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SMART HYDROGELS FOR THE TREATMENT OF ORAL CAVITY DISEASES

BY

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Abstract. The unique environment specific to the oral cavity is suitable for the proliferation of pathogenic bacteria and infections. The effectiveness of drug treatment is often reduced due to the fact that saliva dilutes the mediating formulation and reduces the interaction between the drug and its site of action. An efficient way to solve this problem is the creation of polymeric systems sensitive to the action of stimuli that command the release of the drug at the right place, time and in suitable doses. Due to their ability to respond to stimuli, hydrogels have been applied as an excellent drug-delivery system for treatments that include caries, endodontic diseases, periodontal diseases, bone diseases, mucosal diseases, oral cancer. The present paper proposes a review of recent research in the field of obtaining hydrogels that respond to physical (temperature, UV and visible light) chemical (pH, glucose) and biological stimuli (enzymes) - smart hydrogels -, with applications in the treatment of oral cavity diseases.

Keywords: hydrogels, oral cavity diseases, drug delivery system, stimuli sensitive systems, topical administration.

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1. Introduction

The oral and maxillofacial region, located at the beginning of the respiratory and digestive tract, constitutes a complex system, with various anatomical structures such as periodontal tissue, skin, mucous membrane, teeth and other organs and tissues. They fulfill various physiological functions (mastication, breathing, articulation) and even social ones, if we refer to the facial appearance and esthetic maintenance (Matichescu *et al*., 2020; Ulaganathan *et al*., 2020; Hatcher, 2022).

There is a number of diseases specific to this region, such as pulpitis, periodontitis, alveolar osteitis, apical periodontitis, caries, candida infections or cancer (Liu *et al.*, 2023). Their treatment is an important challenge for doctors, because they can cause to the patient a series of defects and dysfunctions of the affected anatomical structures (periodontal tissue, skin and mucosa, salivary glands, mandibular joints, teeth). Their impact, in addition to the suffering caused, can later even influence the physical and mental state of the patient and ultimately decrease the quality of life.

The conventional treatment of these diseases, by taking systemic or even local (topical) administration of drugs, does not prove to be highly effective. This is due to the fact that the passive target does not ensure a sufficient, constant and long-term concentration of the drug at the site affected by the disease, given being that the dynamic anatomical structure and the complex vascular system often lead to inadequate release and limited efficiency of drug absorption. The experience accumulated until now has proven that the key to an adequate and effective treatment is the use of drug release systems applicable *in situ* and capable of ensuring a concentration located in the therapeutic range as long as possible.

Drug (and other biologically active principles) delivery systems (DDS), constitute a separate class of biomaterials, being formulated in various ways, depending on the specific desired application: films, micro/nanoparticles, micro/nanocapsules, implants, inserts, etc. They are mostly built on the basis of polymers, but they can also be made of other biocompatible materials such as lipids (liposomes), metals and metallic oxides (gold, silver), non-metallic oxides (silica) or their combinations, carbon nanostructures (fullerenes, carbon dots, graphene, carbon nanotubes). However, the overwhelming majority is made on polymers, which must meet a series of constraints: to be biocompatible, biodegradable under physiological conditions and not to provide toxic products through degradation. That is why biopolymers are preferred in medical applications - polymers of natural origin from the class of polysaccharides and proteins - and more rarely some synthetic polymers that meet these conditions. In recent years, DDSs have also been developed based on combinations of natural polymers with some synthetic polymers or their composites with inorganic materials (silicates, clays, carbo dots, etc.) (Kuperkar *et al.*, 2024).

Within DDS, a dominant place is occupied by hydrogels that show a promising potential in terms of ensuring an efficient therapeutic effect at the place affected by the disease and simultaneously allow the repair of some structural defects (Annabi *et al*., 2010; Bencherif *et al*., 2013). This type of biomaterial is characterized by a three-dimensional structure made by creating transverse bonds between hydrophilic polymer chains, which gives them mechanical stability but especially the ability to retain large amounts of water and water-soluble compounds. However, it must be emphasized that the hydrogels themselves do not allow the treatment of various diseases (including oral ones) or the repair of defects, but they constitute a platform that can include/encapsulate drugs or other compounds with therapeutic potential, ensuring their integrity until the target, where they are released by diffusion or disintegration assuring a long therapeutic effect. Moreover, due to their structure and biocompatible character, hydrogels are similar to the extracellular matrix (ECM) being able to encapsulate and ensure the development of stem cell cultures or cytokines with important applications in tissue engineering (Ahmed, 2015).

Currently, hydrogels have found applications in many fields of medicine, becoming important candidates for the treatment of oral cavity and maxillofacial disorders, involving injection (Zhao *et al*., 2017), use as a scaffold (Gelain *et al*., 2020), dressings (Francesko *et al.*, 2018), inserts, 3D bio-printing (Mandrycky *et al.*, 2016). Figure 1 illustrates the applications of hydrogels in the treatment of oral disorders (Liu *et al*., 2023).

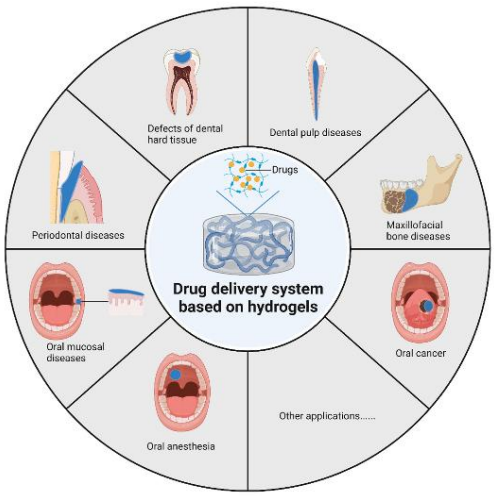


Fig. 1 − Applications of hydrogels in the treatment of oral and maxillofacial diseases (Liu *et al*., 2023, reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license http://creativecommons.org/licenses/by/4.0/).

Some hydrogels show, in addition to the other specific properties of these materials, the ability to respond to external stimuli: physical stimuli (temperature, light, electric or magnetic field, mechanical stress), chemical stimuli (pH, glucose), as well as biological stimuli (enzymes).

This special category of materials is generically called "intelligent hydrogels" or "smart hydrogels" and constitutes an intensively investigated field. Fig. 2 presents in a suggestive form the most important types of intelligent hydrogels used in the encapsulation and release of drugs (DDS) and suggests how they release the biologically active principle under the action of external stimuli (Wei, 2024).

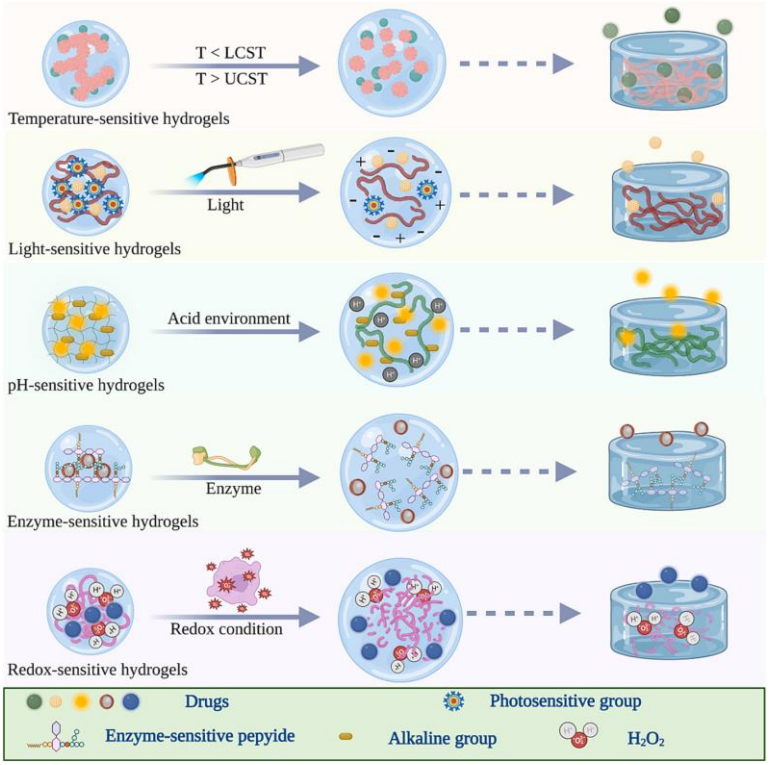


Fig. 2 − Schematic illustration of some types of smart hydrogels used as DDS (Wei *et al.*, 2024, reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license http://creativecommons.org/licenses/by/4.0/).

