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Merkli, Alain; Tabatabay, Cyrus A.; Gurny, Robert

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REVIEW

Use of Insoluble Biodegradable Polymers in Ophthalmic Systems for the Sustained Release of Drugs*

Alain Merkli, Cyrus Tabatabay, Robert Gurny
University of Geneva, School of Pharmacy, Geneva, Switzerland

Key words: Biodegradable polymers; Ophthalmic application; Glaucoma; Poly(ε-caprolactones); Poly(ortho esters); Copolymers of lactic and glycolic acids; Poly(alkyl cyanoacrylates); Polyanhydrides; Review

Abstract

Biomaterials have made a great impact on medicine. However, numerous challenges remain. The eye presents special challenges for drug delivery in the treatment of various ocular diseases. Many of the conventional therapeutic modalities have not adequately solved these problems. Medicated biodegradable devices used for drug delivery may offer several advantages over conventional ocular drug delivery methods. In this review, we discuss firstly the different mechanisms of erosion leading to the dissolution of the polymeric drug delivery systems. The principal investigation using polymer exhibiting a biodegradation (erosion type III) characterized by the cleavage of the polymeric chain, and the formation of small molecules is presented. These biodegradable polymers discussed include poly(alkyl cyanoacrylates), poly(lactic acids), poly(glycolic acids) and their copolymers, polycaprolactones, polyanhydrides and poly(ortho esters).

In the last part of this review the application of these biodegradable polymers to the treatment of glaucoma is presented.

Symbols Used

DETOSU	3,9-bis(ethylidene)-2,4,8,10-tetraoxaspiro (5.5) undecane
IOP	Intraocular pressure
5-FU	5-fluorouracil
5-FUR	5-fluorouridine
MMC	Mitomycin C
MP	Microparticles
MS	Microspheres
NC	Nanocapsules
NP	Nanoparticles
PBCA	Poly(butyl cyanoacrylate)
PCL	Poly(ε-caprolactone)
PCPH-SA	Copolymer of bis(carboxyphenoxy)hexane and sebacic acid
PCPP-SA	Copolymer of bis(carboxyphenoxy)propane and sebacic acid
PECA	Poly(ethyl cyanoacrylate)
PHCA	Poly(hexyl cyanoacrylate)
PIBCA	Poly(isobutyl cyanoacrylate)
PLA	Poly(lactic acid)
PLG	Poly(glycolic acid)
PLGA	Copolymer of lactic and glycolic acids
PMCA	Poly(methyl cyanoacrylate)
POE	Poly(ortho ester)
PTA-SA	Copolymer of terephthalic anhydride and sebacic acid
PVM/MA	Copolymer of methyl vinylether and maleic anhydrid

* Dedicated to Dr. h.c. Paul Reisen on the occasion of his 70th birthday

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Correspondence to: Prof. Robert Gurny, University of Geneva, School of Pharmacy, 30, quai Ernest-Ensermet, CH-1211 Geneva 4, Switzerland

1 Introduction

From the anatomical and physiological standpoint, the human eye is a very special organ in that it contains many different structures, characterized by specific physiological functions. They include for example non-vascularized areas such as the cornea and the crystalline lens or highly vascularized areas such as the ciliary processes and the choroid. As to the retina, it provides an area which is rich in synapses and which functions together with the optical nerve to transmit vision to the brain.

This very special organ has been subjected to much scientific research in the past aimed at remedying certain physiopathological dysfunctions. In this context, the development of special therapeutic systems is a subject which is attracting considerable attention for the treatment of certain eye diseases.

At the present time, a topical application into the conjunctival cul-de-sac is the most common mode of administration for an active principle. Ophthalmic preparations most frequently presently used are solutions, suspensions, gels or ophthalmic ointments. Although these preparations are highly effective, they are rapidly cleared from the eye surface, owing to the movements of the eyelid and to the drainage of the lacrimal fluid, thus significantly reducing the contact time between the preparation instilled or applied and the conjunctival and corneal epithelia (1, 2).

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Table 1 Classification of various techniques used for achieving controlled release of therapeutic agents

1. Physical systems
   - A. Reservoir systems with rate-controlling membrane
   - B. Reservoir systems without rate-controlling membrane
   - C. Matrix-based systems
     1. Dissolution in a polymeric matrix
        - a. Non-erodible
        - b. Swellable
        - c. Erodible
        - d. Degradable
     2. Physically dispersed throughout a polymeric matrix
        - a. Non-erodible
        - b. Swellable
        - c. Erodible
        - d. Degradable
   - D. Other physical systems
     1. Osmotic pumps
     2. Ion-exchange resins
2. Chemical systems
   - A. Chemical erosion of the polymeric matrix
     1. Heterogeneous
     2. Homogeneous
   - B. Biological erosion of the polymeric matrix
     1. Heterogeneous
     2. Homogeneous

To overcome these drawbacks, two approaches have been investigated. The first one consists in increasing the transcorneal passage by using absorption enhancers, such as surface-active agents and also, already from the seventies, by using pro-drugs. This technique further increases the duration of action and decreases the secondary systemic and ocular side-effects (3). In a second approach, use is made of viscosifiers which ensure a longer contact time between the active principle and the corneal and conjunctival epithelia.

These various improvements have, however, not provided a satisfactory answer to the problem of insufficient bioavailability of ophthalmic drugs. To achieve higher intraocular concentration levels, methods of a more invasive nature have been resorted to, such as for example subconjunctival or retro-ocular injections. In this context, a higher intraocular concentration can be achieved by direct injection into the vitreous cavity. These methods have remained in use despite the fact that the injections are often accompanied by clinical complications or by side-effects, and cause a real discomfort to the patient. This situation has stimulated research on the development of ophthalmic delivery systems of a more sophisticated nature, which would be capable of releasing an accurate amount of drug and of maintaining an optimal concentration over an extended period of time.

In Table 1, different systems are listed available for controlling and prolonging the action of therapeutic agents.

These systems have grown in importance during the recent years with the development of biodegradable polymers. Actually, and more particularly in the case of implants, the use of this type of polymers makes it possible to eliminate the step of removing the implant after completion of the release of the drug, which, in some applications, can represent a decisive advantage over other systems.

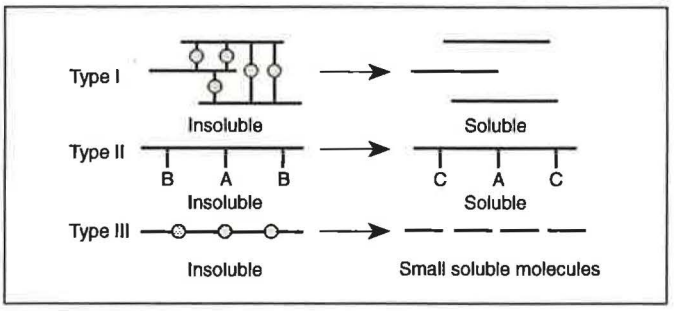

Fig. 1 Schematic representation of three different breakdown mechanisms ○: hydrolytically unstable bonds, A: hydrophobic substituent, B → C: hydrolysis, ionization, protonation (8)

This review is directed at updating existing information on various erodible polymers currently available and more particularly on the use of biodegradable polymers for ophthalmic drug delivery. These different polymers are classified according to their erosion mechanism.

