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Hydrogels

From Tradition to Innovative Platforms with Multiple Applications

Edited by Lăcrămioara Popa, Mihaela Violeta Ghica and Cristina-Elena Dinu-Pîrvu

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Meet the editors

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Contents

Preface

This book discusses hydrogels, presenting pioneering studies on their use in modern "smart" applications, multiutility delivery platforms, 3D and 4D printing, and more.

Hydrogels have demonstrated great impact in many medical and biomedical fields in diagnostics and therapeutics (aesthetic medicine, tissue engineering, drug screening, cancer therapy, etc.). This book highlights the design and engineering of hydrogels for use as efficient drug carriers. It describes stimuli-responsive hydrogels, nanogels, and therapeutic release from 3D printed hydrogels.

The beneficial characteristics of hydrogels are very well known and include biodegradability, biocompatibility, porosity, elasticity, flexibility, and biological properties similar to the extracellular matrix. This book discusses the latest advances in multifunctional hybrid hydrogels with responsiveness to electric and magnetic fields and with applications in biomedicine. In combination with certain nanomaterials, hydrogels are considered a new class of materials that offers new opportunities for living organisms, such as machine interfacing for application biomedical engineering, soft robotics, soft electronics, and environmental and energy science.

Important aspects related to the hydrogel's unique applications in tissue engineering and regenerative medicine are closely related to their self-healing power, interactive structure, low cost, non-toxicity, bio-adhesion, conductivity, elasticity, softness, swelling behavior, transparency, stimuli-responsive ability, and controlled release of various bioactive agents. As presented in the book, hydrogels represent versatile systems with desirable properties, such as viscoelasticity, degradability, biocompatibility, and stimuli-responsiveness, being explored for 4D bioprinting of organs and tissues. However, present outcomes are far from manufacturing an outstanding human-scale tissue construct.

Hydrogels have potential to be combined with mesenchymal stem or stromal cells. These composites could represent valuable alternatives in tissue engineering, as is also discussed in the book.

Three-dimensional hydrogel networks, which tend to imbibe water, have hydrophilic tendency and are excellent super-absorbent materials that still remain water insoluble.

Supramolecular hydrogels could be generated via spontaneous self-assembly with various peptides, proteins, or other biomolecules. These materials have attracted attraction as next-generation drug delivery substitutes to synthetic polymers.

To conclude, hydrogels have proven adaptability and versatility, which makes them particularly interesting for the newest and most modern applications, even artificial intelligence. This book contributes to the understanding of hydrogels and their many beneficial uses.

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Chapter 1

Introductory Chapter: Hydrogels in Comprehensive Overviews, Recent Trends on Their Broad Applications

Lăcrămioara Popa, Mihaela Violeta Ghica, Cristina Elena Dinu-Pîrvu and Elena-Emilia Tudoroiu

1. Introduction

Initial research of hydrogels started in 1894 when the usage of inorganic salts led to a colloidal gel [1]. Once they come into contact with fluids, hydrogels proceed to incorporate and expand to create a three-dimensional (3D) structure considering the presence of hydrophilic groups (amino, hydroxyl, carboxyl, and amide) in their structure [2].

Bemmelen was the first who established the term "hydrogel" to characterize hydrophilic polymeric systems, with high efficiency to absorb huge amounts of water or other fluids (e.g., biological fluids) in their interstitial networks [3]. The first presence on the market for a 3D network is registered in 1949 when a hydrogel based on poly(vinyl alcohol) was crosslinked with formaldehyde, which was retailed with the name Ivalon, utilized as a biomedical implant [4]. The current definition of hydrogel was established on the groundbreaking work of Lim and Wichterle, who used in 1960 gels based on poly (2-hydroxymethyl methacrylate) to create soft contact lenses. This novelty represented the onset of hydrogel investigation for applications in the biological field [1].

2. Classification, source, and structure of hydrogels

The progress of these semisolid systems is characterized by three generations of hydrogels. The first one is represented by chemically crosslinked hydrogels that show excellent swelling and high mechanical stability. The second generation was influenced by Kuhn's research about the configuration of ionizable polymeric particles [5]. The last generation of hydrogels was encouraged by the stimuli-receptivity of the hydrogel second generation. Hence, smart hydrogels are stimuli-responsive with adjustable mechanical and physicochemical characteristics [6].

The water aspect in a hydrogel can establish the general permeation of nutrients into and biological products out of the hydrogel. When a moistureless hydrogel starts to swallow the water, primary particles of water that penetrate the cellular matrix will hydrate the most hydrophilic groups, which conduces to "primary bound water" [7]. Consequently, the polar parts hydrate, the network absorbs the water, and lets out hydrophobic groups that likewise connect with molecules of water; therefore, the water is hydrophobically bound, which means the "secondary bound water" [8]. Primary and secondary bounds of water usually link, and the resulting combination is named

"total bound water." After the hydrophobic and hydrophilic sites have been connected and linked water molecules, the structure will assimilate supplementary water, due to the osmotic power of the conformation chains to limitless dilution. The new swelling is neutralized by the physical and covalent crosslinks that go to a flexible structure retraction power. Accordingly, the hydrogel will attain an equilibrium swelling level [9]. The supplementary swelling water which is imbibed after the hydrophilic, hydrophobic, and ionic groups turn into saturated with linked water is named "free or bulk water." This is estimated to saturate the space between the conformation conglomerates and the middle of the longer pores, blank spaces, or macropores [10]. As the hydrogel structure absorbs, if the structure crosslinks or chains are degradable, the hydrogel will start to decompose and dissolve, at a percentage that depends on its distribution. It is very important to mention that a hydrogel, which is used as a scaffold for tissue engineering can never be dehydrated, but the total water in the hydrogel consists of "bound" and "free" water [11].

The exclusive sources of hydrogels consist of two major groups: natural which comprises two principal classes based on polysaccharides and polypeptides (proteins) and the other group is artificial one, which is based on petrochemicals. Natural hydrogels are often manufactured through the addition of a few synthetic units to the natural parts. The synthetic way for the preparation of most synthetic hydrogels is represented by the multifunctional vinyl monomers that are free of radicals. Each monomer has a carbon double linkage where an effective center can disseminate to determine polymer chains [12].

Hydrogels result through chemical or physical crosslinking. Chemically cross-linked systems present durable junctions, whilst physically cross-linked systems present limited junctions [13]. The chemically crosslinking method involves monomers grafting on polymers' backbone. On the other side, physical crosslinking generates reversible hydrogels [14] and includes the interaction between ions (e.g., hydrophobic association, hydrogen linkages, and polyelectrolyte complexation) [15]. Most of the physical gelation methods rely on the intrinsic features of the component polymers, which diminish the capacity to adjust the qualities of hydrogels, but gelation can be efficiently obtained without the necessity to change the polymer chains. The chemical path can be used to admit for more manageable and specific management of the crosslinking method, possibly in a dynamically and spatially detailed process [16].

Hydrogels can be prepared from each water-soluble polymer; there is a vast and various range of polymers that can be used to fabricate multiple hydrogels with particular properties. Thus, for their formulation, there are natural polymers (hyaluronic acid, chitosan, collagen, dextran, dextran sulfate, gelatin, alginic acid, fibrin, agarose, pectin, chondroitin sulfate, pullulan, carrageenan, polylysine, and carboxymethyl chitin), synthetic polymers (poly(ethylene glycol), poly(lactic acid), poly(lactic-glycolic acid), polycaprolactone, poly(hydroxy butyrate), poly(butylene oxide), poly(acrylic acid), polyacrylamide, and poly(glucosylethylmethacrylate), or any combination of natural and synthetic polymers [17, 18]. Consequently, depending on the polymeric composition, these semisolid systems can be homopolymeric (a single variety of monomer), copolymeric (two or more different monomer varieties), and multipolymer (known as interpenetrating polymer networks, IPNs, which are composed of two separate cross-linked natural or synthetic polymers) hydrogels [19].

3. Properties and applications of hydrogels

Hydrogels exhibit noteworthy physical, chemical, mechanical, and biocompatible properties. Thus, due to their significant water volume, porosity, permeation,

biocompatibility, nontoxicity, and soft consistency, hydrogels firmly imitate natural living tissues, greater than any other group of synthetic biomaterials [20]. Besides these attractive features, hydrogels also exhibit other characteristics, such as versatility, low immunogenicity, availability, elastic structure, flexibility, responsiveness to stimuli, tensile strength, conductivity, washability, cooling effect, tolerability, transparency, safety, and excellent adhesion on the skin surface and different mucosa; they are also nonocclusive and nongreasy [21]. Therefore, hydrogels represent an exceptional substrate for utilization in cell culture due to their structural similarity to the extracellular matrix [3].

Regarding the technical properties of these semisolid systems, it can be mentioned the following: maximum stability and adherence in a swelling medium and also during storage; stability at neutral pH, odorless, colorless; suitable absorption rate and particle size; utmost biodegradability without toxic compounds generation; photostability, small soluble volume, re-wetting capacity, and the maximum absorbency under load [22].

Regarding all the outstanding properties that were highlighted above, hydrogels exhibit numerous applications in miscellaneous domains, extending from engineering to biological areas. Presently, the materials based on hydrogels mean a $22.1 billion market, with a substantial expansion to $31.4 billion by 2027. It is anticipated that the market for wearable sensors will reach $2.86 billion in 2025 and for medical sensors, $2.23 billion in 2027 [23]. The main applications of these 3D systems involve biomedical and pharmaceutical fields, bioanalysis, hygienic products, dyes, heavy metal ions elimination, artificial snow, pH sensors, agriculture, food industry, and supercapacitors. Considering the biomedical and pharmaceutical fields, hydrogels can be used for 3D bioprinting, tissue engineering, wound dressings, drug delivery systems, biosensors, regenerative medicine, biomolecules and cells separation, diagnostics, contact lenses, cosmetic medicine, and barrier materials to manage biological adherence [24].

Nowadays, 3D bioprinting has a notable place between other techniques that develop tissue matrices, having considerable uses in the biomedical field (e.g., cancer therapy, tissue engineering, drug screening, or transplantation). Considering the significant interest in this domain, the universal market had a noticeable increase, from $487 million in 2014 to $1.82 billion in 2022 [25]. Hydrogels are "soft biomaterials" utilized for the advancement of cell-laden networks, offering a conducive medium for cellular expansion. These 3D matrices can be created and printed into a range of forms, shapes, and sizes to accomplish the final product specifications [26]. 3D printing based on the nozzle is the most popular method to design hydrogel scaffolds. Viscous liquids are pushed out of the nozzle or syringe and solidified on a construction level. 3D structures are engineered layer by layer by sequential extruding matrices that pursue a predesigned line created by computer modeling [27]. Hydrogels have become principal candidates for several applications due to the current evolution in the 3D bioprinting area. The outstanding feature of hydrogels is that they can be engineered to imitate the extracellular matrix, with large applicability in tissue engineering, immunomodulation, or stem cell therapy for malignant diseases [28]. Hydrogels consist of 3D hydrophilic molecules that assure excellent water absorption; thus, they can encapsulate growth factors and nutrients into their hydrophilic network, mimicking the biological tissue. An adequate bioink for use in 3D bioprinting needs to satisfy certain conditions, such as bioactivity, cytocompatibility, and printability [29]. Regarding the polymers that make up the hydrogel structure, polysaccharides are extensively used to produce bioinks, such as cellulose, hyaluronic acid, alginate, pectin, chitosan, carrageenan, or agarose [30]. 3D bioprinted hydrogels have a large use for tissue bioprinting, including skin, muscles, bones, cartilages, neurons, cardiac fibers, and blood veins [31].

Tissue engineering and regenerative medicine represent recent areas where hydrogels have found their applicability. Due to their biocompatibility, hydrogels can interact directly with biological tissues without causing any disturbance [32]. These scaffolds can consist of large pores that have the role to integrate living tissues, or they can be formulated to deteriorate, discharge growth factors, or generating pores in which human cells can infiltrate and multiply [33]. Hydrogels can be handled as space-filling agents, delivery vectors for bioactive substances, or 3D networks, which can regulate cells and stimuli to assure the expansion of vital tissue. Hydrogels as space-filling agents are used for bulking and to avoid adherence. Hydrogel platforms can be applied in many applications, such as angiogenesis, transplant cells, and organizing various human tissues (bone, cartilage, or muscles) [20].

The applicability of hydrogels in the wound healing domain as wound dressings is due to the excellent combination between their biocompatibility, high water content, and plasticity. Hydrogels can furnish a suitable moisture medium at the lesion site and at the same time allow acceptable gas exchange between the foreign medium and the lesions, promoting wound healing. Hydrogels have the ability to reduce the temperature of the lesion and their high water volume helps to alleviate the injured surface, especially if the wound is dry [34]. Moreover, hydrogels absorb a large amount of lesion exudate and sustain it away from the lesion bed. Due to their non-irritant and non-reactive behavior with human tissues, hydrogels are proper dressings for various types of cutaneous lesions. Hydrogels are flexible and soft semisolid systems, they are easy to apply and remove, being comfortable and soothing the pain for damaged skin tissues; therefore, hydrogel dressings are attractive for patients [35].

Hydrogel scaffolds for drug delivery have firmly developed in their style, increasing further synthetic and covalently crosslinked networks to an extreme group of biomaterials platforms. Hydrogel drug release systems can be utilized for oral, transdermal, ophthalmic [36], vaginal, or rectal applications [21]. Particularly, these models can manage the drug carriers' design and they can reach the conditions of a specific application, or they can aid researchers to explicate the transport mechanisms, which control the release kinetics from innovative formulations [37]. By regionally drugging target tissues, hydrogel drug transporters furnish imperative safety advantages by diminishing drug exposure in off-target tissue. Exceptionally, cancer therapies rise to benefit remarkably from this type of hugely concentrated drug exposure. As long as hydrogels can narrowly target drug exposure, they can also maintain a constant delivery ratio of drugs over an extended period (from hours to months, according to the formulation) [38]. This prolonged drug delivery is notably favorable for decreasing the doses administrations needed to cure a patient over time which is promising for chronic disease treatment, which requests permanent medication (e.g., diabetes). This prolonged release kinetic offers particular conveniences to augment the efficiency of several therapies like vaccines for infectious diseases. Hydrogels can also integrate properly into soft tissues, performing as possible scaffolds for endogenous cells, which can promote their applicability in the field of regenerative applications [39].

Hydrogels also represent a main part of biosensors development because the necessity for adaptable chemical or biochemical sensors has raised greatly. Moreover, many hydrogel precursors are accessible from the industrial and ecological zones as platforms for sensor geometries. Different sensing mechanisms can be included for sensor progression [40]. A modification in resistance, conductance, and electric charge transmission represents the most commonly utilized procedures and fragile interactions like hydrogen linkage are also effective. Sensor geometries were also

soft because the hydrogels were flexible and adjustable. Hydrogels are appealing systems to develop flexible biosensor matrices due to their fundamental properties and structural benefits [41]; thus, they contain elastic materials like polymer, carbohydrates, elastomer, biocompatible molecules, and additives. Hydrogels can also furnish a benign environment for better action of resulting devices. A fast inflow of substance into the hydrogel could be averted essentially. Signal transduction of these semisolid matrices is available through the internal space of them if an adequate sensing medium is favorably imported. Hydrogel biosensors are extensively used in the biomedical field, especially for drug delivery [42].

4. Concluding remarks

Taking into account all the perspectives mentioned above, hydrogels had a significant evolution, from traditional to innovative platforms, with an important impact in biomedical and pharmaceutical fields, including 3D bioprinting, tissue engineering, wound dressings, drug delivery scaffolds, and biosensors. Nevertheless, their huge potential is still being explored, because hydrogel represents versatile systems, with desirable properties, such as viscoelasticity, degradability, biocompatibility, and stimuli-responsiveness, being presently explored for 4D bioprinting of organs and tissues, but the present outcomes are far away from manufacturing an outstanding human-scale tissue construct [43]. The primary challenge distributed by all researchers in this area of tissue engineering and regenerative medicine is ensuring acceptable vascularization because the cell viability of the bioprinted materials in long term is closely related to vascularization. The major test is to incorporate the printed vascular matrix into a living host and to simulate the biological processes and conformational complexity of in vivo graft. The 4D bioprinting can lead to the formulation of vascularized models but expanding them into an entire organ is still a provocation and opened a new paradigm for future explorations [44].

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Chapter 2

Promising Hydrogels-Based Dressings for Optimal Treatment of Cutaneous Lesions

Mihaela Violeta Ghica, Cristina Elena Dinu-Pîrvu, Lăcrămioara Popa, Elena-Emilia Tudoroiu, Diana-Georgiana Ionescu and Claudia-Maria Benga

Abstract

Worldwide, cutaneous lesions care represents a daily challenge for the medical system, with an increasing prevalence from year to year (from ~5 million in 2005 to about 8 million in 2018) and high costs for their treatment (between ~$28 billion and ~$97 billion). Injuries are the most frequent and destructive form of skin damage, affecting patients' quality of life. To promote wound healing, an ideal treatment involves proper dressings that can manage the local pain, inflammation, or infection. Passive or dry traditional dressings, such as cotton, gauze, or lint, have limited therapeutic actions and demand periodic replacement of the dressing. Therefore, an optimal alternative for advanced wound care is represented by hydrogels, one of the five classes of modern dressings, which assure excellent local moisture, due to their high ability to absorb a large volume of water inside their three-dimensional networks. Moreover, hydrogels possess suitable biocompatibility, biodegradability, porosity, elasticity, flexibility, and biological properties similar to the extracellular matrix. This chapter presents the main characteristics of the hydrogels and the recent research regarding the development of new hydrogel dressings, based on natural, semi-synthetic, or synthetic biopolymers, loaded with varied therapeutic agents to stimulate the tissue regeneration of different etiologies cutaneous lesions.

Keywords: different etiologies wounds, hydrogel dressings, wound healing, wound management, tissue regeneration, therapeutic agents sustained release

1. Introduction

With a length of ~2 m^2 and weight of ~15% of the body mass, the skin represents a sophisticated tissues complex of the human body, being the largest and the heaviest organ [1]. Due to its optimal physicochemical characteristics, the skin is a dynamic and effective outermost barrier, defending the body against the external surroundings [2]. In addition to the role of physical protection, the skin is involved in the regulation of the body's homeostasis, synthesis of vitamin D [3], and control of the temperature

and blood pressure. Furthermore, it impedes dehydration, maintains an optimal level of moisture and body nutrients, and exhibits self-healing properties [4]. Skin is also an essential sensory organ when it connects with the environment, and the stimulation is perceived on the human body as pain, temperature, and pressure [5]. Normal skin represents a stratified epithelium that is composed of three principal layers: epidermis, dermis, and subcutaneous tissue. The epidermis is made up of many cells, including melanocytes, Merkel, and Langerhans cells, but keratinocytes are the most numerous (~95%). This stratum has a thickness of 0.05–0.1 mm, and it does not contain blood vessels and sensory nerve endings [6]. Dermis represents a hard fibrous layer, due to its composition in collagen and elastic tissues. It is based on a supporting network that furnishes elasticity and toughness to the skin. Dermis exhibits a noticeable ability to absorb the water. Its thickness varies from 0.5 mm to 5 mm or more according to the skin region. Compared to the epidermis, the dermis is vascularized [7]. Hypodermis (subcutaneous tissue) represents the profound stratum of the skin, and it is made of fat cells among which are found elastin fibers, collagen, nerves, lymphatic, and blood vessels. The main roles of this layer are to store energy, to thermally insulate the body, and to defend against physical trauma [8].

Being the main organ that interacts directly with the environment, the skin is principally disturbed by external agents, such as chemicals, microorganisms, UV and electromagnetic radiations, allergens, heat, pollution, and mechanical trauma [9]. On the other hand, the skin can also suffer various modifications due to behavioral factors (smoking, alcohol, and nutrition), physiological factors (obesity), demographic factors (age and gender), and pathological factors (numerous local and systemic diseases) [10, 11]. All these mentioned factors often generate a skin injury and a delay in the healing process, so the restoration of healthy and functional skin is still a big challenge for the medical community [12] and an increasing problem worldwide [13]. Depending on the degree of the skin damage, cutaneous lesions can necessitate a long-term treatment, which involves a huge financial cost for global healthcare systems [14]. Statistics showed that the number of people with skin injuries of different etiologies worldwide is constantly growing from ~5 million in 2005, ~6 million in 2015 to about 8 million in 2018, and the total costs for their medical care are estimated to be between ~$28 billion and ~ $97 billion. Taking into account the dynamics of the factors that cause damage to the skin tissue, in the coming years, the total costs for their treatment are expected to rise [15, 16]. From all types of wounds, chronic lesions have the highest incidence in the population. Thus, in developed countries, approximately 1–2% of people will suffer a chronic lesion during their lifetime [17]. The highest increase is in the case of injuries caused by diabetes because it is estimated that in 2025 there will be at least 400 million people with diabetes globally, most cases being in South Africa, Asia, and Africa. About 15–25% of these people will develop throughout their life one of the major complications of diabetes which is the diabetic foot ulcer [18].

Most often a wound is accompanied by pain that can vary from mild to severe depending on the degree of the skin impairment. Hence, the personal life quality of the patients is considerably affected because they have to limit their daily activities, which negatively influences their physical, psychological, and social conditions [19, 20].

Optimal wound management needs physicians to comprehend the etiology of the wound, its healing time and complexity, the mechanism of injury healing, and the factors which affect the skin regeneration to make the right decision regarding the most efficient treatment for a proper cutaneous tissue restoration [21]. Since ancient

times, the care of a lesion involves its cleaning and applying a patch (traditional dressing) that allows protection from the external environment, but it cannot absorb high amount of exudates and requires regular application that produces soreness when changing the patch; moreover, the common patch owns modest adhesive characteristics and cannot furnish an adequate drainage for the injury. Consequently, the wound healing process is delayed, and the quality of the patient's life is seriously affected [22]. Nowadays, those patches have been switched with new wound dressings (modern dressings) that function as a physical and defensive barrier, swallowing the exudate and facilitating the healing process [23]. Over the last few years, modern dressings have been developed, which include hydrogels, hydrocolloids, semi-permeable films, foams, and alginates [24]. Comparing to the traditional dressings, these modern wound dressings, due to their improved structure, have a high capacity to generate a moist environment all over the skin lesion and to keep it, promoting the healing process and the reepithelialization by developing the proliferation of fibroblasts and enhancing the synthesis of collagen [25]. Moreover, they are semi-permeable and highly absorbent dressings and semi-occlusive or occlusive that stimulate the granulation tissue production and promote the epithelial cells movement from the injury margins to its center, providing an enlarged functionality [22].

Thus, this chapter highlights the main structural and functional properties of hydrogels, which are hydrophilic macromolecular networks, formed by crosslinking of diverse polymers, physically or chemically [26]. Also, this chapter presents recent studies regarding the broad applicability of hydrogels as bioactive dressings, which, after application to the wound bed and alleviate the pain, inflammation, and infection that generally follow a lesion [27]. Primary results consist of anatomical, functional, and esthetic restoration of the skin, improving the patient's quality of life [28].

2. Complexity of cutaneous lesions and skin regeneration process

Cutaneous lesions appear while the skin tissue is broken, or the cellular stability is imperiled under the action of physical, chemical, mechanical, and thermal agents or because of genetic diseases and metabolism-linked factors [29].

In the first instance, skin injuries can be clinically partitioned into acute and chronic injuries. Acute lesions are those wounds that often heal totally, with minimal scarring, in a period between 8 and 12 weeks [30]. Mainly, acute lesions can be produced by mechanical trauma; thus, these types of lesions can be classified inside one of these eight types: abrasions (it happens when a mechanical power scratches away a limited thickness of the skin) [31], avulsions (occurs when the primary layers of the skin are cut from the underlying fascia, for example, injury produced by animal bites) [32], contusions or bruises (fist leads to a contusion), crush wounds, cuts (knife or paper can cause a cut), fish hook injuries, incised wounds (it is the result of a surgical cut inside the skin) [33], and lacerations or tears (it means a break in the skin, which can be generated by a sharp object, for example, metal, glass, or wood) [34, 35]. Also, in the category of acute wounds are found burns and chemical lesions. On the other hand, chronic wounds heal slowly, their healing time exceeds 3 months, and they often reoccur. According to the Wound Healing Society, in this category of cutaneous lesions are included: pressure, venous, and arterial insufficiency, diabetic ulcers, and also malignant wounds [17].

Furthermore, from an etiological point of view, cutaneous lesions can be categorized as follows: surgical wound, which is a mechanical lesion produced by surgical

incisions, for example, to eliminate tumors [36]. Traumatic injury is an accidental and a spontaneous lesion that can vary from a small wound, such as a scraped knee, to a serious injury, such as a gunshot lesion. Abrasions, lacerations, skin tears, bites, burns, crush, and stab injury are some examples of traumatic wounds [37]. Radiation lesion is the result of radiotherapy and surgery, two treatment methods that are generally used for the therapy of cancerous tumors, lesions whose delayed healing produces physiological and psychological stress to the patient [38]. Chemical and thermal injuries (burns) are produced by a diversity of factors such as radiation exposure, electricity, corrosive chemicals, or thermal agents [39]. In these types of injuries, it is very important to know how deep the wounds are and how much of the body surface is affected, all these for good management that can lead to a decrease of wounds healing time [40]. According to World Health Organization, there are reported globally every year more than 11 million burn wounds and their medical care passes $12 billion per year [41]. A lesion becomes malignant when cancerous cells attack the epithelium, penetrate blood and lymph vessels, and invade the epidermis; mostly, this type of wound produces death and necrosis of the tissue [42]. Melanoma is metastatic skin cancer, with an increased risk of death, produced by uncontrolled growth of melanocytes that spread abnormally in neighboring tissues. This type of cancer produces severe wounds, requiring special treatment for optimum treatment [43]. Psoriasis is an autoimmune disease, characterized by erythematous-scaly lesions (crumbly white peels on irritated skin background) on the scalp, elbow, and knees, lesions to the face caused by sun exposure, and lesions at the level of the inguinal, axillary, or interfacial skin folds [44]. A pressure ulcer (pressure lesion, pressure sore, decubitus ulcer, or bedsore) is a surface of localized disturbance to the skin and hidden tissue, and it is induced by pressure, shear, or rubbing. The main risk factors that can lead to a pressure ulcer are incomplete nutrition, peripheral vascular disease [45], elderly people, obesity, diabetes, inadequate posture, pregnancy, smoking, or an increased frequency of infection (osteomyelitis) [46]. The most frequent complication of diabetes mellitus is diabetic foot ulcer, which affects 15–25% of diabetic patients. This is a condition that requires a long period for healing, or in some cases, it does not heal and can lead to infection, the major consequence being lower limb amputation [47, 48]. In close relation with diabetic foot ulcer is vascular ulcer, which is caused by disorders of the circulatory system; there are two principal types: venous ulcer (varicose ulcer) and arterial ulcer [49].

Based on contamination and postoperative infection risk, wounds can be classified in classes I, II, III, or IV. Class I or clean wound includes injuries that are infection-free, although current bacteria on the skin contaminate the injury [50]. Class II or clean-contaminated wound involves injuries, which affect the respiratory and digestive system, characterized by no loss of tissue fluid [51]. Class III or contaminated wound contains non-purulent inflammation and class IV or dirty/infected wound contains purulent inflammation [52].

According to appearance and injured tissue coloration, a wound can present necrotic tissue (characterized by a black or olive green coloration, often at pressure ulcer) [53], sloughy tissue (characterized by yellow coloration, related with excess exudates, produced during the inflammatory stage) [54], granulation tissue (characterized by red or deep pink coloration, typical for proliferative phase) [55], epithelializing tissue (characterized by pink coloration and formation of a new epidermis; it develops in migratory and proliferative phases) [56], and infected (malodorous) tissue (characterized by red coloration, hot inflamed tissue, pus formation, and unpleasant odor) [57].

An injury is classified according to complexity in simple and complex (complicated). A simple wound affects the skin tissue without any complication. On the other hand, a complex wound leads to a major tissue loss and a complicated wound involves an infected complex wound [58, 59].

Conforming to the depth of injury or number of skin layers affected, a wound can be superficial, partial thickness, or deep dermal and full thickness. A superficial wound is characterized by affecting only the epidermal skin surface, with minimum scars and a short period for healing, less than 10 days [60, 61]. A partial thickness or deep dermal wound represents a type of injury that affects the epidermis and also the inner dermal layers, containing blood vessels, sweat glands, and hair follicles; it requires between 10 and 21 days for healing, with the formation of scar and reepithelialization [62, 63]. A full thickness wound appears when hypodermis and also epidermal and dermal layers are damaged and the healing time is longer than the other two types of wounds (more than 21 days) [64, 65].

The regeneration of cutaneous lesions represents a fundamental physiological process that consists of a succession of cellular and biochemical events, which begin when a skin lesion occurs in order to reestablish the impaired tissue. The wound healing process involves more consecutive stages, but which still overlap: hemostasis, inflammation, proliferation, reepithelialization, and remodeling; therefore, skin tissue repair is one of the most complex processes that occur in the human body [66].

Multiple factors can delay the wound healing process, such as: different underlying physiological diseases (diabetes mellitus, human immunodeficiency virus, tumor resection, after organ transplantation, inborn genetic immunodeficiencies, burns, hypoxia, and vascular and autoimmune disease or cancer), obesity, continuous infection, stress, elderly population, sex hormones, gender, smoking, and malnutrition [67, 68]. Another cause for this delayed wound healing and epithelialization is represented by high levels of proteolytic enzymes and cytokines [69]. These factors lead to the production of a substantial amount of exudate [70], which decreases the mobility of lymphocytes and produces maceration of healthy tissue around the injury, the major problem which results being the inhibition of the wound repair process [71].

3. Bioactive hydrogel-based wound dressings

Traditionally, wound dressings have to protect lesions from physical impairment and secondary infection, to ensure thermal isolation, to be comfortable, and to be quickly changed by a new dressing, without producing any trauma on the lesion site, facilitating the dermal regeneration, playing a passive role in the evolution of the wound healing process [72]. Presently, these functions are constantly evolving. Medical healthcare systems demand for new "intelligent" products, which function not only as a protective barrier but also strongly promote the skin repair process [73]. Over the last few decades, there were developed numerous modern (advanced) wound dressings to stimulate the regeneration of cutaneous lesions, such as semi-permeable films and foams, hydrocolloids, alginates, hydrofibers, and hydrogels. These advanced products for optimal clinical management of skin wounds represent, in 2019, about $7.1 billion of the international market, and their manufacture is expected to increase to about $12.5 billion in 2022 [74]. Of all these modern products, the most competitive candidate is represented by hydrogels.

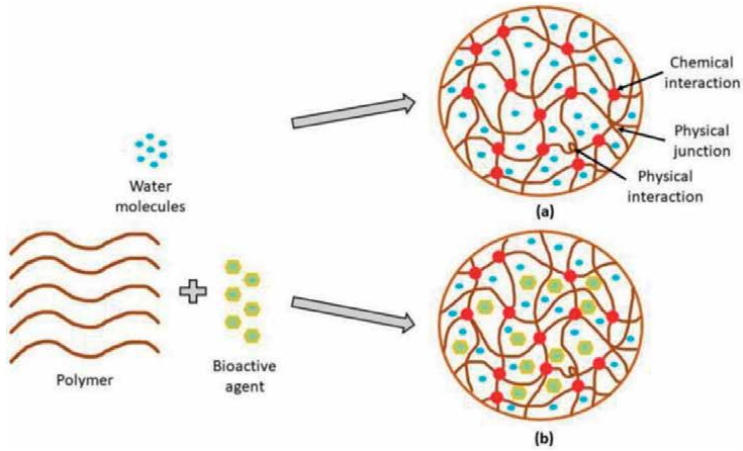

Figure 1.
Molecular structure of hydrogel: (a) without bioactive agent, and (b) with bioactive agent.

3.1 Molecular structure of hydrogels

Hydrogels, also known as aquagels, are a three-dimensional (3D) and crosslinked network of polymer chains, which can absorb massive quantities of water and body fluids due to their hydrophilic functional groups (hydroxyl, carboxyl, amide, and amino), adhering to the polymeric backbone [75]. The term "hydrogel" has been invented for the first time in 1894 by van Bemmelen. Due to their 3D structure, the molecular weight goes to infinity. The fundamental feature that characterizes the molecular structure of the hydrogel is the mesh size. There are two ways to crosslink the hydrogels: physically through hydrogen bonds and chemically through covalent bonds. The main property of the hydrogel is the super-absorbent capacity of water molecules that diffuse into the hydrogel network [76].

The molecular structure of hydrogel loaded or not with a bioactive agent is illustrated in **Figure 1**.

