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PATENT LITERATURE REVIEW OF OPHTHALMIC INSERTS

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ABSTRACT

In the area of topical ocular administration, important efforts concern the design and the conception of new ophthalmic drug delivery systems able to prolong the residence time. The use of inserts, which are solid devices to be placed in the cul-the-sac or on the cornea represents one of the possibilities to reach increased residence time. These solid ophthalmic devices present the advantage of avoiding a pulsed release due to multiple applications.

In the scientific literature, patents are often not mentioned resource and this remark is particularly true in the case of ophthalmic inserts: there is no review yet describing patented ophthalmic inserts. Thus the review presented herein essentially takes into account patented ophthalmic inserts. The solid ophthalmic devices are classified into three major categories based upon their solubility behavior: the insoluble, the soluble and the bioerodible inserts. When necessary, these groups are subdivided into more specific sub-groups. The discussion essentially takes into account the design, the conception, the release mechanisms, the in vivo and in vitro assays, the limitations, and the therapeutic rationale for their use.

INTRODUCTION

Traditional topical ophthalmic formulations have poor bioavailability because of rapid precorneal elimination, conjunctival absorption, solution drainage by gravity, induced lacrimation and normal tear turnover [1]. This leads to frequent instillations of concentrated medication to achieve a therapeutic effect [2-3]. Systemic absorption of the drug and additives drained through the nasolacrimal duct may result in some undesirable side effects.

These observations suggest that increasing the contact time between drug and corneal tissue could both be beneficial for patient compliance and improve the therapeutic effect. The main approaches investigated and practiced in sustained release ophthalmic formulations have led to the use of viscous preparations or inserts. Nowadays, ophthalmic viscous solutions are mostly aqueous solutions of the hydrogel type. Hydrogels are polymers that have the ability to swell in water or in aqueous solvent systems. The polymer structure is capable of forming a swollen gel phase which retains the solvent and which in the case of cross-linked polymers will not dissolve, regardless of the solvent [4].

Ophthalmic soft hydrogels belong to two separate groups: preformed hydrogels and *in situ* formed hydrogels. The first group includes components such as polyacrylic acid [5-9], cellulose derivatives [6-7;10-12] and a number of special compounds like the hyaluronate derivatives [13-18]. The *in situ* formed hydrogels can be divided into three subgroups depending upon their activation process, which can be the pH [19-27], the temperature [28-32] or the ionic concentration [33-36].

All of these ophthalmic preparations present some disadvantages. The amount of drug delivered during external application may vary despite accurate prescription: the drop size of commercial ocular medication or its volume is not uniform and those delivered is generally not correct [37]; moreover, the presence of a viscous vehicle can cause blurred vision [38] while the presence of additives such as preservatives may have undesirable side effect.

The information presently available suggests that solid ophthalmic dosage forms are more effective, requiring less frequent administration, avoiding pulsed release and diminishing the number of additives needed; these solid forms are usually named inserts. Over the last decade, an impressively large number of patents have been published in that field (Fig. 1) and the primary objective of the present review is to analyze and to categorize the various technologies proposed.

OPHTHALMIC INSERTS

Ophthalmic inserts are defined as sterile preparations, with a solid or semisolid consistency, and whose size and shape are especially designed for ophthalmic application. They are composed of a polymeric support containing or not drug(s), the latter being incorporated as a dispersion or a solution in the polymeric support. The inserts can be used for topical or systemic therapy. The main objective of the ophthalmic inserts is to increase the contact time between the preparation and the conjunctival tissue to ensure a sustained release suited to topical or systemic treatment. In comparison with the traditional ophthalmic preparations (i. e. eye drops) the solid ophthalmic devices present some advantages such as:

- Increasing contact time and thus improving bioavailability.
- Possibility of providing a prolonged drug release and thus a better efficacy.
- Reduction of systemic side effects and thus, reduced adverse effects.
- Reduction of the number of administrations and thus better patient compliance.
- Administration of an accurate dose in the eye and thus a better therapy.

In the field of ophthalmic inserts, the patent literature is an under-utilized source of information for two principal reasons: it is not always easy to appraise the proposed concepts properly and the dense legal style in which they are written makes their reading fastidious. Thus this review essentially takes in account the concepts proposed, the drug

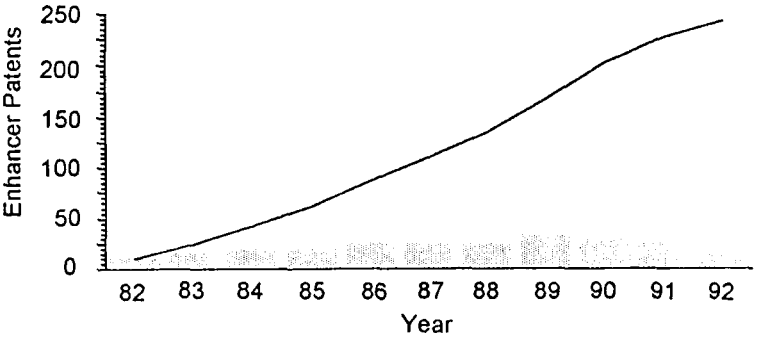

FIGURE 1: Estimation of the annual and cumulated number of insert patents during the last decade.

release mechanism and certain particularities of the ophthalmic inserts described in the patents published over the last decade.