The present work proposes a review of the types of intelligent hydrogels, based on the consultation of the recent literature in the field, highlighting the concept, methods of synthesis and the benefits of such material that can be used as DDS in the treatment of specific disease of the oral cavity and of the maxillofacial region.

2. Temperature-responsive hydrogels

Among the smart hydrogels, those that respond to changes in temperature are the most investigated, being used to release drugs when this parameter changes (Milcovich *et al*., 2017).

Numerous such materials have known applications, especially in the treatment of oral cavity diseases, the explanation being relatively simple: compared to the skin or even other parts of the body, its temperature is relatively higher and stable (Hao *et al*., 2023).

We can talk about two categories of thermo-responsive hydrogels, namely: ***(i)*** injectable thermosensitive hydrogels which in their initial state are liquid (sol state) but upon injection into the organism, a reversible sol-gel state transition can be achieved through slight changes in ambient temperature, specific to the physiological conditions; ***(ii)*** preformed hydrogels that are introduced into the body in the form of implants, inserts, micro/nanoparticles, and that undergo conformational changes at the physiological temperature that result in the release of the included bioactive principle.

Injectable temperature-sensitive hydrogels can be obtained starting from amphiphilic copolymers (block or grafts), which therefore contain both hydrophilic and hydrophobic segments in the structure, and whose physical state depends on the relative balance of these segments (Chen *et al*., 2022a; Huang *et al*., 2019). The mechanism of the sol-gel transition is determined by the change in the hydrophilic/hydrophobic balance, and depending on the chemical structure of the polymer, two types of transition are possible. In the first case, by increasing the temperature, the interactions between water and polymer molecules weaken, so that the latter begin to associate, forming the hydrogel; the process is known as the lowest critical solution temperature (LCST) type phase transition, and the hydrogels that show such behavior are called "*negatively sensitive hydrogels*". Changing the hydrophilic-hydrophobic balance can result in changing the LCST. The second case is specific to polymers that have a critical maximum temperature of passing into solution, so gelation is favored by the decrease in temperature; they therefore present a upper critical solution temperature (UCST) and the hydrogels generated by these polymers are called "*positively sensitive hydrogels*", being typical of polysaccharides such as carrageenan, agarose, and proteins (gelatin) that require high temperatures to go into solution. However, excessively high temperatures can harm the viability of cells and tissues in organisms.

LCST-type polysaccharide hydrogels are better for injectable hydrogel systems as they are free-flowing solutions at ambient temperature and transform into gels at body temperature. From the point of view of the molecular mechanism of the sol-gel transition, the following considerations can be made. At temperatures below the LCST, the hydrophilic effect is the main force. The hydrophilic groups on the polymer molecular chains connect with water

molecules through hydrogen bonding, resulting in a sol state. When the temperature rises above the LCST, hydrophobic interactions become dominant, which contributes to formation of bulky aggregates by the association of hydrophobic polymer chains, resulting in a gelation phase transition (Wang *et al*., 2018). The sol-gel transition is reversible, because of the dynamic interactions between polymer chains and water molecules. From the thermodynamic point of view, when temperature rises above LCST, the entropy of the system increases and becomes dominant, because the system goes into a more orderly state. As a result, the free energy variation ΔG becomes negative, which represent the gel state and is favorable for the association of polymer chains. So, thermodynamically, the sol-gel phase transition of thermosensitive polymers is driven by an increase in entropy.

There is a wide range of thermosensitive polymers with LCST type transition, either of synthetic nature, or natural polymers or their derivatives. Some examples of thermosensitive hydrogels will be presented in the following.

A first category of such hydrogels is those originating from synthetic polymers or copolymers. Copolymers of poly(N-isopropylacrylamide) (PNIPAAm) (which have an LCST value of 30ºC) are probably the most extensively studied temperature sensitive systems (Coughlan *et al*., 2004; Yin *et al*., 2006). By PNIPAAm grafting or copolymerization with other vinyl or acrylic monomers, precursors of some thermo-injectable hydrogels can be obtained characterized by a LCST temperature close to the physiological one (37˚C). For example, by copolymerisation of NIPAM with propylacrylic acid (PAA) (Garbern *et al*., 2010) (Fig. 3) a thermo-responsive hydrogel was obtained and the LCST was adjusted closer to body temperature.

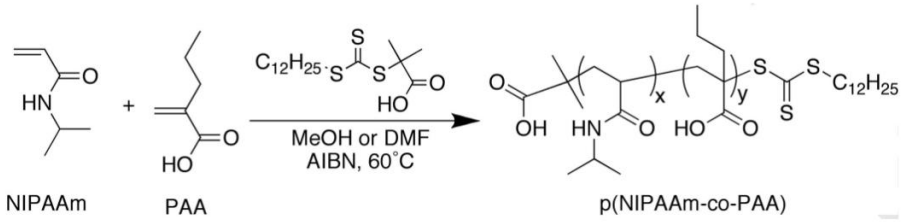
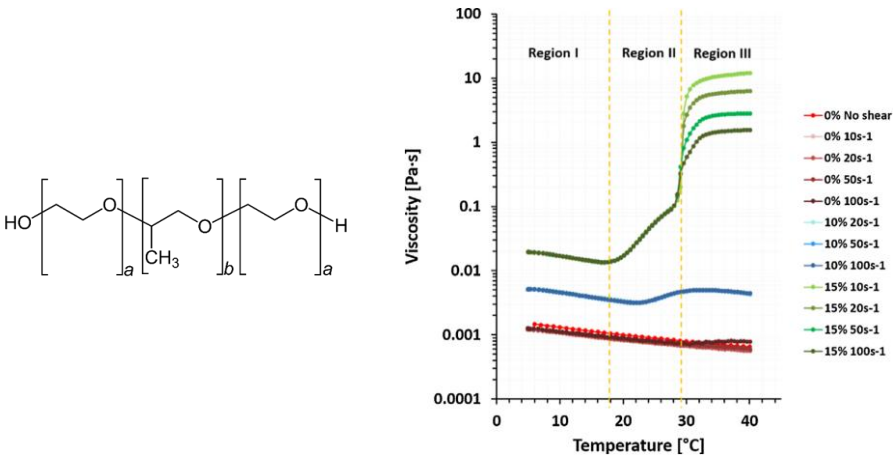


Fig. 3 – Synthesis of p(N-isopropylacrylamide-*co*-propylacrylic acid) [p(NIPAAm-co-PAA)] by reversible addition fragmentation chain transfer (RAFT) polymerization. (Garbern *et al*., 2010, reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license http://creativecommons.org/licenses/by/4.0/).

Similarly, by copolymerisation of NIPAM with acrylic acid (AA) and hydroxyethyl methacrylate (HEMA) another type of hydrogel was obtained. It is important to note that the gelation occurs, practically, at the physiological value of the temperature (Huang *et al*., 2019).

NIPAM copolymers with vinylic and acrylic monomers mentioned above have proven effective in loading with azithromycin, obtaining thermosensitive systems with applications in the treatment of periodontitis

Poloxamer hydrogels are thermos-responsive hydrogels that become fluid when cooled and gel-like when heated. Poloxamer (Pluronic) is a triblock copolymer which is composed of a central hydrophobic poly(propylene oxide) (PPO) core with hydrophilic poly(ethylene oxide) (PEO) chains on both sides (Fig. 4a). Due to its amphiphilic character, it can form micelles in aqueous solutions, its core being made up of the hydrophobic segment (Popovici *et al.*, 2022). By heating, upon reaching the LCST, the micelles come into contact with each other, forming a hydrogel-like network, highlighted by the increase in viscosity. Through rheological measurements of Poloxamer solutions, three temperature ranges were highlighted on the viscosity evolution curves, finding that the polymer goes into a gel state at a temperature of around 30ºC, when the viscosity becomes higher depending on the concentration of the solution (Fig. 4b) (Shriky *et al.*, 2020). An injectable Poloxamer hydrogel loaded with gentamicin sulfate (antibiotic) was studied for its antibacterial properties against *Escherichia coli*, *Bacilus cereus*, and *Staphylococcus aureus*, and the antibacterial tests carried out proved that the system can be a potent drug carrier for infected cavity wounds (Niyompanich *et al.*, 2021).



a b

Fig. 4 − General chemical structure of a poloxamer (a) (https://en.wikipedia.org/wiki/Poloxamer and the variation of the viscosity of poloxamer aqueous solutions of different concentrations, depending on the temperature) (b) (Shriky *et al.*, 2020, reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license http://creativecommons.org/licenses/by/4.0/).