The swelling hydrogel includes three major phases:

1. Primary bound water—the molecules of water adhere to the hydrophilic moieties from the hydrogel structure;

2. Secondary bound water—the molecules of water combine with the hydrophobic moieties from the hydrogel structure;

3. Free water—the molecules of water totally swell into the empty spaces from the hydrogel structure.

The swelling ratio varies in accordance with polymers' content and the density of crosslinking [77].

3.2 Classification of hydrogels

Hydrogels products can be classified according to different measurable parameters as detailed below:

a. source: natural, synthetic, or hybrid (mixture of natural and synthetic polymers);

b. physical aspect: film, gel, matrix, or micro−/nanoparticles (microspheres) according to the method of the polymerization used in the preparation process;

c. dimensions: macro−/micro−/nanogel;

d. polymer composition: homopolymeric, heteropolymeric, copolymeric, hybrid, composites, or interpenetrating polymer network (IPNs);

e. network structure: permanent (chemical or irreversible crosslinking) or non-permanent (physical or reversible crosslinking);

f. preparation method: copolymerization, complex coacervation, irradiation, or using enzymes;

g. sensitivity to stimuli: physical (pressure, sound, temperature, light, and magnetic and electric fields), chemical (pH, molecular species, solvent content, and ionic strength), or biochemical (enzymes, antigens, and ligands) stimuli;

h. polymer network charge: amphoteric, non-ionic, ionic (cationic and anionic), or zwitterion (polybetaines);

i. chains configuration: non-crystalline (amorphous), semi-crystalline, crystalline, hydrogen-bonded, or hydrocolloids;

j. physical properties: smart or conventional;

k. biodegradability: biodegradable or non-biodegradable;

l. sensitivity to environmental factors: temperature, electric and magnetic fields, sound, enzymes, pH, or light;

m. equilibrium swelling grade (SWD): low (20–50%), medium (50–90%), high (90–99.5%—these hydrogels exhibit proper biocompatibility and permeability, which make them the most suitable for use in the medical domain), or superabsorbent hydrogels (>99.5%) [78–80].

Regarding the network structure, hydrogels are mostly manufactured from crosslinking networks, so there are two major categories of hydrogels: physically and chemically crosslinked hydrogels. Physically crosslinked hydrogels have gained importance due to the fact that they are easy to produce because no crosslinking agents are used during the synthesis process; thus, these types of hydrogels are used in biomedical, pharmaceutical, and food industries. Many methods are used to generate physically crosslinked hydrogels: freeze-thawing, stereocomplex formation, ionic interaction, hydrogen bonding, maturation (heat-induced aggregation), noncovalent interaction, and thermoreversible gels [81]. Chemically crosslinked hydrogels present covalent bonds in the middle of the polymeric network that generate permanent hydrogels formation. These types of hydrogels are formed through reactions between functional groups of polymeric chains. Many methods are used to generate chemically crosslinked hydrogels: condensation reactions, polymer–polymer crosslinking, high energy irradiation, enzymatic reaction, grafting, and radical polymerization [82].

3.3 Functional and technical properties of hydrogels

Hydrogels are of huge interest for the development of new wound dressings due to their outstanding mechanical and biochemical traits (biocompatibility, biodegradability, hydrophilicity, and the porous structure similar to the extracellular matrix) [83]. They are composed of 90 wt% water and 10 wt% different nature biopolymers. This high water content produces soothing and cooling effects, which reduce the perceived pain. Hydrogels stimulate the healing process through their moisture exchanging actions, which generate a proper microclimate between the dressing and the injury bed [74]. Depending on their composition, hydrogel-based dressings present a high power to swallow up to 1 kg of injury exudate per gram of dressing [84]. Thus, hydrogel-based dressings furnish optimal moisture on the lesion site, which has various advantages: to avoid the injury from drying out, to mitigate the pain perception, to damage the fibrin and dead tissues, and to allow the communication between target cells and growth factors [85].

Regarding the polymeric component, hydrogels can be produced from natural polymers (cellulose and its derivatives, collagen, hyaluronic acid, chitosan and its derivatives, gelatin, alginate, keratin, fibrin, pectin, elastin, dextran, chitin, and gums) and synthetic polymers (polyvinyl alcohol, polylactic acid, polyethylene oxide, polyglycolic acid, polyacrylic acid, poly ε-caprolactone, polyethylene glycol, polyacrylamide, vinyl acetate, N-vinyl-2 pyrrolidone, 2-hydroxyethyl methacrylate, methoxyl polyethylene glycol, ethylene glycol diacrylate, and poloxamer) [78, 83].

Hydrogels are colorless and odorless; they also exhibit the highest capacity to absorb fluids in saline medium, a high absorbency under load, low price, proper stability, and durability during the storage and in swelling conditions, neutral pH after swelling in water, nontoxicity, and photostability [75]. Hydrogels allow an excellent mechanical safety, a suitable gases exchange (CO_2 and O_2), the stimulation of angiogenesis, and the absorption of local exudates; thus, epithelial cells can flourish, and the healing process accelerates to restore the skin layers with minimal scars. Also, hydrogels exhibit non-adhesive characteristics, malleability, and smoothness, so they are easy to applicate and remove without tissue impairment [86].

Moreover, the transparent structure of these dressings allows a suitable evaluation of the wound healing progress, without the dressing being removed. Therefore, hydrogel-based dressings are the first option to treat dry, necrotic lesions, superficial

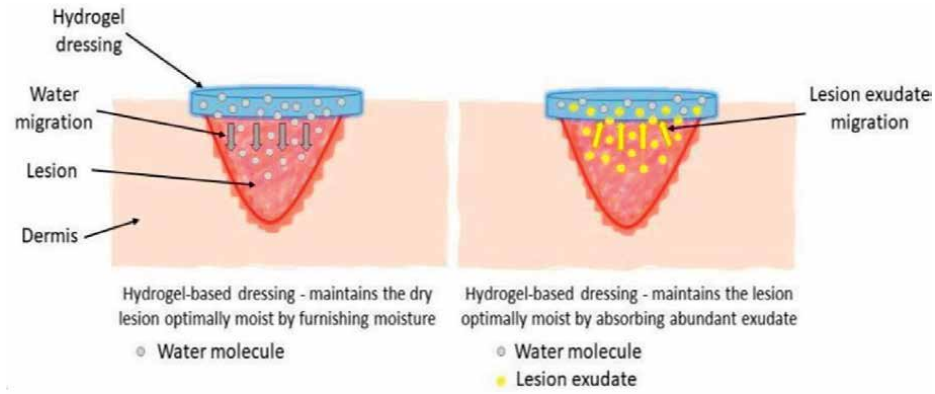

Figure 2.
The action mode of hydrogel-based dressing on cutaneous lesion for accelerating the wound healing process.

Type of lesion	Polymer composition	Bioactive agent/–s	Obtaining method/hydrogel type and properties	Ref.
Post-surgical lesion	Chitosan	Naproxen	Dissolution/thermosensitive; analgesic effect, postoperative adhesions treatment	[89]
	Polyglutamic acid/ pluronic F127	Paclitaxel	Double crosslinking/self-healing after surgical removal of melanoma, proper hemostatic effect, antibacterial activity, and mechanical properties	[90]
	Poloxamer 407/sodium hyaluronate	Ropivacaine	Physical blending/thermosensitive; analgesic effect, efficient long-term pain alleviation	[91]
Radiation-induced lesion	Carbopol	Sildenafil citrate	Physical blending/notable wound contraction, minimization of skin impairment, excellent tensile strength, enhanced production of granulation tissue, mature collagen fibers, and less inflammatory infiltrates	[92]
	Alginate/hyaluronic acid/polylysine	Curcumin and epigallocatechin gallate	Crosslinking/angiogenesis stimulation, inflammation relief, and reactive oxygen species (ROS) scavenge	[93]
Burns	Alginate	Vancomycin, gentamicin, or minocycline	Physical blending/infection treatment and burn depth reduction	[94]
	Chitosan	Gold nanoparticles and Aerva javanica	Crosslinking/antimicrobial and antioxidant activities	[95]
	Keratin	Ciprofloxacin	Physical blending/antibacterial effect, collagen deposition, tissue remodeling, and macrophage recruitment	[96]
	Hydroxypropyl methylcellulose/ hydroxyapatite	Silver nanoparticles	Crosslinking/3D porous network, high antibacterial, mechanical, optical, and spectral properties, proper swelling and degradation ratio, wound closure improvement with rapid reepithelialization, and minimal scar tissues	[97]
Pressure ulcer	Chitosan	Genipin	Crosslinking/pH-responsive; antimicrobial, hemostatic, and mucoadhesive characteristics, wound site pH neutralization, and high swelling capacity	[98]
	Polyvinyl alcohol	Poly(lactic-co-glycolic acid) nanoparticles loaded with ciprofloxacin hydrochloride	Crosslinking (gamma radiation)/antimicrobial activity, good gel fraction, and excellent swelling ability	[99]
	Gelatin/silk fibroin	Growth factors (adipose-derived stem cells and platelet-rich plasma)	Photocrosslinking (UV light)/optimal swelling ratio, rheological and mechanical properties, rapid reepithelialization and collagen deposition, inflammatory infiltration decrease, increased angiogenesis, and nerve regeneration	[100]

Type of lesion	Polymer composition	Bioactive agent/–s	Obtaining method/hydrogel type and properties	Ref.
Venous and arterial leg ulcers	Chitosan	Gallic acid	Enzymatic crosslinking/antibacterial and antioxidant activity, inhibition of matrix metalloproteinase, myeloperoxidase, and collagenase	[101]
	Pluronic F-127	Antisense oligodeoxynucleotides	Crosslinking/thermoreversible; anti-inflammatory effect (neutrophil cell infiltration reduction)	[102]
	Polyvinyl alcohol/ chitosan	Ibuprofen-β-cyclodextrins	Physical blending/macroporous network, optimal mechanical and morphological properties, anti-inflammatory effect, and scab formation prevention	[103]
Diabetic foot ulcer	Alginate	Polydeoxyribonucleotide	Crosslinking/stimulation of cell promotion and angiogenesis	[104]
	Gelatin methacryloyl	Cerium-bioactive glass	Photocrosslinkin/proper swelling ratio, cell adhesion, compressive features, antibacterial activity, granulation tissue formation, increased angiogenesis, and collagen deposition	[105]
	Hydroxypropyl methyl cellulose	Valsartan	Physical blending/antimicrobial effect, decrease of the level of the proinflammatory factors	[106]
	Chitosan/hyaluronic acid	Insulin glargine	Crosslinking/pH-responsive; inflammatory phase reduction, enhanced collagen deposition, granulation tissue production, reepithelialization, neovascularization, and peripheral neuropathy	[107]
	Poly(ε-caprolactone)/ poly-(glutamic acid)	Ciprofloxacin	Physical blending/inhibition of superoxide free radicals and high antibacterial effect	[108]
Psoriatic lesion	Carbopol	Apremilast	Crosslinking/proper anti-inflammatory effect (reduction of TNF-α level) and mechanical properties	[109]
		Methotrexate	Physical blending/anti-inflammatory effect, proper viscoelastic and bioadhesive behavior	[110]
		Clobetasol propionate	Crosslinking/anti-inflammatory, antioxidant, and immunomodulatory properties, pseudoplastic behavior, spreadability, and mechanical properties	[111]
	Pluronic F-127	Cyclosporine	Physical blending/suitable mechanical properties, viscosity, and pH, reduction of hyperplasia, and tissue impairment	[112]
	Pluronic F-127/ hyaluronic acid	Curcumin	Physical blending/optimal anti-inflammatory activity and mechanical properties	[113]

Table 1.
Recent studies regarding the development of new hydrogel dressings based on different polymers composition and bioactive agents for tissue regeneration.

injuries (burns and skin tears), surgical wounds, radiation burns, sloughy and dehydrated lesions, and shallow ulcers. Depending on the hydration level required by the lesion, hydrogel dressings need to be changed every 1–3 days [87]. The schematic illustration of the action mode of a hydrogel-based dressing on cutaneous lesion for accelerating the wound healing process is illustrated in **Figure 2**.

3.4 Recent studies regarding the development of new hydrogel-based dressings for damaged skin regeneration

Hydrogel-based dressings are bioactive dressings, which are extensively used to cure different etiologies wounds because they furnish an optimum pH, suitable exchange of gases, proper regulation of temperature, and adequate local moisture, accelerating the fibroblasts' proliferation and angiogenesis [88]. These dressings present biomimetic characteristics, which make them suitable vehicles for sustained release of various bioactive agents, such as plants extracts, growth factors, nucleotides, inorganic compounds, and analgesic, anti-inflammatory, anesthetic, or antimicrobial active substances, ideal for scaffolds that target the fundamental structures involved in the healing process of the injured skin. Therefore, hydrogel-based dressings can reduce, prevent, and treat the tissue maceration, pain, inflammation, and infection that usually accompany a skin lesion [87]. Recent studies regarding the development of new hydrogel dressings based on different polymers composition and bioactive agents for tissue regeneration are summarized in **Table 1**.

4. Conclusions

Cutaneous lesions care leads to a vast socioeconomic burden, with a huge impact on the patient's quality of life. Thus, this chapter presents a brief approach of hydrogels, which are the most outstanding competitors for the development of new wound dressings from all five classes of modern (advanced) dressings. Hydrogels have attracted the attention of researchers due to their particular 3D structure similar to the extracellular matrix, which has a high capacity to absorb large amounts of water and biological fluids, and which can also retain in their network external microorganisms. These dressings assure optimal moisture at the wound site and a cooling effect, being so comfortable for the patient. Furthermore, hydrogels exhibit a self-healing power, interactive structure, biocompatibility, biodegradability, low cost, nontoxicity, bioadhesion, conductivity, elasticity, softness, swelling behavior, transparency, stimuli-responsive ability, and controlled release of various bioactive agents. As a result of the last feature, this chapter also emphasizes recent studies regarding the development of new wound dressings manufactured using different polymeric supports loaded with various therapeutic agents to stimulate the regeneration of impaired skin tissues.

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Conflict of interest

We, the authors of this paper: Mihaela Violeta Ghica, Cristina-Elena Dinu-Pîrvu, Lăcrămioara Popa, Elena-Emilia Tudoroiu, Diana-Georgiana Ionescu, and Claudia-Maria Benga, declare no conflicts of interests.

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Chapter 3

Hydrogel Biomaterials for Drug Delivery: Mechanisms, Design, and Drugs

Wanis Nafo

Abstract

Due to their unique physical and chemical properties, hydrogels have attracted significant attention in several medical fields, specifically, drug delivery applications in which gel-based nanocarriers deliver drug molecules to the region of interest in biological organs. For different drug delivery applications, hydrogel systems can be manipulated to provide passive and/or active delivery. Thus, several drug targeting, loading, and releasing mechanisms have been devised and reported in the literature. This chapter discusses these mechanisms and their efficacy with respect to different drug delivery applications. Furthermore, the drug dosage is dependent on the design and shape of the hydrogel systems, which in turn depend on the route of the drug administration. This chapter covers the types of hydrogel-based products applied via different routes of drug administration. Lastly, this chapter addresses different classifications of delivered drugs including small molecular weight drugs; therapeutic proteins and peptides; and vaccines.

Keywords: drug delivery, loading, targeting, releasing, routes of administration

1. Introduction

Hydrogels are three-dimensional polymeric networks that are utilized in various medical applications due to their unique properties: hydrophilicity, biodegradability, non-toxicity, and their controllable mechanical properties to mimic the mechanics of biological tissues [1, 2]. Furthermore, their structural properties exhibit similarities with biological extracellular matrix components which makes them ideal for cell culture and growth [3].

From the mechanical perspective, the concentration of the polymer network in hydrogels controls, to large extent, their mechanical strength allowing them to mimic the mechanics of physiologically loaded tissues [4]. Consequently, due to their availability and relatively low cost, hydrogels have become an attractive option when developing quantitative techniques that measure the mechanics of biological tissues [5–8].

On structural level, hydrogels can be produced by chemical or physical cross-linking. In chemical (permanent) hydrogels, the network is crosslinked with strong

covalent bonds that connect the molecular chains [9]. In physical (reversable) hydrogels, the gel's molecular chains are connected with weaker forces such as hydrogen-bonding and ionic forces, thus, they can be easily dissolved by altering their environmental conditions (e.g., temperature, ionic strength, or pH of the gels [10]). These crosslinking methods allow the synthesis of multi-network hydrogels. For instance, hydrogels can be fabricated to have highly crosslinked rigid chains that are entangled with weakly crosslinked chains to provide a functional network system used in synthesizing biomaterials for several medical applications [11, 12].

One of the medical applications the hydrogels used in is contact lenses, mainly due to their unique physical properties and ease of processing; for example, Bauman et al. [13] developed Silicone Hydrogel lenses with nano-textured surface that mimics the surface of human cornea. Hydrogel lenses are also known for their wettability, a property necessary to avoid tear deposits [10], thanks to plasma treatment during the synthesis process [14]. Gas permeability is also a key characteristic of contact lenses to provide the cornea with efficient supply of oxygen at sufficient rates. Hydrogel lenses can be designed to meet this requirement thanks to their hydrated polymer matrix [10]. Hydrogels are also commonly used in wound dressing; they have been used in combination with other materials to form composite products efficient for different dressing applications; for example, a gauze impregnated with thermoplastic hydrogels allows for absorbing wound exudate while maintaining relative slimy consistency, as a result, it prevents adherence to the wound that normally results in pain during gauze changes [15]. Moreover, flexibility and transparency of hydrogels also made them an attractive option in wound dressing. While flexibility facilitates easy removal of the dressing products, transparency allows for continuous observation of the wound healing process [16].

Nowadays, delivery and release of drug molecules is receiving significant attention in many fields of medicine in which therapeutic drugs are loaded in polymer-based-carriers. These carriers transport the drugs to the targeted location [17, 18]. The efficacy of gels as drug-carriers relies in their adjustable porosity through controlling the crosslinking density of their matrix. Their porous structure allows for drug loading and releasing with high efficiency [19, 20]. Numerous studies have been published on the potential applications of hydrogels in drug delivery focusing on their mechanism, shape of the gel-carriers, and types of transported drugs. Therefore, this chapter, will discuss different drug loading and releasing mechanisms with respect to their corresponding medical application. Furthermore, the drug dosage is dependent on the design of the hydrogel systems, which in turn depend on the route of the drug administration (e.g., rectal, ocular, peroral, etc.), thus, this chapter will shed the light on the types of hydrogel-based carriers applied via different routes of drug administration. Lastly, this chapter will cover different classifications of the delivered drugs using gel-based delivery systems including small molecular weight drugs; therapeutic proteins and peptides; and vaccines.

2. Drug loading, targeting and releasing

2.1 Drug loading

Drug loading is an important property of a drug delivery system, and it is defined as the process of incorporating a drug into a carrier. The therapeutic agents can be introduced into gel-carriers by ionic interaction, dipole interaction, hydrogen

bonding, physical encapsulation, covalent bonding, precipitation, or surface absorption. It's common that more than a loading mechanism is used in drug delivery systems, and the ideal loading strategies are determined based on the compatibility between the physicochemical properties of the drug and the carrier.

The drug-loading process can take place during the formation of the carriers, or by incubating carriers into a concentrated drug solution to allow the loading through adsorption on their surface area [21]. However, this method has limited loading capacity, and the incubation time can influence the drug loading efficacy [22, 23]. In general, the entrapment and loading of drug molecules into polymer carriers depend on several characteristics: polymer and crosslinker concentrations, molecular weight of the polymer, and drug-polymer interactions [24–26]. The higher the polymer concentration the more efficient the drug entrapment is; at a high concentration, the polymer viscosity is increased, which delays the drug diffusion within the polymer particles [27]. Similarly, the high concentration of the crosslinker yields tangible increase in the loading efficiency [28]. Conversely, Fu et al., 2004 reported that the encapsulation efficiency decreases when the molecular weight of the polymer increases [29]. In protein based drugs, the interaction between the polymer and the drug molecules contribute to the entrapment efficiency; it increases if the protein molecules are entrapped into hydrophobic polymers, moreover, ionic interaction between the molecules and the polymer particles increase the efficiency of encapsulation, specifically, in polymers that belongs to carboxylic end groups [30].

2.2 Targeting

The delivery of therapeutics by nanocarriers can be passive: transport of drug-carrying nanoparticles through permeable vessels due to the enhanced permeability and retention (EPR) effect; or active: based on molecular recognition in which peripherally targeting moieties that interact with specific cell receptors [31].

In localized cancer therapy, the mechanism of passive targeting relies heavily on the tumor characteristics; tumor hypoxia causes rapid growth of leaky vessels, which increases the permeation of nano-delivery systems into the tumor, the lack of lymphatic filtration allows for the retention of these systems on the tumor's interstitial space [32]. Moreover, this targeting strategy also depends on the carriers' size; delivery systems larger than 50 kDa permeate through leaky vessels and retained in the tumor, smaller molecules are washed out quickly (very short circulation time) from the tumor [33]. The charge and the surface chemistry affect the circulation time of carriers; mononuclear phagocyte system (MPS) cells tend to opsonize largely hydrophobic and charged systems. Thus, water-soluble and neutral (or slightly anionic) compounds (e.g., Polyethylene Glycol) are used to coat the nanocarriers surface [31, 32, 34]. Active targeting also depends on the EPR effect to accumulate the delivery nanocarriers in the tumor region, however, the efficacy of this strategy capitalize on equipping the nanocarriers' surface with ligands that bind to specific receptors of cancer cells, thus, enhancing the penetration and efficiency of the chemical therapeutics. **Figure 1** illustrates passive and active targeting strategies.

2.3 Drug releasing

Biodegradation of the nanocarriers is essential for the release of the drug molecules over extended periods of time (days or weeks). It is also crucial for the removal of delivery systems from the body [35]. The carrier size has an effect on the efficacy

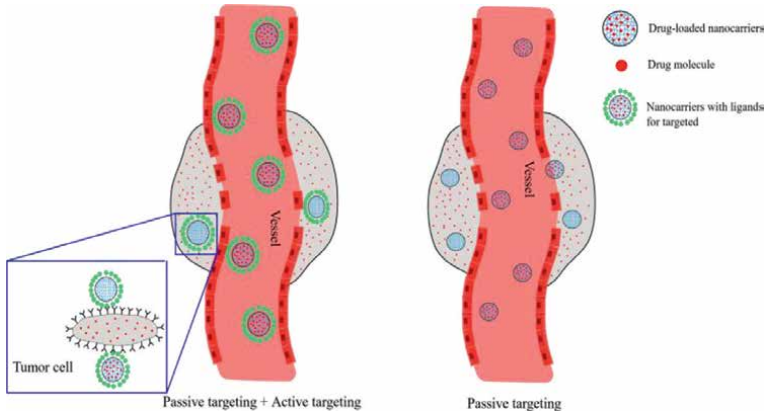

Figure 1.
Schematic illustration of active and passive delivery of drug molecules.

of the releasing process; drug molecules loaded at or in proximity to the surface of small particles are released at a fast rate due to the large surface-to-volume ratio. On the other hand, slower release rates are associated with larger particles, nevertheless, more drug molecules can be loaded. Modulation of the drug release can also be controlled by the molecular weight of the gel composition; higher molecular weight tends to exhibit slower release rates [36, 37]. In general, the mechanism of releasing drugs is dependent on three main parameters: drug diffusion and dissolution, gel matrix design, and interaction between the drug and the gel matrix.

The transport of the therapeutic molecules out of the gel matrix is a complex process that depends on the dissolution and diffusion of the drug [38]. Several studies have been conducted to develop mathematical models that describe this process [39–41]. The basic equation of the dissolution rate as a function of diffusion can be described as [42].

$$\frac{dM}{dt} = \frac{DA}{\mathrm{h}}\left(\mathrm{C_s} - \mathrm{C}\right) \tag{1}$$

Where dM/dt is the rate of dissolution, A is the surface area of solid in contact with the dissolution milieu, D is the diffusion coefficient, $\mathrm{C_s}$ is the drug solubility, and C is the drug concentration at time t, and h is the diffusion boundary layer thickness at the solid's surface. This equation shows that the dissolution rate is directly dependent on the surface area of the particle and the solubility of the drug. Conversely, larger thickness of the diffusion boundary layer reduces the dissolution rate. When the size of the nanocarriers is reduced from the micro-domain to nano-domain, the surface area increases resulting in a higher rate of dissolution as reported in [43].

There are several mechanisms to release the drug, most common strategies are diffusion and swelling controlled. In diffusion-controlled delivery systems, drug molecules diffuse from a region of high drug concentration (reservoir) through the gel matrix or membrane. The design of these systems is commonly available as spheres, cylinders, slabs, or capsules. These systems can have a constant rate of release as described by Eq. (1), or their release rate can be proportional to the square

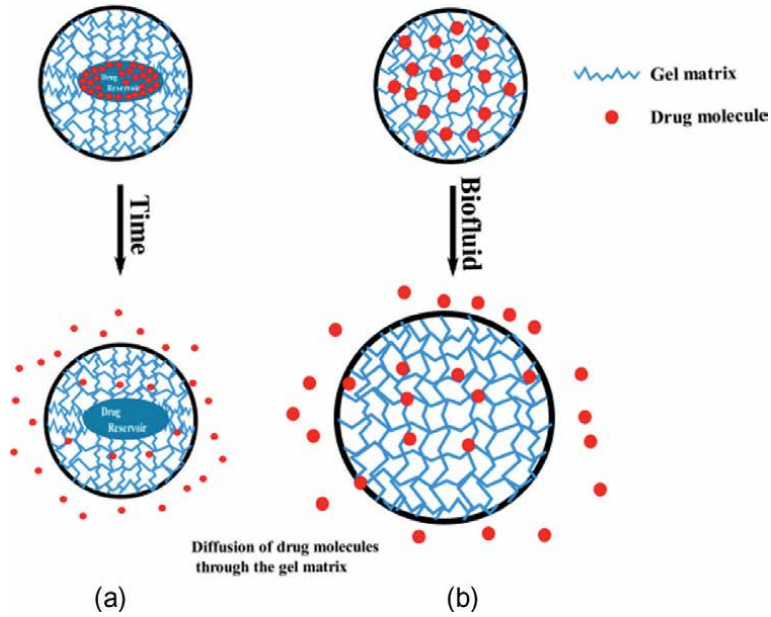

Figure 2.
Schemes of drug release systems: (a) from a reservoir system; (b) from a matrix system.

root of time. In the latter case, the drug is usually dispersed or dissolved uniformly through the matrix of the hydrogel [10]. In swelling controlled systems, the drug is dispersed within carriers made of a glassy gel, and upon contact with biofluids, they swell beyond their boundary which results in the diffusion of the drug during the relaxation of the gel chains, this process is known as anomalous transport [10, 44]. Illustrations of the two releasing mechanisms provided in **Figure 2**. The structure of the nanocarriers' controls the release of the drugs; using hydrogels alone in synthesizing the nanocarriers can result into fast premature release of drugs and poor tunability [45]. Therefore, using additives can enhance the control of the drug delivery process; using Polydopamine (PDA) as an additive to the hydrogel materials in making the nanocarriers provides an on-demand capability to release the drug. In high glutathione (GSH) and acidic condition, the bond between the drugs and PDA experience weakening. This is a useful property to release the drugs in inflammatory areas or tumor cites where pH levels are low. While at neutral pH levels such as in normal tissues, the bond between the PDA and the therapeutic dugs is not affected [46–50]. Furthermore, PDA generates heat upon exposure to near infrared (NIR) laser, which makes it ideal for NIR triggered drug delivery [51].

3. Hydrogel administration

Besides long-term stability and release properties, passing the toxicity screening is essential for hydrogel formulations to be used in drug delivery. This is mainly due to the rise of inflammatory reactions that occur as a result of the degradation of synthetic polymers [52]. Therefore, achieving biocompatibility is necessary to use hydrogels in an environment of living organisms. Most in-vivo tests are conducted on animal models to provide reliable biomedical mimicry. As a result, several

hydrogel-based drug delivery systems have been developed and approved for clinical use through different administration routes. Currently, the common accessible routes of these systems are Oral [53], rectal [54], subcutaneous [55], transdermal [56], ocular [57], and intraperitoneal [58]. These administration routes are illustrated in **Figure 3**. **Table 1** provides examples of gel-based products used in drug delivery through different administration routes.

3.1 Oral route

Oral administration currently is the most common and convenient for hydrogel drug delivery systems, thanks to their bioavailability and nontoxicity they provide [67, 68].

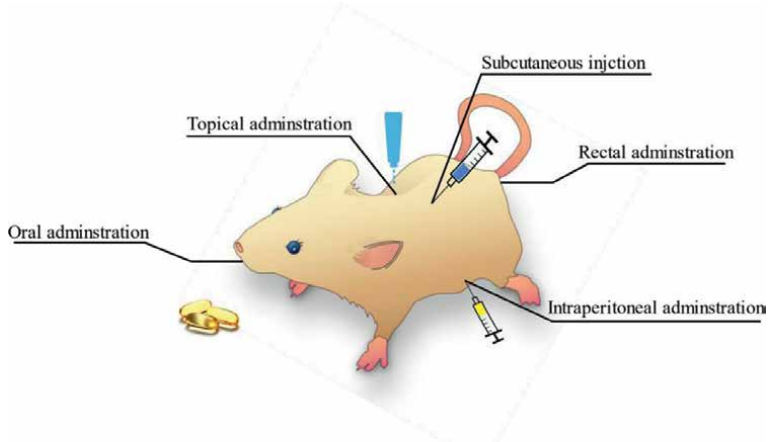

Figure 3.
In-vivo hydrogel-based drug delivery in most common routes of administration. The schematic illustration is reproduced from [59].

Route of administration	Shape	Typical dimensions	References
Oral	Spherical beads; Discs; Nanoparticles	1 μm–1 mm Diameters of 8 mm and thickness of 1 mm 10–1000 nm	[35, 60, 61]
Rectal	Suppositories	Conventional adult suppositories dimensions (32 mm in length) with central cavity of 7 mm and wall thickness of 1.5 mm	[62]
Transdermal	Dressing	Variable	[63]
Subcutaneous	Injection (hydrogel spacers in prostate cancer therapy)	N/A	[64, 65]
Intraperitoneal	Injection (hyaluronic acid hydrogel loaded with chemotherapeutics)	N/A	[66]

Table 1.
Types of hydrogel-based products applied via different routes of drug administration [10, 59].

However, such systems have limitations due to the metabolic effect these systems have on the living organism including but not limited to denaturation and reduction of epithelial membrane permeability [52]. Delivery systems in this strategy are usually made from caprolactone, MPEG, itaconic acid pH-sensitive hydrogels as they were reported to have no signs of toxicity [68].

3.2 Rectal route

This route provides an alternative to intravenous and subcutaneous medication delivery. It has faster absorption of the medication through rectum's blood vessels, which makes it ideal for therapeutics that have high bioavailability and shorter duration [69, 70]. Moreover, it provides a stable environment in which the drugs are released since this administration strategy bypasses the gastrointestinal tract. As a result, minimal alterations occur to the drug concentration when it reaches the circulation system [71]. Hydrogel-based delivery systems such as catechol-chitosan gels have shown excellent biocompatibility and were reported to have no toxicity in-vitro and in-vivo [54, 72].

3.3 Subcutaneous route

This route is very common in studies that involve animal models when developing gel-based injectable biomaterials such as alginate [73], gelatin [74], poly-acrylamide [75], ellagic acid [76], and pectin [77]. While these biomaterials have shown no toxic response when deployed in-vivo into the animal model, the majority of the studies have reported inflammatory effect due to the vascularized nature of the subcutaneous region that is associated with reactions against foreign moieties [78].

3.4 Transdermal route

In topical delivery, the therapeutics reach the circulation system through penetrating the skin layers; the drug passes through the startum corneum to deeper epidermis and dermis until it is absorbed by the dermal microcirculation [79, 80]. The hydrophilic nature of hydrogels allows them to hold considerable amounts of fluid content that ranges between 10% to 1000 times gels' dry weight [81], which makes them ideal for carrying drugs such as insulin, theophylline, sodium fluoride, and progesterone and heparin. Transdermal hydrogel patches can provide a controlled rate of drug delivery in addition to providing a cooling effect at the location where they are applied [81]. Hydrogels can also be combined with bio-adhesives to prolong the therapeutic effect of the delivered drug when applied topically [82].

3.5 Intraperitoneal route

Intraperitoneal injections of hydrogel systems are considered a successful delivery strategy for various therapeutic agents. The injected hydrogels compounds can achieve efficient drug delivery while exhibiting anti-adhesiveness properties on the peritoneum [83]. Although intraperitoneal hydrogels were reported to be non-toxic [84], their hydrophilicity can compromise the concentration of the delivered pharmaceutical agents [58].