A classification of patented ophthalmic inserts based primary upon their solubility behavior once placed is shown in Figure 2.

These inserts may be placed in the lower fornix and less frequently in the upper fornix or on the cornea; some of them can be inserted either in the lower or in the upper fornix.

INSOLUBLE OPHTHALMIC INSERTS

The insoluble inserts have been classified in three groups: the diffusional systems, the osmotic systems and the hydrophilic contact lenses. The two first classes (patents listed in Tables 1 and 3) include a reservoir in contact with the inner surface of the drug rate controller and supplying drug thereto. The reservoir contains a liquid, a gel, a colloid, a semisolid, a solid matrix or a carrier containing drug homogeneously or heterogeneously dispersed or dissolved therein. Carriers can be made of hydrophobic, hydrophilic, organic, inorganic, naturally occurring or synthetic material. The drug release profile is different for each class of inserts. The third class including the contact lenses is a particular group of insoluble ophthalmic devices. The insolubility of these devices is their main disadvantage, since they have to be removed after use.

DIFFUSIONAL INSERTS

The diffusional systems (Tables 1 and 2) are composed of a central reservoir of drug enclosed in specially designed semipermeable or microporous membranes which allow the drug to diffuse from the reservoir at a precisely determined rate. The drug release from such a system is controled by the lacrimal fluid permeating through the membrane until a sufficient internal pressure is reached to drive the drug out of the reservoir.

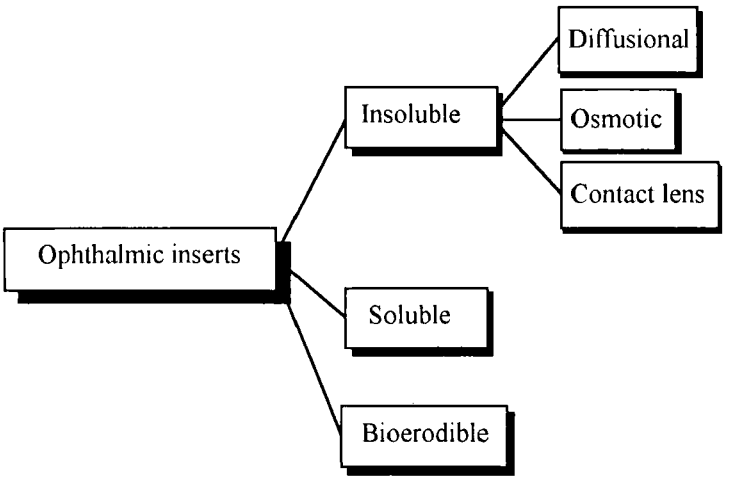

FIGURE 2: Classification of ophthalmic inserts.

TABLE 1: Diffusional ophthalmic inserts.

Author	Year	Patent #	Size mm	Shape	Assays	Spec.	Ref.
Darougar	1988	EP 262893	0.5-1 x 0.5-1 x 8-25	cylindrical	-	a	[39]
Darougar	1992	US 5,147,647	12 x 5 x 1	oval	in vivo remanence	a	[40]
Gould et al.	1972	US 3,641,237	not specified	cylindrical, film	in vitro release	-	[41]
Ness	1973	DP 2140557	4-20 x 1-10 x 0.1-1	various	-	-	[42]
Ness	1974	US 3,828,777	4-20 x 1-12 x 0.1-2	elliptic	-	-	[43]
Shell et al.	1981	US 4,304,765	2-20 x 1-15 x 0.1-4	various	in vitro water uptake	-	[44]
Shell et al.	1984	US 4,432,964	2-20 x 1-15 x 0.1-4	various	-	-	[45]
Shell et al.	1984	US 4,478,818	2-20 x 1-15 x 0.1-4	various	-	-	[46]
Zaffaroni	1980	US 4,186,184	2-20 x 1-15 x 0.1-4	various	in vivo release	b	[47]

[a] flexible, [b] unidirectional drug release device.

