The concept of ocular inserts as drug delivery systems: An overview

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Ocular diseases require localized administration of drugs to the tissues around the ocular cavity. The existing ocular drug delivery systems are fairly primitive and inefficient. However, the design of ocular system is undergoing gradual transition from an empirical to rational basis. In the recent years, there has been explosion of interest in the polymer based delivery devices. Utilization of the principles of controlled release as embodied by ocular inserts offers an attractive approach to the problem of prolonging pre-corneal drug residence times. In the present update, the authors discuss the basic concept of ocular inserts as drug delivery system and examine the few inserts, which are available in the market or are being developed by pharmaceutical companies for drug delivery. The article discusses soluble ocular drug insert (SODI), Ocusert, Collagen Shields, Ocufit, Minidisc and new ophthalmic delivery system (NODS) with special attention to biological/clinical performances, and potential for future applications and developments.

Key words: Basic concept, collagen shields, minidisc, NODS, ocufit, ocular diseases, ocusert, SODI

INTRODUCTION

The eye as a portal for drug delivery is generally used for local therapy against systemic therapy to avoid the risk of eye damage from high blood concentrations of the drug, which is not intended. The unique anatomy, physiology, and biochemistry of the eye render this organ impervious to foreign substances, thus presenting a constant challenge to the formulator to circumvent the protective barriers of the eye without causing permanent tissue damage. Most ocular treatments like eye drops and suspensions call for the topical administration of ophthalmically active drugs to the tissues around the ocular cavity. These dosage forms are easy to instill but suffer from the inherent drawback that the majority of the medication they contain is immediately diluted in the tear film as soon as the eye drop solution is instilled into the cul-de-sac and is rapidly drained away from the pre-corneal cavity by constant tear flow and lacrimo-nasal drainage. Therefore, the target tissue absorbs a very small fraction of the instilled dose. For this reason, concentrated solutions and frequent dosing are required for the instillation to achieve an adequate level of therapeutic effect. One of the new classes of drug delivery systems, polymeric film ocular drug delivery systems/ocular inserts, which are gaining worldwide accolade, release drugs at a pre-programmed rate for a longer period by increasing the pre-corneal residence time.¹³

Ocular inserts are defined as preparations with a solid or semisolid consistency, whose size and shape are especially designed for ophthalmic application (i.e., rods or shields). These inserts are placed in the lower fornix and, less frequently, in the upper fornix or on the cornea. They are usually composed of a polymeric vehicle containing the drug and are mainly used for topical therapy.⁴⁷

History of ocular inserts

The first solid medication (precursors of the present insoluble inserts) was used in the 19th century, which consisted of squares of dry filter paper, previously impregnated with dry solutions (e.g., atropine sulphate, pilocarpine hydrochloride). Small sections were cut and applied under eyelid. Later, lamellae, the precursors of the present soluble inserts, were developed. They consisted of glycerinated gelatin containing different ophthalmic drugs.³⁴ Glycerinated gelatin ‘lamellae’ were present in official compendia until the first half of the present century. However, the use of lamellae ended when more stringent requirements for sterility of ophthalmic preparations were enforced. Nowadays, growing interest is observed for ophthalmic inserts as...
demonstrated by the increasing number of publications in this field in recent years. Examples of the various types of inserts available or in development are presented in the Table 1.