4. Types of therapeutics delivered using hydrogels-based delivery systems

4.1 Small molecular weight drugs

Budhian et al. [85] categorized the release of this class of drugs into three stages; (i) initial burst, during which the drugs immediately released into the medium; (ii) induction, in which the release of drugs is gradual; and (iii) slow release, in which the release reaches a steady slow rate [85]. These stages are controlled by three unique properties of the gel in use to synthesize the delivery systems: hydrophobicity, surface coating, and particle size [35]. The lower the hydrophobicity the higher the release of drugs during the burst stage; for example, the percentage of released drugs after 1 day is 45% for 220 nm strongly hydrophobic PLA particles, on the other hand, the release percentage is 70% for the same size of the moderately hydrophobic PLGA particles. The release stages are also affected by the surface coating of the nanoparticles; coating PLGA particles reduces the number of drugs released by 40%. The rate of release and the initial burst are affected by the size of the particles; increasing the size decreases the total surface area which reduces the burst period, furthermore, the larger the size, the longer the pathways the drug molecules take during the diffusion which increases the induction period [85].

4.2 Therapeutic peptides and proteins

Among several peptides- and proteins-based therapeutics that are used in drug delivery, enzymes are the most studied class of drugs [86]; examples of such enzymes include L-asparaginase, cysteine desulfatase, cysteine oxidase, arginase, and arginine decarboxylase [87]. Currently, only a few protein- and peptide-based drugs have been used in medicinal setting. The clinical use of this class of drugs is hindered by several factors: enzymatic degradation, renal filtration, inefficient cell entry, accumulation in nontargeted organs, immune system response that causes allergic reaction, and protein inactivation due to intrinsic properties such as low stability in an environment of physiological pH and temperature [88].

A simple approach to overcome the elimination of this class of drugs is introducing it via injection to the targeted organ. However, this strategy has its own limitations such as difficulty or delocation of the targeted site, drug toxicity, and long-term hospital setting administration [88]. Other delivery strategies were proposed such as microfabricated chips and implantable devices [89, 90]. While these strategies have shown promising results, their deployment and extraction require surgical intervention. To overcome these challenges and to stabilize the therapeutic proteins and peptides in the physiological environment, they are encapsulated into nanocarriers. This technique protects the enzymes from the degradation parameters imposed by the physiological environment while delivering different types of protein-based drugs [88].

Shimizu et al. [91] developed nanocarriers that efficiently encapsulates bone morphogenic proteins (BMPs), which have significant capability to convince bone formation. When BMPs are encapsulated by the developed nanocarriers, they provided sustained delivery of the BMPs over a time period of 14 days. In cancer therapy, polymersomes are used to deliver therapeutics; Danafar et al., 2016 investigated the delivery of drug molecules encapsulated into mPEG-PCL hydrogel nanocarriers in treating breast cancer. Their mPEG-PCL carriers provided suitable pH-dependent delivery of therapeutics to breast cancer cells [92].

Hydrogel based system	Applications	References
Thermo-sensitive	H5N1 Influenza vaccination; Ebolavirus glycoprotein antigen; prevention of ovine brucellosis	[100–102]
Capsules	Oligopeptide antigen delivery	[103]
Bio bullets	Bacterial vaccines (Brucella Abortus strain RB51 live vaccine)	[104]
Injections	Swine H1N1 influenza killed vaccine; fibroblast growth factor (bFGF); codelivery of immune check point inhibitor and tumor vaccine	[105–107]
Nanogels and peptides	Adjuvant for the vaccine delivery systems for West Nile and respiratory syndrome viruses	[108, 109]
Micro-scale particles	Oral delivery of bovine serum protein; intramuscular delivery of "transmission blocking malaria" vaccine	[110, 111]
Gel patches	Tetanus and diphtheria vaccination	[112, 113]
Micro-needles	Influenza vaccine; DNA vaccine against hepatitis B; Japanese encephalitis vaccine; and rabies vaccine	[114, 115]

Table 2.
Hydrogel-based delivery systems and their applications.

4.3 Vaccines

Establishing an immunological memory and provoking sufficient immune response are the two primary factors that determine the efficacy of a vaccine delivery system [93, 94]. The main administration routes of vaccine delivery systems are parenteral and non-parenteral. The first is administered using hypodermic needles inserted through subcutaneous, intramuscular, and intradermal routes [95, 96]. On the other hand, non-parenteral delivery systems capitalize on needle-free devices such as jet injectors, liquid, powder, and polymeric (including hydrogel) systems [97]. In hydrogel-based systems, gel particles encapsulate the vaccine molecules and deliver it through intramuscular, oral, and transcutaneous routes [98, 99]. In recent years, different hydrogel delivery systems were developed to increase the efficiency of the vaccine delivery, **Table 2** summarizes these systems and their applications.

5. Conclusion

Drug carriers are revolutionary delivery systems in the field of medicine. While there have been several studies that reported different types of polymers that has been used to synthesize the carriers, hydrogel-based systems seem to be very promising due to their affordability, production simplicity, and their unique ability to load different types of drugs. Although several gel-based systems have been investigated, designed and IP-protected, it seems only limited number of these product has actually reached the market, which indicates the need for further investigations on improving the performance of current products and develop new ones. This chapter addressed different hydrogel-based drug delivery systems from different perspectives including mechanisms (loading, releasing, and targeting), design (shape and route of administration), and the classes of delivery drugs. These elements are essential when designing and investigating state-of-the-art hydrogel-based delivery systems.

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Chapter 4

Hydrogels: Smart Materials in Drug Delivery

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Abstract

The prominence of hydrogels in various fields of life sciences is due to their significant and functional three-dimensional biopolymeric networks, which tend to imbibe water due to -OH, -CONH2, -SO3H, -CONH,-COOR groups which have a hydrophilic tendency enabling them to be an excellent super absorbent and remain insoluble in water. Hydrogels can embed physiologically active molecules in their water-swollen network and are appealing materials for the controlled release of medicines. Several significant advancements in the realm of hydrogels for therapeutic delivery have resulted from recent advances in organic and polymer chemistry, bioengineering, and nanotechnology. We offer our perspective on the state-of-the-art in the field in this chapter, focusing on several intriguing issues such as current trends in hydrogel-based drug delivery, stimuli-responsive hydrogels, nanogels, and therapeutic release from 3D printed hydrogels. We also discuss the obstacles that must be solved to promote translation from academia to the clinic, as well as our predictions for the future of this quickly changing field of research.

Keywords: hydrogel, nanogel, drug delivery, nanocarrier

1. Introduction

Recent innovations have statured hydrogels as noteworthy drug carriers which have found their eminent application in tumor drug delivery. As it has lesser side effects than the existing systemic chemotherapy and is known to be an accurate delivering agent at specific tumor sites. In addition to this, it has salient features like biocompatibility, biodegradability, and lower toxicity than nanoparticle carriers. This has paved the way for researchers to delve into and explore more on the functionality of hydrogels. Smart hydrogels can respond to stimuli in the environment (e.g., heat, pH, light, and ultrasound), enabling in situ gelations and controlled drug release, which greatly enhances the convenience and efficiency of drug delivery [1]. The repeated monomers like homopolymers or copolymers containing hydrophilic polymer chains lead to the formation of hydrogels and these monomers are arranged in different ways, as shown in **Figure 1** [3].

The (3D) network of hydrogels can intake water and remain swelled in any condition without dissolving in the medium. Hydrogel carrier is trending in drug delivery

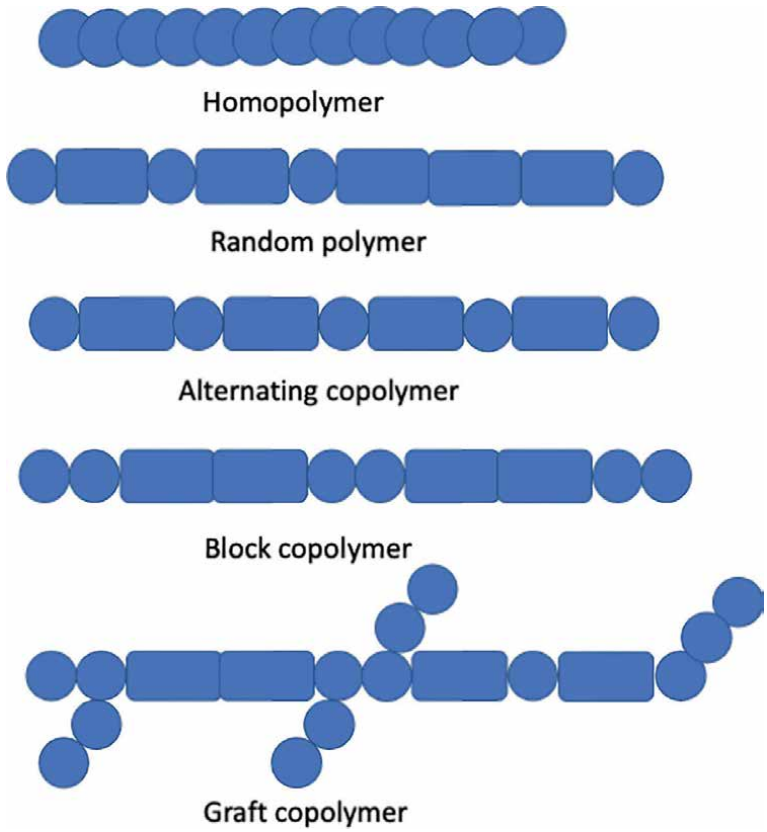

Figure 1.
Chemical diversity of hydrogel polymer chains (adapted from [2]).

due to their extended biocompatibility and tunable mechanical strength. Synthetic hydrogels are explored more because of their peculiarities like long life, higher capacity for water absorption, and high gel firmness. These can be synthesized from purely synthetic materials and these are having defined structures that can be modified to yield tailorable degradability and functionality [4].

Hydrogels are good carriers of drug delivery, and it has resulted in the elevation of therapeutic outcomes tremendously, used in clinical arenas. The delivery of cells, molecules, and macromolecular drugs in hydrogel encapsulation via spatial and temporal delivery has improved. Improving the design for the hydrogel drug delivery has overcome the limitations partially and it results in the progression of a better carrier. Current trends and different types of hydrogel drug delivery with the translation to clinical use will be discussed in this chapter [5]. There is extensive research carried out on hydrogel drug delivery. To add on, properties for drug delivery systems that were under modification, in terms of the ligands and various polymer types are researched meticulously. A wonderful disposition of a positive results was shown in the ophthalmic field i.e., from comfortable contact lenses to biodegradable drug delivery, the applications in eye care have been enormous. These possess 90% water for the drug release for a long period to deliver small or large molecules [6]. Thus, a long road of success waits for hydrogels if they are observed, studied, experimented with, and translated to clinical research.

2. Hydrogels for drug delivery: mechanism

Hydrogels are encompassed of 3-D hydrophilic polymer networks [7]. Since hydrogels have hydrophilic functional groups attached to the 3-D polymeric network they can absorb a huge volume of water [4]. The capability to hold water within the interconnected polymeric network aids them to swell and shrink appropriately and in turn, helps them in the application of drug delivery. Hydrogels possess porosity and compatibility with aqueous conditions hence they are considered highly promising materials for drug release [8]. Moreover, the tunable properties of hydrogels make them excellent materials for specific therapeutic applications such as oral drug administration, ocular route, nasal route, and transdermal route [9].

Hydrogels have the potential ability in oral drug delivery in particular for the delivery of macromolecules and hydrophilic drug molecules [10]. Hence the application of hydrogels has been extended to the treatment of patients with cancer and diabetics. In oral drug delivery, the drug is delivered to the following specific sites: mouth, stomach, small intestine, and colon. Hydrogels with mucoadhesive ability are mainly used for this application (**Figure 2**) [9].

Nowadays the significance of protein and peptide drugs is increasing due to their potent action and high selectivity but the vital problem arises due to the enzymatic activity in the GI tract that results in the degradation of these drugs. However, studies have shown that hydrogels equip a platform that aids to deliver the drugs to specific sites in the GI tract and thus have significant importance in the delivery of protein and peptide drugs through the GI tract [10]. Crosslinked hydrogels can be used to

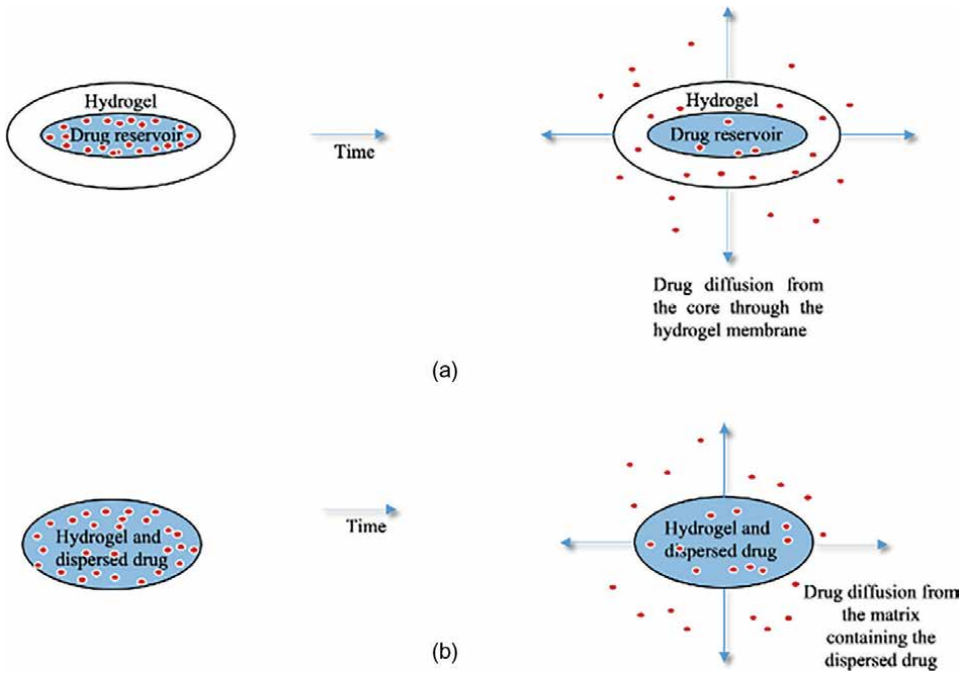

Figure 2.
(a) The drug-containing component is coated with a hydrogel membrane and, the drug concentration is greater in the center of the system, allowing for a constant rate of release in the reservoir delivery system; and (b) Matrix delivery allows for uniform drug dissolution or dispersion across the hydrogels 3D structure (adapted from [8]).

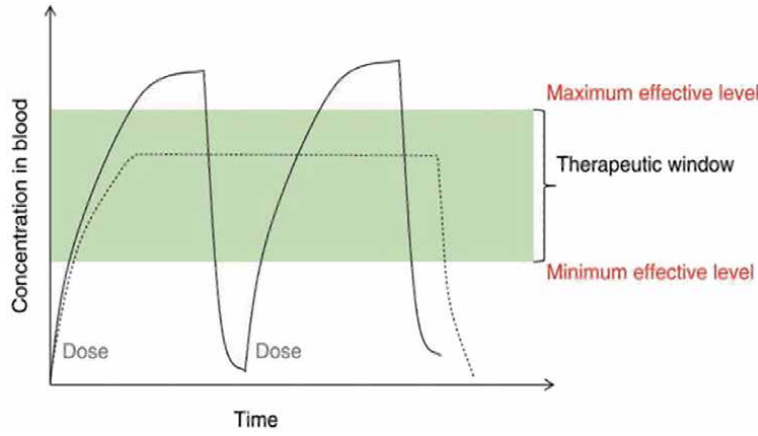

Figure 3.
Illustration of drug level in the blood with repeated dosing (solid line) and controlled delivery dosing (dotted line) (adapted with permission from [10]).

safeguard drugs from detrimental conditions including low pH in the stomach and enzymes due to the crosslinked nature of networks. Controlled diffusion of water-soluble drugs is possible in the hydrogel network. The density and chemical structure of the crosslinking agent determines mesh size [10]. An illustration of drug levels in the bloodstream is shown in **Figure 3**.

Another type of hydrogel called stimuli-responsive hydrogel is considered a potential substance for oral drug delivery. The peculiarities of stimuli-responsive hydrogel include the capability to respond to the changes in the environment, permeability, swelling nature, and ability to control drugs. The major objective of controlled drug delivery is to maintain a stable concentration of dose in the blood which cannot be achieved through a traditional drug release mechanism [10].

The field of eye treatment is currently employing the characteristics of hydrogels to treat the health problems such as blinking, tear drainage, and low permeability of the cornea, and the method is known as ocular route drug delivery [9].

The transdermal route of administration is another way of using hydrogels in drug delivery. This method helps to avoid drug degradation, side effects, and aids in maintaining a steady drug release. It is important to note that in comparison with conventional ointments water holding hydrogels can provide a better feeling to the skin hence this is highly preferred [9].

In reality, designing and synthesizing environmentally sensitive hydrogels offers a lot of potential in healthcare and nanotechnology applications in the future. The creation of advanced materials that can specifically address applications in biomedical issues is important to the achievement of these materials. This progress will be made through the introduction of unique polymers or the modification of existing polymers.

3. Current trend in hydrogel based targeted drug delivery

3.1 Supramolecular hydrogels

Supramolecular hydrogels generated by the spontaneous self-assembly of peptides, proteins, and other biomolecules have recently gathered attraction as

next-generation drug delivery substitutes to synthetic polymers. Due to the comparatively expensive synthetic peptide hydrogels compared to synthetic polymer gels, self-assembling peptides are a promising class of supramolecular gelators for in vivo drug delivery that has been sluggish to catch on despite benefits in biocompatibility. Supramolecular hydrogels' superior biocompatibility and simplicity of formulation in comparison with polymer hydrogels have sparked study into the self-assembly events that lead to gelation and how to engineer the emergent features of supramolecular gels to generate excellent drug delivery materials. The development of stimuli-responsive hydrogels for medication administration has gained the attention of researchers. Changes in pH, temperature, ionic strength, and also exposure to light, electric, and magnetic fields, are all examples of external stimuli that might cause drug release. pH-sensitive smart hydrogels have been widely used as self-regulating drug delivery systems.

The supramolecular hydrogel framework comprises non-covalent intermolecular interactions that collectively hold two or more molecular units. The non-covalent cross-linking of these hydrogels is a particularly appealing feature since it avoids the challenges of restricted drug loading capability and drug integration for use solely as implantable, which is the only option with a covalently cross-linked system. These hydrogels achieve drug loading and gelation concurrently in aqueous conditions without the need for covalent cross-linking, in addition to providing the necessary physical stability for the hydrogels. Supramolecular hydrogels based on self-assembled inclusion complexes between cyclodextrins and biodegradable block copolymers have recently made headway in providing sustained and regulated release of macromolecular medicines [8].

In recent times, supramolecular hydrogels that are responsive to biological stimuli have gained a significant amount of interest for their potential as smart materials. A macroscopic sensor could, for instance, be a stimulus-responsive gel-to-sol phase transition. In response to the stimulus-responsive gel-to-sol phase transition, a drug-encapsulated supramolecular hydrogel could deliver the drug. However, supramolecular hydrogels with a gel-to-sol phase change in response to biological stimuli must be developed under physiological settings to exploit the uses.

Supramolecular hydrogels are generally synthesized by heating followed by cooling a mixture of an LMWHG (low molecular weight hydrogelator) and an aq. solvent whereas external stimuli-triggered gelation enables the spontaneous synthesis of supramolecular hydrogels. Supramolecular hydrogels with high biocompatibility are desirable materials for medical and pharmaceutical applications. Nevertheless, the challenging preparation procedures for LMWHGs and the unavailability of very resistant supramolecular hydrogels restrict the potential possibilities of these materials. Several studies have shown that various LMWHGs can be prepared within a few steps from commercially available chemicals.

The structural tailoring of LMWHGs allows for the development of a more strong supramolecular hydrogel. Small quantities of a dimer with a similar structure to LMWHG can be added to a supramolecular hydrogel to enhance its physical characteristics. Supramolecular hydrogels with stimuli-responsive characteristics will be more beneficial. The formation of biological-stimuli-induced supramolecular hydrogels can be considered as a novel therapeutic technique based on the biological activity of self-assemblies. It is important to produce more specific and precise stimuli-responsive materials for the effective use of biological-stimuli-responsive supramolecular hydrogels [11]. The presence of competitive binders in the physiological surroundings, such as proteins or ions, is another factor to consider when designing supramolecular drug

delivery vehicles. Competing interactions can impact the supramolecular hydrogel's mechanical characteristics and/or change the release profile of loaded medicines [12].

3.2 Multicomponent hydrogels

Hydrogels that were multi-functional and carriers of anti-cancer drugs are a typical example of the versatility of these delivery vehicles and their amenability to chemical modifications to enhance their therapeutic effects. The cytocompatibility and excellent biocompatibility of the materials make them promising materials in biological applications including drug delivery, wound healing, and tissue engineering. However, during the material selection process, the potential toxicity of the breakdown products may be neglected. For instance, amazingly (polyacrylamide) is a popular breast implant that is nontoxic and has a low rate of rejection. On the other hand, the breakdown product acrylamide has medium toxicity for the neurological system and kidneys and has been classified by the World Health Organization (WHO) as one of the suspect carcinogens.

It is necessary to examine the biocompatibility of hydrogels and their degradation products for medical applications. The invention of new cost-effective biomimetic materials or natural products from high throughput processing, such as hyaluronic acid, chitosan, gelatin, collagen, and so on, could improve material safety. Stimuli-responsive hydrogels, as a kind of smart materials, offer promise for tailored drug delivery. The hydrogel structures can be triggered automictically in response to diseased microenvironments and deliver cargos with better spatial/temporal resolution thanks to an elaborate design. Nevertheless, uneven circulatory networks raised interstitial fluid pressure, and diffusion of target stimuli around the tumor microenvironment could result in unintended medication leaks and possibly off-target effects during transportation.

Furthermore, improper drug deposition in solid tumors can lead to drug resistance and a significant reduction in therapeutic benefit. This field could be advanced by drug-loaded hydrogel capsules that react to target biomarkers. Hydrogel capsules with high specificity and permeability provide a new outlook for cancer therapy250, thanks to the modification of aptamers that target certain cells. Multi-triggered hydrogels with programmable functions are also a promising technique for overcoming the challenges stated above and improving therapeutic effects. The off-target scenario might be considerably decreased if the medicine could be released in a planned logic operation in response to multiple disease/therapy-related parameters. A programmable ON/OFF switch is required for improving drug dose in various therapeutic circumstances. Incorporating cell regulators (such as peptides, proteins, and nucleic acids) into hydrogel frameworks to attract cancer cells inside and execute in situ contact-killing is another potential strategy that should be explored [13].

3.3 DNA-hydrogels

Active body regeneration scaffolds are obtained from the nucleic acid molecule of living organisms, sometimes these are known to be DNA nanostructures. Hydrogels that are made out of DNA have a uniqueness in the following characteristics; degradability, non-immunogenicity, high sensitivity, and drug delivery. The self-assembling of biomaterials works on the principle Watson–Crick base pairing and this is how the DNA hydrogels are formed. The unique mechanical and biochemical properties of DNA, along with its biocompatibility, make it a suitable material for the assembly of hydrogels with controllable mechanical properties and composition that could be used in several biomedical applications, including the design of novel multifunctional

biomaterials [14]. Recent studies reported that DNA hydrogels are responsive to stimuli such as; light, biomolecules, and temperature. This stimuli-responsive helps in improving the therapeutic field as well as may decrease the side effects. **Table 1** below shows the two types of triggers; nonbiological and biological [15].

When a drug carrier holds features like upkeeping of intact bioactivity of drugs and inhibiting chemical and enzymatic degradation and improved retention effect it means a successful drug carrier. The benefited properties such as biocompatibility, available binding for cargos, easily triggered stimuli responsiveness, and effective active targeting ability uplifted DNA hydrogel. In a small loading efficiency, drug molecules and inorganic nanoparticles can be incorporated into the porous structured network [16]. Another highlight is to capture high performance in the deliveries of chemotherapy, immunotherapy, and gene by allowing the co-delivery agent with various physicochemical properties [17]. To inhibit the permeation of enzymes a highly crosslinked cage or network is used to deliver nucleic acid drugs and this way will protect the biological activity of the proteins. The trending research on inorganic materials delivery has inspired. Cutting down edge research has put down the obstacles and made the hydrogel drug delivery system a great progression stage over the past 2 years. To fabricate DNA hydrogel in a low-cost method with a high yield end product is a challenge in application. To overcome this challenge, it is necessary to check on the synthetic approach and it is very crucial to find a way in low-cost production for the same. Toward this end, a highly parallel gene synthesis method based on DNA microchips and specific oligonucleotide pool amplification was demonstrated. It led to a remarkable cost reduction for scale-up DNA production [18].

3.4 Stimuli-responsive hydrogels

For example, malignant tissue (pH 6.8) and endosomes/lysosomes (pH 5.5) are more acidic than normal tissue (pH 7.4), necessitating hydrogels that can deliver payload medications in response to a pH change. Several polymers have been intensively explored for the construction of intelligent hydrogels throughout the last few decades. Because of their intrinsic biocompatibility, renewability, and availability, natural-resourced polysaccharide-constructed hydrogels have gotten a lot of attention, fueling the urge to use them as drug carriers. Many polysaccharide-based hydrogels, on the other hand, lack mechanical strength rigidity and are susceptible to rapid erosion, making them unstable. This makes it difficult to use polysaccharide hydrogels for medication administration. Physical diffusions, on the other hand, are commonly used to release medicines from gel matrices, which might result in premature burst release. It's difficult to tailor drug delivery in a predictable and on-demand manner [19].

Nonbiological triggers	Biological triggers
Light	Antigens
pH	Nucleic acid
Metal ions	Enzymes
Temperature	ATP
Reducing agents	Biomolecules

Table 1.
Different types of triggers [15].

Transitional changes occur in stimulus-responsive hydrogels in reaction to environmental factors. The concentration of certain biomolecules such as enzymes can cause them to expand, shrink, degrade, or undergo a sol-gel phase transition if there is a change shown in the temperature, pressure, ionic strength, and insolvent. This type of hydrogels is particularly valuable for therapeutic delivery because of their unique ability to perform specialized activities, such as the release of drug and in situ gel formation, in response to tiny changes in ambient circumstances.

Stimuli-responsive hydrogels that change structural or mechanical properties in reaction to environmental cues/triggers are categorized as vital subgroups in hydrogels. These hydrogels are very beneficial in robotics and biological fields. Several stimuli including light, temperature, magnetic fields, electric field, pH, and chemical and biological triggers could be used to stimulate phase transition or stiffness change of these materials implying a wide range of applications in separation, drug delivery, sensing, bionic devices, regenerative medicine, and more.

Two types of bio-stimuli called endogenous stimuli that exist naturally within the bio-environment and exogenous biocompatible stimuli that activate smart functionalities of the hydrogel system have been garnering attention for the building of bio-functional materials. pH value, metal ions, enzymes, redox environment, antigen, and other endogenous stimuli are examples of endogenous stimuli. In wounds or bacterial infections, for instance, reactive oxygen species are produced, resulting in an oxidative environment; the exocellular pH of tumor tissues is lower than normal tissues caused by abnormal metabolism, particularly glycolysis overactivity; and lung cancer cells have a particular protein that could be recognized by antibody-functionalized microgels. The application with the various stimuli is illustrated in **Figure 4**.

Hydrogels ingrained with efficient cross-linkers or chemical modifications will recognize abnormal signals in pathological or wounded tissues and accomplish endogenous initiation, resulting in automated and focused behaviors such as drug delivery, cell capture, or warning signal output, with proper designing. Light, temperature, magnetic fields, electric fields, ultrasonic waves, and other exogenous stimuli are examples. Exogenous stimuli-responsive hydrogels, in contrast to endogenous stimuli-responsive hydrogels outlined above, are developed to function remotely and non-invasively [20].

It has been found that Magnetic nano-participles embedded in DNA hydrogels provide the networks with shape-adaptive and locomotion-controllable features. Light-guided fibroblast migration and angiogenesis were achieved using hydrogels treated with photo-caged RGD. The sensible integration of endogenous and exogenous stimuli-responsive units into a single hydrogel system could provide a comprehensive "toolbox" for customizing intelligent materials. The addition of programmable, multi-stimulus responsiveness enables the integration of multiple functionalities into a single hydrogel system, such as searching, recognizing, and curing. The gelator-gelator and gelator-solvent interactions are implicated in the stimuli-response pathway, which includes volume change, phase transition, and structural change.

3.5 Nanogels

The nanostructures comprising drug molecules with innovative structures represent the new frontier in the biological and medical fields. The application of nanogel in various biological fields is shown in **Figure 5**. The crosslinked polymer network with a three-dimensional structure and having a nanoscale size range are known to be nanogels. These nanogels can hold a large volume of water but they

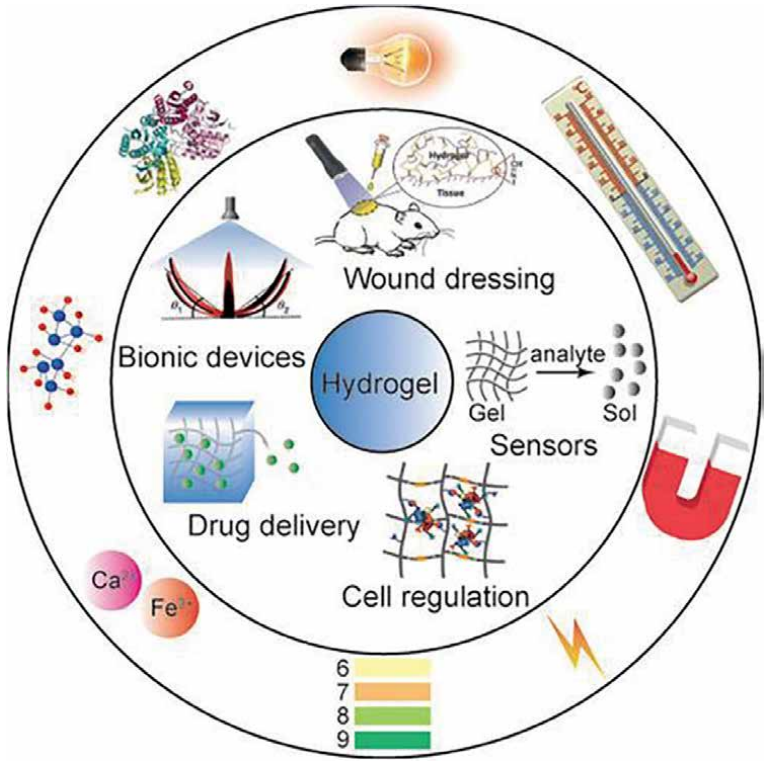

Figure 4.
Stimuli-responsive hydrogels and their applications [13].

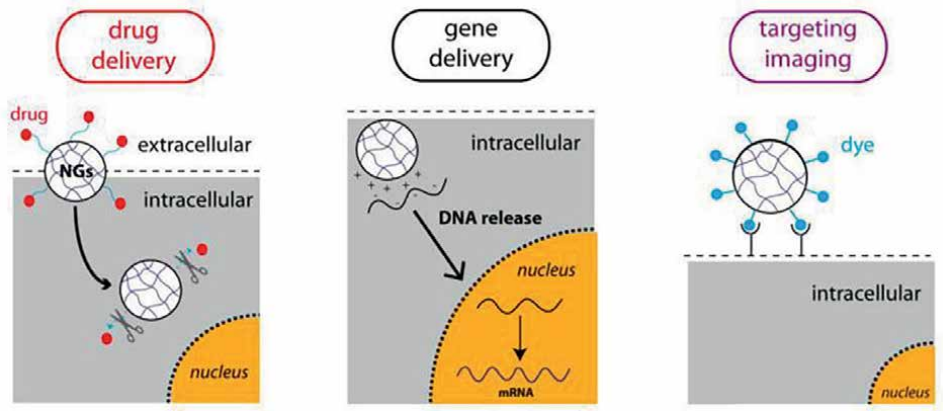

Figure 5.
Schematic representation of nanogels in the various biological applications (adapted from [21]).

will not dissolve in an aqueous medium [16]. They are common in spherical shape but they can vary in the synthetic strategies [22].