2 Erodible Polymers

Firstly, the terms "bioerodible" and "biodegradable" should be precisely defined, since some authors use them indiscriminately. In the case of polymers considered as being biodegradable, drug release is achieved by the gradual dissolution of the matrix. This dissolution can be caused by hydrolytic or enzymatic cleavage of the polymeric structure but can also occur by simple dissolution. Several definitions of the term "biodegradation" are given in the literature. Williams (4) defines biodegradation as a biological cleavage of the polymeric structure, a definition also adopted by Gilbert (5). As to Gilding (6), he uses this term for any polymer which undergoes breakdown in vivo. Further, Graham and Wood (7) define biodegradable systems as those capable of being broken down after a certain time into soluble products which are readily excreted via the normal routes. It should however be noted, that according to the classification made by Heller (8) for biodegradable polymers (Fig. 1), the breakdown of certain polymers does not always produce molecules of a sufficiently small size to be eliminated from the body. The three types of mechanisms described by Heller and which lead to dissolution by erosion are the following :

(1) Breakdown of water-soluble polymers which are made water-insoluble by hydrolytically unstable crosslinks (type I).
(2) Breakdown of linear polymers which are initially water-insoluble and which become solubilized by ionization resulting from hydrolysis or protonation of a pendant group, but without backbone cleavage (type II).
(3) Breakdown of polymers which are water-insoluble and break down to small soluble molecules by backbone cleavage (type III).

The breakdown of polymers does not necessarily proceed through one mechanism only, and various combinations of these mechanisms are possible. Generally, breakdown occurs through a hydrolytic reaction when the system is placed into an aqueous biological environment. In many cases, the presence of enzymes has produced a considerable increase in the rate of the breakdown (9–12).

Table 2 Main classes of bioerodible polymers

Polymer	Mechanism of erosion
Poly(N-vinylpyrrolidone)	Type I
Polyvinylalcohol	Type I
Polyacrylamides	Type I
Gelatin	Type I
Collagen	Types I and III
Copolymers of methylvinylether and maleic anhydride	Type II
Polyanhydrides	Type III
Polyurethanes	Type III
Polycaprolactone and their copolymers	Type III
Poly(ortho esters)	Type III
Poly(alkyl cyanoacrylates)	Type III
Poly(lactic acids), poly(glycolic acids) and their copolymers	Type III

Based on this definition, it is possible to categorize the main bioerodible polymers according to the mechanism of their breakdown (Table 2).

For our purposes, we will consider as being biodegradable, those polymers undergoing a type III erosion leading to a small molecule which can be eliminated by usual routes (urinary, faecal, pulmonary) and as being bioerodible those polymers undergoing a significant loss of weight during their breakdown in a biological medium.

2.1 Erosion of type I

Those polymers undergoing a type I hydrolysis, such as gelatin, collagen, polyacrylamides, poly(vinyl alcohol), poly(N-vinylpyrrolidone) are cross-linked materials and provide matrices which are highly hydrophilic (13, 18). These materials are therefore not suitable for immobilizing active species which have a low molecular weight and which are highly soluble in water, since such products diffuse rapidly through the polymeric network independently of the rate of erosion of the matrix (19). These polymers are therefore primarily used for the release of molecules which are sparingly water-soluble, such as hydrocortisone acetate (13) or macromolecules such as enzymes and antigens (16, 17).

Such materials are used for the ophthalmic administration of drugs mainly in the form of inserts and also, in the case of collagen, as corneal shields (20–23). It should be noted that collagen, because of its erosion combining type I and type II mechanisms, can also be used for implants (24, 25). These soluble inserts obtained from synthetic polymers, often calls SODI, which stands for "Soluble Ophthalmic Drug Inserts" have been largely developed and experimented on humans in Russia by Maichuk and col. (26–29), with active species such as antibiotics, sulfamides pilocarpine, atropine, dexamethasone, etc. Despite a rapid dissolution taking place in about 60 to 90 min, these systems have demonstrated a therapeutic activity extending over more than 24 h. Accordingly, a daily application produces the same result as instillations repeated 6 to 8 times every day.

2.2 Erosion of type II

The erosion of type II has the particularity of not causing any significant change in the molecular weight of the polymer. Actually, no cleavage of the chains normally occurs during the dissolution of the polymer. These polymers cannot therefore be used for a systemic administration or for implants, because of the difficulty of their elimination. Because of the influence of the pH of the medium on their rate of dissolution, these polymers had initially been developed as film-forming materials for coating enteric tablets (30). The half esters of the copolymer of methyl vinylether and maleic anhydride (PVM/MA) have however been the object of several investigations, for delivery of drugs by other routes than oral or topical.

Heller and col. (31) have demonstrated using rabbits the usefulness of this polymer for ophthalmic delivery. They obtained, by making PVM/MA disks containing hydrocortisone and by placing them in the lower part of the conjunctival culde-sac, a hydrocortisone release following zero order kinetics.

Trials with pilocarpine, a substance which is highly water-soluble, were carried out by Urtti and col. (32, 33). Increasing the size of the alkyl ester moiety enabled them to increase the hydrophobicity of the polymeric matrix and thus to obtain a constant release of pilocarpine. The importance of the solubility of the insert loaded with pilocarpine into the lacrimal fluid is also described by Saettone and col. (34). A low solubility seems to be essential to ensure complete release at a constant rate of the pilocarpine before the elimination of the insert from its site of application. The addition of poly(vinyl alcohol) (PVA) appears to be a satisfactory method for controlling this solubility. Actually, by increasing the proportion of PVA in the PVM/MA matrices, Seattone and col. (34) have demonstrated a decrease in the solubility of the matrices, resulting in a better bioavailability of pilocarpine. The use of this method is however limited by an excessive swelling of the matrices, which leads in most cases to the expelling of the insert or to the empty insert remaining in place a long time after the pharmacological effect has ceased.

In relation to the mechanism of dissolution described by Heller (8), the presence of carboxylic moieties on the polymeric chains causes a decrease of the pH at the surface of the matrix during its dissolution. This effect is very little apparent in vitro when the medium is well-buffered. However, in biological fluids, characterized by a poor buffer capacity, this decrease of the pH causes a decrease of the dissolution of the polymer and consequently a decreased release of the active principle through diffusion. Finne and col. (35–41) have studied extensively the effect of adding a basic salt to the polymeric matrix, in order to control the pH of the medium. By this method, they could achieve a constant and prolonged release of timolol.

