Journal of Biology & Pharmacy
and Agricultural Management

ISSN 1983-4209

Journal of Biology & Pharmacy and Agricultural Management, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

HYDROGELS: PRODUCTION, CLASSIFICATION, AND PHARMACEUTICAL APPLICATION

Joyce Cristina da Silva[1], Magda Rhayanny Assunção Ferreira[1], Luiz Alberto Lira Soares[1,2]

[1]Laboratory of Pharmacognosy, Federal University of Pernambuco, Recife-PE, Brazil.

[2]Postgraduate Program in Pharmaceutical Sciences, Federal University of Pernambuco, Recife-PE, Brazil.

**Autor para Correspondência: luiz.albertosoares@ufpe.br*

ABSTRACT

Polymers are macromolecules made up of smaller units, the monomers, offering advantages for their different physical and chemical properties; being classified according to their nature in natural (biopolymers) and synthetic. Among the polymeric biomaterials are hydrogels, which are 3D polymeric networks with the ability to absorb a large volume of water. Characteristics such as flexibility, chemical and physical versatility, response to stimuli, and resilient structure are the main advantages of hydrogels, which are classified based on their origin, crosslinking, polymerization method, biodegradability, physical properties, and ionic charge. Hydrogels are used in various fields, yet most of the research is taking place in the field of biomedical applications because of their similarity to tissue, biocompatibility, and biodegradability. Based on this, this narrative type of literature review was conducted by searching articles indexed in the databases: PubMed, SciELO, Science direct, BVS, MedLine and Lilacs. As inclusion criteria, the articles should be between 2015 to 2020, freely available in the databases, with the following descriptors in the title and/or abstract: Hydrogels, Polymeric biomaterials, Obtaining, Classification and Pharmaceutical applications, those that did not have these criteria were excluded from the review. After the inclusion criteria 41 articles were used, aiming to detail the main

ISSN 1983-4209 *Journal of Biology & Pharmacy and Agricultural Management*, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

characteristics and classifications of hydrogels that enable their use in various pharmaceutical applications. Based on the studies, the use of hydrogels in biomedical applications has been acquiring a key role, since due to their characteristics they have the ability to adapt to the needs of the desired application, although studies are still needed to improve them even more.
Keywords: polymeric biomaterials; hydrogels; applications.

1 INTRODUCTION

Hydrogels are three-dimensional networks of connected hydrophilic components, usually of polymeric origin, containing a large amount of undissolved aqueous phase attached to the network formed by interconnections called *crosslinks* that are intermolecular interactions or chemical bonds between the chains of the hydrogel-forming polymer (KASIŃSKI *et al.*, 2020; MILCOVICH *et al.*, 2017).

The hydrophilic nature of this formulation allows them to increase in volume in water by up to several hundred folds of the dry gel mass. Before crosslinking, the polymers are easily dissolved in water, but after crosslinking, they are in a gel state with a stable defined shape (KHAJOUEI; RAVAN; EBRAHIMI, 2020).

Hydrogels can be synthetic or natural, natural being those obtained, with gelatin, agar, polysaccharides, bacterial biofilms and extracellular matrices, found in all areas of life and nature, while synthetic polymers were only amenable to use after 1960 (FENNELL; HUYGHE, 2019). Synthetic biodegradable polymers are considered more commercially competitive for medical applications, they are also biocompatible, combine preferred properties and biosafety, and are used for the manufacture of various devices such as bone fixation devices, controlled release drug vehicles, implants, screws, *stents*, sutures, plates, and tissue engineering materials (KASIŃSKI *et al.*, 2020)..

The chemical and physical versatility of hydrogels can be exploited for *in situ* use in disease-triggered wear situations, such as programmed degradation of the hydrogel with

Journal of Biology & Pharmacy
and Agricultural Management
ISSN 1983-4209
Journal of Biology & Pharmacy and Agricultural Management, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

consequent drug release, while also serving as a biocompatible depot for local delivery of stimuli-responsive therapeutic cargo (OLIVA *et al.*, 2017).

Hydrogels and polymers have a long history of use in biology, including providing physical support of tissues during cutting and imaging, as well as for a number of important clinical applications in regenerative medicine and tissue engineering (GRADINARU *et al.*, 2018). Given the above, considering the versatility of applications, this work aims to perform a narrative literature review on obtaining, classification and pharmaceutical applications of hydrogels.

The present work consists of a literature survey conducted by searching articles indexed in the scientific databases: PubMed, SciELO, Science direct, BVS, MedLine and Lilacs between the years 2015 and 2020. The articles were selected with inclusion criteria in which the texts that presented, in the title and in the abstract the terms: "Hydrogels", "Polymeric biomaterials", "Obtaining hydrogels", "Classification of hydrogels" and "Pharmaceutical applications of hydrogels" were reviewed, while those that did not present these terms, were not between the years 2015 to 2020, were duplicates or did not have the full text available were excluded from the review.

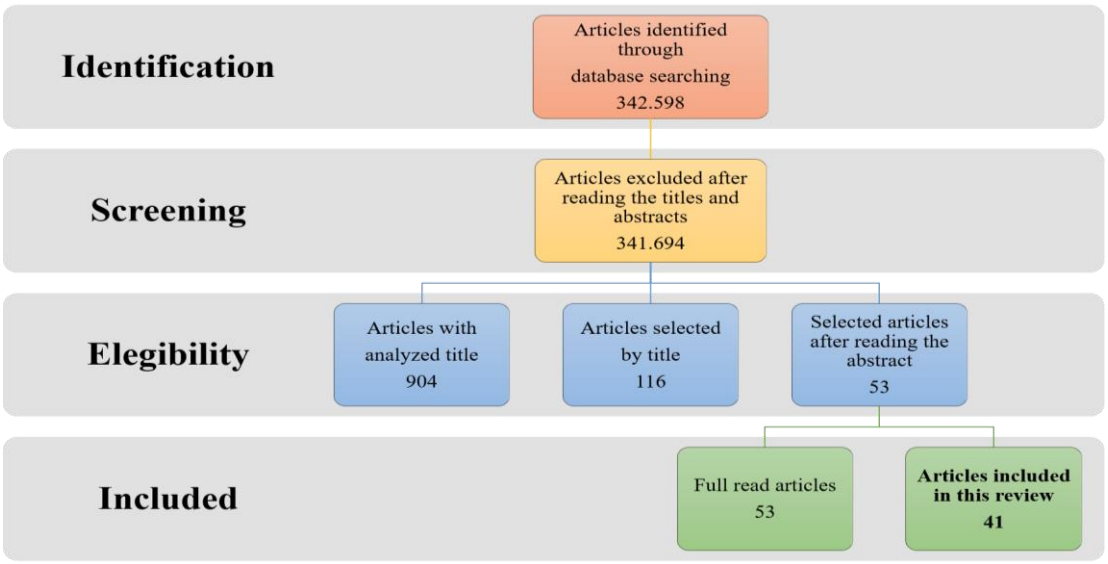

Figure 1. Flowchart of research and selection of articles.