Nanogels have been identified recently by researchers and it has been used as a promising tool in response to the critical issues of intracellular delivery: due to their peculiar properties, including swelling behavior, nanogels can cross the cellular membrane (clathrin-mediated endocytosis, caveolin-mediated endocytosis, phagocytosis,

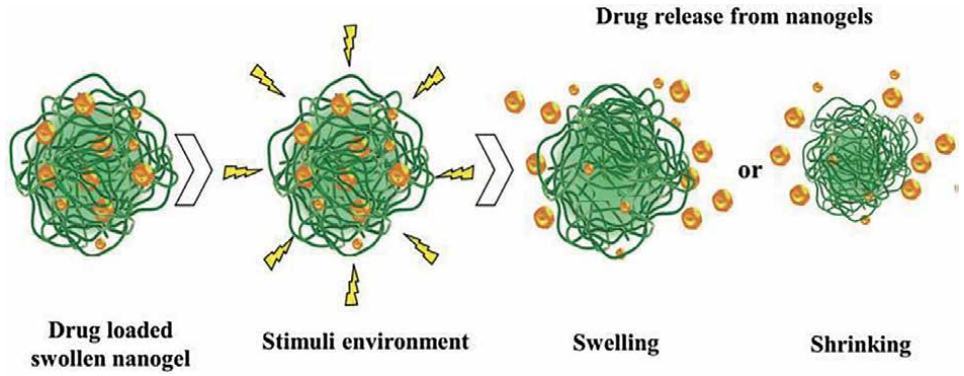

Figure 6.
The schematic of drug release from the nanogel network (adapted from [27]).

and macropinocytosis) and release their cargo in the cytosol, avoiding the activation of immune responses. These can be fabricated using natural polymers, synthetic polymers, or a combination of both. The distinct characteristics of nanogels can be varied by their chemical composition [23].

The properties like swelling and encapsulation and the prior response in the specifically targeted sites put them in the frontline of drug delivery and gene delivery. The nanosized gel can be synthesized by two approaches; top-down and bottom-up. Generating nanoparticles from large clusters of particles by different methods (physical, chemical) is known to be a top-down approach. The imperfections in particle surfaces can be a limitation of this method. The designing and arranging of molecules by direct polymerization of monomers and assembling of polymer precursors bonding can be the bottom-up approach [24, 25]. In the biomedical application, nanogels size distribution with their stability is very important. The stability depends on the chemical composition of the polymer matrix and the crosslinking type of the polymer chains. In comparing the physical and chemical nanogels, physically crosslinked nanogels are weaker and have lesser stability, due to their stability and reproducibility the chemically crosslinked nanogels are much more attractive [26].

The schematic representation in **Figure 6** shows that under a specific environmental condition the hydrogel loaded with the drug will start swelling or start shrinking and it leads to the release of a drug. This completely depends on the interaction of hydrophobic, hydrogen links, complexation, and/or coordination of drug molecules with the polymer chain networks [28]. The thermoresponsive polymeric nanogels allow the interaction of water molecules with hydrophilic groups help in swelling by maintaining its native structure. This occurs in the lower critical solution temperature (LCST), the removal of water content occurs during the hydrophobic nature. This further decreases the size of nanogel and the drug is released by the triggered temperature stimuli [29, 30]. Nanogels can be used to incorporate small nanosized molecules such as drugs and fluorophores, proteins, peptides, nucleic acids. The nanogel can act as multi-drug carriers and nanostructured gels can encapsulate multi-agents too.

4. Translation to the clinic research

The vast area of the potential application of hydrogel formulations has overcome barriers of in vitro/pre-clinical studies and finally found fit into the market. It is very

Study	Hydrogel	Application	Additional effects
(29)	Cardiac ECM in PBS	Bulk delivery IM	Improved cardiac differentiation of BADSCs
(30)	Transglutaminase cross-linked gelatin	Bulk delivery IM	Improved retention and reduced fibrosis compared to ASC in PBS, improved MIT assay, decreased ANP and TNP mRNA
(31)	Alginate hydrogel	Microencapsulation IM	Decreased fibrotic area and increased infarct thickness
(32)	PEG hydrogel	Bulk delivery IM	Improved retention
(33)	RADA hydrogel	Bulk delivery IM	improved retention; hydrogel effect in itself better than BMMSCs; decreased fibrosis
(34)	Alginate cross-linked with calcium glucuronate	Bulk delivery IM	No difference in thickness, perfusion, or fibrosis
(35)	Hyaluronate hydrogel	Bulk delivery IM	Improved retention, myocardial velocity, and strain
(36)	RADA hydrogel	Bulk delivery IM	Decreased collagen content, infarct size, number of vessels, and decreased number of apoptotic MSCs
(37)	TMTD alginate hydrogel	Capsules delivered epicardially	Only decreased fibrosis in die hydrogel group

Table 2.
Lists of the widespread practical applications of the hydrogel concept that have been translated to the clinical level.

important to have the uniqueness and the salient feature to cover the clinical-stage studies. There is a lot of research going on in the background and some of them are in the pre-clinical stage. The time to fabricate these carriers for the delivery was not at all wasted and it has all been the best and the most versatile drug delivery. Here, in **Table 2**, the list on the research on different hydrogel carriers for exploring the new era of therapeutic delivery is shown.

5. Conclusions

Although myriad chemical moieties of the hydrogel are readily available for drug delivery. The specific problem related to hydrogel fabrication is the need to evaluate the polymer that can produce versatile hydrogels that is apt for a certain intervention that mandates the final goal of the delivery system and route of administration. Understanding the influencing elements that influence swelling behaviors, hydrophilicity, biodegradability, biocompatibility, and targetability of the selected polymer is necessary for the development of a successful hydrogel-based delivery system. Hydrogels as targeted drug delivery have several advantages, including biocompatibility, low toxicity, and good swelling behavior. There have been certain impediments in the processing of hydrogels depending on the chemical moieties of the gel-forming polymers and the route of administration, some limitations in the delivery of active pharmaceuticals, such as slow stimuli-sensitive hydrogel responsiveness, the possibility of rapid burst drug release, the possibility of drug reactivation, limited hydrophobic drug delivery, and low mechanical strength. Thus, the field of nanoscience is

contributing positively to the fundamental advances in intelligent hydrogel formulation that can mimic tissues by changing their swelling and non-swelling mechanisms that directly contribute to their property as intelligent carriers that can be made use in pharmaceutical sciences.

Conflict of interest

The authors declare no conflict of interest.

Acronym

LMWHGs	low molecular weight hydrogelator

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Chapter 5

Sustained Drug Release from Biopolymer-Based Hydrogels and Hydrogel Coatings

Jon Andrade del Olmo, Virginia Sáez Martínez, Raúl Pérez González and José María Alonso

Abstract

Biopolymer based hydrogels are three-dimensional physically or chemically crosslinked polymeric networks based on natural polymers, with an intrinsic hydrophilic character due to their functional groups. They display high water content, softness, flexibility, permeability, and biocompatibility and possess a very high affinity for biological fluids. These properties resemble those of many soft living tissues, which opens up many opportunities in the biomedical field. In this regard, hydrogels provide fine systems for drug delivery and sustained release of drugs. Moreover, biopolymer based hydrogels can be applied as coatings on medical implants in order to enhance the biocompatibility of the implants and to prevent medical conditions. In this chapter we review the latest achievements concerning the use of biopolymeric physical and chemically crosslinked hydrogels as well as hydrogel coatings as sustained drug release platforms.

Keywords: sustained release, drug delivery, biopolymers, hydrogels, hydrogel coating

1. Introduction

Gels can be defined as three-dimensional cross-linked polymeric networks which swollen in contact with a liquid. When the polymers forming the gel contain mainly hydrophilic functional groups, the liquid that causes the swelling is water, and the gel is called hydrogel [1]. Biopolymers are often used for the synthesis of hydrogels as the natural composition of the polymer leads to extremely high biocompatibility and potential applications in the biomedical field [2].

Hydrogels can be classified as physical hydrogels when the properties of the gel depend on chain entanglements and other interactions, mainly hydrogen bonds or hydrophobic interactions [3]. In this case, properties are highly dependent on chain molecular weight as well as concentration, as mobility of the chains modifies the structure of the hydrogel and therefore its physical properties. Water temperature, salt content, and pH can also affect the mobility of the chains and interactions and must be controlled [4].

Chemically crosslinked hydrogels present a much more stable structure than physical hydrogels. In chemical hydrogels, the polymeric chains are covalently bonded

using one or more crosslinking agents, using a chemical process [5]. In general, crosslinked hydrogels are less biocompatible than physical hydrogels, but this is compensated by other advantages: cross-linked hydrogels are insoluble, more stable, and rheological properties such as elasticity or viscosity, their pore size, and their degradation rate can be more optimized than with physical hydrogels.

Hydrogels can present different physical forms: from macrogels to micro and nanogels, which are particulate systems with similar chemical structure but different macroscopic size; implantable gels, with strong physical properties, or injectable gels, more fluids or composed of nano-microparticles which can pass through a needle; hydrogel coatings, where hydrogel nano or microlayer is immobilized on a surface; thermoresponsive or pH-responsive gels, where a trigger modulates the sol–gel properties, can be easily injected in a liquid form before gelation in physiological conditions [6].

Physical properties of physically and chemically crosslinked hydrogels, are similar to several soft biological tissues, and therefore they can be used as substitutes or supplements when the biological function of these soft tissues is compromised. Such hydrogels have been widely used as medical devices for different applications: in traumatology, as substitute or supplement of synovial fluid in osteoarthritis; in ophthalmology, as a substitute of aqueous humor during in cataract surgery; in esthetics and reconstructive surgery, as dermal fillers for rid correction and lipoatrophy for patients with VIH; in wound healing, as wound dressings to promote regeneration and healing of wounds [7].

The biomedical use of the hydrogels can be expanded by the employ of the hydrogels as a sustained release system. Concerning this the controlled release of pharmaceutical ingredients leads to important advantages as a control of the biodisponibility, dose control, local delivery and less side effects [8]. This chapter aims to cover a general overview concerning the sustained drug release from hydrogels and hydrogel coatings. In that regard, *Section 1 Introduction* presents the topic and outlines the content of the chapter; *Section 2 Mechanism of drug release form hydrogels*, reviews the most significant theories on drug release mechanism; *Section 3 Drug release from physical hydrogels* summarizes the recent advances on the area; *Section 4 Drug release from chemically cross-linked hydrogels* revises the latest works on sustained release from chitosan, hyaluronic acid and other biopolymers; *Section 5 Drug release from hydrogel-based bioactive coatings* introduces the most relevant concepts on drug release form coatings; finally *Section 6 Conclusion* synopsizes the content of this chapter.

2. Mechanism of drug release form hydrogels

The release of drugs from hydrogels can be achieved by different mechanisms such as swelling/deswelling, diffusion, and chemical mechanism. As previously mentioned, hydrogels are three-dimensional crosslinked polymeric networks that swelled in the presence of water. The crosslink can be physical (hydrophobic interactions, electrostatic interactions and hydrogen bonding) or chemical (covalent bonding) and is responsible of the network structure of the hydrogel. Such networks display open spaces, the size of which is referred to as the mesh size of the hydrogel [9]. Importantly, the mesh size of the hydrogels is one of the main parameters that affect how drugs diffuse through the hydrogel network, being dependent on polymer and crosslinker concentrations, as well as external stimuli. The gelation of hydrogels

by polymerization means leads to network irregularities and polymer polydispersity upon formation, and as a result, the mesh size is usually heterogeneous. A number of approaches exist to determine the mesh size [9].

When the mesh is larger than the drug ($r_{mesh}/r_{drug} > 1$), the drug release process is dominated by diffusion. Small drug molecules migrate freely through the network, and diffusion is largely independent of the mesh size. The diffusivity, D, in this situation depends on the radius of the drug molecule (r_{drug}) and the viscosity of the solution (η) via the Stokes–Einstein equation Eq. (1) [10]:

$$D = \frac{RT}{6\pi\eta r_{drug}} \tag{1}$$

where R is the gas constant and T is the absolute temperature.

When the mesh size is close to the drug size ($r_{mesh}/r_{drug} \approx 1$), the effect of steric hindrance on drug diffusion becomes relevant. Finally, for an extremely small mesh size and/or very large drug molecules ($r_{mesh}/r_{drug} < 1$), strong steric hindrance immobilizes the drugs and it remains physically entrapped inside the network, unless the network degrades or the mesh size expands in response for example, to external stimuli.

Several methods accompanied by mathematical model development have been created in parallel to hydrogel technology, in order to predict drug release from the network. The drug release fitting models (i.e. the zero order equation; the first order equation; the Higuchi's equation; the Korsmeyer-Peppas' equation; the Hixon-Crowell's equation, the Weibull equation, among others) are the most abundant, however, they are not predictive but simple mathematical fitting equations. In the last years, mechanistic and statistical models are growing quite fast. Mechanistic models combining the mass transport with the system mechanics developed with a "fully coupled" approach considers the influence of the mass transport on the mechanics as well as the opposite, which makes this approach the only candidate to produce reliable first-principle models.

Statistical models, are receiving a lot of attention due to the consensus of the regulatory authority and the possibility to predict the hydrogels behavior, in the analyzed design space, regardless the complicate phenomenology, with quick and inexpensive experimental designs [11]. Recently, Wu and Brazel developed a method for the simulation of water uptake profile and drug release from homogeneous hydrogels. This model successfully predicted the initial burst release observed experimentally [12]. Sheth et al. developed a mathematical and computational model using time snapshots of diffusivity and hydrogel geometry data measured experimentally as inputs to predict release profiles of two model proteins of varying molecular weights from degradable hydrogels [13].

3. Drug release from physical hydrogels

Physical hydrogels are those formed by reversible and dynamic crosslinks grounded on noncovalent interactions. In this regard the network of physical hydrogels is reversibly held together by molecular entanglements, resulting from a dynamic competition between pro-assembly forces (for example, hydrophobic interactions, attractive electrostatic forces and hydrogen bonding) and anti-assembly forces (for example, solvation and electrostatic repulsion [3]. These interactions that occur in

this type of hydrogels are usually weak. However, they are numerous and contribute to the presence of complex behaviors.

Polyampholytes may also be used to construct physical hydrogels, with randomly dispersed cationic and anionic groups. The randomness leads to a wide distribution of strengths: The strong bonds serve as structural crosslinks, imparting elasticity, whereas the weak bonds reversibly break and re-form, dissipating energy. Consequently, physical hydrogels have reversible liquid to solid transition, also called sol–gel transition, in response to different changes in environmental conditions such as temperature, ionic strength, pH, or others [14]. Since the interactions depend significantly on external stimuli, they allow hydrogels to be highly versatile concerning the environment, unlike covalently bonded materials [15].

Physical hydrogels can be engineered to undergo spontaneous biodegradation under physiological conditions, which constitutes another way of controlling the release of active molecules [16]. Degradation is typically mediated by hydrolysis [17, 18] or enzyme activity [19]. The erosion or loss of polymer mass through degradation, can take place simultaneously in the bulk or on the surface of the hydrogel. For a variety of hydrogels, the bulk and surface erosion can be tuned to obtain desirable release kinetics ranging from weeks to months. Bulk erosion occurs because of the permeability to water or degrading enzymes when the rate of diffusion of these agents is rapid compared to the rate of bond degradation. Surface erosion, in contrast, results when the rate of bond breakage is more rapid than the rate of enzyme or water diffusion from the exterior into the bulk of the gel [13].

Representatives of reversible physical hydrogels are the shear-thinning hydrogels which flow like low-viscosity fluids under shear stress during injection, but quickly recover their initial stiffness after removal of shear stress in the body [3]. Alginate hydrogels are shear-thinning, formed via electrostatic interactions between alginate and multivalent cations (for example, calcium and zinc). They can be readily injected via a needle after gelation in a syringe and have been used to achieve sustained local delivery of bioactive vascular endothelial growth factor (VEGF) in ischemic murine hindlimbs for 15 days [20, 21].

3.1 Peptide based physical hydrogels

Another example of physical hydrogels forming materials are the self-assembling peptide systems, where amino acid-based chains undergo the sol–gel transition without the need of any chemical crosslinking agent. This property makes them useful materials to safely in situ encapsulate living cells or sensitive drugs, among others. In addition, this peptide-driven self-assembly into physical hydrogels is highly specific, sourced mainly by the biorecognition of peptide segments scattered among the macromolecular chains. They form dynamic well-defined, hierarchically organized 3D structures with reversibility of the assembly and disassembly processes [22]. Another example are elastin-like polypeptides cross-linked via electrostatic interactions between their cationic lysine residues and anionic organophosphorus cross-linkers [23]. Non-covalent interactions between heparin and heparin-binding peptides and proteins can also be used to form hydrogels for growth factor delivery [24, 25].

Peptide self-assembly can also be achieved by taking advantage of interactions between metal cations and amino acid residues of the peptides. This was demonstrated with gelation of a β-sheet-rich fibrillar hydrogel with zinc ions [26].

3.2 Chitosan based physical hydrogels

Additional interesting example of physical hydrogels for drug release applications are pectin-chitosan hydrogels, which showed to be thermo-reversible and capable of prolonging the release of three different model hydrophobic drugs: mesalamin, curcumin and progesterone. In vitro drug-release studies revealed that lower percentage of pectin in the hydrogel led to slower release rates owing to smaller mesh size arising from stronger interactions between the polyelectrolytes. Also, the release was slower when the total polymer concentration was higher. Finally, a slower release in PBS solution compared to HCl solution was attributed to the fact that at pH 7.4, both polymers are charged, with strong electrostatic forces and consequently, smaller mesh size. At the molecular scale, the polymer chains can possess abundant binding sites for the drugs. DSC and FTIR analysis exhibited some interactions between the drugs and both chitosan and pectin that can contribute to the prolonged release of the drugs [27]. Another in situ-gelling hydrogel was formed with a polyelectrolyte complex, which showed a sustained release of insulin and avidin proteins [28].

4. Drug release from chemically cross-linked hydrogels

Crosslinking of biopolymers provide a stable and non-soluble biomaterial which preserves the properties of the original biopolymer and displays a longer durability. Consequently, the half-life time of the hydrogels is increased when performing its biological application [5].

Usually, biopolymer crosslinking can be accomplished in two ways: by direct addition of a cross-linking agent followed by formation of a the three-dimensional (3D) network, or by chemical modification of the biopolymer chains with functional groups suitable for crosslinking with a compatible cross-linker. The first approach takes advance of the functional groups already present in the biopolymer, typically amine (NH_2), hydroxyl (-OH), carboxylic acid (-COOH), amide (-CONH-, $-CONH_2$), thiol (-SH) or sulfate ($-SO_3H$) groups [29]. Examples of cross-linkers are dialdehyde derivatives, NH_2-PEG-NH_2 molecules, COOH-PEG-COOH derivatives, diglycidyl ether compounds, vinyl sulfone groups, etc. These agents cross-link through Michael-type addition, thiol exchange/disulfide cross-linking or Schiff-base processes among others [30]. In some case the addition of coupling agents such as carbodiimides derivatives, N-hydroxysuccinimide (NHS) or N-hydroxybenzo triazole (HOBt), is required for the cross-linking. In the second approach new active functionalities are created in the biopolymer [31, 32] which are appropriate for a broad range of cross-linking processes such as azide–alkyne cycloadditions, Diels–Alder reactions, ultraviolet (UV) photoinitiated crosslinking, (meth)acrylation reactions [5, 32]. Examples of cross-linkers are oxanorbornadiene, cyclooctyne, maleimide, trans-cyclooctene, norbornene, PEG-di(meth)acrylates among others.

The crosslinking of biopolymers produces hydrogels with elastic and deformable structures and great topochemical accessibility which is able to accommodate different kind of active molecules, such as drugs, for sustained release (**Figure 1**).

4.1 Chitosan based chemically crosslinked hydrogels

Chitosan (CHI) is a linear polysaccharide formed by arbitrarily allocated β-(1 → 4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine

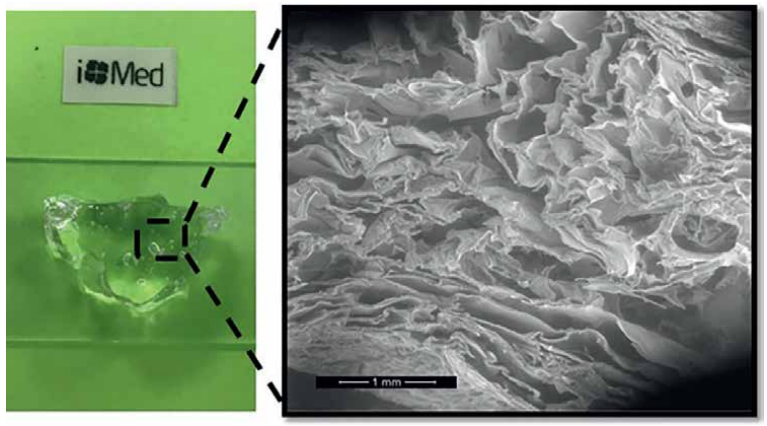

Figure 1.
Left: Image of a hydrogel based on crosslinked hyaluronic acid. Right: Scanning electron microscopy (SEM) picture of the hydrogel. Figure produced by the authors.

(acetylated unit). Chitosan is one of the most versatile biopolymers due to its unique properties: biodegradability, biocompatibility, non-toxicity, antioxidant, anti-inflammatory, antifungal, and antibacterial "contact killing" [33]. Therefore the applicability of this polysaccharide extends to a wide range of various biomedical areas, such as cosmetics, drug delivery, and tissue engineering, among others [34].

In this regard a covalently crosslinked chitosan hydrogel was produced Diels Alder reaction of furan and maleimide functionalized CHI. The resulting biopolymer held the typical pH sensitivity and antibacterial properties of non-functionalized CHI. The drug delivery capabilities of this system were evaluated with model drug antibiotic chloramphenicol (ClPh). Drug release experiment did not show an initial burst, which indicated that the ClPh was successfully encapsulated, whereas it displayed a sustained delivery of the drug with a complete release of the total amount of drug loaded (2.61 ± 0.036 mg ClPh/g hydrogel) after 4 hours [35].

CHI was also crosslinked with genipin (GP) to obtain biocompatible, antibacterial and anti-inflammatory hydrogels with wound healing properties. Sustained release of acetylsalicylic acid (ASA), cefuroxime (CFX), tetracycline (TCN) and amoxicillin (AMX) from the hydrogels displayed a Pharmacologic Half Life t1/2 values of 88 h, 62 h, 135 h, and 240 h for ASA, CFX, TCN and AMX respectively. These antibiotic releases generated antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* that reached almost 100% bacterial reduction and an antibacterial efficacy R > 2. The synergistic anti-inflammatory activity was confirmed by the reduction in the amount of pro-inflammatory cytokines when ASA was mixed with CFX (5.39 ± 0.81 ng·mL^{-1} TNF-α), TCN (4.70 ± 0.21 ng·mL^{-1} TNF-α and 49.06 ± 9.64 ng·mL^{-1} IL-8), and AMX (2.28 ± 0.36 ng·mL^{-1} TNF-α, 14.84 ± 5.57 ng·mL^{-1} IL-8, and total IL-6 removal) [36].

Moreover, dialdehyde-β-cyclodextrin (DA-β-CD) crosslinked carboxymethyl chitosan (CMCS) hydrogels were prepared from carboxymethyl chitosan (CMCS) and periodate oxidized β-CD. Phenolphthalein (PhP), a formerly used laxative agent, [16] was selected as a model molecule to investigate the drug loading and sustained release capabilities of such hydrogels. PhP release results show that increasing crosslinking rate between DA-β-CD and CMCS delays the drug liberation process. On the other hand, DA-β-CD/CMCS system displays faster releases, with a 50% release in 2 h

and about 90% within 12 h, compared to CMCS crosslinked with glyoxal dialdehyde which only releases 19% of PhP after 24 h [37].

CHI based hydrogels (N-succinyl chitosan-g-Poly(acrylamide-co-acrylic acid) were synthesized by free radical mediated cross-linking of N-succinyl chitosan, acrylamide and acrylic acid [38]. Drug delivery capabilities of the system were tested by encapsulation of theophylline, a phosphodiesterase inhibiting drug used for the treatment of respiratory diseases. The drug release experiments showed a pH dependent behavior. In this regard, at pH 1.2 the theophylline released rate was found to be between 14 and 24% whereas at pH 7.4 the release of the drug reached 67–93%. CHI itself has been used as a cross-linking agent for poly(acrylic acid). The resulting hydrogels display pH sensitive properties that have been exploited to control the release of antibiotic amoxicillin and anti-inflammatory drug meloxicam. Concerning this, the release rates of these molecules rise with increasing pH due to the disruption of hydrogen bonds between the hydrogel components and the drugs. As a result 30%, ~60% and ~80% of amoxicillin is released after 800 min at pH 1.2, 6.8 and 7.4, respectively. The corresponding release data for meloxicam are ~20%, ~70% and ~90% at pH 1.2, 6.8 and 7.4, respectively [39].

4.2 Hyaluronic acid based chemically cross-linked hydrogels

Hyaluronic acid (HA) is a non-sulfated glycosaminoglycan constituted by repeating disaccharide β-1,4-D-glucuronic acid–β-1,3 N-acetyl-D-glucosamine units that form hydrogels in aqueous solutions. This naturally occurring polysaccharide is found in connective tissues, skin, and synovial joint fluids of the human body. HA displays bio-functionality, biocompatibility, and physicochemical properties, such as viscoelasticity and high-water retention. As a result hyaluronic acid is used for the treatment of dry eye disease, dermatological conditions as well as a as a viscosupplement for the treatment of osteoarthritis [5].

Biocompatible antibacterial hydrogels of HA were synthetized by crosslinking HA solution with divinyl sulfone (DVS) followed by loading with antibiotic molecules. This way cefuroxime (CFX), tetracycline (TCN) and amoxicillin (AMX) loaded hydrogels displayed in vitro antibacterial activity against S. aureus. The antibacterial properties of the hydrogels were synergically enhanced by merging antibiotics with anti-inflammatory agent acetyl salicylic acid (ASA). Consequently it was observed an increase in the log10 reduction value (R) from 3.2, in the absence of ASA, to R 5.55 when TCN or CFX were combined with ASA [40].

Hyaluronic acid was crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and loaded with quetiapine (QTP), an antipsychotic drug, and quercetin (QCT), a hyaluronidase (HAase) inhibitor that decreases the biodegradation of HA. Subcutaneous injection in rats of the system showed that the cHA hydrogel with QCT exhibited a lower maximum QTP concentration (Cmax. 782.6 ± 174.4 ng/mL) and longer half-life (t1/2 23.5 ± 2.7 h) and mean residence time values (MRT 30.9 ± 3.9 h) compared to the hydrogel without QCT (Cmax. 1827.6 ± 481.3 ng/mL, t1/2 13.4 ± 4.9 h, MRT 14.3 ± 4.8 h). These results demonstrated that HAase containing HA hydrogels are suitable systems for sustained drug delivery applications [41].

A thiol functionalized hyaluronic acid HA-SH was used, together with DMSO, for the fabrication of HA-SS-HA hydrogels. This system was loaded with antitumoral drugs such as doxorubicin (DOX), zinc phthalocyanine (ZnPc), and indocyanine green ICG, for implant post peritumoral administration. In vivo experiments validated that drug loaded hydrogel implant possessed satisfactory biocompatibility and

succeeded in long term sustained release of drugs. As a result the system to ensured high tumor aggregation efficiency and adequate tumor suppression [42]. Hyaluronic acid (HA) functionalized with thiol and hydrazide moieties has been combined with oxidized sodium alginate (ALG)to produced cross-linked hydrogels (HA/ALG). These materials display tunable physicochemical properties and drug release behavior as a function of the HA/ALG precursor concentration. In this regard for HA2/ALG2 (2% w/v), HA3/ALG3 (3% w/v) and HA4/ALG4 (4% w/v) the yield stress of hydrogels were 1724, 4349 and 5306 Pa, and the degradation percentage were about 64%, 51%, and 42% after 35 days incubation, respectively. Thus, in vitro cumulative release of Bovine serum albumin (BSA) for HA2/ALG2, HA3/ALG3 and HA4/ALG4 were 79%, 72%, and 69% respectively for a 20 day release assay [43].

Near-infrared (NIR) light-triggered and reactive oxygen species (ROS)-degradable hyaluronic acid hydrogels (HPTG) were synthesized through the formation of dynamic covalent acylhydrazone bonds. Such system was loaded with photosensitizer protophorphyrin IX (PpIX) and anticancer drug doxorubicin (DOX), to obtain a with light-tunable on-demand drug release for chemo-photodynamic therapy. In this regard NIR light irradiation generated ROS that induced the required degradation of hydrogel and subsequent on-demand DOX release for cascaded chemotherapy. In vivo imaging-guided antitumor study using 4 T1 tumor- mouse model demonstrated that the treatment of DOX-loaded HPTG with laser irradiation nearly accomplished the suppression of tumor growth without noticeable regrowth [44].

Tyramine functionalized HA solutions were combined silk fibroin (SF) to produce a series of HA/SF hydrogels for application in cartilage tissue engineering an and drug delivery. These hydrogels were loaded with Vanillic acid (VA) or Epimedin C (Epi C), both with anti-catabolic, anti-inflammatory and anabolic effects on human cartilage cells. Hydrogels with HA20/SF80 polymeric ratios displayed the longest and the most sustained release profile with 70.1% release of VA after 60 days of release assay and 54% release of Epi C after 7 days of release. Such behavior makes HA20/SF80 hydrogels a prospective material for the treatment of osteoarthritic joint conditions [45].

Polyethylene glycol (PEG)-HA was modified also with a small biologically active molecule, as dopamine, to fabricate a HD-PEG polymer. This polymer was crosslinked with α -cyclodextrin (α-CD) to afford a polypseudorotaxane supramolecular complex HD-PEG/α-CD. The system was loaded with poly(lactic-co-glycolic acid) (PLGA)/ donepezil microspheres (PDM) in order to evaluate the drug delivery capabilities of the system. The released amounts of donepezil, a drug used for the treatment of mental conditions, reaches 39.9% and 56.7%, after 7 and 14 days respectively. These results demonstrate that the HD-PEG/α-CD/PDM system could be used for the subcutaneous injection of long acting donepezil [46]. Similarly, poly(L-lactide-co-glycolide) (PLGA) – dexamethasone (DEX) nanoparticles PLGADEX were combined with crosslinked HA for drug release applications. In this case the chemical crosslinking occurred doubly, by mixing amino-hyaluronic acid and aldehyde-hyaluronic acid in the presence of genipin as a cross-linker agent. Drug delivery experiments showed full DEX release after 2 months for a HPLGADEX hydrogel [47].

Oxidized hyaluronic acid (OHA) was combined with carboxymethyl chitosan (CMC) via Schiff base reaction to fabricate a hydrogel (OHA-CMC) with antibacterial and hemostatic activities. The drug delivery potential of the system was exploited by encapsulating PLGA-PEG nanoparticles of curcumin (CNP) and epidermal growth factor (EGF) that afforded a OHA-CMC/CNP/EGF hydrogel. This system displayed outstanding anti-inflammatory, antioxidant and cell migration-promoting effects *in vitro* and improved wound healing *in vivo* with optimal granulation tissue

formation, re-epithelialization, and skin appendage regeneration. The cumulative release percentage of CNP reached 55.3% on day 1, 75.5% on day 3 and ~ 90% after 6 days of release experiment. EGF displayed a 28.6% of release on day 1, 51.3% on day 2 and 88.1% in 9 days. These results demonstrate the potential of the hydrogel for the treatment of diabetic wound healing [48].

Finally, HA has been used as well as a biopolymer for the fabrication of a 3D printable dual-network hydrogel with drug delivery capabilities. For that acrylamide-modified HA was synthesized and subsequently mixed with folic acid and Fe3+ to form a physical crosslinking network. Afterwards acrylamide residues were polymerized by ultraviolet radiation affording a material suitable for wound dressing with high elasticity and fatigue resistance. The drug delivery properties were investigated using acetylsalicylic acid (ASA) as a drug model and resulted in a pH responsive hydrogels with the sustained release of ASA over 300 hours [49].

4.3 Other chemically cross-linked biopolymers

Lignin is a sustainable biopolymer derived from lignol precursors that has been historically related to the paper industry. Hydrogels of hardwood lignin (TCA) have been synthesized through crosslinking with poly(ethylene) glycol diglycidyl ether (PEGDGE) and loaded with paracetamol for drug release applications. Here, decreasing amounts of crosslinker diminishes the interaction paracetamol - hydrogel network and, as a result, the release of paracetamol increases. In this regard, hydrogels produced with a lignin:PEGDGE 1:1 ratio displayed up to 30% of paracetamol release after 120 h assay. The release data follow a pseudo-Fickian behavior of diffusion when fitted to the Korsmeyer-Peppas model [50]. Furthermore, lignin polymers have been mixed with cellulose to generate drug delivery systems. Mechanical and sustained release performances of these gels are tailored by varying the ratio of the precursors: cellulose, hardwood lignin (TCA), and epichlorohydrin (ECH) cross-linker. TCA containing hydrogels display the best release rate (>90%) for drug model paracetamol comparing to the pure cellulose hydrogels (~40%) after 7 hours of release experiment. This behavior is attributed to the lower affinity of paracetamol for lignin compared to cellulose [51].

