Introduction

Although continued effort is being devoted to the improvement and optimisation of ocular drug delivery, progress in this area does not appear to proceed at the fast pace that is typical of other delivery routes (oral, transdermal, transmucosal, etc.). A cautious advancement is evidently imposed by the delicacy and the many restraints of the site of application. The vast majority of existing ocular delivery systems are still, as defined by Lee and Robinson in 1986, “fairly primitive and inefficient”. However, in the words of Hughes and Mitra: “ophthalmic drug delivery is one of the most interesting and challenging endeavours facing the pharmaceutical scientist...The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances...The challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage...The primitive ophthalmic solutions, suspensions and ointment dosage forms are clearly no longer sufficient to combat some present virulent diseases...”

The aforementioned traditional, or “primitive”, dosage forms are solutions, ointments and suspensions. According to J C Lang, in 1995, these accounted for nearly 90% of available ophthalmic formulations in the US, and a similar percentage is still presumably valid for the current global market.

The relative percentages were 62.4% for solutions, 17.4% for ointments and 8.7% for suspensions. Solutions, in spite of their limitations (a quick elimination from the precorneal area, resulting in poor bioavailability), are still given top priority by formulators since they are relatively simple to prepare, filter and sterile.

More efficient ocular delivery systems that have been commercialised recently and/or are still under evaluation aim at enhancing the drug bioavailability either by providing prolonged/sustained delivery to the eye or by facilitating transcorneal penetration.

Drug Absorption and Disposition in the Eye

It is common knowledge that the ocular bioavailability of drugs applied topically as eye-drops is very poor. The absorption of drugs in the eye is severely limited by some protective mechanisms that ensure the proper functioning of the eye, and by other concomitant factors, for example:

- drainage of the instilled solutions;
- lacrimation and tear turnover;
- metabolism;
- tear evaporation;
- non-productive absorption/adsorption;
- limited corneal area and poor corneal permeability; and
- binding by the lacrimal proteins.

The drainage of the administered dose via the nasolacrimal system into the nasopharynx and the gastrointestinal tract takes place when the volume of fluid in the eye exceeds the normal lacrimal volume of seven to 10 microlitres. Thus, the portion of the instilled dose (one to two drops, corresponding to 50–100 microlitres) that is not eliminated by spillage from the palpebral fissure is drained quickly and the contact time of the dose with the absorbing surfaces (cornea and sclera) is reduced to a maximum of two minutes.

The lacrimation and the physiological tear turnover (16% per minute in humans in normal conditions) can be stimulated and increased by the instillation of mildly irritating solutions. The net result is a dilution of the applied medication and an acceleration of drug loss. It is now definitively established that the rate at which instilled solutions are removed from the eye varies linearly with instilled volume. In other words, the larger the instilled volume, the more rapidly the instilled solution is drained from the precorneal area.

Ideally, a high concentration of drug in a minimum drop volume would be desirable. However, there is a practical limit to the concept of minimum dosage volume. Droppers delivering small volumes are difficult to design and produce. In addition, their practical usefulness could be reduced by the fact that...
most patients cannot detect the administration of small volumes.

The conjunctival absorption, which occurs via the vessels of the palpebral and scleral conjunctiva, concurs in reducing the drug available for absorption into the eye. Any instilled drug that has not been swept away from the precorneal area by the drainage apparatus is subject to protein binding and to metabolic degradation in the tear film. All of these factors may result in transcorneal absorption of 1% or less of the drug applied topically as a solution. In summary, the rate of loss of drug from the eye can be 500 to 700 times greater than the rate of absorption into the anterior chamber.

Drugs applied topically are potentially available for absorption by the scleral and palpebral conjunctiva (the so-called ‘non-productive’ absorption). Although direct transscleral access to some intraocular tissues cannot be excluded, it is well documented that drugs that penetrate the conjunctiva are rapidly removed from the eye by local circulation and undergo systemic absorption. This may range, for example, from 65% for dipivalylepinephrine to 74% for flurbiprofen and 80% for timolol. These effects are frequently not anticipated, recognised or treated appropriately.

In conclusion, the fluid dynamics in the precorneal area of the eye have a huge effect on ocular drug absorption and disposition. When the normal fluid dynamics are altered by, for example, toxicity, pH or irritant drugs or vehicles, the situation becomes more complex. The formulation of ophthalmic drug products must take into account not only the stability and compatibility of a drug in a given formulation, but also the influence of that formulation on precorneal fluid dynamics.

The concepts exposed in this section are summarised in Figure 1, which illustrates the various factors and pathways involved in the ocular disposition of formulations applied topically to the eye.

