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# Photocrosslinkable Polymers for Biomedical Applications

P. Ferreira, J. F. J. Coelho, J. F. Almeida and M. H. Gil  
*Chemical Engineering Department, University of Coimbra  
 Portugal*

## 1. Introduction

Photopolymerization techniques provide a number of economic advantages over the usual thermal techniques. These include: rapid cure reaction, low energy requirements, use of room temperature and solvent free formulations as well as low cost. Light beams are used to start the photochemical reactions in organic materials (monomers, oligomers, polymers) to form a new polymeric system. This technique allows us to prepare materials with several applications in industry (UV curable inks, printing plates and adhesives, among others). Photopolymerization has also been used in electronic materials, optical materials, membranes, coatings and surface modifications. The efficiency of the polymerization reaction is dependent on the monomers, the photoinitiator and the beam wavelength.

More recently, this technique has been used in the preparation of biomaterials with applications in important areas as tissue engineering, (Nguyen & West, 2002), biosensors, (Alves et al., 2009), development of drug delivery systems (Rydholm et al., 2007) dental restorations in situ (Gatti et al. 2007)) and surface modifications to control the materials cell adhesion (Alves et al., 2011). Photopolymerizable polymers have found numerous applications in the field of tissue engineering for the engineering of tissues as bone, cartilage and liver (Ifkovits & Burdick, 2007) as they may be photopolymerized in vivo and in vitro.

Here we will report some of the literature scientific reports in this field.

Ortega and co-workers (2008) showed that the photopolymerization kinetics as well as the resulting structure of the methacrylate based structures are influenced by the monomers and oligomers properties, the reaction conditions, e.g. light intensity, reaction temperature and type of photoinitiator.

Gatti et al. (2007) referred that photopolymers have been widely used in several dentistry applications. Different monomers have been used for this purpose. Gatti et al. (2007) prepared and characterized copolymers obtained from bisphenylglycidyl dimethacrylate, triethylene glycol dimethacrylate and urethane dimethacrylate. These copolymers were used to obtain dentistry resins. The kinetic parameters of the reaction were evaluated by using photocalorimetry.

As it is well known, hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids. They represent an important class of materials to be applied in biotechnology and medicine. These networks have been used as membranes for separating solutes, wound dressings, delivery systems for gene therapy and protein controlled-released systems. Hydrogels have also been applied as

bioadhesives, for immobilization of enzymes and cells and in tissue engineering. These photocrosslinked polymers can be obtained either from natural polymers (eg. hyaluronic acid) or from synthetic monomers in the presence of a photoinitiator, using visible or ultraviolet light (Nguyen & West, 2002).

Tai et al. (2009) prepared and characterized photocrosslinked hydrogels from synthetic monomers to be used as advanced injectable biomaterials. They observed that the PEGMEMA-PPGMA-EGDMA copolymers, with both thermoresponsive and photocrosslinkable properties, have excellent mechanical properties above the LCST. They suggested that the biodegradability of these gels could be increased by copolymerization with biodegradable blocks.

Other authors (Seiffert et al., 2007) prepared hydrogels by crosslinking a dimethylmaleimide functionalized polyacrylamide. They observed that this method could give a very efficient method to synthesize hydrogels in a selective and controlled manner.

Tae Il Son group developed a visible light-crosslinkable porcine gelatine containing furfuryl groups by using Rose Bengal (4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein) as a visible light sensitizer. These authors referred that the material could be used in the dental field as well as a visible light induced crosslinkable biosolvent.

Schuster and co-workers (2009) developed gelatine based photopolymers for bone replacement materials. For this purpose, as a first step, they prepared different methacrylate based gelatine derivatives by reaction of this polymer with glycidylmethacrylate and other acrylate monomers. In this way, they obtained polymerizable gelatin that was polymerized with a polyethyleneglycol monomethacrylate comonomer. They were then able to prepare cellular structures by using stereolithography.

Nichol and colleagues (2010) prepared a photopolymerizable gelatine methacrylate for tissue engineering applications. They modified gelatine with methacrylic anhydride, which was subsequently photopolymerized with UV irradiation, in the presence of Irgacure 2959. These authors suggested that these hydrogels could be applied in microscale applications to create endothelial-lined vessels within engineered tissues.

Hu and co-workers (2010) used a carboxymethylated chitosan modified with 4-nitrocinnamate acid to obtain a photopolymerizable derivative without initiator. They were able to prepare a gel with good mechanical properties that was efficiently used as a matrix in a drug delivery system.

Although the extension of described works, the photopolymerization/photocrosslinkage are processes which are still being studied and therefore explored by many researchers. In this chapter, we wish to report some of the highlights of our work, in this field, still on course in our research group.

## 2. Photoinitiators

The photocrosslinking technology by using ultraviolet (UV) or visible light has been used extensively in several applications including several types of coatings and biomedical applications. When this technology is used in combination with biodegradable polymers very interesting solutions can be found for drug delivery and tissue engineering applications. The photoinitiators are one of most important compounds used in the formulation due to its influence on different reaction parameters. The chemical nature of the photoinitiator determines the reaction rate, the spectral sensitivity (wavelength of absorption), the light resistance and the stability of the materials under storage conditions.

In order to obtain crosslinked polymers, it is necessary to generate free radicals in the system that will induce a free radical chain polymerization of monomers and oligomers. Both have reactive functional groups that can be activated under the presence of reactive radicals, resulting in the formation of crosslinked structures (Corrales et al., 2003). In the mechanism involved in the process we can consider three main reactions: initiation, propagation and termination. Photoinitiators have an essential role in this process, since they are excited under UV radiation leading to the formation of the active radicals that start the polymerization mechanism (initiation). The crosslinking can occur by the reaction of the functional groups that exist in the monomer or polymer structure, which results in a direct intermolecular crosslinking (Figure 1).

