



Review

Hydrogels Based Drug Delivery Synthesis, Characterization and Administration

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Abstract: Hydrogels represent 3D polymeric networks specially designed for various medical applications. Due to their porous structure, they are able to swollen and to entrap large amounts of therapeutic agents and other molecules. In addition, their biocompatibility and biodegradability properties, together with a controlled release profile, make hydrogels a potential drug delivery system. In vivo studies have demonstrated their effectiveness as curing platforms for various diseases and affections. In addition, the results of the clinical trials are very encouraging and promising for the use of hydrogels as future target therapy strategies.

Keywords: hydrogels; drug delivery; target therapy; polymers; biocompatibility; in vivo administration

1. Introduction

Hydrogels are three-dimensional (3D) polymeric networks, whose hydrophilic structure allows the absorption of large amounts of water (thousands of times their dry weight) [1]. Hydrogels consisting of synthetic polymers are currently gaining more interest than natural-derived polymers due to their enhanced life-time, higher capacity to absorb water [2], improved mechanical properties [3] and finely-tuned degradation [4]. Depending on their structure, hydrogels can be chemically stable or easily degradable [5]. According to the type of cross-linking between the polymers, hydrogels can be classified in physical, held together by non-covalent, reversible interactions and chemical hydrogels, linked by non-reversible covalent bonds [4].

Their unique properties, including reliable biocompatibility, tunable mechanical and degradation features, sensitivity to various stimuli and the ability to be easily conjugated with hydrophilic and hydrophobic therapeutic compounds [4] has made them important candidates in biomedical applications including drug delivery [6], tissue engineering [7–9], 3D cell cultures [10], in vitro diagnostics and stem cell research [1] (Figure 1).

In the therapeutic area, drug delivery approaches require outstanding improvements in obtaining safe transport systems in order to achieve the desired therapeutic effect and to avoid the side effects. Biomimetic strategies involving polymers describe innovative industrial products orientated to target therapy and controlled release. Hydrogels inspired design offer favorable conditions for therapeutic compounds encapsulation and protection. Furthermore, they are becoming biological responsive structures which ensure adequate biocompatibility and biodegradability.

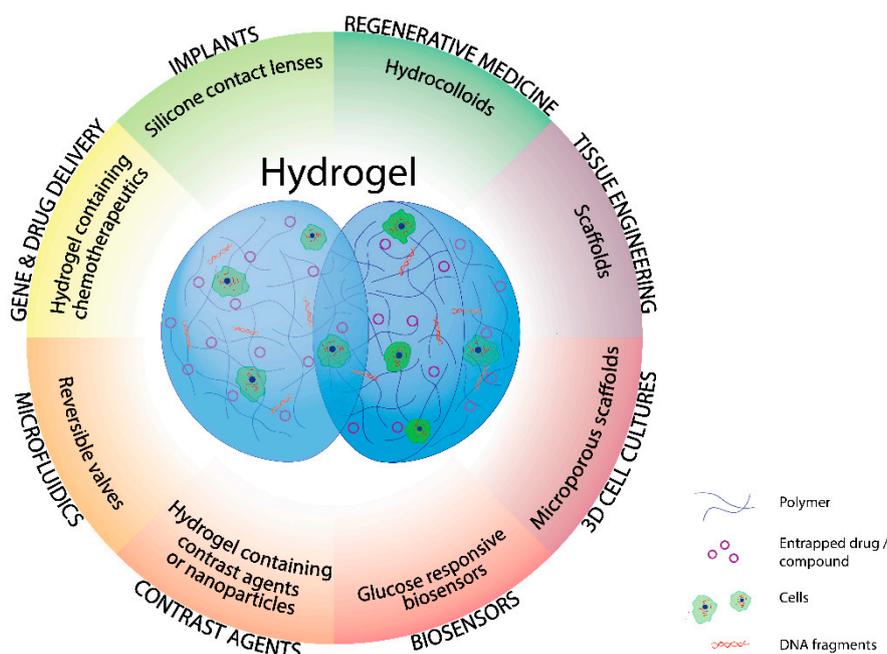


Figure 1. Hydrogel medical applications.

2. Hydrogel Synthesis Methods

Hydrogel synthesis is an essential step in developing new structures with beneficial properties for drug delivery action. The hydrogel structure is defined by the hydration of hydrophilic groups and domains of the polymers involved. Therefore, these groups and their interconnected chains create three-dimensional networks via crosslinking, avoiding their dissolution in the aqueous phase [2,11].

The standard synthesis procedures imply polymerization and crosslinking. These techniques can happen in parallel in one step, or one after the other in multiple steps [2].

Polymerization process is part of the gelation process. The structure and the conformation of the starting material influence the formation of soluble branched polymer networks [12]. The starting material refers to polymer monomers, prepolymers, or hydrophilic polymers [13]. The monomers and polyfunctional comonomers act as crosslinkers in network development. Sometimes polymerization is generated by radical initiators [14,15] or photoinitiators [16,17] like irradiation [18–20].

Hydrophilic polymers are often used for hydrogel synthesis due to their biocompatibility [21,22] in aqueous environments [23] and mostly due to their loading drug potential [24].