**Traditional Ophthalmic Vehicles**

The traditional ophthalmic dosage forms (solutions, suspensions and ointments) have been described and discussed in detail. Solutions are undoubtly the most commonly used and accepted forms. They are relatively simple to make, filter and sterilise. Suspensions, while not as common as solutions, are widely used for formulations involving anti-inflammatory steroids (for example, prednisolone alcohol and acetate). Much published data suggests that a proper particle size and a narrow size range, ensuring low irritation and adequate bioavailability, should be sought for every suspended drug. Other formulation factors, i.e. the use of correct wetting, suspending and buffering agents, protective colloids, preservatives, etc., should also be considered attentively.

Semisolid, petrolatum-based ointments presented problems for years because they could not be filtered to eliminate particulate matter, could not be made truly sterile and no adequate tests had been devised to indicate the suitability of added preservatives. In time, most of these problems have been solved, and sterile, filtered ophthalmic ointments are currently available on the market. These preparations, however, occupy a position of minor importance since they are ill-accepted on account of their greasiness, vision-blurring effects, etc., and are generally used as night-time medications.

Two particular physical factors in ocular formulations that, among others, have been investigated attentively are the drug solubility and physical form and the vehicle viscosity. In the case of poorly soluble drugs, as in steroids, two aspects of the solubility parameter are relevant to ocular absorption: the presence in the cul-de-sac of the eye of a reservoir of insoluble particles could lead to a sustaining effect, and different esters of the drug could show different transcorneal permeation characteristics.

Poorly soluble ophthalmic drugs can be solubilised by the use of cyclodextrins (CDs), a group of cyclic oligosaccharides capable of forming inclusion complexes with many drugs. In ophthalmic preparations, co-administration of CDs has been reported to increase corneal penetration, ocular absorption and the efficacy of poorly water-soluble drugs such as dexamethasone, cyclosporin, acetazolamide, etc. These positive results are attributed to the ability of CDs to increase the aqueous solubility of lipophilic drugs without affecting their intrinsic ability to permeate biological membranes. It is thought that CDs act as true carriers by keeping the
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hydrophobic drug molecules in solution and delivering them to the surface of the corneal epithelium where they partition.

While normal saline is an acceptable vehicle for ophthalmic drugs, slightly viscous solutions are generally recognised as more satisfying to use by the patients. Increasing the viscosity is also exploited as a means to increase the bioavailability of drugs, since an augmented viscosity corresponds to an increased time of residence of the medication in the eye. However, there appears to be only a narrow band of acceptable viscosity (15–18 centipoises (cps)), since the products must have negligible visual effects, should not obstruct the puncti and canaliculi and should be filterable and sterilisable.

Recently, much research has been dedicated to mucoadhesive polymers, i.e. macromolecules capable of retaining the medication in the precorneal area not only by viscosity effects, but also by establishing physicochemical interactions with the mucin layer covering the corneal epithelium.

In recent years, extensive investigation has been dedicated to prolonging the retention time of medications on the eye surface and to the improvement of transcorneal penetration of traditional and of novel therapeutic agents such as protein and peptide drugs. Exhaustive reviews on different ocular delivery systems can be found.

Some recently developed systems aim at prolonging the precorneal retention and therefore reducing the frequency of administration. Other delivery systems are designed to provide controlled, continuous drug delivery with the dual goal of avoiding or minimising the initial drug concentration peak in the aqueous humour (with its associated side effects) and of avoiding the periods of underdosing that may occur between eye-drop instillations.

In-situ Activated Gel-forming Systems

These (liquid) vehicles undergo a viscosity increase upon instillation in the eye, thus favouring precorneal retention. Such a change in viscosity can be triggered by a change in temperature, pH or electrolyte composition. Poloxamer 407 (a polyoxyethylene-polyoxypropylene block copolymer) is a polymer with a solution viscosity that increases when its temperature is raised to the eye temperature. Cellulose acetophthalate (CAP) is a polymer undergoing

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coagulation when the original pH of the solution (4.5) is raised to 7.4 by the tear fluid.

Both systems, however, are characterised by a high polymer concentration (25% for Poloxamer 407 and 30% for CAP). By contrast, Gelrite® is a polysaccharide (low-acetyl gellan gum) that forms clear gels at a much lower concentration in the presence of mono or divalent cations typically found in tear fluids. It is marketed as a once-a-day dosing vehicle for timolol maleate (Timoptic XE, Merck & Co., Inc.).

**Mucoadhesive Formulations**

This approach relies on vehicles containing polymers that adhere via non-covalent bonds to conjunctival mucin, thus ensuring contact of the medication with the precorneal tissues until mucin turnover causes elimination of the polymer.