TABLE 2: Examples of components of diffusional inserts.

central reservoir	glycerin, ethylene glycol, propylene glycol, water, methylcellulose mixed with water, mixtures of propylene glycol monostearate and oils, gum tragacanth, sodium alginate, poly(vinylpyrrolidone), polyoxyethylene stearate, fatty acids.
microporous membrane	polycarbonates, polyvinyl chlorides, polyamides, polysulfones, polyvinyl acetates, polyamides, polysulfones, polyurethane, polyethers, acrylic resins, cellulose esters, crosslinked poly(ethylene oxide), crosslinked polyvinylpyrrolidone, crosslinked polyvinylalcohol.

These diffusional systems prevent a continuous decline in release rate through the utilization of a barrier membrane of fixed thickness. The release rate of these diffusional devices presents three distinct periods as shown in Figure 3: an initial usually high drug release rate (region A) corresponding to the establishment of an equilibrium between the reservoir and the eye surface; this rate decreases to a plateau corresponding to a steady drug release rate (region B), followed by a final decrease of the release rate corresponding to the exhaustion of the drug (region C). An illustration of such release kinetics is given by the Ocusert® (developed by Alza Corporation, Palo Alto, California) in which the first period lasts about 1 day and the second one 7 days; the third one has never been fully investigated because the drug concentration is beneath therapeutic levels [48-49].

The patent literature on diffusional ophthalmic inserts is generally concerned with improvements in the construction and the design of such inserts. These patents rarely relate in vivo or in vitro assays, so that it seems that the patented diffusional inserts are the fruit of a technological know-how rather than a real therapeutic need. In fact, the majority of devices described in the patents are designed for achieving a zero order release rate. Generally, these patents claim that to obtain a zero order release rate for the drug, it is preferable that the drug be only partially solubilized, so as to retain substantially the same thermodynamic activity of the drug throughout the release period. Moreover, for optimal results, the rate of diffusion of the drug through the semipermeable membrane should not exceed the rate of removal or clearance of the drug from the lachrymal fluid by eye tissues; this ensures that the drug delivery rate is controlled by diffusion through the membrane, which one can be controlled.

OSMOTIC INSERTS

The group of osmotic ophthalmic inserts (Tables 3 and 4) corresponds to a class of devices mostly described in the patent literature, rarely elsewhere. The osmotic inserts are generally composed of a central part surrounded by a peripheral part. The first central part can be composed of a single reservoir or of two distinct compartments. In the first case, it is composed of a drug with or without an additional osmotic solute dispersed through a polymeric matrix, so that the drug is surrounded by the polymer as discrete small deposits. In the second case, 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 semipermeable membrane. The second peripheral part of these osmotic inserts comprises in all cases a covering film made of an insoluble semipermeable polymer.

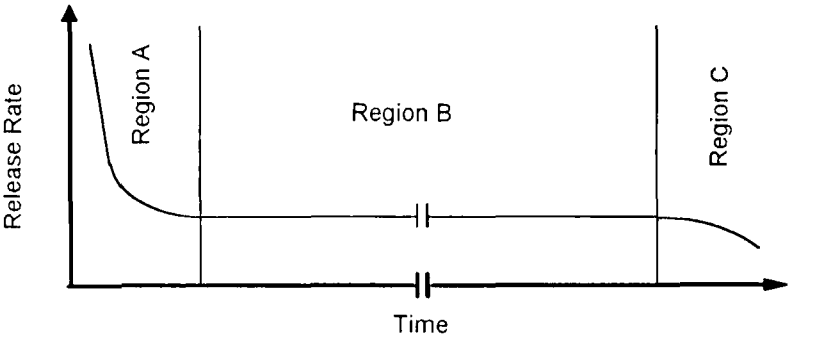

FIGURE 3: Schematic representation of the release rate from reservoir devices.

TABLE 3: Osmotic ophthalmic inserts.

Author	Year	Patent #	Size mm	Shape	Assays	Spec.	Ref.
Darougar	1988	EP 262893	0.5-1 x 0.5-1 x 8-25	cylindrical	-	a, b, c	[39]
Darougar	1992	US 5,147,647	12 x 5 x 1	oval	in vivo remanence	a, b, c	[40]
Gale et al.	1980	US 4,190,642	2-20 x 1-15 x 0.1-7.5	various	in vivo efficacy	d	[50]
Gale et al.	1977	DP 2633987	6-25 x 4-10 x 0.1-1	elliptic	in vitro release	e	[51]
Michaels et al.	1979	US 4,177,256	6-25 x 4-10 x 0.1-2	elliptic	in vitro release	f	[52]
Sanders et al.	1990	US 4,959,217	40 x 1.4 x 0.44	oval	in vitro release	g	[53]
Sanders et al.	1987	EP 246653	40 x 1.4 x 0.44	oval	in vitro release	g	[54]
Shell et al.	1981	EP 037622	2-20 x 1-15 x 0.1-7.5	various	in vitro release	d	[55]
Shell et al.	1981	US 4,303,637	2-20 x1-20 x 0.1-7.5	various	in vitro release	d, f	[56]
Shell et al.	1981	US 4,304,765	2-20 x 1-15 x 0.1-4	various	-	-	[57]
Shell et al.	1984	US 4,432,964	2-20 x 1-15 x 0.1-4	various	-	-	[45]
Shell et al.	1984	US 4,478,818	2-20 x 1-15 x 0.1-4	various	-	-	[46]
Wong	1988	US 4,786,500	various	rectangle	-	h, i	[58]
Zaffaroni et al.	1977	US 4,036,227	16 x 6.75 x 4.2	elliptical	in vitro release	b, j	[59]
Zaffaroni	1980	US 4,186,184	2-20 x 1-15 x 0.1-4	various	-	-	[47]