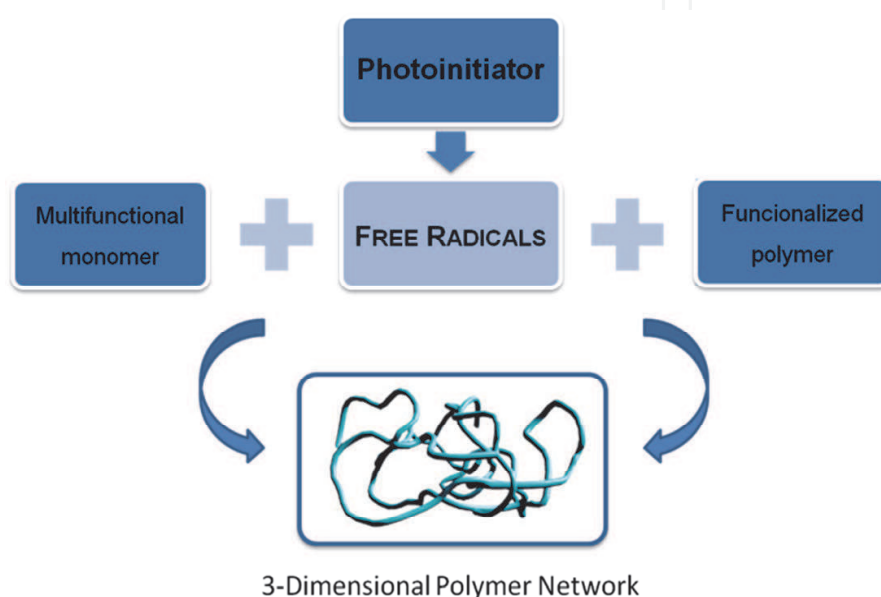


Fig. 1. Representation of the photopolymerization/photocrosslinking processes (Adapted from Decker, 2002).

The crosslinking density plays a critical role in the performance of the biomaterial since it controls properties including permeability, degradation, thermal and mechanic and water uptake (Martens et al., 2003). The use of the proper photoinitiator allows the fine tuning of the reaction rate and therefore the control of the density of crosslinking.

We can consider the existence of two basic types of photoinitiators (Allen et al., 1999): Type I, and Type II. Type I photoinitiators when exposed to UV radiation suffer a fragmentation process that origins the formation of the active radicals with the capacity to start the radical polymerization. Examples of such compounds are the acetophenone derivatives and the  $\alpha$ -hydroxyalkyl phenones. The  $\alpha$ -hydroxyalkylphenones, as for example 4-(2-hydroxyethylethoxy)-phenyl-(2-hydroxy-2-methyl propyl) ketone (Irgacure® 2959, Ciba) are extremely reactive and present a high thermal stability. Once irradiated, benzoyl and alkyl radicals are formed and although both radicals are reactive to initiate the polymerization, the benzoyl presents higher reactivity.

Type II photoinitiators require the presence of molecules, in the system, that suffer a primary process of hydrogen abstraction. These molecules are often referred as co-initiators and are usually tertiary amines. The reaction starts with the formation of the intermediary species resulting from the interaction between the amine and the photoinitiator carbonyl group. The

process continues with an electron and a hydrogen transfer resulting in the radical formation.

When biomedical applications are concerned, the biocompatibility of the photoinitiator is a critical issue to be considered. Williams and co-authors have studied the biocompatibility of the three different photoinitiators (2-hydroxy-1-[4-(2-hydroxyethoxy)phenyl]-2-methyl-1-propanone (Irgacure® 2959); 1-hydroxycyclohexyl-1-phenyl ketone (Irgacure® 184) and 2,2-dimethoxy-2-phenylacetophenone (Irgacure® 651)) commonly used in the preparation of biomaterials using six cellular lines (Williams et al., 2005). Their results revealed that different cell types react differently to the same concentrations of the same photoinitiator. Among the three compounds tested, Irgacure® 2959 presented the better results since very high cell tolerance (in all cell lines) was observed for a broad range of photoinitiator concentrations.

### 3. Biomedical applications

The UV irradiation is frequently used in the area of biomaterials as a strategy to modify both surface and bulk properties of polymers. These modifications allow us to improve some of their assets such as hemo and biocompatibility. It is also possible, by using radiation, to prepare crosslinked systems that may be used to encapsulate cells (Cruise et al., 1999; Hill et al., 1997; Li et al., 2006), proteins (Leach et al., 2005) or other compounds to be controlled delivered (Vieira et al., 2008; Tripodo et al., 2005).

In the following sections a literature review in some of the possible applications of photocrosslikable polymers will be presented. Also, some examples of some of the work that has been done in our own research group will be given.

#### 3.1 Bioadhesives

Primary wound healing of a plan-to-plan oriented scar formation is usually accomplished by hand sewing or stapling the corresponding layers of each side of the incision (Sheikh et al., 2000). However, both methods have been associated to wound infection and granule formation due to their degradation in the organism. They also present other disadvantages, such as the need to be removed, in most cases and the pain associated with their use.

Topical skin adhesives are increasingly being used by health professionals to replace sutures, staples and adhesive strips for wound closure. The use of adhesives provides several advantages that include: rapid application, unnecessary administration of anesthetics, no trauma is induced to tissues, less pain, unnecessary sutures or staples removal and improved cosmetic results.

Tissue adhesives may also be used as delivery systems and can be engineered for slow, localized release of bioactive molecules (Spicer & Mikos, 2010), such as pain treatment drugs or antibiotics (Fujimoto et al., 1997). They can be used as vehicles to growth factors (Catelas et al., 2008), and cell lines to assist on healing, namely, in poorly healing tissues like cartilage (Hoemann et al., 2005). Very recently, Spicer & Mikos (2010) reported several studies concerning the entrapment of drugs and growth factor in fibrin gels. Entrapment of such bioactive compounds was achieved by simply mixing the components before crosslink of the fibrinogen. At the end of the process a fibrin gel containing a bioactive molecule was obtained (Figure 2). The authors concluded that controlled delivery of drugs or factors by this method was in fact possible, and that release kinetics could be tailored through composition, affinity and covalent linkage between the bioactive molecules and fibrin.