Mucoadhesive polymers are usually hydrocolloids with numerous hydrophilic functional groups such as carboxyl, hydroxyl, amide and sulphate. These groups can establish electrostatic interactions, hydrophobic interactions, van der Waals intermolecular interactions and hydrogen bonding with mucus substrates. For many polymers, hydrogen bonding appears to play a significant role in mucoadhesion, thus the presence of water seems to be a prerequisite for a majority of mucoadhesive phenomena.

The following synthetic, semi-synthetic and naturally occurring polymers (hydroxypropylcellulose, polyacrylic acid, high-molecular-weight (>200,000) polyethylene glycols, dextrans, hyaluronic acid, polygalacturonic acid, xyloglucan, etc.) have been evaluated for mucoadhesion, sometimes with interesting results.

Active investigations on mucoadhesive polymers as ingredients for ophthalmic vehicles, now underway in many laboratories, will hopefully lead to the development of more efficient ocular delivery systems.

**Ocular Penetration Enhancers**

The use of substances facilitating drug penetration through the corneal tissues is a potentially interesting, still little-explored approach to improving ophthalmic bioavailability. The effect of these substances (mainly surface active agents) on the cornea is to enhance the permeability of superficial cells by destroying the cell membranes and causing cell lysis in a dose-dependent manner.

Among the promoters that have been investigated, sometimes with positive results, the following can be mentioned: benznalolinium, chloride, polyoxyethylene glycol lauryl ether (Brij® 35), polyoxyethylene glycol stearil ether (Brij® 78), polyoxyethylene glycol oleyl ether (Brij® 98), ethylenediaminetetraacetic acid (EDTA), sodium salt, digitonin, sodium taurocholate, saponins and Cremophor EL, etc. Unfortunately, some agents, while effective, cause transient irritation or produce irreversible damage to corneal tissues.

**Inserts**

Ophthalmic inserts are solid devices intended to be placed in the conjunctival sac and to deliver the drug at a comparatively slow rate. These devices might present valuable advantages, such as:

- increased ocular permanence with respect to standard vehicles, hence prolonged drug activity and a higher drug bioavailability;
- accurate dosing (theoretically, all of the drug is retained at the absorption site);
- capacity to provide, in some cases, a constant rate of drug release;
- possible reduction of systemic absorption, which occurs freely with standard eye-drops via the nasal mucosa;
- better patient compliance, resulting from a reduced frequency of medication and a lower incidence of visual and systemic side effects;
- possibility of targeting internal ocular tissues through non-corneal conjunctival-scleral penetration routes; and
- increased shelf life with respect to eye-drops due to the absence of water.

An interesting device developed by Alza Corp. is the Ocusert®, a diffusion unit consisting of a drug reservoir (for example, pilocarpine HCl in an alginate gel) enclosed by two release-controlling membranes made of ethylene-vinyl acetate copolymer and enclosed by a white ring, allowing position of the system in the eye. Clinical studies with the pilocarpine Ocusert® demonstrated that slow release of the drug can effectively control the increased intraocular pressure in glaucoma, with a minor incidence of side effects such as miosis, myopia, browache, etc.

Other inserts, both erodible and non-erodible (for example, medicated contact lenses, collagen shields, the Minidisc®, etc.) have also been shown to be capable of diminishing the systemic absorption of ocularly applied drugs as a result of a
decreased drainage into the nasal cavity, which is one of the major systemic absorption sites of topical ocular medications. Another potential advantage of insert therapy is the possibility of promoting non-corneal drug penetration, thus increasing the efficacy of some hydrophilic drugs that are poorly absorbed through the cornea.

It is surprising that these delivery systems, in spite of the advantages demonstrated by extensive investigations and clinical tests, have not gained acceptance. The commercial failure of inserts has been attributed to psychological factors such as the reluctance of ophthalmologists and of patients to abandon the traditional liquid and semisolid medications, to price factors and to occasional therapeutic failures (for example, unnoticed expulsion from the eye, membrane rupture, etc.). Still, the prolonged, constant-rate release pattern achievable by inserts, resulting in increased therapeutic efficacy and reduction of ocular and systemic side effects, can be considered as the most desirable condition for long-term therapy.

Conclusions

Constant progress in the understanding of principles and processes governing ocular drug absorption and disposition and continuing technological advances have surely brought some improvements in the efficacy of ophthalmic delivery systems. However, ocular drug delivery still faces the challenges enunciated by Lee and Robinson several years ago. These are:

- the extent to which the protective mechanisms of the eye can be altered safely to facilitate drug absorption;
- delivery of drugs to the posterior portion of the eye from topical dosing;
- topical delivery of macromolecular drugs;
- improved technology, allowing non-invasive monitoring of drug transport in the eye; and
- predictive animal models for all phases of ocular drug evaluation.

Additional Information

The complete version of this article, including an additional graphic and references, can be found in the Reference Library on the CD-ROM accompanying this business briefing.