Table 1: Sort of ocular inserts

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name</th>
<th>Reported by</th>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>OcuSert[6,29]</td>
<td>Quigley et al. and Urquhart et al.</td>
<td>1975,1980</td>
<td>Flat, flexible elliptical insoluble device consisting of two layers enclosing a reservoir, used commercially to deliver pilocarpine for 7 days. Small oval wafer, composed of a soluble copolymer consisting of acrylamide, N-vinyl pyrrolidone and ethyl acrylate, softens on insertion.</td>
</tr>
<tr>
<td>3.</td>
<td>Collagen shields[7,8]</td>
<td>Bloomfield et al.</td>
<td>1977,1978</td>
<td>The inserts tested were based either on unmodified or thiolated poly (acrylic acid) for the controlled delivery of ophthalmic drugs and to evaluate its efficacy in vivo.</td>
</tr>
<tr>
<td>4.</td>
<td>Lacrisert[18]</td>
<td>Lamberts et al.</td>
<td>1978</td>
<td>Rod-shaped device made from hydroxypropyl cellulose used in the treatment of dry eye syndrome as an alternative to artificial tears.</td>
</tr>
<tr>
<td>5.</td>
<td>NODS[12]</td>
<td>Lloyd et al.</td>
<td>1985</td>
<td>A preservative-free drop of hydrophilic polymer solution (hydroxypropylmethyl cellulose) that is freeze dried on the tip of a soft hydrophobic carrier strip, immediately hydrates in the tear film.</td>
</tr>
<tr>
<td>7.</td>
<td>BODI[25]</td>
<td>Gurtler et al.</td>
<td>1995</td>
<td>Gelatin hydrogels and lyophilisates with potential application as ocular insert[56]</td>
</tr>
<tr>
<td>8.</td>
<td>Silicone rubber/hydrogel composite ophthalmic inserts[29]</td>
<td>Chetoni et al.</td>
<td>1998</td>
<td>Hydrogels and lyophilisates were obtained by chemical crosslinking of gelatin using N-hydroxysuccinimide and N,N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride. Pilocarpine hydrochloride was used as a model drug.</td>
</tr>
<tr>
<td>9.</td>
<td>Gelfoam[27]</td>
<td>Simamora et al.</td>
<td>1998</td>
<td>Hydrogels and lyophilisates were obtained by chemical crosslinking of gelatin using N-hydroxysuccinimide and N,N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride. Pilocarpine hydrochloride was used as a model drug.</td>
</tr>
<tr>
<td>10.</td>
<td>‘Dry drops’[28]</td>
<td>Diestelhorst et al.</td>
<td>1999</td>
<td>The inserts tested were based either on unmodified or thiolated poly (acrylic acid) for the controlled delivery of ophthalmic drugs and to evaluate its efficacy in vivo.</td>
</tr>
<tr>
<td>11.</td>
<td>Mucoadhesive ocular insert[30]</td>
<td>Hornof et al.</td>
<td>2003</td>
<td>The inserts tested were based either on unmodified or thiolated poly (acrylic acid) for the controlled delivery of ophthalmic drugs and to evaluate its efficacy in vivo.</td>
</tr>
<tr>
<td>12.</td>
<td>One-side-coated ocular insert[31]</td>
<td>Sasaki et al.</td>
<td>2003</td>
<td>The inserts tested were based either on unmodified or thiolated poly (acrylic acid) for the controlled delivery of ophthalmic drugs and to evaluate its efficacy in vivo.</td>
</tr>
<tr>
<td>13.</td>
<td>Molecularly imprinted soft contact lenses[34]</td>
<td>Hiratani et al.</td>
<td>2004</td>
<td>The inserts tested were based either on unmodified or thiolated poly (acrylic acid) for the controlled delivery of ophthalmic drugs and to evaluate its efficacy in vivo.</td>
</tr>
<tr>
<td>14.</td>
<td>New ophthalmic mydriatic insert[55]</td>
<td>Stephane et al.</td>
<td>2006</td>
<td>The inserts tested were based either on unmodified or thiolated poly (acrylic acid) for the controlled delivery of ophthalmic drugs and to evaluate its efficacy in vivo.</td>
</tr>
<tr>
<td>15.</td>
<td>Gelatin hydrogels and lyophilisates with potential application as ocular inserts[56]</td>
<td>Madalina et al.</td>
<td>2007</td>
<td>The inserts tested were based either on unmodified or thiolated poly (acrylic acid) for the controlled delivery of ophthalmic drugs and to evaluate its efficacy in vivo.</td>
</tr>
<tr>
<td>16.</td>
<td>OphthaCoil[57]</td>
<td>Pijls et al.</td>
<td>2007</td>
<td>The inserts tested were based either on unmodified or thiolated poly (acrylic acid) for the controlled delivery of ophthalmic drugs and to evaluate its efficacy in vivo.</td>
</tr>
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</table>

SOD: soluble ophthalmic drug insert; NODS: new ophthalmic delivery system; BODI: bioadhesive ophthalmic drug insert