2.3 Erosion of type III

The erosion of type III of polymers leads to the formation of small soluble molecules, by cleavage of the polymeric chains. Because of the easy elimination of these small molecules, this mechanism corresponds to the definition of biodegradability given by Graham and Wood (7). One can consider these polymers as being truly biodegradable. As we had previously mentioned, the polymers of this class are particularly well suited as carriers for the systemic administration of active principles or for making surgical implants. They can be administered to any organ, provided the breakdown products are not toxic. Such

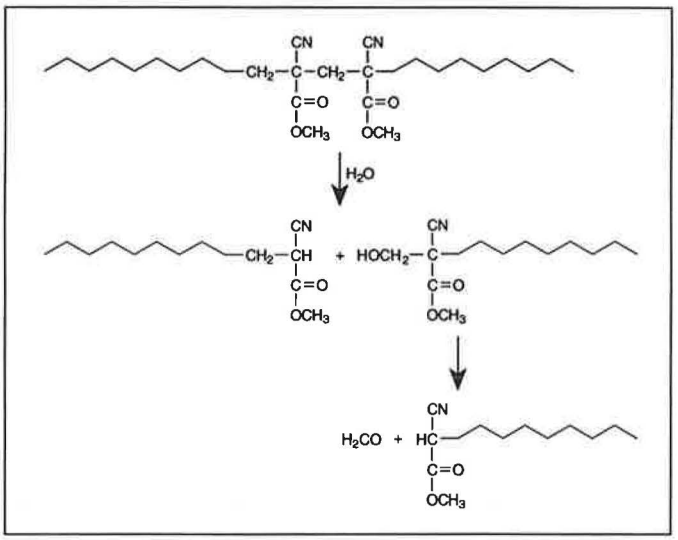

Fig. 2 Mechanism of PIBCA breakdown in an aqueous medium (46)

biodegradable systems have several advantages over conventional systems for ophthalmic delivery. They can be applied on the surface of the eye or be used as intraocular implants, to produce a controlled and extended release of the therapeutic agent. Quite a number of diseases could benefit from the release of therapeutic agents from these biodegradable systems. Amongst these diseases, are eye infections, corneal ulcers, endophthalmites, eye tumours such as melanomas and retinoblastomas. They can further be considered for promoting wound healing after cataract and glaucoma filtering surgery or after vitreoretinal surgery, against inflammatory diseases of the eye such as acute chronic uveitis or against proliferative diabetic retinopathies. This enumeration clearly demonstrates the numerous possibilities of these polymers in ophthalmic applications. The size, shape, rate of breakdown or of release, the pharmaceutical drug and the intraocular positioning of these systems will depend upon the disease and the exact location to be treated.

3 Biodegradable Polymers

3.1 Poly(alkyl cyanoacrylates)

This class of polymers has been largely used for making nanoparticles (42). The first aqueous colloidal suspensions based on polyacrylamide or on poly(methyl methacrylate) offered the advantage of a better stability than liposomes in biological fluids and enabled a better loading of the active principle, but on the other hand, they had the drawback of not being biodegradable, neither enzymically nor chemically. The development of biodegradable poly(alkyl cyanoacrylates) has obviated this drawback and accordingly decreased the risk of chronic toxicity resulting from the intracellular accumulation of non-biodegradable material (43).

These biodegradable nanoparticles or nanospheres are prepared by emulsion polymerization of alkyl cyanoacrylates. The water-insoluble monomer is emulsified in the aqueous phase which often contains dextrans to prevent aggregation phenomena, and glucose to ensure isotonicity (44). The polymerization proceeds spontaneously at ambient temperature to form matrix structures of a small diameter (< 1 μm), of a spherical shape, consisting of a porous polymeric framework having a high specific area. The rate of the polymerization reaction is controlled by the pH of the medium. Generally, the polymerization is carried out under acidic conditions to lower reaction rate. The active principle, can be added directly to the medium before polymerization, to achieve a homogeneous dispersion throughout the particles, or can be added to the suspension of nanoparticles after polymerization to achieve adsorption on the surface of the particles (45).

The mechanisms leading to the breakdown of these polymers have been described by several authors (46, 47). They can involve a hydrolysis of the polymeric chains producing formaldehyde and alkyl cyanoacetate or releasing cyanoacetic monomers, or further enzymic reactions resulting in a solubilization of the polymer by hydrolysis of its ester functions (Fig. 2). Both mechanisms are likely to occur in the case of ophthalmic implants, because of the composition of the lacrimal fluid.

The distribution and the clearance of nanoparticles of poly(hexyl cyanoacrylate) (PHCA) labelled with ^{14}C after instillation into the eyes of albino rabbits was investigated by Wood and col. (48). Their work demonstrates that the nanoparticles are very rapidly removed from the precorneal region, with about 1% of them remaining adhering to the surface of the cornea and of the conjunctiva. This clearance is however less extensive than that found with the control solution. Diepold and col. (49) demonstrated in similar tests, but on inflamed eyes, that the residence time in inflamed tissues is four times greater than in healthy tissues. The application of anti-inflammatory or antiallergic substances with this type of carrier should therefore prove quite useful.

A study by Fitzgerald and col. (50) by gamma scintigraphy of the clearance of nanoparticles of poly(butyl cyanoacrylate) (PBCA) labelled with ^{111}In showed that the retention of the polymeric particles takes place at the internal canthus and not on the surface of the cornea. The use of PBCA nanoparticles loaded with pilocarpine by Harmia and col. (51) enabled these authors to achieve a prolongation of myosis in rabbits, by comparison with a commercial solution. This prolongation is obtained only if the pilocarpine is adsorbed on the surface of the particles. In the case of its inclusion into the polymeric matrix, no significant prolongation is observed.

Diepold and col. (52) achieved a reduction of the intraocular pressure (IOP) over a period of time exceeding 9 h, through the use of PBCA nanoparticles loaded with pilocarpine. With a control solution, this reduction lasted a mere 5 h. This comparison was made on an animal model, namely on albino rabbits, in which the IOP had been increased by injecting subconjunctivally betamethasone.

Studies conducted by Marchal-Heussler and col. (53) have shown that the load of nanoparticles and the manner in which the active principle – in their case betaxolol, an antiglaucoma drug – is linked to the particle, have a considerable effect on the therapeutic response. A better response is achieved with a lesser load of betaxolol and a less negative surface charge than under the inverse conditions.

Less conclusive results were obtained when incorporating substances such as amikacin sulfate (54, 55) or progesterone. In the case of nanoparticles of progesterone, Li and col. (56) demonstrated that the active principle is released too slowly and that nanoparticles are cleared from the eye before an effective release of progesterone has taken place.