[a] two compartments, [b] single aperture, [c] flexible, [d] encapsulated drugs, [e] for a non ionic drug, [f] micronized drug, [g] for hydrophilic macromolecules , [h] multilayer system, [i] unidirectional release, [j] peripheral bioerodible layer.

TABLE 4: Examples of components of osmotic inserts.

water-permeable matrix	**ethylene-vinyl esters copolymers** ester, acetate, hexanoate, propionate, butyrate. **divers** plasticized polyvinyl chloride, plasticized polyamides, polyisoprene, polyisobutylene, polyethylene, cross linked polyvinylpyrrolidone, polyurethane.
semipermeable membrane	**cellulose acetates derivatives** cellulose acetate, plasticized cellulose triacetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate phthalate, cellulose acetate succinate. **divers** ethylene-vinyle acetate, highly plasticized polyvinyl chloride, polyesters of acrylic and methacrylic acid, polyvinylalkyl ethers, polymeric epoxides, polystyrenes.
osmotic agents	**inorganic** magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfate, calcium sulfate, potassium phosphate monobasic, potassium phosphate dibasic. **organic** calcium lactate, magnesium succinate, tartaric acid, acetamide, choline chloride. **carbohydrates** sorbitol, mannitol, glucose, sucrose, lactose.

The release of the drug is different for the system including two distinct compartments (EP 262893 [39] and US 5,147,647 [40]) and for that having a single central reservoir (all others patented systems). The release of drug from systems having a central reservoir subdivided into two compartments starts as soon as the device is placed in the aqueous environment of the eye; the tears 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. Thus, these systems are characterized by two distinct compartments and a single aperture having a very small diameter (the US 4,036,227 patent [59] describes an ophthalmic insert of this category having an aperture diameter lesser than 15 μm) which may become blocked when brought in contact with the eye environment. The described osmotic insert can induce a zero order drug release in vitro, but no in vivo test are reported. The release of drug from a system having a unique central reservoir presents two distinct release characteristics: an osmotic and a diffusional release. The release starts as soon as the insert is placed in the ocular environment. The tear fluid diffuses to the peripheral deposits through the semipermeable polymeric membrane, wets them and induces their dissolution; thus as long as the fluid imbibes the deposits, it continuously dissolves the solutes and progressively reaches other deposits. The solubilized deposits generate a hydrostatic pressure against the polymer matrix causing its rupture under the form of apertures. Drug is then released through these apertures from the deposits near the surface of the device which is against the eye, by the sole hydrostatic pressure. This corresponds to the osmotic part characterized by a zero order drug release profile. Ideally, the drug is continuously released from the osmotic insert by the increasing formation of apertures in the device forming a lattice of composition dispensing paths in the polymer on all sides of the insert. In fact, the paths are interconnected, forming tortuous microchannels of irregular shapes and size causing a second drug release corresponding to a diffusional

non-constant release. Thus, the release profile is quite similar to the one of diffusional systems as shown in Figure 3. In the US 4,177,256 patent [52] three distinct periods are observed: a 22 hours initial phase of rapid release (region A on the graph of the Figure 2) followed by a second period corresponding to a steady state release lasting about 6-7 days (region B) and finally the third period characterizing by a decreasing drug concentration (region C).

CONTACT LENSES

The group of contact lenses (Table 5) is certainly one of the classes of ophthalmic inserts that will expand owing to continued progress in polymer chemistry which is the driving force behind the rapid development of this type of inserts. However in the case of drug administration, there are not many examples to be found in the patent literature. Actually, a classification for contact lenses has been proposed by Refojo [60] who subdivided the contact lenses in five groups: rigid, semi-rigid, elastomeric, soft hydrophilic and biopolymeric. Because of the limited use of these devices for drug administration reported in the patents literature, all the contact lenses designed or potentially conceivable are discussed together.

