The eye is a unique organ, both anatomically and physiologically, containing several widely varied structures with independent physiological functions. For example, the cornea and the crystalline lens are the only tissues in the body besides cartilage that have no blood supply. The complexity of the eye provides unique challenges to drug delivery strategies.

Pharmaceutical treatment and drug delivery methods for treating eye diseases and disorders vary considerably depending on the nature and extent of the disease or disorder. Diseases such as diabetic retinopathy and age-related macular degeneration are associated with tissues at the back of the eye (BOTE). Methods used for ocular drug delivery for the front of the eye (FOTE) differ significantly and pose considerably less risk than subcutaneous or back of the eye therapy. Methods for subcutaneous or BOTE delivery can range from injections to sustained-release implants and can be associated with greater risk of infection, internal ocular bleeding and retinal damage, etc. Excellent reviews of drug delivery for treating posterior eye disease have been developed. A popular alternative drug delivery method to invasive approaches for delivering a drug to non-FOTE eye tissue that may be useful for treating BOTE diseases and disorders is iontophoresis. This method involves the use of a low electrical current, administered through a removable temporary applicator placed under the lower eyelid, to transport an ionised drug to eye tissues.

**Special Considerations for Effective Front-of-the-eye Drug Delivery**

In FOTE drug therapy, a significant degree of the topically applied drug is immediately diluted in ocular tear liquid. As a direct result, excess fluid can spill over the lower eyelid, with some of the remaining drug draining into the nasolachrymal duct. As a result, corneal contact time has been estimated to be in the order of only a couple of minutes or less, with drug bioavailability as low as <10%. In order to optimise FOTE drug delivery systems, it is important to consider a number of factors, including effective corneal application to promote good corneal penetration, prolonged contact time with the corneal epithelium and the use of a drug solution with appropriate rheological properties that is non-irritant to the eye in order to limit lachrymation and reflex blinking.

Traditional FOTE drug delivery methods have included solutions, ointments and suspensions, accounting for nearly 90% of available ophthalmic formulations in the US. Generally, these products are delivered via an eye-drop bottle, which relies on gravity as the primary motive force to propel the drop into the eye. Of these formulations, approximately 62% are for solutions. In the limit of the implications associated with rapid elimination for the pre-corneal area, resulting in poor bioavailability, solutions are still given high priority by formulators since they are relatively simple to prepare, filter and sterilise. More effective ocular delivery systems that have been commercialised recently or are under development all aim at enhancing drug bioavailability by providing prolonged or sustained delivery to the eye or by facilitating transcorneal penetration.

A recent review indicated that, typically, the bioavailability of ocular drugs topically applied in eye-drops is very poor, with ocular drug absorption limited by protective mechanisms that promote proper functioning of the eye, as well as by a number of concomitant limiting factors related to the efficacy of FOTE drug application. Drainage of an administered drug dose by the nasolachrymal system can occur when the volume of fluid in the eye exceeds the normal lachrymal volume of about 7–10µl. In contrast, the application of one to two drops of a drug medication applied by an eye-dropper as the drug delivery device represents roughly 50–100µl. Much of this dose is wasted or rapidly drained. The remaining applied drug solution is diluted by induced increased lachrymation and physiological tear turnover produced by the applied drug solution. In addition, any remaining drug is subject to non-selective transcorneal adsorption. All these factors taken together can result in a loss of drug from that applied to the eye that can be 500–700 times greater than the rate of absorption of the drug into the anterior chamber.

**Technology Advances in Front-of-the-eye Drug Delivery Systems**

Advanced technology based on the use of nanocarriers (nanoparticles, liposomes, dendrimers) has been investigated recently with the aim of enhancing FOTE ocular drug delivery. These systems are claimed to provide a prolonged residence time at the ocular surface, minimising the effect of natural eye clearance systems. It has been argued that, when combined with controlled drug delivery, it should be possible to provide drug therapeutic levels for a prolonged time at the site of action. The use of nanoparticles and other forms of ocular drug delivery have been reviewed in several excellent texts, such as that by Edman. Advances in recent years in topical ocular drug delivery have ranged from primitive eye-drops to iontophoretic drug delivery, in situ gelling systems, dendrimers, penetration enhancers, lipid emulsions, ocular inserts, the use of muco-adhesive and thiolated polymers and site-specific drug delivery systems. Nonetheless, very few drug delivery systems have successfully appeared on the market: currently, 95% of FOTE products are delivered via the traditional eye-drop bottle.

**Front-of-the-eye Drug Delivery Applications**

Common eye problems requiring FOTE drug delivery include glaucoma, dry-eye syndrome and ocular allergy. Glaucoma is estimated to affect 5.2 million people worldwide and primarily affects older people, which frequently means it is necessary to address and overcome patient compliance issues and use methods that are both physically facile.
and user-friendly. Current therapy involving beta-blockers can pose cardiovascular and respiratory risks, hence drug delivery must be carefully controlled. The incidence of dry-eye syndrome, which is thought to affect over four million Americans, also increases with age. The increasing growth in the elderly sector of the US and world populations will result in a marked increased incidence in ocular disease requiring drug therapy and effective and precise drug delivery systems.

**A New Standard for Effective Front-of-the-eye Drug Delivery**

Challenges for effective FOTE drug delivery include: somehow circumventing the physics of eye-drop delivery, which can result in chronic overdosing, which in turn can produce unwanted adverse effects; minimising the use of preservatives in the eye-drop drug solution being applied; and avoiding excess eye-drop solution being drained through the nasolachrymal duct with potential systemic absorption into the circulatory system. Currently available devices for improving FOTE drug delivery using eye drops include the Visine® Pure Tears Single Drop dispenser, which contains no preservatives, the Pfizer Xal-Ease® FOTE drop delivery device, which encloses a traditional eye-drop bottle, and the Autosqueeze and Autodrop devices developed in the UK with the Royal National Institute for the Blind, which clip onto bottles of eye drops. The characteristics of a successful FOTE drug delivery device should be: the ability to provide consistent drop volumes, preferably 7–15µl; the use of a stable, sterile drug solution that can be delivered consistently and reproducibly and that is preservative-free to avoid patient eye irritability; and affordability. Recent innovations in FOTE drug delivery devices include the Eye-Instill produced by Med-Instill, Inc., which has a one-way valve to ensure multiple dosings of sterile, preservative-free drug solutions, and the OptiMyst device, which dispenses medication as a mist rather than as a drop. The latter provides much less medication per dose, below blink and lachrymation thresholds.

The VersiDoser™ Drug Delivery System under development by Mystic Pharmaceuticals, Inc. holds the near-term potential for setting a new standard for effective FOTE drug delivery. The VersiDoser platform utilises aseptic unit dose packaging combined with novel multidose delivery devices that dispense the drug into the eye in a predictable and consistent manner irrespective of the orientation of the device and the eye. These devices are capable of self-administered precision dosing in the 12–15µl range and provide automatic dose counters. Preservative-free packaging and ergonomic design will significantly enhance compliance, ease of use and therapeutic benefits for elderly and paediatric patients.