Table 3 Various types of poly(alkyl cyanoacrylates) used for preparing ophthalmic nanoparticles

Polymer	Drug	Dosage form	Model	Year	Author
PBCA	In^{111}	NP	Rabbit	1987	Fitzgerald (50)
PBCA	Pilocarpine HCl and nitrate	NP	In vitro	1986	Harmia (51)
PBCA	Pilocarpine nitrate	NP	Rabbit	1986	Harmia (59)
PBCA/PHCA	Pilocarpine HCl and nitrate	NP	In vitro	1986	Harmia (60)
PBCA/PHCA	Pilocarpine HCl and nitrate	NP	Rabbit	1987	Harmia (61)
PBCA	Pilocarpine nitrate	NP	Rabbit	1988	Kreuter (62)
PBCA	Pilocarpine nitrate	NP	Rabbit	1989	Diepold (52)
PBCA	Amikacine sulfate	NP	Rabbit	1989	Alonso (54)
PBCA	Amikacine sulfate	NP	Rabbit	1991	Losa (55)
PBCA	Progesterone	NP	Rabbit	1986	Li (56)
PIBCA	Betaxolol HCl	NP	Rabbit	1990	Marchal-Heussler (53)
PIBCA	Betaxolol HCl	NP NC	Rabbit	1992	Marchal-Heussler (63)
PIBCA	Metipranolol	NC	Rabbit	1993	Losa (57)
PHCA	C^{14}	NP	Rabbit	1985	Wood (48)
PHCA	C^{14}	NP	Rabbit	1989	Diepold (49)
PMCA/PECA/PBCA	Timolol base and maleate	NP	In vitro	1986	Harmia-Pulkkinen (64)

PHCA: Poly(hexyl cyanoacrylate); PBCA: Poly(butyl cyanoacrylate)
PIBCA: Poly(isobutyl cyanoacrylate), PMCA: Poly(methyl cyanoacrylate)
PECA: Poly(ethyl cyanoacrylate), NP: Nanoparticles, NC: Nanocapsules

Table 4 Properties of polymers according to the configuration of the lactic acid used

Polymer	Physical state	Tg (°C)	Tm (°C)	Solubility in organic solvent
PGA	semi-crystalline	35	230	not soluble
L-PLA	semi-crystalline	59–67	159–178	low
D-PLA	semi-crystalline	59–67	159–178	good
DL-PLA	amorphous	50–57	–	good

Recently, Losa and col. (57) have shown that it was not possible to control the release of metipranolol from nanoparticles of poly(isobutyl cyanoacrylate) (PIBCA), but that their use could produce a reduction of the side-effects, probably through a reduction of the systemic absorption of metipranolol. Table 3 lists the main types of poly(alkyl cyanoacrylates) used for preparing ophthalmic nanoparticles.

It is further to be noted, that this class of polymers has already been used experimentally or clinically in the sixties as a tissue adhesive for cases of corneal perforations or for application on sutures after various surgical interventions (58). These adhesives will not be examined in the present review.

3.2 Poly(lactic acids), poly(glycolic acids) and their copolymers

The main polymers in this class of biomaterials, are poly(lactic acids) (PLA) and their copolymers with glycolic acid (PLGA). As to poly(glycolic acids) (PGA), they are far too sensitive to hydrolysis to be considered for use as a carrier for sustained drug delivery.

These homo- and copolymers of lactic and glycolic acids are generally synthesized by a condensation reaction at elevated temperature, via the ring opening of the corresponding lactide and glycolide dimer (65). A direct condensation reaction can also take place by using the monomers, but leads to the formation of polymers of a relatively low molecular weight.

The presence of a centre of asymmetry on the lactic acid makes it possible to obtain levorotatory (L), dextrorotatory (D) or racemics (DL) forms of the corresponding polymers. The different physicochemical characteristics, summarized in Table 4, of these monomers, make it possible to synthesize an important range of polymers. Actually, the mechanical characteristics as well as the release profiles of the homo- and copolymers synthesized will depend upon the configuration of the lactic acid used and on the proportion of the two monomers (66).

The biodegradation of these polymers proceeds by a homogeneous erosion of the core. The polymeric chains are first cleaved by hydrolysis, thereby releasing acidic monomers which are subsequently eliminated from the body via the Krebs cycle, in the form of CO_2 and H_2O (Fig. 3) (11, 65).

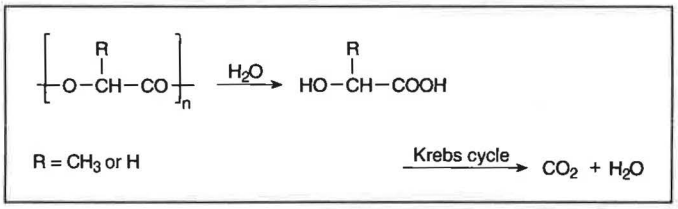

Fig. 3 Mechanism of breakdown of PLGA in an aqueous medium

The rapid clearance, as well as good biocompatibility (67, 68) of these polymers has enabled their use since the seventies as sutures which resorb with time, sold as Dexon™ in the case of PGA and as Vicryl™ and Polyglactin 910™ in the case of PLGA (69). Their use in the form of implants or of injectable microparticulate systems, for controlled release of therapeutic agents (narcotic antagonists, contraceptive steroids, vaccines, LHRH analogs, anticancer agents, local anesthetics, antibiotics and antimalarial agents) has also been extensively described in the literature (70).

The use of these polymers in ophthalmology stems from the need to reduce the number of injections of the active principle into the vitreous body of the eye. In the treatment of chronic or acute affections of the posterior segment of the eye, such as proliferative vitreoretinopathy, endophthalmitis, or further recurrent uveitis, repeated injections of the active principle are necessary, in order to maintain the drug concentration at therapeutic levels. These repeated and painful injections are often the cause of clinical complications both at the anterior segment and at the posterior segment of the eye and can cause infections and hemorrhages in the eye (71). To overcome these problems, several authors have developed microspheres of PLA and PLGA. Although microparticulate systems ensuring a controlled delivery to the eye were already described in several US patents (72, 73) granted in the late seventies, it is only in the late eighties and more recently that the injection of microspheres into the vitreous body of rabbit's eyes was investigated.

Moritera and col. (74, 75) have prepared by solvent evaporation PLA and PLGA microspheres having a diameter of 50 µm, which were loaded with 5-fluorouracil (5-FU), an agent used in this case for inhibiting the cellular proliferation in proliferative vitreoretinopathies. When they injected the microspheres into rabbit eyes, they obtained a release of the antimetabolite over a period of time ranging from 2 to 7 days, depending on the polymer used and on its molecular weight. A complete clearance of the microspheres was found after an average of 48 days. In another study, Moritera and col. (76) obtained a release of the adriamycin over a period of two weeks from PLA microspheres. The study carried out on rabbits demonstrates a decrease in the incidence of detached retinae after 4 weeks, as well as an absence of toxicity by comparison with the control solution of adriamycin.