Cellulose itself have been used for the fabrication of hydrogels with drug release properties. In this regard, carboxymethyl cellulose (CMC) functionalized with β-cyclodextrin and nucleic acids have been crosslinked by using of arylazopyrazoles (AAPs) and loaded with anti-cancer molecule Doxorubicin (DOX). The resulting hydrogel behaves as a functional matrix for the UV light mediated ON/OFF release DOX. Irradiation of the matrix provokes the photoisomerization of the trans-AAP to cis-AAP residues and the generation of the low-stiffness hydrogel that releases DOX. Therefore, the liberation of the DOX could be changed between ON and OFF states by oscillating the photoisomerization of the hydrogel by employing UV/Vis irradiation [52].

Xanthan is a heteropolysaccharide produced by fermentation from the bacteria *Xanthomonas campestris* with applications as thickening agent in food industry as well as pharmaceutical aid and release retarding polymer in drug delivery systems [53]. Hydrogels form this biopolymer have been produced by crosslinking oxidized xanthan, with a PEG hydrazine derivative through pH-responsive hydrazone linkages. The drug delivery properties of the hydrogel were assessed by performing release studies of the antitumoral drug Doxorubicin (DOX), at pH 5.5 (tumoral) and 7.4 (physiological). At pH 5.5 the cumulative release of DOX from 3, 4, and 5% hydrogels was 81.06, 61.98, and 41.67% respectively whereas the release at pH 7.4 was 47.43, 37.01, and 35.34% after 30 days of assay. Moreover DOX-loaded hydrogels possessed cytotoxicity against

A549 cells after exposure to DOX containing released media [54]. Curdlan is another example of polysaccharide produced by fermentation and with applications in the food industry. Phosphorylated curdlan (PC) was crosslinked with,4-butanediol diglycidyl ether (BDDE) and loaded with tetracycline (TCN) to fabricate hydrogels with drug delivery applications. Drug release profiles at equilibrium release (3.5 h), pH 6.8, 37°C reached 87% for hydrogels produced exclusively from phosphorylated curdlan (PC), whereas release from curdlan hydrogels achieved 48% of release [55].

Casein is a proline-rich, open-structured protein found in raw milk. It displays high hydrophilicity, good biocompatibility and a lack of toxicity that makes of it a potential candidate for hydrogel development. Casein can be chemically cross-linked with enzymes such as microbial transglutaminase (MTG). This feature was utilized to produced crosslinked casein -γ-polyglutamic acid (PGA) hydrogels in 1/5 and 1/9 ratio. Drug release experiments showed that both composition displayed similar release rate values for aspirin (~ 100% after 10 h), while 1/9 hydrogels possessed a higher release rate for vitamin B12, ~100% after nearly 12 h versus ~20% for 1/5 casein/γ-PGA hydrogels [56].

5. Drug release from hydrogel-based bioactive coatings

Historically, the development of medical implants has been a great concern for biomedical community. Besides, their need has risen dramatically due to the increased number of surgical procedures that are predicted to be even higher in 2030 [57]. Thus, improving the performance of implantable biomaterials has become a high-priority trend, which is reflected in the large number of research realized to successfully meet the upward demand [58].

Implantable medical devices (e. g. coronary stents, cardiac pacemakers, prostheses, insulin pumps) are classified in four main groups: ceramics [59], polymers [60], composites [61], and metals [62]. Among them, metallic biomaterials as titanium and its alloys are of outmost interest thanks to their inert chemical and biological behavior *in vivo* [63]. Even so, their bioactivity can be improved creating coatings by surface modification techniques and thereby, add other beneficial properties [64].

The use of these bioactive coatings entails the development of an improved version of bioactive materials that modulates biological systems response by the establishment of interactions with adjacent tissues and bones [65]. Nevertheless, these coatings require the most suitable physicochemical, mechanical, and biological functionality for a successful implantation and integration so as not to produce any counterproductive disorder in humans [66]. Therefore, it is imperative to develop functional bioactive coatings onto the surface of biomaterials (**Figure 2**, produced by the authors) that combine biocompatibility [67], antibacterial [68], anti-inflammatory [69], self-healing [70], wound healing [71], bone tissue engineering [72], and osseointegration [73] properties.

Such features can be incorporated onto the surface of biomaterials by the use of biopolymer-based coatings, mostly based on hyaluronic acid and chitosan [74]. Moreover, these coatings acquire hydrogel-like three dimensional microstructure after crosslinking for bioactive agents delivery applications (**Figure 3**, produced by the authors). In such manner, bioactive properties that already possess biomaterials can be upgraded or even provide novel outstanding properties [75]. Specifically, hydrogel coatings take advantage of hydrogels peculiar ability of releasing in a controlled space–time manner to the therapeutic target the entrapped bioactive agents (drugs, proteins, peptides, growth factors, inorganic or polymeric nanoparticles, and nucleic acids) through their polymeric network [76].

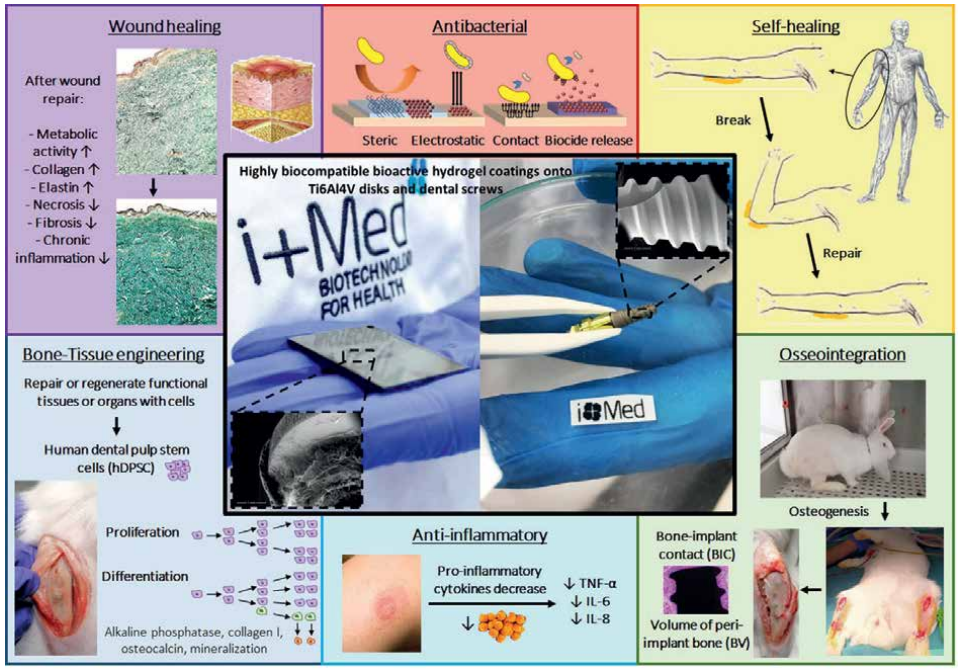

Figure 2.
Bioactive properties of functional hydrogel coatings for biomaterials successful implantation. Figure produced by the authors.

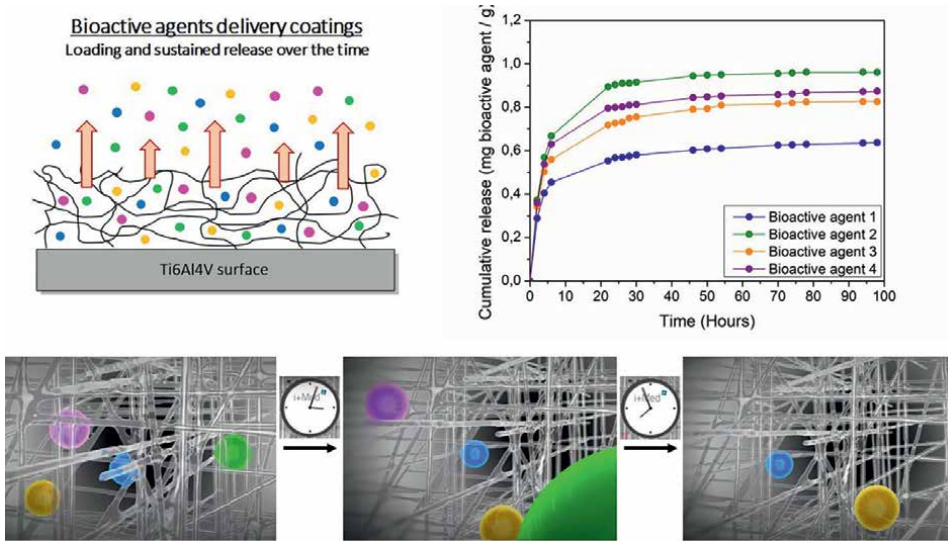

Figure 3.
Bioactive agents loading and controlled release ability from hydrogel-based coatings. Figure produced by the authors.

Bioactive agents controlled delivery reduces side effects in patients undergoing implant procedures. In addition, highly stable (from hours to months) hydrogel coatings with great loading ability provide a not sudden, uniform, and prolonged

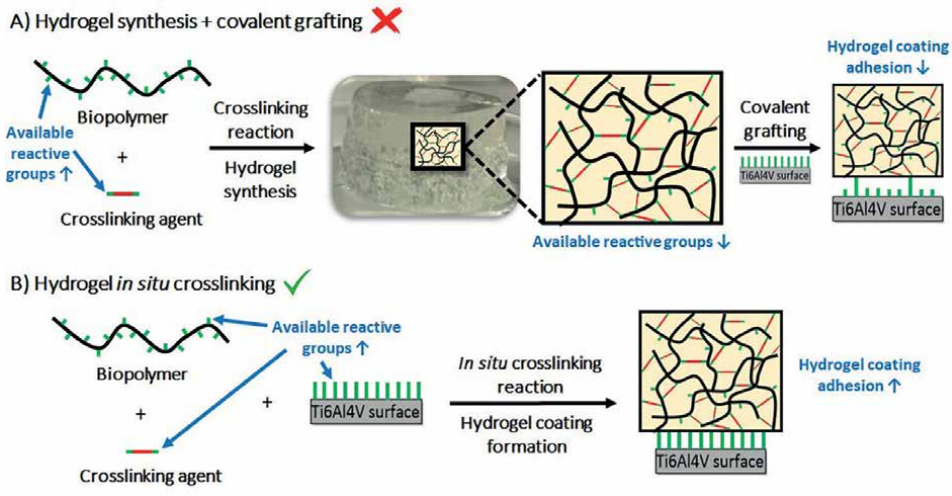

Figure 4.
A) Conventional and B) in situ crosslinking strategies to form hydrogel coating onto the surface of biomaterials. Figure produced by the authors.

release of specific low- to high-doses [77]. This way, therapeutic effect of bioactive substances is extended, and the over-excessed concentration peaks of conventional methods are diminished. These features endow hydrogel coatings with privileged pharmacokinetic profiles, which can be modulated for personalized therapies [78]. Further, hydrogel coatings do not need to modulate specific linkages to release bioactive agents since their release mechanisms are mainly governed by simple diffusion, swelling, and degradation processes [79].

Nowadays, researchers are focusing their attention is the hinder of hydrogel coatings attachment to surfaces, which occurs due to hydrogels excessively huge swelling and macroscale thickness. One promising alternative approach to create highly adhesive hydrogel coatings with strong and resistant hydrogel-surface attachment is the *in situ* hydrogel crosslinking onto the surface of biomaterials (**Figure 4B**, produced by the authors) [80]. This way, hydrogel crosslinking and hydrogel coating formation occurs almost at the same time, and thereby, all the active groups available in the structure of biopolymers react equitably with crosslinking agent and surface. Conversely, the conventional strategy of first synthesizing hydrogel followed by covalent grafting to the surface (**Figure 4A**, produced by the authors) limits hydrogel-surface adhesion since hydrogel formation consumed almost entirely reactive functional groups and therefore, few of them remain available for the subsequent linkage formation the surface. Additionally, although this method requires purification steps to eliminate toxic unreacted monomers, crosslinkers and initiators, common dialysis processes are used to easily remove these harmful molecules from coatings before their biomedical real-life application [1].

6. Conclusions

The number of works related to the development of novel biopolymer-based hydrogel systems, mainly those synthesized with hyaluronic acid and chitosan,

that promote the sustained release of bioactive agents increases year by year. In the current chapter we have summarized the recent accomplishments of biopolymer based physical and chemically crosslinked hydrogels, as well as hydrogel coatings for drug delivery and sustained release applications. The future perspectives in this field involve the development of hydrogel based medicines with specific temporal and spatial controlled release of drugs. Such medicines afford dose control, local delivery and reduced side effects that increase the efficacy and security of the treatment and the adherence of the patient to it. This strategy will lower pharmaceutical costs and improve the quality of life of the patient and the society overall.

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Conflict of interest

All the authors are employees of the company i+Med S. Coop.

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Chapter 6

Hybrid Hydrogels with Stimuli-Responsive Properties to Electric and Magnetic Fields

Jose Garcia-Torres

Abstract

Hydrogels are a promising type of soft material featuring great similarity to biological tissues due to their inherent characteristics, such as high-water content, flexibility, softness, or low elastic modulus. Imparting multifunctionality to hydrogels to be triggered by external stimuli is considered to have a high potential for innovative application in the biomedical field by regulatory agencies, such as FDA and EMA. Thus, functional hybrid systems based on the combination of nanomaterials and hydrogels are a new class of materials offering new opportunities for living organisms-machine interfacing for application in a wide variety of fields ranging from biomedical engineering to soft robotics, soft electronics, environmental or energy science. The objective of this chapter is to review the latest advances in multifunctional hybrid hydrogels with responsiveness to electric and magnetic fields and with applications in the biomedical field.

Keywords: hydrogels, nanomaterials, hybrid composites, stimuli-responsive, electric and magnetic field

1. Introduction

Human body is a complex system where multiple processes and reactions take place simultaneously to give an efficient system. A lot of functions in the body are regulated by chemical substances (e.g., proteins) but also by physical (e.g., electric fields, temperature, light, etc.) and mechanical stimuli, such as neuronal communication, embryo development, tissue repair after an injury, or heartbeat [1–3]. Scientists and engineers have been inspired by the natural world in general, but in the human body in particular, to develop materials with new functionalities and unique skills [4, 5]. Recently, hydrogels have been revealed as a promising new class of materials due to their intrinsic properties, such as high-water contents, high porosity, flexibility, or biocompatibility, showing great similarities to biological systems as a result of the 3D porous polymeric structure [6, 7]. Hydrogel flexibility and elasticity are important to diminish the mechanical mismatch with living systems; meanwhile, the high-water contents provide a humid environment rich in ions, such as biological media. Hydrogels also show some other interesting properties, such as self-healing

and self-adhesive capacity, biocompatibility, and biodegradability [8, 9]. For all those reasons, hydrogels have been suitable for different biomedical applications, such as wound healing [10], passive drug delivery [11], or contact lenses [12]. However, one of the main drawbacks of hydrogels is the lack of bioactivity.

To overcome hydrogel's inertness, hydrogels can be successfully modified with nanomaterials (e.g., metallic nanoparticles and carbon nanomaterials) to develop smart nanocomposite hydrogels with improved functionality [13–15]. Thus, nanomaterials can improve the mechanical properties of the nanocomposite hydrogels (e.g., stiffness, toughness, and ductility) but also confer physical properties (e.g., electrical conductivity, magnetism, thermal properties, etc.) to be able to respond to different stimuli, such as electric and magnetic fields, temperature, pH, light or biomolecules, among others. Hydrogel's response is based on phase changes, change in stiffness, or change in volume in response to those stimuli [16]. These nanocomposite hydrogels, named as smart, intelligent, or stimuli-responsive, are being applied in a wide range of applications including bioelectronic devices (e.g., biosensors) [17, 18], energy and environmental science [19, 20], soft robotics [21, 22], or regenerative medicine [23, 24], with promising advances in all those fields. Moreover, these stimuli-responsive hydrogels show the capacity to respond in a reversible and controllable way to different stimuli but also to adapt and conform onto curvilinear and dynamic surfaces improving their performance [25].

Due to the different length scales and physicochemical properties of the two main components of the stimuli-responsive composites—hydrogels, nanomaterials-, hybrid hydrogels with variable and tunable designs are being possible. Hydrogels have similar mechanical properties to biological tissues and they also mimic several features of the extracellular matrix. They also have compliant and permeable structures that can be modified to suit the requirements to create not just a physical but also a chemically favorable environment [6, 7]. To obtain the characteristic three-dimensional hydrogel networks, with the abovementioned innate properties making them very interesting in comparison to other polymer groups, it is required to transform the liquid viscous precursor solution to the final gelled material by inducing crosslinking. The liquid-gel transition can be achieved either via physical (e.g., ionic crosslinking) or chemical (e.g., photo-crosslinking), leading to the formation of non-covalent and covalent hydrogels, respectively. Moreover, hydrogels can be classified as natural and synthetic depending on the source used to fabricate them [26]. Natural polymers have high interest due to their inherent biocompatibility, low toxicity, and biodegradability. There are two main types, polysaccharides and fibrous proteins that are both components of the extracellular matrix, such as alginate (Alg), chitosan (CS), or collagen (Col), among others. Synthetic polymers, such as poly(ethylene glycol) (PEG), poly-(N-isopropylacrylamide) (PNIPAAM), poly(vinyl alcohol) (PVA), or poly(hydroxyethyl methacrylate) (PHEMA), have controllable and good mechanical properties but they lack bioactivity to promote cell-material interaction, the reason why they are required to be modified. On the other hand, the nanometric size of nanomaterials (<100 nm at least in one dimension) confers them higher specific surface areas compared to their bulk counterparts and very unique physical properties as they are size-dependent, such as the electronic, magnetic, and optical properties, due to the quantum size effect [27]. Nanomaterials are very versatile since they can be synthesized using different materials (e.g., metals and metal oxides, carbons, polymers, etc.), sizes (e.g., 0–100 nm), and shapes (e.g., nanoparticles, nanowires, nanotubes, 2D layers, etc.) and can be modified by combining different materials (e.g., core-shell structures)

or functionalized with biomolecules (e.g., peptides, enzymes) [28]. However, some requirements are needed for their application in the biomedical field, such as biocompatibility, non-cytotoxicity, and stability in biological media [29].

Stimuli-responsive hydrogels are able to respond to different stimuli that can be classified as endogenous—pH, enzymes, antigen—or exogenous—light, electric field, magnetic field—depending on if they are present at the implantation site or not, respectively. However, the most common form of classification is as chemical or physical stimuli if the changes in the hydrogels are induced by chemical entities (e.g., molecules and biomolecules) or physical variables (e.g., temperature, light, electricity, etc.). Chemical stimuli include molecules and biomolecules present in the environment where the hydrogel will be located. For example, reactive oxygen species (ROS) are generated in wounds, bacterial infections, or tumors creating a more oxidation environment. Or pH values are lower in cancerous cells than in normal cells due to abnormal metabolism. Thus, chemically responsive hydrogels must be designed to respond to changes in those (bio)molecules that sometimes are very low, making the development more difficult. Meanwhile, physical stimuli include magnetic and electric fields, temperature, light, or ultrasounds. Among them, electrically- and magnetic-responsive hydrogels have been widely researched as they have the advantage to be remotely and non-invasively operated even in narrow and small areas. Moreover, the use of adjustable electric (e.g., voltage) or magnetic (e.g., field intensity) signals as stimulation sources make them even more interesting to develop hydrogels with reversibility and controllability compared with, for example, pH or temperature-responsive hydrogels. Thus, stimuli-responsive scaffolds capable of responding to either electric or magnetic fields have emerged as a promising technology for biomedical applications, including drug delivery systems, tissue regeneration, or soft actuation. For this reason, in this chapter, the author will focus on electrically- and magnetic-responsive hydrogels.

2. Electrically-responsive hydrogels

Electroresponsive hydrogels have been the most studied among the physically stimuli-responsive hydrogels due to their broad applicability in many fields, such as bioelectronics (e.g., sensors), bioengineering (e.g., drug delivery systems and actuators), tissue engineering (e.g., bone regeneration), or soft robotics applications. They are able to undergo changes in their shape and size when swell/deswell under the application of an electric field. Very briefly, the deformation generated by the electric field can be explained by a combination of Coulombic, electrophoretic, and electroosmotic interactions. As a result of the migration of mobile ions from the electrolyte under the applied field, the generated osmotic pressure increases or decreases causing hydrogel swelling or deswelling, respectively [30, 31]. Electrical conductivity has been conferred to the hydrogel mainly following two approaches—(i) The incorporation of conductive nanofillers, and (ii) the preparation of intrinsic conductive hydrogel networks. Multiple electroconductive fillers have been tested, such as metallic nanomaterials (e.g., nanoparticles (NP), nanorods (NR), and nanowires (NW)), made of noble metals, such as Au, Ag or Pt, carbon nanomaterials (e.g., carbon nanotubes (CNT) and graphene) or conducting polymers (CP) (e.g., polypyrrole (PPy), polyaniline (PANI), poly(3,4-ethylenedioxyhiophene) (PEDOT)) [32, 33]. Any of those materials can confer, apart from electrical conductivity, many other properties to develop multifunctional hydrogels. More recently, preparing inherently

conductive hydrogels using pure CP or blends with other synthetic/natural polymers has been outstanding [34, 35].

Regarding the first strategy, electrically conductive nanomaterials have been successfully employed to develop electrically-responsive hydrogels. Different hydrogel matrices either natural, Alg, CS, and Col, or synthetic, PVA, PEG, and PNIPAAM, have been used to incorporate the conductive fillers [32, 33]. These conductive nanomaterials that are nanometer-sized particles show different properties (e.g., electrical, optical, etc.) depending on the size, shape, and type of material that make them very useful to tailor hydrogel properties. Among the conductive fillers, metal nanomaterials in general, but Au and Ag in particular, have been by far the most employed. Gold shows excellent electrical, optical, and catalytic properties together with biocompatibility, ease of functionalization, and resistance to oxidation; meanwhile, silver has a unique electrical, optical, chemical, and antibacterial properties to develop multifunctional hydrogels. On the other hand, carbon nanomaterials, especially CNT and graphene, are also excellent conductive materials to incorporate into non-conductive hydrogels. Properties, such as high electrical conductivity, high strength, high specific surface area, or low density, have conferred them very interesting applicability within the biomedical field.

Regarding the second strategy, CP have been essential in the development of intrinsic conductive hydrogels. CP are conjugated polymer materials showing electronic conductivity due to the free motion of the delocalized π-electrons throughout the double bonds and aromatic rings present in the polymeric chain originating electrical pathways for charge carriers' motion. The π-orbitals of these conjugated systems are overlapped along the chain that allows the delocalization of the electrons throughout the macromolecule's backbone [36]. The most employed CP for conductive hydrogels has been PANI, PPy, and PEDOT due to properties, such as high conductivity, high stability, biocompatibility, or water dispersibility [37]. However, their main drawback is their fragility and low mechanical strength. For this reason, CP have been mixed with other non-conductive natural and/or synthetic polymers to form interpenetrated (IPN) or semi-interpenetrated hydrogels (s-IPN) to improve the mechanical properties [38]. The addition of electrically conductive nanomaterials into the blended hydrogels has also been done to overcome the decrease in electrical conductivity attributed to the presence of the non-conductive polymer.

Researchers have employed different methodologies to develop electrically conductive hydrogels—(i) blending, (ii) in situ formation, and (iii) covalent bonding (**Figure 1**). Blending has been one of the most used approaches to develop such hybrid hydrogels due to its simplicity and the wide range of nanomaterials that can be incorporated into the hydrogel. This method consists of mixing the hydrogel precursors with the colloidal NP suspension followed by crosslinking to entrap the NP within the hydrogel network. For example, Baei and collaborators fabricated a AuNP-chitosan (AuNP-CS) hydrogel for cardiac tissue engineering. Gold NP with a diameter of 7 nm were embedded in the hydrogel precursor solution by chemically reducing the tetrachloroauric acid ($HAuCl_4$) with sodium citrate followed by chitosan crosslinking with β-glycerophosphate. The presence of the NP slightly increases the compressive modulus from 6.1 kPa for the bare chitosan to 6.9 kPa for the AuNP-CS hydrogel. Moreover, they observed that the presence of the NP conferred electrical conductivity to CS in a value close to the native myocardium (0.13 S/m). The sole presence of the NP allowed detecting an increase in the cardiac differentiation-related markers (e.g., Nkx-2.5 and α-MHC) of the mesenchymal stem cells (MSC) seeded on the scaffold [43]. Navaei et al. successfully incorporated Au NRs into gelatine-methacrylate solution that after

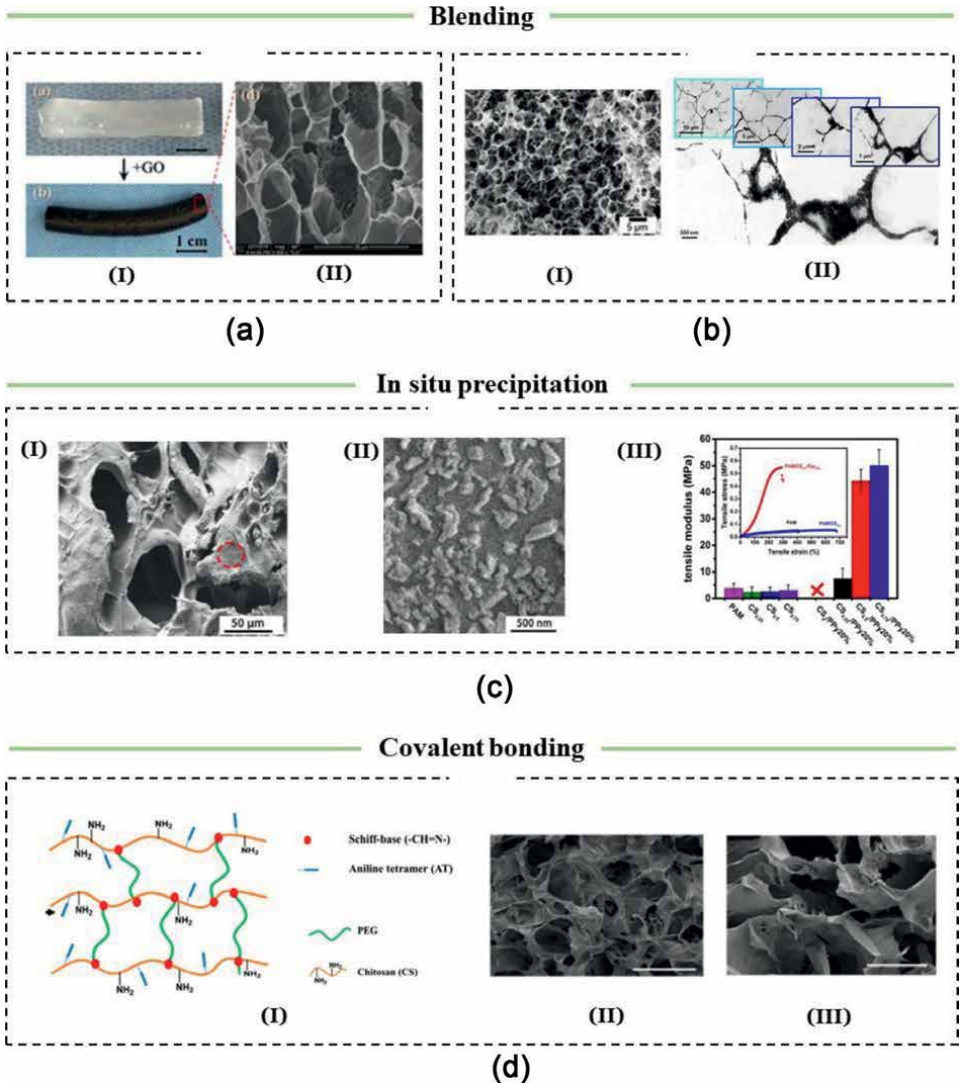

Figure 1.
(a) (I) Photograph of PVA/PEG hydrogel (top) and PVA/PEG/GO (bottom). (II) SEM image of the PVA/PEG/GO hydrogel cross-section. Reproduced with permission from Ref. [39]. (b) (I) SEM image of the PEDOT/Alg hydrogel cross-section. (II) Transmission electron microscopy (TEM) micrographs with different magnifications (from low at the left to high at the right and bottom) of a stained PEDOT/Alg hydrogel. Adapted with permission from Ref. [40]. Copyright (2020) American Chemical Society. (c) (I) SEM image of the PPy/PAM/CS hydrogel and (II) magnified SEM image showing the PPY NR embedded in the hydrogel. (III) Variation of the tensile modulus of PPy/PAM/CS hydrogels with various contents of CS. Adapted with permission from Ref. [41]. Copyright (2018) American Chemical Society. (d) (I) Scheme of the hydrogel showing the covalent crosslinking between the CS and PEG. SEM images of hydrogels (II) before and (III) after swelling. Scale bar: 300 μm. Adapted with permission from Ref. [42]. Copyright (2016) American Chemical Society.

UV-crosslinking led to hydrogels with improved properties for cardiac regeneration. The incorporation of Au NRs (16 ± 2 nm width and 53 ± 4 nm length) led to an increase in the mechanical and electrical properties compared to the pure hydrogel. This hydrogel induced excellent cell retention and proliferation resulting in the formation of cardiac tissue layers with beating behavior [44]. Carbon nanomaterials—CNT, graphene oxide (GO)—have also been widely explored in electrically conductive hybrid

hydrogels. Xiao and collaborators prepared a PVA/PEG/GO hybrid hydrogel with high electrical conductivity and mechanical strength (**Figure 1A**). First, PVA and PEG were dissolved in water at 90°C and cooled to room temperature. After that, GO was dispersed in water, subsequently added to the PVA-PEG solution and mixed until obtaining a homogeneous distribution of GO. Finally, the crosslinking was obtained by the cyclic freezing-thawing method [39]. The blending method has also been employed to develop hybrid hydrogels between CP and insulating polymers either natural or synthetic to confer mechanical properties to the blended hydrogel. It is important to highlight that the electrical performance is normally directly proportional to the content of CP. For example, A. Puiggalí-Jou et al. fabricated an electrochemically active blended hydrogel between PEDOT and alginate biopolymer by an easy one-step process. After thoroughly mixing an aqueous PEDOT:PSS (poly(styrene sulfonate)) dispersion with a fixed amount of an Alg solution, the mixture was placed in a mold and immersed in a $CaCl_2$ solution to crosslink Alg. As observed by the authors, both polymers showed high porosity and they were organized as segregated PEDOT- and Alg-rich regions (**Figure 1B**). The incorporation of curcumin as a model hydrophobic drug allowed demonstrating that the application of a negative potential allowed controlling its release [40]. Gan et al. prepared an IPN based on CS and polyacrylamide (PAM) by UV photopolymerization [41]. First, CS was dissolved in deionized water followed by the addition of given amounts of the monomer (acrylamide (AM)), the crosslinking agent (e.g., N,N′-methylene bisacrylamide) (MBAM), and the initiator (e.g., ammonium persulfate (APS)). The mixture was crosslinked under UV irradiation for 5 min. The resultant hydrogel also showed high porosity to allow its further modification with PPy NWs. Generally, two main drawbacks have been found with the blending methodology—(i) aggregation of the conductive nanomaterials or phase separation between insulating and CP leading to heterogeneous properties across the hydrogel limiting its electrical conductivity and weakening its mechanical strength and (ii) weak nanomaterial-polymer or CP-insulating polymer interaction hindering the full exploitation of nanomaterials or CP. Therefore, the surfactants, polymer-stabilized dispersions, or functionalized nanomaterials are required to properly disperse, and therefore, process them into homogeneous hybrid hydrogels hindering, in most cases, their electrical properties [45].

