Mediterranean Journal of Basic and Applied Sciences (MJBAS)
Volume 7, Issue 1, Pages 58-74, January-March 2023

Polyelectrolyte-based Hydrogels for Biomedicine

María I. León-Campos[1], Jesús A. Claudio-Rizo[1*], Martín Caldera-Villalobos[1], Denis A. Cabrera-Munguía[1], Juan J. Mendoza-Villafaña[1], Lucía F. Cano-Salazar[1] & Tirso E. Flores-Guía[1]

*[1]Department of Advanced Materials, Faculty of Chemistry Science, University Autonomous of Coahuila, Saltillo, Coahuila, México. Corresponding Author (Jesús A. Claudio-Rizo) - jclaudio@uadec.edu.mx**

DOI: https://doi.org/10.46382/MJBAS.2023.7106

Article Received: 11 January 2023 *Article Accepted: 25 February 2023* *Article Published: 17 March 2023*

ABSTRACT

Hydrogels have a three-dimensional structure of polymer chains composed of hydrophilic end groups. The aim of this review is to show how polyelectrolytes have emerged as a promising and innovative toolkit for delivering and targeting therapeutic bioactive substances. Also, here the most relevant contributions related to hydrogel systems based on polyelectrolytes are presented, highlighting of these systems their main characteristics for applications in biomedicine.

Keywords: Hydrogels; Polyelectrolytes; Biomaterials; Biomedicine; Polymers; Scaffolds.

1. Introduction

Polyelectrolyte hydrogels are very important as they have the ability to respond to external physical or chemical stimuli [1]. A polyelectrolyte hydrogel has a three-dimensional (3D) network that is made up of charged polymer chains which have the ability to swell and retain a significant amount of water, allowing to maintain its structural integrity [2].

In 1960, Wichterle and Lim were the first to describe a hydrogel based on poly-2-hydroxyethylmethacrylate (PHEMA) as a synthetic biocompatible material useful for contact lens applications [3]. Hydrogels are used for a variety of biomedical applications, such as drug delivery, tissue engineering for wound dressings, as well as cell culture and antimicrobial applications. Most of these applications require multifunctional hydrogels and dynamic interactions with cellular microenvironments [4]. Polyelectrolytes, composed of polymers that contain ionizable groups, have generated great interest in the design of biomaterials for their application in biomedical, biotechnological, and pharmaceutical fields, among others. Polyelectrolyte applications are primarily focused on polyelectrolyte adsorption on solid surfaces to obtain thin films that can modulate the chemical nature and charge of the modified surface [5].

There are polymers that have an ionic nature, highlighting mainly polyelectrolytes are an intriguing class of macromolecules, which contain dissociated ionic groups. These have been used for decades in different applications, highlighting biomedical. [6]. This review highlights the synthesis of hydrogels that have been synthesized by various methods and using natural and synthetic polymers and have been used for various biomedical applications.

2. Polyelectrolytes

Polyelectrolytes (PEs) have remained one of the most attractive subjects of scientific research in recent decades owing to their great importance in advanced technologies and molecular biology. A PE is defined as any

macromolecular material that has repeating units and dissociates into a highly charged polymeric molecule upon being placed in any ionizing solvent forming either a positively or negatively charged polymeric chain [7].

2.1. Classification of polyelectrolytes

Polyelectrolytes (PE) can be classified into different categories depending upon their origin, charge, pH dependence, morphology, position of ionizable sites, and composition (Table 1). Some natural polyelectrolytes include carbohydrates, alginates, chitosan, carrageenan, pectin, and nucleic acids, while synthetic polyelectrolytes, like poly(acrylic acid), poly(vinyl amine), poly(vinylsulfonic acid), and polyvinylpyridine, are also common [8].

Table 1. Classification of polyelectrolytes based on different criterion [8]

Criterion	Classification	Examples
Origin	Natural	Protein
	Semi-synthetic	Xanthan gum
	Synthetic	Poly (styrene sulfonic) acid
	Polycation	N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride (HTCC)
Charge	Polyanion	Poly (sodium styrene sulfonate)
	Polyampholyte	Protein
pH dependence	Strong: pH-independent charge	Poly (vinyl sulfate)
		Poly(ethyleneimine)
	Weak: pH-dependent charge	
Position of ion sites	Integral (Ions on the backbone)	Poly (2,20-disulfonyl-4,40-benzidine terephthalamide
	Pendant (Ions at the periphery or sidechain)	Poly (2-methacryloyloxyethyl 4-vinyl pyridinium bromide)

We distinguish between natural and synthetic polyelectrolytes. Natural polyelectrolytes are usually produced from starch, while the synthetic kind is produced as a result of polymerisation of organic monomers with unsaturated bindings [9].

Depending on the nature of the ionic charge, polyelectrolytes can be classified into polyanions (PA) (polyacids, have negative charges), polycations (PC) (polybases, have positive charges), polyampholytes (PAm) (amphoteric, have both positive and negative charges) [10]

Many polyanions have been used to form polyelectrolyte complexes in order to provide the physicochemical properties required for the design of specific drug delivery systems. In addition, it has been used: chitosan, pectin,

alginate, carrageenan, xanthan gum, carboxymethylcellulose, chondroitin sulfate, dextran sulfate, and hyaluronic acid within said polyelectrolyte formulations [11].

The ionic type determines the charge carried by the ionized polymer (positive, negative or both), and PE are defined as cationic, anionic, and polyampholytes, respectively. The strength of the PE charge controls PE behaviour in a polar solvent through electrostatic forces [12].

Normaly prevailing cationic PEs incorporate quaternary ammonium groups that provide almost inexhaustible combinations of nitrogen substituents for tailor-made polymer synthesis [13]. In addition, quaternary ammonium-based PEs exhibit basic properties, are relatively stable and cost-efficient [14]. Other heteroions in the cationic moieties could also be used, i.e., phosphonium, sulphonium, boronium.