Karthikeyan, et al.: An overview on ocular inserts
Advantages of ocular inserts
Ocular inserts offer several advantages,\(^\text{[1-3]}\) which can be summarized as follows:

(a) Increased ocular residence, hence a prolonged drug activity and a higher bioavailability with respect to standard vehicles;
(b) Possibility of releasing drugs at a slow, constant rate;
(c) Accurate dosing (contrary to eye drops that can be improperly instilled by the patient and are partially lost after administration, each insert can be made to contain a precise dose which is fully retained at the administration site);
(d) Reduction of systemic absorption (which occurs freely with eye drops via the naso-lacrimal duct and nasal mucosa);
(e) Better patient compliance, resulting from a reduced frequency of administration and a lower incidence of visual and systemic side-effects;
(f) Possibility of targeting internal ocular tissues through non-corneal (conjunctival scleral) routes;
(g) Increased shelf life with respect to aqueous solutions;
(h) Exclusion of preservatives, thus reducing the risk of sensitivity reactions;
(i) Possibility of incorporating various novel chemical/technological approaches.

Such as pro-drugs, mucoadhesives, permeation enhancers, microparticulates, salts acting as buffers, etc.

The potential advantages offered by inserts clearly explain why an active interest has been dedicated to these dosage forms in recent years, and why efforts to introduce them on the pharmaceutical market continue. Of course, not all of the benefits listed above can be present in a single, ideal device. Each type of insert represents a compromise between the desirable properties inherent to solid dosage forms and negative constraints imposed by the structure and components of the insert itself, by fabrication costs, as well as by the physical/physiological constraints of the application site.

Disadvantages of ocular inserts
The disadvantages\(^\text{[1-3]}\) of ocular inserts are as follows:

(a) A capital disadvantage of ocular inserts resides in their ‘solidity’, i.e., in the fact that they are felt by the (often oversensitive) patients as an extraneous body in the eye. This may constitute a formidable physical and psychological barrier to user acceptance and compliance.
(b) Their movement around the eye, in rare instances, the simple removal is made more difficult by unwanted migration of the insert to the upper fornix,
(c) The occasional inadvertent loss during sleep or while rubbing the eyes,
(d) Their interference with vision, and
(e) Difficult placement of the ocular inserts (and removal, for insoluble types).

MECHANISM OF DRUG RELEASE
The mechanism of controlled drug release into the eye is as follows:

A. Diffusion, B. Osmosis, C. Bio-erosion.

A. Diffusion
In the Diffusion mechanism,\(^\text{[32,33]}\) the drug is released continuously at a controlled rate through the membrane into the tear fluid. If the insert is formed of a solid non-erodible body with pores and dispersed drug. The release of drug can take place via diffusion through the pores. Controlled release can be further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions.

In a soluble device, true dissolution occurs mainly through polymer swelling. In swelling-controlled devices, the active agent is homogeneously dispersed in a glassy polymer. Since glassy polymers are essentially drug-impermeable, no diffusion through the dry matrix occurs. When the insert is placed in the eye, water from the tear fluid begins to penetrate the matrix, then swelling and consequently polymer chain relaxation and drug diffusion take place. The dissolution of the matrix, which follows the swelling process, depends on polymer structure: linear amorphous polymers dissolve much faster than cross-linked or partially crystalline polymers. Release from these devices follows in general Fickian ‘square root of time’ kinetics; in some instances, however, known as case II transport, zero order kinetics has been observed.

B. Osmosis
In the Osmosis mechanism,\(^\text{[33]}\) the insert comprises a transverse impermeable elastic membrane dividing the interior of the insert into a first compartment and a second compartment; the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by an impermeable material and the elastic membrane. There is a drug release aperture in the impermeable wall of the insert. The first compartment contains a solute which cannot pass through the semi-permeable membrane and the second compartment provides a reservoir for the drug which again is in liquid or gel form.

When the insert is placed in the aqueous environment of the eye, water diffuses into the first compartment and stretches the elastic membrane to expand the first compartment and...
contract the second compartment so that the drug is forced through the drug release aperture.