Contact lenses are shaped structures. The coherent system is a covalently crosslinked hydrophilic or hydrophobic polymer that forms a three dimensional network or matrix capable of retaining water, aqueous solution or solid components. The polymeric network consists in repeating units of the same or different monomers that form long chains, joined together by internal bridges or cross-links that are responsible for the coherent structure of the system. This crosslinked structure cannot dissolve, but it will swell by absorbing water. The tendency to swell, caused by the osmotic pressure of the polymer segments is opposed by the elastic retractive forces arising along the chains as cross links are stretched until a final swelling is reached; this is called the equilibrium swelling of the gel under the given conditions. The contact lenses are the only class of ophthalmic inserts that have the ability to correct any refractive errors the patient may have and thereby provide improved visual acuity while the medication is being administered and if correcting vision is not necessary, the contact lens does not have to cover the entire cornea.

The drug incorporation into contact lenses depends on wether their strucutre is hydrophilic or non-hydrophilic. When a hydrophilic contact lens (including 35 to 80 % water) is soaked in a drug solution, it absorbs the drug, but does not give a delivery as precise as that provided by other non-soluble ophthalmic system, because the amount of drug, the soaking time of the contact lens and the drug concentration in the soaking solution contribute markedly to differences in drug release, so that it is often necessary to determine the drug concentration before using it for drug release. The drug release from such a system is generally very rapid at the beginning, and then declines exponentially with time [66]. Several processes are described in the patent literature which enable to decrease the release rate and/or to ensure a precise drug content. These processes consist in incorporating the drug homogeneously during the manufacture (US 3,786,812 [65]), in decreasing the hydrophilicity by adding a hydrophobic component (EP 219207 [62;63]), in decreasing the release rate of the drug by introducing some component capable of bringing about such a decrease (US 4,668,506 [61] and US 4,931,279 [64]) or in introducing the drug into the monomer mixture and polymerizing the monomers in the presence of the drug (EP 219207 [62;63]). In the US 4,668,506 [61] an interesting release assay is described: it compares a diffusional system (Ocusert®, Alza Corporation), a hydrophilic soft contact lens (Permalens®, Bausch & Lomb) with the device described in this patent. The release time

TABLE 5: Contact lenses.

Author	Year	Patent #	Assays	Spec.	Ref.
Bawa	1987	US 4,668,506	in vitro release	c	[61]
Bawa	1987	EP 219207	in vitro release	d, e	[62-63]
Bawa	1990	US 4,931,279	-	f	[64]
Neefe	1974	US 3,786,812	-	a, b	[65]

[a] incorporation of drug during the manufacture, [b] rechargeable by immersion in drug solution, [c] includes an amino acid polymer, [d] includes a hydrophobic polymer, [e] multilayer system, [f] includes an ion-exchange resin.

for both the described device and the diffusional system extends over about one week and only over about two hours with the soft hydrophilic contact lens. These results are obtained in buffer solutions and distilled water but no correlation with an in vivo release is provided. In fact, the ophthalmic drug administration using contact lenses presents two main problems. Firstly, the patient or wearer of contact lenses will obviously have to handle the lenses, and the cleaning and rinsing procedures can induce a deterioration of the devices and especially a loss of drug. The second problem is the cost of medicated contact lenses. In the future, it seems conceivable to develop contact lenses for drug administration designed to be worn continuously during the entire treatment period. For example, the patent WO 8805060 [67] describes a corrective contact lens that can be worn continuously for about 30 days. Concerning the high cost of contact lenses, it should be mentioned that disposable contact lenses have been commercially available for five years already and it should be possible to incorporate a drug into such devices at an acceptable cost. Contact lenses have certainly good prospects as ophthalmic drug delivery systems.

SOLUBLE OPHTHALMIC INSERTS

Soluble inserts correspond to the oldest class of ophthalmic inserts. They offer the great advantage of being entirely soluble so that they do not need to be removed from their site of application, thus limiting the interventions to insertion only. The patent literature concerning this very important class of ophthalmic inserts proposes a variety of devices which have been evaluated both trough in vivo and in vitro tests. They can be broadly divided into two types, the first one being based on natural polymers and the other on synthetic or on semisynthetic poymers.

NATURAL POLYMERS

The natural polymers used presently to produce soluble ophthalmic inserts (Tables 6 and 7) include the oldest components of ophthalmic inserts described in the literature: collagen. This component has already been described for ophthalmic lamellae already in the 1948 British Pharmacopeia. Inserts containing natural polymer were initially

TABLE 6: Soluble inserts including natural polymers.