These molecules can exhibit interesting phenomena owing to their dual character of macromolecular chain plus high charge. The classification of the PEs and some PEs are exemplified in Table 2 based on their nature.

Table 2. Some of the polyelectrolytes (PEs) and their ionic nature [7]

PE type	Polyanion	Polycation
Natural	Nucleic acids, poly(L-glutamic acid), carrageenan, sodium alginate, hyaluronic acid, chondroitin sulfate, gellan gum.	Poly(L-lysine), lysozyme, gelatin, chitosan, dextran, starch.
Chemically modified/semi-synthetic	N-carboxymethyl chitosan, cellulose-based (sodium carboxymethyl cellulose), carboxymethyl konjac glucomannan, pectin, sodium dextran sulfate, xanthan gum.	Chitosan (deacetylation of chitin), N-trimethyl chitosan, chitosan-g-poly(ethylene glycol) monomethyl ether.
Synthetic	Poly(acrylic acid)/carbopol, poly(methacrylic acid), poly(acrylamide-2-methyl-propane sulfonate), poly(3-sulfopropyl methacrylate), dextran sulfate, poly(metaphosphoric acid).	Poly(ethyleneimine), poly (acrylamideco-dimethyldiallylammonium chloride), poly(vinylbenzyl trialkyl ammonium), poly(acryloyl-oxyalkyl-trialkyl ammonium).

Polyampholytes are polymers containing mixed cationic/anionic groups, and polyzwitterions in general [15].

Polyelectrolytes present electrostatic interactions (attraction/repulsion) between the charges present in the monomeric units. These make macromolecules rich in a variety of physicochemical properties. Electrostatic repulsion between the same charges of monomeric units of a macromolecule can result in significant chain elongation, which can vary almost linearly with the degree of polymerization [16].

An important factor to consider in selecting a polyelectrolyte is pH. Due to the sensitivity to pH, it occurs with cationic polymers, mainly in which quaternary ammonium groups are dominant, and with anionic polymers [17].

The polyelectrolytes are classified into various types. Based on origin they are classified as natural polyelectrolytes, synthetic polyelectrolytes and chemically modified biopolymers. Based on composition they are homopolymers and copolymers. Based on molecular architecture linear, branched and cross linked. Based on electrochemistry they are classified as polyacids/polyanions, polybases/polycations and polyampholytes. Some of the important polyelectrolytes are exemplified in table 3 [18].

Table 3. Some important polyelectrolytes [19] [18]

Name	**Category (based on the charge type)**
Natural polyelectrolytes	
Nucleic acid	Polyanion
Poly (L-lisine)	Polyanion
Poly (L-glutamic acid)	Polyanion
Carrageenan	Polyanion
Alginates	Polyanion
Hyaluronic acid	Polyanion
Chemically modified biopolymers	
Pectin	Polyanion
Chitosan	Polyanion
Cellulose-based	Polyanion or polycation
Starch-based	Polyanion or polycation
Dextran-based	Polyanion or polycation
Synthetic polymers	
Poly (vynilbenzyl trialkyl ammonium)	Polycation
Poly (4-vinyl-N-alkyl-pyridimium)	Polycation
Poly (acryamidoalkyl-trialkyl	Polycation
Polyampholyte	
Acrylamide	Weak cation
2-(Dimethylamino)ethyl methacrylate	Weak cation
[2-(Acryloyloxy)ethyl]trimethylammonium chloride	strong cation
Polyzwitterion	
Alanine	Polycation
L-Glutamic acid	Polycation

There are many studies of the synthesis and characterization of polyelectrolytes that have anionic, cationic, or both covalently bonded groups [20].

These include experimental studies of mechanism and reaction conditions, physicochemical properties and design of chemical structure. The design of chemical structure of polyelectrolytes includes the appropriate selection of the kind of ionic group in the polymer structure. The cationic polyelectrolytes generally have in their structures basic groups such as amino, phosphonium, sulfonium, boronium, imidazolium, or pyridinium. While the anionic polyelectrolytes have acid groups like carboxylates, sulfates, sulfonates, phosphates, phosphonates, and arsenates [21].

2.2. Synthesis of polyelectrolyte

The most innovative developments in the synthesis of polyelectrolytes stand out, focused on the nature of the ionic groups, the polymeric skeletons, the synthesis methods and the additional functionality granted to the polyelectrolytes. It should be noted that the synthesis of new polyelectrolytes is mainly driven by material aspects, currently [14].

To produce polymeric substances, free-radical polymerization is the most used industrial method, inclusive plastics, rubbers and fibers production. This method is comparatively tolerant to functional groups on the repeating units as ionic moieties, ligands, nucleophilic and electrophilic sites, acids and bases, and is possible to operate in various solvents. Numerous impurities, even water are not a genuine issue. This method does not require confusing procedures and modern types of gear to work under strict humidity-free situations. Polymerizations should even be possible straightforwardly in (water functioning as a solution, bulk, precipitation, suspension, or emulsion) given that oxygen is rejected. This method can be performed in a wide temperature range, relying on the monomer-initiator couple [22]. In the table 4 shows the polyelectrolyte preparation methods.

Table 4. Polyelectrolyte preparation methods [23]

Type of polymerization	Preparation method	Characteristics
Solution polymerization	In solvents bearing both polymers and monomers.	The rate of polymerization and the characteristics of the polymer thus obtained are controlled by factors like solvent type, pH, temperature, surfactant, chain-transfer agent, and complexing agent.
Bulk polymerization	Without solvents or diluents. By this technique, high-molecular-weight polymers can be prepared.	The reusing and purification of solvents or dispersants and also the discard of liquid wastes are not required in this method, so economically and ecologically it has great advantages.