The swelling property of a hydrogel is significant for further use in medical applications because most of the body tissues are composed of large amounts of water [25]. Swelling features of various polymers are advantageous for functionalization with therapeutic agents. On the other side, the effectiveness of such systems could consist of their capacity to deliver these agents without side outcomes.

The crosslinker agent plays a significant role in hydrogel swelling [26] and degradation [27]. It influences the physical properties of the final hydrogel product [28]. Crosslinking methods imply covalent or non-covalent interactions between polymer monomers providing elastic characteristics [2,11,29,30]. For this reason, two different types of hydrogels were identified: chemical gels based on covalent interactions (Figure 2C) and physical gels based on non-covalent interactions [11] (Figure 2B).

On the other hand, there are factors involved in altering hydrogels assembly [31]. Chemical stimuli (pH [32,33], ionic strength [34,35], solvent composition [36], and molecules [37]) (Figure 2A) lead to permanent gels. Physical stimuli (temperature [38], electric field [39], magnetic field [40], light [16,41], pressure [42]) (Figure 2A) determine the reversible conversion between un-swollen and swollen state called phase transition. Biological stimuli (enzymes [43], antigens [44], and nucleic acids [45])

(Figure 2A) affect the physical properties of the hydrogels like solubility [46]. These stimuli-responsive polymers belong to the group of intelligent or smart materials [47,48].

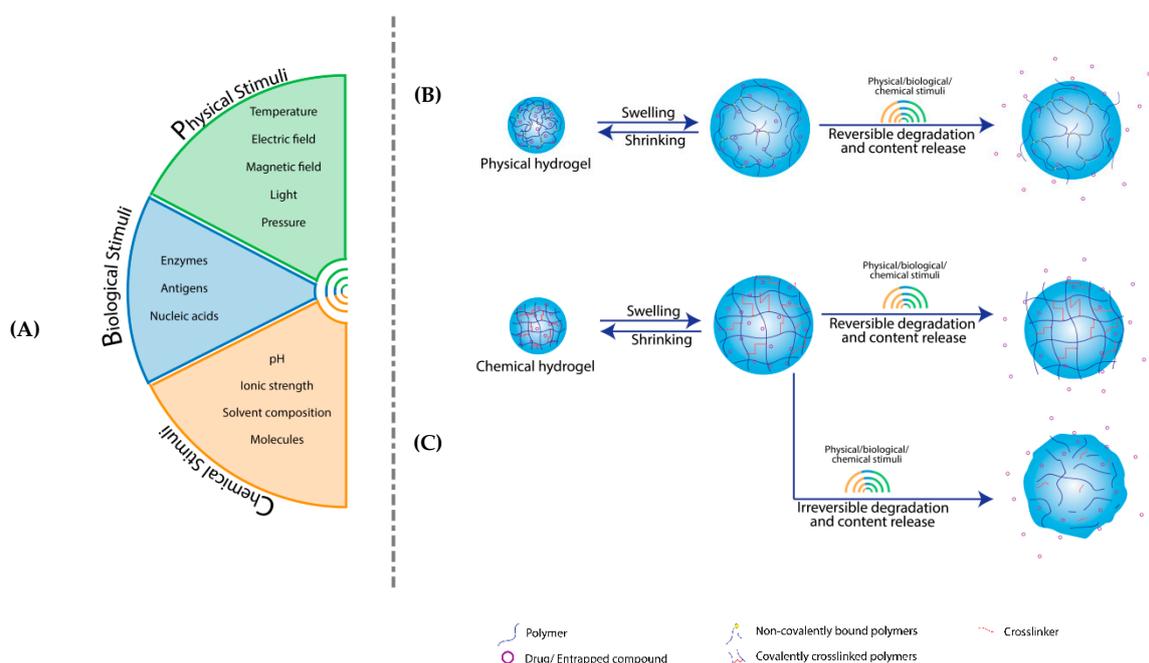


Figure 2. Stimuli sensitive hydrogels structural changes. (A) Stimuli categories: physical, biological and chemical. (B) Physical hydrogels are non-covalently crosslinked and in an aqueous environment, they swell. Under various stimuli presence, they undergo reversible structure modifications and release the compound. (C) Chemical hydrogels describes covalently crosslinked formulation that swells in aqueous conditions and then suffers reversible or irreversible alterations depending on stimuli presence and crosslinking strength, which influence their discharge.

Smart polymers can form self-assembly structures through two significant procedures: using peptide/protein materials or using hybrid systems containing minimum a synthetic macromolecule and a peptide/protein motif [49]. Their synthesis includes supramolecular chemistry and the control of the dynamic of supramolecular interactions and bonds for future media conditions [50]. Proteins and peptides extend the system properties to degradability, stimuli-responsive phase transition, and also biological molecules targeting [51]. Such smart hydrogels own convenient characteristics for drug delivery systems through their structural, morphological, and functional modifications occurred due to stimuli detection [52]. These modifications ensure a time-dependent controlled release of the therapeutic agent with long circulation time converging to minimal side effects [53].

3. Classification

Hydrogels can be classified considering different parameters like: polymer origin, ionic charge and biodegradability [54].