An alternative methodology to synthesize the conductive hybrid hydrogels avoiding aggregation is the in situ formation of the conductive material within the hydrogel to improve their interaction and therefore integration. Although this approach is dependent on the type of conductive material, generally is based on homogeneously mixing both the conductive (nano)material and the hydrogel precursors followed by the formation of the (nano)materials and crosslinking of the hydrogel. More specifically, metallic nanomaterials can be incorporated by in situ process by mixing the metal ions with the hydrogel precursors. One important point is achieving a homogeneous dispersion of ions before the metallic NPs are grown in the hydrogel. For example, Dolya and colleagues have reported the in situ formation of Au NP within PAM hydrogels following a one-step process. This step consisted of dissolving AM, MBAAM, and APS involved in the hydrogel formation together with $HAuCl_4$, poly(ethyleneimine) (PEI), and the ionic liquid (IL) ethyl-3-methylimidazolium ethylsulfate as a gold precursor, reducing and stabilizing agent, respectively. The formation of the hydrogel and Au NP took place simultaneously by heating the solution at 80°C for 30 min. Results show that hydrogels have high porosity and Au NP are better dispersed and stabilized within the hydrogel when PEI and IL form a shell around the NP preventing their aggregation. While the lack of aggregation was

observed by UV-Vis spectroscopy, better immobilization was detected through kinetic studies of the release of unbound charged compounds [46]. Au NP have been successfully synthesized within many natural (e.g., pectin and κ-carrageenan) and synthetic (e.g., poly(N-vinylpyrrolidone) (PVP), PEG, etc.) hydrogels following the in situ method [47]. Incorporation of CP inside a hydrogel can also be achieved by in situ polymerization. First, CP monomers are incorporated either with hydrogel precursors or after crosslinking by immersing it into the monomer solution and followed by introducing the oxidative reagents (e.g., APS, ferric ions, etc.) to initiate the polymerization. Thus, Gan et al. incorporated PPy NW inside a PAM/CS hydrogel by first immersing the template hydrogel into a pyrrole (Py) solution and second adding the ferric chloride as oxidation agent. The PPy NW, clearly observed by scanning electron microscopy (SEM), enhanced the mechanical properties of the PAM/CS hydrogel (**Figure 1C**) [41]. Or Hur and coworkers reported the fabrication of an interpenetrated network of agarose and PPy by pyrrole polymerization within the agarose gel. First, the authors mixed an agarose aqueous solution with $CuCl_2$ as an oxidizing agent at 40°C. After that, they added a pyrrole monomer to initiate polymerization within the solution. The temperature was decreased down to room temperature to induce agarose gelation, while PPy formation still took place. The addition of the monomer helped to get a homogeneous distribution between agarose and PPy. They developed an electrically conductive hydrogel with self-healing and stretchability [48]. Wu et al. showed the preparation of a conductive hydrogel composed of gelatin methacrylate (GelMA) and PANI. First, GelMA was prepared by UV photopolymerization using irgacure 2959 as initiator. After that, the hydrogel was immersed first in an HCl and APS solution for 4 h followed by immersion in a hexane solution containing the aniline monomer for another 4 h for the polymerization to take place. No significant differences in terms of mechanical properties, swelling, and cell adhesion were observed between the bare GelMA and the GelMA/PANI hydrogel except for an increase in the electrical conductivity of the latter [49]. In situ polymerization can also be achieved by electropolymerization in which an electrical potential or current plays the role of an oxidative reagent inducing polymerization within the template hydrogel [50].

Finally, another strategy to improve even more the interaction between the hybrid hydrogel components (e.g., nanomaterials and polymers), which is normally weak if the previous strategies are used, is through covalent bonding. Here, a covalent bond is formed between the different materials to, for example, stabilize the NP inside the hydrogel but also to boost the chemical and biological properties of the hybrid hydrogel. Skardal et al. synthesize hyaluronic acid (HA), gelatin, and Au NP hydrogels using non-functionalized and thiol-functionalized NP. What they observed is a significant increase in the hydrogel stiffness when the functionalized NP were used, which they attributed to the covalent bond formed with the hydrogel matrix [51]. This methodology has also been explored with carbon nanomaterials. For example, poly(acrylic acid) (PAA) has been grafted onto CNT surface for the promotion of neuron differentiation. First, the authors treated CNT with 4 M nitric acid by reflux to increase surface hydrophilicity. After that, those CNT were dispersed by sonication for 30 min in an acrylic acid-acetone solution followed by the addition of 2′-azobisisobutyronitrile (AIBN) to obtain the PAA. They successfully induced selective differentiation of MSC into neurons [52]. Dong et al. created a covalent bond between a chitosan-graft-aniline tetramer (CS/AT) and a dibenzaldehyde-terminated poly(ethylene glycol) (PEG/DA) to obtain a covalent IPN that they used as drug delivery for cardiac regeneration (**Figure 1D**) [42].

2.1 Biomedical applications

One of the main applications of hybrid hydrogels with electrical conductivity is in the tissue engineering field where hydrogels aim to restore the electrical/electrochemical intercommunication between cells and tissues. These hybrid hydrogel scaffolds have been developing for many tissues especially electroactive ones, such as cardiac, nerve, skeletal muscle, bone, or cartilage. Baei et al. developed a Au NP/CS hydrogel for cardiac tissue engineering. The authors seeded MSC onto the hydrogels, and although they did not observe any significant difference in cell density, morphology, and distribution between bare chitosan and Au NP/CS hydrogels they did observe higher levels of cardiac markers, such as alpha myosin heavy chain (α-MHC) and homeobox protein Nkx-2.5, indicating that the presence of Au NPs electrically stimulating the differentiation of MSC into cardiac cells (**Figure 2A**) [43]. Gan et al. also developed an electrically conductive hydrogel based on PAM, CS, and different amounts of PPy NR as previously explained for skin regeneration. After seeding the scaffolds with muscle myoblasts, the authors analyzed their morphology, adhesion, and proliferation under different electrostimulation voltages (0–900 mV). They found out that not only the incorporation of PPy NR had a clear effect on proliferation and elongation (e.g., 20 v/v% PPy NR led to the highest cell aspect ratio) but also the application of an electric voltage promoted cell activity and elongation (e.g., 300 mV showed the highest elongation) (**Figure 2A**) [41].

Drug delivery has also been widely studied due to the possibility to control the release of the drug out of the conductive hydrogels by the application of different electrical signals (e.g, voltage). A. Puiggalí-Jou et al. fabricated Alg/PEDOT hydrogels incorporating curcumin (CUR) as a hydrophobic model drug during the hydrogel fabrication process. Interestingly, the authors showed a different release profile depending on the applied voltage (0, +1 V, −1 V). Thus, they observed a higher release when −1 V was applied during 2 h to the hydrogel (e.g., ~25%) compared to the 0 V (e.g., ~3%) or + 1 V (e.g., ~8%), indicating a controlled release of curcumin (**Figure 2B**) [40]. Cho et al. also developed a collagen-CNT hydrogel containing a nerve growth factor (NGF). First, a solution containing the collagen and the NGF was prepared followed by mixing with a COOH-functionalized CNT suspension. Then, the mixture was poured into a mold and heated to induce crosslinking. The hydrogels were electrically stimulated immersing them in PBS solution at 37°C and by applying a voltage of 0.5 V for 2 h per day. The application of the voltage led to an increase in the NGF release during the same period of time. Thus, the 5% collagen hydrogel led to a 10-fold increase compared to the non-stimulated one. Moreover, collagen content in the hydrogel had an effect on the drug release observing a higher release in the order 5% > 1% > 0.5% > 20% collagen. The authors attributed the lower release of the 20% collagen hydrogel to the presence of electrical insulating regions limiting the electrical stimulation [54].

Although less studied, these electrically-responsive hydrogels have been also applied for wound healing or as actuators. For example, the hydrogel PAM/CS/PPy was observed to induce skin reparation in *in vivo* experiments with rats. The authors observed that the wound closed with new epithelial tissue and hair in lesser days than with PAM/CS hydrogels. The good results were attributed to the electroactivity of PPy promoting the electrical communication between cells that at the end controls tissue growth (**Figure 2C**) [41]. On the other hand, Yang et al. developed electrically active hydrogels by incorporating GO into a poly(2-acrylamido-2-methylpropanesulfonic acid-co-acrylamide) (AMPS-co-AM) hydrogel to be used as actuator under an

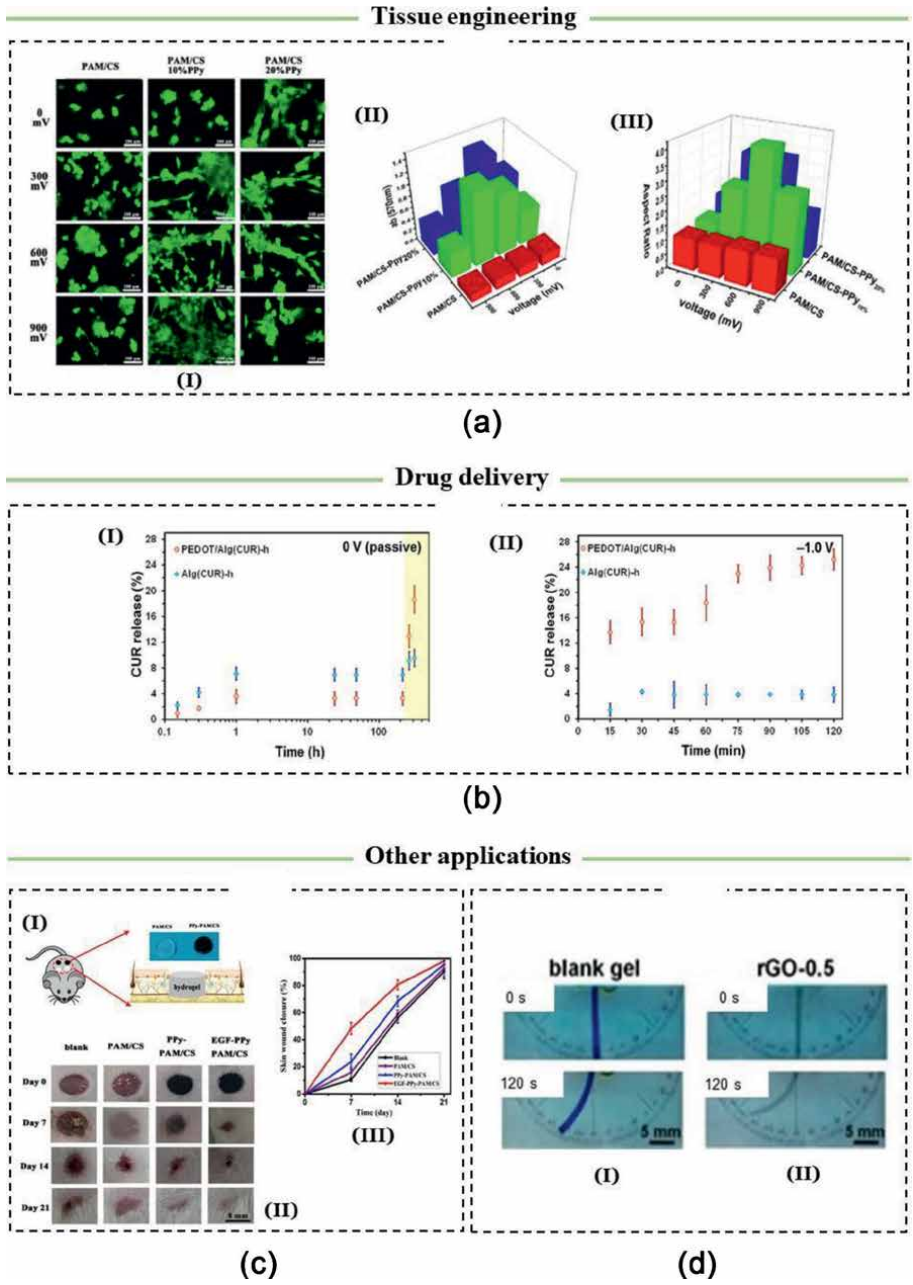

Figure 2.
(a) (I) Fluorescence micrographs of C2C12 cells seeded on PPy/PAM/CS hydrogels and electrostimulated at different electric potentials. (II) Proliferation of cells evaluated by MTT analysis and (III) cell aspect ratio as a function of hydrogel composition and applied voltage. Adapted with permission from Ref. [41]. Copyright (2018) American Chemical Society. (b) Release profile of curcumin from Alg/PEDOT/CUR and Alg/CUR hydrogels by (I) passive diffusion (0 V) and (II) by applying a voltage of −1 V. Adapted with permission from Ref. [40]. Copyright (2020) American Chemical Society. (c) (I) Scheme showing the implantation of hydrogels onto skin defects on rats. (II) Photos of the defects treated with PAM/CS, PAM/CS/PPy, and PAM/CS/PPy loaded with EGF at different time periods. (III) Graph showing the wound closure percentage. Adapted with permission from Ref. [41]. Copyright (2018) American Chemical Society. (d) (I) Optical photographs of the electro-responsive bending behaviors of (I) poly(AMPS-co-AAm) (blank) and (II) rGO/poly(AMPS-co-AAm) hydrogels. Adapted with permission from Ref. [53]. Copyright (2017) American Chemical Society.

electric field. The preparation of the composite hydrogel, which was performed in a two-step process, allowed a good dispersion of the GO leading to a hybrid hydrogel with improved electrical and mechanical properties. An electric field originated the deformation (e.g., bending) of the hydrogel that was reversible and repeatable when a cyclic electric field was applied showing great potential as a remotely controlled electro-responsive actuator (**Figure 2D**). The authors explained the actuation based on the different osmotic pressure between hydrogel's inside and outside as a consequence of ionic flux created during the application of the electric field [53].

3. Magnetic-responsive hydrogels

Hydrogels with magnetic responsiveness have also recently received great attention to developing the next generation of stimuli-responsive hydrogels that possess unique functional structures with controllability, actuation, and spatiotemporal response properties controlled by an external magnetic field. Such magneto-responsive hydrogels have also been used in a multitude of applications in the biomedical field, such as enhancement of cell growth and differentiation for tissue regeneration, drug delivery controlled by magnetic fields, magnetic hyperthermia for the treatment of cancer or magnetic actuators [55]. Magnetic nanomaterials are composed of magnetic elements (e.g., Fe, Co, and Ni) and their oxides (e.g., Fe_3O_4, Fe_2O_3, and $CoFe_2O_4$) [56], and although widely investigated in terms of their physical, structural, and magnetic properties, little is still known about their full potential impact on the biomedical field. Among those nanomaterials, magnetite (Fe_3O_4) has become the most used for medical applications not only because of its biocompatibility and non-cytotoxicity but also for its tunable magnetic properties [55]. Thus, the size of the NP has an effect on the induced magnetic moment and the magnetic properties (e.g., ferromagnetic, superparamagnetic, etc.), which in turn can be used to control their orientation and accumulation, or aggregation, within the hydrogel. For example, NP aggregation affects the biological fate of the magnetic NP that prevents their internalization into the cells and therefore their further excretion, increasing their cytotoxicity. Therefore, it is essential to control the chemical (e.g., composition) and physical (e.g., size, shape, etc.) characteristics of magnetite NP since they impact the former properties. For more details, see reference [55].

As with the electrically conductive hydrogels, magnetic nanocomposite hydrogels can also be fabricated by following the same strategies—(i) blending, (ii) in situ precipitation, and (iii) covalent bonding. Again, blending methodology has been widely employed for its simplicity since the polymer and the magnetic nanomaterials are physically mixed followed by the polymer chains crosslinking to get the hydrogel network. Sapir et al. successfully developed a magneto-responsive hydrogel by properly dispersing magnetite NP by sonication in an Alg solution and followed by crosslinking with Ca^{2+} ions. The magnetic NP, ranging from 5 to 20 nm, did not seem to have any significant effect on the physicochemical properties of the hydrogel, such as porosity, stability, and wetting, as the NP were perfectly embedded within the polymer network but the mechanical and magnetic properties were improved. However, some NP aggregation was observed [57]. Fuhrer and coworkers developed a more complex magnetic hydrogel formed by the incorporation of 4-vinylbiphenyl functionalized carbon-cobalt core-shell NP into an aqueous solution containing 2-hydroxy-ethyl-methacrylate (HEMA), ethylene glycol dimethacrylate (EGDMA), and styrene-maleic anhydride (SMA). A rheology additive (tetramethyl

ethylenediamine) and a crosslinker (APS) were added and the reaction took place in a casting mold for 1 h at room temperature (**Figure 3A**). Although the magnetic properties of the nanomagnets were not reported, the authors did observe an influence of an external magnetic field on cell differentiation [58].

In situ precipitation was employed as a method to avoid NP aggregation since first a mixture of the metal salts (e.g., $FeCl_2$ and $FeCl_3$), precursors of Fe_3O_4, were better mixed within the polymeric solution before cross-linking. After that, formation of magnetite was achieved by precipitating the Fe^{2+} and Fe^{3+} ions with NaOH following the reaction:

$$Fe^{2+} + 2Fe^{3+} + 8OH^- \rightarrow Fe_3O_4 + 4H_2O \quad (1)$$

Albertsson et al. fabricated a hemicellulose magnetic hydrogel by a one-step method. First, O-acetyl-galactoglucomannan and epichlorohydrin (crosslinking agent) were dissolved in NaOH followed by the addition of an aqueous solution of the metal salts ($FeCl_3{\cdot}6H_2O$, $FeCl_2$ (Fe^{3+}:Fe^{2+} molar ratio = 2:1)). Different concentrations were added to incorporate variable amounts of magnetite (5, 10, and 15%). The crosslinking reaction and the magnetite formation simultaneously took place at 60°C for 20 min. The resultant hydrogel contained Fe_3O_4 NP with an average size of 5.8 nm conferring a superparamagnetic behavior to the hydrogel. Moreover, it was observed that the higher the Fe_3O_4 content, the higher the magnetization of the hydrogel. The presence of the magnetic NP also improved the mechanical properties but a decreased swelling ratio, thermal stability, and pore size was observed as magnetite content increased [62]. Another example by Miyazaki et al. was the in situ incorporation of Fe_3O_4 NP within chitosan hydrogels with different crosslinking degrees achieved changing molar ratios of the crosslinker (glutaraldehyde) from 0.5 to 30 with respect to the amino groups in chitosan. The authors immersed the hydrogels with different crosslinking densities in a 0.1 M $FeCl_2$ solution for 6 h at room temperature to allow hydrogel swelling and Fe^{2+} diffusion into it. After that, hydrogels were dipped into 0.5 M NaOH solution at 60° to precipitate the magnetic NP. An influence of the hydrogel network structure on magnetite growth was observed. On one hand, the amount of Fe_3O_4 generated in the hydrogel decreased as the crosslinking density increased, which they attributed to the lower swelling meaning that the Fe^{2+} intake was impeded. On the other hand, larger crystallite sizes were obtained as the crosslinking degree was increased. The authors did not show the magnetic properties of the hydrogels but they did analyze the influence of an alternating magnetic field in heat generation for hyperthermia applications. The heat generation was enhanced in hydrogels with higher crosslinking due to the larger crystallite and particle sizes and despite the lower amount of magnetite [63]. Zhou et al. also fabricated hydrogels based on PVA or PVA/PNIPAAM and containing Fe_3O_4 NP as the magnetic material. The one-step process consisted of mixing a PVA or PVA/PNIPAAM solution with the Fe^{2+}/Fe^{3+} ions followed by dropwise addition into an alkaline NH_3 solution to obtain the magnetite NP and crosslink the PVA chains in the form of beads (**Figure 3B**). PVA played different roles, the stabilizer to avoid magnetite aggregation and the matrix to support the NP. On the other hand, the Fe_3O_4 NP interacted with the hydroxyl groups of PVA via hydrogen bonds favoring also gelation. Although the authors did not provide the size of the magnetite NP, they did report their superparamagnetic behavior indicating a nanometric size. They finally incorporated congo red inside the magnetic scaffold to be used as a drug delivery system. They found out a different profile release with and without an applied magnetic field [59].

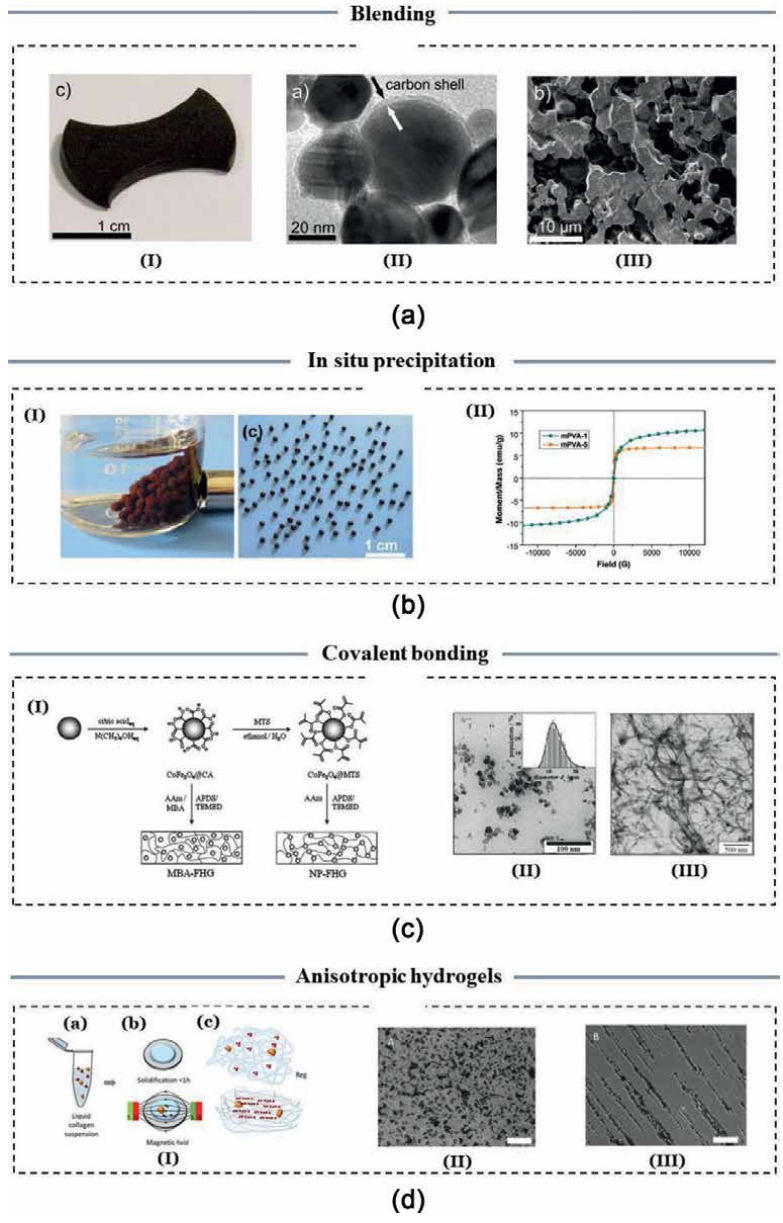

Figure 3.
(a) (I) Photo of the magnetic hydrogel with a dog-bone shape. (II) TEM image of the carbon-coated metal nanomagnets. (III) TEM image of the nanomaterials incorporated into the hydrogel. Reproduced with permission from Ref. [58]. (b) (I) Images of magnetic PVA hydrogels in the form of beads. (II) Magnetization-magnetic field curves for the hydrogels with different magnetic contents at 300 K. Adapted with permission from Ref. [59]. Copyright (2012) American Chemical Society. (c) (I) Scheme showing the synthesis of $CoFe_2O_4$ NP coated with citric acid (CA) ($CoFe_2O_4$@CA) and 3-methacryloxypropyltrimethoxysilane (MTS) and the corresponding hydrogels MBA-FHG and NP-FHG. TEM images of the (II) $CoFe_2O_4$ NP coated with and (III) the swollen and freeze-dried magnetic hydrogel. Adapted with permission from Ref. [60]. Copyright (2011) American Chemical Society. (d) Scheme showing the experimental procedure to align the magnetic particles and collagen fibres: (a) Liquid collagen suspension with neurons (orange) and magnetic NP (red). (b) Placement of the suspension onto coverslips and allowed to solidify with (bottom) or without (top) magnetic field. (c) Final scheme of the random and aligned hydrogels. SEM image of (II) the random distribution of magnetic NPs within collagen hydrogel and (III) the magnetic strings in the hydrogel solidified under a magnetic field. Adapted with permission from Ref. [61]. Copyright (2016) American Chemical Society.

A third strategy to incorporate magnetic NP has been covalent bonding, which implies the formation of a covalent bond between the functionalized magnetic nanomaterials and the polymer chains. Although this method usually involves more complicated steps and is more time-consuming, the advantage is the prevention of NP leaching out from the hydrogel network. For example, PAA and methacrylic surface-functionalized $CoFe_2O_4$ NP were employed to assure a covalent bonding between them. First, the $CoFe_2O_4$ NP were synthesized by precipitation from a $CoCl_2$ and $FeCl_3$ (1:2 molar ratio) solution after alkalinization and stabilized with citric acid and tetramethylammonium hydroxide in water. And second, functionalization was obtained after mixing the NP first with NH_4OH solution (25%) and second with 3-methacryloxypropyltrimethoxysilane (MTS) allowing the reaction (e.g., condensation of siloxane groups onto particle surface) to take place at room temperature for 15 h. The resultant particles were single-crystalline and had an average size of 12.2 ± 0.23 nm, resulting in a pseudo-superparamagnetic behavior. Finally, the authors synthesized different PAA hydrogels with the citric acid- and methacrylic-functionalized $CoFe_2O_4$ NP to investigate the effect of the particle-to-polymer interaction (hydrogen bonding in citric acid- and covalent bonding in methacrylic-functionalized particles) on the hydrogel magnetic and mechanical properties [64]. Another example was the formation of covalently bonding hydrogels between siloxane-functionalized $CoFe_2O_4$ NP and the PVA matrix (**Figure 3C**). The procedure was very simple as they first mixed the monomer (AAM) and the functionalized $CoFe_2O_4$ NP followed by the crosslinker (N,N,N′,N′-tetramethylethylenediamine) and the initiator (ammonium peroxodisulfate). The reaction proceeded at room temperature for 2 h. The magnetic NP had a size around 12 nm showing a superparamagnetic behavior. Moreover, they also showed that the hydrogel swelling was lower when the NP were covalently bonded to the hydrogel compared to the NP physical entrapped [60].

In all previous strategies, a more or less homogeneous but random distribution of the magnetic NP can be achieved. Recently, the development of complex hydrogels architectures has grown by controlling the spatial distribution and orientation of the magnetic nanomaterials within the hydrogel scaffold by using an external magnetic field. Normally, the magnetic nanomaterials are mixed with the hydrogel precursors and subsequently aligned by placing the mixture in an external magnetic field. The nanomaterials become magnetized and reorient along the magnetic field direction. This anisotropic and well-ordered structure is then fixed by crosslinking the precursor solution into the hydrogel. Although this approach can be applied to magnetic nanomaterials with different shapes (e.g., NP, NR, and NW), magnetic NP have been extensively used for the preparation of such anisotropic hydrogels [61, 65]. For example, Fe_3O_4 NP have been successfully aligned within the hydrogel precursor solution containing AM (monomer), MBAM (crosslinker), APS (initiator), and tetraethylethylenediamine (accelerator) using a static magnetic field. After that, the hydrogel formation was triggered by increasing temperature up to 50°C. Such alignment led to an enhanced magnetothermal effect under an external alternating magnetic field compared to the disordered hydrogel [66]. Or Antman-Passig and Shefi embedded Fe_3O_4 NP in a collagen fiber suspension, aligned the NP into strings under an external magnetic field, which also forced the alignment of the fibers, and finally, collagen was allowed to solidify keeping the magnetic field (**Figure 3E**). The seeded neurons had normal electrical activity and viability and their growth was induced and controlled along the fibers and NP string direction acting as a physical cue for the cells [61].

3.1 Biomedical applications

These magnetically-responsive hydrogels have enabled a wide range of potential applications in the biomedical field, such as tissue engineering, drug delivery, artificial muscles, soft actuators, and magnetic hyperthermia, among others. Tissue engineering has been one of the fields where magnetic hydrogels have been widely applied covering a wide range of tissues, such as bone, cartilage, cardiovascular, or neuronal tissues. The ultimate aim of scaffolds is to foster the natural reparative process by guiding the new tissue formation and recovering their functionality, where multiple biochemical, biophysical, and biological cues need to be controlled. Magnetic hydrogels are key in this discipline since hydrogel architectures can be magnetically controlled in a way to confer directionality and or concentration gradient mimicking complex anisotropic tissues. Moreover, these hydrogels can be remotely actuated with external magnetic fields inducing mechanical deformation within the scaffold (e.g., magnetomechanical stimulation or mechanotransduction effect), which has an impact on cell behavior (e.g., growth, migration, proliferation, and differentiation). For example, Huang et al. have reported an effective regeneration of cartilage using magnetic hydrogels composed of PVA, hydroxyapatite particles, and maghemite (Fe_2O_3) NP. The incorporation of the NP improved not only the mechanical properties of the hydrogel but also induced the proliferation and differentiation of the seeded MSC into the chondrogenic lineage [67]. Other approaches have applied either static or time-varying magnetic fields to the cells-containing hydrogels. Thus, Brady et al. developed a three-layer agarose-Fe_3O_4 hydrogel with a stiffness gradient that was achieved using a different agarose concentration in each layer (1, 2, and 3 wt.%). Bovine chondrocytes were embedded in each layer under the application of a 500 mT static magnetic field (**Figure 4A**). After 14 days of magnetic stimulation, they observed an increase in both strain and sulphated glycosaminoglycan content from the 1 wt.% agarose layer to the 3 wt.% agarose layer [68]. Fuhrer and collaborators also observed that the application of a non-continuous (2 s on, 10–225 s off) 800 mT magnetic field to the Fe_3O_4-styrene-maleic anhydride hydrogel seeded with MSC induced their chondrogenic differentiation without the need of any other chondrogenesis transcription factors [58].

More recently, magnetic hydrogels with anisotropic architectures have been fabricated trying to mimic native tissues. For example, an anisotropic collagen-agarose bilayer containing Fe_3O_4 NP was obtained when a 2 mT magnetic field was applied during hydrogel formation. Collagen fibers aligned as a consequence of the NP alignment parallel to the field direction but only in the layer where the agarose content was lower (0.5 w/v%). The layer with the higher agarose concentration (1 w/v%) hindered collagen and magnetite NP alignment. The authors observed that seeded chondrocytes in the anisotropic scaffolds expressed more collagen type II when compared with the isotropic hydrogels [72]. These anisotropic structures were also recently explored by Araújo-Custódio et al. who reported the fabrication of gelatin hydrogels containing rod-shaped cellulose nanocrystals decorated with magnetite NP that were aligned by applying a static magnetic field (108 mT). The hydrogel, that tried to mimic tendon tissue, showed a directional structure with anisotropic mechanical properties being the storage modulus higher in the direction parallel to the rod long axis. This anisotropy also had an impact on the embedded cells as it induced an elongated morphology and a directional growth again on the rod long axis (**Figure 4B**) [69].