Precipitation polymerization	Precipitation occurs as the polymer is prepared. Acetone, acetonitrile, dioxane, ethanol, tert-butanol, and Tetrahydrofuran (THF).	Toward the start of the process, the reaction mixture is homogeneous, though, during the procedure, precipitation of the polymer happens, and the process continues under heterogeneous conditions.
Suspension polymerization	In the presence of stabilizers, when aqueous monomer solution is dispersed in an organic solvent and stirred mechanically, a suspended system is gotten.	The size of droplets in the aqueous monomer solution varies in diameter within the range of 0.1 to 5 mm for the preparation of dispersion medium, hydrocarbons (aliphatic or aromatic, or their mixtures) with carbon number 6-10 can be used as the organic medium
Emulsion polymerization	Requires the charging of the reactors with a solution of emulsifier in an organic médium.	During this, the aqueous solution containing 20-60% monomer concentration is scattered in an organic solvent by continuous stirring.

3. Polyelectrolyte complexes

Polyelectrolyte complexes (PECs) or polysalts are precipitates formed when two oppositely charged polyelectrolytes are allowed to co-react in aqueous solution. These PECs have been shown to display unique physical and chemical properties due to the considerably stronger electrostatic interactions compared to most other secondary binding interactions (Lee et al. 2002). PECs are formed by increasing entropy through the release of ions from low molecular weight counter polyelectrolyte complexes (PECs). Hydrogen bonding and hydrophobic interaction are also known to play a role [24]

Polyelectrolyte complexes (PECs), composed of natural and biodegradable polymers, (such as positively charged chitosan or protamine and negatively charged glycosaminoglycans (GAGs)) have attracted attention as hydrogels, films, hydrocolloids, and nano-/micro-particles (N/MPs) for biomedical applications [25].

PECs have important application, it contains microencapsulation of drugs, enzymes, cells and microorganism, control of proteins by the complex development and polycation complexes with poly nucleotides or oligo nucleotides as vectors in gene treatment [26].

Polyelectrolyte complex (PEC) hydrogels are the networked structure of polymer chains crosslinked to each other and surrounded by an aqueous solution. The polymer chains contain acidic and basic groups bound to them. The acidic groups on the chains deprotonate at a high pH, whereas the basic groups protonate at a low pH. In the presence of a salt solution, the polymer chains absorb water, and the association and dissociation of various ions to and from polymer chains determines the degree of hydrogel swelling [27].

The structure and properties of PEC hydrogels are similar to those of many biological tissues, such as cartilage and the corneal stroma in the eye. PEC hydrogels are capable of undergoing large, reversible deformations in response to changes in several environmental factors [28]. For example, hydrogel volume is sensitive to solution pH, salt concentration, temperature, and electric fields. The sensitivity of hydrogels to a large number of physical factors makes them candidates for a broad range of biological applications including control of microfluidic flow, musclelike actuators, and drug delivery [29].

3.1. PEHs hydrogels

Polyelectrolyte complexes possessing hydrogel character: polyelectrolyte hydrogels (PEHs) recently they have gained great importance due to their characteristics such as: ability to respond to chemical or physical stimuli (pH, ionic strength, solvent polarity, external electricity) field, they are known as "smart hydrogels [30].

PEHs are three-dimensional networks formed by the electrostatic interactions of oppositely charged polyelectrolytes when ionic forces cross-link the polymers forming a network. Ionic crosslinking is reversible; at high ionic strength, the polyelectrolyte complex decomposes slowly. This behavior has an advantage because hydrogels of this type are more biodegradable compared to hydrogels formed by covalent interbreeding [31].

There is a chemical difference between physical hydrogels and polyelectrolyte complex (PEHs) hydrogels, these are held together by non-covalent bonds without toxicity organic crosslinkers are needed. Although some PEHs have been recently used in flexible solid-state supercapacitors (SC), these electrolytes are made from synthetic polymers, such as poly(styrenesulfonic acid) and poly(ionic liquid). Therefore, these hydrogels are expensive, dangerous for the environment and even toxic [32].

Polyelectrolyte complexes (PEHs), composed of natural and biodegradable polymers, (such as positively charged chitosan or protamine and negatively charged glycosaminoglycans (GAGs)) have attracted attention as hydrogels, films, hydrocolloids, and nano-/micro-particles (N/MPs) for biomedical applications. This is due to their biocompatibility and biological activities. These PECs have been used as drug and cell delivery carriers, hemostats, wound dressings, tissue adhesives, and scaffolds for tissue engineering [25].

4. Hydrogels

Hydrogels are 3D networks of hydrophilic nature, which have the ability to ingest large amounts of water or biological fluids, in addition, they are drug delivery vectors, energy harvesting devices, potential candidates for biosensors, and carriers or matrices for cells in tissue engineering [33].

Hydrogels may be chemically stable or could degrade and eventually disintegrate and dissolve. They are also called physical gels when their networks are held together by secondary forces, including hydrogen bonding, ionic or hydrophobic forces, and molecular entanglements [34].

In this sense, hydrogels are polymeric structures that are held together as water-swollen gels by: (1) covalent bonds; (2) ionic forces; (3) hydrogen bonds; (4) affinity interactions or "bio-recognition"; (5) hydrophobic interactions; (6) crystalline polymers; (7) physical entanglements of individual polymer chains; or (8) a combination of two or more of the above interactions [35].