According to the polymer origin, the hydrogel composition can be synthetic, natural or it can contain both synthetic and natural polymers and is called hybrid [55]. Lately, the synthetic hydrogels are preferred due to their high water absorption properties, long life, and also a variety of chemistry which confers better strengths and resistance in different conditions [2].

Ionic charge influences the uptake of the charged drug molecules. A positively charged hydrogel will embed and release negatively charged low molecular weight molecules [56]. Furthermore, the ionic charged hydrogels have implications on cellular interactions and behavior [57].

Biodegradable hydrogels need to meet some specific features as biocompatibility and adaptability to various media conditions and preparation procedures. Such hydrogels are potential candidates for

drug delivery applications because of their flexibility. Biodegradation process describes a chemical decomposition of a complex hydrogel into a simple structure through solubilizing or hydrolysis dictated by various external stimuli like pH, ionic strength, temperature or enzymes [27]. Therefore, these hydrogels can be divided into chemical, physical and biological stimuli responsive categories.

Otherwise, non-biodegradable hydrogels offer multiple possibilities for tissue engineering applications by encapsulating growth factors, proteins [58]. Other medical fields that are exploiting these type of hydrogels are plastic and reconstruction surgery, orthopedic implants, ocular lens, and microfluidic devices [59].

Table 1 summarizes important classes of hydrogels and their properties and applications.

Table 1. Hydrogel classification according various parameters, their properties and corresponding applications.

Parameter	Hydrogel Type	Hydrogel Composition	Properties	Applications
Chemical stimuli	pH responsive	Carboxylated agarose/tannic acid hydrogel scaffolds cross-linked with zinc ions [60] Poly(acrylamide-co-acrylic acid) poly(AAm-co-AAc) hydrogels [61]	Sustained release of the incorporated drugs [60] Biocompatibility [60] Strong electrostatic interactions and stability [61] Increased hydrophilicity and swelling [62]	Drug delivery [54,60] Sensing [63]
	Ionic strength responsive	2-acrylamido-2-methylpropane sulfonic acid crosslinked with <i>N,N'</i> -methylene(bis)acrylamide [34] Poly(<i>N</i> -isopropylacrylamide) crosslinked with imidazolium-based dicationic ionic liquid [64]	Increased swelling properties [34] Controllable porous structure [34] Biodegradability [65]	Depollution of aqueous ecosystems [64] Drug and gene delivery [47] Tissue engineering [47]
	Solvent composition responsive	Fluorenylmethoxycarbonyl diphenylalanine [36] Poly(<i>N</i> -isopropylacrylamide) and poly(<i>N,N</i> -dimethylacrylamide) mixtures [66] Poly(<i>N</i> -isopropylacrylamide) [67,68]	Uniform networks [36] Swelling behaviour responsive to temperature too [66] High porosity, Heterogeneous structure [67]	Sensing [68]
	Molecules responsive	<i>N</i> -isopropylacrylamide crosslinked with <i>N,N'</i> -methylenebis(acrylamide) [69] Acrylamide crosslinked with polyethylene glycol [70]	Achieves molecular recognition, High affinity and specificity [71] Controlled assembly [72] Controlled release [43] Enzyme responsive [70] Antigen responsive [69]	Sensing [73] Drug delivery [37] Cell culture [72]
Physical stimuli	Temperature responsive	<i>N</i> -trimethyl chitosan chloride polymers crosslinked with poly(ethylene glycol) and glycerophosphate [74] Poly(<i>N</i> -vinylcaprolactam) grafted with poly(ethylene oxide) [75] Poly(<i>N</i> -isopropylacrylamide) and aminated alginate [76] Poly(<i>N</i> -vinylcaprolactam) [77] Methoxy poly(ethylene glycol)-poly(pyrrolidone-co-lactide) [78]	Two categories: low critical solution temperature [74] and upper critical solution temperature [75] Sol-gel transition at 37 °C [79] Easy functionalization with drug molecules [80] Unique physical properties similar to extracellular matrix [81] Controlled degradation [76]	Tissue engineering [76–78,82], Drug delivery [80,82]
	Electric field responsive	Polypyrrole polymeric nanoparticles loaded in poly lactic-co-glycolic acid and poly(ethyleneglycol) hydrogel [83]	Controlled release of the cargo [84] depending on the strength or the duration of applied electric field [83] Biocompatibility, Minimal invasiveness [83]	Drug delivery [84]
	Magnetic field responsive	Hemicellulose crosslinked with O-acetyl-galactoglucomannan [85] Gelatin hydrogels loaded with magnetic nanoparticles [86]	Successful absorption and controlled release of drugs [85] Some of them dispose of anisotropic properties [87]	Tissue engineering [86] Microfluidics, drug delivery, contrast agents [88]

Table 1. Cont.