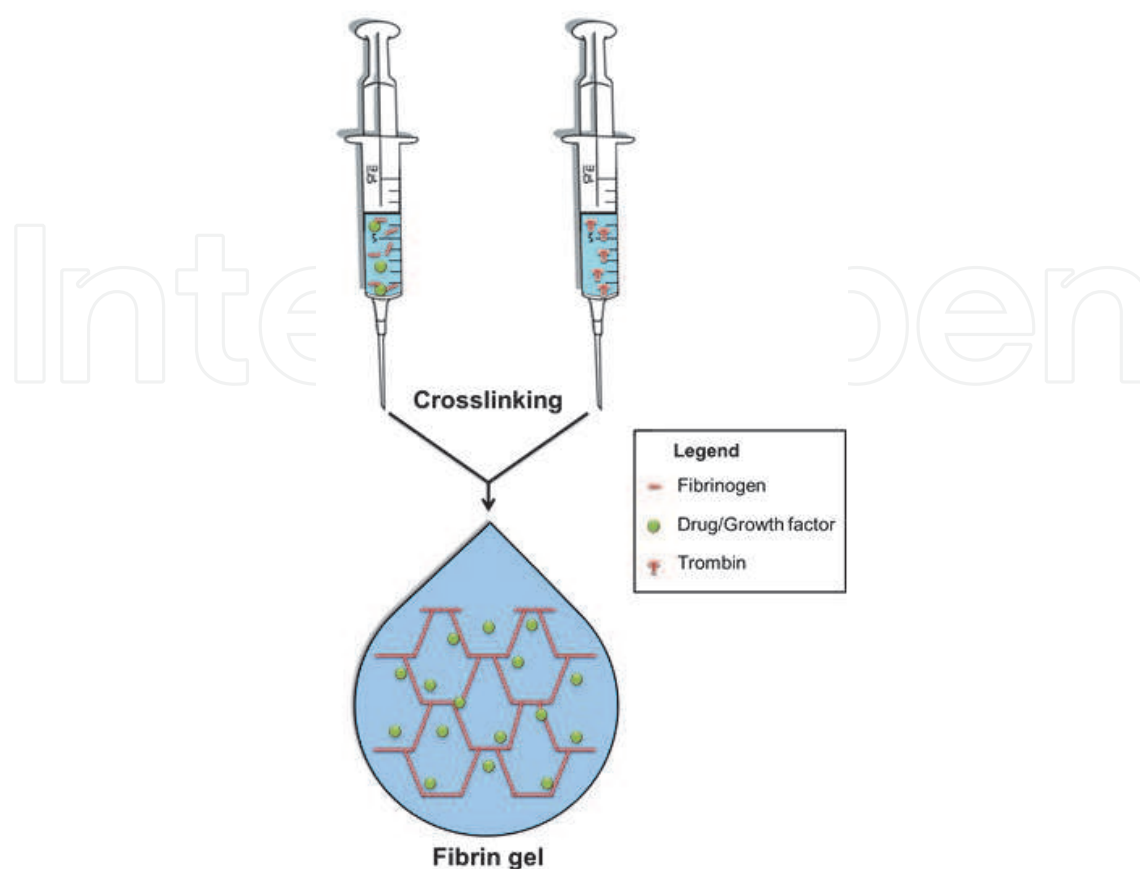


Fig. 2. Fibrin gel preparation and drug/growth factor entrapment. (Adapted from Spicer and Mikos, 2010).

Regardless their nature, surgical adhesives must obey some clinical requirements. They must hold the two sides of the tissue together, until it is no longer necessary, and then they should be degraded to biocompatible products (Lipatova, 1986). Also, an adhesive would ideally present the ability to cure in a moist environment.

Among the adhesives available on the market, the most applied are the ones based either on fibrin (Silver et al., 1995; Dunn & Goa, 1999) or cyanoacrylates (Leahey et al., 1993; King & Kinney, 1999). Both classes present some advantages as well as some disadvantages. Although fibrin glues contribute efficiently to hemorrhage control at bleeding wounds, their application is limited by their possible immunogenicity and risk of blood transmission diseases such as HIV and BSE. On the other hand, cyanoacrylates present a fast curing rate and a very strong adhesion to tissues but have been reported to degrade in aqueous media to produce formaldehyde, which causes inflammation and has got carcinogenicity potential.

Considering the described limitations, other options are now being considered, and among synthetic materials, urethane-based adhesives have been considered to be quite promising for this application. However, although several studies have already been conducted by other authors (Lipatova, 1986; Sheikh et al., 2000) and also by our research group in trying to develop urethane pre-polymers to be applied as bioadhesives (Ferreira et al., 2007, 2008a), these have proved that despite the good adhesion results, the curing time is too long to face surgical demands. UV curable adhesives offer major advantages

compared to pre-polymers systems, such as fast-curing rate, control of the polymerization heat evolution and are ideal for application to weakened and diseased tissue (Benson, 2002).

The photopolymerization and photocrosslinkage of polymers intending the preparation of bioadhesives has been largely developed during the second half of the 20<sup>th</sup> century. Throughout this period, several works translated into patents and scientific papers were published focusing on the development of various aspects of photopolymerization. Among them, new UV radiation sources, functionalized monomers and oligomers as well as new technologies for preparation of particles stand out (Moon et al., 2005).

A biological adhesive must present a combination of biocompatibility, performance and effectiveness. It should also present a fast curing rate when in contact with the living tissues. UV curable adhesives offer major advantages, such as fast-curing rate, control of the polymerization heat evolution, superior control over the final properties of the material and are ideal for application to weakened and diseased tissue (Benson, 2002). Another great advantage of such UV sensitive systems is allowing the adhesive to cure almost instantaneously, however selectively, in strongly illuminated areas such as the operating rooms (Decker, 2002).

Kao et al. (1997) have synthesized UV irradiation curable bioadhesives based on *N*-vinylpyrrolidone. The obtained results showed that these adhesives presented suitable adhesive strength. However, the UV induced setting time was of approximately 3 min which is a value that should be improved when surgical applications are concerned. A few years later, Ono and co-workers developed another photocrosslinkable adhesive based on chitosan. Its UV sensitivity and consequent crosslinking was dependent on azide groups that were introduced to the chitosan molecules. In vivo tests were conducted to evaluate its efficacy as well as the organism response (Ono et al., 2001). The final results showed that, 30 days after the surgical procedure, the adhesive was still present at implantation site surrounded by fibrous tissue. Also, inflammatory cells were observed around the material.

Since then, some work has been published describing attempts to develop a bioadhesive based on photosensitive polymers (Ho & Young, 2006; Grinstaff, 2007; Brigham et al., 2009). As an example, in our research group, Ferreira and co-workers (2008b) developed a photocrosslinkable biodegradable bioadhesive based on polycaprolactone (PCL). PCL is a semi-crystalline linear biodegradable aliphatic polyester that has been used in several medical applications already approved by the US Food and Drug Administration. Its structure presents several aliphatic ester linkages (Figure 3) that can undergo hydrolysis and its products of degradation are either metabolized by being included in the tricarboxylic acid cycle or eliminated by renal secretion.