**C. Bioerosion**

In the Bioerosion mechanism,[33,34] the configuration of the body of the insert is constituted from a matrix of bioerodible material in which the drug is dispersed. Contact of the insert with tear fluid results in controlled sustained release of the drug by bioerosion of the matrix. The drug may be dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix.

In truly erodible or E-type devices, the rate of drug release is controlled by a chemical or enzymatic hydrolytic reaction that leads to polymer solubilization, or degradation to smaller, water-soluble molecules. These polymers, as specified by Heller,[34] may undergo bulk or surface hydrolysis. Erodible inserts undergoing surface hydrolysis can display zero order release kinetics; provided that the devices maintain a constant surface geometry and that the drug is poorly water-soluble.

**CLASSIFICATION OF OCULAR INSERTS**

The inserts have been classified, on the basis of their physico-chemical behavior, as soluble (S) or insoluble (I). Only the latter types can usually deliver drugs by a variety of methods at a controlled, predetermined rate, but need removal from the eye when ‘empty’. Soluble (S) inserts, also generally defined by some authors[21] as erodible (E), are monolithic polymeric devices that undergo gradual dissolution while releasing the drug, and do not need removal. It should be pointed out that, as indicated in the article by Saettone[5], the terms ‘soluble’ and ‘erodible’ are not interchangeable, and correspond to distinct chemical processes, even if a clear-cut distinction between the two mechanisms is sometimes difficult. True dissolution occurs mainly through polymer swelling, while erosion corresponds to a chemical or enzymatic hydrolytic process.[33]

Hence, ocular inserts are classified as given below:

1. Insoluble ocular inserts; II. Soluble ocular inserts; III. Bio-erodible ocular inserts.

**I. Insoluble ocular inserts**

Inserts made up of insoluble polymer can be classified into two categories:

A. Reservoir systems; B. Matrix systems.

A. Reservoir systems

Each class of inserts shows different drug release profiles. The reservoir systems can release drug either by diffusion or by an osmotic process. It contains, respectively, a liquid, a gel, a colloid, a semisolid, a solid matrix, or a carrier containing drug. Carriers are made of hydrophobic, hydrophilic, organic, natural or synthetic polymers.

They have been sub-classified into:

1. Diffusional inserts, e.g., ‘Ocuserts’; 2. Osmotic inserts.

1. Diffusional insert or Ocuserts

Ocusert system is a novel ocular drug delivery system based on porous membrane. The release of drug from diffusional inserts/Ocusert is based on a diffusional release mechanism. It consists of a central reservoir of drug enclosed in specially designed microporous membrane allowing the drug to diffuse from the reservoir at a precisely determined rate.

As pointed out by Urquhart,[24] the Ocusert pilocarpine ocular therapeutic system, developed by Alza Corporation, is notable for several reasons. This product was the first rate-controlled, rate specified pharmaceutical for which the strength is indicated on the label by the rate(s) of drug delivery in vivo, rather than by the amount of contained drug. It provides predictable, time-independent concentrations of drug in the target tissues, a feat impossible to achieve with conventional, quantity-specified, pulse entry opthalmic medications. The near-constant drug concentration in ocular tissues markedly improves the selectivity of action of pilocarpine. A major advantage is that two disturbing side effects of the drug, miosis and myopia, are significantly reduced, while reduction of intraocular pressure (IOP) in glaucoma patients is fully maintained.

Two types of Ocusert are available: the Pilo-20 and Pilo-40. The former delivers the drug at a rate of 20 µg/h for 7 days, and the latter at a rate of 40 µg/h for 7 days. This device, which is certainly well familiar to the readers of this review, has been exhaustively described and discussed in a series of specialized papers.[14 17-19] Briefly, it consists of a reservoir containing pilocarpine alginate enclosed above and below by thin EVA (ethylene-vinyl acetate) membranes. The insert is encircled by a retaining ring of the same material, impregnated with titanium dioxide. The dimensions of the elliptical device are (for the 20 µg/h system): major axis-13.4 mm, minor axis-5.7 mm, thickness-0.3 mm. The membranes are the same in both systems, but to obtain a higher release rate, the reservoir of the 40 µg/h system contains about 90 mg of di (2-ethylhexyl) phthalate as a flux enhancer.

