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Review Article

HYDROGEL: RESPONSIVE STRUCTURES FOR DRUG DELIVERY

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ABSTRACT

Hydrogels are water-swollen 3D networks made of polymers, proteins, small molecules, or colloids. They are porous in structure and entrap/encapsulate large amounts of therapeutic agents and biopharmaceuticals. Their unique properties like biocompatibility, biodegradability, sensitivity to various stimuli, and the ability to be easily conjugated with hydrophilic and hydrophobic drugs with a controlled-release profile make hydrogels a smart drug delivery system. Smart hydrogel systems with various chemically and structurally responsive moieties exhibit responsiveness to external stimuli including temperature, pH, ionic concentration, light, magnetic fields, electrical fields, and chemical and biological stimuli with selected triggers includes polymers with multiple responsive properties have also been developed elegantly combining two or more stimuli-responsive mechanisms. This article emphasized the types, features, and various stimuli systems that produce responsive delivery of drugs.

Keywords: Stimuli-responsive, Smart hydrogel, Triggers, Environment-sensitive, Biocompatibility, Biodegradability

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INTRODUCTION

Hydrogels are water-swollen networks usually formed of a crosslinked polymer having hydrophilic properties. A three-dimensional network of polymers made of natural or synthetic materials possessing a high degree of flexibility due to large water content. Hydrogel molecules or colloidal particles are either chemically or physically cross-linked. While hydrogels are generally prepared based on hydrophilic and hydrophobic monomers under physiological conditions, they can retain a large amount of water or biological fluids [1, 2].

Hydrogels can be classified into two groups depending on the nature of the cross-linking reaction. If the cross-linking reaction involves the formation of covalent bonds, then the hydrogels are termed as a permanent hydrogel. Hydrogels are held together by either physical and chemical interactions cross-links are covalent bonding and physical interactions such as chain entanglements, van der Waals forces, hydrogen bonds, crystallite associations, and ionic interactions. Hydrogel molecule size of the pores affects their deformability and the diffusion of cells, which leads to the release of drugs through diffusion. This can be altered through degradation and swelling of the matrix, either time-dependent or triggered. Specific interactions between the gel matrix and the drug also impact the release of drugs [3, 4].

Hydrogel drug delivery systems include applications in regenerative medicine and cell therapy. Hydrogels present a wide range of design options in terms of the nature of the constitutive molecules, their functionality, and therapy, programmable and controlled release such as attaching ligands, combining them with nanoparticles, attaching drugs, etc.;. For all these reasons, they provide a versatile platform for drug delivery. Hydrogels play a critical role in many tissue engineering scaffolds, biosensors and BioMEMS biomedical (or biological) microelectromechanical system devices, and drug carriers. Among these applications, hydrogel-based drug delivery devices have become a major area of research and commercial products for development [5].

Approaches for the designing and processing of a speci fic hydrogel for a specfic application are required to show maximum mechanical strength, chemical properties, stimuli response, density, biodegradation, and biological and environmental response. Solution polymerization and suspension polymerization are the most common techniques for the production of a variety of hydrogel networks with molecular-scale control over the structure, such as crosslinking density, initiator, emulsifier and reaction conditions and tailored properties like chemical, physical and biological response to stimuli, mechanical strength, biodegradation, and solubility.

Smart hydrogels systems with various chemically and structurally responsive moieties exhibit responsiveness to external stimuli, including physical, chemical, and biological stimuli. The Physical stimuli responses include temperature, light, magnetic fields, electrical fields, and ultrasounds. Chemical stimuli responses pH, ionic concentration sensitive hydrogels and the biological stimuli responses; glucose, antigens, and enzymes sensitive hydrogels. Intelligent polymeric hydrogels change their structural and extent phase transition response to external stimuli resulting in clinical observations and advanced technology [6].

Intelligent network designs have accurate mathematical modeling of drug release profiles. The polymer engineering technology can design and synthesize polymeric networks with a molecular structure that incorporates cross-linking properties, such as biodegradation, mechanical strength, chemical and biological response to stimuli [7].

Hydrogels are required to avoid side-effects for the drug delivery system, such as transdermal drug delivery systems appear as a promising alternative strategy to carry antineoplastic agents, including increased in drug solubility, bioavailability, and stability, prolonged half-life, distribution, and reduction of the total dose required.

Search criteria

The source and range of years used to write this review article are Elsevier, Research scholar, Pubmed, Science direct and 2015-2020 respectively.

Design criteria for hydrogels

Type of Materials, stimuli responses, and process which governs that rate and mode of drug release from hydrogel matrices. These design properties are lead to an increase the efficient drug loading have to be evaluated for drug delivery. The main criteria for designing hydrogel-based drug carriers are drug diffusion, transport which leads to affect the molecular size and characteristics of the drug-polymer network.

The physical and chemical properties are especially modeling molecule release. The physical properties of the hydrogel affect drug release. For example, polymer molecular weights, composition, and polymer/initiator concentrations influence hydrogel swelling and degradation. The stimuli-responses of a hydrogel network can also mediate the amount and rate of drug delivery. The properties of the hydrogel are always critical in designing biocompatible hydrogel formulations for controlled release [8, 9].

Classification

Hydrogels were generally classified into two distinct categories of natural and synthetic based.

Natural hydrogel

The natural polymers which are used to produce natural hydrogels are proteins such as collagen, gelatin, lysozyme, fibrin, dextran, and polysaccharides such as hyaluronic acid and alginate and Chitosan [10].

Synthetic hydrogels

These are prepared by chemical polymerization of monomers and having a wide range of mechanical and chemical properties. They have interpenetrating polymeric network hydrogels such as homopolymeric, copolymeric, and multipolymeric by polymerization techniques. Synthetic Hydrogels are Poly (vinyl alcohol) poly (acrylamide), poly (ethylene glycol), poly (N-isopropyl acrylamide) [11].

Hydrogels can be classified into physical and chemical hydrogels based on their cross-linking mechanism

Physical hydrogels

Physical crosslinks include polymeric chains, hydrogen bonding, hydrophobic interaction, and crystallite formation. While these physical crosslinks may not be permanent junctions, they are sufficient to keep the hydrogel from dissolving in an aqueous media.

Chemical hydrogels

Chemical or covalent crosslinks are permanent junctions formed by covalent bonds. Which creates a covalently crosslinked network is to polymerize end-functionalized macromers [12, 13].

Miscellaneous

Hydrogel networks may include both permanent junctions and semipermanent junctions like chain entanglements. The hydrogel properties, like swelling properties, elastic modulus, and transport of molecules. Hydrogels can further be classified by their ionic charge (neutral, cationic, anionic, and ampholytic), structure (amorphous, semicrystalline, and hydrogen-bond), and preparation methods (homopolymer, copolymer, multi polymer, and interpenetrating polymer network) [14, 15].