An *in situ* thermo-sensitive hydrogel based on Poloxamer 407 was fabricated to incorporate chlorhexidine digluconate - loaded β-cyclodextrin-jeffamine-based microgel particles for periodontitis treatments (Morelli *et al*., 2017). The system is capable to undergo rapid thermally induced sol-gel phase transition at body temperature. The effectiveness of system to achieve sustained release of antimicrobial agents was demonstrated *in vitro*, and results achieved disclose his potential in effectively treating periodontitis lesions. Generally, *in vitro* release tests for systems based on Pluronic proved that they could control the release of drugs over 10 days (Yu *et al*., 2021).

A mixture of Poloxamer and Carbopol P934 mixed with borax and choline salicylate led to obtaining a thermosensitive hydrogel that gels at the temperature of the oral cavity and has important mucoadhesive properties. Tests on mice demonstrated the potential of its use in the treatment of oral ulcers, finding that it completely disappears after 5 days of treatment (Wang, 2020; Gurav and Husukale, 2023). Other research has proven the potential of Pluronic-based hydrogels carrying drugs, for more effective treatment of periodontal tissue degradation. An interesting result is reported by Nasra *et al.*, who found that the *in vivo* testing of a hydrogel based on Poloxamer and Carbopol loaded with curcumin on patients with adult periodontitis could aid in significant clinical reduction of probing depth, bleeding index, and to less extent of plaque (Nasra *et al*., 2017).

Poly(ethylene glycol) (PEG) is intensively used in obtaining copolymers that can generate thermos-sensitive hydrogels. By copolymerization with biodegradable polyesters, non-toxic, biocompatible compounds can be obtained. An example is the triblock copolymer poly((lactic acid)-co-(glycolic acid) and poly(ethylene glycol) (PLGA-PEG-PLGA) whose synthesis is carried out starting from PEG and cyclic esters (D,L-lactide and glycolide) (Fig. 5)(Fan *et al*., 2022). As can be seen (Fig. 6b), The sol-gel transition temperature of the copolymes located at the intersection of the two rheological modules, is approximately 28ºC (Shinde *et al*., 2012). The thermal response properties can be improved by adjusting the length of the hydrophobic polyester block and the PEG block appropriately (Petit *et al*., 2012).

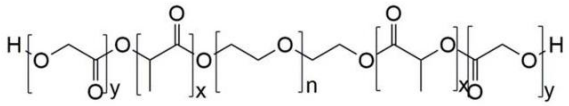


Fig. 5 – Structure of PLGA-PEG-PLGA copolymer (Fan *et al*., 2022), reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license http://creativecommons.org/licenses/by/4.0/.

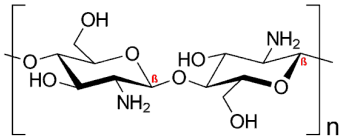
Such a hydrogel can be used to release antibacterial drugs specific to the treatment of typical oral cavity conditions (Liu *et al*., 2023). A triblock copolymer

of PEG (central block) with poly(D,L – lactide) (side blocks), capable of micellization due to its amphiphilic character, reported by Chen *et al.* is characterized by the sol-gel transition at 37°C, after only 24 sec. The encapsulation of gambogic acid (antitumor) in the micelles and the topical administration of the hydrogel by injection facilitated the release of the drug directly into the tumor, which has the effect of increasing the antitumor activity of the system against oral squamous cell carcinoma (Chen *et al*., 2022b).

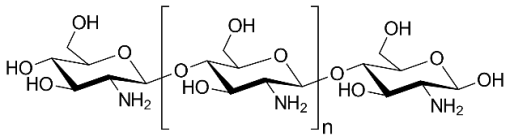
Recently, thermo-responsive PCL-PEG [poly(ε-caprolactone)-poly(ethylene glycol)] hydrogels have attracted extensive attention as a promising alternative hydrogels based on PLGA-PEG copolymers. An excellent review was recently published, discussing the existing literature on this subject (Mithun *et al*., 2022). Triblock copolymers were synthesized, in two variants, namely with the central block formed by PEG, respectively by PCL-(Wei *et al*., 2009). Copolymers have the ability to gel at a slightly higher than physiological temperature, which makes them useful as release systems for antitumor drugs, especially due to the fact that in the tumour the temperature is higher than in the rest of the body, which favours instant gelation. Another important advantage is that the usually intense burst effect present in hydrogel release systems is greatly reduced. The possibility of encapsulating and releasing from the hydrogel drug (in this case diclofenac) suggests the application of such a hydrogel in the treatment of some forms of cancer of the oral cavity. The disadvantage of such hydrogels is the rapid degradation with the formation of acidic compounds, and poor mechanical properties.

Polysaccharides constitute a wide class of natural polymers, preferred in obtaining biomaterials. Some of the native ones possess thermosensitive properties: agarose, carrageenan which form “positively sensitive hydrogels”. However, numerous other polysaccharides can be chemically modified to acquire thermosensitive properties and to generate “negatively sensitive hydrogels”. A strategy for obtaining such hydrogels is grafting with NIPAM.

Some examples of polysaccharides that can generate, following chemical transformations or by association with other polymers, thermosensitive hydrogels, are presented in Fig. 6.



Hydroxypropyl methyl cellulose (HPMC)



Chitosane

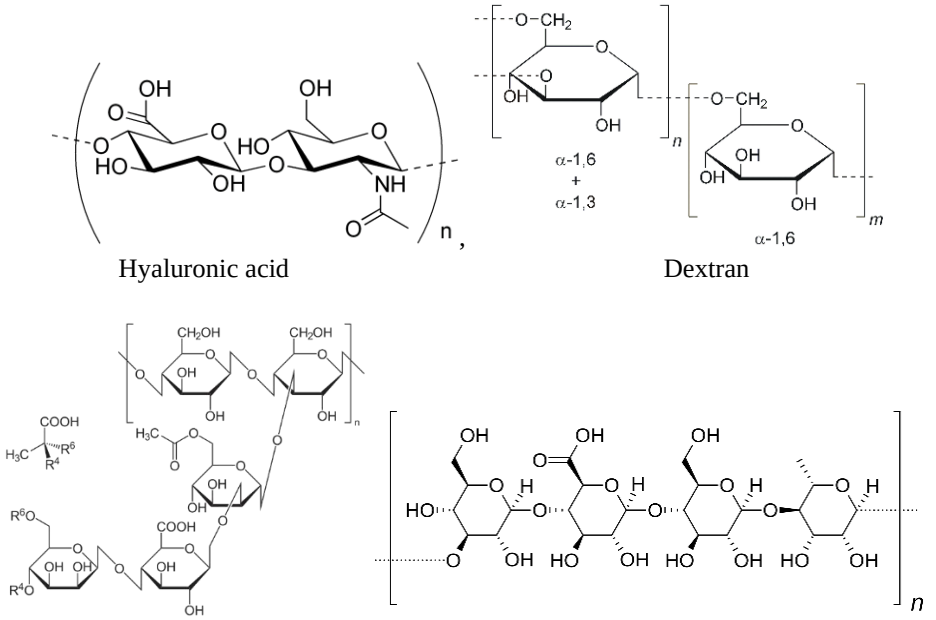


Fig. 6 − Some examples of polysaccharides that can generate thermosensitive hydrogels (https://de.wikipedia.org/wiki/Hydroxypropylmethylcellulose, https://fr.wikipedia.org/wiki/Chitosane, https://fr.wikipedia.org/wiki/Acide_hyaluronique https://fr.wikipedia.org/wiki/Dextrane, https://en.wikipedia.org/wiki/Xanthan_gum, https://en.wikipedia.org/wiki/Gellan_gum).

Chitosane (CS) is a polymer widely used in biomedical applications due to its abundance, high reactivity due to amino and hydroxyl groups in the structure and intrinsic antibacterial properties. The presence of amino groups in the structure facilitates its thermal gelation in the presence of ionic crosslinkers, such as β-glycerophosphate (β-GP). Figure 7 shows the crosslinking reaction that takes place *in situ*, when the polymer and crosslinking solution is injected at the affected site (Chenite *et al*., 2000).