Kimura and col. (77) also used PLA microspheres loaded with adriamycin to prevent the proliferation of fibroblasts after glaucoma filtering surgery. After a subconjunctival injection, the release of the antimetabolite extending over a period of 20 days produced a decrease of the IOP between the 6th and the 16th day after the injection of microspheres, and maintained the filtration bleb for a duration of 15 days. Mild corneal opacities as well as a slight epithelial erosion with return to normal after 4 weeks were however noted with the microspheres highly loaded with adriamycin.

Khoobehi and col. (78, 79) used the sodium salt of fluorescein to study the kinetics of release of the tracer from PLA and PLGA microspheres after their subconjunctival and intravitreous injection. They describe release profiles which differ depending on the polymer used, as well as a release over a longer period of time than in the case of a control solution. In the case of the intravitreous injection, the concentration of the sodium salt of fluorescein is maximum after 24 h, and then decreases during 5 days and remains measurable to about the 16th day. The subconjunctival injection of PLGA microspheres loaded with cyclosporin A for the purpose of decreasing cornea graft rejection, and also the injection of PLGA microspheres loaded with fluconazol for combating fungal endophthalmitis were also investigated (80, 81).

Another approach also described in the literature consists of using implantable matrices. These implants are generally in the form of small cylinders having a diameter of 0.9 mm and a length of 6 mm, and they can be implanted by means of a conventional syringe with a needle of a sufficient diameter. The subconjunctival or intravitreous implantation of PLGA implants loaded with 5-FU has also demonstrated that they could be used for the treatment of glaucoma or of proliferative vitreoretinopathies (82–85).

Mention should also be made of two topical applications of PLA nanoparticles loaded with indometacin (86) and of PLGA nanoparticles loaded with betaxolol (87). An increase of the ocular bioavailability of the active principles is obtained by the accumulation of nanoparticles inside the conjunctival culde-sac. Table 5 lists the different articles concerned with the ophthalmic uses of PLA and PLGA.

3.3 Polycaprolactones

The successful use of PLA and PLGA as biodegradable systems with an prolonged action has prompted investigators to assess other aliphatic polyesters and in particular polycaprolactones (PCL) for medical applications. By comparison with PLA and PLGA, the homopolymer hydrolyzes very slowly and this was put to use in the development of the contraceptive implant Capronor™ for the controlled release of levonorgestrel over a period of one year (90). The rate of biodegradation can however be increased by copolymerization with other monomers, such as lactic acid (91).

PCL are synthesized through a catalyzed polymerization via an ring opening of the coresponding lactone through an anionic, a cationic, or a radical reaction, or further by coordination (92). The PCL synthesized are semi-crystalline and exhibit a melting range from 59 to 64 °C and a glass transition temperature ranging from –70 °C to –60 °C, depending on their degree of crystallinity. Accordingly, the polymer is rubbery at room temperature.

PCL hydrolyzes to ε-hydroxycaproic acid by cleavage of the polymeric chains at the ester linkage (Fig. 4). This cleavage of the polymeric chains by hydrolysis produces initially a decrease of the intrinsic viscosity, without any significant loss of weight. When a number molecular weight of about 5000 is attained, the cleavage of the chains is accompanied by a loss of weight resulting from the diffusion of small polymeric fragments from the matrix, which subsequently fragments and undergoes phagocytosis (92).

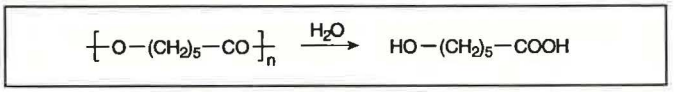

Fig. 4 Mechanism of breakdown of PCL in an aqueous medium

Table 5 List of publications describing the use of PLA and PLGA for ophthalmic drug delivery

Polymer	Drug	Dosage form	Model	Year	Author
PLA	Adriamycin	MS	Rabbit	1992	Moritera (76)
PLA	Adriamycin	MS	Rabbit	1992	Kimura (77)
PLA	Indometacin	NC	Rabbit	1992	Masson (86)
PLA/PLGA	5-fluorouracil	MS	Rabbit	1989	Moritera (74)
PLA/PLGA	5-fluorouracil	MS	Rabbit	1991	Moritera (75)
PLA/PLGA	Fluorescein Na	MS	Rabbit	1990	Khoobehi (78)
PLA/PLGA	Fluorescein Na	MS	Rabbit	1991	Khoobehi (79)
PLGA	–	Matrix MP	–	1976	Michaels (72)
PLGA	–	MP	–	1978	Shell (73)
PLGA	Fluconazol	MS	Rabbit	1992	Kimura (81)
PLGA	Cyclosporin A	MS	Rabbit	1992	Harper (80)
PLGA	–	Film	Rabbit	1989	Portugal (89)
PLGA	5-fluorouracil	Matrix	Rabbit	1992	Davis (82)
PLGA	5-fluorouracil	Matrix	Rabbit	1992	Villain (84)
PLGA	5-fluorouracil	Matrix	Rabbit	1992	Rubsamen (83)
PLGA	Gancyclovir	Film	Rabbit	1992	Davis (88)
PLGA	–	Ring	–	1992	Parel (85)
PLGA	Betaxolol HCl	NP NC	Rabbit	1992	Marchal-Heussler (87)

MS: Microspheres, MP: Microparticles, NP: Nanoparticles, NC: Nanocapsules

Table 6 Use of PCL for the preparation of ophthalmic nanocapsules and nanoparticles

Polymer	Drug	Dosage form	Model	Year	Author
PCL	Betaxolol	NC	Rabbit	1991	Marchal-Heussler (93)
PCL	Betaxolol	NP NC	Rabbit	1992	Maincent (95)
PCL	Betaxolol	NP NC	Rabbit	1992	Marchal-Heussler (63)
PCL	Carteolol	NP NC	Rabbit	1993	Marchal-Heussler (96)
PCL	Metipranolol	NC	Rabbit	1992	Losa (97)
PCL	Metipranolol	NC	Rabbit	1993	Losa (57)
PCL	Indometacin	NP NC	Rabbit	1992	Masson (86)

NP: Nanoparticles, NC: Nanocapsules

The copolymerization of PCL with lactic acid causes a decrease of the crystallinity of the copolymer and, consequently, an increase of its permeability to the biological medium. By synthesizing homopolymers of different molecular weights, as well as copolymers containing different proportions of lactic acid, it is possible to obtain, as in the case of PLA and PLGA, a whole range of polymers characterized by a variable duration of hydrolysis.