The control of the hydrogel network structure allows for the proper design and characterization of the degradation of hydrogel scaffolds, diffusion of bioactive molecules, and migration of cells through the network [16, 17].

Types of stimuli-responsive hydrogels

Hydrogels present a wide range of design options in terms of the nature of the constitutive molecules, functionality, and properties. The design approaches as well as improved activation strategies, are required to provide the control and biological responses required for human translation.

Macromolecular networks present in hydrogels absorb and reversibly release water solutions; these responses depend on specific environmental stimuli. The environment-sensitive hydrogels, also called "smart" hydrogels, smart hydrogels are also known as Stimuli-responsive hydrogels. Modalities and mechanisms associated with externally triggered drug delivery for enhanced drug release of stimuli-responsive gels, with selected triggers [18].

Responsive properties of special hydrogels to the environmental stimuli are especially desirable for clinical applications. In response to internal or external stimuli, hydrogels undergo significant changes in their network structure, swelling behavior, and permeability. External stimuli such as light and electric field have been applied with stimuli generating devices, whereas internal stimuli occur within the native environment of the body [19, 20].

Factors such as the type of monomers, hydrophilic and hydrophobic balance, cross-link density, osmotic pressure, confirmation of chemical groups, etc, which results in changing the stimuli responses of gels.

Physical stimuli

Chemical stimuli

Biological stimuli

Many physical, chemical and biochemical stimuli have been applied to induce various responses to the smart hydrogel systems. The physical stimuli include temperature, electric fields, light, sound, and magnetic fields, while the chemical stimuli include pH, ions, and speci fic molecular species and biological stimulus involves the responses to enzyme, antigen, and other biochemical agents are represented in fig. 1.

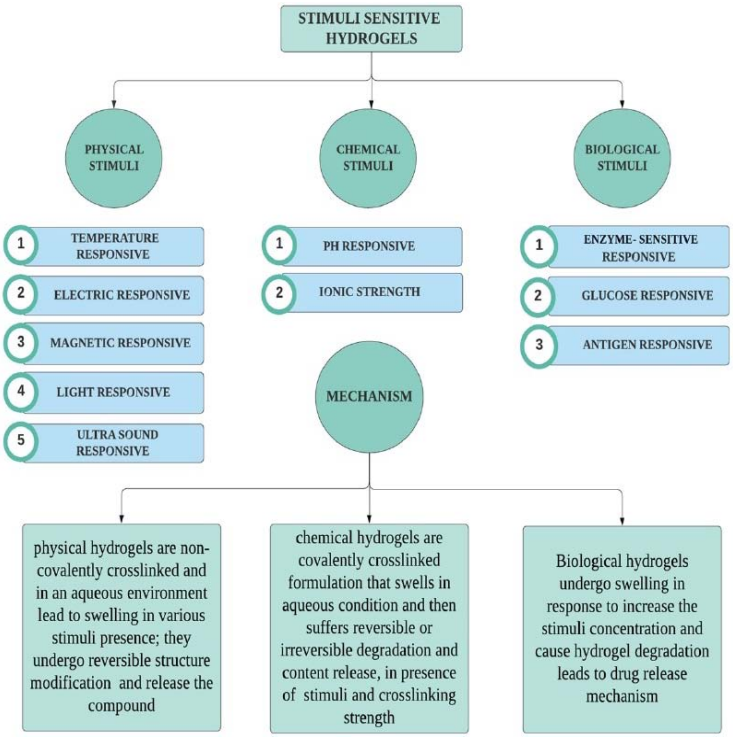

Fig. 1: Stimuli sensitive hydrogels and its mechanism [21]

Physical stimuli hydrogels

Temperature responsive hydrogels

Temperature-sensitive hydrogels are also called as thermo-gels. The temperature is one of the important reaction parameters determining the grafting kinetics. These stimuli sensitive hydrogels show changes in their swelling behavior of the network structure according to the external environments [22, 23].

The characteristic feature of thermoresponsive polymers is the presence of hydrophobic units such as methyl, ethyl, and propyl groups. Critical solution temperature is a key parameter in temperature-sensitive polymers. At a specific temperature, the polymer phase changes according to its composition. If the polymer solution has a lower critical solution temperature (LCST), its solubility in water decreases upon heating. Otherwise, it is called an upper critical solution temperature (UCST). For the case of hydrogels, the solubility decreases, and hydrogels shrink as temperature increases above the LCST [24, 25].

The other category is irreversible hydrogels; the non-covalent cross-linking in the hydrogels tends to undergo sol-gel phase transition instead of swelling and shrinking transitions. Such hydrogels exhibit inverse temperature-dependent sol-gel behavior; they become sol as the temperature increases. At the critical temperature, physically cross-linked thermals undergo a sol-gel transformation, while the chemically cross-linked thermals prominently undergo volume transition. Certain molecular interactions such as hydrogen bonding, Vander Waals forces, molecular entanglements, and hydrophobic interaction assist in the formation of the physical hydrogels [26, 27].

Environmentally sensitive hydrogels exhibit temperature-sensitive swelling behavior due to a change in the polymer or swelling agent, which is compatible over the temperature range. Temperature-sensitive polymers typically exhibit an (LCST), above the temperature, polymers are typically hydrophobic and below which the polymer is soluble. The cross-linked gel swells to significantly higher degrees because of the increased compatibility with water. Examples: poly (n-isopropyl acrylamide) [28].

Thermally-induced gelation is based on hydrophobic and hydrophilic interactions. The thermo-responsive polymer, systems mainly characterized by the presence of hydrophobic groups, such as methyl, ethyl, and propyl groups, which are used in the synthesis of hydrogels. These hydrogels are classified into positive thermosensitive, negative thermosensitive, and thermally irreversible hydrogels [29]. The schematic representation of thermoresponsive hydrogel is as shown in fig. 2.