Another application where magnetic nanocomposite hydrogels have been investigated is drug delivery due to the possibility to release the drug on demand

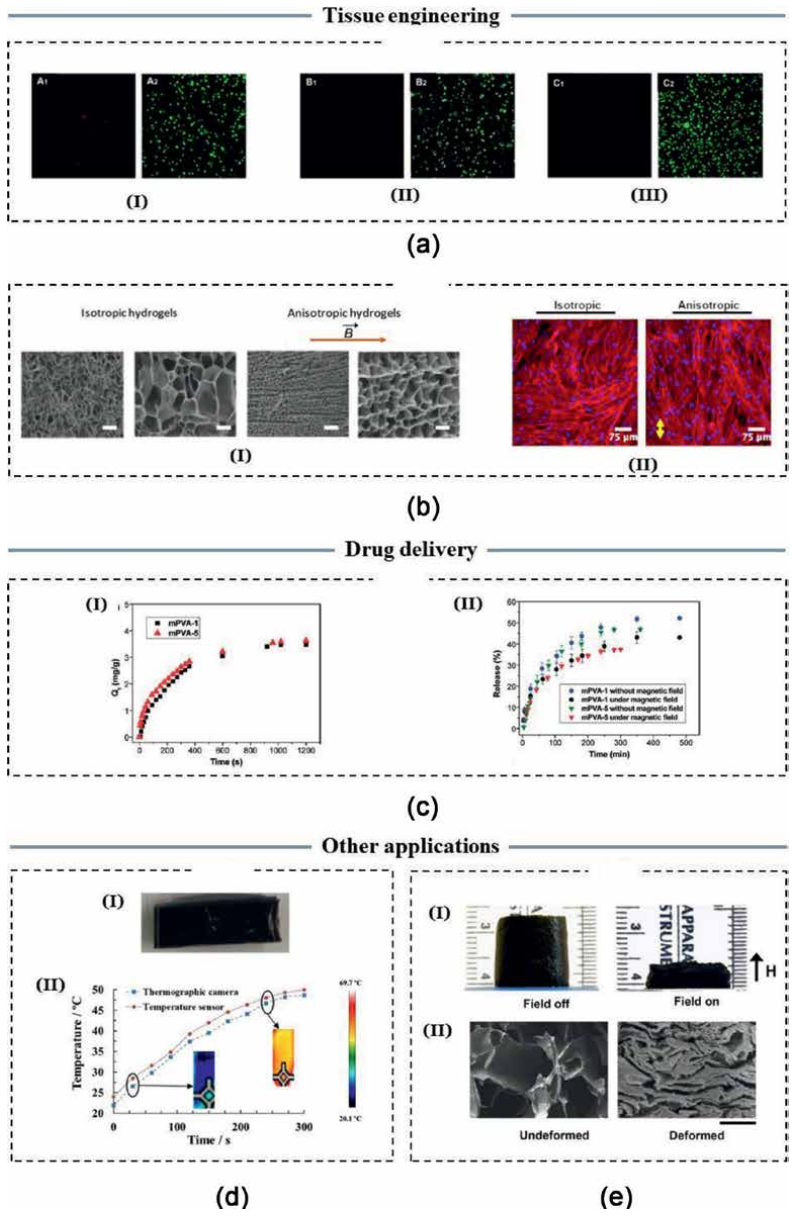

Figure 4.
(a) Live/dead stain images (dead cells (red), live cells (green)) showing the cell viability of chondrocytes embedded into the different layers of the agarose-Fe_3O_4 NP hydrogel at different times (I) day 1, (II) day 7 and (III) day 14. Reproduced with permission from Ref. [68]. (b) (I) SEM images of isotropic and anisotropic hydrogels. Scale bar = 10 μm. (II) Confocal microscope images showing the effect of isotropic and anisotropic hydrogels on cell alignment (red, cytoskeleton; blue, nucleus). Adapted with permission from Ref. [69]. Copyright (2019) American Chemical Society. (c) (I) Graph showing the amount of congo red loaded onto the hydrogels with different magnetic contents with time. (II) Graph showing the release profiles of the hydrogels with different magnetic contents over time with and without applied magnetic field. Adapted with permission from Ref. [59]. Copyright (2012) American Chemical Society. (d) (I) Photo of the Alg/PEDOT/Fe_3O_4 NP hydrogel. (II) Graph showing the variation of temperature of the Alg/PEDOT/Fe_3O_4 NP hydrogel with time subjected to an alternating magnetic field (200 Hz, 8 kA m^{-1}). Adapted with permission from Ref. [70]. Copyright (2021) American Chemical Society. (E) (I) Image of the hydrogel without (left) and with an applied magnetic field (right). (II) SEM images of the hydrogel in the undeformed and deformed states. Scale bar: 500 μm. Reproduced with permission from Ref. [71].

and at certain concentrations when magnetic fields are applied. Moreover, the delivery of the therapeutic drug in situ to the specific target can be done remotely. In this line, Mahdavinia and collaborators fabricated a magnetic IPN hydrogel network containing k-carrageenan and PVA as well as $FeSO_4$ and $FeCl_3$ to precipitate Fe_3O_4 NP by adding NH_3. After that, diclofenac sodium as a model drug was added to the previous mixture and further crosslinked by the freezing-thawing method followed by immersion in K^+ solution. The hydrogel, that showed a superparamagnetic behavior with magnetization saturation values between 3.4 and 8.2 emu/g depending on the magnetite content, was subjected to an alternate magnetic field with variable strength in the range 100–500 G. They observed a controlled diffusion of the drug such that the higher the magnetic field was, the higher the amount of diclofenac sodium released. They attributed this behavior to the higher mechanical stress conferred as the magnetic field increased [73]. Another example by Zhou et al. showed that the amount of congo red loaded onto the hydrogels was the same independently of the amount of magnetite inside the PVA hydrogel. However, they did observe a change in the amount of congo red released in the absence and presence of a static magnetic field. After 500 min, the released content was around 55% with no magnetic field and around 42% with the applied magnetic field for the hydrogel with the lowest amount of magnetite (**Figure 4C**) [59].

Some other applications of magnetic hydrogels are magnetic hyperthermia as experimental cancer therapy or soft actuators to develop artificial muscles. Magnetic hyperthermia, which basically consists of the delivery of heat when a high frequency oscillating magnetic field is applied, has been investigated into magnetic nanocomposite hydrogels. For example, Puiggalí-Jou et al. observed that when an alternating magnetic field (frequency = 200 kHz) was applied to a Alg/PEDOT/Fe_3O_4 NP hydrogel, the temperature increased from room temperature to around 50°C after a few minutes, which was attributed to the presence of the magnetic NP (**Figure 4D**) [70]. More recently, hydrogels with ordered structures like the one fabricated by aligning magnetite NP with a PAM hydrogel have also shown magnetothermal effect but direction-dependent. When the magnetic NP chains were aligned parallel to the applied field, the heating rate and the plateau temperature were higher than the values achieved with the non-ordered hydrogels [66]. Magnetically responsive hydrogels can also be used as soft actuators due to the change in volume, shape, or position they experience in response to a magnetic field. Thus, Zhao et al. developed an Alg hydrogel crosslinked with adipic acid dihydrazide (AAD) and containing magnetite NP with a diameter around 10 nm. The application of a magnetic field (38 A/cm^2) induced deformation of the hydrogel with a volume change of 70% (**Figure 4E**) [71]. Zhou et al. developed the amphiphilic pentablock copolymer PAA-PC5MA-PEO-PC5MA-PAA (PC5MA: poly(5-cholesteryloxypentyl methacrylate), PEO: poly(ethylene oxide)) and the Fe_3O_4 NP that were directly bonded to the carboxylic groups of PAA. These magnetic hydrogels were bent under the application of a magnetic field [74]. Recently, significant efforts have been put into developing dual electric- and magnetic-responsive hydrogels with even enhanced properties compared to the single stimuli-responsive systems. For example, Liu et al. fabricated a flexible hydrogel containing CNT, PPy NP, and iron oxide with electrical conductivity and magnetic properties with potential applicability as biosensor and bioactuator [75]. Or Garcia-Torres and collaborators synthesized an Alg/PEDOT/Fe_3O_4 hydrogel for magnetic hyperthermia application and simultaneous measurement of temperature [70].

4. Conclusions

In this chapter, the author has reviewed recent developments in electric- and magnetic-responsive hydrogels from the perspective of materials and properties and applications. Many hydrogels have been employed so far for the fabrication of the hybrid systems comprising natural (e.g., Alg and Col) and synthetic polymers (e.g., PVA and PEG) but mainly a mixture of different polymers to improve the performance of the interpenetrated hydrogel obtained. The different strategies to confer hydrogels with electric and magnetic responsiveness—blending, in situ precipitation, covalent bonding—have been presented. The different methodologies allowed modifying the structure of the hydrogels (e.g., different distribution of the NP within the hydrogel framework) and therefore their properties. The main applications for the electric- and magnetic-stimuli hydrogels have been presented, including tissue engineering, drug delivery, and actuation. It has been shown that the unique presence of the nanomaterials either with electrical conductivity or magnetic properties already improved cell adhesion, proliferation, and differentiation, but it was enhanced even more when the hydrogel was either electrically or magnetically stimulated. These hydrogels can also be used as drug delivery systems with the ability to control the amount of drug release just by modifying the applied signal (e.g., voltage and magnetic field strength). Thus, this field is rapidly emerging with new electric- and magnetic-responsive hybrid hydrogels providing significant advances in the biomedical field. And it has been possible thanks to the versatility in the main components—hydrogels, nanomaterials—providing unique features and properties to the hybrid hydrogels.

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Chapter 7

Mesenchymal Stem/Stromal Cells and Hydrogel Scaffolds for Tissue Engineering

Leisheng Zhang and Zhihai Han

Abstract

Hydrogels are splendid biomaterials and play a critical role in multiple applications for disease management via offering a microenvironment for drug metabolism and exerting the bonding effect attribute to the preferable physical and chemical properties. State-of-the-art renewal has indicated the combination of hydrogels with mesenchymal stem/stromal cells (MSCs), which are heterogeneous populations with unique hematopoietic-supporting and immunoregulatory properties. For decades, we and other investigators have demonstrated the promising prospects of MSCs in regenerative medicine, and in particular, for the administration of recurrent and refractory disease. Very recently, we took advantage of the hydrogel/MSC composite for the applications in osteoarthritis, burn wounds, and refractory wounds associated with diabetic foot as well. Strikingly, the composite showed superiority in continuous improvement of the biological functions of the injured areas over hydrogels or MSCs, respectively. Collectively, hydrogel-based biomaterials are of importance for disease treatment and the accompanied regenerative medicine. Therefore, in this chapter, we will summarize the latest updates of hydrogel/MSCs composite in tissue engineering and put forward the direction of hotspot issues in the future including hydrogel/MSC and hydrogel/MSC-exosome in preclinical and clinical studies.

Keywords: mesenchymal stem/stromal cells, exosomes, hydrogel scaffolds, tissue engineering, regenerative medicine

1. Introduction

Mesenchymal stem/stromal cells (MSCs) have been acknowledged as medicinal signaling cells as well as the most important niche cells in the microenvironment, and possess advantaged properties such as immunomodulatory capacity, hematopoietic-supporting effect and multi-lineage differentiation potential towards adipocytes, osteoblasts and chondrocytes, which thus hold promising prospects for tissue engineering and regenerative medicine [1–3]. MSCs were first isolated from bone marrow in the 1960s, and followed by various stromal fractions of adult tissues [4, 5], perinatal tissues [6–8], and even derived from stem cells [9–11]. For decades, due to the limitation of unique biomarkers and the wide range of cell sources, MSCs

are recognized as heterogeneous populations with great heterogeneity in cellular phenotypes and transcriptome characteristics [12–14]. Generally, MSCs with diverse origins mainly function via direct- or trans-differentiation, paracrine or autocrine, homing, dual immunomodulation, neovascularization, and constitutive microenvironment [4, 15, 16]. To date, more than 1340 MSC-based clinical trials have been registered for various disease treatment according to the ClinicalTrials.gov website. For instance, we and other investigators have indicated the therapeutic effects of MSCs upon multiple refractory and recurrent disorders including acute graft-versus-host diseases (aGVHD) [17], aplastic anemia [18, 19], osteoarthritis [11, 20], critical limb ischemia (CLI) [9], acute-on-chronic liver failure (ACLF) [21], Parkinson's syndrome [22], acute myocardial infarction (AMI) [23], rheumatoid arthritis (RA) [24], and coronavirus disease 2019 (COVID-19) [15, 25]. It's noteworthy that the variation of the therapeutic efficacy of MSCs upon acute liver failure and aGVHD has also been respectively observed by Zhang et al. and us, which further indicated the necessity and urgency of developing tissue engineering including biomaterials, three-dimensional (3D) printing, and MSC-based gene therapy [26, 27].

Simultaneously, state-of-the-art updates have further suggested the preferable application of biomaterial/MSC composite as well [11, 28, 29]. Of the current natural extracellular matrices (ECMs), hydrogels have been regarded as the most promising alternative biomaterials attribute to their excellent swelling property and the resemblance to soft tissues [11, 30]. In particular, synthetic biomimetic hydrogels with appropriate mechanical behavior and predictable biodegradation property can be easily synthesized and modulated for facilitating the biological phenotypes and bioapplications of the encapsulated MSCs such as adhesion, migration, differentiation, proliferation, and apoptosis [30]. For instance, Gwon et al. and Huang et al. reported the influence of heparin-hyaluronic acid (HA) hydrogel upon cellular activity and hydrogel scaffolds for the differentiation of adipose-derived stem cells, respectively [30, 31]. Very recently, we took advantage of the HA hydrogel/MSC composite and demonstrated the reinforced cell vitality of human pluripotent stem cell-derived MSCs (hPSC-MSCs) over monolayer-cultured MSCs for chondrogenesis and the management of osteoarthritis rabbits [11].

Herein, we summarize the current progress in MSCs or MSC-derived exosomes and hydrogel scaffold for tissue engineering, and in particular, the potentially reinforcing or attenuating effects of hydrogel scaffold with unique biochemical and biophysical properties upon the MSC-based cytotherapy for regenerative medicine.

2. The cell sources of MSCs for tissue engineering

Not until 2006, the International Society for Cellular Therapy (ISCT) defined the preliminary criteria of defining multipotent MSCs including adherent property, multi-lineage differentiation capacities *in vitro* towards adipocytes, osteoblasts, and chondrocytes, together with high-levels of mesenchymal biomarker expression (CD73, CD90, and CD105) whereas minimal expression of hematopoietic or endothelial markers (CD31, CD34, and CD45) [32]. After that, numerous studies aiming at dissecting the similarities and differences in biological phenotypes and biofunctions as well as transcriptome characteristics of MSCs derived from adult tissue, perinatal tissue, and PSCs have been extensively conducted (**Table 1**).

Classification	Type of scaffold	Disease	Applications	Reference
Adult tissue-derived MSCs	PF-127 hydrogel/ AD-MSC	Diabetic wound healing	Preclinical study	Kaisang et al. [33]
	AdhHG hydrogel/G-MSCs	Craniofacial bone tissue regeneration	Preclinical study	Hasani-Sadrabadi et al. [34]
	HPCH-PCL-nHA hydrogel/BM-MSC	Massive bone defects	Preclinical study	Ji et al. [35]
Perinatal tissue-derived MSCs	PF-127 hydrogel/ UC-MSC-exo	Chronic diabetic wound healing	Preclinical study	Yang et al. [36]
	Chitosan hydrogel/P-MSC-exo	Hindlimb ischemia	Preclinical study	Zhang et al. [37]
	Collagen/UC-MSCs	POF	Clinical study	Ding et al. [38]
Pluripotent stem cell-derived MSCs	HA hydrogel/ PSC-MSCs	Osteoarthritis	Preclinical study	Zhang et al. [11]
	Hydrogel/ iPSC-MSCs	Endometrial injury	Preclinical study	Ji et al. [39]

Table 1.
Representative applications of HA/MSC-based scaffold in tissue engineering.

2.1 Adult tissue-derived MSCs

As mentioned above, adult tissue-derived MSCs hold vast prospect in tissue repairing and organ reconstruction [3]. To date, massive literatures have reported the isolation and identification of MSCs from various adult tissues such as adipose tissue, bone marrow, synovium, dental pulp, peripheral blood, muscle tendon, and menstrual blood [40, 41]. According to the ClinicalTrials.gov website, a total of 1096 trials have been registered worldwide against disorders such as acute respiratory distress syndrome (ARDS), CLI, AMI, anoxic or hypoxic brain injury, moderate-to-severe Crohn's disease, idiopathic pulmonary fibrosis (IPF), and COVID-19. For example, a phase I interventional trial was led by Dr. Jesus JV Vaquero Crespo in Puerta de Hierro University Hospital was aiming to evaluate the security of local administration of autologous bone marrow-derived MSCs (BM-MSCs) in traumatic injuries of the spinal cord (NCT01909154), which was consistent with another study by Geffner and their colleagues [42]. In details, 12 participants received 1×10^8 BM-MSCs by intrathecal injection (subarachnoid and intramedullary), and another 3×10^7 BM-MSCs by subarachnoid administration after 3 months depending on centromedullary post-traumatic injury. The safety outcomes of the patients were evaluated according to vital signs (ECG, blood pressure, and heart rate) and possibility of adverse reaction (headache, meningeal irritation, and infectious complications). The secondary outcomes were quantized from the view of sensitivity recovery (e.g., surface sensitivity and pain sensitivity), level of chronic pain, neurophysiological parameters, maximum cystometric capacity, and the decrease in volume and hyperintensity of intramedullary lesions. Very recently, Oraee-Yazdani et al. further verified that BM-MSCs in combination with autologous Schwann cell co-transplantation was safe and effective for treating 11 patients of spinal cord injury (SCI), and in particular for spinal cord regeneration during subacute period [43].

Notably, cutting-edge advances have also put forward the variations and limitations of adult tissue-derived MSCs in both preclinical and clinical studies [1, 14, 44].

For example, among the indicated adult tissue-derived MSCs, BM-MSCs are recognized as the widest application in clinical practices whereas with inherent disadvantages such as ethical risk, pathogenic risk, invasive pain, replicative senescence and individual diversity for cell source, and in particular, the limitation in healthy donors and declined long-term *ex vivo* amplification further restrict the large-scale application in future [11, 44]. Interestingly, despite the variations in signatures and functions, we recently verified the potential conservative properties in adipose tissue-derived stem cells (AD-MSCs) from type 2 diabetics and healthy donors [4]. However, multifaceted diversity among BM-MSCs, AD-MSCs, dental pulp stem cells (DPSCs), and supernumerary teeth-derived apical papillary stem cells (SCAP-Ss) were observed by investigators in the field [16, 45–47].

2.2 Perinatal tissue-derived MSCs

Perinatal tissues are abundant sources of MSCs and extracellular matrix with a wide range of therapeutic purposes in tissue engineering, which thus act as particularly interesting candidates for regenerative medicine [48, 49]. To date, a variety of perinatal tissue-derived MSCs have been identified such as placental-derived MSCs (P-MSCs), umbilical cord-derived MSCs (UC-MSCs), cord blood-derived MSCs (CB-MSCs) [49, 50], amniotic-derived MSCs (A-MSCs) [51], amniotic fluid-derived MSCs (AF-MSCs) [52], decidua-derived MSCs (D-MSCs) [53], and chorionic villi-derive MSCs (CV-MSCs) [54]. Of the aforementioned perinatal tissue-derived MSCs, UC-MSCs are promising sources with preferable properties in long-term proliferation *in vitro* and immunoregulation, and most of all, without ethical risks and limitation in supply, and thus hold great prospect for large-scale clinical investigation and investigational new drug (IND) purposes [18, 44]. Up to November 11th of 2021, a total of 317 interventional clinical trials have been registered for the administration of numerous refractory diseases by UC-MSC infusion such as diabetic nephropathy, heart failure, perianal fistulas with Crohn's disease, lumbar discogenic pain, chronic obstructive pulmonary disease (COPD), Duchenne muscular dystrophy (DMD), and cerebral hemorrhage sequela (CHS) according to ClinicalTrials.gov website.

Similarly, other types of MSC sources are of equal importance in offering "seeds" for tissue engineering and regenerative medicine (e.g., umbilical cord, placenta, amniotic membrane, and amniotic fluid). For instance, Liu and the colleagues took advantage of A-MSCs and conducted intragastric administration and intraperitoneal injection for the management of hydrogen peroxide-induced premature ovarian failure (POF) model. As expected, POF mice with A-MSC transfusion in bilateral ovaries revealed increased estrogen levels, decreased follicle-stimulating hormone level, and evaluated ovarian index and fertility rate, which collectively suggested the ameliorative effects of MSCs in improving the follicular microenvironment and recovering ovarian function in POF [55].

2.3 Pluripotent stem cell-derived MSCs

Pluripotent stem cells (PSCs), including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), possess self-renewal and multi-lineage differentiation potential, which thus provide advantaged "seeds" for disease modeling and drug validation as well as unprecedented opportunities for cytotherapy against intractable diseases [56–58]. Since the year of 2005, a number of literatures have reported the generation of MSCs from ESCs and iPSCs [59, 60]. Strikingly, the PSC-derived MSCs

(PSC-MSCs) revealed multifaceted superiority over those derived from adult tissues such as unlimited source, homogeneity, large-scale generation without pathogenic or ethical risks, and in particular, PSC-MSCs could be used for exploring the early development and molecular mechanism of MSCs [10, 53, 61, 62]. Notably, current studies have suggested the considerable efficacy of MSCs or MSC-derived exosomes in preclinical application including experimental inflammatory bowel disease (IBD) [63, 64], allergic tracheal inflammation (e.g., asthma and anaphylactic rhinitis) [65], experimental autoimmune encephalitis (EAE) of multiple sclerosis [66], lupus nephritis [67], acute colitis [68], kidney fibrosis [69], and hematopoietic reconstitution [70].

Generally, there are three strategies for PSC-MSC generation including monolayer induction, PSCs and stromal cell coculture and the embryoid body (EB) models. However, most of the existing strategies with drawbacks such as laborious manipulations (e.g., handpicking and scraping), time-consuming (3–8 weeks), low efficacy (approximately 5–20%), cell sorting (e.g., $CD73^+$ and $CD105^+$), and serial passages [10, 71, 72]. For instance, Wei et al., Deng et al., Vainieri et al., Wang et al., and Tran et al. reported the elevated generation of PSC-MSCs by modulating intracellular JAK-STAT [9], IKK/NF-κB [73], PDGF-BB [74], bone morphogenetic protein 4 (BMP) [68], and ABB (activin A, 6-bromoindirubin-3′-oxime, and BMP4) [75] signaling pathways in feeder or serum-free model, respectively. Notably, we recently took advantage of the Msh homeobox 2 (MSX2) and small molecule library-based cell programming strategies for high-efficient induction of PSC-MSCs within 2 weeks, respectively [9–11]. Even though the convenience in practice as well as the promising prospects in tissue engineering and regenerative medicine [76, 77], the potential risks of PSCs attribute to genome editing and their inherent characteristics such as tumorigenicity, heterogeneity, and immunogenicity should cause enough attention [56, 78, 79].

3. Hydrogels/MSCs scaffolds for tissue engineering

The therapeutic effects of MSC transplantation largely attributed to the paracrine including soluble factors and extracellular vehicles (e.g., exosome and secretome), which could be rapidly sequestered and cleared [80]. Hydrogels are ideally suited for MSCs cultivation and are adequate to offer splendid delivery platforms, enhance vehicles retention rates and thus enhance immunomodulation and tissue regeneration after *in vivo* transplantation (**Figure 1**, **Table 1**) [80–82].

3.1 Hydrogels/MSCs scaffolds for wound healing

Wound healings are regulated by series of events with overlapping phases, which represent an intractable issue in clinical practice [83, 84]. State-of-the-art renewal has indicated the prospective applications of hydrogel in combination with MSCs or MSC-derived exosomes in skin wound healing, and in particular, the recurrent and refractory cutaneous types (**Table 1**) [83, 85]. Of them, chronic refractory wounds are disorders attribute to multifactorial comorbidity with characteristics of inflammation and impaired vascular networks, which eventually result in unfavorable prognosis due to the lack of effective treatments [36, 86]. Recently, Yang and the colleagues topically applied UC-MSC-derived exosomes encapsulated into the thermosensitive PF-127 hydrogel (hydrogel/MSC-exo) and demonstrated that hydrogel/MSC-exo scaffold significantly upregulated expression of multiple cytokines (e.g., VEGF and TGFβ-1), enhanced regeneration of granulation tissue and accelerated wound closure

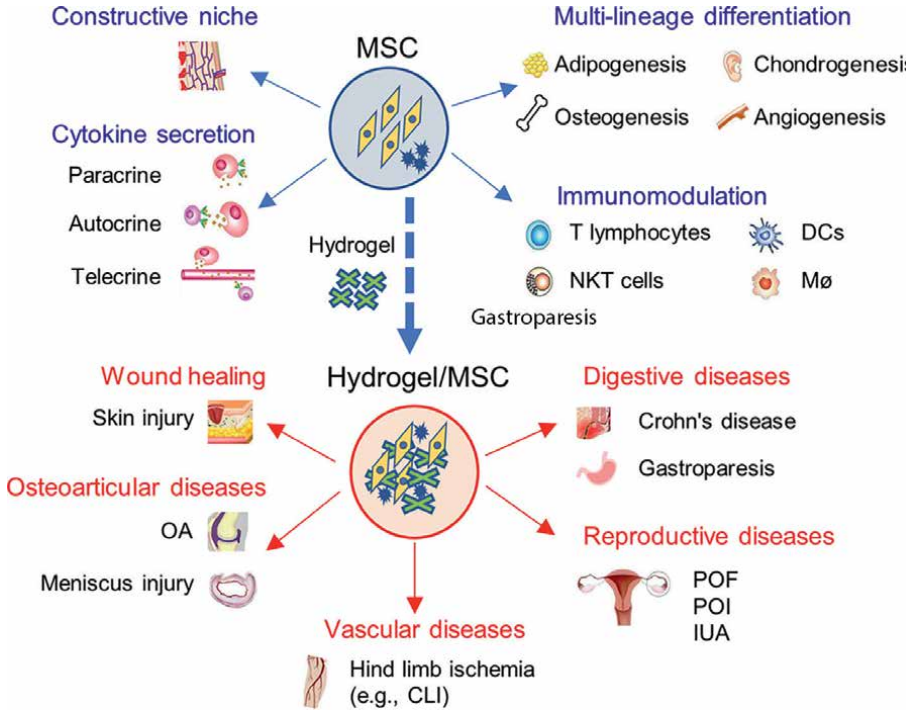

Figure 1.
Illustration of hydrogel/MSC-based cytotherapy for tissue engineering.

rate in a streptozotocin-induced diabetic rat model, which was further verified by another study in a streptozotocin-induced diabetic model with hydrogel/AD-MSC composite [33, 36]. Marusina et al. and Xin et al. reported the influence of tunable bio-inert poly (ethylene glycol)-based hydrogels and microporous annealed particle hydrogels on MSCs and the optimization of cell-degradable hydrogels/MSCs delivery for wound re-epithelialization [81, 87]. Zhang et al. took advantage of the bioluminescence imaging (BLI) technology and further demonstrated the therapeutic effects of prostaglandin E2 (PGE2) and chitosan (CS) hydrogel (PGE2 + CS hydrogel) in a murine wound healing model via modulating the M1 and M2 paradigms of macrophage activation [88]. Meanwhile, a full sheet consisting of A-MSCs on thermoresponsive polymers have been considered as advantaged skin substitute for the management of burn wounds [89]. Collectively, these studies suggested that hydrogel-based MSC/MSC-exo therapy represent a novel therapeutic approach for refractory cutaneous regeneration of chronic wounds.

3.2 Hydrogels/MSCs scaffolds for osteoarticular diseases

Despite the dramatic progress in bone reconstruction, the osteoarticular diseases and bone regeneration in clinical practices are still challenging [82]. Hydrogels have been extensively investigated in numerous osteoarticular diseases (e.g., osteoarthritis) and bone regeneration (e.g., craniofacial bone tissue) largely attribute to the high cell compatibility [34]. For example, Ji et al. recently combined MSCs with a newly synthesized hybrid scaffold consisting of thermosensitive hydroxypropyl chitin hydrogel (HPCH) and 3D-printed nano-hydroxyapatite (nHA)/poly

(ε-caprolactone) (PCL) for bone regeneration. Strikingly, they found the vascularization and osteogenesis and immunomodulation of encapsulated MSCs as well as cytokine secretion of macrophages were collectively orchestrated in bone defect mice model [35].

Osteoarthritis (OA) is recognized as the most prevalent chronic joint disease, which increases in prevalence with age and resultant in functional loss or decline in quality of life, and in particular, act as a major socioeconomic cost worldwide and a leading musculoskeletal cause of impaired mobility in individuals over 65-year-old [90, 91]. Despite joint replacement is an effective strategy for symptomatic end-stage disease, yet most of the functional outcomes are poor and the lifespans of prostheses are largely limited [91, 92]. Current studies have shown that MSC-based cytotherapy are promising for osteoarticular disease administration. For example, Portron et al. and Merceron et al. found that the *in vivo* chondrogenic potential of AD-MSCs encapsulated in a cellulose-based self-setting hydrogel (Si-HPMC) preconditioned by hypoxia (5% oxygen) was significantly enhanced compare to that in the control (20% oxygen) group, which was confirmed by subcutaneous transplantation of AD-MSCs with an injectable hydrogel in rabbits [93, 94]. Very recently, our group also found that the application of hyaluronic acid (HA) hydrogel/PSC-MSCs and HA hydrogel/hydroxyapatite/UC-MSC (HA/HAP/UC-MSC) composite with reinforced efficacy upon OA rabbits and mice, respectively (**Table 1**) [11]. It's noteworthy that Chung and their colleagues have systematically explored and detailed dissected the efficacy of articular cartilage repair *in vivo* by combining UC-MSCs with various hydrogels such as alginate, pluronic, HA, and chitosan. They finally concluded that HA hydrogel/UC-MSC composites resulted in preferable cartilage repair and collagen organization pattern, which were similar to adjacent uninjured articular cartilage [95]. Additionally, the gingival MSC-laden photocrosslinkable hydrogels were also confirmed with preferable biocompatibility, biodegradability, and osteoconductivity for craniofacial bone tissue engineering in rat peri-implantitis model as well [34]. Taken together, the biodegradable and biocompatible hydrogels can serve as advantaged scaffolds and supply structural integrity for cellular organization and morphogenic guidance of hydrogel scaffold-laden MSCs [88].

3.3 Hydrogels/MSCs scaffolds for reproductive diseases

Premature ovarian failure (POF) is a refractory disorder with declined fertility in females [96, 97]. In 2019, Yang and their colleagues took advantage of collagen scaffold loaded with UC-MSCs (collagen/UC-MSCs) and verified the efficacy in POF mice via increasing estrogen (E2) and ovarian volume, and promoting granulosa cell proliferation and ovarian angiogenesis [96]. Similarly, Ding et al. reported the rescue of E2 concentrations and activation of follicles in the dormant ovaries of premature ovarian failure (POF) patients with long history of infertility after transplantation of collagen/UC-MSC scaffold (**Table 1**) [38].

As to premature ovarian insufficiency (POI), an intractable endocrine disease that severely restricts the reproductive and physiological function of females and resultant in menopausal symptoms, a series of literatures have suggested the ameliorative effect of hydrogel/MSC composite or hydrogel/MSC-derived microvesicles/secretomes via facilitating angiogenesis, enhancing granulosa cell generation and steroidogenesis, and accelerating follicular regeneration [98–101]. Notably, Li et al. have summarized the current renewal of the therapeutic effects and molecular mechanisms of MSC-based cytotherapy in both preclinical research and clinical trials [102].

3.4 Hydrogels/MSCs scaffolds for vascular diseases

Peripheral arterial diseases (PAD) are severe medical conditions, which are characterized by blood vascular blockage and low limb Doppler signals and commonly associated with hind-limb ischemia or critical limb ischemia (CLI) [103]. For decades, we and other investigators have primarily suggested the therapeutic of MSCs or MSC-derived exosomes in hind limb ischemia models by alleviating the severity, promoting angiogenesis, and enhancing immunomodulation [9, 104, 105]. In recently years, a certain number of outstanding researchers turned to injectable hydrogels such as self-assembled Nap-GFFYK-Thiol hydrogel, nitric oxide-releasing hydrogels, and the novel hydrogel composed of pooled platelet lysate (PL) to enhance the efficacy of MSCs or derivations upon peripheral artery diseases (PADs) [37, 106–108]. For example, Lee et al. found that fucoidan was adequate to improve the bioactivity and vasculogenic potential of MSCs in hind limb ischemia murine with chronic kidney disease (CKD) whereas Nammian et al. further compared the variations of efficacy between BM-MSCs and AD-MSCs for CLI [109, 110]. Notably, Ding and their colleagues systematically dissected an injectable nanocomposite hydrogel consisting of chitosan, gelatin, β-glycerophosphate and Arg-Gly-Asp (RGD) peptide for potential applications of facilitating vascularization and tissue engineering [111]. Collectively, the aforementioned studies suggest that hydrogel/MSC-based composites occupy a greater angiogenic potential over single hydrogel- or MSC-based treatment for PADs.

3.5 Hydrogels/MSCs scaffolds for digestive diseases

Gastroparesis is characterized by pyloric dysfunction, vomiting, severe nausea, delayed gastric emptying and impaired fundamental structures, which is related with consume of enteric neurons and interstitial cells of Cajal [112]. Meanwhile, stem cell therapy has also been extensively explored in inflammatory bowel diseases (IBDs) including ulcerative colitis (UC) and Crohn's disease (CD) in both preclinical studies and clinical trials [113–115]. State-of-the-art updates have indicated the mitigatory effects of MSCs in gastrointestinal diseases such as acute ulcerative colitis and perianal CD [8, 10, 68, 116]. For example, we recently reported the spatio-temporal metabolokinetics and efficacy of placenta-derived MSCs (P-MSCs) on intractable CD with enterocutaneous fistula in mice via simultaneously accelerating neovascularization and downregulating reactive oxygen species (ROS) [8]. Interestingly, Joddar et al. conducted delivery of the MSC-alginate/gelatin/poly-l-lysine hydrogel atop stomach grafts facing the luminal side, and confirmed the significant advance towards the entire tissue-engineered "microgels" or "gastric patch" [112]. Of note, the therapeutic effects of MSCs via systemic administration are still contradictory largely due to the localization in the lungs, which is confirmed by the outcomes of two clinical trials with BM-MSC transplantation [117, 118]. Therefore, the local administration of hydrogel/MSC or hydrogel/MSC-exosomes are promising alternatives for resolving refractory digestive diseases.

