Cellulose-based hydrogels: Designing concepts, properties, and perspectives for biomedical and environmental applications

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Development of new products and materials, especially those which are based on renewable organic resources using innovative sustainable processes, represents an increasing interest in both academic and industrial research. Cellulose and its derivatives have demonstrated to be versatile materials with unique chemical structure which provides a good platform for the construction of hydrogel networks with distinctive properties as respects of swelling ability and sensibility to external stimuli. Indeed, the high density of free hydroxyl groups in the cellulose structure makes them become a solid substrate that can undergo functionalization, allowing the production of new materials for novel advanced applications. Moreover, the smart behaviour of these materials, in response to specific environmental stimuli, namely temperature, pH, ionic strength, determines the obtained hydrogels especially attractive for *in vivo* applications. Consequently, cellulose-based hydrogels are promising materials, biodegradable, biocompatible, and the low cost, which exhibit properties that make them attractive in many applications, particularly in biomedical and environmental applications.

Keywords: cellulose-based hydrogels; biocompatibility; biomedical and environmental applications

1. General remarks

Hydrogels are material that exhibit three-dimensional network of hydrophilic polymers, capable to swell and retain a large amount of water within its structure [1]. The chemical crosslinking [2], physical entanglement [3], hydrogen bonds [4], and ionic bonds [5] are responsible to achieve the network of hydrogels. They can be obtained from the synthetic and natural polymers [6], and depend on various parameters, including the preparation method, charge, as well as mechanical and structural characteristics. Due to their excellent hydrophilicity, permeability, compatibility, and low friction coefficient, polymer-based hydrogels have been used extensively as drug delivery, food, cosmetics, high water-absorbing resin, contact lenses, corneal, implant, substitutes for skin, tendons, ligaments, cartilage, and bone [7,8]. Furthermore, an exclusive class of hydrogels - superporous hydrogels - can potentially be used for both short- and long term applications, as superdisintegrant, controlled release platform, and a gastroretentive drug delivery system. Also, superporous hydrogels have been successfully used as soil improvers [9], slow release fertilizers [10,11], pesticide release devices [12].

Recently, hydrogels have captured progressively the interest of researchers, due to the intrinsic properties corresponding of the medical applications. They can serve as scaffolds that provide structural integrity to tissue constructs, control drug, and protein delivery to tissues and cultures, and serve as adhesives or barriers between tissue and material surfaces. The advantages provided by hydrogels for drug delivery applications include the possibility of sustained release, leading to the maintenance of a high local concentration of an active pharmaceutical ingredient over an extended period of time [13]. Their biocompatibility, ability to release water-soluble compounds from the polymeric matrix, and versatility in modeling the physico-chemical properties, permit the generation of new biomaterials with applications in controlled drug release. Among them, polymers of natural origin are one of the most attractive options, mainly due to their similarities with the extracellular matrix (ECM), chemical versatility, as well as typically good biological performance.

It is worth noting that natural polymers have better biocompatibility and less latent toxic effect than most synthetic polymer hydrogels [14], so pure natural polymer hydrogels would be more suitable for biomaterials [15]. Indeed, polysaccharide-based hydrogels behave as smart materials and offer a variety of properties that can be exploited in several applications. Moreover, polysaccharides are gaining a particular attention as components of stimuli-responsive drug delivery systems, especially since they can be obtained in a well characterized and reproductible manner from natural sources [16]. In this context, they can be promising for application in the biomaterial domain, due to their unique benefits, like non-toxicity, abundance, biodegradability, biocompatibility, and biological functions [17]. The most important properties of polysaccharides are derived from natural sources, and their difficulty imposed new synthetic chemical modification methods, the aim being to promote new biological activities and to modify their final properties for specific goals. Furthermore, polysaccharide-based materials have opened new roads in the biomedical domain, namely in the tissue engineering of controlled drug delivery systems and cell immobilization. According those above-mentioned, cellulose represents the most abundant renewable and biodegradable polymeric material, being considered as the main constituent of plants and natural fibers. Also, cellulose is an environmentally friendly alternative to conventional materials and exhibit properties that make them very attractive in many applications [18]. Nowadays, cellulose derivatives-based hydrogel have gained a great popularity in agriculture and pharmaceutical industry, and become more and more important in these fields, owing to production of the new derivatives with extended applications.

Considering the extensive possibilities to use the new materials, this work introduces the information on the intelligent cellulose hydrogels, which are able to respond to environmental changes by modification their characteristics and finally, presents their possible applications in different fields. From this reason, the present chapter covers the applications of cellulose–based hydrogels in the pharmaceutical and biomedical area. Furthermore, the cellulose-based hydrogels can become green via replacing the synthetics with the bio-based materials, and implicitly are suitable in the environmental protection, being developed for the optimization of water resources in agriculture.