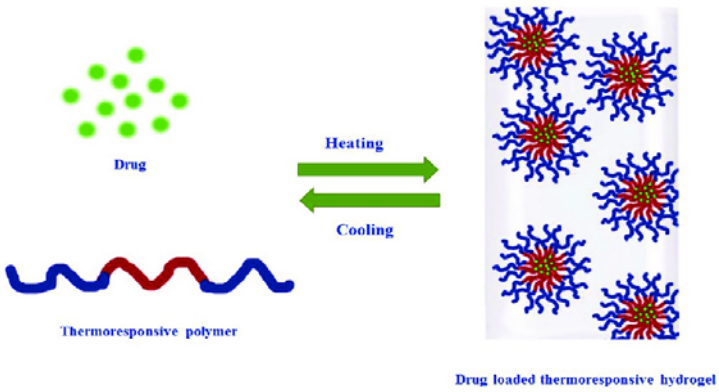

Fig. 2: The schematic representation of thermoresponsive hydrogel formation loaded with drug-using temperature as a stimulus [30]

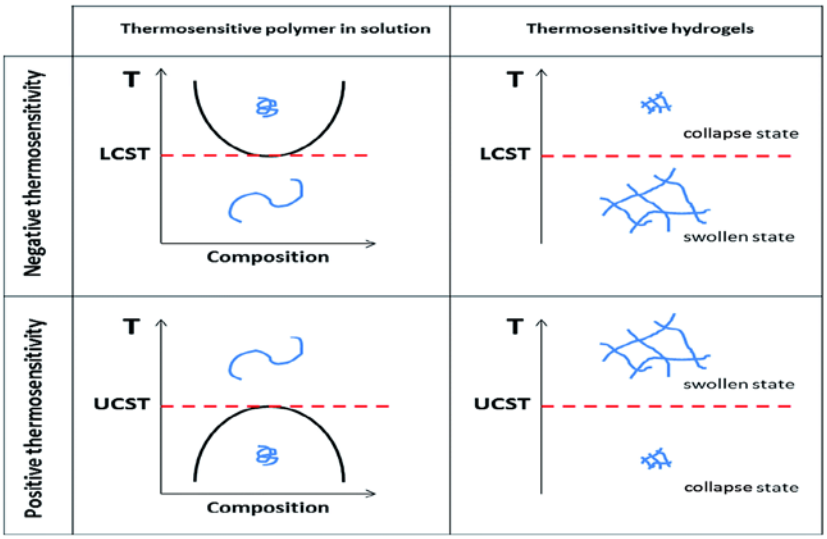

Fig. 3: Thermosensitive behaviors of polymers in solution and hydrogels [34]

Positive temperature hydrogels

Hydrogels prepared from upper critical solution temperature (UCST) polymers exhibit shrinking to swelling transition with increasing temperature, and these are referred to as "positive thermosensitive gels". Shrinking occurs at low temperatures because of a complex structural formation by hydrogen bonding and swells at high temperatures. For example, the hydrogels prepared

from polymer networks of poly `1(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly (acrylamide-co-butyl methacrylate) display this positive temperature dependence [31].

Negative temperature hydrogel

Negative thermosensitive gels are characterized by the (LCST) low critical solution temperature of the backbone polymer forming the gel. Rising the temperature above LCST collapses or shrinks the gel, whereas cooling below LCST causes the swelling of the gel. This specific temperature-dependent swelling or shrinking is due to the change in the hydration state of the polymer chains. When the interaction between the polymer chains increases, a sudden and reversible transition in the volume of the network occurs, this is referred to as "volume phase transition (VPT)". At a critical temperature, these crosslinked hydrogels show this behavior is referred to as "volume phase transition temperature (VPTT)" [32, 33].

Thermo responsive hydrogels include different mechanisms such as inclusive of passive diffusion, erosion, swelling, and dictate the discharge of the drugs. The drug delivery systems based on synthetic thermosensitive polymers such as PNIPAAm, Pluronics are usually non-degradable. Thermoresponsive polymers exhibiting this negative temperature dependence are polyacrylamides, polyvinyl ethers, polyoxazolines, and poly (oligo-ethylene oxide) methacrylates. The schematic representation of the thermosensitive behaviors of polymers is as shown in fig. 3.

Applications

Due to the ability of good biocompatibility and mimic the extracellular matrix environment, hydrogels become the potential candidates for many biomedical applications include soft contact lenses, wound healing, tissue engineering, and sensors.

The porous structure of hydrogels can be adjusted by cross-linked density, thus the release behavior of different bioactive agents like proteins or drugs can be controlled. Temperature-sensitive hydrogels are used for the delivery of drugs, genes, cells, therapeutic agents, and tissue engineering.

Electro responsive hydrogels

Electric field-responsive hydrogels are polymers that swell, shrink, or bend in response is carried out to an applied electric field. They are usually made of polyanions, polycations, or amphoteric polyelectrolytes. The electric-sensitive hydrogels are formed, depending on their composition, such as charge density, nature, hydrophobicity of cross-links, monomers, groups, shape, and position relative to the electrodes. In general, electrically responsive polymers are conducting polymers. For example, polythiophene or sulfonated-polystyrene shows swelling, shrinking or bending in response to an externally applied field [35, 36].

Electrically activated microchips represent another interesting strategy for triggerable pulsatile release of tunable drug combinations with high spatial and temporal precision and integrating a degree of automation that is not easily achievable using other pulsatile delivery strategies [37].

Electro-sensitive hydrogels can be easily controlled the drug release rate in drug delivery by modulating the electric field. Most of the electrolytes are develop drug delivery modules based on electro-sensitive hydrogels under physiological conditions. Hydrogels made poly (2-acrylamide-2-methylpropane sulfonic acid–co-n-butyl methacrylate) were able to release edrophonium chloride and hydrocortisone in a pulsatile manner using an electric current.

Applications

Electro-responsive hydrogels have been used in controlled drug delivery. These hydrogels are used as electroactive sensors or actuators in electronic devices because they swell or shrink differentially on two electrode side anode and cathode [38].

The fast release pattern was also attributed to the electrostatic force, squeezing effect, and electro-osmosis of the gel. Chitosan gels were also used as matrices for electrically modulated drug delivery. Among many electro responsive polymers, electro-responsive hydrogels have become appealing both because of their use for controlled drug delivery as well as their biocompatibility [39].

Magnetic field responsive hydrogels

Magnetic field hydrogels generally consist of a polymer matrix and a magnetic component embedded in the matrix. The properties of magnetic hydrogels contain several factors, including the type of hydrogel used, concentration, size, and distribution of hydrogels. Methods such as the blending method, an in situ precipitation method, and the grafting method have been used to develop to fabricate magnetic hydrogels [40].

Magnetic fields represent another method for external activation of drug release, usually relying on the incorporation of superparamagnetic nanoparticles into the hydrogels, and the use of either static or alternating magnetic fields. The gels are sensitive to magnetic fields and undergo volume change after the application of the external magnetic field.

The polymer network through this combination of solid-like and fluid-like behavior is induced; the influence of the external field on the hydrogels the responsiveness is enhanced. CMC hybrid hydrogels containing CoFe2O4 nanoparticles, chitosan, and CMC-coated Fe3O4 nanoparticles, etc. are used as magnetic field-responsive hydrogels. The Fe3O4 magnetic nanoparticles were used to generate heat through the application of an alternating magnetic field [41]. The schematic representation of magnetic hydrogels design as shown in fig. 4.