Although these polymers were initially investigated for the manufacture of environmentally friendly packaging material, because of their biodegradability by micro-organisms, they were subsequently investigated as biomaterials for administration by different routes and in particular for ophthalmic delivery.

Table 6 lists the main investigations reported in the literature.

Marchall-Heussler and col. (93) instilled a colloidal suspension of PCL nanocapsules containing a β-blocker, namely betaxolol, into the eye of a rabbit with induced glaucoma. The nanocapsules were prepared by a technique of interfacial precipitation of the polymer (94). This method produces nanocapsules formed of oily droplets surrounded by a polymeric membrane, allowing the encapsulation with high yields of lipophilic active principles. Following the instillation of the suspension, a reduction of the IOP is obtained, which is more important both in intensity and duration, than that induced by the aqueous solution or by a commercially available preparation. The authors explain this phenomenon by the accumulation and the longer residence time of nanocapsules in the conjunctival cul-de-sac. In another study, they demonstrate that by comparison with other polymers (PLGA, PIBCA), the PCL nanocapsules loaded with betaxolol base are more effective against IOP than nanoparticles loaded with betaxolol hydrochloride (63). This effect seems to be due to a better agglomeration of the PCL carrier inside the conjunctival cul-de-sac, by comparison with other carriers, as well to the fact that the active principle is in

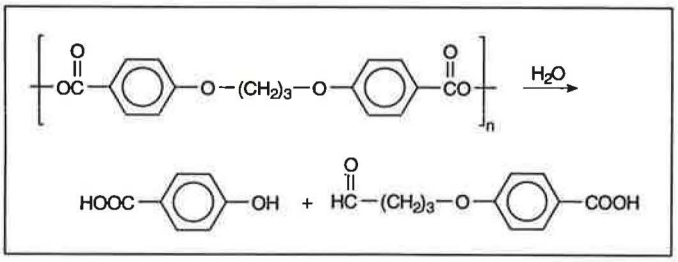

Fig. 5 Mechanism of breakdown of PCPP in an aqueous medium (100)

its non-ionized form. The better corneal absorption of betaxolol in its non-ionized form (betaxolol base) from PCL nanocapsules is also reported by Maincent and col. (95).

One of the important advantages associated with this type of carrier is the achievement of a more important therapeutic effect with small doses of active principle, which avoids a number of systemic side-effects, specially when β-blockers are used. Thus, Marchal-Heussler and col. (96) demonstrated that by instilling PCL nanocapsules loaded with carteolol, a decrease of the secondary cardiovascular effects, by comparison with the control solution. This decrease is explained by the possible reaction of β_1 and β_2-receptors to the injection of isoprenaline after the instillation of nanocapsules. In contrast, when a control solution is instilled, it blocks the receptors and prevents any cardiovascular reaction after the injection of isoprenaline. This difference probably arises from a decrease of the systemic absorption of the β-blocker after the instillation of nanocapsules. Losa and col. demonstrated by their investigations (97) the same effects by instilling PCL nanocapsules loaded with another β-blocker, namely metipranolol. They also demonstrate that the rate of release of the therapeutic agent depends only a little on the polymeric envelope, but rather on the coefficient of partition of the drug between the encapsulated oil and the aqueous release medium (57).

Weighton and col. (86) have also obtained good results following the nanoencapsulation of indometacin in PCL nanocapsules. A better availability is achieved by comparison with the commercial solution owing to the accumulation of the carrier inside the conjunctival cul-de-sac.

3.4 Polyanhydrides

This class of polymers can, due to the great lability of the anhydride links, undergo a so-called heterogeneous surface erosion. This breakdown mechanism is made possible by the fact that the rate of hydrolysis of the polymeric chains on the surface is much faster than the penetration of water into the core of the matrix. This surface erosion makes it possible to obtain zero order release profiles, as well as a good control over the rate of release and over the duration of the release.

Polyanhydrides can be synthesized by three different methods, namely through dehydrative coupling, dehydrochlorination and melt-polycondensation (98). The two first methods lead to the formation of low molecular weight polymers, but the last one, produces polymers of a higher molecular weight (98). The polymer of this class which has been most frequently used is a copolymer of bis(carboxyphenoxy)propane and sebacic acid (PCPP-SA). The ratio of the two monomers has an important effect on the rate of the breakdown of the resulting polymer. Actually, by increasing the proportion of sebacic acid, one decreases the hydrophobic nature of the polymer, which results in a faster hydrolysis of the polymeric chains at the surface. In addition to hydrophobicity we also must consider changes in crystallinity. Leong and col. (99) calculate by extrapolation that breakdown of PCPP requires over three years. The copolymerization with sebacic acid can reduce the duration of this breakdown to a few days, by using a proportion of this acid at 80%. Conversely, by using homologous poly(biscarboxyphenoxyalcanes) with a number of methylene groups increased from 1 to 6, one decreases the reactivity of the anhydride links, through an increased hydrophobicity of the polymer. A 3-fold decrease of the rate of erosion is thus obtained (99). It should also be noted, that the polyanhydrides break down less rapidly in an acidic medium than in a basic medium. PCPP breaks down by hydrolysis into *p*-hydroxybenzoic acid, which can be eliminated directly or after conjugation with amino acids, and into an aldehyde (Fig. 5). This aldehyde can further undergo an oxidation before being eliminated as a carboxylic acid or as *p*-hydroxybenzoate.

Polyanhydrides have first been investigated for the production of textile fibres. While their low resistance to hydrolysis has considerably limited applications in the textile industry, this property has promoted their use as biomaterials.

Results of biocompatibility tests carried out by Leong and col. (100) have also contributed to the use of these materials in the medical field. They found that no inflammatory reaction occurred after implantation of polyanhydrides into the rabbit cornea or under the conjunctiva. The breakdown products are neither mutagenic, nor cytotoxic and they carry only a very small risk of teratogenesis.

The main use of these biomaterials in ophthalmology is in the post-surgical treatment of glaucoma. The failure of glaucoma filtering surgery is due, in most cases, to an uncontrolled proliferation of subconjunctival fibroblasts which obstruct the passage surgically opened (101). This is in fact a normal healing process, but which in this case is undesirable, since it reduces the chances of success of the filtering surgery. A post-surgical implantation of a cylinder of a copolymer of bis(carboxyphenoxy)hexane and sebacic acid (PCPH-SA) containing 5-FU, an antimetabolite inhibiting healing mechanism by preventing the proliferation of fibroblasts, was studied by Lee and col. (102) in rabbits. Results show that the IOP remains lower over two weeks and that the filtering bleb remains operative longer than in the eyes of control animals. A similar study confirming these results was carried out by the same authors by using this time a disk, a shape which is better tolerated by the eye, made of PCPP-SA and loaded with 5-FU (103). One should note that in the two studies a time lag was found between the end of the release of the 5-FU and the disappearance of the polymer, as well as a release of the antimetabolite which did not follow zero order kinetics. This is certainly due to the fact that, because of its greater hydrophilicity, 5-FU diffuses rapidly through the polymer.

