International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Issue 4, 2024

Review Article

GASTRORENTENTIVE HYDROGELS RESPONSIVE TO EXTERNAL STIMULI FOR NOVEL DRUG DELIVERY

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Received: 04 Apr 2024, Revised and Accepted: 06 Jun 2024

ABSTRACT

Hydrogels, or water-swollen polymers, are three-dimensional networks of polymeric chains with a high capacity for holding water inside their structure. Because of this special quality, they are helpful in many applications, such as tissue engineering, drug delivery, and wound healing. Tissue engineering, controlled drug release, smart devices, and magnetic fields are all made possible by their sensitivity to temperature, ionic strength variations, electric fields, pH changes, magnetic fields, and ultrasounds. The interesting potential of stimuli-dependent hydrogels for gastroretentive drug delivery in the Gastrointestinal Tract (GIT) is examined in this review article. A new strategy is provided by stimuli-responsive hydrogels, which change their characteristics in response to particular GIT environment triggers like pH, enzymes, or pressure. The article explores a range of stimuli-dependent hydrogels, such as those that react to enzymes, pH, and other stimuli. Hydrogel's latest developments and their use in GIT medication delivery are also examined. Promising research on these innovative drug delivery systems is highlighted in the review. The paper also examines patents about stimuli-dependent hydrogels, offering information about the intellectual property environment surrounding this technology. In summary, hydrogel systems combine the targeted response to GIT stimuli with the controlled release properties of hydrogels to hold immense potential for improved drug delivery and therapeutic efficacy.

Keywords: Hydrogel, Crosslinking, Gastroretentive, Stimuli-responsive, Drug delivery, Recent advancement, Patents

DOI: https://dx.doi.org/10.22159/ijap.2024v16i4.51051 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Hydrogels are classified as 3D cross-linked macromolecular polymers (homopolymer or copolymer) which have a swelling property with water or any aqueous solvent [1, 2]. After coming in contact with the solvent, liquid sorption takes place due to which the dry powder or bead changes to a gel-like substance. When these hydrophilic cross-linked polymers are in smaller dimensions, they are known as “microgels“ and when the size of these microgels is further reduced to submicrometer, they are known as “nano gels” remain insoluble due to these cross-linking [3, 4].

They have a soft consistency, are highly filled with water, and have a porosity that can be chemically stable degrade disintegrate, or dissolve [5]. If molecular entanglements and secondary forces like ionic, H-bonding, or hydrophobic forces play the primary role, hydrogels are also known as "reversible" or "physical" gels [4, 6]. Physical gels are always reversible and easily dissolve by altering factors like temperature, solution ionic strength, and pH [7]. By using cross-linking polymers in dry or in solution state, it is possible to create a network of covalent connections that connect various macromolecular chains in "permanent" or "chemical" gels [8]. Depending on the functional groups of their structure, these gels can be classified as charged or non-charged. When the pH of the charged hydrogels varies, they often experience changes in swelling (stimuli effect) [8, 9].

They show swelling behavior due to various factors like types of polymers used (hydrophilic or hydrophobic), method of preparation of hydrogel, and the cross-linking or osmotic pressure difference act as driving force for water sorption [10].

Super porous Hydrogel (SPH) is a hydrophilic polymer network with specific ingredients. Foam stabilizers, initiators, crosslinkers, foaming agents, and foaming aids that are three-dimensional. Because of their enormous size and ability to absorb large fluids in their surroundings, these hydrogels cannot pass through the constrained pylorus and reach the next organ. Instead, their volume increases dramatically in a short amount of time [11, 12]. They can be utilized as gastric retention carriers thanks to their special swelling feature, which provides continuous release over prolonged stomach residence [11, 13]. Upon exposure to the acidity of the stomach, SPHs ought to expand and function as a gastroretentive apparatus. Cationic ($-NH_2$,$-SO_3H$) functional groups on the backbone of polymers can be used to accomplish this. Because of this, the polymers are pH-sensitive to the environment but swell only in acidic environments [14].

Here are some details about the structure of SPHs

- High Porosity: SPHs typically have porosities ranging from 60% to 99%, creating a network of void spaces within the material. This high porosity allows for the absorption and retention of large amounts of water or other solvents, making them suitable for applications such as absorbent materials and drug delivery systems [14].
- Interconnected Pores: The pores within SPHs are interconnected, forming a continuous network throughout the material. This interconnected structure facilitates the rapid diffusion of water or solutes into and out of the hydrogel, enabling fast response times and efficient mass transport [15].
- Macroporous Structure: SPHs typically contain macropores with diameters ranging from tens to hundreds of micrometers. These macropores provide pathways for fluid flow and contribute to the high permeability of the hydrogel [14].
- Polymeric Scaffold: The structure of SPHs is often based on a polymeric scaffold that provides mechanical support and stability. Common polymers used in superporous hydrogels include natural polymers like alginate, chitosan, and gelatin, as well as synthetic polymers such as poly(acrylic acid) and poly(vinyl alcohol) [15, 16].
- Crosslinking Networks: Crosslinking is used to stabilize the polymeric scaffold and create the porous structure of SPHs. Crosslinking agents such as chemical crosslinkers, physical crosslinkers (e.g., temperature or pH-responsive interactions), or radiation (e.g., UV or gamma irradiation) are employed to crosslink the polymer chains and form a stable network [17].
- Swelling Behavior: Due to their high porosity and hydrophilic nature, SPHs exhibit significant swelling in the presence of water or aqueous solutions. The extent of swelling can be controlled by adjusting factors such as the polymer composition, crosslinking density, and environmental conditions (e.g., pH, temperature) [11, 18].

- Stimuli-Responsive Properties: SPHs can be designed to exhibit stimuli-responsive behavior, where changes in environmental conditions such as pH, temperature, or ionic strength trigger reversible changes in the hydrogel's structure and properties. This responsiveness makes them suitable for applications such as controlled drug release and tissue engineering [19].

One of the most practicable ways to achieve a longer and more consistent profile of medication delivery in the gastrointestinal system is to regulate the food in the stomach. To achieve gastric retention, the dosage form needs to be strong enough to withstand the forces produced by the stomach's peristaltic waves as well as continuous contractions, grinding, and churning mechanisms [20-22].