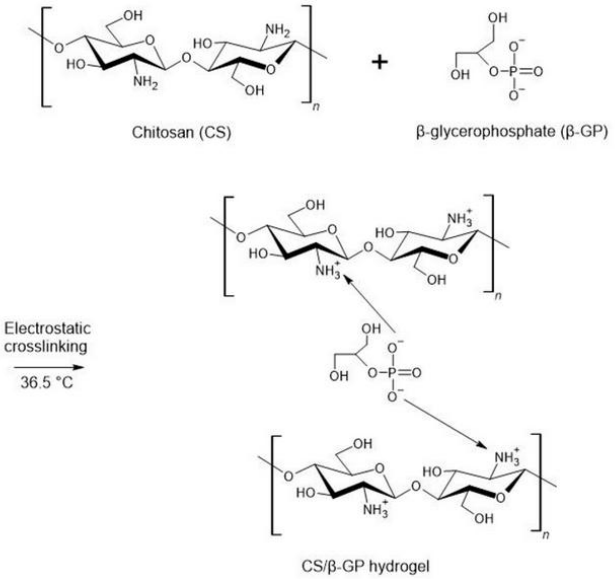


Fig. 7 − Physical cross-linking of (CS) with β-GP (Jeong *et al.*, 2021, reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license http://creativecommons.org/licenses/by/4.0/).

Dental pulp stem cell-derived exozomes were included in a CS and β-GP hydrogel, to teat periodontitis (Shen *et al*., 2020). The authors demonstrated that this drug delivery system can accelerate the healing of alveolar bone and the periodontal epithelium in mice with periodontitis. Zang *et al.* included ornidazole (bone morphogenetic protein-7) in the same type of hydrogel demonstrating periodontal regeneration activity and an effective antibacterial activity against *Porphyromonas gingivalis* (Zang *et al*., 2019). An important antibacterial effect, prolonged, against *Porphyromonas gingivalis* and *Prevotella intermida* was reported by Ji *et al.*, using the same hydrogel-drug system (Ji *et al*., 2009).

CS derivatives know many uses for the synthesis of thermo-sensitive hydrogels. Peng *et al.* (2023) uses acetylated carboxymethyl chitosan to create a release system of caffeic acid phenethyl ester (CAPE), a natural polyphenolic compound with anti-inflammation, anti-oxidation and tissue repair efficacy. The system applied in the periodontal pocket has the advantage of being formed practically instantly at the temperature of the oral cavity, slightly higher than the physiological one, and of achieving a sustained release that maintains almost constant the concentration of the drug at the affected site, compared to traditional systemic administration. The study highlights the possibility of this system to improve the therapeutic potential of CAPE for periodontitis therapy.

Grafting of CH and CS derivatives with poly(ethylene glycol) (PEG) is able to add new physicochemical properties to the cationic polysaccharide

polymers, thereby overcoming some limitations, especially regarding their solubility and their use in drug delivery. The obtained derivatives show lower toxicity than CS, higher capacity of permeation of physiological membranes and formation of thermosensitive hydrogels. An excellent review regarding their production and bioapplications was published by Casettari *et al.* (2012). A PEG grafted CS derivative was recently obtained by Vijayan *et al.* (Vijayan and Kumar, 2019) It starts to gel at 26ºC and becomes a hydrogel at 37ºC. The duration of gelation depends on the concentration of the polymer solution, varying between 1 min and 1 h. Prolonged quasi-linear release of bovine serum albumin (BSA) (up to 40 days) with reduced initial burst release of protein was achieved recommending this hydrogel for sustained *in vivo* drug release and tissue engineering in maxilofacial and oral cavity affections.

The association of CS with other synthetic polymers allows obtaining thermos-sensitive hydrogels with potential applications in medicine. For example, Poloxamer 407/poly(vinyl pyrrolidone)/chitosan temperature-sensitive hydrogels can maintain sol status at the room temperature and rapidly occur gelation at the oral temperature. This complex can be prepared into oral spray which is able to efficiently relieve pain and strengthen the drug–mucosa interaction for the treatment of oral mucositis (Pagano *et al*., 2020).

A thermosensitive porous CS, PEG and hydroxy propylmethyl cellulose (HPMC) based hydrogel with fast phase transition was prepared in the presence of a sodium carbonate and acetic acid mixture as porogen (Ma *et al*., 2023).

The duration at which the phase transition occurs decreases, in principle, with the increase in the amount of porogenic agent used in the synthesis. The hydrogel has a high capacity to include some hydrophilic drugs (antitumorals), due to its hydrophilicity and high porosity and is a potential candidate with applications in the treatment of some diseases of the oral cavity (cancer).

Hyaluronic acid (HA) is a polysaccharide widely used in bio-applications, in the field of tissue engineering or drug release. Thermosensitive hydrogels based on hyaluronic acid grafted with PNIPAM, containing drug-carrying particles intended especially for the tissue engineering of cartilage were reported by Atoufi *et al.* (2019). Depending on the active biological principle loaded in particles, such a composite hydrogel can be used in the treatment of some diseases of the oral cavity. By grafting with poly(NIPAM) and the subsequent reaction with gelatine, it generates porous hydrogels capable of including a wide variety of drugs (Santos *et al.*, 2010; Chen *et al*., 2011). whose gelation occurs at a temperature of approx. 33ºC.

The *in vitro* and *in vivo* studies led to the conclusion that this thermos-sensitive hydrogel can be used for the immobilization of a cisplatin release system that can be administered intravesically.

Curdlan is a polysaccharide of microbial synthesis with high potential for use in the creation of drug release systems. It was used by Tong *et al.* to create a thermosensitive hydrogel, in which chlorhexidine was immobilized - an

antimicrobial drug used in the treatment of some diseases of the oral cavity (Tong *et al*., 2020). It was found that the topically administered system (in the periodontal pocket for example) releases the drug in a controlled manner and ensures a practically total bacteriostatic efficacy (99.9%). Subsequent studies will aim to obtain such systems for periodontal antibacterial treatment by combining simultaneously a photothermal and antimicrobial effect.

Gellan is another microbial culture polysaccharide with multiple uses in medicine, pharmaceuticals, cosmetics, and the food industry. A mixture of Poloxamer 407 with gellan led by injection into the periodontal pocket, in contact with the divalent cations found in saliva and at physiological temperature, to a hydrogel in which moxifloxacin hydrochloride was immobilized. It was found that the system thus formed *in situ* releases the drug sustainably, demonstrating antibacterial activity against *Staphyloccoccus aureus* and *Escherichia coli* whose development it effectively inhibits (Swain *et al*., 2019).

Combinations of polysaccharide derivatives with Pluronic and even other types of polysaccharides have also proven the ability to gel at physiological temperature and to encapsulate drugs intended for the treatment of oral cavity conditions. For example, a mixture of methylcellulose, sodium alginate and Poloxamer 407 can generate hydrogels at temperatures varying between 25-27ºC, characterized by high mucoadhesiveness (tested on porcine buccal mucosa). *Scutellaria baicalensis* - known for its anti-inflammatory effect and antibacterial properties due to the presence of flavonoids (baicalin, baicalein, and wogonin) - was immobilized in the hydrogel, as well as chitosan which improves mucoadhesion without affecting the in vitro permeation behavior of the active principle. It is obvious that, through its proven advantages, the system constitutes a novel approach for periodontal diseases treatment (Chanaj-Kaczmarek *et al*., 2021). A thermos-responsive hydrogel based on hydroxyethyl cellulose, and Pluronic 127 was obtained to include Azithromycin. By injecting it into the periodontal pocket, the authors note an improvement in clinical parameters such as gingival index, probing pocket depth, clinical attachment level, bleeding index and plaque index, which demonstrates the potential of the system to be used in the treatment of chronic periodontitis. Moreover, it reduces the dose and side effects, bypasses the usual surgical procedures and improves patient compliance (Venkatesh *et al*., 2013).