2. Cellulose-based hydrogel applications

Excellent biocompatibility of the cellulose and cellulose derivatives determine their wide use in different applications, such as in pharmaceutical compounded and industrialized products. Cellulose esters and cellulose ethers are two main groups of cellulose derivatives with different physicochemical and mechanical properties. Thus, cellulose esters compounds are water insoluble polymers with good film-forming characteristics which find a variety of applications, as classical material-coatings and controlled-release systems, hydrophobic matrices, and semipermeable membranes for applications in pharmacy, agriculture, and cosmetics. Additionally, cellulose esters (*e.g.,* cellulose acetate (CA), cellulose acetate phthalate (CAP), cellulose acetate butyrate (CAB), cellulose acetate trimelitate (CAT), hydroxypropylmethyl cellulose phthalate (HPMCP)) are used extensively as binders, fillers, and laminate layers in composites and laminates, as excellent material for photographic films, and as membrane-forming materials applicable for gas separation, water purification, food and beverage processing, medicinal and bioscientific fields [19-21]. On the other hand, cellulose ethers which present a good solubility, high chemical resistance, and non-toxic nature are utilized in drilling technology and building materials, as additives for drilling fluids and processing of plaster systems, as well as stabilizers in food, pharmaceutical, and cosmetics formulations as the main component. Moreover, cellulose ethers are widely used as important excipients for designing matrix tablets [22,23]. The most commonly used cellulose ethers are: methyl cellulose (MC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), carboxymethyl cellulose (CMC), sodium carboxymethyl cellulose (NaCMC), hydroxypropyl cellulose (HPC) and hydroxypropylmethyl cellulose (HPMC) [24,25]. Cellulose ethers are generally hydrophilic and convert to hydrogel after exposing to water. Both types of soluble and insoluble cellulose ethers can absorb water and form a gel. After exposing of these coated dosage forms with water, the soluble coating polymers form hydrogels which gradually dissolve in water until disappear (dissolution-controlled drug delivery system), but the insoluble cellulose ether coatings remain as a viscose gel around tablets and drug release allowing the diffusion of drug molecules within this layer (diffusion-controlled drug delivery system).

Cellulose-based hydrogels can be achieved by the chemical or physical stabilization of cellulosic materials aqueous solutions. Also, for obtaining the hydrogels with specific properties, cellulose can be combined with synthetic or natural polymers [26]. Moreover, can be employed a number of crosslinking agents and catalysts to form hydrogels. Thus, the most widely used crosslinkers for cellulose are epichlorhydrin, aldehydes, aldehyde-based reagents, urea derivatives, carbodiimides and, multifunctional carboxylic acids. The crosslinking reactions between the cellulose chains activated by chemical agents may occur in water solution, organic solvents or even in the dry state [27-30]. Also, literature data reveal new methods for obtaining cellulose-based hydrogels, namely by radiation [31,32] or by absorption a monomer solution into a dried porous cellulose network, followed by the crosslinking inside the network [33,34]. Furthermore, cellulose and some cellulose derivatives can play vital roles in the enhancement of the performance of absorbent products. Cellulose itself, in the form of cellulosic fibers or nano-fibers can provide water-holding capacity and channeling of fluids over a wide dimensional range [35]. Special hydrogels, as superabsorbent materials, are widely employed in hygienic domain (*e.g.,* disposable diapers and female napkins). Moreover, in agricultural domain such hydrogels are used as granules for holding soil moisture in arid areas.

Consequently, hydrogels are used as water absorbents for various applications, namely as water reservoirs for dry soils, underwater devices, personal hygiene products or as biomedical devices, like soft contact lenses, lubricating surface coatings, phantoms for ultrasound-based imaging, controlled drug release devices, wound healing dressings, cell immobilization islets, three-dimensional cell culture substrates, and bioactive scaffolds for regenerative medicine [28,32,36,37]. Thus, it will describe in more detail below, the potential applications of cellulose-based hydrogels that varies from the traditional use of hydrogels as water absorbents to more innovative biomedical applications.

2.1 Superabsorbents for personal hygiene products

Superabsorbent polymers (SAPs) are the most commercially successful materials of the hydrogel class. The superabsorbent hydrogels (SAHs) with the ability to absorb urine and blood are used in hygiene products, such as in baby diapers and feminine incontinence products. SAHs are crosslinked hydrophilic polymers insoluble in water, but capable to absorb large amounts of water through a swelling process. Hydrogels swell to a volume much larger than their original size, with a weight 10-1000 times higher than their initial one. For this feature, hydrogels have been widely used in many areas such as diapers and napkins for personal care, drug delivery systems in pharmaceutical area, in catalysis, and in bio-sensing [38-40].