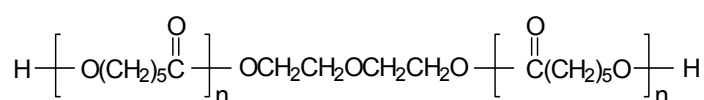


Fig. 3. Chemical structure of PCL.

The authors modified the polymer with 2-isocyanatoethylmethacrylate (IEMA) to form a macromer that was crosslinked via UV irradiation using Irgacure® 2959 by CIBA as the photoinitiating agent. Results showed that after 60s of irradiation the curing of the polymer was complete and membranes were obtained. The resultant films were then

characterized by several techniques that included swelling evaluation, thermal characterization, surface energy determination, electronic microscopy, biodegradation in human plasma and haemocompatibility (haemolysis and thrombogenicity). In a global appreciation, it was concluded that the obtained membranes presented a porous morphology and that biodegradation occurred although in a slow rate (10% of weight loss after 6 weeks). Also, the material was haemocompatible (no significant value of haemolysis was measured) and presented thrombogenic character (which would contribute to control wound bleeding). Finally, the adhesive was also able to promote efficient adhesion between the aminated substrates (gelatin was used as a model material), since during the binding strength tests, the gelatin pieces broke without compromising the glued section. The adhesive was posteriorly tested *in vivo* using Wistar rats, in two organs (skin and liver) and it proved to be efficient in keeping the glued surfaces together (even in moisture conditions) for the entire experimental protocol. After this period, the animals were euthanized and histological study of these organs was performed (hematoxylin & eosin coloration technique). No signs of necrosis or inflammation were detected in any of the target organs. Figure 4 presents a scheme summarizing the steps involved in this study.

### 3.2 Drug delivery systems

Drug delivery systems aim to control and sustain the distribution of drugs to attain optimal therapeutic efficiency. The earliest drug delivery systems were introduced in the 1970s and were based on poly(lactic acid). Nowadays, polymers are still the most used materials in this field of research mainly because of their ease of processing and also because of the possibility of researchers to control both their physical and chemical properties.

#### 3.2.1 Ophthalmology

Recently, significant advances have been made in optimizing the delivery of drugs to target tissues within the eye and in maintaining effective drug doses within those tissues (Geroski & Edelhauser, 2000). However, and despite all efforts, conventional ocular therapy for the treatment of acute and chronic diseases makes use of topical appliance of eye drops. This type of therapeutics represents nearly 90% of the marketed formulations. Still, this kind of appliance has a limited efficacy that is due to several factors, namely lacrimation, tear drainage and turnover, and the composition of the precorneal tear film itself.

One of the major limiting factors for drug absorption from the lachrymal fluid into the anterior chamber, after eye drop administration, is the low permeability of the corneal epithelium that results in a very low (around 5%) drug absorption by the cornea. The corneal epithelium consists of approximately five to seven cell layers (Figure 5) which make it a strong barrier to drug permeation.

The remaining amount of drug flows with tears through the upper and lower canonically into the nasolachrymal ducts and consequently may cause unwanted systemic side effects (Ali & Lehmussaari, 2006). The self-protective mechanisms of the eye, such as rapid tear turnover, limit the absorption of the instilled drug in the eye. In addition, application of ophthalmic drugs as drops results in rapid variation in drug delivery rates to the cornea that limits the efficacy of therapeutic systems.