Gastroretentive Drug Delivery Systems (GRDDS) are useful for drugs that have short half-lives, are unstable and poorly soluble at alkaline pH, have low absorption in the lower half of the GIT, and have local activity in the upper intestine for H. pylori eradication [23, 24].

Gastro-retentive hydrogel assembly containing a core shell is recommended to release the drug and control the gastro-retentive time. In vivo, the hydrogel assembly can sustain a constant blood drug concentration for more than 80 hours, and in vitro, it can continuously release medication for up to 72 h. The hydrogel assembly may naturally break down in the stomach environment after usage [25].

By increasing the gastric retention, absorption increases. A prolonged release is brought on by gastric floating and mucoadhesion [23, 26]. The capacity to float is dependent upon the stomach fluid that is available for buoyancy, and this is usually lost at night after the stomach is emptied. The pyloric sphincter allows a medication to enter the body as a result of supine sleeping [27].

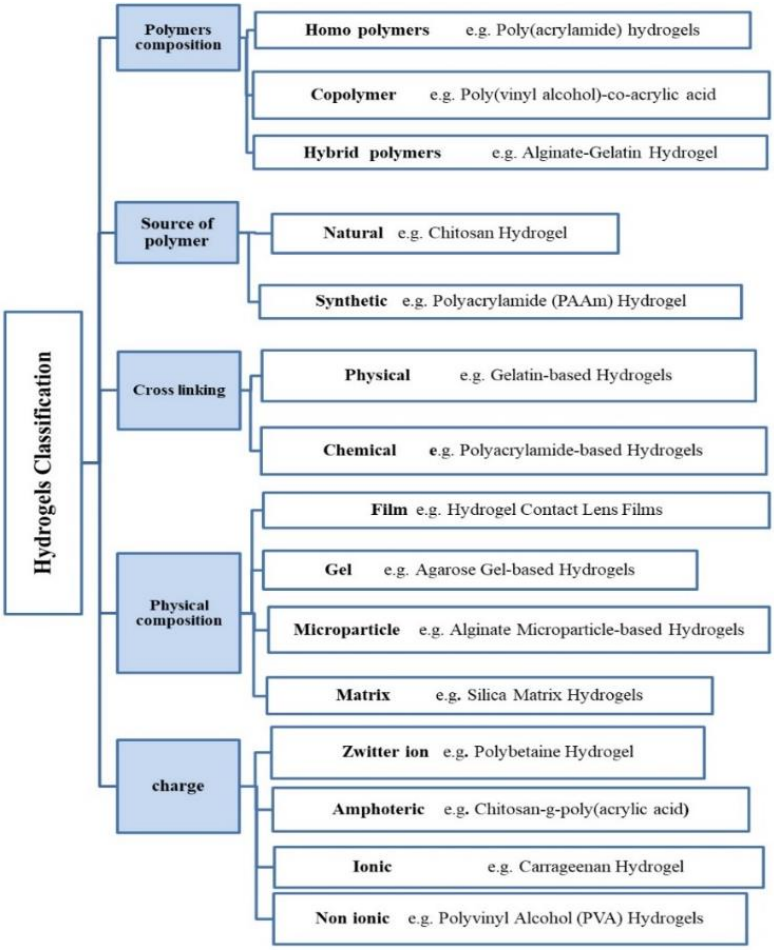

Fig. 1: Classification of various types of hydrogel [28]

Table 1: Various stimuli effect utilized to affect the release of drugs from hydrogels

S. No.	Stimulus	Hydrogel type	Release mechanism	References
1.	pH	Acidic or basic hydrogel	pH change-swelling-drug release	[29]
2.	Enzyme substrate	Hydrogel containing immobilized enzymes	Substrate present-conversion of enzyme-changes gel swelling-drug release	[30]
3.	Ionic Strength	Ionic hydrogel	Change in ionic strength-concentration of ions inside the gel changes-swelling-drug release	[31]
4.	Magnetic	Magnetic particles dispersed in microspheres	Magnetic field applied-pores in gel changes-swelling-drug release	[32]
5.	Chemical	Hydrogel containing electron-accepting groups	Electron-donating compounds-charge-transfer complexes formation-swelling-drug release	[33]
6.	Thermal	Thermo-responsive hydrogel	Temperature change-polymer-polymer and water-polymer interactions change-swelling-drug release	[34]
7.	Ultrasound irradiation	Ethylene–vinyl alcohol hydrogel	Ultrasound irradiation-temperature increase-release of drug	[35]

Classifications of hydrogels

Natural polymers overcome synthetic polymers due to various advantages like high biocompatibility, biodegradability, and excellent tissue and cell response [2, 28]. The different types of hydrogels are explained in fig. 1 as follows.

External stimuli effect

Table 1 shows different types of drug release with their mechanism.

Phase transition results from changes in the external environment in each of these situations, and these changes affect the polymer's ability to absorb water or its swelling behavior. These changes can be attributed to changes in ionic strength, pH, current, ultrasonic velocity, and other variables which are explained in fig. 2.

pH-responsive hydrogels

Variations in pH levels can be found in the vagina, GIT, blood vessels, and other body parts. These pH-sensitive hydrogels are made to specifically target organs and tissues that have particular pH values [37]. These formulations can swell when the pH changes because they contain an acidic or basic group (like an amino group or carboxyl group) that is easily protonated or hydrolyzed. The drug release from hydrogel after changing pH is shown in fig. 3.

They include hydrogels that are both cationic and anionic. Anionic groups that break down in an alkaline medium, such as -COOH, deprotonate at lower pH and become protonated at higher pH. These hydrogels come upon contact with molecules of water [29]. Because they contain an alkaline group like NH_2, cationic hydrogels have an entirely different swelling characteristic.

Chitosan, a bio-based polymer, is the most prevalent ionic polymer that exhibits behavior due to changes in pH. Taking alginate orally is safe and biodegradable because it's a copolymer containing polyanions of sugar residue that is mannuronic and guluronic [30, 38]. To stop drug release, it reduces at low pH, such as in the GIT. At pH values below 3, the Alginate chain contains carboxylate groups, which change into-COOH, which limits the hydrogel's ability to expand and form a hydrogen bond with the hydroxyl group in Alg. However, due to their high content of water and restricted mechanical properties, basic hydrogels face problems such as burst drug release. There are a few more varieties of hydrogel drug release in addition to films [38, 39].