4.1. Classification of hydrogel

Hydrogels are formed primarily from biopolymers and/or polyelectrolytes. Depending on the type of source, hydrogels can be classified into those made from natural polymers and those made from synthetic polymers. The ionic charges of the linked groups must also be considered, in addition, hydrogels can be cationic, anionic, or neutral. Another criterion for classifying them is crosslinking agents [36]

By their crosslinking, hydrogels can be physical, chemical, or biochemical. Physical gels can undergo a transition from liquid to a gel in response to a change in environmental conditions such as temperature, ionic concentration, pH, or other conditions such as mixing of two components. Chemical gels use covalent bonding that introduces mechanical integrity and degradation resistance compared to other weak materials. In biochemical hydrogels, biological agents like enzymes or amino acids participate in the gelation process [37].

Depending on their preparation method, ionic charge, or physical structure characteristics, hydrogels can be classified into several categories. Depending on the method of preparation, they can be: (1) homopolymer hydrogels; (2) copolymer hydrogels; (3) multipolymer hydrogels; and (4) Interpenetrating Network (IPN) hydrogels, these are shown in Figure 1 [38].

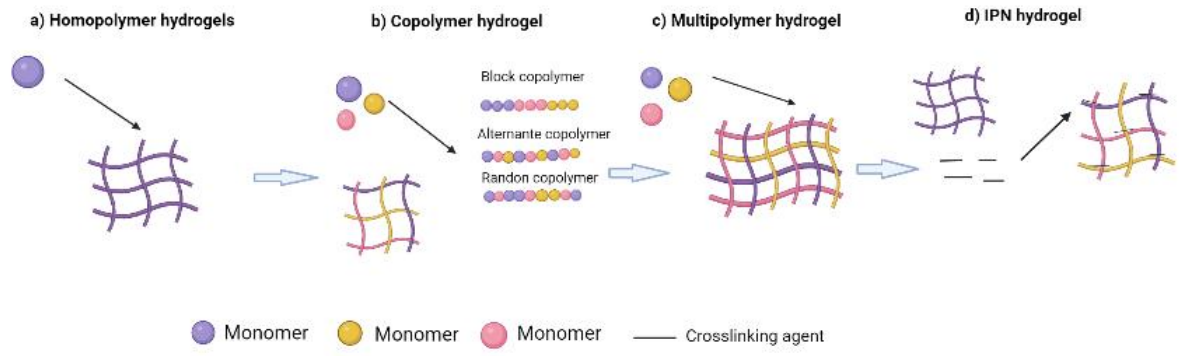

Figure 1. Chemical classification of hydrogels: a) homopolymer hydrogels, b) copolymer hydrogels, c) multipolymer hydrogels, and d) interpenetrating network hydrogels

The polymer chains of homopolymer hydrogels are derived from one monomer species, whereas copolymer hydrogels are produced by the crosslinking of chains composed of two monomer units, at least one of which must be hydrophilic, so they can swell in water [39].

The polymers in the hydrogels can be homopolymers, copolymers, semi-interpenetrating networks (semi-IPNs), or IPN hydrogels, which are dependent on their chemical composition. The simple diagrams of homopolymer hydrogels, copolymer hydrogels, semi-IPNs, and IPN hydrogels can be seen in figure 1. The polymer chains of the homopolymer hydrogels are derived from one species of monomer, whereas copolymer hydrogel are derived from two or more species of monomers.

The copolymer can be further classified as block, alternate, or random copolymer, based on their composition order of monomer. The active side of copolymers can be linked with another monomer or copolymer. Both, homo and copolymer hydrogels contain one type of polymer chain. In contrast, both semi-IPNs and IPN hydrogels have

two or more types of polymer chains. Semi-IPN hydrogels are a polymer network embedded with the linear polymer chains. The linear polymer chains are embedded without a crosslinking agent. IPN hydrogels are formed by two or more polymer networks that are crosslinked with each other by using a crosslinking agent. In comparison with the homo- and copolymer hydrogels, the semi-IPN and IPN hydrogels present higher mechanical strength and swelling properties [40]. In the figure 2 clearly represents the classification of hydrogels based on their source and properties.

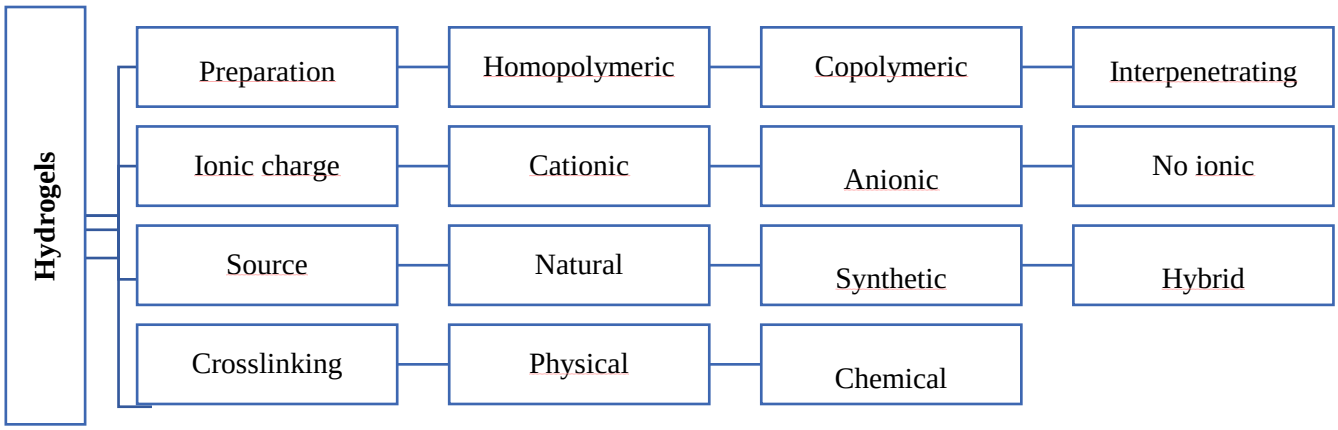

Figure 2. Classification of hydrogels based on the different properties [5]

Hydrogels could also show a swelling behavior dependent on the external environment. These polymers are physiologically-responsive hydrogels, where polymer complexes can be broken, or the network can be swollen as a result of the changing external environment. These systems tend to show drastic changes in their swelling ratio as a result. Some of the factors affecting the swelling of physiologically-responsive hydrogels include pH, ionic strength, temperature, and electromagnetic radiation [41].