4. Conclusions

Tissue engineering is an inveterate and promising area in the field of regenerative medicine, which also has long-lasting limitations in engineering and regenerating tissues. MSCs of different origins are splendid "seeds" for the efficient administration of various refractory and recurrent diseases. As mentioned above, MSCs as well as the

released extracellular vesicles (EVs) reveal substantial therapeutic effect in numerous pathophysiological conditions and potentially reconstructing an extensive range of diseased or damaged tissues and organs in tissue regeneration engineering, which have been predominantly demonstrated from pre-clinical or clinical *in vitro* and *in vivo* studies. MSC-encapsulated hydrogel scaffolds demonstrate enhanced cell vitality and committed differentiation, prolonged fundamental and operational consistency, which thus hold promising prospects for tissue engineering and the resultant regenerative medicine. Meanwhile, the exosomes and other nano-scale secretions released from the multivesicular MSCs encapsulated into appropriative hydrogel formulations (e.g., HA, nHAP, PLGA, pDA, and FHE) have manifested higher therapeutic potential in both fundamental research and clinical application. Overall, the current progress of regenerative medicine will extensively benefit from the "advantaged" artificial hydrogel/MSC-based cytotherapy in the near future.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

Not applicable.

Appendices and nomenclature

MSCs	mesenchymal stem/stromal cells
aGVHD	acute graft-versus-host diseases

CLI	critical limb ischemia
ACLF	acute-on-chronic liver failure
AMI	acute myocardial infarction
RA	rheumatoid arthritis
COVID-19	coronavirus disease 2019
ECMs	extracellular matrices
HA	hyaluronic acid
PSC-MSCs	pluripotent stem cell-derived MSCs
BM-MSCs	bone marrow-derived MSCs
ARDS	acute respiratory distress syndrome
IPF	idiopathic pulmonary fibrosis
DPSCs	dental pulp stem cells
UC-MSCs	umbilical cord-derived MSCs
P-MSCs	placental-derived MSCs
AF-MSCs	amniotic fluid-derived MSCs
A-MSCs	amniotic-derived MSCs
D-MSCs	decidua-derived MSCs
CV-MSCs	chorionic villi-derive MSCs
COPD	chronic obstructive pulmonary disease
CHS	cerebral hemorrhage sequela
DMD	Duchenne muscular dystrophy
POF	premature ovarian failure
EAE	experimental autoimmune encephalitis
IBD	inflammatory bowel disease
ESCs	embryonic stem cells
iPSCs	induced pluripotent stem cells
nHA	nano-hydroxyapatite
CKD	chronic kidney disease
PADs	peripheral artery diseases
CD	Crohn's disease
UC	ulcerative colitis
IUA	intrauterine adhesions
PGE2	prostaglandin E2
ROS	reactive oxygen species

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Chapter 8

Smart Polymer Hydrogels as Matrices for the Controlled Release Applications in Agriculture Sector

Dhanapal Venkatachalam and Subhapriya Pushparaju

Abstract

Synthetic polymer hydrogels and modified natural polymer hydrogels are widely and increasingly used in agriculture, health care textiles, effluent treatment, drug delivery, tissue engineering, civil concrete structure, etc. Among them, the use of hydrogels in agricultural and horticultural sectors as matrices for the controlled release of water, various primary and secondary nutrients has drawn significant attraction from researchers, scientists, and industry persons due to their smartness with reference to controlled release characteristics based on plant requirement. Since the use of these hydrogels for controlled release application ensures the minimum utilization of water and plant nutrients in fields. Besides, this will bring down the overloading of fertilizer, soil contamination, and water pollution such as eutrophication, nitrate pollution, and micronutrient imbalance. This chapter is focused on the class of hydrogels that are used for the controlled release application in the agricultural and horticultural sectors as matrices, the possible methods of fine-tuning their structures for improving their fertilizer uptake and release behavior, safety aspects, and environmental issues.

Keywords: swellability, controlled release, reusability, environmental protection, water conservation

1. Introduction

The smart polymers hydrogels are the class of functional polymers, which finds extensive use [1, 2] in diverse areas like agricultural, medical, pharmaceutical, effluent treatment, textile, etc. They have physicochemically crosslinked three-dimensional network, which are derived from water-soluble acrylic monomers, crosslinkers and natural pre-polymers. These smart hydrogels are capable of imbibing and retaining water or aqueous fluids such as urine, blood, electrolyte solution, etc. to the extent of 200 g to 1–2 kg of fluids without dissolving [3–5]. This hydrophilic nature of hydrogel leads to managing drought conditions in arid and semi-arid regions as a matrix for the controlled release of water and fertilizers [5]. To serve this, polymers with different chemical architecture are essential for diverse soil characteristics [5].

Agrochemicals such as primary and secondary fertilizers are used to hike crop yield with substantial quality foodstuff [6]. However, the traditional method of growing foodstuffs using synthetic fertilizers will not ensure a high-quality

environment [6]. Depending on the method of application and climatic conditions, about 90% of conventionally applied fertilizers never reach their objectives to realize the desirable biological response at the precise time and in the quantities required [6]. Such a mode of application provides a higher initial concentration than required for quick results. The conventional method of fertilizer amendment provides an initial concentration far above that required for immediate results to ensure the availability of sufficient nutrients. But such overdosing will result in waste of fertilizers [6] and produce undesirable side effects in the environment. Hence, there is a need for more controlled application of fertilizer, affording lower amounts of active ingredients without diminishing the efficacy. Controlled-release formulations were used to maintain an effective local concentration of active ingredients in the soil and to reduce runoff [6]. Besides, the application frequency required in the growing season could be minimized through controlled release technology. The controlled release was defined [6] as a technique or a method by which water or active chemicals were made available to a specified target at a definite rate and duration designed to accomplish an intended effect [7–15]. The method of choice to achieve controlled release in a particular application depends on the cost, release rate, potency and properties of the active compounds [14–16]. This chapter addresses the synthesis, characterization and controlled release applications of synthetic and natural polymer modified hydrogels in agriculture as matrices [16], different types of hydrogel used for controlled release, advantages, limitations and challenges.

2. Synthesis of hydrogels for controlled release

The smart hydrogels with controlled release characteristics have been prepared either from water-soluble acrylic monomers, crosslinkers and modified natural polymer by grafting.

2.1 From hydrophilic monomers

The hydrogels with good swelling ability are synthesized from water-soluble hydrophilic acrylic monomers such as acrylamide, acrylic acid, acrylates, itaconic acid, etc. using suitable initiators and crosslinkers through radical or photochemical polymerization methods [17]. This will be achieved either by solution or suspension or emulsion or bulk polymerization methods [17]. Free-radical polymerization mechanism is predominantly employed to synthesize hydrogel using olefinic monomers. The initiation of monomers is carried out by the initiators such as peroxides (benzoyl or t-butyl peroxides), azo-compounds (azobisisobutyronitrile) and persulphates. Peroxides and peroxy compounds can facilitate ambient temperature polymerization under the influence of tetramethylene diamine, sodium metabisulfite/ferrous salts, triethylamine, etc. [17, 18]. Benzyl alcohol, ethanol, water, and ethanol-water mixtures are commonly used solvents to achieve solution polymerization. The monomers (**Table 1**), cross-linkers (**Table 2**) and natural polymers (**Table 3**) that are used for hydrogel synthesis are given in the respective Tables.

2.2 Modification of natural pre-polymers

Water swellable hydrophilic hydrogel polymer can also be synthesized by performing appropriate chemical modification of natural polymers such as gelatin,

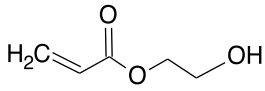
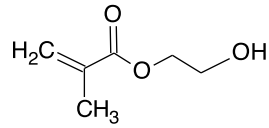
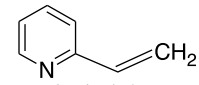
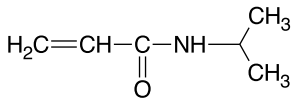
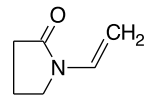
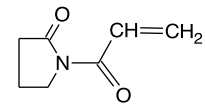
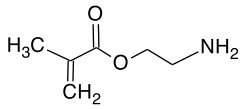
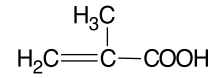
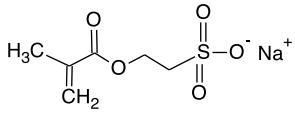
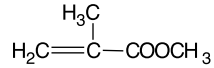
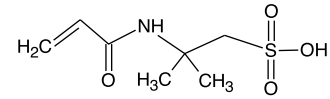
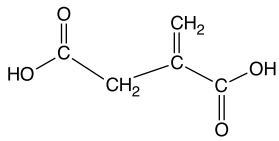
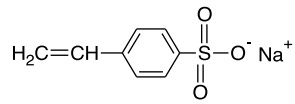
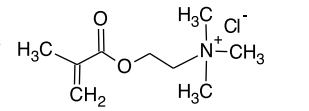
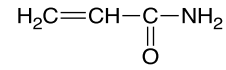
Chemical structure of monomers		
 Hydroxyethyl acrylates (HEA)	 Hydroxyethyl methacrylates (HEMA)	 2-Vinylpyridine (VP)
 N-Isopropylacrylamide (NIPAm)	 N-vinyl-2-pyrrolidone (NVP)	 N-acroylpyrrolidone (ANVP)
 2-Aminoethyl methacrylate (AEM)	 2-oxazoline (OZ)	 Methacrylic acid(MAA)
 Sodium – 2 sulfoxyethyl methacrylate (SSM)	 Methyl methacrylate (MMA)	 2-Acrylamido-2-methylpropane sulfonic acid (AMPS)
 Itaconic acid (IA)	 Sodium styrene sulfonate (SSS)	 2-methacryloyloxyethyl trimethylammonium chloride
CH_2=CH-COOH Acrylic acid(AA) Acrylic acid(AA)	CH_2=CH-CN Acrylonitrile (AN) Acrylonitrile (AN)	 Acrylamide (Am)

Table 1.
Typical monomers used for hydrogel synthesis.

starch, alginate, cellulose, chitosan, pectin, etc. via grafting using acrylic monomers. In-situ incorporation of micronutrient (boron) on acrylic acid grafted guar gum-based hydrogel [19], acrylic monomers grafted chitosan hydrogel [20], urea loaded cellulose [21], carboxymethylcellulose-hydroxyethylcellulose cross-linked with citric acid [22], etc. can also be used as matrices for the controlled release of fertilizers and water in agricultural field.

3. Characterization

3.1 Analytical methods

The potential applicability [23] of smart polymers are gauged based on their chemical structure, the extent of chemical and physical crosslinking, crosslink density, mechanical properties, degrees of swelling (hydrophilicity), release characteristics, hydrophobicity, surface morphology, biodegradability, biocompatibility, glass-transition temperature, thermal stability, photo-stability, bio-resorbability,

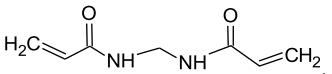
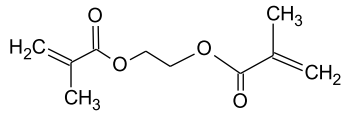
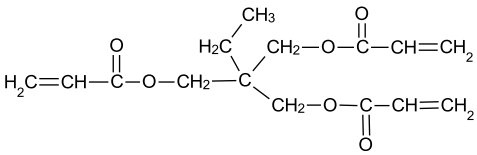
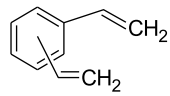
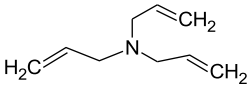
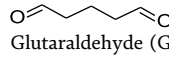
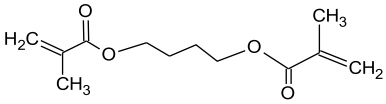
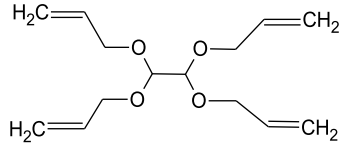
Chemical structures of crosslinkers	
 N,N'-Methylenebisacrylamide (N, N[1]MBA)	 Ethylene glycol dimethacrylate (EGDM)
 Trimethylol propane trimethacrylate (TMPTA)	 Divinylbenzene (DVB)
 Triallylamine (TA)	 Glutaraldehyde (GA)
 1,4-butanediol dimethacrylate (BDDM)	 Tetraallylethoxy ethane (TAEE)

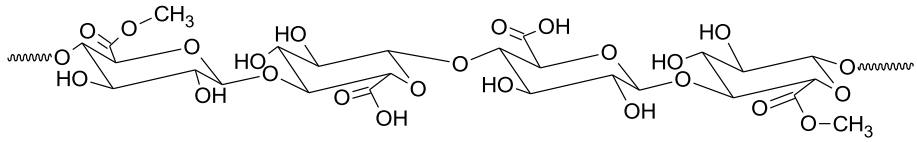
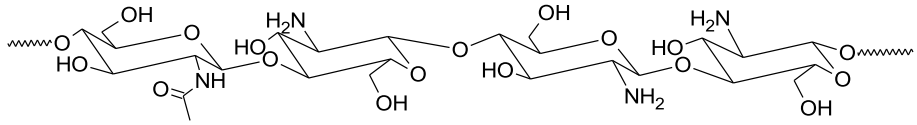
Table 2.
Typical crosslinkers used for hydrogel synthesis.

interaction with biological fluids, environmental sensitivity, dielectric properties, toxicity, the toxicity of the degraded products, etc. For instance, the nature of functional groups, crystallization deformation of polymers, biodegradation, moisture uptake properties, nature of interactions between components are evaluated using Fourier Transform Infrared Analysis (FTIR) and Nuclear Magnetic Resonance (NMR) spectroscopy. The modification after polymerization such as chemical composition, grain size, the extent of crosslinking, pore size, pore volume are evaluated using Atomic Force Microscopy (AFM) or Scanning Electron Microscopy (SEM) and X-ray diffraction analysis. The oxidative thermal degradation, glass transition temperature, lifetime prediction, melting point, etc. are assessed through Thermal Analysis (TGA and DSC). The mechanical characteristics such as tensile strength and elastic moduli and strain are evaluated using a tensile-compressive tester.

3.2 Swelling measurements

The swelling ability of hydrogel is a significant characteristic for field application. The absorption capacity of the hydrogel can be evaluated [23] gravimetrically at successive time intervals using tea-bag, sieves, centrifugal, volumetric, microwave, gravimetric, NMR, DSC methods based on the required precision. The extent of swelling (DS) was measured using Eq. (1) by performing triplicate measurements.

$$DS = \frac{W_t - W_0}{W_0} \tag{1}$$

Chemical structures of natural polymers

Pectin

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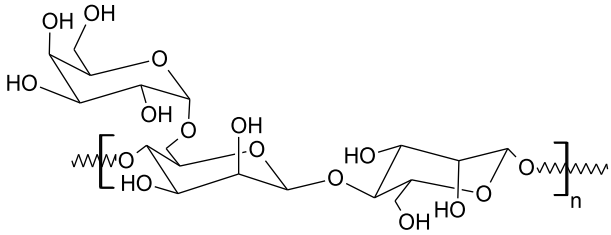
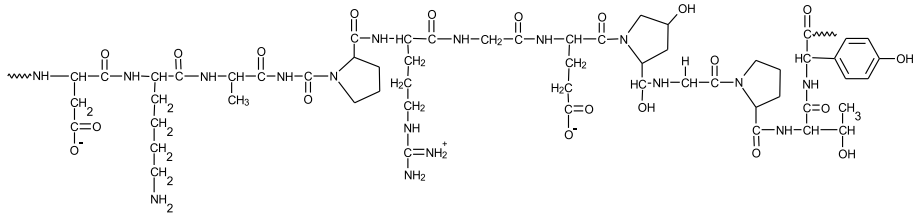

Guar gum

Gelatin

Table 3.
The representative natural pre polymers used for hydrogel synthesis.

The weight of dried (W_0) and swollen polymers (W_t) at a particular time are measured gravimetrically.

3.3 Absorption under load (AUL)

The extent of water absorption under load is determined by performing AUL of hydrogel samples [24] using the Eq. (2). The AUL test will display the absorption capacity of smart polymer hydrogel under stressed conditions (load) and ionic strength.

$$AUL(g/g) = \frac{W_2 - W_1}{W_1} \tag{2}$$

W_1 and W_2 represents weight of dry and swollen hydrogel respectively.

3.4 Fertilizer uptake and release studies

The quantum of fertilizer absorption and release characteristics of smart hydrogels are measured based on Eq. (3). The percentage release of fertilizer from the loaded

hydrogels are measured gravimetrically [12]. This procedure was followed for every two-day interval to ensure maximum fertilizer release. The percentage of urea/potash release was calculated [12] using Eq. (3).

$$\text{Percentage of fertilizer released} = \frac{(\Delta W)n \times [100 - (n-1) \times 2]/2 + \sum_{i=1}^{n-1}(\Delta W)i}{Wo} \tag{3}$$

The amount of fertilizer released from the hydrogel in 2 and i^{th} ml are represented by W_0 and $(\Delta W)i$ respectively. The number of nutrient releases at different time intervals for the single experiment is denoted by the term "n".

3.5 Transport kinetics

The rate of nutrient absorption by the plants depends on various parameters such as plant age, nature of fertilizers, and the concentration of fertilizers. However, the micronutrients are supplied as chelates or complexes (using synthetic complexing agents such as salicylic, lactic, formic, citric, succinic, propionic, ascorbic, tartaric and gluconic acids and their sodium, potassium and ammonium salts. Amino acids such as glutamine cysteine, glycine, and lignosulfonates can also be used as complexing agents [25]. The water, nutrients uptake and release behavior of hydrogels are regulated by their chemical constituents namely sulfonic acid, amide, hydroxyl, amine, carboxylic acid, carboxylate groups, etc.

The uptake and release mechanisms are clearly understood by analyzing the transport kinetics. The movement of solvent and solute either into or out of hydrogel is also regulated by the shrinking and swelling of hydrogels. The second-order kinetic model [Eq. (4)] was used to explain the swelling of hydrogel [23].

$$\frac{dM}{dt} = k_s \ (M_\infty \ - M)^2 \tag{4}$$

where, M: uptake at time t, $M_{\infty:}$ uptake at equilibrium condition, and $k_{s:}$ kinetic rate constant.

The swelling rate (S_R), and swellability (S_t) and($S_{t+\Delta t}$) at time 't' and '$t+\Delta t$' respectively are measured using the Eq. (5).

$$S_R = \frac{S_{t+\Delta t} - S_t}{\Delta t} \tag{5}$$

3.6 Diffusion

A random molecular process causes the movements of solvent or solute molecules from one part to another part of hydrogels. Further, this movement is also influenced by temperature, pressure, solute size and viscosity. Generally, in hydrogel water molecules diffusion is connected to the extent of polymer-solvent interactions. Based on hydrogel relaxation rate, the diffusion is categorized as non-Fickian and Fickian [26], and the power-law Eq. (6) is used to evaluate the penetration characteristics of solvent into the hydrogel [26].

$$M_t = kt^n \quad (6)$$

The value of diffusion exponent (n) is ranged from 0.5 to 1 and the parameter k represents the rate constant.

3.7 Fickian and non-Fickian

The diffusion mechanism [26] of solution in the hydrogel during network collapse or swelling was analyzed using Fick's law. Fickian diffusion was noticed when the operating temperature of the system was greater than the glass transition temperature (T_g) of the hydrogel. Fickian type diffusion was also predicted if the solvent diffusion rate (R_{diff}) was slower than hydrogel relaxation rate (R_{relax}) i.e., ($R_{diff} << R_{relax}$). Besides, the diffusion distance and the square root of time were found to have a direct relationship [Eq. (7)]

$$M_t = kt^{1/2} \quad (7)$$

The value of 'n' provides the diffusion characteristics, for instance, if n = 0.5 in Eq. (6) Fickian diffusion is followed, and the 'n' values lie between 1 and 0.5 non-Fickian (anomalous) transport mechanism is followed. Further, non-Fickian model was noticed below glass transition of the hydrogel.

4. Application of hydrogel in agriculture field

The substantial foodstuff production requires an adequate amount of primary and secondary nutrients [6] along with water during cultivation. To achieve expected yield farmers used to feed an additional amount of fertilizers than the required quantity [6] during each amendment. However, 90% of the applied fertilizers are going as waste due to different climatic conditions and the application method [6]. An excess dose of fertilizers leads to economic losses, toxicity problems and effects on aquatic organisms [6] which cause uninvited effects such as water and soil pollution. Hence, there is a necessity to adopt the method, which facilitates the controlled release of fertilizers without affecting efficacy. An execution of controlled release using polymer based matrix is being used for a long time [6]. The loaded fertilizers have been released through chemical cleavage of the polymer-active agents or by depolymerization reaction (originated other factors) [6]. However, the implementation of a controlled release technique for the particular application depends on the factors namely release rate, cost, effectiveness and properties of synthetic fertilizers.

4.1 Advantages

In agricultural field, smart hydrogels have discharged numerous applications [27] and the notable merits are minimum use of fertilizers and water through controlled a release mechanism. The list of noteworthy advantages of hydrogel amendment in the soil is displayed in **Figure 1**. However, hydrogels used for the controlled release of fertilizers and water in the field must have

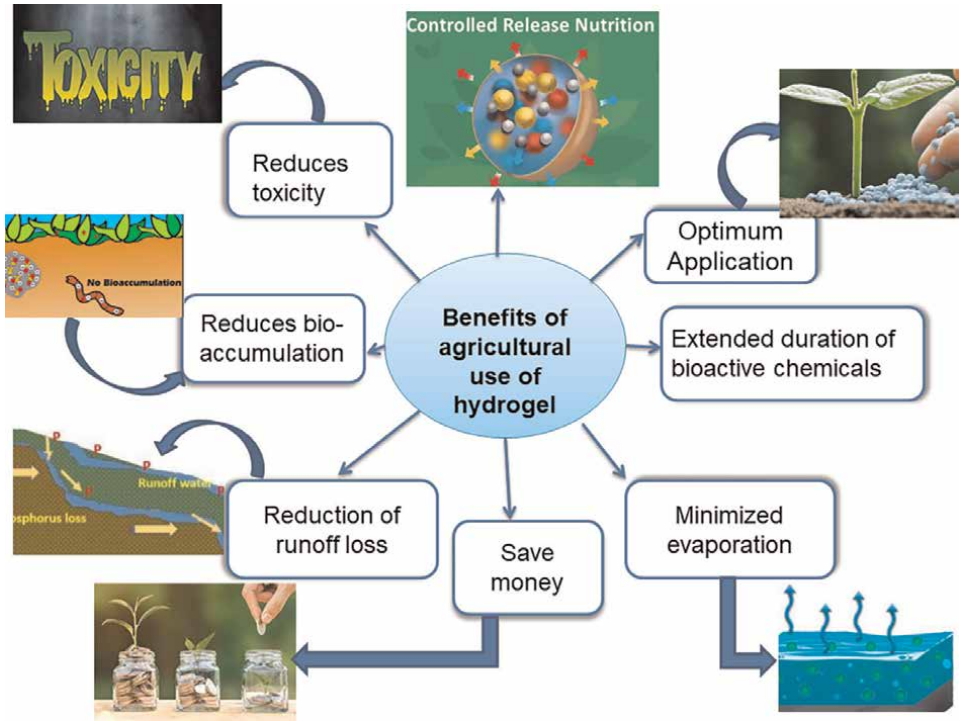


Figure 1.
Advantages of hydrogel in field.

a. High water retaining ability with slow-release behavior

b. Excellent efficiency

c. Appreciable permeability and infiltration rate

d. Highly stable enough under various environmental conditions for the prolonged use

e. Reduced frequency of irrigation

f. Ability to undergo biodegradation without affecting soil fertility

g. Enhanced plant growth in arid and semiarid conditions

The use of smart hydrogels in agricultural sector have attracted great attention as water management material in soil and matrices for the controlled release of primary and secondary fertilizers. The release rates of hydrogels [23, 27] are depends on the functional groups that are present in the polymer, functionality of crosslinker, pH, temperature, ionic strength of the medium, etc. Besides, the incorporation of natural pre-polymers in synthetic polymer hydrogel will bring down the operation cost, since they are readily available at a low cost and highly biodegradable. Nevertheless, natural polymer incorporation may induce a few limitations such as the lack of solubility of monomers in aqueous

and non-aqueous solvents during hydrogel synthesis [16]. This characteristic behavior will result in excess utilization of pre-polymers to enhance agricultural yield.

The additional expected physicochemical and mechanical properties from the synthesized hydrogel for field applications are good stability during swelling (without dissolving), photostability, ability to uptake and hold maximum water with good swelling rate, particle size, maximum fertilizer uptake, porosity, odorless, neutral pH, colorless, low residual monomer content, non-toxicity, biodegradability without yielding toxic reside, and low cost [28, 29]. However, it should be remembered that the synthesis of hydrogel with all these features is difficult to achieve. However, some of its features namely porosity, stimuli responsiveness (pH and temperature), residual monomer content and swellability [30–32] are fine-tunable. The extent of hydrogel swellability, which are amended in the soil can be fine-tuned based on the requirement by making modification in the functional groups such as $-NH_2$, $-COOH$, $-OH$, $-CONH_2$, $-CONH-$ and $-SO_3H$. Besides, osmotic pressure, movable counter ions and capillary effect have also influenced swelling and release phenomena [33]. During swelling, the process of water uptake by the hydrogel will follow multiple steps that include hydration of polar hydrophilic and hydrophobic groups leading to the formation of primary and secondary bound water respectively. Meanwhile, infinite dilution of the hydrogel network will be resisted by the formation of either chemical or physical cross-links. Hence, the water molecules that are entering into the network during the initial and equilibrium stages are known as total bound and bulk water/free water respectively. During swelling these water molecules shall occupy the gaps available between chains and the midpoint of pores. The quantum of water uptake by the hydrogel networks is influenced by various parameters such as temperature, pH, nature of interactions, etc. that exist between networks and water molecules [33]. The list of representative hydrogels that are used as water-retaining agents and matrices for the controlled release of nitrate, potash, phosphate fertilizers are presented in **Tables 4–7**.

Representative hydrogel	**Reference**
Starch-modified poly(acrylic acid)	[15]
Hydrogels based on polyacrylamide and natural cashew tree gum	[34]
Wheat straw cellulose hydrogel based hydrogel	[35]
Hyaluronate-Hydroxyethyl acrylate blend	[36]
Acrylic acid and acrylamide copolymers	[37]
Polyacrylamide based hydrogel	[38]
Guar gum-g-poly(sodium acrylate)	[39]
Radiation induced crosslinked polyacrylamide	[40]
Glycerol and poly(vinyl alcohol) hydrogel	[41]
Gum ghatti-poly(acrylic acid–aniline) hydrogels	[42]
Acrylamide and hyper-branched polyethyleneimine based hydrogel	[43]
Acrylic acid-co-acrylic amide based hydrogel	[44]
Poly(acrylamide-co-acrylic Acid)/$AlZnFe_2O_4$	[45]
Poly(ethylene glycol) and Poly(acrylate) copolymer	[46]
Partially neutralized acrylic acid and NVP	[47]
Oxyethylene segments of poly(ester-amide) and poly(tartaramide)	[48]

Representative hydrogel	Reference
Aluminum sulfate octadecahydrate crosslinked carboxymethyl cellulose and aluminum sulfate octadecahydrate crosslinked starch	[49]
Modified poly(ethylene glycol) crosslinked with poly(sodium acrylate)	[50]
Poly(acrylic acid) grafted on carboxymethyl chitosan copolymer	[51]

Table 4.
Hydrogel used as soil conditioner and water retention material in soil.

Typical hydrogel	Reference
Microwave-mediated biochar-hydrogel composites	[52]
Polyvinylpyrrolidone (PVP)/carboxylmethyl cellulose	[53]
Acrylamide and acrylic acid based hydrogels	[54]
Glutaraldehyde crosslinked chitosan-poly(vinylalcohol) hydogel	[55]
Borassus aethiopum starch and Maesopsis eminii hydrogels	[56]
Poly(acrylonitril)-based poly acrylic acid hydrogels,	[57]
Acrylamide and N-hydroxymethyl acrylamide hydrogel	[58]
Natural rubber, cassava starch crosslinked by glutaraldehyde hydrogel	[59]
Starch phosphate carbamate hydrogel	[60]
Starch cross-linked acrylic acid and acrylamide hydrogel	[61]
Poly (acrylamide-*co*-acrylic acid)/kaolin gel	[62]
Poly(maleic anhydride-*co*-acrylic acid) hydrogel	[63]
Poly(acrylic acid)/attapulgite/sodium humate composite hydrogel	[64]
Poly(acrylamide) and methylcellulose based hydrogels	[65]
N,N^1-MBA crosslinked acrylic acid	[12]

Table 5.
Representative Hydrogel used for the controlled release of nitrogen fertilizer.

Chemical nature of hydrogel	Reference
Biodegradable Gelatin-Tapoica/polyacrylamide	[66]
N,N'-MBA crosslinked starch hydrogel	[67]
Poly(vinyl alcohol)/chitosan crosslinked with glutaraldehyde	[68]
Methylcellulose and hydroxypropyl methylcellulose based hydrogel	[69]
Arabic gum-based hydrogel	[70]
Pine resin backbone based hydrogel	[71]
Clay-based nanocomposites hydrogel	[72]
κ-carrageenan-based hydrogel	[73]
poly(lactic acid)/cellulose-based hydrogel composite	[74]
poly(acrylic acid-co-acrylamide)/kaolin hydrogel	[75]

Table 6.
Typical hydrogels used as matrices for the controlled release of potassium.

Name of the hydrogel	Reference
Carboxymethyl cellulose based hydrogel	[76]
Alginate-cellulose nanofibers–poly(vinyl alcohol) hydrogel	[77]
Hybrid nanocomposite banana peel cellulose and layered double hydroxides nano-sheets	[78]
Carboxymethyl starch-g-polyacrylamide	[79]
pH sensitive sodium alginate, acrylic acid, and acrylamide based hydrogel	[80]
Biodegradable crosslinked acrylic acid based hydrogel	[81]
sulfonated-carboxymethyl cellulose, acrylic acid and polyvinylpyrrolidone based hydrogel	[82]
Poly(acrylic acid) and sugarcane bagasse hydrogel	[83]
Poly(vinylalcohol)-phosphate gels	[84]
Alginate-graft-polyacrylamide hydrogel	[13]

Table 7.
Representative hydrogels used for the controlled release of phosphate fertilizer.

4.2 Effects of hydrogel amendment

Smart hydrogel amendment in the soil during cultivation process will alter the hydraulic conductivity and pore size of soil to some extent due to water absorption [85, 86]. However, it will improve residual and saturated water content, which results in the reduction of subsequent water loss and infiltration due to percolation, this will facilitate aeration in soil due to expansion and contraction of hydrogel through absorption and evaporation [85]. The suitability of hydrogel for semi-arid and arid regions was due to the release of water and fertilizers with reference to environmental temperature, which results in increased survival [85] of plants. Besides, the hydrogel amendment has reduced the uptake of toxic metals and soil salinity by plants [87, 88].

4.3 Safety aspect and environmental concern

The practical applicability of hydrogel in field applications is dependent on safety, toxicity and eco-friendly degradability under soil conditions after its service and other environmental issues. Most of the hydrogels used in agricultural sector have stable service life (5–7 years), but their degradability is suspected. Hydrogels amended in the soil will experience stress from various factors such as microbes, light, pH, temperature, etc. The degradability of hydrogels depends on their structures and other environmental factors such as intensity of light, soil microbes, heat, pH, etc. The degradability of hydrogels could be attained by incorporating favorable functional groups such as ester, amide, urethane, anhydride, glycocidic (ether), urea, orthoester, carbonate, etc. in the backbone. The degradation sequence of polymers have predicted as anhydride > ester> orthoester> carbonate> urea>urethane> ether [89].

The monomers of hydrogels are known to be toxic and carcinogenic, but the polymer derived from the same monomers are proved to be non-toxic [18]. This characteristic behavior could be attributed to low boiling point and the low molecular weight of acrylic monomers and crosslinkers, which may effortlessly enter into the human body through skin absorption and inhalation [90, 91]. The studies have also recorded that these acrylic monomers imposed wide a range of health effects such as

skin and eye irritation, allergic action, asthma, nerves problem, internal organ toxicity and impacts on fertility [90, 91]. The contentious exposures of acrylates will yield acrylic acid [90, 91] in the human body during metabolic activity. However, the crosslinked hydrogels will not cause any harmful effects on living organisms due to their insolubility and non-volatile nature [90, 91].

5. Conclusions

The chapter is focused on the development of smart hydrogels derived from synthetic monomers and natural pre-polymer for agricultural application as water retaining material and matrices for the controlled release of fertilizers. However, in the majority of the report, the mechanical properties of those hydrogels are not good enough for prolonged application in the field. Hence, this chapter addressed the route in which the mechanical properties of such hydrogel are fine-tuned. Besides, it focused on the typical hydrogels that are used for the controlled release of water, urea, potash and phosphate fertilizers, their advantages in the field, effects on the hydraulic conductivity of soil and their safety aspects.

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Conflicts of interests

The authors declare that no conflicts of interests.

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