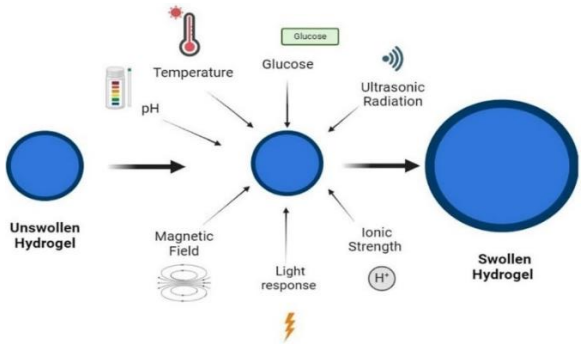

Fig. 2: Various stimuli acting on hydrogel [31, 36]

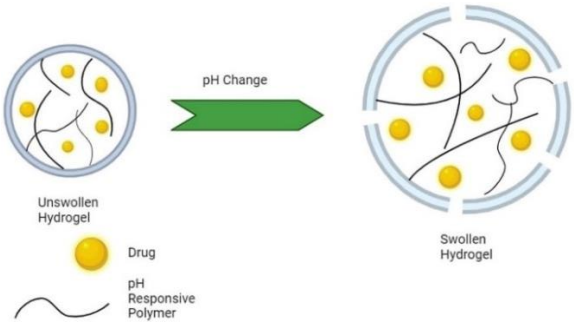

Fig. 3: Drug release by a change in pH resulting in swelling of the hydrogel [29, 37]

Mechano-responsive hydrogels

Mechano-responsive, also known as a mechanically-activated system for drug delivery, uses mechanical force that is either naturally occurring in humans or applied externally to control the spatiotemporal release of medications and active ingredients [40]. It is possible to apply three different mechanical stimulation techniques-tension, shear, and compression-to deliver drugs and other therapeutic agents. To optimize the delivery performance of each type of mechanoresponsive DDS for a variety of intended applications, distinct materials in various forms are required for both in vitro as well as in vivo testing. More precisely, Hydrogels or elastomeric matrices that tolerate cyclic compressive stresses in addition to responding to compression forces are commonly used in systems activated by compression. Composites with payload separation capabilities are frequently used in tension-sensitive systems [40, 41].

Mechanoresponsive hydrogel drug delivery systems release drugs in response to mechanical stimuli through various mechanisms. Here are some common mechanisms by which drug release can be triggered in mechanoresponsive hydrogels:

- Pore Size Modulation: Mechanical forces applied to the hydrogel can cause changes in the pore size or network structure of the hydrogel. A decrease in pore size or collapse of the network can lead to the expulsion or diffusion of encapsulated drugs from the hydrogel matrix [42].

- Swelling and Deswelling: Some hydrogels undergo significant swelling or deswelling in response to mechanical forces. Swelling may lead to increased drug release due to enhanced diffusion, while deswelling may result in compression and expulsion of the drug payload [43].

- Fracture-Induced Release: Mechanical stress can induce fracture or rupture of the hydrogel matrix. Fracture-induced release occurs when the fractures expose drug-loaded regions, allowing for rapid release of the encapsulated drugs into the surrounding environment [40].

- Osmotic Pressure: Mechanical compression of the hydrogel can alter the osmotic pressure within the system. Changes in osmotic pressure may drive the diffusion or expulsion of drug molecules from the hydrogel matrix [44].

- External Triggering: In some cases, mechanical stimuli may be used to trigger external mechanisms that, in turn, lead to drug release.

For example, mechanical deformation of the hydrogel may trigger the release of encapsulated drugs through the activation of embedded microspheres containing drug payloads or through changes in the local environment (e.g., pH or temperature) [40, 45].

Applications for mechanoresponsive hydrogel drug delivery systems can be found in wound healing, tissue engineering, regenerative medicine, and drug delivery, among other biomedical domains. By enabling targeted and localized drug delivery, these systems reduce systemic side effects and increase the effectiveness of treatment.

Electric field-responsive hydrogels

Electro-responsive systems, or medication delivery systems that react to electric fields are a rapidly developing field of study. These devices can precisely and flexibly control the time and space in which drugs are delivered. Easy and accurate tools like external electroconductive patches for skin or small, ultrasound-controlled implants that can be inserted deeper into the body to provide the necessary voltage to start the release of the medication [46]. Electro-responsive hydrogels, electro-responsive lBL films, and conducting polymers are the three most prevalent electro-responsive delivery systems that have been documented to date. Drugs are released from hydrogels made of polyelectrolytes by physical changes (bending, shrinking, distorting, or swelling) or general changes in the polymer structure. However, the drawback of using high applied voltages (2 to 25 V) to initiate drug release must be partially addressed by electro-responsive hydrogel systems [47, 48].

Ultrasound (US)-responsive hydrogels

There are numerous enticing advantages to using ultrasonic response systems (USRs) for drug release. US-triggered platforms are useful, affordable, and discrete. It is important to note that the US has been used in the past to treat various conditions, like thrombosis, osteoporosis, and strokes [49]. Reports state that the US is capable of disassembling hydrogen bonding networks and working with hydrogels. Studies have shown that US stimulus greatly accelerates the release of medications [35]. Usually, carriers are dissolved by ultrasound-responsive devices to start the drug's release some researchers developed a cellulose hydrogel matrix-based ultrasound drug delivery system to activate the liver and release mimosa. The hydrogel system significantly increased the rate of mimosa release. The efficiency of the mimosa release was roughly six times higher than that of the release without US exposure [45, 50].

To achieve ultrasonic responsiveness in hydrogels, ultrasonic-sensitive structures or elements are typically integrated into the hydrogel framework, as shown in fig. 4. The hydrogel's structure undergoes reversible modifications upon exposure to ultrasonic waves, which can lead to alterations in its mechanical properties, swelling behavior, or drug release properties [51, 52]. Key considerations for ultrasonic responsive hydrogels include:

Polymer Selection: Selecting polymers with appropriate acoustic characteristics that can change back when exposed to ultrasonic radiation is crucial. Poly(N-isopropyl acrylamide) (PNIPAAm), polyvinyl alcohol (PVA), and polyethylene glycol (PEG) are a few examples of commonly used polymers [51].