Journal of Biology & Pharmacy
and Agricultural Management
ISSN 1983-4209 Journal of Biology & Pharmacy and Agricultural Management, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

2 POLYMERIC BIOMATERIALS

Polymers are found everywhere, even inside the human body. They can be produced by living organisms, in which case they are called biopolymers; while polymers that have the ability to be in contact with a living system without producing any adverse effects are referred to as polymeric biomaterials, and these can be of natural or synthetic origin (KOWALCZUK, 2020).

Among the existing biomaterial candidates, one of the most promising are the inherent components of biological organisms. Without the introduction of any foreign materials, such biomaterials have the distinct advantages of being naturally biocompatible, biodegradable, and resorbable (SHAN *et al.*, 2018). The term "biocompatibility" reflects the ability of a polymeric material to function with an appropriate host response in a specific application. Thus, biocompatibility is a property of a polymeric host-biomaterial system (WILLIAMS, 2017).

Polymeric biomaterials are designed to interact with biological systems for therapeutic, diagnostic, repair, replacement, or enhancement of human tissue or organ functions; they generally possess heterogeneity arising from a partially disordered network of polymer chains and macromolecules. Their optical, mechanical, chemical, and biological properties are crucial for their applications (SHAN *et al.*, 2018; YIN; LUAN, 2016).

The most synthetic biomaterials are obtained from lactic acid, caprolactone, or glycoside monomers to form poly(L-lactide), or poly(ε-caprolactone), or poly (L-glycolic acid), respectively; and/or their combination to form copolymers; or the physical mixture of these polymers. Natural polymers, on the other hand, can be formed from chitosan, alginate, starch, collagen, hyaluronic acid, cellulose, fibrin, silk, and their derivatives (CHOUDHARY; SARASWAT; VENKATRAMAN, 2019; LIU *et al.*, 2020).

Polymers that possess hydrophilic properties form three-dimensional (3D) cross-linked networks known as hydrogels, a type of new smart biomaterial that responds to external stimuli and exhibits a potential application for tissue regeneration and delivery of bioactive molecules (KHAN; TANAKA, 2017).

Journal of Biology & Pharmacy
and Agricultural Management

ISSN 1983-4209 *Journal of Biology & Pharmacy and Agricultural Management*, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

3 HYDROGELS

The term hydrogel describes 3D network structures obtained from a class of synthetic and/or natural polymers that can absorb and retain a significant amount of water. Due to high water retention and physicochemical similarity with the native extracellular matrix they are considered highly biocompatible (CATOIRA *et al.*, 2019; LARRAÑETA *et al.*, 2018)

The three-dimensional network is made up of crosslinking polymers with covalent bonds or non-covalent interactions, and their structure can be designed to suit the end application. Their unique ability to absorb and retain water is directed by their hydrophilic nature; the amount of water they absorb depends on factors such as the structure of the hydrogel, the density of the crosslinker, the composition of the solution, and the technique used to synthesize it (LEE *et al.*, 2019).

Hydrogels in general have many characteristics that make them an interesting subject of research: they have a great versatility because their chemical and physical properties can be manipulated to create a gel best suited for the desired application. The unique ability of hydrogels to form intumescent 3D networks gives them the possibility to diffuse molecules and cells, although their similarity to natural soft tissue is also of great interest to the biomedical field (FRANCIS *et al.*, 2018).

The possible uses of hydrogels are an extremely broad topic with still a lot to offer, from domestic use to biomedical applications. Hydrogels provide a physiologically similar environment for cell growth and are often used to simulate the extracellular matrix, and in general have been extensively studied for different applications, which include drug delivery systems, 3D cultures, tissue implants, tissue regeneration, contact lenses, and use in healthcare products. Each different type of hydrogel can be tailored to suit the application for which it was designed, therefore, hydrogels are obtained from different techniques to provide the required chemical and physical properties (JABBARI *et al.*, 2016; PENG *et al.*, 2019; XU; LIU; HSU, 2019).

Journal of Biology & Pharmacy
and Agricultural Management
ISSN 1983-4209
Journal of Biology & Pharmacy and Agricultural Management, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

3.1 Classification of hydrogels

Depending on the preparation methods, ionic loadings, sources, nature of intumescence with changes in the environment, rate of biodegradation, or the nature of crosslinking, hydrogels can be classified in various ways. A detailed classification of hydrogels is presented in Figure 2, where one of the important classifications is based on their nature of crosslinking (IQBAL, 2018).