Parameter	Hydrogel Type	Hydrogel Composition	Properties	Applications
Physical stimuli	Light responsive	Hydroxypropyl methylcellulose and Carbopol hydrogels containing diclofenac-sodium chitosan microspheres [89] Poly[2-((4,5-dimethoxy-2-nitrobenzyl)oxy)-N-(2-(methacryloyloxy)ethyl)-N,N-dimethyl-2-oxoethan-1-aminium] [90]	Reasonable strengthens according to application [89] Reversible and irreversible, Spatiotemporal control over functional groups, Controlled release [91]	Drug delivery [89] Self-sterilization and self-cleaning [90] Microfluidics [92]
	Pressure responsive	Polyacrylamide and poly(acrylamide-hydroxyethyl methacrylate) [93]	Thermo- and pH sensitive [94] Adhesion capacity, elasticity [93]	Sensing [95] Drug delivery [96]
Polymer origin	Natural	Nanofibrillar cellulose [97] Thiolated gelatin-poly(ethylene glycol) diacrylate [98] Methacrylated gelatin [99] Polycaprolactone sandwiched in a gelatin-chitosan hydrogel [100]	Biomimetic and adhesion capacity [101] Mechanical support for cell development [102]	Tissue engineering [101,103,104], Drug delivery, Sensing [102]
	Synthetic	Low acyl gellan gum bilayered hydrogel scaffolds [105] N-isopropylacrylamide and itaconic acid [106] Poly(ethylene glycol)—poly(propylene glycol) copolymers [107]	Controllable structure and other physico-chemical properties [102] Stimuli responsive [106]	Drug delivery [106] Tissue engineering [108]
	Hybrid	Alginate-polymethacrylate [109] Chondroitin sulfate and poly(ethylene glycol) [110] Chitosan/hyaluronic acid hydrogels loaded with poly(lactic-co-glycolic acid) microspheres [111]	Biomimetic capacity [109] Multicomponent [112] Heterogeneous composition [113] Responsive to environment changes [114]	Tissue engineering, drug delivery [112] Wound-healing [111]
	Biodegradable	Chitosan-gelatin [115] Pectin-co-poly(methacrylic acid) [116]	Stable and biocompatible [116] Biomimetic capacity [117] Natural and synthetic polymeric structure [117] Stimuli responsive [118]	Drug delivery [116] Tissue engineering [117]
Biodegradability	Non-biodegradable	Poly(2-hydroxyethyl methacrylate) [58] Poly(2-hydroxyethyl methacrylate)/trimethylolpropane trimethacrylate [119]	Biocompatibility [58] Sustained release and recharge [119]	Tissue engineering [58] Drug delivery [119] Plastic and reconstruction surgery [120]

4. Hydrogel Functionalization with Therapeutic Agents

Crosslinking synthesis methods make possible the functionalization with drugs and other therapeutic agents in order to develop new delivery systems [121]. The hydrogel design describes cross-linked polymers and meshes that allow compound solution loading and diffusion. When functionalizing, the size of the meshes is to be taken into consideration [122]. This procedure can be performed at two different times of hydrogel synthesis: at the beginning by mixing the drug with the other reagents or at the end after hydrogel is done [29]. In situ loading method suits for hydrophilic drugs and is based on dissolving the drug into the water together with the polymer powder. The other technique is called post-loading and refers to dry hydrogel films immersion into drug solution for a certain period of time. In both of these cases, after drug incorporation, the hydrogel has a dried state and confers protection. In addition, cross-linkers are essential factors in controlled release of high or low molecular weight therapeutic agents, and in most cases the degradable cross-linkers are preferred [56].

Wong and Dodou, 2017, synthesized poly(ethylene oxide) hydrogels cross-linked with pentaerythritol tetra-acrylate using ultraviolet light for cross-linking reaction. These hydrogel films were loaded with various drugs (lidocaine hydrochloride, diclofenac sodium and ibuprofen) using post-loading and in situ loading methods. The study results revealed that in situ loading procedure was more successful regarding drug encapsulation [123].

Prince et al., 2019, used in situ loading technique for thermoresponsive poly(ϵ -caprolactone-co-lactide)-block-poly(ethylene glycol)-block-poly(ϵ -caprolactone-co-lactide) hydrogels functionalization with celecoxib. PEG's length affects hydrogel loading capacity and 2000 g/mol was found to be the optimal length for drug delivery applications [124].

Many drugs and small molecules, especially the hydrophobic ones, can be encapsulated in order to enter the gel for further medical applications. For instance, many nanosystems (metallic [125], lipid [126], polymeric [127], peptides [128]) are used for targeted delivery [129]. Nanoparticles are fashioned to ensure drug pharmacokinetics and pharmacodynamics [130].

The use of nanoparticles can help the crosslinking reaction by adsorbing or attaching to polymer chains [131], but also they can modify the hydrogel assembly properties [132]. Due to the porous hydrogel structure, nanoparticles are easily embedded within a polymeric 3D network. This aspect is mandatory for achieving controlled release profile and can impede in choosing the right nanoparticles for drug molecules delivery, respectively those for hydrogel functionalization [133]. Other nanoparticle physico-chemical properties like size, polydispersity index, and spatial orientation inside the gel need to be carefully adjusted [134].

High loading capacity combined with controlled drug release and prolonged stability, will represent advantages for the newly designed system [135].

Nanoparticle functionalized gels can perform targeted drug delivery in different ways: passive [136], stimuli-responsive [137], site-specific [138] or detoxification manner [139].