2. Osmotic insert

The osmotic inserts are generally composed of a central part surrounded by a peripheral part and are of two types:

Type 1: The central part is composed of a single reservoir of a drug with or without an additional osmotic solute dispersed throughout a polymeric matrix, so that the drug is surrounded by the polymer as discrete small deposits.
The second peripheral part of these inserts comprises a covering film made of an insoluble semi-permeable polymer. The osmotic pressure against the polymer matrix causes its rupture in the form of apertures. Drug is then released through these apertures from the deposits near the surface of the device.\[53\]

Type 2: The central part is composed of two distinct compartments. The drug and the osmotic solutes are placed in two separate compartments, the drug reservoir being surrounded by an elastic impermeable membrane and the osmotic solute reservoir by a semi-permeable membrane. The second peripheral part is similar to that of type 1. The tear diffuse into the osmotic compartment inducing an osmotic pressure that stretches the elastic membrane and contracts the compartment including the drug, so that the active component is forced through the single drug release aperture.\[53\]

B. Matrix systems
The second category, matrix system, is a particular group of insoluble ophthalmic devices mainly represented by contact lenses. It comprises of covalently cross-linked hydrophilic or hydrophobic polymer that forms a three dimensional network or matrix capable of retaining water, aqueous drug solution or solid components. The hydrophilic or hydrophobic polymer swells by absorbing water. The swelling caused by the osmotic pressure of the polymer segments is opposed by the elastic retroactive forces arising along the chains or crosslinks are stretched until a final swelling (equilibrium) is reached.

II. Soluble ocular inserts
These soluble inserts offer the advantage of being entirely soluble so that they do not need to be removed from their site of application, thus limiting the intervention to insertion only.

They can be broadly divided into two types, the first one being based on natural polymers and the other on synthetic or semi-synthetic polymers.

A. Natural polymers
The first type of soluble inserts is based on natural polymer.\[8\] Natural polymer used to produce soluble ophthalmic inserts is preferably collagen. The therapeutic agent is preferably absorbed by soaking the insert in a solution containing the drug, drying, and re-hydrating it before use on the eye. The amount of drug loaded will depend on the amount of binding agent present, the concentration of the drug solution into which the composite is soaked as well as the duration of the soaking. As the collagen dissolves, the drug is gradually released from the interstics between the collagen molecules.

B. Synthetic and semi-synthetic polymer
The second type of soluble insert is usually based on semi-synthetic polymers (e.g., cellulose derivatives)\[41\] or on synthetic polymers such as polyvinyl alcohol.\[41,42\] A decrease of release rate can be obtained by using Eudragit, a polymer normally used for enteric coating, as a coating agent of the insert\[40,41\]. Saettone et al.\[40\] have observed in rabbits that Eudragit coated inserts containing pilocarpine induced a miotic effect of a longer duration, compared to the corresponding uncoated ones. However, the inherent problems encountered with these soluble inserts are the rapid penetration of the lacrimal fluid into the device, the blurred vision caused by the solubilization of insert components and the risk of expulsion due to the initial dry and glassy consistency of the device.\[41\] Ethyl cellulose, a hydrophobic polymer, can be used to decrease the deformation of the insert and thus to prevent blurred vision.\[25,42\] As for the risk of expulsion, several authors have incorporated carbomer, a strong but well tolerated bio-adhesive polymer.\[25,43\]
The soluble inserts offer the additional advantage of being of a generally simple design, of being based on products well adapted for ophthalmic use and easily processed by conventional methods. The main advantage is decreased release rate, but still controlled by diffusion.

III. Bio-erodible ocular inserts
These inserts are formed by bio-erodible polymers (e.g., cross-linked gelatin derivatives, polyester derivatives) which undergo hydrolysis of chemical bonds and hence dissolution. The great advantage of these bio-erodible polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis and by addition of anionic or cationic surfactants.

A cross-linked gelatin insert was used by Attia et al. [42] to increase bioavailability of dexamethasone in the rabbit eye. The dexamethasone levels in the aqueous humor were found to be four-fold greater compared to a dexamethasone suspension.

However, erodible systems can have significantly variable erosion rates based on individual patient physiology and lachrimation patterns, while degradation products and residual solvents used during the polymer preparation can cause inflammatory reaction.