4.2. Biomedical applications of hydrogels based on polyelectrolytes

Polyelectrolytes have been used for the development of polymeric materials with potential application in the area of biomaterials, this is favored given the variety of functional groups and ionizable groups that they contain in their structure. The structural variety influences on the ability to attract or repel biological systems such as cells and proteins, affecting the behavior of adhesion, growth and viability on the polymeric material [41].

There are various biomaterials focused on biomedical uses, such as hydrogels which are used for tissue regeneration, they have the capacity to absorb water. Crosslinking changes a liquid polymer to a solid or gel by modifying the movement of the molecules that make up the hydrogel. These biomaterials have diverse biomedical applications, highlighting their role as scaffolds in tissue lesions and sustained drug release systems. They are also 3D scaffolds for various cell therapies, providing a microenvironment with biomimetic properties that favor the recovery of damaged tissue [42] [43].

Interestingly, the first publication on hydrogels for biomedical applications was in the early 1950s, when Wichterle and Lim reported on crosslinked poly(hydroxyethyl methacrylate) (pHEMA). The aim was to create a new biomaterial for ophthalmic applications, which led later to the first soft contact lens [44].

Hydrogels can be useful for many applications, it has been reported its use in sustained drug release systems, as an alternative for the regeneration of damaged tissues; They are also 3D scaffolds for various cell therapies, in order to provide a microenvironment with biomimetic properties that allow the differential expression of cell behaviors that favor the recovery of damaged tissue.

This characteristic makes it very relevant in regenerative medicine focused on the repair of the nervous system in different neuropathologies, since the anatomy of this system is very complex and delicate. Currently, the study of hydrogels as possible biomaterials that promote axonal regeneration is a very dynamic topic with great potential for possible preclinical applications [45]. In figure 3 presents some biomedical applications of hydrogels comprised from polyelectrolytes.

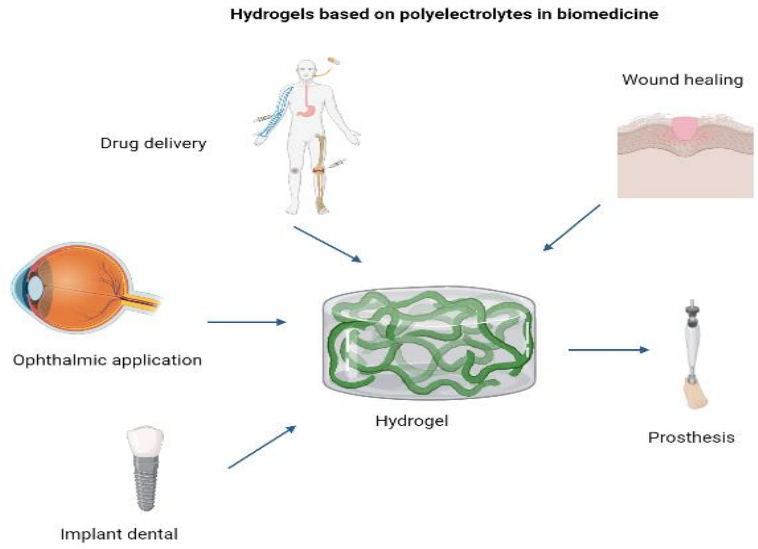

Figure 3. Use of hydrogels based on polyelectrolytes in biomedicine

Natural polymers have been reported to have explicit biomedical applications in tissue regeneration because of their biocompatibility, biodegradability, and macromolecular similarity to parent ECMs, which can provide superb bioactivity and a natural adhesive surface for cells required for bioactivity. There are natural polymers that have been used for hydrogel preparation, these include protein-based materials (such as gelatin, collagen, fibrin, and silk fibroin) and polysaccharide-based materials (such as hyaluronic acid, chondroitin sulfate, alginate, chitosan, etc.) [46]. In the table 5 and 6 polyelectrolyte hydrogels based on natural polymers and synthetic polymers with biomedical applications are summarized.

Table 5. Polyelectrolyte hydrogels including natural polymers for biomedical applications

Chemical Composition	**Preparation method**	**Properties**	**Potential biomedical use**	**Reference**
Novel p(HEMA-co-METAC)/alginate semiinterpenetrating hydrogels	Were synthesized by copolymerization of	Hydrogels proved	Potential biomedical	[47]

(semi-IPNs) were developed in the attempt to improve poly(hydroxyethylmethacrylate)	2-hydroxyethylmethacrylate and 2-methacryloxy ethyltrimethyl ammonium chloride monomers in the presence of aqueous solutions of alginate	noncytotoxic; moreover, semi-IPN surfaces allowed cell attachment and proliferation	use	
Glycol chitosan PEG	Chemical crosslinking of glycol-chitosan (GCS), by applying a one-step procedure, in water, at 37 °C.	In a highly pronounced pro-angiogenic activity suggesting important tissue regeneration properties	Wound dressing applications	[48]
Two alginate-graft-poly(N-isopropylacrylamide) (Alg-g-PNIPAAm) copolymers and aimed to prepare smart hydrogels through formation of polyelectrolyte complex (PEC)	Between the negatively charged Alg-g-PNIPAAm copolymers and the positively charged chitosan (Cts) in aqueous solutions.	Are a kind of smart hydrogels that could respond to both temperature and pH changes	Great potential for Drug delivery application	[49]