A significant drawback for traditional hydrogels (usually, crosslinked with sodium polyacrylates) is given by their environmental impact. Acrylate-based superabsorbent hydrogels are currently extensively used in personal care products to absorb fluids; they keep moisture and promote skin health and consumer comfort. Furthermore, a number of studies have showed the advantages resulting from the use of superabsorbent materials in personal care products, and their safety and effectiveness [41,42]. In addition to keeping skin dry and preventing diaper rash, the SAP helps control the spread of germs in care medical units. For example, the leakage diapers prevention is very important for reducing the risk of fecal contamination and thus, the potential for the spread of illness [43]. Medical studies have provided clear evidences on disposable diapers which play an important role in reducing the risk of spread of gastrointestinal malady, emphasizing significantly their efficiency than double cloth diapers and plastic over pants [44]. For the recycle of disposable diapers, napkins, hospital bed sheets, sanitary towels, and other similar products have been done various attempts [45].

Instead, cellulose-based products have been used for the absorption of water and other aqueous fluids throughout recent history [46]. Among such products, the paper towels and tissue papers are some of the most widely used absorbents [47]. Fluff pulps, which are generally based on kraft pulping and optimized for high bulk and absorbency products, are in widespread use, *e.g.*, disposable diapers [48]. The idea for diaper recycling is to recover separately the cellulose, which is biodegradable and recyclable, the plastic cover material and the SAP, both of which are not biodegradable, but might be recycled for other applications. Therefore, obtaining recyclable disposable diapers, napkins, hospital bed sheets, sanitary towels, and other similar products is therefore, one of the vital targets for the modern industry. Recently has been proposed an innovative solution to this problem, which involves the use of cellulose-based hydrogels that are totally biodegradable. The first superabsorbents were made from renewable resource, such as chemically-substituted cellulose and grafted cellulose or starch, but today more than 95% of superabsorbents come from synthetic SAP, mainly consisting of crosslinked poly-acrylic acids [49]. Microfibrillated cellulose (MFC) is a renewable material that may be used as a highly absorbent and retentive material. Literature data reveal that the first methods developed for producing MFC, are those who treat dilute slurries of cellulose fibers in a high-pressure homogenizer [50,51]. Moreover, literature [52] show a highly absorbent material obtained by freeze drying dilute suspensions of MFC, which had a retention value of 10 g/g in 1% sodium chloride solution under a load of 3.5 kPa. Later, was found that, crosslinking with glutaraldehyde determines improvement the properties of the MFC absorbents and allows the material to be air-dried. After compression, it is observed that this material had an absorption capacity of 16 g/cm^3 and a retention capacity of 8 g/g [53]. Literature specify that the novel types of hydrogels, containing sodium carboxymethyl cellulose and hydroxyethyl cellulose crosslinked with divinylsulfone (DVS), can swell like SAPs, and exhibit high water retention under centrifugal loads. These improvements were achieved by introducing microporous structures into the hydrogel, by means of a phase inversion desiccation technique in acetone, which increases water retention and swelling kinetics, due to capillarity effects [54,55].

The advantage of cellulose-based hydrogels over current SAP consists in their biodegradability and environmentally friendly nature. Further developments in this domain are expected with the formulation of the materials containing enzymes and other additives to prevent infections and disagreeable odors. Moreover, considering the production importance of these materials, there is a clear necessity in environmentally friendly hygiene products that undergo the biodegradation. SAPs control the market of personal hygiene products; however, there are a number of other applications of SAPs in agriculture, horticulture, waste management, electronics, and construction.

2.2 Water reservoirs in agriculture

Hydrogels have been widely proposed horticultural purposes over the last 40 years, due to the water release properties and swelling necessary to water availability for plants [56]. This has offered solutions to the present problems in agriculture, namely to maximize land productivity and water, without threatening the environment and the natural resources. Superabsorbent polymer hydrogels influence soil permeability, structure, texture, density, evaporation, and infiltration rates of water through the soils. Particularly, the hydrogels reduce irrigation frequency and compaction tendency, stop erosion and water run off, and increase the soil aeration and microbial activity. Recently, their application has been expand in agriculture, since can represent a appropriate solution for water depositing and controlled release [57]. The hydrogels also act as a controlled release system by favouring the uptake of some nutrient elements, holding them tightly, and delaying their dissolution. Consequently, the plant can access some of the fertilizers, resulting in improved growth and performance rates [58,59]. As is well known, the material turns from a glassy to a rubber-like state that is able to store water even under significant compression during the swelling process of a hydrogel. In this context, the swollen hydrogel can release easy water through a diffusion-driven mechanism, if a gradient of humidity between the inside and the outside of the material exists. Moreover, another benefit in utilization of hydrogels in this application is related to the effect of the swelling itself on the soil. The hydrogel granules, that are in the dry form have almost the same dimensions with the substrate granules and increases their dimension after swelling, thus increasing the soil porosity and providing a better oxygenation to the plant roots. The effect of hydrogel swelling on soil porosity (dry hydrogel and swollen hydrogel) is represented in Fig. 1 [60,61].