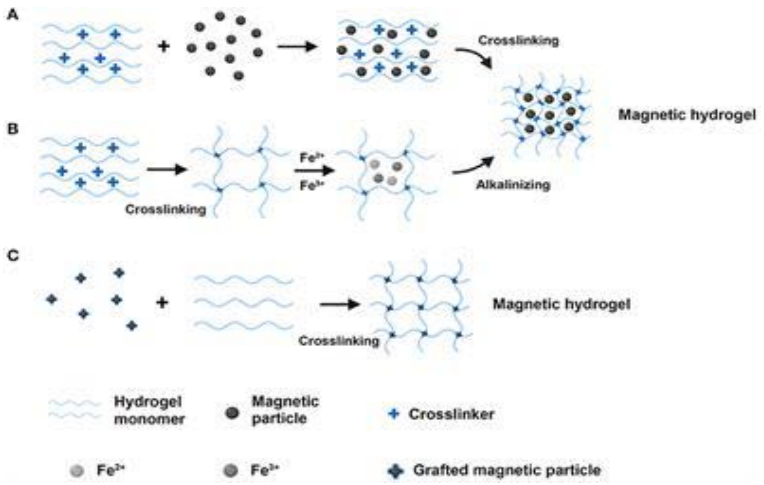

Fig. 4: The schematic diagram of the main three routes for the synthesis of the magnetic hydrogels. (A) The blending method. (B) The in situ precipitation method. (C) The grafting-onto method [42]

Applications

These hydrogels have found their applicability in biomedical sectors, such as cell separation, gene and drug delivery, and magnetic intracellular hyperthermia treatment of cancer. These hydrogels are prepared through the precipitation polymerization method for the controlled release of the anti-cancer drug.

Drug release can be magnetically triggered from delivery systems containing superparamagnetic iron oxide nanoparticles SPIONs using either static or alternating magnetic fields. The application of a static magnetic field can be used to mechanically deform or move all or parts of a composite delivery system to induce triggered release [43].

Light responsive hydrogels

Light-responsive hydrogels are composed of a polymeric network possessing light-reactive groups such as photochromic moieties. Novel light-sensitive hydrogels are fabricated by grafting or incorporating photo-sensitive moieties photo chromes into the polymer chain. Light-sensitive polymers are significantly reversible modifications in its chemical and physical properties due to the exposure to light. Such polymers are also known as "photo-sensitive polymers" [44].

Photo-sensitive molecules respond to light via three main mechanisms: isomerization or cyclization, degradation, and dimerization. The physical properties such as mechanical stiffness, shape, swelling/deswelling behavior size, degradation rate, and the chemical properties such as surface hydrophilicity and hydrophobicity ratio of the light-sensitive hydrogels [45].

Visible light-sensitive hydrogels were prepared by introducing a light-sensitive chromophore hydrogel. When hydrogels are exposed to light, the chromophore absorbs light which is then abandoned regionally as heat by using radiationless transitions, which increasing the 'local temperature of the hydrogel. The temperature increase alters the swelling behavior of hydrogels, which are rate limited by thermal diffuse-sensitive hydrogels. The temperature increase is proportional to the light intensity and chromophore concentration [46].

Applications

Light-sensitive hydrogels can be used in the development of photo-responsive artificial muscles, switches, and memory devices. The hydrogels served as an in situ hydrogel-based drug delivery system for controlled drug release.

Photosensitive hydrogels are the next-generation polymer-based materials for biomedical applications such as photo mediated delivery of therapeutic payloads in a controlled manner and 4-D culture of cells, with an ability to mimic the dynamic and the heterogeneous *in vivo* microenvironments [47].

Ultrasound responsive hydrogel

Ultrasound refers to the high-frequency waves generated from a piezoelectric material due to the mechanical vibrations when it is subjected to alternating current. Ultrasounds may be classified as low-frequency (<1 MHz), medium-frequency (1–5MHz), and high-frequency (5–10MHz) ultrasounds. The low-frequency ultrasound has a higher penetration depth in tissues.

The ultrasound having a frequency>2MHz possesses a low tissue penetration depth due to increased scattering, which in turn, causes heating and tissue damage. But, the increase in the frequency of the ultrasound is associated with a decrease in the focus point, thereby leading to an increase in the intensity at the focus point [48]. The ultrasound causes thermal and non-thermal effects on tissue fluids. Ultrasonic waves can trigger drug release through either thermal or mechanical effects generated by cavitation or convection forces [49, 50].

Applications

The ultrasounds responsive hydrogel is used for transdermal delivery, thus improving the permeability of the skin such as diclofenac sodium (DS) patches. These strategies are embedded in the hydrogel patch [51].

Based on the properties like mechanical, self-healing, and sensitiveness to ultrasound, the hydrogels can potentially be explored for diverse medical applications such as biomedical implants to smart drug delivery.

High-intensity focused ultrasound (HIFU), having a frequency of 0.8–3.5MHz is getting importance as an exogenous trigger for the treatment of cancer either by direct application or via controlled release of anticancer drugs from nanocarriers [52].

Chemical stimuli sensitive hydrogels

pH-responsive hydrogel

The two main strategies are used for the design of pH-responsive drug delivery systems are (a) the use of polymeric systems with ionizable pendant moieties on their backbone structure and (b) the use of polymers bearing acid-sensitive bonds were breaking of these bonds contribute to the release of drug molecules attached to the polymer backbone. Depending upon the various kinetic model's drug release from the hydrogels are characterized by swelling behavior [53].

pH-sensitive hydrogels consist of gel structure, which varies a change in pH values. The pH-sensitive hydrogels expand or contract depending upon the pH of the solutions. Appropriate pH and ionic strength generate electrostatic repulsive force results in swelling or deswelling of the hydrogel. pH-responsive hydrogels could offer desirable physical and chemical properties at specific pH ranges [54].

Depending on the ionizable pendant group, pH-responsive hydrogels are categorized into two main groups as cationic and anionic hydrogels as shown in fig. 5. As the external pH increases, the hydrogel network undergoes swelling if it contains anionic pendant groups or shrinks if it contains cationic pendant groups in its polymeric backbone [55].

Anionic hydrogel

Anionic hydrogels exhibit swelling behavior when the pH of the swelling buffer is above acid dissociation constant, pKa, due to a simultaneous effect of electrostatic repulsion and water absorption. The structure of these gels remains collapsed at low pH because of the tight physical interactions in the network. Acrylic acid, p-styrene sulphonic acid, itaconic acid, crotonic acid, maleic acid, and methacrylic acid, etc are precedents that are utilized in anionic hydrogels [56].