Author	Year	Patent #	Size mm	Shape	Assays	Spec.	Ref.
Erwin	1990	WO 9012564	14.5 x 14.5 x 0.05	hemispheric	in vivo treatment in vitro dissolution	a, b	[68]
Fyodorov et al.	1990	US 4,913,904	not specified	hemispheric	in vivo treatment	a, b	[69]
Shah et al.	1992	EP 486294	thickness: 0.5-1.0	not specified	in vitro dissolution in vitro water uptake	a, c	[70]
Yamamoto et al.	1993	WO 9300890	not specified	-	in vitro release in vitro drug uptake	a, b	[71]

[a] covering system, [b] collagen and derivatives, [c] chitosan and derivatives.

TABLE 7: Examples of components of soluble inserts including natural polymers.

soluble natural polymers	**collagen derivatives** collagen type I; II; III and IV, cross linked collagens **chitosan derivatives** chitosan base, acetylated chitosan
additives	**binding agents** anionic: carboxylated collagens, sodium alginate, carboxylated celluloses, polyacrylic acid, pectin. cationic: aminated collagen, quaternized celluloses, chitin, chitosan **plasticizers** water, polyethylene glycol, propylene glycol

developed by Fyodorov as corneal bandage following surgical operation and eye disease. The coverings with systems including collagen make it possible to reduce the number of post-operative complications, accelerate healing of injured tissues of the eye (US 4,913,904). All the devices presented in Table 6 correspond to covering systems which can be used for releasing medical agents.

The therapeutic agent is preferably absorbed by soaking the insert in a solution containing the drug, drying and rehydrating it before use on the eye. The insert can also be rehydrated just before use by soaking in a solution containing the drug. It will be realized that the amount of drug which will be loaded onto the composite will depend upon the amount of binding agent that is present, upon the concentration of the drug solution into which the composite is soaked, as well as the duration of the soaking. It is within the skill of those "versed in the art" to determine the proper amount of loading depending upon the release profile and instantaneous dosage that is desired for the drug at the site of delivery. As the collagen dissolves, the drug is gradually released from the interstices between the collagen molecules. Actually, the drug release profile is comparable to that obtained with hydrophilic contact lenses. The patents concerned with

soluble inserts listed in Table 6 are all aimed at improving the release profile and the drug loading. In the case of collagen, it has thus been proposed to adjust the net charge of the collagen depending of the type of drug that is to be incorporated (WO 9012564 [68]). Another chemical modifications of the collagen is to decrease its hydrophilic nature by incorporating binding agents during preparation to create cross-links or introduce covalent links into the collagen structure (WO 9300890 [71]).

SYNTHETIC AND SEMISYNTHETIC POLYMERS

The ophthalmic inserts most frequently described in the patent literature are soluble ophthalmic inserts containing (semi)synthetic polymers (Tables 8 and 9). Both the production methods and trial results are described. These soluble inserts offer the additional advantages of being of a generally simple design, of being based on products well adapted for ophthalmic use and easily processed by conventional methods (slow evaporation, extrusion, compression or injection molding).

The release of the drug from such systems is characterized by two distinct phases: the first one corresponds to the penetration of tear fluid into the insert that induces a high release rate of drug by diffusion and forms a gel layer around the core of the insert; this external gelification induces then the second period corresponding to a decreased release rate, but still controled by diffusion. The drug release from such devices which are initially dry and glassy is, however, also affected by many factors other than drug diffusion. These include penetration of the aqueous solvent into the matrix, swelling of the matrix, dissolution of the drug and the polymers, and relaxation of the polymeric chain. In three patents (US 4,179,497 [74], EP 108661 [77] and US 4,343,787 [78]) ophthalmic inserts are described which are essentially composed of soluble cellulose derivatives including a non-negligible water content (up to 30%). The presence of this water is certainly unfavourable from the standpoint of stability of the drug, but offers the advantage that the insert can be sterilized by exposure to gamma radiation without the cellulose component being altered. The inherent problems of these soluble inserts are the rapid penetration of the lachrymal 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 constitution, and several patents address these disadvantages. A decreased release rate is obtained by using as a component of the matrix a polymer normally used for enteric coatings (EP 077261 [72] and US 4,730,013 [73]) or by introducing a suitable amount of hydrophobic polymer capable of diminishing the tear fluid penetration and thus of decreasing the release of the drug without modifying the solubility of the insert when added in the proper proportion. The blurred vision has been improved by two different methods, the first one involves the use of low molecular weight polymers (US 4,730,013 [73]) and the second one theuse of a hydrophobic polymer decreasing the deformation of the insert (EP 400677 [75]). The last problem often encountered with soluble inserts, which is the risk of expulsion due to their initially glassy constitution, is drastically decreased by the adjunction of a strong but well-tolerated bioadhesive polymer (EP 400677 [75]).

BIOERODIBLE OPHTHALMIC INSERTS

The bioerodible inserts (Tables 10 and 11) are composed of matricial homogeneous dispersion of a drug included or not into a hydrophobic coating which is substantially impermeable to the drug. The main components used for the production of this type of

TABLE 8: Soluble inserts including synthetic polymers.