A study carried out by Charles and col. (104) with PCPP-SA loaded with mitomycin C (MMC), a hydrosoluble antimetabolite, also confirms the potential of these polymers in the postoperative treatment of glaucoma filtering surgery, as well as the importance of the hydrophilicity of the active principle on the release profile.

Jampel and col. (105) also used PCPP-SA in trials on monkeys, but in their case loaded with 5-fluorouridine (5-FUR), an antimetabolite which is 100 times more powerful than 5-FU. They obtained a release of the metabolite lasting 16 days and the operation was successful over a longer period of time for eyes which had received the polymer loaded with 5-FUR. In view of these results they concluded that the release of 5-FUR

Table 7 Polyanhydrides used for the preparation of ophthalmic implants

Polymer	Drug	Dosage form	Model	Year	Author
PCPH-SA	5-FU	Cylinder	Rabbit	1987	Lee (102)
PCPP-SA	5-FU	Disk	Rabbit	1988	Lee (103)
PCPP-SA	MMC	Disk	Rabbit	1991	Charles (104)
PCPP-SA	5-FUR, 5-FU	Disk	Monkey	1990	Jampel (105)
PCPP-SA	VP-16, Taxol	Disk	In vitro	1991	Jampel (106)
PCPP-SA	Taxol, Etoposide	Disk	Monkey	1993	Jampel (107)
PCPP-SA/PTA-SA	Heparin, Cortisone	Disk	Rabbit	1985	Langer (108)

5-FU: 5-fluorouracil, MMC: mitomycin C, VP-16: a semi-synthetic derivative of podophyllotoxin

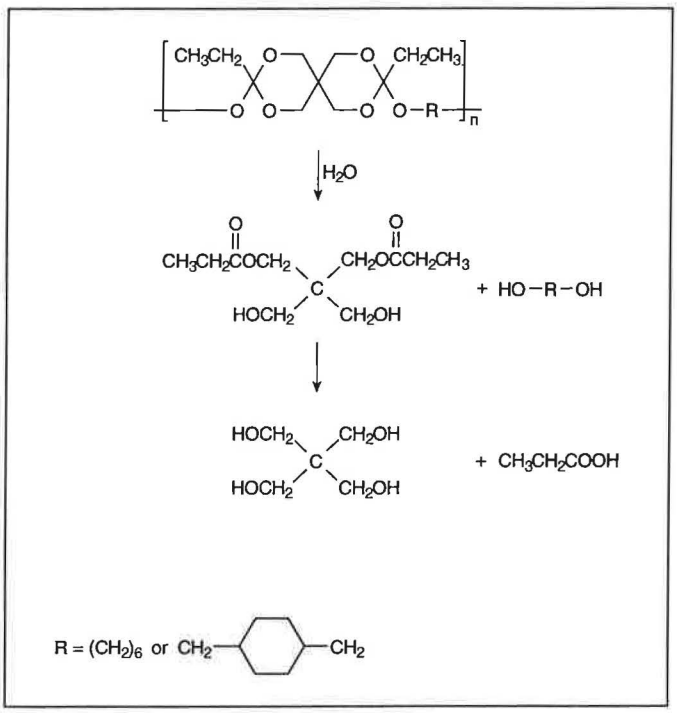

Fig. 6 Mechanisms of breakdown of POE in an aqueous medium (110)

is too fast relative to the rate of breakdown of the polymer. To decrease this rate of release, they incorporated hydrophobic inhibitors of the proliferation of fibroblasts into PCPP-SA disks. The in vitro release of VP-16, a semi-synthetic derivative of podophyllotoxin is complete after 31 days, whereas that of taxol, a substance which is much more hydrophobic, amounts to a mere 10 to 15% after 100 days (106). These results induced Jampel and col. (107) to carry out in vitro trials with PCPP-SA loaded with taxol. The use of this substance of a much more hydrophobic nature than 5-FU or 5-FUR ensured a decrease of the IOP in monkeys over a period of more than 100 days.

In another field, Langer and col. (108) studied the inhibition of the neovascularization of a corneal tumour after the implantation of a disk of polyanhydride loaded with a mixture of heparin and cortisone. The two polymers used are PCPP-SA and the copolymer of terephthalic anhydride with sebacic acid (PTA-SA). The mixture of the two active principles enabled a total inhibition of the neovascularization for three weeks, which was the time necessary for the complete dissolution of the copolymers used. Table 7 summarizes the experimentation carried out with this type of polymers.

3.5 Poly(ortho esters)

Poly(ortho esters) (POE) stem from investigations directed towards obtaining polymers exhibiting a release of the active principle following zero order kinetics. The first poly(ortho ester) was synthesized at Alza. This polymer was hydrophobic and contained bonds that are labile in an acidic environment. Addition of an excipient, generally an alkaline salt, inhibited hydrolysis of the matrix and allowed control over erosion rates.

Another family of poly(ortho esters) was prepared by a simple addition reaction at ambient temperature (109). The polymers which were investigated for ophthalmic applications were obtained through an addition reaction between 3,9-bis (ethylidene)-2,4,8,10-tetraoxaspiro(5.5)undecane (DETOSU) and a mixture of diols, in particular *trans*-cyclohexane dimethanol and 1,6-hexanediol or, in the case of reticulated POE, the triol 1,2,6-hexanetriol.

Hydrolysis of the polymer produces in a first step, which is generally rather fast, the initial diols and pentaerythritol dipropionate which in a second slower step, produces propionic acid and pentaerythritol (Fig. 6) (110). This second slower step prevents an autocatalysis of breakdown of the polymer, due to the acidification of the medium by propionic acid.

Heller and col. (111) used a cross-linked polymer to release 5-FU, for decreasing the proliferation of fibroblasts, after glaucoma filtering surgery. Despite a copolymerization with 9,10-dihydrostearic acid for the purpose of catalyzing the breakdown reaction of the polymer, the release of 5-FU occurs mainly through diffusion and not through surface erosion of the polymer. When the release has ended, the polymer has undergone only a very small loss of weight. This increased residence time of the implant after a complete release of 5-FU causes in most cases an encapsulation of the material implanted, which is generally undesirable, and more particularly so in the case of an ophthalmic therapy.

In another study, Maa and col. (112) synthesized a linear polymer for the release of 5-FU. By using different proportions of diols for its synthesis and by incorporating different amounts of acids having different acidity constants and different solubilities, they were able to obtain dosage forms where the 5-FU was predominantly released by surface erosion. Unfortunately, the optimized formulation had physical properties which makes difficult its use as an implant. Table 8 summarizes the work carried out in ophthalmology with poly(ortho esters).