Selecting a polymer that is UV-active in a hydrogel involves considering several factors:

- UV-absorbing Monomers: Choose monomers with UV-absorbing properties. Some monomers, such as those containing benzene rings or conjugated double bonds, can absorb UV light effectively. Examples include acrylic-based monomers like benzophenone or anthracene derivatives [53].

- Crosslinking Ability: The polymer should have the ability to form a stable hydrogel network through crosslinking. UV-active cross-linkable groups (e. g., vinyl, acrylate, or methacrylate groups) can be incorporated into the polymer structure [54].

- Biocompatibility: Ensure the polymer and its degradation products are biocompatible for biomedical applications [55].

- Tunable Properties: Consider polymers with tunable properties such as swelling behavior, mechanical strength, and degradation rate to meet specific application requirements [56].

- Synthesis Method: Select a synthesis method compatible with UV polymerization, such as photopolymerization, where UV light initiates the crosslinking reaction [57].

- Application Requirements: Assess the specific requirements of your application, such as the desired hydrogel properties (e.g., porosity, responsiveness to stimuli), and choose a polymer that best fulfills those requirements [55].

- Compatibility with Other Components: Ensure compatibility with other components that may be incorporated into the hydrogel formulation, such as drugs or bioactive molecules [58].

- Research and Testing: Conduct thorough research and experimentation to evaluate the performance of the selected polymer in UV-active hydrogel formulations, considering factors like polymerization kinetics, gelation time, and final hydrogel properties [59].

Crosslinking: One important factor is the hydrogel's degree of crosslinking. In addition to providing structural stability to the hydrogel, crosslinks can be designed to react to ultrasonic stimuli.

To achieve the desired responsiveness, crosslinking agents and methodologies must be carefully chosen. Common methods for UV-crosslinking hydrogels include direct UV irradiation, photomask-assisted patterning, and two-photon polymerization (for high-resolution patterning) [60].

Incorporation of Responsive Components: Adding responsive components to the hydrogel matrix, like nanoparticles or microbubbles, is frequently necessary to achieve ultrasonic responsiveness. These elements may alter in reaction to ultrasonography, changing the hydrogel's overall characteristics [52].

Magnetic field-responsive hydrogels

A magnetic stimulus is a non-contact force that can be applied to biomedical devices with ease and convenience [61]. This shows the application of low-frequency oscillating magnetic fields (OMF), high-frequency alternating magnetic fields (AMF), and direct current magnetic fields (DMF), among other common external magnetic fields in drug administration. Researchers have documented the effect of an OMF on the release of dextran from collagen magnetic nanocomposites. The OMF's uses depended on the hydrogel's mechanical deformation brought about by the interactions of magnetic particles, which enabled the controlled extrusion of drug molecules [62].

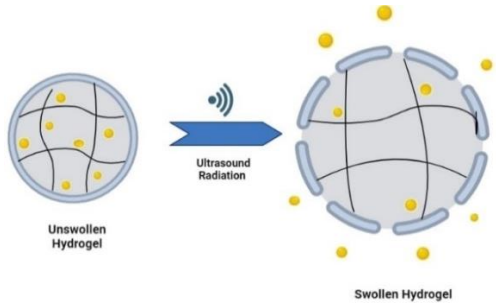

Fig. 4: Drug release by ultrasound as external stimuli [51, 52]

Alginate hydrogels, for instance, have been embedded with MNPs (iron oxide) to control the release of drugs and cells both in vivo and in vitro by using an external force field to induce large volume changes and deformation. (above 70%) [63, 64].

Methods for creating magnetic hydrogels: The typical components of magnetic hydrogels are a polymer matrix and a magnetic component embedded in the matrix. The properties of magnetic hydrogels, such as their magnetic response, are dependent on the kind of hydrogel and MNP utilized, their concentrations, and the size and distribution of the MNPs within the hydrogels. Numerous techniques, such as blending, in situ precipitation, and grafting-onto, have been developed to create magnetic hydrogels [65, 66].

Glucose-sensitive hydrogels

Known by other names, such as "smart" or "responsive" hydrogels, glucose-sensitive hydrogels are hydrogels made primarily of a polymer matrix that reacts to variations in glucose concentration by changing either physically or chemically, as shown in fig. 5.

Hydrogels that are sensitive to changes in glucose concentration are materials known as glucose-sensitive hydrogels. These materials may find application in the biomedical and diagnostics industries, among other fields. These hydrogels play an important role in the management of diabetes, where real-time blood sugar monitoring is essential [67, 68].

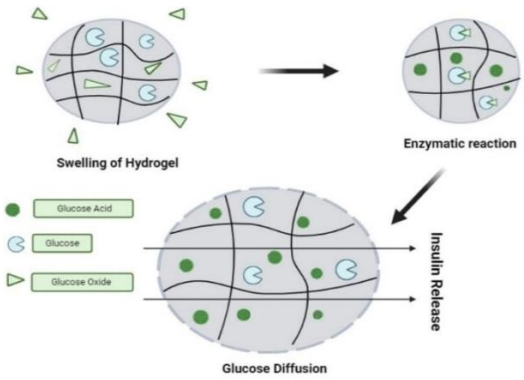

Fig. 5: Insulin release in the presence of glucose as external stimuli resulting in lower glucose levels in the body [67, 68]

Specialized elements, frequently glucose-binding molecules or enzymes, are incorporated into these hydrogels by carefully placing them within their matrix. These responsive elements experience particular structural or conformational changes in response to variations in glucose levels. As a result, the hydrogel undergoes reversible swelling or deswelling, which is directly correlated with changes in the concentration of glucose. Applications such as drug delivery systems, where the hydrogel can release encapsulated substances, like insulin, in a glucose-dependent manner, are made possible by this dynamic behavior. The complex interaction between glucose and the hydrogel produces a responsive system with great potential for novel biomedical applications, especially in the field of diabetes treatment. Researchers are continuously improving their composition and design to maximize these hydrogels sensitivity, accuracy, and general performance for medical and diagnostic applications [69].