5. Characterization Methods

When considering hydrogel characteristics usually investigated, the typical protocol will most probably compose of two kinds of tests: structural and functional. For structural analysis, an assortment of microscopy techniques have become, to a degree, the golden standard. As hydrogels are three dimensional, commonly optically clear, materials, conventional bright field microscopy is sparsely used. By far, the most common technique is Scanning Electron Microscopy (SEM). An extensive review of morphological characterization of hydrogels has been recently published [140], and it implies that an SEM is a go-to instrument for hydrogel characterization regardless of composition. SEM imaging does require specialized sample preparation instrumentation, but the methodology was standardized to most gel types. Briefly, formalin fixed samples are dehydrated and freeze-dried, followed by either Au or Au/Pd sputtering under vacuum before imaging [141]. Newer protocols forgo the fixation and dehydration steps [142] even though there is evidence that liquid nitrogen snap freezing followed by freeze-drying induces gel shrinkage and incorrect evaluation of pore size [143,144]. SEM is generally used to assess pore formation and pore size [145], crosslinking status [146] and the effect certain loading compounds have on general gel structure [147].

While SEM does provide valuable qualitative information, alternatives do exist and can potentially provide complementary information to the limited capacity of regular SEM of generating two-dimensional projections. Laser scanning confocal microscopy (LSCM), used in combination with fluorescent dyes is capable of generating Z-stacks to evaluate similar aspects (i.e., pore dimensions and shape) to SEM [140,148]. Where LSCM shines is the complementary characterization capacity it has. Hydrogel loading and unloading of solutes [149], dispersion and mobility of the solute [150] or distribution of solid loading materials [151] are tested with the condition that the solute (or other compounds of interest) is fluorescent or can be spiked/bound to a fluorescent marker. Structural characteristics, along with mechanical properties, can also be observed by different variations of Scanning Probe Microscopy. It was proved that the elastic modulus of the gel correlates is correlated

with cell differentiation [152] and migration [153]. As the modulus of the hydrogel correlates with the degree of polymer cross-linkage [154] and cross-linkage to solute mobility through the gel [155], Atomic Force Microscopy is a powerful multimodal analysis tool in the characterization of hydrogels, allowing not only topological and roughness investigations but also functional ones. Of course, all the techniques presented can be used in parallel or correlatively to offer complementary information or potentially highly specific characteristics such as individual pore mechanics [156].

Functional analysis is paramount to understanding the effects that solute/external stimuli have on the hydrogel. The most important ones seem to be: absorption capacity and rate, absorbency under load, lowest solute, and extra monomer level, pH, and photostability [2]. Drug release from the hydrogel is usually a function of the diffusion capacity of the drug and the retention capacity of the gel. This is most commonly measured by dynamically probing the concentration of the drug in the medium of interest and plotting the concentration against a certain time interval or as a percentage. The actual analysis is highly dependent of the nature of the tested compound and can range from HPLC for peptides [157], electrochemical probing for gases such as H₂S [158] or various fluorescence/colorimetric/absorbancy tests.

The controlled release can be achieved through various strategies based on hydrogel composition and properties. For instance, there are some molecules that can initiate and enhance the degradation rate [159,160]. Matrix-metalloproteinases family members can cleave the oligo-peptide bonds [161]. Other examples are represented by glucose [162] and thrombin [163], which are playing important roles in physiological processes. On the other hand, external stimuli [164,165] can determine hydrogel networks disruption. Hydrogels swelling capacity is an important target for the sustained release mechanism [166] and is also influenced by stimuli sensitivity [167].

In addition, hydrogel mechanical deformation using magnetic field or ultrasounds is a very common procedure. In this regard, Liu et al., 2006, proposed an intelligent magnetic hydrogel loaded with drug molecules capable of tunable controlled release profile time dependent [168]. Ultrasound guided drug release approach was digitally integrated into ionically crosslinked hydrogels [169].

Many mathematical models are used for predicting the drug delivery efficiency of polymeric hydrogels. These determinations are based on mesh size, mechanical, mass-transport and diffusion behavior using hydrodynamics, obstruction, free volume and combined theories [166,170].

6. In Vivo Biocompatibility and Biodegradability

In order to compare and investigate the effects of hydrogels in vivo, it is necessary to evaluate its biocompatibility, since living organisms are prone to develop inflammatory reactions which are facilitated by the degradation of the synthetic polymers [171]. As stated in a review by Naahidi et al., hydrogel toxicity and biocompatibility is dependent on the breakdown of the polymer into monomers or oligomers, the crosslinking agents or trace polymerization agents [172]. Besides achieving favorable hydrogel formulations for drug delivery, the main challenges are performing toxicity screening [173], maintaining long-term stability, and controlling the release properties of the therapeutic agents. One favorable aspect of hydrogel research has been its longevity. The over 100 years of research have produced gel-like biopolymers with low toxicity and high biocompatibility, especially those derived from natural molecules such as collagen, chitosan, fibrin, and hyaluronic acid [174]. However, while previous in vitro studies have shown promising results regarding the biodegradability and biocompatibility of these compounds, further in vivo studies are necessary at this point [175].