Table 6. Polyelectrolyte hydrogels including synthetic polymers for biomedical applications

Chemical composition	**Preparation Method**	**Properties**	**Potential biomedical use**	**Reference**
Ionic monomers based on methacrylate, methacrylamide, styrene or vinyl imidazolium derivatives in aqueous solution.	Crosslinking ionic liquids	The preliminary findings of this work underline the excellent suitability for the majority of the	Candidates for the development of drug depots for implants.	[50]

		evaluated Of intelligent implant systems hydrogels (HGs)		
Cathionic polyelectrolyte polydimethyldiallylammonium chloride	Physically crosslinked hydrogels were synthesized by copolymerization of acrylamide and acrylic acid monomers	Good mechanical properties and good adhesion with a variety of substrates	Hydrogels were cytocompatible, and can be used for biomedical applications, including pH-triggered small molecule delivery and hydrogel-based hybrids for detecting doses of radiotherapy.	[51]
Polyelectrolyte and poly-ionic liquid based hydrogels. The obtained polymers were covalently crosslinked with N,N'-methylenebisacrylamide (MBAA) or different lengths of poly(ethyleneglycol)diacrylate (PEGDA).	Radical polymerization	Hydrogels revealed an excellent in vitro biocompatibility	Biomedical application	[52]

5. Conclusion

In this review, the use of polyelectrolytes is addressed, focusing mainly on the synthesis of hydrogels with polyelectrolytes using natural and synthetic polymers for their synthesis, as well as the biomedical applications that these materials can present. Polyelectrolytes have shown excellent performance in biomedical applications due to the regulation of their relation structure and properties, which is related to the availability of ionogenic groups in their chemical composition. These ionogenic groups could be exploited in the generation of crosslinkers for the synthesis of novel hydrogels with both tailored swelling and crosslinking, designing devices for the controlled release of drugs depending on the conditions of the release medium, generation of new agents to preparate both ophthalmological and dental devices, 3D printing prosthetics, sutures among others. For this reason,

continuing to generate knowledge that allows synthesizing new polymers with a polyelectrolyte character and knowing their properties represents a current innovative challenge for the construction of novel biomaterials that could be successful in biomedical applications.

Declarations

Source of Funding

This research work is funded by Consejo Nacional de Ciencia y Tecnología (CONACyT) under the grant FORDECYT- PRONACES/6660/2020.

Competing Interests Statement

The authors have declared that no competing financial, professional or personal interests exist.

Consent for publication

All authors contributed to the manuscript and consented to the publication of this research work.

Acknowledgments

María I. León-Campos thanks CONACyT for the scholarship No.958083.

References

[1] X. Jiang, P. Mathew y J. Du, (2014). Polyelectrolyte Hydrogels. Engineering Materials, Pages 183-214. doi: https://doi.org/10.1007/978-3-319-01680-1.

[2] Z. Ahmad, S. Salman, S. Khan, A. Amid, Z. Rahman, Y. O.Al-Ghamdi y K. Akhtar, (2022). Versatility of Hydrogels: From Synthetic Strategies, Classification, and Properties to Biomedical Applications, 8(3): 167. doi: https://doi.org/10.3390/gels8030167.

[3] M. Zare, A. Bighan, M. Zare, H. Luo, E. Ghomi y S. Ramakrishna, (2021). pHEMA: An Overview for Biomedical Applications. Int J Mol Sci., 22(12): 6376. doi: https://doi.org/10.3390/ijms22126376.

[4] F. Wahid, X. Zhao, S. Jia, H. Bai y C. Zhong, (2020). Nanocomposite hydrogels as multifunctional systems for biomedical applications: Current state and perspectives. Composites part B: Engineering, Pages 108208. doi: https://doi.org/10.1016/j.compositesb.2020.108208.

[5] X. Briones, V. Villalobos, Y. Queneau, C. Danna, R. Muñoz, H. Ríos y J. Pavez, (2019). Surfaces based on amino acid functionalized polyelectrolyte films towards active surfaces for enzyme immobilization. Materials Science & Engineering C, Pages 109938. doi: https://doi.org/10.1016/j.msec.2019.109938.

[6] A. Theocharis, S. Skandalis, C. Gialeli y N. Karamanos, (2016). Extracellular matrix structure. Adv Drug Deliv Rev., 97: 4-27. doi: https://doi.org/10.1016/j.addr.2015.11.001.

[7] V. Meka, M. Sing, M. Pichika, S. Nali, V. Kolapalli y P. Kesharwani, (2017). A comprehensive review on polyelectrolyte complexes. Drug Discovery Today, 22(11): 1697-1706. doi: https://doi.org/10.1016/j.drudis.2017.06.008.

[8] G. Chakraborty, A. Bhattarai y R. De, (2022). Polyelectrolyte–Dye Interactions: An Overview. Polymers (Basel), 14(3): 598. doi: https://doi.org/10.3390/polym14030598.

[9] I. Krupińska, (2018). Impact of Polyelectrolytes on the Effectiveness of Treatment of Groundwater with Increased Natural Organic Matter Content. Civil and Environmental Engineering Reports, 28(3): 17-29. doi: https://doi.org/10.2478/ceer-2018-0032.

[10] L. Petrila, F. Bucatariu, M. Mihai y C. Teodosiu, (2021). Polyelectrolyte Multilayers: An Overview on Fabrication, Properties, and Biomedical and Environmental Applications. Materials, 14: 4152. doi: https://doi.org/10.3390/ma14154152.

[11] J. Hamman, (2010). Chitosan Based Polyelectrolyte Complexes as Potential Carrier Materials in Drug Delivery Systems. Mar Drugs, 8(4): 1305–1322. doi: https://doi.org/10.3390/md8041305.

