ocular hypotensive insert or implant has been approved. Why are advances in this area so difficult? One challenge is akin to my difficulties when backpacking (Figure 2). One day of food, even dehydrated, weighs about 750 g. My basic backpacking gear weighs about 18 kg. I can carry approximately 27 kg at most, so I can only transport about 12 days’ worth of food before resupplying. In addition, all of my food has to be stable at ambient temperatures (0°C–40°C). This “payload” issue is common to all ophthalmic drug delivery systems, and it tends to limit options to potent drugs and several months of therapy.

Drug solubility is also key in designing systems; only some systems can work with macromolecules such as antibodies. Another challenge is linking the nature of the timed release of the molecule to the desired therapeutic effect. There is a natural assumption that zero-order is the Holy Grail. That is true for pilocarpine and probably for timolol, but prostaglandin analogues may be different in that more frequent instillation may result in lower efficacy. For the treatment of acute infection or inflammation, it may be desirable to have a higher delivery rate early on followed by a lower maintenance level.

The least risky approach to developing a novel drug delivery product is to select a molecule that is already approved and has an expiring patent. This strategy assumes that the marketplace will recognize the improvement, however, and will compensate for the incremental cost of the new medication over a generic. A higher-risk but higher-reward approach is to select novel medications, especially those for which a delivery system is the only way in which they could be used.

CONCLUSION

It will most likely be several years until a novel drug delivery system is available to patients with glaucoma. I encourage ophthalmologists and their staff members to observe patients using eye drops to check for proper instillation. A host of educational materials is available from the American Academy of Ophthalmology and online. I also encourage clinicians to convey to health care payers that patients’ adherence and performance are major issues in therapeutics and to emphasize that enhancements in this area are of clinical and financial value. Finally, I encourage physicians to be investigators for ongoing and upcoming clinical trials of novel therapies.

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