In the construction of thermosensitive hydrogels, proteins are also used, usually in combination with Pluronic and/or another biopolymer or its derivative. Such a hydrogel was reported by Pham *et al*., which uses a mixture of Pluronic 127, methyl cellulose and silk fibroin. The hydrogel had a high capacity to include metronidazole, to release it at the site of application, a strong and long-lasting action of inhibiting the infection determined in the oral cavity by anaerobic microorganisms (Fig. 8) and reduced the frequency of administration compared to the administration of the free drug (Pham *et al*., 2021). The hydrogels remained in low-viscosity solution form for at least 6 months at 4°C (storage temperature)

and rapidly formed a hydrogel at 37°C within 1 min after injection into the dental pocket. The release of the drug from the system is governed on the one hand by diffusion, as long as the hydrogel maintains its integrity, also by diffusion correlated with the erosion produced by the fluids and the environment characteristic of liquids in the oral cavity (Fig. 8).

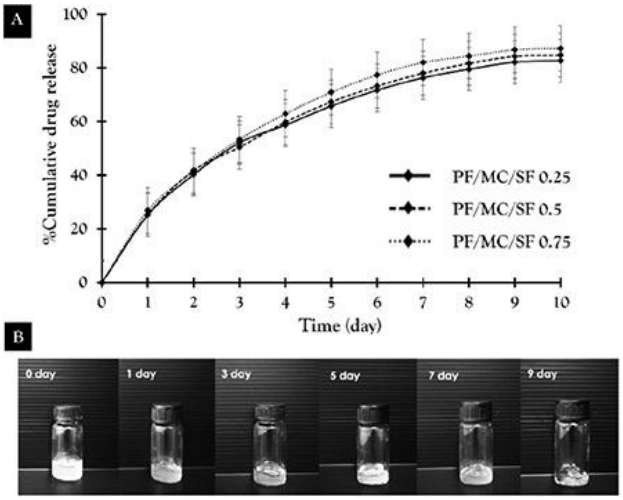


Fig. 8 − (A) Cumulative release of MTZ from hydrogel in phosphate-buffered saline (PBS) within 10 days and (B) erosion of MTZ-thermosensitive hydrogel (PF/MC/SF 0.75) in PBS pH 6.6 within 9 days. MTZ: Metronidazole, PF: Pluronic F127, MC: Methylcellulose, SF: Silk fibroin (Pham *et al.*, 2021, reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license http://creativecommons.org/licenses/by/4.0/).

3. Light-responsive hydrogels

In recent years, photosensitive hydrogels have been a field intensively studied by researchers, due to their multiple applications, starting from systems for encapsulating and releasing drugs, cells or other biologically active principles, materials for tissue engineering, up to biosensors, soft actuators, materials usable in environmental protection (Linsley and Wu, 2017; Ji *et al.*, 2020; Rapp and de Forest, 2021).

Hydrogels that change their physicochemical properties by stimulation with a source of radiation of a certain wavelength, especially UV, are considered photosensitive, which triggers a series of reactions such as isomerization, pyrolysis, dimerization, etc. (Ye *et al*., 2022).

The consequences of exposing the photosensitive hydrogel to UV radiation are manifested by the swelling or contraction (Wei *et al.*, 2024), and if

it carries a drug, its local release can be achieved, which improves biodistribution and reduces toxicity induced by overdoses (Choi *et al*., 2019).

The photosensitive character of a hydrogel is conferred by the presence in its structure of some photosensitive groups, which determine the wavelength to which it responds. On this basis, one can talk about hydrogels sensitive to near-infrared radiation, to visible radiation and especially ultraviolet radiation.

The mechanism by which the hydrogel responds to the stimulus is based on three principles: ***(i)*** the photosensitive groups absorb the light radiation and transform it into thermal energy, which, exceeding the specific LCST of the polymers in the construction of the network, causes its contraction as a response; ***(ii)*** the photosensitive groups become ionized through the absorption of radiation, and the ions thus formed increase the osmotic pressure and cause the movement of water molecules towards or outside the hydrogel to restore the osmotic balance; ***(iii)*** light radiation can cause the structural modification of the hydrogel through reactions that include isomerization, pyrolysis, dimerization or even degradation. The latter occurs when the chemical bonds between the photosensitive groups are broken, which also leads to an increase in the osmotic pressure in the hydrogel, facilitates the expansion of the structure by increasing the meshes of the network and allows the enhanced diffusion and the exit of water and drug molecules from it (Ma *et al*., 2017).

The photosensitive groups that are attached to a hydrogel to give it photosensitivity are chromophores or gelators such as azobenzene, stilbene, alkene, and coumarins, bound as substituents along the macromolecular chain, in the nodes of the network, as substituents at the branches of the basic polymer or in the aqueous medium in which the hydrogel swells (Roth-Konforti *et al*., 2018).

The visible light-sensitive hydrogels consisting of α-cyclodextrin and azobenzene linked by a dimethylamino bond have also been developed (Wang *et al*., 2017; Tai *et al*., 2019). Under the action of visible light, azobenzene undergoes cis–trans isomerization, which plays a critical role in the visible-light responsibility of the hydrogel. A review of them is excellently systematized and presented by Ji et al (Ji *et al*., 2020).

Photosensitive hydrogels can also be obtained by introducing photosensitive nanomaterials (gold nanorods, graphene, and CuS nanoparticles) at the time of creating the reticulated structure. By absorbing the heat generated by photo-irradiation, the nanoparticles determine the local inclusion of the hydrogel. The weak hydrogen bonds with water break, the structure contracts and expels the encapsulated drug. A complete and suggestive picture regarding the construction of photosensitive hydrogels and how they respond to stimulation with light radiation is provided in Fig. 9 (Li *et al*., 2019).

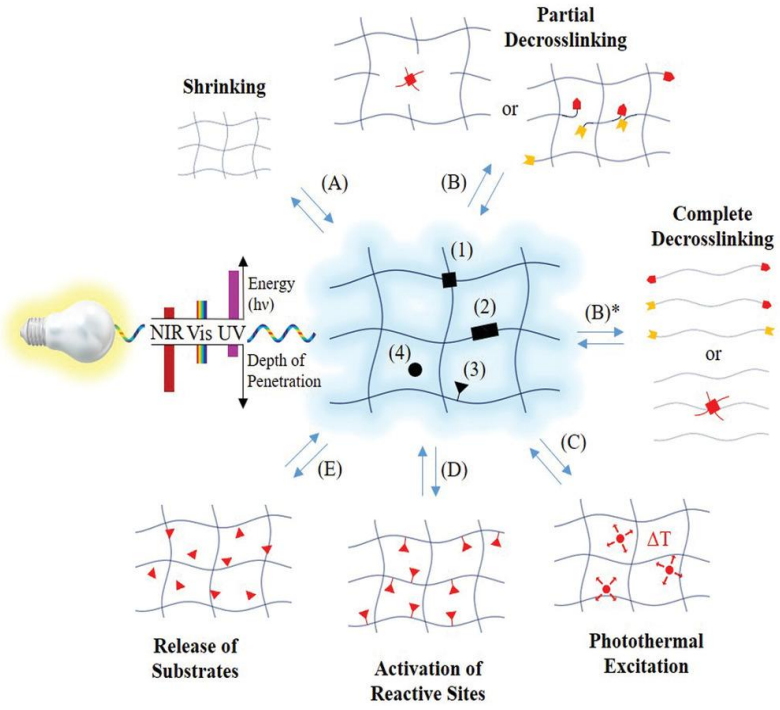


Fig. 9 − The construction of a hydrogel containing the photosensitive groups (black) in the nodes of the network, along the macromolecular chain between the nodes of the network, as a substitute for the side chains or in compounds dissolved in the aqueous swelling medium of the hydrogel. The response to photoactivation consists in: *(i)* contraction of the network, *(ii)* breaking of the bridges between the chains of the network and its folding, *(iii)* erosion of the network with the release of its chains, phenomena accompanied by the release of the included drug. (Li *et al*., 2019, reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license http://creativecommons.org/licenses/by/4.0/).

The literature mentions numerous bio-applications of this type of hydrogel, but less in the field of treating oral cavity conditions. Oral cancer is a form of squamous cell carcinoma that affects the tongue, gums and roof of the mouth. Zhao *et al.* discuss in a recent review the possibility of using smart hydrogels to treat this condition, highlighting their ability to offer an alternative to the classic treatment, advantageous by more effective treatment of oral cavity malignancy (Wu *et al*., 2021; Zhao *et al*., 2022; Wei *et al*., 2024). For example, a way to treat periodontitis is photodynamic therapy, which uses toluidine blue as a photosensitizer. Its association with poly(acrylic acid) (carbomer) leads to obtaining a photo-sensitive hydrogel which, by exposure to UV radiation, prolongs the duration of action of the included active principle by releasing it gradually and even reduces the usual required dose, through its classical

administration. It was found that such a hydrogel exhibits a higher antimicrobial activity after irradiation than without photoexcitation, suggesting that the system is a potential candidate for the treatment of periodontitis (Liang *et al*., 2017).