7. Hydrogel Administration

As mentioned above, a complex problem regarding the administration of various biomaterials in vivo reflects the ability of the material to conserve and promote a biologically safe environment for the subjected animals. In vivo testing is challenging because there still is a need for an established and reliable animal model in order to achieve biomechanical restoration. Following these standards, different injectable hydrogels protocols were developed and optimized, which because the body very

well tolerated them, are ideal candidates for performing *in vivo* testing on rodents [176]. Given the fact that these delivery systems are suitable for clinical use, the most accessible routes of administration are subcutaneous [177], oral [178], rectal [179], topical and transdermal [180], orthotopic [181], intraperitoneal [182] and ocular [183]. Figure 3 represents all these administration routes.

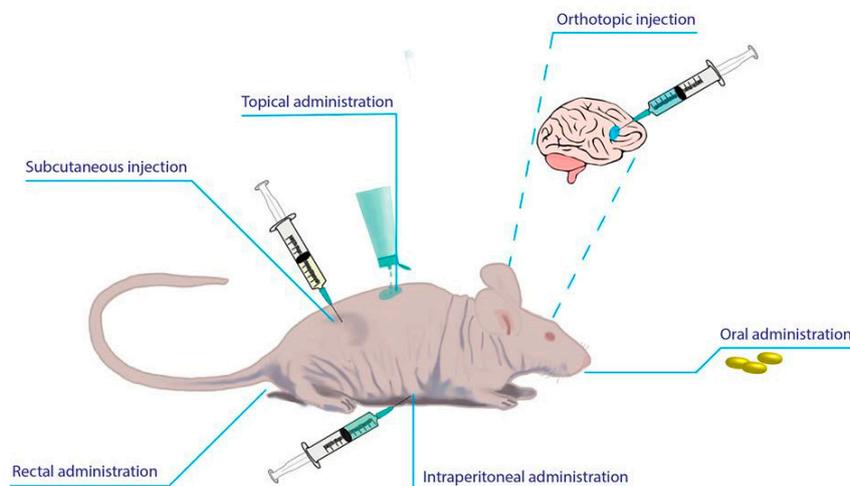


Figure 3. *In vivo* drug delivery hydrogel routes of administration. There are various methods for *in vivo* administration of hydrogel based products depending on the pathological conditions and their localization. Subcutaneous injection plays a crucial role in toxicological effects evaluation. Topical or transdermal application is preferred for skin associated problems. Orthotopic and intraperitoneal injections are non-invasive techniques which ensure good therapy results. On the other hand, oral administration has some limitations because of digestive enzymes.

7.1. Subcutaneous Hydrogel Delivery System

One of the most efficient methods to evaluate the response to the therapy and assessing the toxic response *in vivo* in mice is performing a subcutaneous injection. Since the subcutaneous area is vascularized, the implanted hydrogels or other biomaterials are immune privileged, so a mild reaction to foreign moieties is to be expected [176]. Bare polyethylene hydrogels have been proven to not exhibit cytotoxicity in murine models even after 60 days when injected subcutaneously [184]. Similar results regarding biocompatibility were obtained with ellagic acid hydrogels [185], nano-patterned poly-acrylamide hydrogels [186] chitosan and gelatin hydrogels [187,188], alginate [189] and pectin [190]. It is worth mentioning that the majority of the studies do report mild inflammatory responses.

7.2. Oral Delivery

The oral delivery route represents by far the most convenient solution under adjustable parameters and patient compliance [191]. Orally administered hydrogels should provide bioavailability depending on medium particularities, such as pH variations along the intestinal tract [192]. MPEG, caprolactone and, itaconic acid pH-sensitive hydrogels were tested for acute oral toxicity in BALB/c mice and showed no signs of toxicity [193]. When considering oral ingestion, the metabolic effect that monomers have on the organism is very significant. Poly-glycolic and poly-lactic-*co*-glycolic acid hydrogel degradation have been shown to affect healthy metabolism [172], leading to some limitations in terms of hydrogel therapy such as:

1. Presence of digestive enzymes could lead to denaturation;
2. Low permeability through the epithelial membrane into the bloodstream;
3. Superior and inferior digestive systems can represent potential therapeutic targets [194].

7.3. Rectal Delivery

Rectal administration offers plenty of advantages such as rapid absorption of the compound, avoidance of the gastrointestinal tract, limited adverse reactions of the therapeutics, and provides controlled release of the compound in the context of the stable environmental conditions encountered in the rectum. Based on an earlier study that showed excellent biocompatibility on the digestive tract [195], rectally administered catechol-chitosan-based hydrogels with mucoadhesive properties have been tested in murine models and show no toxic effects after 10 days [196]. Regarding this issue, Afaf A. et al., developed a hydrogel-based product and made a correlation between in vitro and in vivo profile with promising results [179].

7.4. Topical and Transdermal Delivery

Hydrogel therapy is suitable for the topical and transdermal approach. Nowadays, the general concept about nanosystems in the context of skin penetration is that the skin barrier restricts the delivery via epidermis and dermis. In truth, hydrogel penetration through the skin seems unlikely as the macroscale mesh-like structure would prohibit penetration and has been shown, in the case of collagen hydrogels, to not even affect burn models [197]. Various alternative hydrogel formulations are commonly tested on graft donors with no discernable side effects compared to other gel-based formulations commonly used in hospital environments [198]. Recent studies demonstrated that this method of delivery is reliable as a delivery system for nanoparticles with various roles, and it only depends on nanoparticles diameter, charge, and structure. The coating influences the penetration rate. Peptide layered nanocarriers are more efficient than pegylated ones. Ex vivo studies were carried out, using skin samples collected from mouse and human through surgical resection [199].