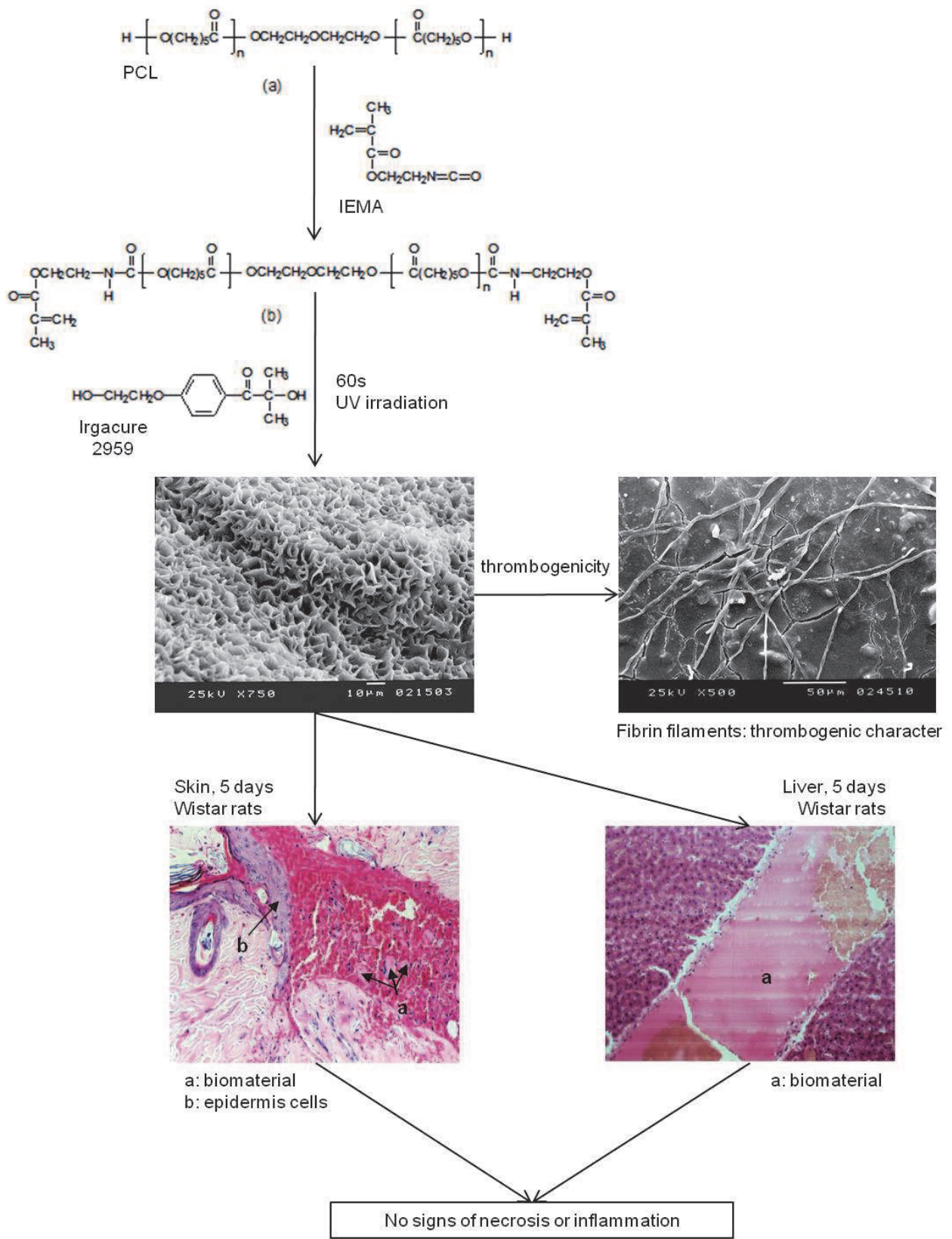


Fig. 4. Summary of the development and characterization of a UV curable PCL based bioadhesive.

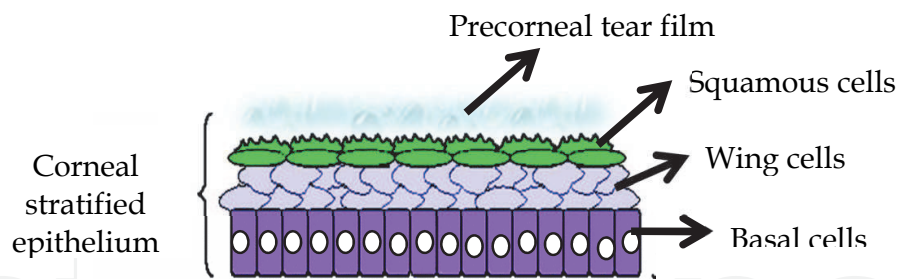


Fig. 5. Diagram showing the various layers of the corneal epithelium.

In order to improve the patient compliance for delivering the medications there is the need for finding some new implantable devices which could deliver the drugs in a long-lasting controlled manner. Using this strategy, the drug loss associated with systemic absorption would be minimized, and the resident time of the drug in the tear film increased (Ludwig, 2005). An alternative approach to optimize ophthalmic drug delivery is the adaptation of bioadhesive systems (Vasir et al., 2003), namely mucoadhesive ones, which have been proved to be successful in oral applications (Bernkop-Schnürch, 2005). Initially, intraocular implants aimed to achieve controlled and long lasting drug delivery for patients with glaucoma, proliferative vitreoretinopathy, cytomegalovirus retinitis, endophthalmitis, and posterior capsule opacification. Nowadays, new ambitions rely on the development of new drug delivery systems namely therapeutic targeting of retinal degenerative diseases and angiogenic reactions which lead to blindness (Bourges et al., 2006). These systems are prepared using different kinds of biodegradable or non-biodegradable polymers and can present several shapes: sheet, pellet, disc, rod, or plug (Figure 6).

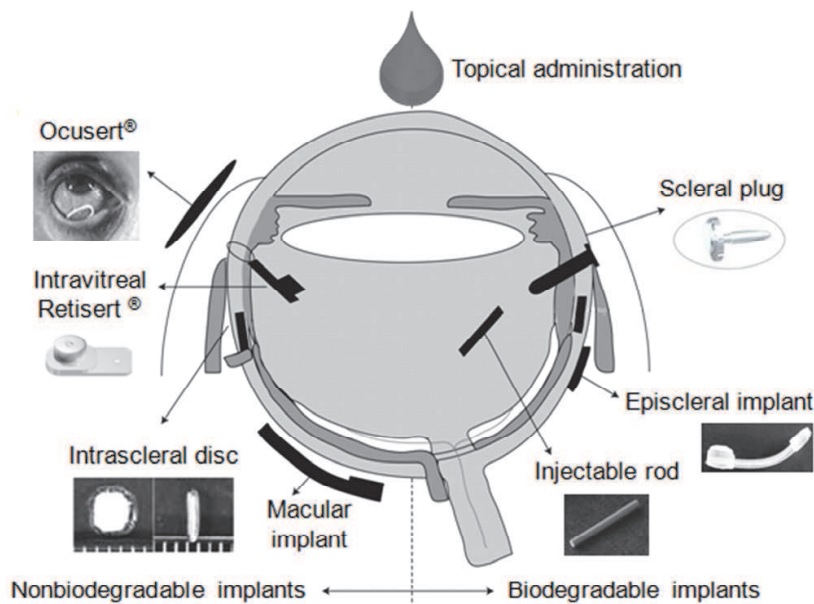


Fig. 6. Routes of ocular drug delivery. (Adapted from Short, 2008).

Among non-biodegradable implants, the best documented are based on polyvinyl alcohol (PVA)-ethylene vinyl acetate (EVA) (Okabe et al., 2003) and polysulfone (under the form of capillary fibers; Rahimy et al., 1994) Although both systems proved to efficiently control drug delivery for a long period of time, they present the disadvantage of being surgically

removed once the entire amount of drug has been released (Bourges et al., 2006). In order of overcoming this limitation biodegradable systems have been prepared based on several different polymers, namely: poly(lactic-co-glycolic acid) (Yasukawa et al., 2005); polycaprolactone (Shi et al., 2005); polyanhydrides (Leong et al., 1986) and poly(ortho esters) (Heller, 2005).

In our research group, a starch-based polymer with urethane linkages to be used as a controlled drug delivery system for biomedical applications was developed (Vieira et al., 2008). Hydroxyl groups present on starch were modified with 2-isocyanatoethyl methacrylate (IEMA) in order to obtain a polymer containing carbon-carbon double bonds. This modified starch was then used to prepare films by UV irradiation using Irgacure® 2959 (CIBA) as the photoinitiator.