The literature of recent years reports the obtaining of hydrogels with a simultaneous response to two stimuli - dual responsive hydrogels (Ye *et al*., 2022). It is known that cancer cells, including those specific to oral cancer, are less resistant to temperature compared to healthy cells. The construction of a hydrogel capable of responding to both the light stimulus and the temperature has proven its effectiveness in destroying cells specific to this type of tumor (Wang *et al*., 2017). Also, photothermal therapy combined with chemotherapy is a way to effectively destroy oral tumor cells (Zhao *et al*., 2022). The antitumor drug can thus overcome the limits of an insufficient penetration that only photodynamic therapy ensures, increasing the sensitivity of tumor cells not only to the hyperthermic effect but also to the action of reactive oxygen species (ROS) essential for their destruction (Li *et al*., 2020).

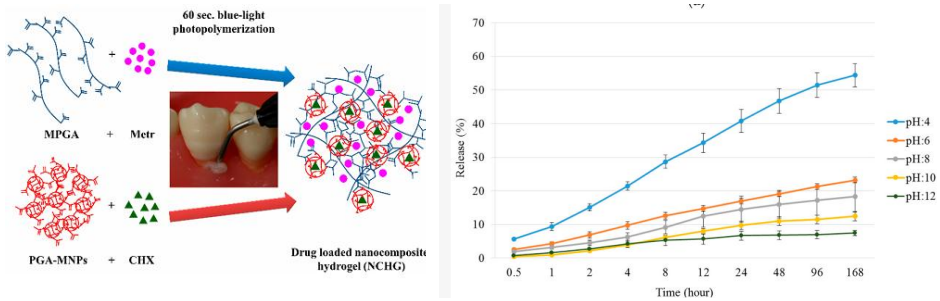
4. pH-responsive hydrogels

This category of hydrogels is notable for its ability to undergo phase transition, respectively to change its shape and volume in response to pH variations. There are two categories of pH-sensitive hydrogels, as they come from polyanions or polycations. Polymers containing carboxylic groups as a substituent lose the proton in alkaline environments, generating negative charges - polyanions (Khan *et al.*, 2019) those that contain basic groups (for example the amino group) accept protons in an acidic environment, generating positive charges – polycations (Deen *et al*., 2018). The specific pKa value of the polymer from which the hydrogel is built is important, determining the pH to which it responds. In the case of polyanions, when pH is lower than pKa, the anionic group (usually the carboxylate one) is protonated, the hydrophobicity of the hydrogel increases and it contracts, expelling water and molecules dissolved in it. On the contrary, in the case of polycations, contraction occurs at pH values higher than pKa (Yu *et al*., 2016; Ding *et al*., 2022).

pH-sensitive hydrogels can be obtained either by combining polymers that respond in the opposite way to pH changes, or by introducing some pH-sensitive substituents on the polymer chain. Poly(methacrylic acid) is used to obtain numerous polyanionic hydrogels with applications in the release of drugs in the oral cavity. Poly(ε-caprolactone) can be esterified by its terminal group to a carboxylic group of the polyanion, creating a pH-sensitive graft copolymer. At lower pH values, the acid groups are protonated and the strength of the hydrogen bonds between the carboxylic groups of the chains increases, so the polymer does not swell. When the pH changes to basic, the hydrogen bonds disappear through the formation of the carboxylate anion, so that the the hydrogel swell and the drug is delivered faster.

Nanoparticles with pH sensitive hydrogel character, loaded with metronidazole and chlorhexidine, were made starting from methacryloil group modified/methacrylated-poly(γ-glutamic acid), by blue-light polymerization (Bako *et al*., 2022). Polymerization is fast (60 sec), and proceeds directly into the periodontal pocket where the reactive mixture containing the drugs was introduced. This fast photo-polymerizable process can help to establish a locally applicable combined drug delivery system which can be loaded with the required amount of drug and can reduce the side effects of the systemic use of drugs that have to be used in high doses to reach an ideal concentration locally.

Figure 10 shows, schematically, the methodology for forming the pH-sensitive hydrogel nanoparticles (a) and kinetics of chlorhdexidine release form the nanoparticles, at different values of pH.



a b

Fig. 10 − Schematic presentation of the methodology for forming the pH-sensitive hydrogel (a) [MPGA - methacrylated poly(γ-glutamic acid); PGA- poly(γ-glutamic acid); MPNs – methacryloil group modified/methacrylated-poly(γ-glutamic acid) nanoparticles; Metr – metronidazole; CHX – chlorhexidine]; (b) kinetics of chlorhexidine release at different values of pH. (Bako *et al.*, 2022, reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license http://creativecommons.org/licenses/by/4.0/).

The nanoparticles are biocompatible, rapidly releasing metronidazole (after 2 h) and much slower chlorhexidine, with speed profiles that depend on the pH value. Fig. 15b shows the release kinetic curves of chlorhexidine at 5 different pH values, the maximum release efficiency being reached after 7 days in an environment with pH=4. Compared with regular hydrogels, nanoparticle hydrogels are more prone to reach the periodontal pocket and correctly release drugs. The *in vitro* tests demonstrated an important effect of reducing the bacterial activity of *Pseudomnas gingivalis*, arguing the possibility of using such a system in the prevention/treatment of bacterial plaque.

Chitosan is a polycation intensely used in the formulation of drug release systems, being an abundant, renewable, biocompatible biopolymer and itself possessing bioactive (antimicrobial) properties. As such, it is widely used in

obtaining pH-sensitive hydrogels, following quaternization, carboxylation, alkylation, thiolation, and graft copolymerization reactions (Du *et al*., 2015).

It is well known that the internal environment of tumors has an acidic character (pH=5), compared to their external environment, which has a pH value of 6.5. The explanation lies in anaerobic glycolysis, which lowers tumor acidity by consuming glucose and hydrolyzing glutamine with the generation of lactic acid. This pH difference between the normal tissue and the tumor microenvironment determines the release of drugs in the pH-sensitive hydrogels. At pH values below that of pKa, the amine groups are protonated, electrostatic repulsion forces appear between the chain segments that increase the network meshes and determine the intensification of the diffusion of water and the drug included in the network.

Liang *et al* report a pH-sensitive hydrogel obtained under physiological conditions by cross-linking a chitosan derivative grafted with di-hydroxycaffeic acid, with oxidized pullulan, which is loaded with doxorubicin or amoxicillin. The obtained system has good injectability, rapid gelation, swelling in a physiological environment depending on pH, and especially mucoadhesive properties. The *in vitro* tests revealed a high antimicrobial activity against *Escherichia Coli* and *Staphylococcus Aureus*, components of the microbial flora in the oral cavity, arguing the possibility of using this injectable system, sensitive to pH changes, for the local release of antimicrobial drugs (Liang *et al*., 2018). The dissociation degree of some groups in the pH-sensitive drug delivery system can change according to the pH, resulting in swelling of the nanogel, thus controlling the release of small molecules from the pores of the hydrogel. A hydrogel based on chitosan cross-linked with citaconic anhydride was loaded with cyclohexidine, one of the most used agents against dental plaque, effective in destroying both Gram-positive and Gram-negative bacteria (Li *et al*., 2022). When the hydrogel reaches an acidic environment, the anhydride groups hydrolyze whereas the amine groups from chitosan are protonated so that the system expels cyclohexidine in a quantity much higher than that released in a non-tumorous, normal tissue. Consequently, the hydrogel can be applied on the surface of a tissue that has ulcers or in the area of caries due to its excellent gelling capacity, releasing the drug and thus preventing the occurrence of some diseases of the oral cavity.