Author	Year	Patent #	Size mm	Shape	Assays	Spec.	Ref.
Bondi et al.	1982	EP 077261	4 x 5-15 x 0.5-1.5	rectangular	in vivo blurred vision	a, b	[72]
			1.0-1.5 x1.0-1.5 x 5	cylindrical	-		
Bondi et al.	1988	US 4,730,013	4 x 5-15 x 0.5-1.5	rectangular	in vivo blurred vision	a, b	[73]
			1.0-1.5 x 1.0-1.5 x 5	cylindrical	in vivo release		
					in vitro dissolution		
Cohen et al.	1979	US 4,179,497	4 x 5-15 x 0.5-1.5	various	in vivo myotic resp.	a, c	[74]
			1-1.5 x 1-1.5 x 10	cylindrical	in vivo remanence		
					in vitro water uptake		
Gurtler et al.	1993	EP 561695	1.5 x 1.5 x 5	cylindrical	in vivo remanence	d, e	[75]
					in vivo expulsion		
Haddad et al.	1974	US 3,870,791	3-7 x 3-7 x 0.3	disk	in vivo myotic resp.	a	[76]
Harwood	1983	EP 108661	4 x 5-15 x 0.5-1.5	rectangular	in vitro sterilization	c, f	[77]
			1.0-1.5 x1.0-1.5 x 5	cylindrical			
Katz	1982	US 4,343,787	various	various	-	b, g	[78]
Khromov et al.	1976	US 3,978,201	3-5 x 6-9 x 0.2-0.6	rectangular	-	h	[79]
Urquhart	1977	DP 2648737	thickness: 0.5-1.25	hemispheric	in vivo release	h	[80]
				elliptical	in vitro release		

[a] comparative efficacy, [b] includes an enteric coating polymer, [c] includes water, [d] includes a bioadhesive polymer, [e] includes a hydrophobic polymer, [f] sterilization method, [g] no drug, [h] original polymeric support.

TABLE 9: Examples of components of soluble inserts including synthetic polymers.

soluble synthetic polymers	**cellulose derivatives** hydroxypropylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose. **divers** polyvinyl alcohol, ethylene-vinyl acetate copolymer, hydoxyalkyl acrylate derivatives.
additives	**plasticizers** water, polyethylene glycol, propylene glycol, glycerine, hydroxypropyl sucrose. **enteric coating polymer** hydroxypropylmethylcellulose phtalate, cellulose acetate phtalate, hydroxypropylmethyl cellulose acid succinate. **complexing agents** polyvinylpyrrolidone. **bioadhesive** polyacrylic acid, methylhydroxyethylcellulose

TABLE 10: Bioerodible ophthalmic inserts.

Author	Year	Patent #	Size mm	Shape	Assays	Spec.	Ref.
Baker et al.	1974	DP 2363963	various	various	in vitro release	c	[81]
Bawa	1992	US 5,137,728	3-6 x 3-6 x 0.8-1.5	curved disk	in vivo release in vivo expulsion	d	[82]
Capozza	1982	US 4,322,323	5 x 8 x 2	various	in vitro release	e, f	[83]
Darougar	1988	EP 262893	0.5-1 x 0.5-1 x 8-25	cylindrical	-	a, b	[39]
Darougar	1992	US 5,147,647	12 x 5 x 1	oval	in vivo remanence	b	[40]
Heller et al.	1974	US 3,811,444	4-20 x 1-12 x 0.1-2	various	in vivo tolerance in vitro erosion rate in vitro erosion time	e, b, c	[84]
Higuchi et al.	1976	CA 989732	4-20 x 1-12 x 0.1-2	various	in vivo remanence in vitro erosion time	b, g	[85]
Michaels	1976	US 3,962,414	4-20 x 1-12 x 0.1-2	various	in vitro erosion rate liquid uptake	e, b, g	[86]
Shell et al.	1981	US 4,304,765	2-20 x 1-15 x 0.1-4	various	-	b	[43]
Shell et al.	1984	US 4,432,964	2-20 x 1-15 x 0.1-4	various	-	b	[45]
Shell et al.	1984	US 4,478,818	2-20 x 1-15 x 0.1-4	various	-	b	[46]
Zaffaroni	1980	US 4,186,184	2-20 x 1-15 x 0.1-4	various	in vivo release	b	[47]

[a] flexible, [b] reservoir, [c] multilayer, [d] asymmetrical shape, [e] matrix, [f] includes a surfactant, [g] micro capsules.

inserts are the so-called bioerodible polymers, i.e. materials that undergo hydrolysis of chemical bonds and hence dissolution; bioerosion is defined here as the property of a material to innocuously disintegrate or break down from a unit structure or entity, over a prolonged period of time, in response to the environment in the eye and particularly hydrolysis.