7.5. Orthotopic Injections

Administration of hydrogels via intratumoral injection is a practical approach, which requires the release of the nanostructure system loaded in a hydrogel matrix. These hydrogel structures are so-called “macroscopic gels” that are coming with the imperative need to decrease potential damages of associated tissues during an injection [200]. Qinjie Wu et al., 2015 synthesized a smart hydrogel responsive to temperature, which prevented the formation of peritoneal adhesion on a damaged abdominal wall [181]. Where orthotopic treatment using hydrogels seems to show promise is in the post-resection cavity where it can act as a slow release to improve long term survival [201,202].

7.6. Intraperitoneal Delivery

Intraperitoneal administration of hydrogel systems shows promising results and is considered to be a noninvasive option, as well as an optimal formulation for various pharmaceutical agents. One of these structures was prepared by Chih-Hao Chen et al., in 2018 and was successfully incorporated in the mouse peritoneum achieving dual action: drug delivery and postoperative anti-adhesiveness [203]. Similarly to orthotopic injected hydrogels, intraperitoneal hydrogels (mostly gelatin based gels) by themselves show no cytotoxicity and high degrees of biocompatibility [204]. It is worth mentioning that the capacity of the gels to absorb high amounts of water could be detrimental in the case of any injectable formulations [182].

7.7. Ocular Delivery

Formulations for ocular delivery are complicated to develop; several implications are creating limitations like inferior bioavailability and absorption [183]. Eye topical applications can be performed but with minimal disease addressability. Delivering therapeutic agents in maximum concentrations needed in the posterior segment encounters failure in most of the cases [205]. However, for a better approach of the posterior segment, intraocular injections are more operative, but in this case, ocular complications are the primary concern. There are still other approaches like intravitreal, intracameral

or peri-ocular injections, but with a significant risk of side effects [206]. Improvements in protocols alongside adaptations of in vivo performance for sustainable results are needed. The standard hydrogels used for contact lenses (silicone and polymethylmethacrylate) are, however, generally highly biocompatible with almost 50 years of results proving it [207]. Some issues with silicone hydrogels causing eye inflammation have been reported [208] but, the only specific limitation to capable hydrogel based therapeutics seem to be those mentioned above.

7.8. Tissue Engineering and Bone Repair

Innovative biocompatible and biodegradable injectable hydrogels have been synthesized for cartilage and bone tissue [209], vascular tissue, skin, and other soft tissues engineering [210]. In this regard, the viscosity of the hydrogel plays a significant role together with sol-gel transition in specific physiological environment [210].

The injectable systems have the flexibility to fill irregular-shaped defects and offer the possibility to reduce surgical invasion [211]. Significant current research strategies have been reported regarding the use of autografts in bone implantation therapy, due to the advantage of minimized rejection rates [212]. Recent attempts have been made in injectable bio hydrogels (collagen [213], chitosan [214], gelatin [215], cellulose [97]) in cell-based therapies to increase biomimetic capacity. For instance, Park and Lee developed an oxidized alginate/hyaluronic acid hydrogel construct and tested it together with chondrocytes in vivo on mice, and obtained positive results on cartilage regeneration [216].

Among these, stem cell delivery systems are focusing on microfluidics to avoid microenvironment interactions. Various hydrogel constructs like microspheres were formulated for stem cells encapsulation. For example, Zhao et al., 2016, synthesized light responsive hydrogel microspheres made by gelatin and methacryloyl chloride. Bone marrow-derived mesenchymal stem cells were encapsulated using post-loading procedures and then tested in vivo on rabbit femoral condyle animal model following orthotopic implantation protocol. This microfluidic approach demonstrates the feasibility of this method in osteogenesis [217].

In situ gel forming tissue implants are suitable for transplantation during invasive surgeries directly into defects. The difficult regeneration of articular cartilage represents a very challenging problem. Due to the fact that this tissue is not presenting vascularization, the immune response is absent and it allows the use of allogenic constructs in the context of tissue engineering matter. Perrier-Groult et al., 2019, implemented a protocol for subcutaneous administration of agarose hydrogels embedded with human chondrocytes in order to promote their differentiation to cartilage matrix. In this regard, humanized mouse models are preferred for the evaluation of such implants acceptance [218].

Considering the aspects mentioned above, when choosing the experimental design for in vivo studies using murine models, the age of the animal should be considered because it can influence the outcomes through various metabolic pathways involved in hydrogels degradation and clearance [175].

Regarding hazard assessment, many different hydrogel systems aim to deliver the therapeutic agent in a controlled manner for better effects at the target site [219]. In a general approach to a pathology, orthotopic murine models simulate clinical conditions with better accuracy than cell line-based models, due to proper exposure to a microenvironment that is more similar to the pathological status in human [220]. Therefore, orthotopic animal models should be implemented in order to improve the response to therapy significantly.