In the following paragraphs, some important ocular inserts are discussed which are available commercially (SODI) or in advanced states of development (collagen shields, Ocufit, NODS, and Minidisc).

Soluble ophthalmic drug insert
Soluble ophthalmic drug insert (SODI) is a small oval wafer, which was developed by soviet scientists for cosmonauts who could not use eye drops in weightless conditions.

SODI is together with the collagen shields, the first modern revival of the gelatin ‘lamellae’, which disappeared from pharmacopoeias in the late forties. The SODIs are the result of a vast collaborative effort between eminent Russian chemists and ophthalmologists, and led eventually (in 1976) to the development of a new soluble copolymer of acrylamide, N-vinylpyrrolidone and ethyl acrylate (ratio 0.25: 0.25: 0.5), designated ABE [9]. A comparison of medicated eye films prepared with different polymers, showed that ABE produced the highest concentration of drugs in rabbit ocular tissues.[10]

After large-scale preclinical and clinical testing, the ABE copolymer was used for the industrial manufacture of the SODI in the form of sterile thin films of oval shape (9 x 4.5 mm, thickness 0.35 mm), weighing 15-16 mg, and color-coded for different drugs (over 20 common ophthalmic drugs, or drug combinations). After introduction into the upper conjunctival sac, a SODI softens in 10-15 s, conforming to the shape of the eyeball. In the next 10-15 min the film turns into a polymer clot, which gradually dissolves within 1 h while releasing the drug. The sensation of an ‘extraneous body’ in the eye disappears in 5-15 min.[11]

Collagen shields
Collagen is the structural protein of bones, tendons, ligaments, and skin and comprises more than 25% of the total body protein in mammals. This protein, which is derived from intestinal collagen, has several biomedical applications, the main of which is probably catgut suture.

Bloomfield et al. are credited for first suggesting, in 1977 and 1978, the use of collagen inserts as tear substitutes [7] and as delivery systems for gentamicin.[8] They compared the levels of gentamicin in tears, cornea, and sclera of the rabbit eye after application of a collagen insert, drops, an ointment or following subconjunctival administration. After 3 h, they found that the collagen insert gave the highest concentration of gentamicin in the tear film and in the tissue.

Other treatments using collagen shields impregnated with gentamicin and dexamethasone have been described.[13] In rabbits, aqueous humor levels of dexamethasone and gentamicin achieved with collagen shields were compared to subconjunctival injections. The authors concluded that the use of collagen shields impregnated with gentamicin-dexamethasone was comparable to the subconjunctival delivery of these drugs over a 10-h period.

Some drawbacks of these devices, however, need mentioning. To apply the collagen shield, the cornea is anaesthetized while the physician uses a blunt forceps to insert the hydrated or unhydrated shield. Contrary to medicated contact lenses, collagen shields often produce some discomfort and interfere with vision. In rabbits, collagen shields have been found to exacerbate ulcerations of alkali-burned corneas.[14]

A new preparation referred to as collasomes consists of small pieces (1 mm x 2 mm x 0.1 mm) of collagen suspended in a 1% methylcellulose vehicle. Kaufman and co-workers [15] recently reported that collasomes provide the same therapeutic advantages of the shields (high and sustained levels of drugs and/or lubricants to the cornea), while not presenting their disadvantages.

Ocufit
The Ocufit is a sustained release, rod shaped device made of silicone elastomer,[16] patented in 1992 and currently developed by Escalon Ophthalmics Inc. (Skillman, NJ). It was designed to fit the shape and size of the human conjunctival fornix. Accordingly, it does not exceed 1.9 mm in diameter and 25-30 mm in length, although smaller sizes for children and newborn babies are planned. The superiority of the cylindrical shape can be traced in an earlier paper by Katz and Blackman. They reported the effect of the size and
shape of the inserts on tolerance and retention by human volunteers.[17] These workers found that expulsion of rod-shaped units was significantly (P < 0.01) less frequent than expulsion of oval, flat inserts. A typical example of a rod-shaped insert is the Lacrisert (Merck and Co., Inc.), a cellulosic device used to treat dry-eye patients.[18]

The insoluble Ocufit reportedly combines two important features, long retention and sustained drug release. When placed in the upper fornix of volunteers, placebo devices were retained for 2 weeks or more in 70% of the cases. Moreover, active disease (bacterial, allergic and adenoviral conjunctivitis, trachoma, episcleritis, anterior uveitis, corneal ulcers or scars) did not overly affect the ability of the patients to retain the inserts. Tetracycline-loaded inserts released in vitro 45% of the drug over the 14-day period with an initial burst in the first day followed by a constant rate over the remaining period.