Cationic hydrogel

In cationic hydrogels, the drug is mostly released at low pH conditions such as the stomach. Cationic hydrogels swell at low pH conditions (pH<pKa) and collapse when exposed to an environment with high pH (pH>pKa). The swelling behavior of pH-responsive anionic or cationic hydrogels is specific in acidic and alkaline buffer solutions [57].

The pH-responsive nature of hydrogels can be applied for biomolecule delivery in neutral or alkaline environments. Polymers such as chitosan, poly (ethylene amine), poly (dimethylamino-ethyl methacrylate), are functional moieties leads to ionized the primary, secondary, and tertiary amines [58].

Most anionic pH-sensitive polymers are based on Carbopol derivatives, which including poly (methacrylic acid) (PMAA), PAA poly(acrylic acid), poly (diethylaminoethyl methacrylate) (PDEAEMA), and phosphoric acid derivatives. These polymers, comprising a large number of ionizable functional groups, are generally referred to as polyelectrolytes. The presence of ionizable groups onto polymer chains results in increased hydrogel swelling compared to nonelectrolyte polymer hydrogels.

pH-responsive hydrogel using poly (lactic acid) (PLA), methoxyl poly (ethylene glycol) (MPEG), and itaconic acid (IA) via heat-initiated free-radical polymerization in the absence of organic solvents. The effect of the pH value on the swelling ratio was determined in buffers with pH ranging from 1.2 to 6.8 [59, 60].

Applications

Both anionic and cationic pH-responsive hydrogels have been investigated for the controlled delivery of therapeutic drugs, genetic agents, and proteins. pH-responsive hydrogels are useful for oral

administration of the drug along the digestive tract because of the distinct pH conditions located at special sites, the targeted drug delivery into a tumor site due to alterations in the acidity of tumor tissue [61].

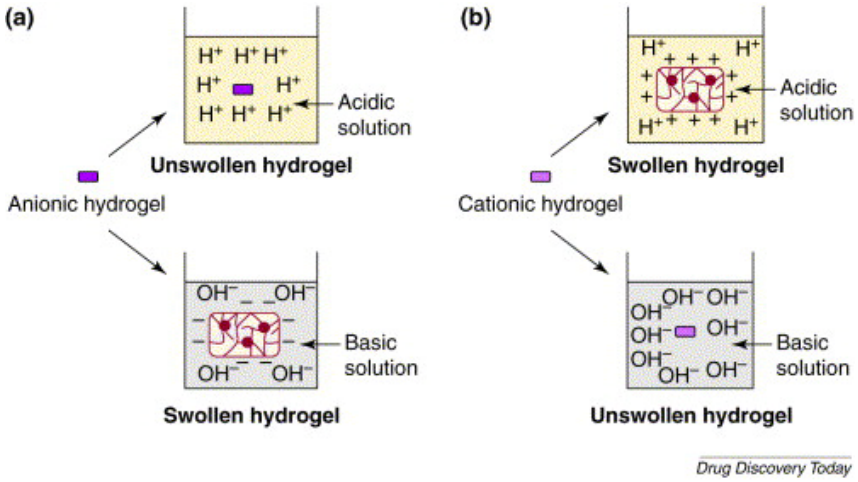

Fig. 5: The pH-responsive swelling of (a) anionic and (b) cationic hydrogels [62]

pH-sensitive hydrogels have been most frequently used as an antibacterial wound dressing. They also have been used in making biosensors and permeation switches. The hydrogels were explored as a carrier for dual model drugs, namely, doxorubicin (DOX) (anti-cancer) and tetracycline (TET) (anti-bacterial). Alginate, dextran, hyaluronic acid, chitosan, and gelatin are some examples of the natural pH-sensitive polymer [63].

Ion-sensitive hydrogels

The polymers having ionizable groups exhibit sensitivity to ionic strength. They can attractive electrostatic force between the oppositely charged species. These polymers become insoluble in deionized water but soluble at a suitable concentration of electrolyte solution. Hence, the polymer properties, like the size of polymer chains and solubility, g*et al.* tered in ion-sensitive polymers as the ionic strength of the solution [64].

The polyelectrolyte gels also demonstrate variation in swelling kinetics in the presence of salts. The introduction of salts results in the growth of the ionic strength of the solution, which ultimately reduces the equilibrium degree of swelling of the polyelectrolyte gels. The hydrogels having high restrained swelling in the presence of ionic solutions having higher ionic valence numbers as compared to low valence numbers.

Applications

The ion-sensitive hydrogels have mainly been applied for the development of delivery systems which are used in applications including nasal and ocular drug delivery.

Ion-sensitive in situ hydrogels that can be used for improved and prolonged ocular pharmacotherapy.

The changes in the properties of the hydrogels due to the alteration in the type or composition of the gelling agent were also analyzed [65].

Biological stimuli sensitive hydrogels

Enzyme-sensitive hydrogels

The most common approach for the design of enzyme-responsive hydrogels involves the incorporation of peptide chains into the gel network as a linker or crosslinker to make the network biodegradable with specific enzymes. These enzymes have been utilized as signals of physiological changes and can be used in site-specific drug delivery [66].

The enzymes used in the organic trigger to induce the biomaterial properties modifications, which can also assist in reaching sustained and controlled release of bioactive molecules upon enzymatic movement [67].

Enzyme-sensitive hydrogels consist of two main functional parts: (i) an enzyme recognizable and accessible substrate, and (ii) a functional component to regulate molecular interactions, which leads to macroscopic transitions in hydrogels. The transitions may be associated with the change in the surface properties, swelling, or shrinking of the gel structures. Molecular interactions that play a significant role in the semacroscopic transitions are VanderWaals forces, hydrogen bonding, electrostatic interactions, hydrophobic interactions, – π π interactions [68].

Applications

Enzyme-sensitive systems imitate the biological matrices which developed in the potential applications of these hydrogels. The preparation of enzyme sensitive hydrogel microparticles is based on poly (ethylene glycol) for pulmonary drug delivery.

These prepared enzyme-sensitive hydrogel particles have great potential to be implemented as drug delivery vehicles. The synthesis of pH-sensitive peptide-based hydrogels could fficiently describe the effect of the peptide concentration on the extent of enzymatic degradation of the hydrogels.