The obtained films were characterized by several techniques and some parameters were evaluated. The swelling capacity in artificial lachrymal fluid (performed both at room temperature and physiological temperature), was determined and even though some hydroxyl groups of starch were modified, it was observed that polymeric matrix remained hydrophilic. The in vitro biodegradation in artificial lachrymal fluid supplemented with lysozyme was also studied for 6 weeks and it was verified that biodegradation of the samples remained almost constant during experimentation time. Scanning electronic microscopy (SEM) was used to characterize the morphology of the materials immediately after synthesis and after biodegradation and it was possible to visualize pore size increasing due to the degradation process. Since the main goal of this work was to develop a controlled drug delivery system for ophthalmic application, timolol maleate and sodium flurbiprofen were immobilized by adsorption inside the polymeric matrix and their in vitro release profiles were followed spectroscopically (for 10 days). As general conclusions, one can mention that it was possible to verify that the drugs' incorporation into the polymer matrix was mainly controlled by the swelling behavior of the polymer, rather than the different characteristics of each tested drug. Also, drug release studies proved that incorporation of the each drug resulted in a different diffusional behavior. Timolol revealed to be a Case II diffusional anomalous process, whereas flurbiprofen diffusion presented a typical Fickian release pattern. However, the main driving force of the release pattern in both cases appears to be diffusion of the drugs from the polymeric matrices. Figure 7 presents a scheme summarizing the steps involved in this study.

### 3.2.2 Responsive hydrogels for dermatologic applications

Human skin is an easily accessible surface for drug delivery and covers a surface of approximately 2m<sup>2</sup> in a young adult. Also, it receives about one-third of the blood circulating through the body. For these reasons, transdermal drug delivery (Figure 8) represents an attractive alternative to oral delivery of drugs as well as to hypodermic injection since is a non-invasive technique and can be self-administered.

The first transdermal drug delivery system was approved by the FDA in 1979 and consisted in a patch with a 3 days release of scopolamine (an alkaloid used in the treatment of nausea and motion sickness). During following years, many systems were developed and some of them remain until now as real best-sellers (Prausnitz and Langer, 2008). Among them, nicotine patches are probably the more broadly used. Other systems available on the market include the ones containing: fentanyl (a synthetic narcotic analgesic), lidocaine (a local anesthetic) and hormones (either for contraception or hormone replacement). In fact,

transdermal patches are so largely used nowadays, that it is estimated that more than one billion are currently manufactured each year.

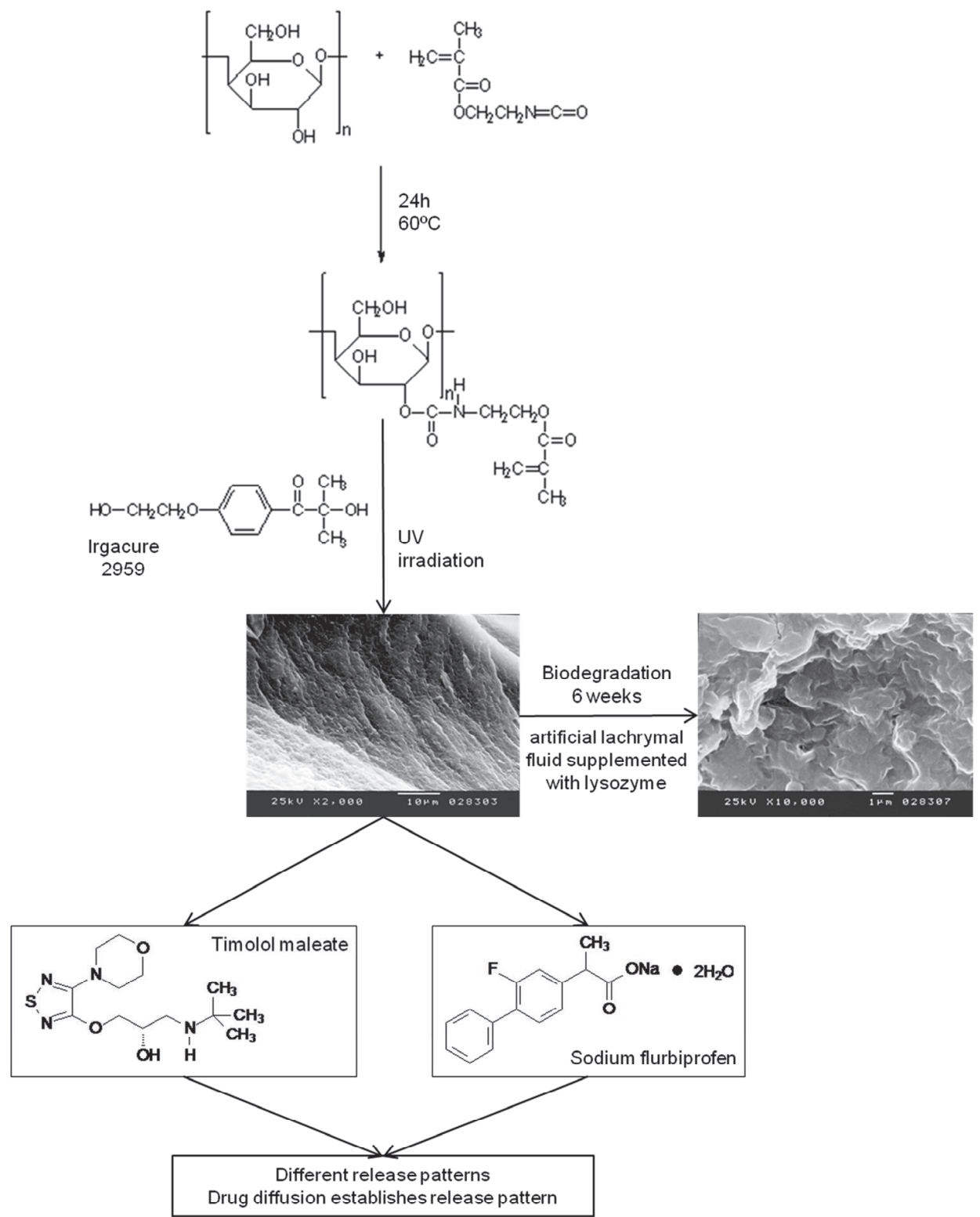


Fig. 7. Summary of the development and characterization of a UV curable starch based drug delivery system.



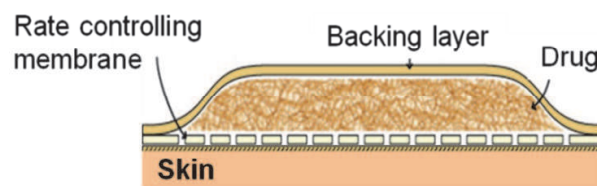


Fig. 8. Scheme of a transdermal drug delivery system.