The **Minidisc ocular therapeutic system**

This monolytic polymeric device, originally described by Bawa et al. (Bausch and Lomb, Rochester, New York)[19] and referred to as Minidisc ocular therapeutic system (OTS), is shaped like a miniature (diameter 4-5 mm) contact lens, with a convex and a concave face, the latter conforming substantially to the sclera of the eye. The particular size and shape reportedly allow an easy placement of the device under the upper or lower lid without compromising comfort, vision or oxygen permeability. When compared with another standard insert, the Lacrisert, the Minidisc was reported to require less time and less manual dexterity for insertion.[21] Different versions of the device have been evaluated, such as, non-erodible hydrophilic, non-erodible hydrophobic and erodible.

In vitro tests showed that the hydrophilic OTS (based on polyhydroxymethyl methacrylate) released sulfisoxazole for 118 h, while the hydrophobic unit (based on a proprietary Bausch and Lomb pre-polymer) released gentamicin sulfate for more than 320 h. Clinical trials on placebo units demonstrated that the devices were well tolerated when placed either in the upper or lower conjunctival sac. In the eyes of healthy volunteers, the hydrophilic OTS released sulfisoxazole continuously for 3 days.[19] Further studies conducted on the hydrophilic Minidisc[20] showed that gentamicin sulfate was efficiently released in rabbit eyes for 14 days.

**THE ‘NEW OPHTHALMIC DELIVERY SYSTEM’**

The ‘New ophthalmic delivery system’ (NODS), originally patented by Smith and Nephew Pharmaceuticals Ltd in 1985, is a method for delivering precise amounts of drugs to the eye within a water-soluble, drug-loaded film.[21] The device consists of a medicated flag (4 mm x 6 mm, thickness 20 µm, weight 0.5 g) which is attached to a paper-covered handle by means of a short (0.7 mm) and thin (3-4 µm) membrane. All components (flag, membrane, and handle) are made of the same grade of water-soluble polyvinyl alcohol (PVA). The devices are individually packaged and sterilized by gamma irradiation. For use, the flag is touched onto the surface of the lower conjunctival sac. The membrane proceeds to dissolve rapidly releasing the flag, which swells and dissolves in the lacrimal fluid, delivering the drug. This relatively simple device appears to offer most of the advantages specified earlier in the advantages of ocular insert, except the possibility of releasing drug at a slow, pre-determined rate.[22]

When evaluated in humans, the NODS produced an 8-fold increase in bioavailability for pilocarpine with respect to standard eye drop formulations.[23] The pre-conveal retention of experimental PVA matrices containing 99mTc-labelled sulphur colloid [12] or 99mTc-diethylene-triaminepentacetic acid [24] was studied in man using the gamma scintigraphy technique. In the latter study, the rate of clearance of the marker was investigated in relation to the duration of pharmacological effect of pilocarpine (also incorporated into the matrix). These studies showed the NODS system to have a t1/2 of approximately 8 min for the film itself and 7 min for the water-soluble drug incorporated into the film, which compares to about 3 s for an aqueous solution of a water-soluble drug.

Currently investigated ocular inserts containing anti-glaucoma, antibacterial, anti-inflammatory or anti-viral drugs for ocular delivery are presented in Table 2.

**CONCLUSION**

The solid drug-releasing devices, in spite of the advantages demonstrated by extensive investigations and clinical tests, have not gained a wide acceptance by ophthalmologists. At this moment, the Ocusert systems are the only medicated inserts marketed in Western countries, and the acceptance of these devices has been, to the present date, far from enthusiastic. According to recent information the NODS project will not be further developed.[19] As said before, the commercial failure of inserts has been attributed to psychological factors, such as the reluctance of ophthalmologists and patients to abandon the traditional liquid and semi-solid medications, to price factors and to occasional therapeutic failures (e.g., unnoticed expulsion from the eye, membrane rupture, etc.).