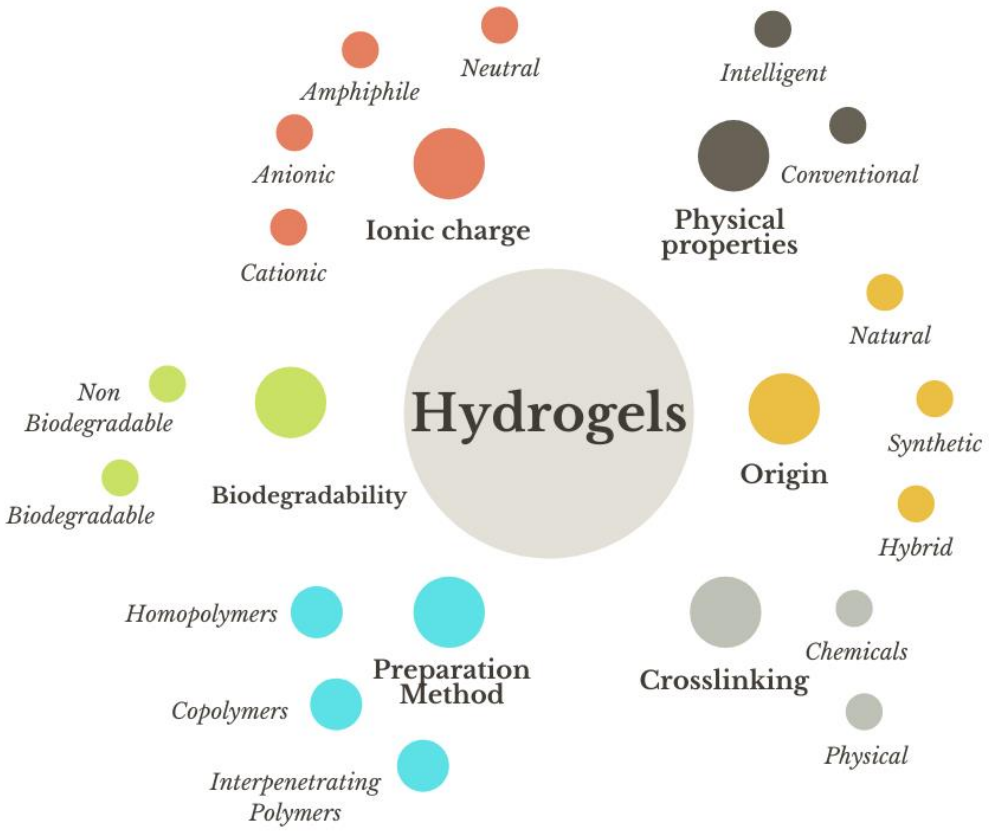

Figure 2. Classification of hydrogels.

3.2 Origin: natural, hybrid or synthetic

As for their origin, as seen in figure 2, hydrogels can be classified as natural, hybrid, or synthetic. Hydrogels of natural origin include collagen, silk fibroin, hyaluronic acid, chitosan, alginate, and hydrogels derived from decellularized tissues. Their properties are

ISSN 1983-4209 *Journal of Biology & Pharmacy and Agricultural Management*, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

biocompatibility, biodegradability, low cytotoxicity, the possibility of adapting the hydrogel into an injectable gel, and their similarity to the physiological environment, while synthetic hydrogels are the exact opposite (LI *et al.*, 2018). However, natural hydrogels have some limitations, such as they do not have strong mechanical properties and are not easily controllable due to their batch-to-batch variation. For these reasons, natural hydrogels are often combined with synthetic ones, creating hybrid polymers, which are still widely experimented (JABBARI *et al.*, 2016).

The mechanical properties of hydrogels can affect the stability of the material and the behavior of cells, including cell propagation, migration, and differentiation, affecting the signal transformation process; for example, mechanical signals that are converted into biochemical signals (NASCIMENTO; LOMBELLO, 2016).

The compressive strength of hydrogel consisting of alginate, chitosan, polyvinyl alcohol, or hyaluronan can range from 0.46 to 5.64 Mpa (PAHLEVANZADEH; BAKHSHESHI-RAD; HAMZAH, 2018). However, hydrogels made by artificial polymers, such as polylactic-co-glycolic acid (PLGA), polymethylmethacrylate (PMMA), polycaprolactone (PCL), and poly(ethylene glycol) (PEG) can reach mechanical strength of ≥ 20-120 Mpa (LI *et al.*, 2018).

Hence the need and importance of hybrid hydrogels that can be prepared by polymer *blends* and exhibit remarkable stability, even under severe conditions such as high temperature or a very acidic or basic environment (ROSA *et al.*, 2020). Moreover, by modifying the polymer chains with stimulus-responsive functional groups, the properties of the hydrogel can be exchanged by stimuli including heat, light, magnetic fields, chemical agents, and pH enriching the applications in the biomedical area, thus allowing the adjustment of the physical and chemical properties of both types of polymers (CHAI; JIAO; YU, 2017).

Journal of Biology & Pharmacy
and Agricultural Management

ISSN 1983-4209 *Journal of Biology & Pharmacy and Agricultural Management*, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

3.3 Reticulation: physical or chemical

Chemically cross-linked hydrogels form the 3D network through dynamic covalent bonds or reversible chemical reactions, which are stable, homogeneous and difficult to degrade (LI *et al.*, 2018) generally including (Table 1) phenylboronic ester bonds (GREGORITZA *et al.*, 2017), dynamic imine bonds (LIU *et al.*, 2018), disulfide bonds, reversible radical reaction, Diels-Alder reaction etc. Physically cross-linked hydrogels re-establish the structure through dynamic non-covalent interactions, such as hydrogen bonds, host-guest interaction, metal coordination (SHAO *et al.*, 2018) or a combination of multiple intermolecular interactions (WANG; NARAIN; ZENG, 2018).

The main advantage of physically cross-linked hydrogels is the absence of chemical agents, which decreases the toxicity of the material. On the other hand, chemically cross-linked hydrogels are prepared by forming covalent bonds and the resulting hydrogel is more resistant to mechanical forces, but generally undergoes greater volume changes than physically cross-linked networks (GUVENDIREN *et al.*, 2016).

Table 1. Different strategies used to obtain hydrogels.

HARNESS MECHANISMS	
Chemical	**Physical**
Complexation of phenylboronic ester	Hydrogen bond
Dynamic Schiff base	Hydrophobic interaction
Disulfide bond	Host-guest interaction
Diels-Alder reaction	Interaction multiple intermolecular

3.4 Method: homopolymers, copolymers or interpenetrating polymers

According to the substrates used and type of polymerization processes, it is possible to distinguish systems in homopolymeric, copolymeric or with intermittent polymers (Table 2). Homopolymeric hydrogels are formed from one type of monomer; whereas copolymeric systems are based on two types of monomers; and finally, in the case of the

Journal of Biology & Pharmacy and Agricultural Management
ISSN 1983-4209
Journal of Biology & Pharmacy and Agricultural Management, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

presence of three or more different monomers, interpenetrating polymers are originated (KASIŃSKI *et al.*, 2020).