Recently, a new generation of POE was developed (113). These POE of a semi-solid consistency have been investigated for use after glaucoma filtering surgery. Their synthesis, physicochemical characteristics, sterilization, as well as the possi-

Table 8 Polymers used for the preparation of implants of poly(ortho esters) designed for ocular delivery

Polymer	Drug	Dosage form	Model	Year	Author
Cross-linked POE	5-FU	Disk	In vitro	1987	Heller (111)
POE	5-FU	Disk	In vitro	1990	Maa (112)
POE	5-FU	Semi-solid	In vitro	1994	Merkli (116)
POE	5-FU and MMC	Semi-solid	In vitro	1995	Merkli (117)

ble in vitro modulated release of antimetabolites, through the use of different excipients is described (114–117).

4 Use of Biodegradable Polymers in the Treatment of Glaucoma

A review of the literature concerned with the main uses of biodegradable polymers in ophthalmic applications shows clearly that the treatment of glaucoma is a major field of investigations. Fig. 7 gives the breakdown as a percentage of total, of the publications dealing with investigations on the ophthalmic delivery of drugs by means of polymeric biodegradable carriers.

Glaucoma is generally characterized by an excessive IOP which can lead to an atrophy of the optic nerve. In healthy eyes, the tissues of the anterior chamber of the eye, such as the trabecular meshwork and Schlemm's canal produce a certain resistance to the drainage of the aqueous humour. Accordingly, the IOP increases in proportion to the production of aqueous humour by the ciliary body, until an equilibrium value is reached, with a pressure which can range from 10 to 25 mm Hg. In the case of eyes affected by glaucoma, this equilibrium is moved to higher pressures (> 26 mm Hg), principally because of an increased resistance to the drainage of the aqueous humour (101).

The oldest antiglaucoma drug is the cholinergic agonist, pilocarpine. The mechanism of action of this drug has not yet been fully elucidated even now, but its administration results in an increased drainage of the aqueous humour. Another approach consists in decreasing the production of the aqueous humour at the ciliary body, by using β-blockers. These two therapies are mainly applicable to primary open-angle glaucoma and they involve the use of a topical treatment.

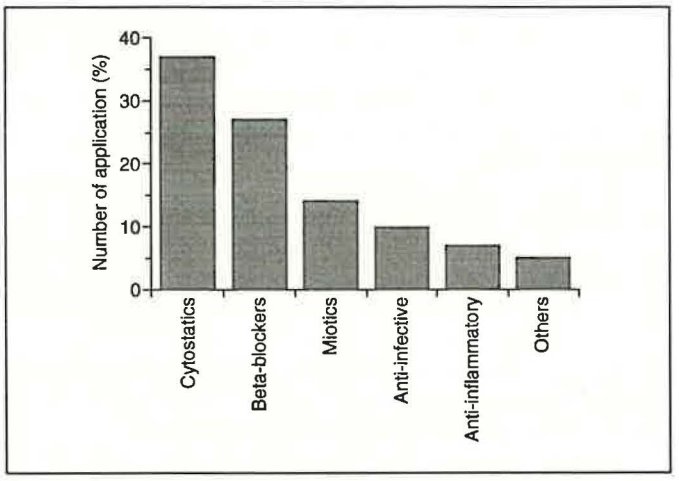

Fig. 7 Breakdown as a percentage of total of publications (1985 up to 1994) dealing with the various drugs investigated for ophthalmic delivery using biodegradable polymeric carriers

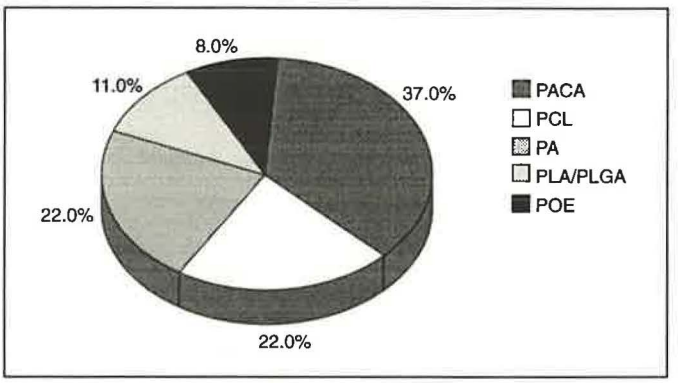

Fig. 8 Breakdown as a percentage of total of the publications (1985 up to 1994) dealing with the different biodegradable polymers investigated for use in the treatment of glaucoma

In the case of glaucomas refractory to topical treatments which needs to be treated by filtering surgery, cytostatics are sometimes used. Filtering surgery consists in creating a passage for the aqueous humour between the anterior chamber of the eye and the subconjunctival space. A conjunctival filtration bleb is thus formed, which allows diffusion of the aqueous humour. Cytostatics such as 5-FU or MMC are used to inhibit the proliferation of subconjunctival and episcleral fibroblasts which obstruct the passage created surgically. This treatment is applied by subconjunctival injections.

Fig. 8 gives the breakdown as a percentage of total, of the publications dealing with the use of various polymers described above in the treatment of glaucoma. Most of the investigations are concerned with poly(alkyl cyanoacrylates) and polycaprolactones and these polymers were mostly used for making nanoparticles or nanocapsules for the topical application of miotic agents or of β-blockers. The four other polymers, namely PLA, PLGA, polyanhydrides and POE were less extensively studied, and the studies were mainly concerned with implants designed for use after complicated cases of filtering glaucoma surgery.

5 Conclusions

Success of ophthalmic therapies is dependant mainly upon three factors, namely the intrinsic activity of the therapeutic agent, its capacity to pass through different biological barriers and finally the targeting and retention of the drug where it is needed, for a sufficient length of time. This last factor is largely influenced by the drug release system used. The progress made in developing new synthetic biodegradable polymers for medical use during the past twenty years has broadened the range of the materials available for ophthalmic use.

The special anatomy and physiology of the eye has forced investigators to carry out their investigations on animal models as closely related as possible to humans. Most of the investigations on the use of polymeric carrier were made on rabbits, but only a very few of them have so far led to commercial applications in human medicine. Despite this, they have increased our knowledge in this field and they have encouraged the development of new polymers with improved biocompatibility or improved drug release profiles, or both. The POE which can undergo a so-called heterogeneous surface erosion ensuring a release of the therapeutic agent over an extended period of time at a constant rate are an example of the progress made in the chemistry of these polymers. A number of these biodegradable polymers appear to have a promising future for the treatment of different ocular diseases and will certainly lead to new therapeutic concepts.

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