Among the systems designed for drug release, the ones based on hydrogels are receiving most of the current attention. Hydrogels used for this purpose are usually prepared outside the organism and impregnated with drugs before placement of the system in the body. Several methods are available to achieve crosslinking of the matrices, namely UV photopolymerization and various chemical cross-linking techniques (Hoare and Kohane, 2008).

Hydrogels are materials that, when placed in aqueous medium absorb and retain large amounts of water without dissolving in the solution (Hennink and van Nostrum, 2002; Hatice Kaplan, 2005). In the polymeric structure of hydrogels, the hydrophilic parts of gels tend to be highly hydrated in the aqueous environment triggering the big water uptake that characterizes these structures (Coviello et al., 2007). Because of their properties, namely hydrophilicity and biocompatibility, hydrogels have been a subject of interest in different areas especially in the preparation of drug delivery systems (DDS) (Hoffman, 2002; Ulbrich, 1995).

Both natural and synthetic polymers can be used to prepare hydrogels. Natural-based hydrogels lack mechanical strength and may contain pathogens that induce immune or inflammatory host responses. However, they simultaneously present some advantages such as their biodegradability, biocompatibility and biologically recognizable moieties that are compatible with cellular activities. Synthetic hydrogels, on the other hand, do not possess these inherent bioactive properties and are often modified in order to improve their bioactivity (Bajpai et al., 2008).

Although the variety of hydrogels already used as DDS, a great interest in this field of research still exists mainly in the development of gels that present a phase transition that responds to changes in external conditions. The most important systems from biomedical point of view are those sensitive to temperature and/or pH of the surroundings. These materials are known as “stimuli-responsive” or “smart” gels and can undergo abrupt volume changes in response to small changes in environmental parameters. Their ability to swell or deswell according to external conditions, leads to a drug release profile that varies with the same specific parameters (Figure 9).

Among stimuli responsive hydrogels, we will be focusing on the ones sensitive to temperature. These materials are prepared using polymers in carefully chosen in order to achieve a delicate balance between hydrophilic and hydrophobic groups. The most extensively studied temperature-sensitive polymer is poly(N-isopropylacrylamide) or PNIPAAm which consists on a non-biodegradable polymer (Figure 10).

PNIPAAm shows a lower critical solution temperature (LCST) at approximately 32°C which means that is soluble in water below this temperature but precipitates rapidly when temperature is raised above 32°C. This means that crosslinked gels prepared using these polymers suffer an abrupt change in their volume when temperature value varies above or below the LCST (Satish et al., 2006). In fact, these materials expand and swell when cooled below the LCST, and shrink and collapse when heated above the LCST. As a consequence, drug release profile undergoes the same variations patterns.



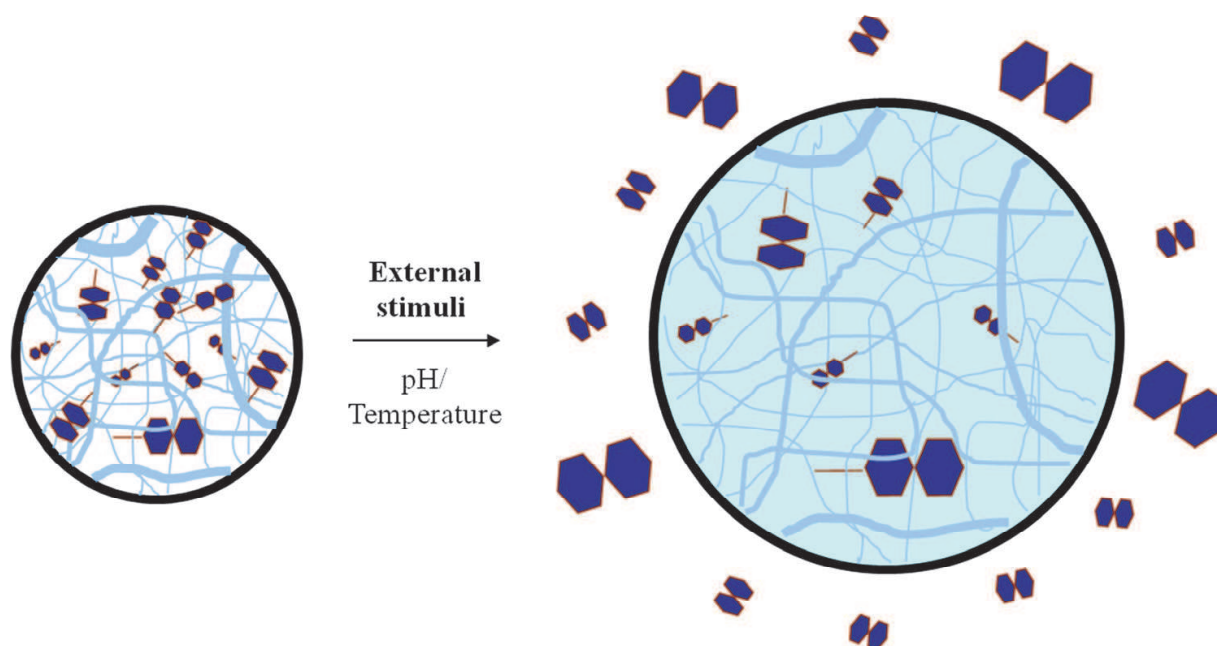


Fig. 9. Schematic representation of the on-off release from an intelligent stimuli-responsive hydrogel designed for drug release.

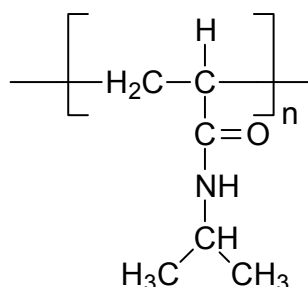


Fig. 10. Chemical structure of PNIPAAm.