Table 2. Classification of polymers according to their monomers.

Monomers	Polymers	Representation
X	Homopolymer	X – X – X – X – X
Y	Homopolymer	Y – Y – Y – Y – Y
	Random copolymer	X – Y – Y – X – Y
	Block copolymer	X – X – X – Y –Y
X + Y	Alternating copolymer	X – Y – X – Y – X
	Graft copolymer	X – X – X Y –Y

In copolymers there are four different basic representations: random copolymers, in which the monomeric unit can be randomly distributed; alternating copolymers, block copolymers, and graphitized (grafted) copolymers (VIEIRA, 2016). Interpenetrating polymer network-based hydrogels are defined as the combination of two or more polymer networks that are prepared from the expansion of a gel, in a solution containing a second monomer that is then cross-linked within the chain of the first one interpenetrating at the molecular level without being covalently linked (SATTARI; DADKHAH TEHRANI; ADELI, 2018).

3.5 Biodegradability: biodegradable or non-biodegradable

Good biodegradability is essential for the application of hydrogels in tissue engineering. If hydrogels are used as scaffolds or drug delivery devices, their biodegradability plays a vital role and affects the performance of the hydrogel products. Compared to non-biodegradable hydrogels, migration and intercellular interaction are significantly enhanced in biodegradable hydrogels (LI *et al.*, 2018).

ISSN 1983-4209 *Journal of Biology & Pharmacy and Agricultural Management*, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

To create biodegradable hydrogels, chemical bonds susceptible to "cutting" by water or enzymes can be readily introduced into the cross-links of the polymer network. By controlling the initial crosslinking density and the choice of degradable bond, the desired macroscopic properties and their evolution over time can be programmed for a given expected chemical structure of the hydrogel (BRYANT; VERNEREY, 2018).

3.6 Physical properties: smart and conventional

Conventional hydrogels generally exhibit poor mechanical properties and are easily deformed or damaged when subjected to mechanical forces. The accumulation of damage can lead to permanent structural change and loss of functional properties of hydrogels (WANG; NARAIN; ZENG, 2018).

The release of the active substance occurs through shrinkage or swelling of the material, diffusion, and matrix decomposition. If the matrix has the ability to change its properties under the influence of environmental factors, such as temperature, pH, or magnetic field, it is referred to as a stimulus-responsive hydrogel and is referred to as a smart hydrogel (KASIŃSKI *et al.*, 2020).

The design of smart polymer-based biomaterials with desired properties and network structure mainly depends on the characteristic nature of functional monomers, polymerization method, molecular architecture construction during synthesis, and *crosslink* network formation (KHAN; TANAKA, 2017). It is known that the properties of smart polymers change reversibly with the variation of external or internal parameters, which can be of physical, chemical or biochemical nature, in the form of pH, temperature, salts, surfactants, light, pressure, biomolecules and magnetic field (DEEN; LOH, 2018).

Therefore, it is desirable to develop mechanically robust hydrogels that have the ability to self-recover in order to not only extend the lifetime of materials, but also increase the durability and reliability of hydrogels in certain applications (WANG; NARAIN; ZENG, 2018).

Journal of Biology & Pharmacy
and Agricultural Management
ISSN 1983-4209
Journal of Biology & Pharmacy and Agricultural Management, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

3.7 Ionic charge: neutral, anionic, cationic and amphiphilic

Considering the charge of hydrogel forming macromolecules; anionic, cationic, amphiphilic, or neutral systems are distinguished. Cationic hydrogels contain in their structure positively ionized portions, anionic systems comprise negatively charged groups, and amphiphilic groups possess both, positive and negative charge (KASIŃSKI *et al.*, 2020).

Hydrogels that contain polycations and are sensitive to external pH changes are called cationic hydrogels. The tertiary amine functional groups present in these hydrogels are protonated below their dissociation constant (*pKa*) in acidic solutions, causing the hydrogels to swell extensively. Hydrogels based on the chemical structures of some pH-sensitive synthetic cationic polymers, such as poly(diethylaminomethyl methacrylate), poly(diethylaminomethyl methacrylate), poly(ethyl pyrrolidine methacrylate), and poly(ethyl piperazine acrylate), increase in size in low pH solutions due to the protonation of tertiary amine functional groups, which leads to the formation of fixed electric charges in the macromolecule (DEEN; LOH, 2018).

4 PHARMACEUTICAL APPLICATION

The possibility of designing a hydrogel according to the desired application requirements is related to the wide range of polymers that can be used. Thus, it is possible to control its biodegradation rate, mechanical strength, swelling capacity and responsiveness to external stimuli by combining natural and/or synthetic polymers (LIMA *et al.*, 2020).

Similar to other biomaterials, the use of a hydrogel for pharmaceutical applications has biocompatibility, non-toxicity, non-inflammation, non-immunogenicity, biodegradability, stability, mechanical property matching with natural tissues, and application specificity as requirements (WANG; HAN, 2017).

The alginate hydrogel has proven to be one of the most relevant, especially in delivery system applications, wound treatment and cosmetic applications because when obtained in high purity, it provides biomedical applications due to its characteristics such as

ISSN 1983-4209 *Journal of Biology & Pharmacy and Agricultural Management*, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

biocompatibility, hydrophilicity, low cost and easy gelation that in the presence of divalent ions and at physiological pH and temperature favor drug retention.

4.1 Delivery System

The need for an effective delivery vehicle for a therapeutic payload is driving the development of materials at various scales. As a mimic of the extracellular matrix, hydrogels have the potential to serve as delivery vehicles for cells and drugs. This class of hydrophilic cross-linked polymers can retain more than 90% water within the mesh of their porous network structure, thus enabling the encapsulation of hydrophilic drugs and cells (WANG; HAN, 2017).

The ability of hydrogels to absorb large amounts of water makes them particularly useful immunotolerant materials. Their flexibility is also another characteristic that makes them very similar to natural tissue, which is important to avoid irritation or other immune responses; it is also possible to work with the balance between hydrophilic and hydrophobic areas of the gel, according to the desired solvent diffusion characteristics being possible, for example, to control the release of a drug (LIMA *et al.*, 2020).