Trichlorsan is a compound with potential uses in the treatment of some diseases of the oral cavity, but its bioavailability is limited due to its insolubility in water. This deficiency can be overcome by including it in a chitosan-based nanogel that can be administered directly into the periodontal pocket, thus forming a system with dual activity that increases the effectiveness of the treatment (Aminu *et al*., 2019; Bikiaris, 2011). Nanoparticles based on chitosan containing triclosan release the drug in a proportion of over 80% at a pH value of 5.64 directly in the periodontal pocket, extending its duration of action, increasing the amount accumulated at the site of action, demonstrating a pronounced

antibacterial effect and reducing thus the symptoms of periodontitis; in conclusion, the system is pH-sensitive, with potential uses in the treatment of bacterial plaque. A chitosan-based hydrogel loaded with *N*-phenacylthiazolium bromide was reported by Yu *et al.* (2016). The release rate of the drug was high at pH=5.5, and decreases considerably with increasing pH up to the value of 7.4. Tests were performed in vivo on mice and rats that were experimentally induced with periodontitis, and the therapeutic effects were evaluated by microcomputed tomographic imaging of periodontal bone level and histomorphometry for inflammatory cell infiltration and collagen density. The obvious conclusion was that the chitosan-based hydrogel loaded with N-phenacylthiazolium bromide has a pH-sensitive character, delays the evolution of experimentally induced periodontitis and facilitates its recovery.

Chitosan can generate pH-sensitive hydrogels by association with other polymers, natural or synthetic, or with mineral materials with the formation of composites. Suggestive are the hydrogels reported by Alvarez *et al*, built on the basis of chitosan and silica, respectively carboxymethylcellulose, (Alvarez Echazu *et al.,* 2018). The composites were loaded with an aqueous extract of *Larrea divaricata Cav*., whose main component is nor-dihydroguaiaretic acid, with a strong antioxidant character. The degree of incorporation of the extract reaches 100%, and the antioxidant properties are kept unchanged for 4 days. The composites show mucoadhesivity, they are not cytotoxic, favouring the proliferation of fibriblasts, they create an environment conducive to biomineralization, and they release the natural active principle due to the acidic pH that causes swelling of the hydrogel. In conclusion, the constructed system is pH-sensitive and can have an effect on the regeneration of periodontal tissue degraded by periodontal diseases.

Chitosan derivatives, such as *N*-carboxymethyl chitosan, cross-linked with dibenzaldehyde terminated poly(ethylene glycol), generate hydrogels whose bridges between the polymer chains are of the Schiff base type (Qu *et al*., 2017). The hydrogels were loaded with doxorubicin, the tests in different pH environments proving a sustained release. The release of the drug is facilitated by the reversible process of association/dissociation of the Schiff base bonds (sensitive in acidic environment). Obviously, the pH-sensitive character is also due to the protonation capacity of chitosan's amino groups. The hydrogel is injectable subcutaneously or in the periodontal pocket, having real prospects of being used in the chemotherapy treatment of oral cancer.

Jommanee *et al.* (2018) obtained a hydrogel with a dual response, respectively to temperature and pH, by grafting a diblock copolymer based on ethylene glycol methyl ether and caprolactone, to chitosan. The copolymer exhibits a variable temperature and pH response to the sol–gel phase transition that is in good agreement with body temperature and pH in the acidic tumor microenvironment. *In vitro* tests demonstrated the ability of the hydrogel created in situ to continuously release encapsulated curcumin and doxorubicin for two

weeks, thus arguing the possibility of its use in the treatment of some forms of cancer of the oral cavity.

Polyphenols isolated from *Turkish gall* play an important role in the treatment of inflammatory conditions due to their antibacterial, antioxidant and anti-inflammatory action. Through oxidative self-polymerization and self-assembly, nanoparticles were prepared, which, by encapsulation in a thermosensitive hydrogel based on Poloxamer, can be administered directly into the periodontal pocket; the gelation practically occurs when the Poloxamer containing the dispersion of polyphenolic nanoparticles comes into contact with the periodontal pain test, so at physiological temperature. At the slightly alkaline pH specific to the oral micro-environment of patients with periodontitis, which achieves the gradual release of the biologically active compound in a proportion of over 80% after 100 h (Qi *et al*., 2022). The system has a strong antibacterial action against oral pathogens, especially against *Porphyromonas gingivalis* which is a major etiological agent in the initiation and progression of chronic periodontitis among the various organisms that reside in the oral tissue. Bacterial lysis is due to the excessive production of reactive oxygen species (ROS), without causing damage to the periodontal tissue through excessive oxidation. The method offers a green and effective option for the therapy of gingivitis associated with periodontal pocket, which could be extended to the treatment of other diseases, especially tumors, with these antioxidant compounds.

5. Enzyme responsive hydrogels

Enzymes are catalysts with very selective action on substrates, exercised in mild reaction conditions. This aspect is very important for the enzymes that work in the body, having maximum activity at temperatures around 37°C, in a weakly acidic, neutral or weakly alkaline environment. (Zelzer *et al*., 2016; Chandrawati, 2016). They are involved in all biological and metabolic processes, serving as the prime protagonists in the chemistry of living organisms at a molecular level (Hu *et al*., 2012). The previously mentioned characteristics allow them to work, and to be used as biological triggers in the controlled release of enzyme-mediated drugs. They can be involved either in the synthesis of hydrogels, or especially in their degradation, resulting in their erosion and the release of the loaded biologically active compounds - in both cases we are talking about enzyme responsive hydrogels. In principle, polymeric materials sensitive to the action of enzymes - polymeric assemblies, nanoparticles or hydrogels - can be classified into three categories namely, enzyme-triggered self-assembly and aggregation of synthetic polymers, enzyme-driven disintegration and structural reorganization of polymeric assemblies and nanoparticles, and enzyme-triggered sol-to-gel and gel-to-sol transitions.

A brief review of hydrogel-type polymer systems containing encapsulated drugs, which are released under the action of enzymes will be

discuss in the following, with the mention that the literature does not offer much information about their application in the treatment of oral cavity disease. The realization of such hydrogels requires compliance with some constraints: in the structure of the hydrogel there must be components (substrate) that the enzyme can recognize; the enzyme must come in contact with these components, which is extremely important for the kinetics of the catalyzed process; the properties of the hydrogel must change as a result of the action of the enzyme on the substrate.

Drugs can be associated with the hydrogel either through physical bonds, or they can create conjugates through chemical binding; their release under the action of the enzyme can be determined either by changing the shape and volume of the hydrogel, or by breaking the chemical bonds with the macromolecular support (Gohil *et al*., 2021).

Among the most used enzymes as triggers of some processes in enzyme-sensitive hydrogels are metalloproteinase, phosphatase, trypsin, tyrosinase - belonging to the class of endopeptidases, therefore capable of cleaving peptide bonds (Vartak and Gemeinhart, 2007).

Metalloproteinases (MMP) play an important role in chronic periodontal disease. Its severity causes an increase in the amount of metalloproteinase-8 (MMP-8) in gingival crevicular fluid, which makes this enzyme frequently used as a marker for disease monitoring and progress (Gursoy *et al*., 2010; Cavalla *et al*., 2017; Zhang *et al*., 2018). Hence the idea of using it as a stimulus for hydrogels specially designed for the release of drugs intended for managing periodontitis. In the synthesis of these hydrogels, a peptide sensitive to MMP was used as a cross-linking agent, so that by breaking the bridges between the chains activated by MMP, the drug is released (Nultsch and Germershaus, 2018).

Nanocapsules based on biodegradable flax poly(D,L-lactide)-poly(ethylene glycol)-poly(D,L-lactide) micelles loaded with doxorubicin, were encapsulated in an injectable hydrogel based on hyaluronic acid with formation in situ, cross-linked with a metalloproteinase-2 (MMP-2)-responsive peptide (GCRDGPQGIWGQDRCG). The obtaining and mode of action of the system are very suggestively presented in Fig. 11.

The *in vitro* tests demonstrated its cytotoxicity against squamous carcinoma cells, and the in vivo tests proved that it degrades faster in the tumor test, being sensitive to the action of the enzyme, but more difficult in healthy tissue. The system thus releases sustained micelles that in turn release doxorubicin, inhibiting the growth of the oral squamous cell carcinoma tumor without causing damage to healthy tissue (Li *et al*., 2019).