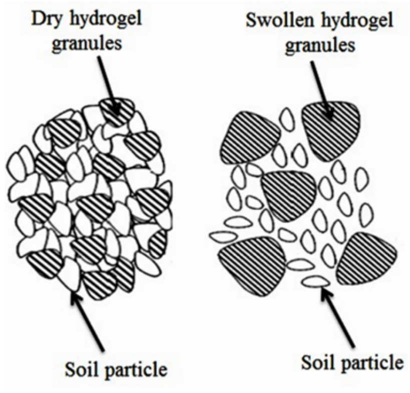

Fig. 1 Effect of hydrogel swelling on soil porosity.

Most of the traditional hydrogels on the market are acrylate-based products, thus not biodegradable and regarded as potential pollutants for the soil. Due to the increasing attention for environmental protection, biodegradable hydrogels present a special interest for commercial applications in agriculture [62]. In this context, the development of new products and materials, especially those which are non-petrolchemical reserves and based on renewable organic resources, using innovative sustainable processes is nowadays of increasing interest of both academic and industrial research. In this regard, several studies from literature were conducted to obtain hydrogels from polysaccharides, *e.g.,* cellulose. The advantages of these biopolymers compared to petroleum-based polymers are the sustainability, biodegradability, and non-toxicity [63,64]. Cellulose and its derivatives, as renewable organic resources, have been used to synthesize novel superabsorbent hydrogels. Although the production of cellulose is one of the causes connected to deforestation, the production of cellulose superabsorbent hydrogel materials has been proposed to preserve water in typically arid areas. Moreover, cellulose derivatives-based hydrogel were used to increase the efficiency of pesticides and herbicides using lower doses, and to indirectly protect the environment by reducing pollution and clean-up existing pollutants. Literature data reveal a novel class of cellulose-based polyelectrolyte hydrogels, totally biodegradable and biocompatible, whose swelling capability can be modulated by adjusting several synthesis parameters [65,66]. For instance, SAP based upon biopolymer like CMC determines increasing interest in scientific and agriculture fields, due to their biodegradable characters and high swelling capacity [67,68]. The rate of biodegradation of CMC increases when starch is introduced into the complex. Furthermore, CMC polymer complexes were crosslinked with aluminum ions to form non-permanent bonds when the complex is swollen with water. The results suggest that, soil amendment using a superabsorbent polymer composed of CMC and starch, can be an alternative to petroleum based superabsorbent polymers for water retention during irrigation [69,70]. Finally, the results presented from literature data suggest that the cellulose-based hydrogel could be a powerful means for optimizing water management in agriculture, which is particularly critical in areas where water scarcity is a severe problem.

2.3 Controlled drug delivery

Cellulose and its derivatives [71-73] are among the excipients frequently used in pharmaceutical compounded and industrialized products with different purposes. Water soluble cellulose derivatives are generally biocompatible and can be used as thickener, binding agents, emulsifiers, film formers, suspension aids, surfactants, lubricants, and stabilizers, especially as additives in food, pharmaceutical, and cosmetic industries. In this context, cellulose derivatives, especially ethers, are used in the pharmaceutical industry as excipients for oral, topical or parenteral administration [74-76]. The cellulose ethers at the contact with water start to swell and the hydrogel layer grows around the dry core of the tablet. The hydrogel represents a diffusional barrier for water molecules, penetrating into the polymer matrix and the drug molecules being released. These cellulose derivatives are frequently resistant to acid environments, such as that of the stomach, and are highly useful as enteric coatings for tablets or capsules [74,75,77]. Additionally, cellulose ethers, such as MC, EC, HPC, HPMC, EHEC (ethylhydroxyethylcellulose) possess a remarkable combination of important properties for pharmaceutical and biomedical applications, *e.g*., as carriers for drug targeting, sustained release of drugs, vaccine bullets, as materials for the disintegration of matrix tablets [78-80]. For example, the cellulose ether HPMC has been widely applied as compressed hydrophilic matrix in which drug release occurs *via* a combination of the diffusion and dissolution processes of the matrix itself, followed by hydration.