The manufacturers of ocular dosage forms appear to show a continued preference for dropper-dispensed medications. Many drugs already in use have been reformulated in new longer acting liquid dosage forms, such as an ‘in situ’ gelling preparation of timolol (Timoptic XE, Merck and Co., Inc.), Semisolid gel type preparations (i.e., Pilopine HS gel, Alcon Laboratories, Inc.), etc., do not seem to occupy an equally important position in the manufacturers’ preferences.

Still, the prolonged, constant-rate release pattern achievable by inserts of the Ocusert and Ocufit type can be considered...
as the most desirable condition for long term therapy, both because of efficacy as well as the reduction of ocular and systemic side-effects. Shorter-acting devices, such as the collagen shields which could effectively deliver gentamicin-dexamethasone combinations, might prove useful for single application after intraocular surgery or other conditions.

Although at this time the advantages of solid ocular dosage forms are understood and appreciated, marketing strategies prevent their further commercialization, unless, of course, their potential use could be extended to applications other than long-term glaucoma or trachoma treatment, or short-term medication after ocular surgery. Nevertheless, recent research suggests a renewed interest based on the efficacy of subconjunctival and intra-vitreal drug delivery devices.

REFERENCES


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### Table 2: Drugs used in ocular inserts

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Drug delivery system</th>
<th>Carriers</th>
<th>Effects</th>
<th>Animal model</th>
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<tr>
<td>Anti-glaucoma Pilocarpine</td>
<td>Soluble insert</td>
<td>HPC/D-lactose/glycercol palmi-</td>
<td>Increased lipophilic character and coating result in an increased pilocarpine bioavailability.</td>
<td>Rabbit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stearate/Eudragit RS PVDF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilocarpine[46] 14%</td>
<td>Soluble insert</td>
<td>PVDF</td>
<td>2.5-fold increased AUC over the aqueous solution.</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Pilocarpine[47] 11%</td>
<td>Soluble insert</td>
<td>HA; HAE</td>
<td>Increased bioavailability of pilocarpine compared to the standard aqueous vehicle.</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Pilocarpine[48] 14%</td>
<td>Bioerodible insert</td>
<td>PVDF</td>
<td>Delayed and decreased peak concentration of pilocarpine in general circulation compared to aqueous solution.</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Pilocarpine 20 µg/h and 40µg/h release[49]</td>
<td>Insoluble insert</td>
<td>Ethylene vinyl acetate; alginate</td>
<td>Pilocarpine levels remained over therapeutic level for 7 days.</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Timolol[50] 0.5%</td>
<td>Soluble insert</td>
<td>HPC/Eudragit RS</td>
<td>Sustained release of timolol in tear fluid and decreased systemic peak concentration with coated and uncoated inserts compared to the aqueous solution.</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Anti-bacterial gentamicin[51] 11%</td>
<td>Soluble insert</td>
<td>Collagen</td>
<td>After 3 h, collagen insert gives the highest tear film and tissue concentration of gentamicin compared to ointment, aqueous solution, and subconjunctival route.</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Gentamicin + dexamethasone[51]</td>
<td>Soluble insert</td>
<td>Collagen</td>
<td>Collagen shields impregnated with gentamicin-dexamethasone are comparable to the subconjunctival delivery of these drugs over a 10-h period.</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Anti-inflammatory dexamethasone[52]</td>
<td>Soluble insert</td>
<td>PVAL; HPC;EC; CAP; Eudragit</td>
<td>Increased dexamethasone concentration in eye tissues compared to suspension.</td>
<td>Rabbit</td>
</tr>
</tbody>
</table>

AUC: area under the curve; HA: hyaluronic acid; HAE: ethyl ester hyaluronic acid; HPC: hydroxypropylcellulose; PVMA-n-butyl half ester of poly(methyl vinyl ether/maleic anhydride); CAP: cellulose acetophtalate; EC: ethyl cellulose; HPC: hydroxypropylcellulose; PVAL: polyvinyl alcohol

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