One of the most important applications of hydrogels is drug delivery, as they are potential candidates for improving accuracy and efficiency, as well as reducing the adverse effects of chemotherapeutic treatment processes, for example. As drug carriers, hydrogels must have suitable mechanical properties, biodegradability and biocompatibility, based on these characteristics the most commonly used polymers are: Collagen, gelatin, hyaluronic acid, dextran, chitosan and alginate in addition to synthetic ones (XU; LIU; HSU, 2019).

Hydrogels can improve oral administration by providing controlled release over prolonged periods, protecting the drug from adverse conditions in the stomach. In addition to being able to be designed containing groups responsive to pH and temperature changes that are able to release their cargoes in specific parts of the gastrointestinal tract (LARRAÑETA *et al.*, 2018).

Journal of Biology & Pharmacy
and Agricultural Management
ISSN 1983-4209
Journal of Biology & Pharmacy and Agricultural Management, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

In this sense, stimulus-responsive systems allow the advantage of delivering the right amount of drug at the right time in response to changes in external stimuli. Cationic gels, for example, can expand as a result of ionization of functional parts present along the macromolecular chain in an acidic condition, thus promoting drug diffusion and release in the stomach (DEEN; LOH, 2018).

4.2 Wound care

Wound dressings are the most successful examples of commercial hydrogel-based materials, these provide several desirable properties: a - maintenance of the moist environment; b - provides a barrier to bacterial contamination; c - allows oxygen access to the injured area; d - can be removed without damage to the healing surface (Figure 3) (LIMA *et al.*, 2020).

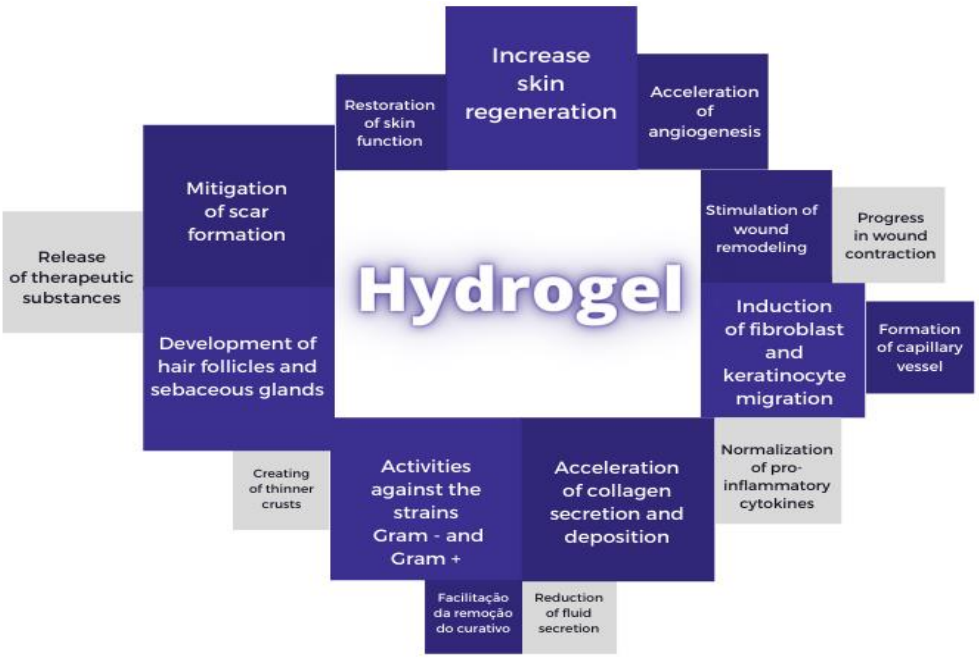

Figure 3. Effect of hydrogels on the wound healing process.

ISSN 1983-4209 *Journal of Biology & Pharmacy and Agricultural Management*, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

The most important reported fact was an increased healing rate compared to dry gauze dressing, and it is possible to reduce abnormal scar formation due to its biomimetic nature, regulated mechanics, ability to cross-link at the target site and the high water retention capacity which are important characteristics in the wound healing process (XU; LIU; HSU, 2019); its non-stick nature causes less discomfort in patients, especially in the case of burns, where the availability of autologous skin is significantly limited; chitin, chitosan, gelatin, alginate, and collagen are examples of natural polymers used (ZAGÓRSKA-DZIOK; SOBCZAK, 2020).

Properly designed hydrogels also allow for minimally invasive filling of free spaces in the human body and delivery of medicinal substances due to the fact that their structures are similar to the extracellular matrix of many tissues; by filling the space after damaged tissues and delivering appropriate bioactive molecules, they can also contribute to the restoration of new tissues (ZAGÓRSKA-DZIOK; SOBCZAK, 2020).

4.3 Cosmetic application

Hydrogels are one of the most interesting groups of medical materials for cosmetology and dermatology. One of the main advantages of hydrogels used in the topical treatment of skin diseases is the ease of application and significant minimization of side effects (ZAGÓRSKA-DZIOK; SOBCZAK, 2020). In addition to their properties such as biocompatibility, elasticity, softness, and high water content, hydrogels can be used to treat problems such as cellulite, wrinkles, pigmentation, skin aging, and hydration, the latter responsible for loosening the skin barrier assisting in drug permeation (ASWATHY; NARENDRAKUMAR; MANJUBALA, 2020).

The hydrogels used in cosmetic preparations can be based on various biopolymers, including collagen, gelatin, hyaluronic acid, alginate, chitosan, xanthan gum, pectin, starch, cellulose, and their derivatives. Biopolymer-based hydrogels are used for the development of several cosmetic products (Figure 4), such as the so-called "beauty

Journal of Biology & Pharmacy and Agricultural Management
ISSN 1983-4209
Journal of Biology & Pharmacy and Agricultural Management, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

masks". These masks aim to hydrate the skin, restore its elasticity and promote an anti-aging performance (MITURA; SIONKOWSKA; JAISWAL, 2020).