Literature shows that, tablets prepared by compression of hydrophilic gums, excipients, and drug in specified ratios leads to prolonged release of drug. Analysis of simulated gastric and intestinal fluids, by *in vitro* tests, show that the drug can be released with a uniform rate after an initial hydration phase [81,82]. Moreover, the release of a number of drugs with varying hydrophilicity was investigated and release near zero-order was achieved for some water-soluble drugs, such as diazepam [82]. It can be mention that, use of carboxymethyl cellulose sodium salt as an excipient sustains the release in solid oral dosage forms. Also, HPMC starts to swell on the tablet surface, leading to the formation of the chain entanglements and a physical hydrogel. Swelling occurs from the surface to glassy core of the tablet and the drug dissolves gradually in water and then diffuses out from the polymer network. Moreover, the rate of drug release depends on the water quantity of the swollen hydrogel, but also by the network parameters (meshes size and degree of crosslinking) [83]. The most recent advances aim not only the sustained release of a bioactive molecule over a long time period (from several hours to several weeks), but also a space-controlled delivery, directly at the site of interest - the organism. The necessity to encapsulate bioactive molecules in a hydrogel matrix or other delivery devices (microspheres) indicates also to the smaller half life obtained for many biomolecules *in vivo*. When using hydrogels to modulate the drug release, drug loading is performed, either after crosslinking or simultaneously, during network formation [84]. To control the space- and time- release profile of the drug, smart hydrogels are especially useful, as swelling-deswelling transition, that change the mesh size of the hydrogel network matrix correlated with the modifications of physiologically variables (pH, ionic strength and temperature) - see Fig. 2 [83,85]. Habitually, the controlled release oral drugs are based on the strong pH variations when crossing from the stomach into the intestine. In this context, cellulose-based polyelectrolyte hydrogels are appropriate for this application. Recently, literature data have investigated anionic hydrogels based on carboxymethyl cellulose for colon targeted drug delivery [86].

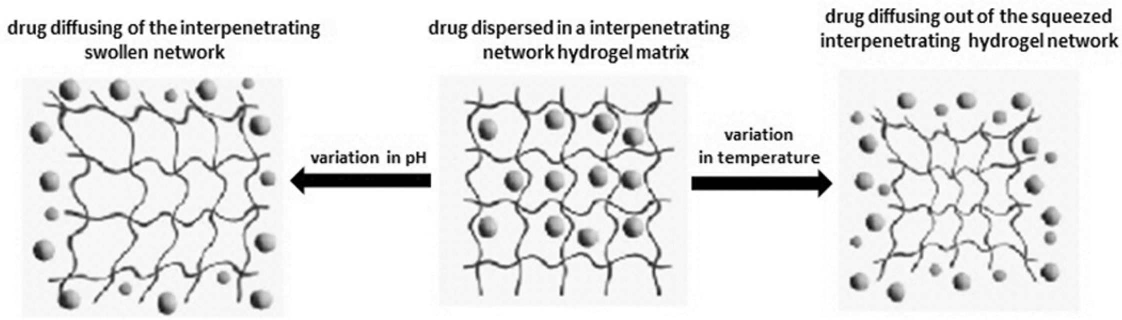

Fig. 2 Swelling and deswelling behaviour of interpenetrating hydrogel network.

In recent years, literature mentions the antimicrobial and antiviral properties of CAP. For several decades, this material has been used in the pharmaceutical industry for enteric film coating of oral capsules and tablets, due to the pH dependent solubility of the aqueous medium. Enteric coatings of CAP are resistant to the gastric acid and easily soluble in the slightly alkaline environment of the intestine. Moreover, micronized cellulose acetate phthalate, used for tablet coating from water dispersions, indicates its potential to adsorb and to inhibit infections by human immunodeficiency type 1 virus, several herpes viruses *in vitro*, and other sexually transmitted disease pathogens. Previous studies reveal that a gel formulation has potential as a topical microbicide for preventing sexually transmitted diseases including acquired immunodeficiency syndrome [87-90].

The latest studies in controlled release of a hydrogel matrix refer to the proteins, growth factors, and genes to specific locations, used in tissue engineering applications. In order to avoid foreign body reactions and further surgical removal, the direct delivery of drugs or proteins to different body places require the hydrogel biodegradation. The most interesting property of cellulose derivatives is the ability to be injected, without any alteration of their chemical, mechanical, and biological properties, by taking advantage of their thixotropic behaviour. Injectable formulations, that contain cellulose derivatives-based hydrogels (*e.g.*, HPMC), have been developed to deliver both biomolecules and exogenous cells *in vivo* [91,92]. Various cellulose derivatives have proved to be efficient on increasing the intranasal absorption of drugs, including soluble cellulose derivatives, such as HPMC, MC, HPC, and CMC, and insoluble cellulose derivatives, such as EC and microcrystalline cellulose. Due to their mucoadhesive property can be extended significantly the residence time of drugs in the nasal cavity [93] and high viscosity following hydration in the nasal cavity, makes these derivatives to sustain the release of drugs [94]. Thereby, using cellulose derivatives as absorption enhancer, can lead to improved intranasal absorption and increased bioavailability [95-97]. For instance, apomorphine administered intranasal with carboxymethyl cellulose, can acquire a relative bioavailability of 102% compared with subcutaneous injection at rabbits [98]; an absolute bioavailability up to 90.77% could be achieved for ketorolac tromethamine administered with microcrystalline cellulose [99]. It is observed that, combination of the cellulose derivatives with other absorption enhancer generates a better effectiveness than using the polymer alone. For example, the intranasal bioavailability of ciprofloxacin at rabbits using methylcellulose and hydroxyethylcellulose alone as enhancer is low (18.2% and 19.46%) and increase, when is combined with the Tween 80 (22.35% and 25.39%) [100]. Moreover, dopamine, which is ineffective by oral administration, due to first pass metabolism, and is usually injected, was administered to dogs via rectal, dermal, buccal and, nasal routes. The effects of the addition of hydroxypropyl cellulose and azone on the nasal absorption leaded to an absolute bioavailability of almost 100%, while for using only HPC it was 25% [96]. Significant progresses were made in enhancing the properties of cellulose-based hydrogels used for drug delivery and expanding the range of drugs and kinetics which can be realized using a hydrogel-based delivery vehicle. However, several challenges remain to improve the clinical applicability of hydrogels for drug delivery.