Ion-sensitive hydrogels

When specific ions are present, polymers can transition into a different phase. Ion-sensitive polysaccharides are a subclass of polysaccharides. I-carrageenan primarily forms elastic gels in Ca2+ presence, whereas k-carrageenan reacts to trace amounts of K+ by forming rigid, brittle gels. An anionic polymer, gellan gum (also

called gelrite) solidifies when it comes into contact with divalent and monovalent cations like Mg2+, Ca2+, Na+, and K+[70, 71]. It has been demonstrated that the presence of divalent cations, specifically Ca2+, causes low-methoxy pectins to partially gel. Alginic acid gels under these circumstances as well because divalent or polyvalent cations, such as Ca2+, interact with guluronic acid blocks in alginate chains. light-sensitive hydrogel [70, 72].

These hydrogels are designed to undergo structural changes or exhibit specific behaviors in response to variations in ion concentrations, particularly hydrogen ions (pH), metal ions, or other specific ions.

The responsiveness is often achieved through the incorporation of ion-sensitive components, such as ionizable groups or molecules, within the hydrogel matrix.

Ion-sensitive hydrogels continue to be a subject of active research, with ongoing efforts to enhance their sensitivity, specificity, and overall performance for various applications across various scientific and technological domains [73].

Hydrogels that are sensitive to metal ions represent an additional notable category. These hydrogels are designed, frequently by adding chelating ligands or ion-binding groups, to react selectively to particular metal ions. These hydrogels are essential for identifying and measuring heavy metal ion concentrations in water sources in environmental monitoring [74]. Ion-sensitive hydrogels are important instruments for guaranteeing water quality and safety because of their capacity to detect and react to environmental pollutants [75].

Light-responsive hydrogels

Light-responsive hydrogels, also known as photo-responsive or photoreactive hydrogels, constitute a class of intelligent materials that experience reversible alterations in their characteristics when exposed to light signals. Due to these hydrogels' versatility and utility, they are attracting a lot of interest. across diverse domains, encompassing tissue engineering, drug delivery, biomedical devices, and soft robotics [76].

Apart from the ones mentioned above, the categories of DDSs, this system is also a desirable drug delivery system because of the advantage of the spatiotemporal regulation of drug release. Light-switchable devices can precisely control the light's intensity, wavelength, irradiation period, and area to achieve "on-demand" or pulsatile drug delivery. Additionally, light irradiation can be precisely targeted to initiate the on-demand release at specific sites, which could enhance the effectiveness of treatment [77, 78].

In addition to the DDSs previously discussed, the advantage of spatiotemporal regulation of drug release makes light-responsive systems appealing for drug delivery. light-switchable devices can precisely control the properties of light, such as wavelength, intensity, irradiation period, and area, to achieve pulsatile or "on-demand" drug delivery. Furthermore, the on-demand release can be activated or triggered at particular locations by tightly directed light irradiation, which may enhance the therapeutic efficacy [77, 79].

Lignin-based hydrogels

One renewable polymer that may be utilized as a foundational ingredient for hydrogel applications is lignin. In the past few years, natural polymers have quickly replaced synthetic ones as the most important components in the development of hydrogels. Natural polymer-based hydrogels are of great interest because of their inherent qualities, which include, but are not limited to, biocompatibility, low toxicity, eco-friendliness, susceptibility to enzymatic degradation, and biodegradability [80, 81]. The domains of water purification, healing systems, biomimetic scaffolds, biomedical, and devices for drug delivery are among the various applications of hydrogels based on biopolymers. Lignin is a desirable option for hydrogels among other natural polymers, because of its previous benefits, which make it a versatile material with a wide range of applications. The use of lignin as the backbone polymer in hydrogel applications is the subject of very few research publications [82].

Lignin-based hydrogels are a type of hydrogel that incorporates lignin, a complex organic polymer derived from plant cell walls, as a key component. These hydrogels have gained attention due to the different properties of lignin, including its abundance in nature, biodegradability, and potential for sustainable material development. Lignin-based hydrogels find applications in various fields, including agriculture, environmental science, and biomedicine [83, 84].

Typically, the synthesis of lignin-based hydrogels involves combining lignin with other polymers or crosslinkers to augment structural integrity and responsiveness to stimuli. This enables the customization of hydrogels for specific applications in fields such as biomedicine, agriculture, and environmental remediation [80]. In the realm of biomedicine, lignin-based hydrogels exhibit considerable potential for applications like wound healing, tissue engineering, and drug delivery capitalizing on their biocompatibility and controlled release features. Additionally, in agriculture, they show promise for tasks such as soil conditioning and controlled fertilizer release [83].

In essence, lignin-based hydrogels represent a versatile and sustainable class of materials with wide-ranging applications, playing a crucial role in the advancement of environmentally conscious solutions and the efficient utilization of natural resources.

Recent works on different stimuli

Table 2 defines various polymers used in the recent advancements in hydrogel.

Table 2: Recent advancements in the hydrogel with their mechanism

S. No.	Recent work	Polymer used	Mechanism	Reference
pH-responsive hydrogels:				
1.	Synthesis of biodegradable enzyme and pH-responsive hydrogels for controlled drug release	Poly (l-glutamic acid)	One kind of hydrogel that responds to temperature changes by changing its solubility or swelling is called biodegradable thermoresponsive hydrogel. polymer with upper or lower critical solution temperatures are used to make them.	[38, 85]
2.	pH-responsive hydrogels inspired by self-healing Mussels	Poly (ethylene glycol)	Hydrogels that draw inspiration from mussels are typically created by crosslinking a polymer with a molecule that contains catechol, like dopamine (DOPA). DOPA is found in mussels' adhesive proteins by nature. The degree of crosslinking between polymer chains can be affected by the Ph of the solution and can occur as a result of coordination complexes that form between DOPA and iron ions.	[29]
3.	pH-sensitive hydrogels that degrade naturally are designed for the controlled release of two drugs simultaneously	Poly (L-lactide)-co-polyethyleneglycol-co-poly(L-lactide) methacrylates	The hydrogels were evaluated for their biodegradability biocompatibility and mechanical properties. The hydrogels were shown to be non-toxic to cells and exhibit a reversible>80% volume reduced at pH 1.2 as compared to that at pH 7.4	[86]
Mechano-responsive hydrogels.				