Glucose responsive hydrogels

The strategies for glucose sensing hydrogels are extensively categorized into enzymatic sensing, natural glucose-binding proteins, and artificial molecular recognition. The stimuli-responsive delivery systems using hydrogels that can release insulin are referred to as glucose-sensitive hydrogels. In the controlled drug delivery area includes the development of self-regulated modulates the insulin delivery systems. The swelling of hydrogel triggers the discharge of insulin while the nearby pH of the device reduces when glucose is converted to gluconic acid via glucose oxidase enzymes within the presence of oxygen. Glucose oxidase has been covalently attached to the hydrogel network for controlling the discharge of insulin [69, 70].

These hydrogels are composed of materials that are “bio-clever” the engineered molecular recognition site is related to actuation, inclusive of HEMA and PMA. The nearby pH of the system is decreased when glucose is converted to gluconic acid through glucose oxidase inside the presence of oxygen, which increases the swelling of cationic hydrogels and releases insulin.

Phenylboronic acid (PBA) as glucose sensing groups that Synthesized smart glucose-responsive hydrogels by immobilizing

the glucose or galactose binding protein (GBP) within an acrylamide hydrogel network which demonstrated a dynamic response in the presence of glucose.

The hydrogel was conjugated with peptide and was also loaded with insulin, glucose oxidase, and catalase. Designed peptides induce self-assembly of the polymer into a hydrogel at physiological conditions [71].

Antigen responsive hydrogels

Antigen responsive hydrogels are designed by using grafting antigens on hydrophilic polymeric backbones to deliver biomolecules at a specific targeted site. These hydrogels may be combined with antibody grafted crosslinked hydrophilic polymeric backbones. In the absence of a free antigen, the structure of the hydrogel shrinks due to intrachain antigen-antibody binding inside the polymer network. Formulating an antigen sensing tool makes them beneficial biomaterial for biomolecules, protein drug delivery at desired sites, where the exceptional feature is specific molecular recognition of antigen-sensitive hydrogels [72, 73].

An antigen responding hydrogel, which may be prepared by using grafting antigen and the corresponding antibody to the polymer network, the binding between the two introduces crosslinks into the network. The competitive binding of the free antigen triggers which exchange the hydrogel volume, display shape, and pulsatile permeation of protein through the network within the antigen concentration.

Applications

Some biomedical applications, it is highly desirable and useful to develop material or devices, which can respond to specific proteins. Sol-gel phase reversible hydrogels and glucose-sensitive phase reversible hydrogels were prepared based on antigen-antibody interactions.

A semi-interpenetrating network hydrogel was prepared by grafting an antigen and a corresponding antibody to different polymer networks. The gel is formed by crosslinking interactions that occur upon antigen-antibody binding. Hydrogel swelling is triggered in the presence of free antigens that compete with the polymer-bound antigen, leading to a reduction in the crosslinking density [74].

Table 1: Summarized table contains types of stimuli, the material used, and features of hydrogels

Type of stimuli	Material used	Features	References
Physical stimuli	Poly(N-vinyl caprolactam), Poly(N-isopropyl acrylamide),	Easy functionalization with drug molecules,	[83-85]
Temperature responsive	Poloxamers Poly(N-alkylacrylamide), N-trimethyl chitosan chloride, Methoxy poly(ethylene glycol)-poly(pyrrolidone-co-lactide), xyloglucan Chitosan	Sol-gel transition at 37 ◦C, Unique physical properties similar to the extracellular matrix, Controlled degradation.	
Electric field responsive	poly lactic-co-glycolic acid and poly(ethyleneglycol) hydrogel Sulfonated polystyrenes, Poly(thiophene)s,Poly(ethyloxazoline) poly (2-acrylamide-2-methylpropane sulfonic acid–co-n-butyl methacrylate)	Undergo shrinking or swelling in the presence of an applied electric field, Biocompatibility, Minimal invasiveness.	[86-88]
Magnetic field responsive	Hemi cellulose crosslinked with O-acetyl-galactoglucomannan, polyurethane acrylate oligomers bioink, and magnetized platelets	Successful absorption and controlled release of drugs, Dispose of anisotropic properties, field strength, field geometry, drug/gene binding capacity.	[89-91]
Light responsive	Hydroxypropyl methylcellulose and Carbopol hydrogels containing diclofenac-sodium chitosan microspheres, Poly[2-((4,5-dimethoxy-2-nitrobenzyl)oxy)-N-(2-(methacryloyloxy)ethyl)-N, N-dimethyl-2-oxoethan-1-aminium]	Reasonable strengthens, Reversible and irreversible, Spatiotemporal control over functional groups, Controlled release, The Light stimulus can be imposed in high accuracy	[92-94]
Ultrasound responsive	poly(d,l-lactide)(PGA),poly(d,l-glycolide)(PLA),poly(bis(p-carboxyphenoxy))alkane–anhydrides (PCPX), and sebacic acid	Mechanical vibrations, cavitation, or convection forces	[95, 96]
Chemical stimuli pH-responsive	Carboxylated agarose/tannic acid hydrogel scaffolds cross-linked with zinc ions, Poly(acrylamide-co-acrylic acid) poly(AAm-co-AAc) hydrogels, Poly(methacrylicacid), Poly(vinylpyridine), Poly(vinylimidazole)s	Sustained release of the incorporated drugs, Biocompatibility, Strong electrostatic interactions, and stability, Increased hydrophilicity and swelling	[97-99]
Ionic strength responsive	2-acrylamido-2-methylpropane sulfonic acid cross-linked with N,N′-methylene(bis)acrylamide, Poly(N-isopropyl acrylamide) crosslinked with imidazolium-based dicationic ionic liquid	Increased swelling properties, Controllable porous structure, Biodegradability	[100-102]
Biological stimuli Enzyme-sensitive hydrogels	Poly(allylamine) Hyaluronic acid/tyramine, Dextran/tyramine, Carboxymethylcellulose/tyramine for hydrogel formulation (Elastase, HRP)	improve their therapeutic potential, sol-to-gel and gel-to-sol phase transitions leads to change in the surface properties, swelling or shrinking of the gel structures	[103]
Glucose responsive hydrogels	phenylboronic acid side chains using m-acrylamidophenylboronic acid (AAPBA), N-vinylpyrrolidone, acrylamide, and (N, N-dimethylacrylamide) DMAAm.	Increases the swelling of cationic hydrogels and releases insulin.	[104, 105]
Antigen responsive hydrogels	Vinyl functionalized antigen or antibody with acrylamide or N, N′-methylene bisacrylamide (MBA).	Hydrogel swelling is triggered in the presence of free antigens, leading to a reduction in the crosslinking density	[106]

Specialized hydrogels

3D printing of hydrogels

3D printing is an emerging technology that allows the fabrication of complex, three-dimensional objects from computer-aided design (CAD). The structure is built layer-by-layer from a series of thin horizontal cross-sections, thus giving a high degree of flexibility in the design. The FDA approved a rapidly dissolving levetiracetam tablet for oral suspension.