2.4 Regenerative medicines

Tissue engineering or regenerative medicine is an interdisciplinary field which involves principles of engineering and life sciences to understand the structure-function relationships and to develop of biological substitutes that restore, maintain or improve the tissue function [101,102]. Scaffolds are designed to serve as a temporary, artificial, extracellular matrix in order to support the cell attachment and guide three-dimensional tissue formation [103,104]. Therefore, an ideal scaffold should be mimic the natural extracellular matrix characteristics, which is a structural and support material that surrounds the tissue cells [105,106]. The most critical factor to be considered here is the interaction of cells with the scaffolds, which is the template to direct the growth of the tissue. The cells should receive all the signals from the scaffolds for cell and tissue differentiation, cell proliferation, cell adhesion, cell migration as well as tissue regeneration and repair [107,108].

Over the past two decades, a wide range of chemicales and pore formers have been examined to create scaffolds for tissue engineering. Natural polymers afford the advantage of being similar to biological macromolecules, which the biological environment is prepared to recognize and deal with metabolically. Owing to their similarity with the extracellular matrix, natural polymers may also avoid the stimulation of chronic inflammation or immunological reactions and toxicity, often detected with synthetic polymers. Because of their large water content, hydrogels are highly biocompatible, possess rubbery mechanical properties close to those of soft tissues and usually, allow the incorporation of cells and bioactive molecules during the gelation [109]. Furthermore, although cells do not readily attach to highly hydrophilic surfaces, the bulk or surface chemistry of hydrogels can be easily modified with extracellular matrix domains, that promote cell adhesion, as well as specific cell functions. Due to their unique biocompatibility, flexible methods of synthesis, range of constituents, and desirable physical characteristics, hydrogels have been the material of choice for many applications in regenerative medicine. They can serve as scaffolds that provide structural integrity of tissue constructions, control drugs, and protein delivery to tissues and cultures, and additionally, serve as adhesives or barriers between tissue and material surfaces.

Hydrogels obtained from natural cellulose derivatives have been extensively used in stem cell engineering applications, either as components of natural native extracellular matrix or exhibit properties similar to the matrix components in native tissues. Lately, utilization of cellulose and its derivatives as biomaterials for the design of tissue engineering scaffold has received a special attention, due to the excellent biocompatibility of cellulose and its good mechanical properties. For optimal tissue regeneration, the scaffold should be biodegradable, with a biodegradation rate matching that of the biological process of interest, but practically a slow degradation is often preferred, in order to minimize the risks associated to a premature resorption of the scaffold. Several studies report the applicability of cellulose-based materials for culturing cells and for implantation; examples include bone regeneration [110,111], hepatocyte culturing for an artificial liver [112,113], expansion of progenitor hematopoetic cells in culture [114], and suppression of matrix metalloproteases action in wound healing [115]. Moreover, cellulose and cellulose derivatives, in the form of sponges, have been used for the treatment of severe skin burns, and in the regeneration of cardiac, vascular, neural, and cartilage bone tissues [116-120]. Also, a few independent investigations show that cellulose-based hydrogels are useful for inducing the regeneration of bone, cartilage and neural tissues [116,120,121]. In an attempt to modulate the *in vivo* degradation behaviour of cellulose, literature suggests the pre-treatment of a cellulose-based scaffold with cellulase prior to implantation. *In vitro* and *in vivo* applications of cellulose-based materials have demonstrated only negligible foreign body and inflammatory response reactions [110,122,123]. In this context, they are considered to be biocompatible. The introduction of small amount of cationic groups can further improve tissue compatibility of cellulose-based materials [122].