S. No.	Recent work	Polymer used	Mechanism	Reference
1.	Utilizing mechanical forces to regulate release: Mechanoresponsive materials for drug delivery with controlled discharge.	Polyurethane	Mechano-responsive hydrogels utilize various mechanisms, with cleavable crosslinks being a common strategy. When subjected to mechanical stress, these crosslinks within the hydrogel network can break, triggered by shear, compression, or tension. This event leads to the release of encapsulated medication as the hydrogel unravels. Another prevalent mechanism involves hydrophobic interactions, where the hydrogel's hydrophobic domains interact during mechanical stress, forming aggregates. This interaction induces structural and characteristic alterations in the hydrogel, affecting permeability and stiffness. Through these modifications, the encapsulated drug release can be controlled, offering a dynamic and responsive system for drug release based on mechanical cues	[87]
2.	Tough and antibacterial hydrogels with mechano-responsive properties and adjustable drug release, designed for applications in wound healing.	Poly (sulfobetaine methacrylate)	Treating frequently deformed acute wounds poses challenges, as external mechanical forces can hinder healing. Using strong, skin-adhesive dressings with stimuli-responsive drug release is necessary due to the limited efficacy of traditional wound dressings because of their poor mechanical properties, difficulties with skin adhesion, and drug delivery issues. To address this, a poly(sulfobetaine methacrylate) mechano-responsive hydrogel was developed. loaded with hydrophobic antimicrobial drugs in diacrylate Pluronic F127 micelles, it demonstrated excellent mechanical qualities, with a tensile strength of 112 kPa and a strain of 1420 %, respectively. The hydrogel maintained skin adhesiveness at 6 kPa, even after repeated cycles.	[43]
3.	Hydrogels are sensitive to mechanical stimuli induced by host-guest complex dissociation.	Poly (N-isopropyl acrylamide)	By utilizing a nonthermoresponsive network with a host like β-cyclodextrin and a thermoresponsive polymer with adamantane in its side chain as the guest, a hydrogel that responds to mechanoelectric forces was created. The host-guest interaction immobilized the polymer above the lower critical solution temperature (LCST), thereby partially blocking its phase transition. Reduced transmittance upon the use of mechanical stress at temperatures above lCST suggests a polymer phase transition induced by host-guest complex dissociation. Resolving the thermoresponsive polymer and cooling the hydrogel would also replicate this mechano-responsive behavior.	[85, 88]
Electric field-responsive hydrogels.				
1.	Transformer Hydrogels	Poly (N-isopropyl acrylamide)	Transformer hydrogels are micro-and mesostructured hydrogels that exhibit a sharp change in form, dimension or shape along with corresponding functional changes as a result of local variations that are engineered, like swelling or stiffness, in response to outside stimuli or controls. This covers techniques like layering, patterning, or creating anisotropy and gradients that can be used to create transformer hydrogels. Transformer hydrogels are categorized according to how they react to various stimuli, including chemicals, biomolecules, electromagnetic fields, and temperature. A review of recent research findings points to use the of transformer hydrogels for soft robotics, tissue engineering, biomimetics, and microfluidics.	[89]
2.	Innovative platforms for diverse biomedical applications and tissue engineering: Hydrogels that are smart or stimuli-responsive.	Poly (acryl amide)	The use of therapeutic protocols combining biomimetic scaffolds, bioactive substances, and cells is a crucial aspect of this track. Smart/stimuli-responsive hydrogels are amazing three-dimensional (3D) bioscaffolds made for tissue engineering and other biomedical applications. They can copy the mechanical, biological, and physicochemical properties of local tissues. Additionally, they provide the aqueous conditions required for cell growth, aid in the conformation of cells in three dimensions, provide mechanical stability to cells, and function as efficient matrices for the delivery of bioactive substances. A wide range of natural and synthetic polymers were used to create these intelligent platforms with special, cutting-edge characteristics and tailored functionalities suitable for such applications	[90]
3.	Hydrogels responsive to environmental cues designed for drug delivery applications	Poly (N-ethylacrylamide)	Because hydrogels are enzymes to absorb large water and have a rubbery, soft texture, they can mimic the physical characteristics of biological tissues. The potential of environment-sensitive Hydrogels, which can alter in response to external stimuli, is being investigated by researchers more and more. Drug delivery has advanced significantly as a result of this focus, enabling improved treatment for a range of pathological conditions. As this study covers various physical, chemical, and biological stimuli influencing drug release from hydrogel details, these advancements include decreased dose frequency, prolonged release duration with fewer side effects, and simplified preparation and administration.	[53]