[12] D. Nicolaeva y P. Luis, (2020). Top-Down Polyelectrolytes for Membrane-Based Post-Combustion CO_2 Capture. Molecules, 25: 323. doi: https://doi.org/10.3390/molecules25020323.

[13] D. Nicolaeva, I. Azcune, E. Sheridan, M. Sandru, A. Genua y M. Tanczyk, (2017). Poly (vinylbenzyl chloride)-based poly (ionic liquids) as membranes for CO_2 capture from flue gas. Journal of Materials Chemistry A, 5: 19808–19818. doi: https://doi.org/10.1039/C7TA05171A.

[14] A. Laschewsky, (2012). Recent trends in the synthesis of polyelectrolytes. Colloid Interface Sci., 17: 56–63.

[15] C. Stubbs, T. Bailey, K. Murray y M. Gibson, (2020). Polyampholytes as Emerging Macromolecular Cryoprotectants. Biomacromolecules, 21(1): 7-17. doi: https://doi.org/10.1021/acs.biomac.9b01053.

[16] R. De y B. Das, (2020). Concentration, medium and salinity-induced shrinkage/expansion of Poly (sodium styrenesulfonate) in 2-ethoxyethanol-Water mixed solvent media as probed by viscosimetry. J. Mol. Struct., 1199: 126992.

[17] B. Baraniak, y E. Waleriańczyk, (2003). FLOCCULATION. de Encilcopedia of Food Science and Nutrition, B. Caballero, Ed., Baltimore, Maryland, Academic Press, Pages 2531-2535.

[18] S. Lankalapalli y V. Kolapalli, (2009). Polyelectrolyte Complexes: A Review of their Applicability in Drug Delivery Technology. Indian J Pharm Sci., 71(5): 481–487. doi: https://doi.org/10.4103/0250-474X.58165.

[19] S. Hang y M. Bernards, (2017). Polyampholyte Hydrogels in Biomedical Applications. Gels, 3(4): 41. doi: https://doi.org/10.3390/gels3040041.

[20] W. Jaeger, J. Bohrisch y A. Laschewsky, (2010). Synthetic polymers with quaternary nitrogen atoms – synthesis and structure of the most used type of cationic polyelectrolytes. Prog. Polym. Sci., 35: 511–577. doi: https://doi.org/10.1016/j.progpolymsci.2010.01.002.

[21] A. Herrera, M. Caldera, J. García y A. Peláez, (2016). Polyelectrolytes with sulfonic acid groups useful in the synthesis and stabilization of Au and Ag nanoparticles. Designed Monomers and Polymers, 19(4): 330-339. doi: https://doi.org/10.1080/15685551.2016.1152543.

[22] J. Poblete, (2010). Cationic polyelectrolytes. Synthesis, characterization and application in analysis and removal of arsenic. Chemical Sciences, 1: 7-138.

[23] Y. Ghimire y A. Bhattari, (2020). A Review on Polyelectrolytes (PES) and Polyelectrolyte Complexes (PECs). International Journal of Engineering Research & Technology, 9(8): 2278-0181. doi: https://doi.org/10.17577/IJERTV9IS080112

[24] M. Buriuli y D. Verma, (2017). Polyelectrolyte Complexes (PECs) for Biomedical Applications. Advances in Biomaterials for Biomedical Applications, 66: 45-93. doi: https://doi.org/10.1007/978-981-10-3328-5_2.

[25] M. Ishihara, S. Kishimoto, S. Nakamura, S. Nakamura y H. Hattori, (2019). Polyelectrolyte Complexes of Natural Polymers and Their Biomedical Applications. Polymers, 11(4): 672. doi: https://doi.org/10.3390/polym11040672.

[26] P. Jagtap, K. Patil y P. Dhatrak, (2007). Polyelectrolyte Complex for Drug Delivery in Biomedical Applications: A Review. Conf. Ser.: Mater. Sci. Eng., Pages 1183.

[27] H. Kang, S. Park, Y. Lee y T. Son, (2006). Polyelectrolyte Complex Hydrogel Composed of Chitosan and Poly (g-Glutamic Acid) for Biological Application: Preparation, Physical Properties, and Cytocompatibility. Journal of Applied Polymer Science, 103(1): 386-394. doi: https://doi.org/10.1002/app.24623.

[28] T. Okano, Y. Bae y S. kim, (1990). Pulsed and Self-Regulated. Boca Raton, FL, CRC Press, 11(1): 17. doi: https://doi.org/10.1016/0169-409X(93)90028-3.

[29] M. Shahinpoor, Kim, K, (1995). Ionic polymer metal composites: III and simulation as biomimetic sensors, actuators, transducers, and artificial muscles. J. Intell Mater Syst Struct., 6(307). doi: https://doi.org/10.1088/0964-1726/13/6/009.

[30] S. Vasiliu, S. Racovita, M. Popa, L. Ochiuz y C. Peptu, (2019). Chitosan-Based Polyelectrolyte Complex Hydrogels for Biomedical Applications. de Cellulose-Based Superabsorbent Hydrogels. Polymers and Polymeric Composites. In: Mondal, Ed., Switzerland AG, Springer, Cham., Pages 1695–1725. doi: https://doi.org/10.3390/gels3030027.

[31] T. Nge, M. Yamaguchi, N. Hori, A. Takemura y H. Ono, (2002). Synthesis and characterization of chitosan/poly (acrylic acid) polyelectrolyte complex. J Appl Polym Sci., 5(83): 1025-1035.

[32] J. Zhao, Y. Chen, Y. Yao, Z. Tong y P. Li, (2018). Preparation of the polyelectrolyte complex hydrogel of biopolymers via a semi-dissolution acidification sol-gel transition method and its application in solid-state supercapacitors. Journal of Power Sources, 378: 603-609.