8. Clinical Trials

Bringing together the advantages of a biocompatible hydrogel with the therapeutic effect of various molecules provides new efficient configurations adapted for medical devices development. Polymer science is holding up the attention of scientists because of the promising properties of biomedical clinical applications.

In the last decade, an increasing number of clinical trials investigated the use of hydrogel structures for drug delivery systems. According to [ClinicalTrials.gov](https://clinicaltrials.gov), over 300 completed studies are

presenting encouraging results for hydrogel use with significant applicability in visual disorders and dermatological affections. Table 2 emphasizes prominent examples of such products.

Table 2. Different completed clinical trials using hydrogel based products ([ClinicalTrials.gov](https://clinicaltrials.gov)).

Condition	Product	Benefits	Reference
Prostate cancer radiotherapy	Hydrogel spacer	Minimal side effects and toxicity Improves rectal dosimetry Reduces the rates of rectal toxicity	[221,222]
Gynecologic laparoscopic surgery	Crosslinked hyaluronan gel	Safety use Minimizes postoperative adhesion formation throughout the abdominopelvic cavity	[223]
Corneal epithelial permeability	Silicone hydrogel contact lenses	Improves epithelial permeability when used with ophthalmic solutions	[224]
Corneal infiltrates		Identification of bacterial species during continuous wear of contact lenses Improved cornea response to contact lenses	[225,226]
Myopia		Good ocular comfort High oxygen transmissibility	[227]
Dry eye syndrome	Crosslinked hyaluronic acid with liposomes and crocin	Safety profile Promotes re-epithelialization	[228]
Urinary incontinence	Polyacrylamide hydrogel	Facilitates urinary incontinence symptoms for patients that are ineligible for midurethral sling surgery Low rate of adverse effects	[229]
Cerebrospinal fluid leak	Fibrin sealant	Efficient adjunct to dural sutures repair Safe profile	[230]
Diabetes, foot ulcer	Hydrogel/hydrocolloid	Promotes wound healing Confers protection Stimulates epithelial migration	[231]
Intracranial aneurysm	Hydrogel coils	Efficient endovascular coil embolization Safe profile	[232]
Cerebral aneurysm		Improves aneurysm packing Decreases major recurrence	[233]
Submucosal tumor of gastrointestinal tract	Calcium-alginate gel	No adverse events and no tissue injuries Increases mucosa-elevating capacity	[234]
Oral mucositis	Mucoadhesive hydrogel	Safety profile and tolerability Reduces oral mucositis symptoms	[235]
Myoma	Resorbable hydrogel	Safety and efficacy Reduces post-operative adhesions formation following myomectomy	[236]
Pulmonary emphysema	Fibrin hydrogel	Safe profile and no major adverse effects Promotes the formation of scar tissue Improves lung function	[237,238]
Lung cancer biopsy	Hydrogel plug	Reduces postbiopsy pneumothorax and other complications associated with CT guided coaxial needle biopsy	[239]

Table 2. Cont.

Condition	Product	Benefits	Reference
Ischemic cardiomyopathy	Gelatin hydrogel	Controlled release of fibroblast growth factor Increases the formation of cardiovascular networks Improves ventricular function	[240]
Heart failure	Alginate hydrogel	Efficiency and safety profile No serious adverse effects Increases exercise capacity	[241,242]
Elective cranial procedures with dural incision	PEG hydrogel	Safe profile Dural closure augmentation Rapid preparation and application	[243]
Neuropathic pain	Lidocaine plaster	Safety and tolerability profile Relevant pain reduction	[244]

9. Future Perspectives

In the frame of current work, hydrogels aim to become feasible tools for microfluidics, biosensing and tissue regeneration engineering (potential scaffold for new tissues and organs). Future proposed designs highlight the control over structural and morphological properties in order to improve their biomimetic capabilities.

Furthermore, hydrogel usage in generating complex 3D multi-cell models offers promise in reducing the number of animals used for testing and while at the same time provides medium that more closely resembles aspects of the human body. All of these considerations will inevitably lead to accelerating pharmaceutical formulation development and deployment on the market. It is truly difficult to exemplify the role and applications that hydrogels have in biomedical research mainly due to their usage not being restricted to the topics described in this review. It is, however, easy to observe the capacity that this technology has to transcend a certain niche and in a very timely manner be implemented in a completely new field of work. The most difficult hurdles for medical and biological research seem to have been overcome and hydrogels have become a common day item in not only researchers' lives but the general public's lives too.

Recently, electronics progress relieves the use of hydrogel technology for healthcare oriented applications. Lab-on-a-chip microfluidic devices are considered practical and compelling for diagnostic and drug screening investigations. The generation of wearable sensors represents an innovative platform able to monitor pathological particularities of the human subject. Such devices can also perform a controlled release of pharmaceutical formulations according to the monitored parameters.

What is clear is the fact that hydrogels have been and are continuing to be relevant "scaffolds" in biomedicine and biomedical research. When it comes to these constructs we have entered an era of fine-tuning already existing structures and technology, where novel hydrogels are quick to reach practical applications in the real world (contact lenses, wound dressing, 3D culture scaffolds) and more exotic ones hold potential in a variety of fields such as robotics, aerospace engineering, solar cells and photoreactors, environmental research and sports science.

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