S. No.	Recent work	Polymer used	Mechanism	Reference
Ultrasound (US)-responsive hydrogels.				
1.	Ultrasound-responsive programmable hydrogel nanogenerators provide wireless electrical stimulation of the vagus nerves for anti-inflammatory treatment in sepsis.	Lipopolysaccharide	The use of hydrogel nanogenerators that respond to ultrasound waves and can be programmed to stimulate vagus nerves wirelessly presents a non-invasive method of treating sepsis-related inflammation. When ultrasound activation is applied to an implant placed close to the vagus nerves, it causes regulated hydrogel deformation and electrical signals that activate the cholinergic anti-inflammatory pathway. This accurate, non-invasive technique offers on-demand therapy by reducing systemic inflammation in sepsis. This novel approach to treating sepsis prioritizes patient comfort and safety while providing precise electrical output control thanks to the programmable hydrogel.	[91]
2.	On-demand drug delivery via ultrasound-activated hydrogel microbeads with release enhancer	poly-l-lysine	Ultrasound-activated on-demand delivery of drugs employs hydrogel microbeads with release-enhancing agents. These microbeads, loaded with therapeutic agents, respond to ultrasound waves by undergoing controlled deformation. The 8 enzylae enhancer, activated by ultrasound, further facilitates the controlled release of drugs. This mechanism enables precise modulation of drug delivery, offering a non-invasive and on-demand approach. The ultrasound-triggered release enhances therapeutic efficacy, allowing tailored drug administration for optimal treatment outcomes. This innovative strategy holds potential for various medical applications where controlled and localized drug delivery is crucial.	[92]
Magnetic field-responsive hydrogels				
1.	Hydrogels' changing shape in an alternating magnetic field	Poly (N-isopropyl acrylamide)	Due to inadequate magnetization, shape-morphing hydrogels-which are essential in soft robotics, biomimetics, and biomedical engineering-have difficulties when exposed to magnetic fields. We suggest a novel approach to tackle this issue, which involves the use of magnetothermal-sensitive hydrogels, like magnetic poly(N-isopropyl acrylamide). Because these hydrogels are heated to high temperatures through induced heating, they significantly shrink in volume when taken to another magnetic field.	[85, 93]
2.	Super-elastic magnetic structure hydrogels	Poly (4-styrene sulfonic acid-co-maleic acid)	Embedded magnetic nanoparticles are specifically used in super-elastic magnetic structural color hydrogels to provide mechanical resilience and structural coloration. The hydrogels exhibit two mechanisms. They consist of a flexible polymer matrix that contains magnetic nanoparticles that respond to external magnetic fields. In these fields, the super-elastic polymer permits deformation and shape recovery, while the alignment of nanoparticles affects structural color. Promising applications in tunable optics, responsive materials, and flexible biomedical devices are presented by this dual functionality driven by magnetism.	[94]
Glucose-sensitive hydrogels				
1.	A 3D-printable hydrogel that is responsive to glucose and temperature, serving as a sacrificial material for the creation of constructs featuring vascular-like channels.	Poly(N-isopropylacrylamide)	The 3D-printable hydrogel operates as a responsive scaffold, integrating glucose and temperature sensitivity in a sacrificial role for constructing vascular-like channels. Imbued with glucose-responsive elements, the hydrogel undergoes selective swelling or degradation in the presence of glucose, influencing its structural integrity. Simultaneously, temperature responsiveness enables controlled physical changes. During 3D printing, the hydrogel serves as a sacrificial template for creating intricate structures with vascular-like channels. Upon subsequent removal or dissolution, these channels are revealed, mimicking vascular networks. This innovative mechanism holds promise for fabrication, regenerative medicine, and tissue engineering, providing a dynamic platform for constructing complex biomimetic structures.	[95]
2.	Using glucose-sensitive hydrogels made of concanavalin A and carboxylated pullulan that have been8enzylamtly modified, a smart controlled release of insulin is achieved.	Pullulan	Glucose-sensitive hydrogels made of concanavalin A and carboxylated pullulan that have been covalently modified enable the smart, controlled release of insulin. The hydrogel responds to glucose levels, facilitated by the specific interaction between concanavalin A and glucose, leading to insulin release. This mechanism enables precise and responsive insulin delivery, mimicking natural glucose regulation for improved diabetes management.	[85, 96]
3.	The preventive effectiveness of insulin and liraglutide in reducing diabetic nephropathy in rats is enhanced by a hydrogel that responds to glucose.	Phenylboronic acid-grafted γ-Polyglutamic acid (PBA-PGA)	The preventive effectiveness of insulin and liraglutide in reducing diabetic nephropathy in rats is improved by the glucose-responsive hydrogel. Sensitive to glucose, the hydrogel optimizes therapeutic delivery by enabling the controlled release of insulin and liraglutide in response to increased glucose. This targeted mechanism improves the management of diabetic nephropathy by regulating blood glucose and minimizing associated complications. The synergistic	[97]

S. No.	Recent work	Polymer used	Mechanism	Reference
			action of hydrogel, insulin, and liraglutide provides a promising strategy for enhanced treatment outcomes in diabetes-related kidney complications.	
Ion-sensitive hydrogels				
1.	Hydrogels sensitive to various stimuli play an important role in cancer treatment, with factors such as light, pH, ionic strength, and magnetic fields influencing their functionality.	Poly-2-hydroxyethyl methacrylate (PHEMA)	Hydrogels sensitive to light, pH, ionic strength, and magnetic fields play a pivotal role in cancer treatment. Their mechanisms involve structural changes in response to stimuli, enabling the controlled release of drugs and targeted therapy. The stimuli-responsive hydrogels offer a versatile platform for designing precision-oriented cancer treatments by exploiting the dynamic microenvironment of tumors	[98]
2.	Micromotors responsive to stimuli and based on hydrogels for applications in biomedicine.	Poly(N-isopropylacrylamide)	Stimuli-responsive micromotors, employing hydrogel-based constructs, operate by integrating pH, temperature, or biomolecule-responsive elements. These stimuli trigger propulsion mechanisms, such as bubble generation or swell-propulsion, allowing precise control. These micromotors find applications in biomedicine, offering potential in drug delivery, diagnostics, and biological sensing through their targeted and adaptable movement in dynamic environments.	[99]
Light-responsive hydrogels				
1.	Hydrogel that responds to near-infrared light for the targeted identification and release of circulating tumor cells from photothermal sites	Gelatin	A mechanism of specific recognition and photothermal site release of circulating tumor cells (CTC) powers a near-infrared light-responsive hydrogel. The hydrogel incorporates molecular recognition elements that selectively bind to CTCs. Upon exposure to near-infrared light, the hydrogel undergoes a controlled photothermal effect, leading to localized release of the captured CTCs. This innovative mechanism enables targeted and precise recognition of tumor cells in the bloodstream, offering a potential strategy for non-invasive detection and therapeutic interventions in cancer by leveraging the advantages of near-infrared light in biomedical applications.	[100]
2.	Light-responsive hydrogels for controlled drug delivery	poly(ethylene glycol) (PEG)	It employs a mechanism rooted in photo-responsive materials. These hydrogels incorporate light-sensitive components, such as photoactive molecules or nanoparticles, that undergo specific changes in response to light exposure. Upon illumination with an appropriate wavelength, the photoresponsive elements induce alterations in the hydrogel's structure, leading to the controlled release of encapsulated drugs. This process enables precise spatiotemporal control over drug delivery, as the release can be triggered with high precision using light stimuli. An effective method for targeted and on-demand drug release is the creation of light-responsive hydrogels. Offering potential applications in various biomedical and therapeutic contexts.	[76]
3.	Robust, Self-Healing, and Reusable Hydrogel Actuators with Visible light Response	poly(methacrylic acid-co-oligo(ethylene glycol) methacrylate)	The supramolecular design has effectively addressed the main drawbacks of light-driven hydrogel actuators, such as their dependence on UV light, slow response times, poor mechanical properties, and restricted functionality. The application of benzylamine-functionalized anthracene groups is the main innovation. Through π-interactions, this modification not only moves the absorption toward the visible region but also improves the stability of the supramolecular network. To maintain the hydrophilicity of the network and release energy during mechanical deformation, acid-ether hydrogen bonds are also added. The simple synthesis process results in a double-crosslinked supramolecular hydrogel that is both wet and dry and has exceptional strength, quick self-healing, and quick shape morphing under visible light. Because all the interactions involved in the architectural design are dynamic, it makes recycling and reprogramming structures into different 3D forms easier.	[101]
Lignin based hydrogels				
1.	Effective preparation and adsorbent of hydrogel based on lignin from shaddock peels	acrylamide	The synthesis of an efficient shaddock peel lignin-based hydrogel adsorbent involves extracting lignin from shaddock peels and integrating it with a suitable monomer and crosslinking agent. Through a polymerization reaction, the hydrogel forms, incorporating shaddock peel lignin for enhanced mechanical strength. The resulting hydrogel, characterized for structural and mechanical properties, exhibits specific surface chemistry and a porous structure. The adsorbent, prepared for practical use, showcases ion exchange and π-π stacking mechanisms, making it suitable for microfluidic applications with high adsorption efficiency, while considerations include regeneration capability and environmental impact.	[102]