[33] A. Karoyo y L. Wilson, (2021). A Review on the Design and Hydration Properties of Natural. Materials, 14(5): 1095. doi: https://doi.org/10.3390/ma14051095.

[34] S. Bashir, Y. Teo, S. Ramesh, K. Ramesh, M. Rizwan y M. Rizwan, (2019). Synthesis and characterization of pH-sensitive n-succinyl chitosan hydrogel and its properties for biomedical applications. J. Chil. Chem. Soc., 64(3): 0717-9707. doi: https://doi.org/10.4067/S0717-97072019000304571.

[35] D. Buddy, A. Ratner y S. Hoffman, (2013). Biomaterials Science: An Introduction to Materials in Medicine. An introduction to materials in Medicine, Academic Press, Pages 1573.

[36] S. Mitura, A. Sionkowska y A. Jaiswai, (2020). Biopolymers for hydrogels in cosmetics: review. J Mater Sci Mater Med, 31(6): 50. doi: https://doi.org/10.1007/s10856-020-06390-w.

[37] M. B. Bahram, N. Mohseni y M. Moghtader, (2015). An Introduction to Hydrogels and Some Recent Applications. L. IntechOpen, Ed., in S. B. Majee (ed.), Pages 10-38.

[38] E. Ahmed, (2015). Hydrogel: Preparation, characterization, and applications: A review. Journal of Advanced Research, 6(2): 105-121. doi: https://doi.org/10.1016/j.jare.2013.07.006.

[39] L. Takashi, T. Hatsumi, M. Makoto, I. Takashi y G. Takehito, (2007). Synthesis of porous poly(N-isopropyl acrylamide) gel beads by sedimentation polymerization and their morphology. J Appl Polym Sci., 104(2): 842. doi: https://doi.org/10.1002/app.25605.

[40] T. Ho, C. Chang, H. Chan, T. Chung, C. Shu, K. Chuang, T. Duh, M. Yang y Y. Tyan, (2022). Hydrogels: Properties and Applications in Biomedicine. Molecules, 27(2902).

[41] N. Peppas, P. Bures, W. Leobandung y H. Ichikawa, (2000). Hydrogels in pharmaceutical formulations. European Journal of Pharmaceutics and Biopharmaceutics, 50: 27-46. doi: https://doi.org/10.1016/s0939-6411(00)00090-4.

[42] Q. Chai, Y. Jiao y X. Yu, (2017). Hydrogels for biomedical applications: their characteristics and the mechanisms behind them. Gels, 3(1): 6. doi: https://doi.org/10.3390/gels3010006.

[43] H. Cao, L. Duan, Y. Zhang, J. Cao y K. Zhang, (2021). Current hydrogel advances in physicochemical and biological response-driven biomedical application diversity. Signal Transduction and Targeted Therapy, 6(1): 426. doi: https://doi.org/10.1038/s41392-021-00830-x.

[44] B. Ilochonwu, A. Urtti, W. Hennink y T. Vermoden, (2020). Intravitreal hydrogels for sustained release of therapeutic proteins. Journal of Controlled Release, 326: 419-441.

[45] A. Reverte, A. Aparicio, J. Molino y D. Reginesi, (2021). Desarrollo de hidrogeles en aplicaciones en biomedicina. Gente clave, 5(1): 8-42.

[46] W. Bao, M. Li, Y. Yang, Y. Wan, X. Wang, N. Bi y C. Li, (2020). Advancements and Frontiers in the High Performance of Natural Hydrogels for Cartilage Tissue Engineering. Front. Chem., 12(8): 53. doi: https://doi.org/10.3389/fchem.2020.00053.

[47] A. La Gatta, C. Schiraldi, A. Esposito, A. D´Angostino y A. De Rosa, (2009). Novel poly(HEMA-co-METAC)/alginate semi-interpenetrating hydrogels for biomedical applications: synthesis and characterization. J Biomed Mater Res A., 90(1): 292-302. doi: https://doi.org/10.1002/jbm.a.32094.

[48] G. Tripodo, A. Trapani, A. Rosato, C. Di Franco, R. Tamma, G. Trapani y D. Ribatti, (2018). Hydrogels for biomedical applications from glycol chitosan and PEG diglycidyl ether exhibit proangiogenic and antibacterial activity. Carbohydr Polym., 198: 124-130. doi: https://doi.org/10.1016/j.carbpol.2018.06.061.

[49] M. Liu, J. Zhu, X. Song, Y. Wen y J. Li, (2022). Smart Hydrogel Formed by Alginate-g-Poly(N-isopropylacrylamide) and Chitosan through Polyelectrolyte Complexation and Its Controlled Release Properties. Gels, 8(7): 441. doi: https://doi.org/10.3390/gels8070441.

[50] A. Brietzke, C. von der Ehe, S. Illner, C. Matschegewski, N. Grabow y U. Kragl, (2017). Promising biocompatible hydrogels of crosslinked polyelectrolytes for biomedical applications. Current Directions in Biomedical Engineering, 3(2): 695–698. doi: https://doi.org/10.1126/science.1214804.

[51] W. Li, R. Feng, R. Wang, D. Li, W. Jiang, H. Liu, Z. Guo, M. Serpe y. L. Hu, (2018). Polyelectrolyte-based physical adhesive hydrogels with excellent mechanical properties for biomedical applications. J. Mater. Chem. B, 6(29): 4799. doi: https://doi.org/10.1039/C8TB01160E.

[52] J. Claus, A. Brietzke, C. Lehnert, S. Oschatz, N. Grabow y U. Kragl, (2020). Swelling characteristics and biocompatibility of ionic liquid-based hydrogels for biomedical applications. PLoS ONE, 15(4): e0231421. doi: https://doi.org/10.1371/journal.pone.0231421.