Polymer solutions can be used as "bio-inks", provided that they are shear-thinning and that gelation can be triggered either by chemical cross-linking or a physical trigger. This technology has been envisaged in ophthalmic drug delivery, to build drug delivery devices that can deliver to the eye, e. g. with implantable pump systems, or Micro-Electro-Mechanical Systems (MEMS), with drug-infused hydrogels. 3D printing is also being employed for diagnostic and targeted delivery applications.

Using 3D printing from the two-photon polymerization of photocrosslinkable hydrogel gelatin mathacryloyl (GelMA), decorated with magnetically responsive nanoparticles, which can be designed to respond to pathological concentrations of metalloproteinase-2 (MMP-2). Recent examples of hydrogel drug matrices using 3D printing include the printing of lactose-crosslinked gelatin scaffolds for the sustained release of dexamethasone [75, 76].

3D printing and smart hydrogels is a potent combination of bioprinting functional 3D tissues. Hydrogel in bioprinting acts as a matrix that supports and regulates the cells encapsulated inside the matrix. At the current stage, computational models have been set up to assess hydrogel contraction and deformation due to cellular events such as migration, proliferation and traction, cellular concentration, and distribution.

Table 2: The updated research work is done on hydrogels

S. No.	Active ingredient	Materials	Method	Result	References
1	Ibuprofen	Ethyl oleate (EO), propylene glycol (PG), tween 80	Microemulsion technique	*In vitro* permeation data showed that microemulsions increased the permeation rate and increase the topical delivery of ibuprofen	[107]
2	Bifonazole	Tween 80, isopropyl alcohol (IPA), and HPMC K100M	Microemulsion technique	The studied micro emulsion-based hydrogel (F5) has a potential for sustained action of drug release and good stability and also to improve its solubility and permeability	[108]
3	Montelukast sodium	Chitosan, anhydrous dextrose, sodium tripolyphosphate, glutaraldehyde, microcrystalline cellulose, magnesium stearate and talc	Direct compression method	CHGL tablets showed more prolonged drug release profiles (86 % to 74 %) as compared to CHDX and CHTPP	[109]
4	Benzydamine Hydrochloride	Hydroxypropyl methylcellulose, Poloxamer 407, Poly (lactic-co-glycolic) polymer	Emulsion solvent evaporation method.	significantly higher reduction percentage in ulcer surface area compared to those treated with BZN-PLGA -NPs.	[110]
5	Poloxamines	Triethylamine (TEA), dithiothreitol (DTT), phosphate-buffered saline	Reverse thermal gelation	Poloxamine-based hydrogels achieved reduced swelling and increased tensile and tissue bonding properties improved stability	[111]
6	Chitosan	Poly(ethylene) glycol, poly (N-isopropylacrylamide) (PNIPAAm)	free-radical polymerization	The chitosan/PNIPAAm system improved the level of crystallinity of the films, thermal, mechanical, swelling properties	[112]
7	Ranitidine hydrochloride	Sodium Carboxymethyl C ellulose (NaCMC), Calcium Carbonate (CaCO3)	Simple mixing method	0.5% of calcium carbonates with 80:20 ĸC: NaCMC showed the Optimum floating properties, swelling ratio, drug entrapment efficiency, and cumulative drug release.	[113]
8	Moxifloxacin hydrochloride	Polyox and HPMC K4M, Sodium alginate	in situ gelation	The selected formulations MF4, MF5, and MF9 were shear thinning and an increase in shear stress was observed with an increase in angular velocity	[114]
9	1-chloroethyl-3-piperidine-ethyl acrylate	acetone, ethanol, dimethylformamide, dimethylsulfoxide	Radical polymerization	The physical and chemical properties of solutions of the obtained hydrogels, including the kinetics of swelling of gels in aqueous solutions, are studied.	[115]
10	Lornoxicam	HPMC K15M, Carbopol 934p, Xanthan gum	Microemulsion technique	They exhibited high flux value, highest release rate, good spreadability and show a significant effect on their physical, rheological, and *in vitro* drug release characteristics	[116]
11	Irbesartan	Sodium alginate, Chitosan, and Calcium chloride	ionotropic-gelation method	The optimized hydrogel microbeads showed controlled release with high % drug entrapment efficiency and swelling index	[117]
12	N, N-dimethyl acrylamide	Hydroxylamine hydrochloride, hexanoyl chloride, ethyl propionate, dimethyl sulfoxide, triethylamine	copolymerization	Kinetics of swelling at neutral pH can be controlled	[118]
13	Monomethoxy poly(ethylene glycol) (MPEG), 3,6-dimethyl-1,4-dioxane-2,5-dione(D,L-lactide) (DLLA),	Ethyl hexanoate, gelatin, toluene, dichloromethane (DCM), diethyl ether, chloroform	ring-opening polymerization method	To obtain a wide range of molecular weight and hydrophilicity shows rapid gelation	[119]
14	Gelatin-polyoxometalate	Acrylic acid, sodium hydrogen sulfite, ammonium persulfate, sodium hydroxide	self-assembling process	Formulation (GP6) shows optimal swelling and maximum release (84%) of the POM at physiological pH 7.4	[120]
15	Doxorubicin	Poly(N-isopropylacrylamide)/dextran-maleic acid	photo-cross-linking /polymerization	A larger and faster release of doxorubicin was found in those hydrogels having a large pore size	[121]
16	N-carboxyethyl chitosan And Dextran	Sodium periodate, sodium hydroxide, acrylic acid, tert-butyl car bamate (TBC), and trinitrobenzene sulfonic acid (TNBS)	gelation method	An increase in polymer concentration increased interacting functional groups per finite volume of solution	[122]
17	Pluronics F127 and F68	Hydroxypropyl methylcellulose (HPMC)	cold method	Rheological analyses showed that both elastic and viscous moduli were higher	[123]
18	Calcitonin	Methacrylic acid (MAA) and methoxy-terminated poly(ethylene glycol) monomethacrylate (PEGMA)	free radical solution polymerization	The loading efficiency was affected by the amount of solvent used during hydrogel preparation	[124]
19	Ciprofloxacin	Dextrin, 2-hydroxyethyl methacrylate (HEMA), N, N'-methylene bisacrylamide (MBA)	free-radical polymerization technique	Good compatibility between the drug and hydrogel matrix, hydrogels shows excellent physical stability	[125]

20	Pantoprazole Sodium	Acrylamide, Methacrylic Acid, N, N-methylene-bis-acrylamide, Pluronic-F127, Ammonium Persulfate, Tetramethylethylenediamine, Sodium Bicarbonate	radical polymerization	The swelling properties, mechanical strength, and stability were affected	[126]

Applications

3D printing technology is used to manufacture dosage forms. The use of hydrogels with 3D printing is emerging, and the use of microfluidic techniques to generate microgels has been particularly focused on applications in regenerative medicine, for the manufacture of complex tissues and 3D printed gels for drug or gene delivery.