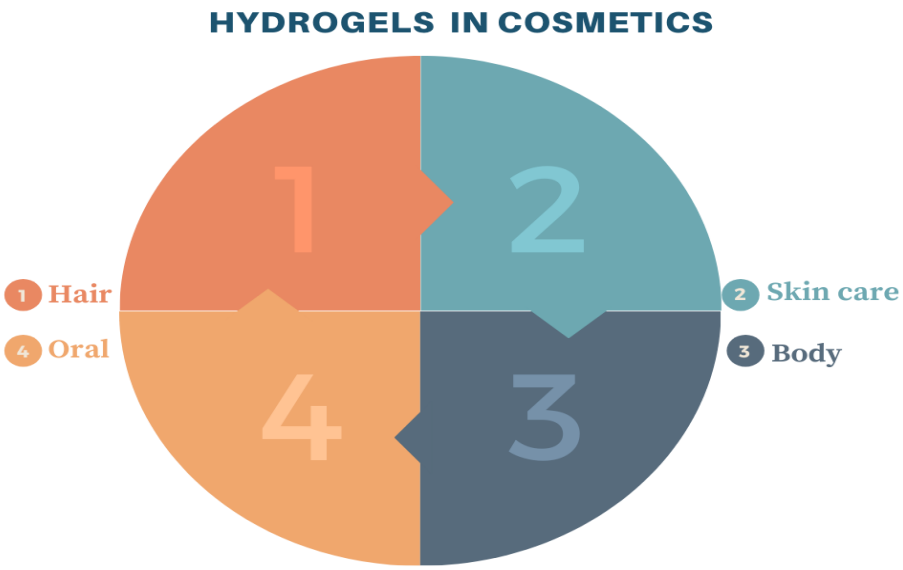

Figure 4. The common use of hydrogels in cosmetics.

4.4 Contact lenses

Silicone-based hydrogels have been used to develop medicated contact lenses for hydrophobic drug delivery that are capable of providing up to two weeks of sustained release of the drug used (LARRAÑETA *et al.*, 2018). Meanwhile, injectable hydrogels have been studied for lens replacement; this type of hydrogel requires refractive index similar with natural lenses, stable dilation behavior, and corresponding mechanical properties. The main polymers used are alginate, chitosan and hyaluronic acid polysaccharides and proteins in ophthalmology, which are biocompatible and have low toxicity (WANG; HAN, 2017).

Oxygen permeability is an important characteristic for the proper functioning of the cornea as it is used to maintain its structure, function, and clarity. The oxygen permeability of hydrogel contact lenses is critically related to the water content and the

Journal of Biology & Pharmacy
and Agricultural Management
ISSN 1983-4209
Journal of Biology & Pharmacy and Agricultural Management, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

thickness of the lens. In addition, it must be biocompatible, comfortable to wear, continuous tear film for clear vision, ion permeable to maintain movement, non-irritating, and resistant to tear film build-up (Figure 5). Light transmittance and refractive index are the important requirements of hydrogel for contact lens manufacturing (ASWATHY; NARENDRAKUMAR; MANJUBALA, 2020).

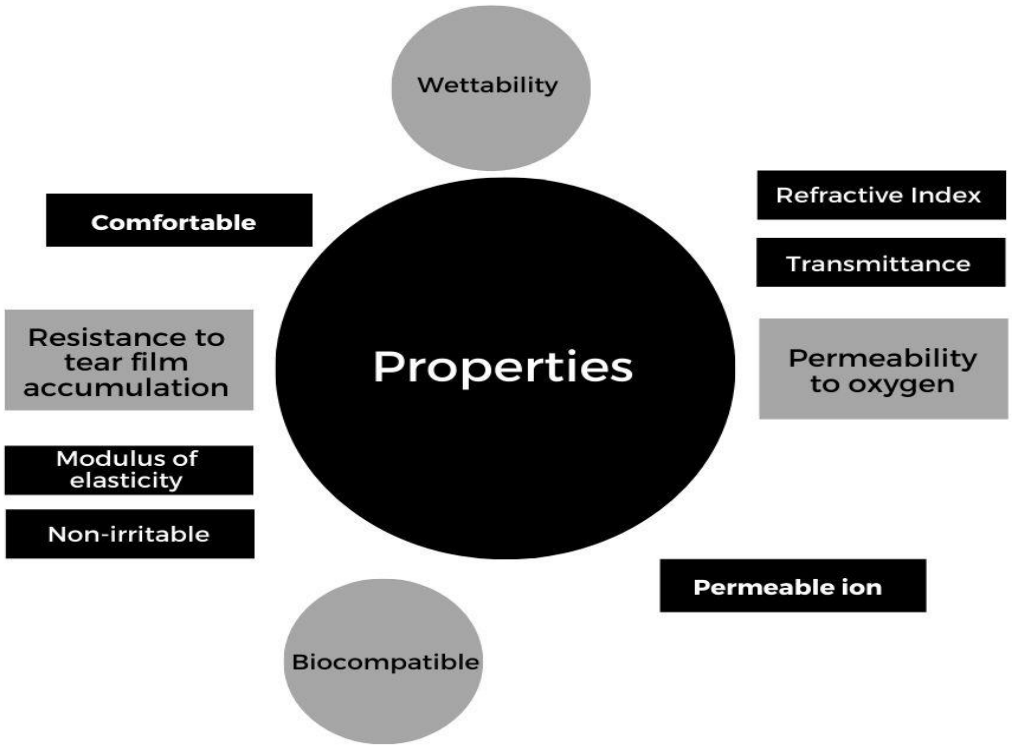

Figure 5. Ideal properties for using hydrogel as a contact lens.

4.5 Tissue engineering

The goal of tissue engineering is to develop new functional tissues and regenerate tissues *in vitro* or *in vivo* to cure diseases when surgical intervention is required. For optimal functional tissue development, the product must interact with cells without any adverse effects to provide cell attachment, proliferation, growth, and mineral matrix accumulation. 3D structured biomaterials can be designed using a variety of natural and

ISSN 1983-4209 *Journal of Biology & Pharmacy and Agricultural Management*, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

synthetic polymers can have a solid structure prior to implantation or be in injectable forms that harden *in situ* (KHAN; TANAKA, 2017).