Literature data have reported the synthesis of novel biomimetic hydrogels, based on cellulose derivatives crosslinking with hyaluronic acid. Hydrogels based on HEC, NaCMC and hyaluronic acid, have been crosslinked with a water-soluble carbodiimide, which is non-toxic. Such hydrogels exhibit also potential as scaffolds for regenerative medicine, with a tunable degradation rate. The presence of hyaluronic acid in the cellulose network assures enzyme sensitive degradation sites, whose density in the bulk of the hydrogel can be easily controlled [124]. Very important is the biocompatibility of the used crosslinking agent, particularly in cases where reactive groups of the crosslinker are integrated into the hydrogel system and can then be released upon degradation. Moreover, in biomedicine it has been employed for preventing postsurgical soft tissue and epidural scar adhesions. Literature data have proposed the use of CMC and HEC-based hydrogels as water absorbents in treating edemas [125]. Also, can be used for the therapeutic application of superoxide dismutase enzyme, shown as hydrogels of CMC carrying the enzyme for its controlled release [126]. Is well-known that carboiimide induce the formation of ester bonds among polysaccharide molecules without taking part in the linkage. Thus, cellulose-based hydrogels crosslinked with carbodiimide present the potential for a tunable biodegradation rate, even when not containing hyaluronic acid. This type of reaction promises the functionalization of cellulose with several biomolecules, capable to promote specific cell functions, due to the ability of the carbodiimide to crosslink different polypeptides. Finally, the key role is played by the scaffold porosity, which increases the attachment, infiltration, and survival of cells within the scaffold [127,128]. Due to their nano-sized mesh structure, hydrogels are currently employed to treat minor tissue defects [129]. In this respect, were tried new techniques for the preparation of porous hydrogels, increasing the contribution of cellulose-based hydrogels in regenerative medicine [130,131]. In summary, tissue engineering is one of the most exciting interdisciplinary and multidisciplinary research areas and growing exponentially over time. Scaffold materials and fabrication technologies play a crucial role in tissue engineering.

2.5 Wound dressings

Wound dressings form an important segment of the medical and pharmaceutical wound care market worldwide. Generally, a wound can be described as a defect or a break in the skin, resulting from physical or thermal damage, or as a result of the presence of an underlying medical or physiological condition, like diabetes and malignancies, persistent infections, poor primary treatment and other patient related factors [132]. Based on the number of skin layers and the area of the skin affected, as well as the nature of the repair process, literature presents various criteria for wounds classification [133-136].

Design of effective dressings is based on an understanding of the healing process, as well as the specific conditions of a patient and the effect that each material used can have on the wound [137]. Since a moist environment favours rapid healing, hydrogels are optimal candidates for the progress of wound dressings, either as sheets or in amorphous form; their viscosity decreases once they absorb physiological fluids. Hydrogels are widely used as debriding agents, moist dressings, and components of pastes for wound care, which may be packaged in tubes or in foil packets [138]. A large scale of hydrogel dressings in the multiple forms of amorphous gels, gel-impregnated gauzes, sheets or plasters are commercially available for the treatment of minor burns and other skin wounds [139,140]. Amorphous gels are preferred for cavity wounds, while sheets and gel-impregnated gauzes find application especially, in the treatment of superficial burns [139,141]. In addition, plaster-like hydrogel dressings (*e.g.*, MySkin®) are mainly attractive for their facile use and elimination [137].

As wound dressings, polymer-based hydrogels give an ideal moisture medium for healing, while protecting the wound, with the advantage of being comfortable to the patient, due to their cooling effect and non-adhesiveness to the wound tissue. Further, recent advances in regenerative medicine demonstrate that bioactive hydrogels can be properly designed to induce at least partial skin regeneration *in vivo* [137]. Many materials, natural and synthetic or their composites and blends have been used as wound dressings and skin repair [142-145]. Literature data reveal that a number of specialized primary wound dressings are currently available for the treatment of partial-thickness burns (both superficial and deep partial-thickness burns) and other types of wounds, with low to high levels of wound exudates [146]. Several dressings might also include specific antibiotics or different antibacterial agents (*e.g.*, silver ions) in their formulation, in order to further protect the wound bed from undesired microbial contaminations [147]. In this context, various types of hydrogel dressings have been patented until now and are commercially available, based on synthetic or natural polymers, or a combination of them. Thus, worth mentioning patents which describe the *in situ* formation of gels, *e.g.,* based on sprayable formulations [148] and on coalescing nanoparticles [149], and those crosslinked obtained in a single step of crosslinking by radiation, as a stabilization technique, and sterile hydrogel films [150]. Furthermore, the most advanced hydrogel dressings include in their formulation antimicrobial agents. Thus, if the local or systemic infection compromise the wound or could compromise the healing process, one possible therapeutic approach can be used the dressings containing antimicrobial agents, such as iodine or silver (the last is useful against *Pseudomonas aeruginosa* and *Staphylococcus aureus*, frequently present in chronic wounds and their mechanism of action includes a biofilm-based infection in the host [151,152]). Moreover, the currently investigations deal with the progress of novel wound dressings with improved performance, and the cellulose-based hydrogels appear to be promising candidates. Nowadays designed dressings, should maintain the temperature of the wound bed and has to accelerate the process of wound healing, as well as reduce the debris influence on the healing process [153-156].