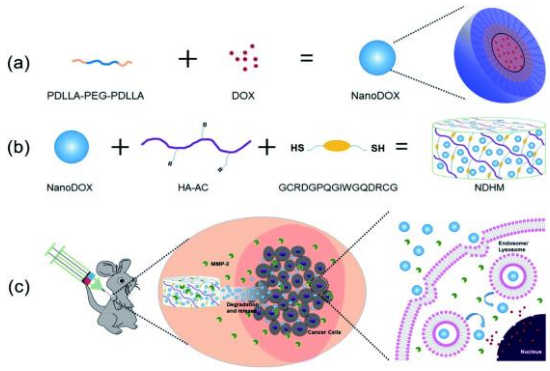


Fig. 11 − Schematic illustration showing the preparation process of micelles loaded with doxorubicin (a) and the preparation process of hydrogel (b). By injecting nanoparticles (NanoDOX), hyaluronic acid (HA), cross-linking protein (G CRDGPQGIWGQDRCG) linked to the enzyme into the experimental animal, the polymer-drug system sensitive to the action of metalloproteinase is formed in situ, which releases the antitumor drug and induces the death of cancer cells (c). (Li *et al*., 2019, reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license http://creativecommons.org/licenses/by/4.0/).

An interesting hydrogel was synthesized by Guo *et al.* from diacrylate-containing poly(ethylene glycol) –based scaffolds and a cysteine-terminated peptide crosslinker (CGPQG↓IWGQC) via a Michael-typ addition reaction (Guo *et al*., 2019). Several active principles were incorporated into the hydrogel: minocycline hydrochloride, bovine serum albumin, or an antibacterial peptide (KSL). The hydrogel proved to be biocompatible, non-toxic, keeping the antibacterial capacity of the encapsulated drugs, biodegradable under the action of co-encapsulated MMP-8. Drug release kinetics could be tuned by varying the loading method as well as MMP-8 concentration. Because MMP-8 is one of the most important biomarkers for periodontitis, the MMP-8-responsive hydrogel has potential to be used for *in situ* adaptive degradation in response to chronic periodontitis and peri-implantitis.

Other hydrogels sensitive to the action of metalloproteinases, bearing doxorubicin, formed in situ by injection, with potential applications in oral cancer therapy, are reported by Najafi *et al.* (2020), Wang *et al* (2019). An interesting hydrogel sensitive to the action of phosphatase is proposed by Coulter *et al.*, being based on a versatile peptoid-peptide structure capable of covalently binding antitumor drugs of low molar mass. The hydrogel is formed in situ by subcutaneous injection in experimental animals (mice) and releases the antitumor drug (zidovudine) by degradation of the hydrogel network under the action of phosphatase, for 35 days without showing a «burst effect». The concentration reached by release represents 90% of the maximum inhibitory (30-130 ng/mL) (Coulter *et al*., 2024).

It should be mentioned that the therapy involving the use of hydrogels sensitive to the action of enzymes is sometimes combined with photodynamic chemotherapy in order to increase the efficiency of the treatment in the treatment of different forms of cancer; however, at our best knowledge, there are no studies regarding this combined treatment in oral cancer therapy, although its potential is very high.

6. Glucose responsive hydrogels

Diabetes melitius, which is characterized by increased blood glucose levels, is one of the most widespread diseases among both the elderly and the young, causing numerous complications (Zhou *et al*., 2015). Since periodontitis is often associated with different forms of diabetes, the periodontal pocket can contain variable amounts of glucose. As a result, glucose-sensitive systems, especially in the form of drug-carrying hydrogels, began to be increasingly studied. They can be used in the detection of abnormal increases in the level of glucose in the body, but also in the release under the stimulus of glucose of some drugs used in the treatment of diabetes (Nasra *et al.*, 2017; Zhang and Huang, 2021). An interesting review discussing these aspects was recently published by Li *et al.* (2023).

Liu *et al.* reports the obtaining of a hydrogel in the form of a film, with important application potential for diabetic's periodontitis therapy in the clinic (Liu *et al.*, 2019). In a first step, maleic anhydride is grafted onto the macromolecular chains of chitosan, obtaining a photopolymerizable derivative. By UV irradiation of the chitosan macromer, films are obtained on the surface of which glucose oxidase has been immobilized. The hydrogel, possessing good mechanical properties, is loaded with metronidazole. In an environment containing glucose in high concentration, the hydrogel hydrolyses forming pores through which the drug easily diffuses. The system thus constructed has proven its effectiveness in increasing antimicrobial activity against *Pseudomonas gingivalis,* the main pathogenic bacterium that causes periodontitis.

Another group coordinated by Xiao (Xiao *et al.*, 2016) created a semi-interpenetrated network type hydrogel, by cross-linking a mixture of chitosan and poly(ethylene oxide) with glutaric aldehyde. Glucose oxidase was immobilized in the hydrogel and metronidazole was encapsulated. The hydrogel is biocompatible and has good mechanical properties, but especially the ability to release metronidazole in response to the specific stimulus of the periodontal pocket - glucose. Metronidazole is released in variable amounts that depend on the amount of immobilized enzyme. The study demonstrated the glucose-sensitive antibacterial hydrogel has a great potential as a new therapeutic material for treatment or prevention of periodontitis in diabetic patients.

An interesting hydrogel was made by crosslinking chitosan into which tannic acid was introduced, with glucose oxidase, using N-

hydroxysuccinimide/1-ethyl-3-(3-dimethylaminopropyl) carbodiimide based coupling chemistry (Liu *et al*., 2022). It was found that the enzyme is much better anchored on the surface of the hydrogel film if it is covalently coupled to chitosan, then if it is adsorbed on the surface. Tannic acid also contributes to the strengthening of the film, through the cross-linking determined by the numerous hydrogen bonds of the phenolic groups and the amine groups in the polysaccharide. The hydrogel film demonstrated adequate biocompatibility and can inhibit *Porphyromonas gingivalis* growth, demonstrating effective antibacterial and anti-inflammatory activity.

Research in the field of hydrogels sensitive to the action of enzymes, with applications in the treatment of diseases of the oral cavity, is currently few, but certainly in the near future many achievements will be reported, especially in what concerns the treatment of bacterial plaque in the oral cavity.

7. Conclusions and Perspectives

Due to the limits of classical drug therapy and the side effects of drugs, especially antitumor ones, on normal tissue, the smart drug delivery system based on hydrogels have become a very attractive research direction. This review summarizes the literature of the last decade related to obtaining hydrogel-type systems that respond to chemical and physical stimuli, whose topical administration in the oral cavity triggers the release of the loaded active principle "on demand", controllable in time and space. Hydrogels are discussed which, after injection into the affected area, respond precisely to stimuli such as temperature, light radiation, pH, the presence of enzymes or high concentrations of glucose, releasing the active principle.

It is obvious that such systems, which can be adjusted a lot in the future, will be beneficial for the expansion of their applications not only in the treatment of oral cavity diseases, but also of other diseases of the human body. Despite the obvious progress recorded so far in the field, there are still many problems that must be solved before their clinical testing. The future needs advanced researches to find solutions to some disadvantages such as a delayed temperature response, weak mechanical characteristics, and poor biocompatibility, which for instant limits their potential use in drug delivery applications. Rigorous *in vivo* testing must be performed on experimental animals, the stability of the system at the site of action and even its biocompatibility must be investigated in detail. It is possible to create intelligent hydrogels that can respond to other stimuli (electrical, mechanical) or to the combined action of two or more stimuli simultaneously. Certainly the near future will bring new, valuable results in terms of obtaining smart hydrogels as drug release platforms in different oral diseases, especially in the treatment of periodontal diseases and oral cancer.

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HIDROGELURI INTELIGENTE PENTRU TRATAMENTUL AFECȚIUNILOR CAVITĂȚII ORALE

(Rezumat)

Mediul unic specific cavității bucale este propice pentru proliferarea bacteriilor și infecțiilor patogene. Eficacitatea tratamentului medicamentos este adesea redusă datorită faptului că saliva diluează formularea medicamentoasă și reduce interacțiunea dintre medicament și locul său de acțiune. O modalitate eficientă de rezolvare a acestei probleme este crearea de sisteme polimerice sensibile la acțiunea stimulilor care comandă eliberarea medicamentului la locul potrivit, la timpul dorit și în doza adecvată. Datorită capacității lor de a răspunde la stimuli, hidrogelurile au fost aplicate ca sisteme excelente de livrare a medicamentelor pentru tratamente care includ carii, boli endodontice, boli parodontale, boli ale sistemului osos, boli ale mucoasei, cancer bucal. Lucrarea de față propune o trecere în revistă a cercetărilor recente în domeniul obținerii de hidrogeluri care răspund la stimuli fizici (temperatură, UV și lumină vizibilă) chimici (pH, glucoză) și biologici (enzime) - hidrogeluri inteligente - cu aplicații în tratamentul afecțiunilor cavității bucale.