The role of most polymer scaffolds is to provide a modified surface of porosity suitable for seeded cell adhesion and interaction, much like the extracellular matrix. The volume of tissue developed depends on the *crosslinking* density and pore size of the polymer scaffolds; polymers, such as cationic chitosan, poly-l-lysine, poly (ethylene-imine) (PEI), etc., have been widely used for this purpose (DEEN; LOH, 2018).

Hydrogels have highly hydrated 3D architectures with high water content and adequate porosity, substance exchange capacity, good biodegradability and extraordinary mechanical properties, providing a suitable environment, efficient biocompatibility and high strength being effective in differentiation and regeneration of the specific MEC extracellular matrix, thus resulting in their wide uses for tissue engineering (BAO *et al.*, 2020).

5 CONCLUSIONS

Based on this review it can be evidenced that hydrogels have played an essential role in biomedical application due to their biocompatibility characteristics and unique biomimetic properties. Additionally, it was found that hydrogels have been widely used mainly in pharmaceutical applications, such as contact lenses, wound dressings, drug delivery vehicles, and tissue engineering, mainly due to their ability to fit the application for which it was designed, which is linked to the great diversity of polymers that can be used and different obtaining techniques, which provide necessary chemical and physical characteristics. Finally, the use of hydrogels for a variety of clinical applications has a long way to go, but it has already shown promise. A combination of *in vitro* and *in vivo* studies is needed to understand the mechanical and material properties, the effects of processing methods on hydrogel performance, the mechanisms by which they influence cell behavior and tissue remodeling, and the safety evaluation of the hydrogels, which should further enhance their clinical utility.

ISSN 1983-4209 *Journal of Biology & Pharmacy and Agricultural Management*, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

ACKNOWLEDGMENTS

The authors acknowledge the fellowships received from Fundação de Amparo à Ciência e Tecnologia de Pernambuco (FACEPE APQ-0493-4.03/14) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 380696/2020-7; 405297/2018-1 and 307110/2018-4).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

ASWATHY, S. H.; NARENDRAKUMAR, U.; MANJUBALA, I. Commercial hydrogels for biomedical applications. **Heliyon**, 6, n. 4, p. e03719-e03719, 2020.

BAO, W.; LI, M.; YANG, Y.; WAN, Y. *et al.* Advancements and Frontiers in the High Performance of Natural Hydrogels for Cartilage Tissue Engineering. **Frontiers in chemistry**, 8, p. 53-53, 2020.

BRYANT, S. J.; VERNEREY, F. J. Programmable Hydrogels for Cell Encapsulation and Neo-Tissue Growth to Enable Personalized Tissue Engineering. **Advanced healthcare materials**, 7, n. 1, p. 10.1002/adhm.201700605, 2018.

CATOIRA, M. C.; FUSARO, L.; DI FRANCESCO, D.; RAMELLA, M. *et al.* Overview of natural hydrogels for regenerative medicine applications. **Journal of materials science. Materials in medicine**, 30, n. 10, p. 115-115, 2019.

CHAI, Q.; JIAO, Y.; YU, X. Hydrogels for Biomedical Applications: Their Characteristics and the Mechanisms behind Them. **Gels (Basel, Switzerland)**, 3, n. 1, p. 6, 2017.

CHOUDHARY, R.; SARASWAT, M.; VENKATRAMAN, S. K. A fundamental approach toward polymers and polymer composites: Current trends for biomedical applications. *In*: **Polymer nanocomposites in biomedical engineering**: Springer, 2019. p. 1-28.

DEEN, G. R.; LOH, X. J. Stimuli-Responsive Cationic Hydrogels in Drug Delivery Applications. **Gels (Basel, Switzerland)**, 4, n. 1, p. 13, 2018.

FENNELL, E.; HUYGHE, J. M. Chemically Responsive Hydrogel Deformation Mechanics: A Review. **Molecules (Basel, Switzerland)**, 24, n. 19, p. 3521, 2019.

ISSN 1983-4209 *Journal of Biology & Pharmacy and Agricultural Management*, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

FRANCIS, L.; GRECO, K. V.; BOCCACCINI, A. R.; ROETHER, J. J. *et al.* Development of a novel hybrid bioactive hydrogel for future clinical applications. **J Biomater Appl**, 33, n. 3, p. 447-465, Sep 2018.

GRADINARU, V.; TREWEEK, J.; OVERTON, K.; DEISSEROTH, K. Hydrogel-Tissue Chemistry: Principles and Applications. **Annu Rev Biophys**, 47, p. 355-376, May 20 2018.

GREGORITZA, M.; MESSMANN, V.; ABSTIENS, K.; BRANDL, F. P. *et al.* Controlled Antibody Release from Degradable Thermoresponsive Hydrogels Cross-Linked by Diels-Alder Chemistry. **Biomacromolecules**, 18, n. 8, p. 2410-2418, Aug 14 2017.

GUVENDIREN, M.; MOLDE, J.; SOARES, R. M. D.; KOHN, J. Designing Biomaterials for 3D Printing. **ACS biomaterials science & engineering**, 2, n. 10, p. 1679-1693, 2016.

IQBAL, H. M. N. The Quest for Materials-Based Hydrogels with Antimicrobial and Antiviral Potentialities. **The open virology journal**, v.12, p. 69-79, DOI: 10.2174/1874357901812010069. Acesso em: 2018.

JABBARI, E.; LEIJTEN, J.; XU, Q.; KHADEMHOSSEINI, A. The matrix reloaded: the evolution of regenerative hydrogels. **Materials today**, 19, n. 4, p. 190-196, 2016.

KASIŃSKI, A.; ZIELIŃSKA-PISKLAK, M.; OLEDZKA, E.; SOBCZAK, M. Smart Hydrogels - Synthetic Stimuli-Responsive Antitumor Drug Release Systems. **International journal of nanomedicine**, 15, p. 4541-4572, 2020.

KHAJOUEI, S.; RAVAN, H.; EBRAHIMI, A. DNA hydrogel-empowered biosensing. **Adv Colloid Interface Sci**, 275, p. 102060, Jan 2020.

KHAN, F.; TANAKA, M. Designing Smart Biomaterials for Tissue Engineering. **International journal of molecular sciences**, 19, n. 1, p. 17, 2017.