When the bioerosion process takes place, the geometry (shape and size) is modified and it is difficult to adequately control the release. The patent literature proposes various methods for controling the release. Thus in Eur. Pat. Appl. 262893 [39], the inventor suggests for overcoming this to use a dispersion of the drug concentrated in the outer layer of the device. But this idea of dispersing the medicinal agent essentially on the outer portion of the device presents two disadvantages. The first one is that the incorporation of the drug as defined in this patent certainly presents considerable problems of feasibility and reproducibility and the second one is that when such an insert releases the drug by bioerosion, there is a first phase characterized by a quite constant

TABLE 11: Examples of components of bioerodible inserts.

bioerodible polymers	**polyesters derivatives** poly(orthoesters) **polycarbonates derivatives** polyorthocarbonates **poly(carboxylic acid) derivatives** **crosslinked gelatin derivatives**
rate controlling membrane (bioerodible polymers)	**modified natural polymers** pectin, pectinic acid , gum arabic, gum gatthi, agar, carboxymethyl starch. **modified synthetic polymers** carboxymethyl cellulose, polystyrene sulfonic acid, polyvinyl sulfuric acid.
additives	**surfactants** anionic: sulfated derivatives (esters, amides, alcohols, ethers, carboxylic acid), sulfonated derivatives (aromatic and aliphatic), hydrocarbons derivatives, esters, amides, ethers), acylated polypeptides. cationic: alkylammonium derivatives (primary, secondary, tertiary and quaternary), benzylammonium salts. nonionic: esters of polyhydric alcohols, alkoxylated amines, esters and ethers of polyoxyalkylene glycols, alkalonamine fatty acid condensates. **plasticizers** epoxidized soy bean oil, glycerol monoacetate, polyethylene glycol, propylene glycol

release followed by a second phase where no drug is released any more from the device which continues to undergo bioerosion. A second method described in the DP 2363963 and US 3,811,444 patents [81; 84] involves the use of a device composed of two compartments containing the drug and separated by a third compartment: this insert construction improves drug release, but the absence of drug in the middle compartment will certainly induce a release profile with two distinct phases, the first one corresponding to the release from the peripheral compartment and the second one, after that the middle compartment has been bioeroded, corresponding to the release from the third compartment. Another possibility is suggested in the US 4,322,323 [83] patent which teaches the use of a surfactant for increasing or decreasing the rate of erosion of the device by influencing the transition state formed during the erosion of the polymer and thus concomitantly the release rate. Generally, anionic surfactants accelerate the erosion process and cationic surfactants slow it down. Another possibility is described in the US 3,962,414 and CA 989732 patents [85; 86] which teach the use of a bioerodible device including a reservoir. These bioerodible inserts are composed of an inner reservoir which is formed by a biodegradable matrix material having drug dispersed therein surrounded by a bioerodible matrix controlling the release rate of the drug to ensure a zero order release rate, but this is only a theoritical because no in vivo or in vitro assay is given which would demonstrate this zero order release. Another possibility for controlling drug release is described in the US 3,811,444 [84]: a six layer ophthalmic insert is provided, each layer being characterized by a different erosion rate, to control the release rate over the entire drug release process. The development of new bioerodible materials represents certainly a promising solution for improving the control of drug release. Successful bioerodible materials for ophthalmic use are the patented poly(orthoesters) and poly(orthocarbonates) [87-92]. The release of drug from such a

system is the consequence of the contact of the device with the tear fluid inducing a superficial bioerosion of the matrix, but the great advantage of these bioerodible polymers is the possibility of modulating their erosion rate by modifying their final structure during the synthesis.

CONCLUDING OBSERVATIONS AND FUTURE OUTLOOK

As mentioned in the introduction, the advantages offered by ophthalmic drug delivery devices are numerous, but the ophthalmic devices either soluble, insoluble or bioerodible described in the patent literature and in the scientific literature are not successful in modern therapy: only very few of them have gained commercial acceptance. This may be because prescribers have not yet acquired the conviction that the replacement of the traditional ophthalmic solutions and semi-solid preparations by these solid devices is beneficial for the patients. As other explanations for the poor success of the ophthalmic inserts one can mention the cost, the need to train both the prescribers and the patients to place correctly the inserts in the eyes and the reluctance to use an unfamiliar type of ophthalmic medication.

In the future, the use of solid ophthalmic devices will certainly increase owing to the development of new polymers, the emergence of new drugs having short biological half-lives or systemic side effects and the need to improve the efficacy of ophthalmic treatments by ensuring an effective drug concentration in the eye over an extended period of time.

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