The use of 3D printing in the field of wound healing to design hydrogel-based skin with complex nanostructured layers, which can incorporate growth factors or NSAIDS such as lidocaine.

The use of 3D printing technology for tissue engineering, artificial tissue mimics can indeed be delivered of signaling molecules; 3D printing for cartilage and osteochondral tissue engineering have been recently reviewed [77, 78].

Drug delivery of hydrogels

Hydrogels are widely used in the development of intelligent systems for drug delivery. Smart or intelligent hydrogels have been studied for use in drug delivery systems for the delivery of various drugs ranging from low molecular weight drugs to macromolecular drugs such as peptides, growth factors, and insulin. To develop new drug delivery systems hydrogels can entrap drugs and protect it against hostile environments for slow release via diffusion or erosion depending on the state of hydration.

By utilizing their characteristics, hydrogels can be directed to the desired area, and the drug to which they are attached can be released using the response of the hydrogel to that environment.

They can also control the rate of drug delivery by changing the structure in response to environmental stimuli such as temperature, pH, electrical and magnetic fields, solvent composition, light, ions, etc. Hydrogels are intelligent from this aspect that they can exhibit corresponding physical and chemical behaviors under the influence of various stimuli which result in controlled drug release.

Targeted drug delivery is a way of delivering a drug to a certain area rather than releasing the drug into the entire body so that side effects are reduced and the bioavailability of the cells is increased. Hydrogels are advantageous materials in drug delivery because of their characteristics, such as hydrophilic nature is similar to that of biological tissue. Also, their biocompatibility and the least mechanical irritation to tissues are other advantages in their use as a biomaterial. Moreover, because of the lowest interfacial stress between the hydrogel surface and surrounding fluid, protein adsorption, and cell adhesion onto the gel can be minimized [79].

Smart hydrogels change their properties when in contact with distinct stimuli for controlling drug delivery. At the molecular level, the physical and chemical properties such as permeability, environment-responsive nature, surface functionality, biodegradability, and surface biorecognition sites were optimized in controlled drug delivery applications. Drug incorporation and release of model molecules are the factors that are taken into consideration while fabricating a hydrogel for drug delivery.

Drug incorporation

Ligands which are metabolically cleavable and have a specific affinity for active agents are used to perform drug loading by physical entrapment, with either post-fabrication drug absorption or in-situ encapsulation. Drug loading just before cross-linking helps to maintain its stability as well as its biological potency. Thus, during the fabrication process, this prevents the drug from exposure to rough fabrication conditions or from leaching out.

Release of model molecules

Molecule release occurs by the process of diffusion, as a function of porosity, degradation, or swelling of hydrogels. Physical cross-linking through ultraviolet radiation or thermal and ionic or covalent cross-linking methods can be employed to estimate the permeability and the swelling of hydrogel for the release of the model molecule [80-82].

Table 3: The various routes of administration of hydrogels

S. No.	Administration	Description	Reference[s]
1	Hydrogels in oral drug delivery	The drug is incorporated into hydrogels and delivers to the oral cavity for local treatment of diseases of the mouth, such as stomatitis, fungal diseases, periodontal disease, viral infections, and oral cavity cancers.	[127]
2	Gi tract drug delivery	GI tract drug delivery contains the facility of administration of drugs locally to the specific sites in the GI tract and its large surface area for systemic absorption. For example, stomach-specific antibiotic drug delivery systems for the treatment of Helicobacter pylori infection in peptic ulcer disease.	[128]
3	Ocular drug delivery	Hydrogels are most widely used in ocular drug delivery system. Most hard and soft contact lenses are formed of polymers in form of hydrogel films. hydrogels are attractive as an ocular drug delivery system because of their facility in dosing as a liquid, and their long-term retention property as a gel after dosing.	[129]
4	Rectal delivery	Drugs absorbed from the lower part of the rectum drain into the systemic circulation directly. Thus, the rectal route is useful for the drug administration having first-pass metabolism. It is used for local treatment of diseases associated with the rectum, such as hemorrhoids.	[130]
5	Topical drug delivery	To treat skin infection various hydrogels are used to prepare and apply topically for local action. The active component like Desonide which is a synthetic corticosteroid usually used as an anti-inflammatory. The hydrogels have been formulated for better patient compliance and have moisturizing properties.	[131]
6	Subcutaneous delivery	Hydrogel formulations for subcutaneous delivery of anticancer drugs are being prepared viz. cross-linked PHEMA was applied to cytarabine. Subcutaneously inserted exogenous materials may more or less evoke potentially undesirable body responses, such as inflammation, carcinogenicity, and immunogenicity.	[132]
7	Protein drug delivery	Interleukins which are conventionally given as injection are now given as hydrogels. These hydrogels have shown better patient compliance. The hydrogels form in situ polymeric network and release proteins slowly. These are biodegradable and biocompatible.	[133]
8	Hydrogels in tissue engineering	The micronized hydrogels have been used to deliver macromolecules like phagosomes into the cytoplasm of antigen-presenting cells. The release is because of acidic conditions. Such hydrogels mold themselves to the pattern of membranes of the tissues and have sufficient mechanical strength. This property of hydrogels is also used in cartilage repairing.	[134]

CONCLUSION

This review aims to introduce briefly the hydrogels: a class of natural or synthetic polymeric materials that can hold huge amounts of water because of their specific structures and subsequent swelling properties and described recent progress in stimuli-responsive polymers. The various types of stimuli-responsive hydrogels properties and their applications were discussed. An important aspect to be considered while developing these smart hydrogels is controlled biodegradability and biocompatibility. Research into stimuli-responsive polymers as a means of achieving this is steadily gaining momentum, and more novel polymers are being synthesized.

Hydrogels are widely used in the development of intelligent systems for drug delivery. To develop a new drug delivery of stimuli-responsiveness represents a key property in medical applications because it enables a controllable response from biological compartments, such as the release of an encapsulated/entrapped active compound, the triggering of a signaling process, or the detection of a specific biomolecule. The various routes of administration and updated research work done on hydrogels and types, features, and various stimuli systems that produce responsive delivery of drugs were discussed in this article.

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CONFLICTS OF INTERESTS

Declare none

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