KOWALCZUK, M. Intrinsically Biocompatible Polymer Systems. **Polymers**, 12, n. 2, p. 272, 2020.

LARRAÑETA, E.; STEWART, S.; ERVINE, M.; AL-KASASBEH, R. *et al.* Hydrogels for Hydrophobic Drug Delivery. Classification, Synthesis and Applications. **Journal of functional biomaterials**, 9, n. 1, p. 13, 2018.

LEE, J.; SONG, B.; SUBBIAH, R.; CHUNG, J. J. *et al.* Effect of chain flexibility on cell adhesion: Semi-flexible model-based analysis of cell adhesion to hydrogels. **Scientific reports**, 9, n. 1, p. 1-8, 2019.

LI, L.; YU, F.; ZHENG, L.; WANG, R. *et al.* Natural hydrogels for cartilage regeneration: Modification, preparation and application. **Journal of orthopaedic translation**, 17, p. 26-41, 2018.

LIMA, C. S. A. d.; BALOGH, T. S.; VARCA, J. P. R. O.; VARCA, G. H. C. *et al.* An Updated Review of Macro, Micro, and Nanostructured Hydrogels for Biomedical and Pharmaceutical Applications. **Pharmaceutics**, 12, n. 10, p. 970, 2020.

LIU, G.; ZHANG, Q.; LI, Y.; WANG, X. *et al.* High-Throughput Preparation of Antibacterial Polymers from Natural Product Derivatives via the Hantzsch Reaction. **iScience**, 23, n. 1, p. 100754, Jan 24 2020.

ISSN 1983-4209 *Journal of Biology & Pharmacy and Agricultural Management*, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

LIU, J.; ZHANG, X.; CHEN, X.; QU, L. *et al.* Stimuli-responsive dendronized polymeric hydrogels through Schiff-base chemistry showing remarkable topological effects. **Polymer Chemistry**, 9, n. 3, p. 378-387, 2018.

MILCOVICH, G.; LETTIERI, S.; ANTUNES, F. E.; MEDRONHO, B. *et al.* Recent advances in smart biotechnology: Hydrogels and nanocarriers for tailored bioactive molecules depot. **Adv Colloid Interface Sci**, 249, p. 163-180, Nov 2017.

MITURA, S.; SIONKOWSKA, A.; JAISWAL, A. Biopolymers for hydrogels in cosmetics: review. **Journal of materials science. Materials in medicine**, 31, n. 6, p. 50-50, 2020.

NASCIMENTO, M. H. M. d.; LOMBELLO, C. B. Hidrogéis a base de ácido hialurônico e quitosana para engenharia de tecido cartilaginoso. **Polímeros**, 26, p. 360-370, 2016.

OLIVA, N.; CONDE, J.; WANG, K.; ARTZI, N. Designing Hydrogels for On-Demand Therapy. **Accounts of chemical research**, 50, n. 4, p. 669-679, 2017.

PAHLEVANZADEH, F.; BAKHSHESHI-RAD, H. R.; HAMZAH, E. In-vitro biocompatibility, bioactivity, and mechanical strength of PMMA-PCL polymer containing fluorapatite and graphene oxide bone cements. **J Mech Behav Biomed Mater**, 82, p. 257-267, Jun 2018.

PENG, L.; ZHOU, Y.; LU, W.; ZHU, W. *et al.* Characterization of a novel polyvinyl alcohol/chitosan porous hydrogel combined with bone marrow mesenchymal stem cells and its application in articular cartilage repair. **BMC Musculoskelet Disord**, 20, n. 1, p. 257, May 29 2019.

ROSA, E.; DIAFERIA, C.; GALLO, E.; MORELLI, G. *et al.* Stable Formulations of Peptide-Based Nanogels. **Molecules (Basel, Switzerland)**, 25, n. 15, p. 3455, 2020.

SATTARI, S.; DADKHAH TEHRANI, A.; ADELI, M. pH-Responsive Hybrid Hydrogels as Antibacterial and Drug Delivery Systems. **Polymers**, 10, n. 6, p. 660, 2018.

SHAN, D.; GERHARD, E.; ZHANG, C.; TIERNEY, J. W. *et al.* Polymeric biomaterials for biophotonic applications. **Bioactive materials**, 3, n. 4, p. 434-445, 2018.

SHAO, C.; WANG, M.; MENG, L.; CHANG, H. *et al.* Mussel-inspired cellulose nanocomposite tough hydrogels with synergistic self-healing, adhesive, and strain-sensitive properties. **Chemistry of Materials**, 30, n. 9, p. 3110-3121, 2018.

VIEIRA, G. A. Síntese e Caracterização de Polímeros Verdes: Poliésteres do Glicerol e do Ácido Isoftálico. 2016.

WANG, K.; HAN, Z. Injectable hydrogels for ophthalmic applications. **Journal of controlled release : official journal of the Controlled Release Society**, 268, p. 212-224, 2017.

WANG, W.; NARAIN, R.; ZENG, H. Rational Design of Self-Healing Tough Hydrogels: A Mini Review. **Frontiers in chemistry**, 6, p. 497-497, 2018.

WILLIAMS, D. F. Biocompatibility pathways: biomaterials-induced sterile inflammation, mechanotransduction, and principles of biocompatibility control. **ACS Biomaterials Science & Engineering**, 3, n. 1, p. 2-35, 2017.

ISSN 1983-4209

Journal of Biology & Pharmacy and Agricultural Management, v. 17, n. 4, out/dez 2021
revista.uepb.edu.br/index.php/biofarm

XU, J.; LIU, Y.; HSU, S.-H. Hydrogels Based on Schiff Base Linkages for Biomedical Applications. **Molecules (Basel, Switzerland)**, 24, n. 16, p. 3005, 2019.

YIN, J.; LUAN, S. Opportunities and challenges for the development of polymer-based biomaterials and medical devices. **Regenerative biomaterials**, 3, n. 2, p. 129-135, 2016.

ZAGÓRSKA-DZIOK, M.; SOBCZAK, M. Hydrogel-Based Active Substance Release Systems for Cosmetology and Dermatology Application: A Review. **Pharmaceutics**, 12, n. 5, p. 396, 2020.