Several works have been reported using crosslinked gels based on PNIPAAm starting with Tanaka (1981). Later, this same polymer was used to develop materials to be applied as biomaterials (Dong and Hoffman, 1990). These authors recognized its potential to entrap enzymes or cells and regulate their activity by manipulating swelling/deswelling of the hydrogel (Dong and Hoffman, 1986; 1987). They also studied the possibility of delivering drugs or removing toxins by such hydrogels when controlling external stimuli (Dong and Hoffman, 1991; Park and Hoffman, 1992). Since then, PNIPAAm hydrogels have been prepared under several forms and for various purposes. Vernon and co-workers synthesized gels with entrapped cells to be used as artificial organs (Vernon et al., 2000). A few years later, Dubé and co-workers (Dubé et al., 2002) prepared drug carriers for tumoral cells by synthesizing folate-PNIPAAm conjugates that were fluorescently labeled. They evaluated the targeting specificity of this complex by measuring its cellular uptake. They also conducted direct competition experiments with free folate and demonstrated that the PNIPAAm-folate conjugates effectively target the cells even at folate concentration above

normal serum levels. PNIPAAm nanoparticles have also been prepared and their potential applications in biotechnology and in medicine evaluated. Koňák and colleagues (2007) prepared thermoresponsive nanoparticles by heating PNIPAAm solutions with low surfactant additions above the LCST. More recently the preparation of a poly(*N*-isopropylacrylamide)-co-poly(ethylene glycol) (PNIPAAm-PEG) injectable scaffold platform for the repair of spinal cord injury (SCI) was reported (Comolli et al., 2009). The authors stated that this scaffold allows cell attachment, provides mechanical support and allows a sustained release of neurotrophins (growth factors that induce the survival, development, and function of neurons).

Another approach on the synthesis of crosslinkable hydrogels is grafting of PNIPAAm linear chains onto natural polymers (Hoare and Kohane, 2008). As an example, temperature-sensitive injectable gels were prepared by grafting amino-terminated semi-telechelic PNIPAAm onto hyaluronic acid (HA) backbones (Ha et al., 2006). Riboflavin was entrapped in the resulting gel and *in vitro* tests results showed a more sustained release behavior when the grafting yield of PNIPAAm onto the HA backbone was increased. Another example is the work performed by Bae and co-workers (2006). These authors prepared two types of injectable systems using thermosensitive chitosan (chitosan grafted with PNIPAAm): a hydrogel and microparticles-embedded hydrogel. Both systems were developed as drug carriers for controlled release of 5-fluorouracil (5-FU). The results from this study showed that 5-FU release profile from microparticles-embedded hydrogel reduced the burst effect from the beginning of each initial stage. Therefore, the authors suggest that this combined system could be used as an injectable drug carrier for local drug delivery.

PNIPAAm networks interpenetrated in alginate- $\text{Ca}^{2+}$  networks were synthesized and the release of bovine serum albumin (BSA) from the hydrogels was evaluated by Moura and co-workers (2008). The authors concluded that the amount and rate of BSA release could be tailored by the tuning up of the PNIPAAm and/or alginate quantity in the hydrogel and by the control of temperature.

Recently a combination of biodegradable microspheres with a PNIPAAm hydrogel was prepared by Yang and colleagues (2011). They studied the release of BSA from the system and concluded that controlled release of BSA encapsulated in the microspheres embedded in PNIPAAm scaffold was better controlled than when encapsulated in the hydrogel alone.

Temperature-sensitive hydrogels can also be useful for topical delivery of drugs to skin or mucous membranes such as the nose or the eyes. Although the temperature of such surfaces is slightly below 37°C, its value is still above ambient temperature which means that it would be possible to deliver a drug through a thermo-responsive polymer.

One example of such application is the work developed by Almeida and co-workers (2010) at our laboratory during which, graft polymer hydrogels based on dextran and *N*-isopropylacrylamide (NIPAAm) were prepared and characterized. For that purpose, dextran was firstly modified in order to incorporate carbon-carbon double bonds and then NIPAAm was added to the modified polymer. The resultant material (dextran-grafted-PNIPAAm) was obtained by crosslinking using UV irradiation in the presence of the photoinitiating agent Irgacure® 2959 by CIBA. The drug Ondansetron® (an antiemetic used to treat nausea and vomiting, frequently following chemotherapy, Figure 11) was entrapped in the final system and its release profile was determined at 25 and 37°C. The authors

concluded that controlled release of the drug occurred for at least one week and that temperature influenced drug release pattern.

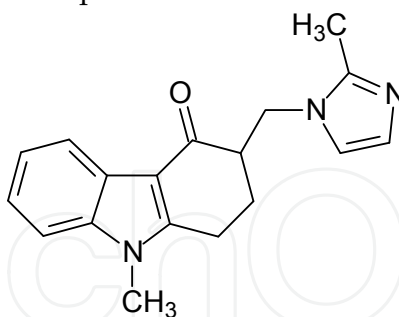


Fig. 11. Chemical structure of Ondansetron®.

These results are extremely important as they show that these systems can be adjusted to have different transition temperatures according to the applications needed giving them a wide range of use.

#### 4. Conclusions

Photocrosslinked polymers may be very useful for biomedical applications.

The use of photopolymerization is advantageous in comparison with other conventional crosslinking methods, since we can obtain biomaterials in situ and in a minimally invasive manner.

The photopolymerizable polymers based either in natural (starch, chitosan and dextran) or synthetic polymers (polycaprolactone), were used for the development of biomaterials, mainly hydrogels.

These materials were applied in the development of bioadhesives, drug delivery systems for ophthalmology and wound dressings.

The results of our research indicate that the systems are suitable for medical applications and make feasible innovative strategies for photocrosslinked polymers in clinical use.

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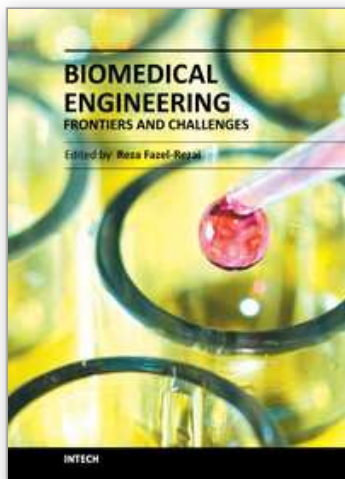
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## **Biomedical Engineering - Frontiers and Challenges**

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In all different areas in biomedical engineering, the ultimate objectives in research and education are to improve the quality life, reduce the impact of disease on the everyday life of individuals, and provide an appropriate infrastructure to promote and enhance the interaction of biomedical engineering researchers. This book is prepared in two volumes to introduce recent advances in different areas of biomedical engineering such as biomaterials, cellular engineering, biomedical devices, nanotechnology, and biomechanics. It is hoped that both of the volumes will bring more awareness about the biomedical engineering field and help in completing or establishing new research areas in biomedical engineering.

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Phone: +86-21-62489820  
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