Commercially available hydrogel wound dressings containing cellulose or cellulose derivatives-based hydrogel are:

- Woundtab® (First Water) - Sulphonated copolymer, CMC, glycerol, and water. The dressing contains a superabsorbent polymeric gel able to absorb bacteria and retain them in its structure. Described as a wound 'kick-starter' patch for chronic wounds, it can also be used as a secondary absorbent.
- Granugel® (ConvaTec) - Pectin, CMC, and propylene glycol. A clear, viscous hydrogel for the management of partial and full-thickness wounds may be used as a filler for dry cavity wounds to provide a moist healing environment.
- Aquacel®Ag™ (ConvaTec) – is a primary wound dressing made from NaCMC containing 1.2% silver in an ionic form.
- Intrasite Gel® (Smith and Nephew) - Modified carboxymethylcellulose (2.3%) and propylene glycol (20%). Amorphous sterile hydrogel dressing for use in shallow and deep open wounds.
- Purilon Gel® (Coloplast) - NaCMC and more than 90% of water indicated in conjunction with a secondary dressing for necrotic and slightly wounds, and first and second degree burns.
- Silvercel Dressing® (Johnson and Johnson) - Antimicrobial Alginate Dressing is a sterile, non-woven pad composed of alginate, CMC and silver coated fibers. Use as a primary dressing on the moderate- to heavily-exudate, partial- and full-thickness chronic wounds.
- XCell® Cellulose Wound Dressing - provides the optimum moisture required for wound healing. Absorbs and/or donates moisture depending upon requirements of microenvironments within a wound. Most wound dressings presented are available in two forms, either as sheets or as amorphous gels. Also, products containing silver ions show antimicrobial activity.

Additionaly, bacterial cellulose (BC) is an interesting material used as a wound dressing, since it can control wound exudates and can provide moist environment to a wound, resulting in better wound healing [157]. For instance, wound dressings from bacterial cellulose are today commonly available on the market, such as: Biofill®, Bioproces®, and XCel® [158]. A commercial product Biofill® which was a partially dried BC membrane was developed for wound healing of burns and chronic ulcers. Studies revealed that Biofill® present a high performance compared to other wound dressing materials, in accelerating the healing process, pain relief, etc. [159]. Another BC wound dressing, named XCel®, has been applied to heal chronic venous ulcers. Once again, the BC dressing showed satisfactory effect in treating these chronic skin abnormalities [160]. Literature data show that cellulose-based hydrogels crosslinked with hyaluronic acid induce a good proliferation of keratinocytes, as a result of a scratch wound model in *in vitro* culture [161]. Also, a microbial cellulose membrane has been successfully used as a wound-healing device for severely damaged skin and as a replacement of small-diameter blood vessel. In fact, the various studies indicate that, local applications of microbial cellulose membranes improve the healing process of burns and chronic wounds [156]. A recent study used the never-dried microbial cellulose membranes in order to treat patients with severe second-degree burns. Results indicate that, skin of the patients whose burns were covered with never-dried microbial cellulose membranes healed faster than the wounds of patients who received a conventional wound dressing [162]. Also, literature [163] reported that swelling, flexibility, and elasticity properties of NaCMC gels was changed by addition of the sodium fucidate (0.2%) and crosslinker, polyvinyl alcohol (PVA, 2.5%) during the hydrogel formulation. Hydrogel adsorbed on the wound surface, maintain the moisture sufficiently in wound area. Consequently, it was recommended as an ideal wound dressing material. Future advances in wound care products will depend on continued requests of the healthcare professionals [164]. The important challenge for the future is to establish the suitable wound care strategy for every patient, by offering the optimal products.

3. Conclusion

Hydrogel based networks have been designed and tailored to meet the needs of different applications. The favorable property of these materials is their ability to swell when put in contact with an aqueous solution. Unlike many other materials, significant progress has been made in improving the properties of cellulose-based hydrogels used in a diverse array of applications, ranging from biomedical to environmental applications. This fact involves technologies adopted for hydrogel production together with the process design and optimized conditions of the preparation process. Extending the duration of release would be useful in many applications and could allow hydrogels to supplant hydrophobic systems for long-term release applications. The application of new physicochemical strategies to simultaneously control not only the gelation process, but also the interactions between the gel and native tissues would further expand the utility of hydrogels for both in drug delivery and tissue engineering-based applications. As in many other branches, convergence the fields of science will guide the future development of hydrogel design.

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