S. No.	Recent work	Polymer used	Mechanism	Reference
2.	Lignin-based hydrogels having "super-swelling" capacities for dye removal	poly (methyl vinyl ether co-maleic acid)	Lignin-based hydrogels having the "super-swelling" ability of dye removal operate by incorporating lignin into a hydrogel matrix. The hydrogel structure, designed for high porosity, allows extensive water absorption, leading to a "super-swelling" capability. This property enhances the hydrogel's efficacy in adsorbing and removing dyes from aqueous solutions, making it a promising material for water purification and wastewater treatment applications.	[103]
3.	Development and Evaluation of lignin-Based Hydrogel for Application in Farm Soils: Initial Proof	d poly(ethylene glycol) diglycidyl ether (PEGDGE)	The development of this hydrogel for farm soils involves synthesizing a hydrogel by incorporating lignin with a suitable monomer and crosslinking agent. Characterization includes evaluating its structural and mechanical properties. Preliminary evidence suggests that the lignin-based hydrogel, when applied to agricultural soils, enhances water retention, soil structure, and nutrient availability. The hydrogel's mechanism involves forming a water-absorbing matrix, improving soil properties for potential benefits in crop growth and sustainable agriculture.	[85, 104]

Table 3: Patents related to hydrogel with their approach

S. No.	Patent	Approach	Year	Reference
1	"Fiber-hydrogel composite surgical meshes for tissue repair"	Offer composite materials and techniques that support the regeneration of soft tissue while repairing soft tissue defects.	2022	[105]
2	"Hydrogels having charged surfaces for cartilage replacement"	This innovation concerns surgical implants designed for the replacement or repair of hyaline cartilage in joints like knees, hips, and shoulders. The term "implants" or "surgery" in this context denotes the surgical, including arthroscopic, implantation of a device into a mammalian joint for the specified purpose.	2013	[106]
3	"Methods for administering certain VMAT2 inhibitors"	Techniques for delivering particular VMAT2 inhibitors are offered by the current invention. [Remedy] ()-α-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido and valbenazine[2,1-a]isoquinoline-2: A technique is presented for giving a patient in need of one of the vesicular monoamine transporter 2 (VMAT2) inhibitors listed above—a patient with mild, moderate, or severe liver damage—a pharmaceutically acceptable salt and/or isotopic variant of the inhibitor. [Diagram for selection] Not one	2023	[107]
4	"Gastro-retentive swellable sustained release composition"	The invention relates to a swellable, sustained-release composition that is gastro-retentive and contains at least one ingredient in the active phase, along with a copolymer of substituted acrylic acid and, optionally, a cellulose derivative and excipients that are approved by pharmaceutical companies. The formulation's goal is to extend the gastric residence time for predetermined periods by including delayed and/or insoluble pH-independent film coating phases.	2023	[26, 108]
5	"Hydrogel implants with porous materials and methods"	There is an implant available that can be placed into a bone segment. It is made up of two parts: a first part that has a porous material portion and hydrogel, and a second part that has an annular rim and a bottom that defines a cavity that can hold the porous material portion of the first part at least partially. Additionally, the second component has a barb that protrudes from the cavity at its bottom.	2023	[106, 109]
6	"Addressing injection site reactions associated with the administration of elamipretide"	The reactions at the injection site relating to elamipretide injection subcutaneously are described in this disclosure. The strategies include the use of specific substances like flavonoids, mast cell degranulation inhibitors, and MRGPRX2 receptor inhibitors. During a subcutaneous injection of 60 mg of elamipretide, certain interventions, such as the application of mometasone furoate or quercetin, are intended to treat or prevent these reactions.	2023	[110]
7	"Compositions for controlled release of cysteamine and systemic treatment of cysteamine sensitive disorders"	The invention includes formulas, procedures, and kits that contain precursor compounds of cysteamine, compounds that can be converted to cysteamine in vivo, and optional agents that facilitate conversion. The goal of these elements is to produce diverse cysteamine pharmacokinetic profiles that are customized for certain patients and circumstances. The invention emphasizes sustained cysteamine plasma concentrations through combinations of pharmaceutical excipients, and it addresses conditions such as cystinosis by providing a variety of administration methods.	2021	[111]
8	"Chemosensory receptor ligand-based therapies"	Treatments for obesity, diabetes, and other metabolic diseases, disorders, or conditions involving chemosensory receptor ligands are provided here. Chemosensory receptor ligand compositions and their preparation for use in the present invention's methods are also included here.	2014	[112]
9	"Modified release drug powder composition comprising gastro-retentive raft forming systems having trigger pulse drug release"	The invention describes a drug powder composition that can be taken orally and forms a dual-trigger, gastro-retentive RAFT. It contains a non-toxic gas-generating agent, medications with both immediate and delayed release, and an RAFT system. After swallowing, it forms a self-contained	2022	[113]

S. No.	Patent	Approach	Year	Reference
		floating RAFT that traps medications and gas produced, guaranteeing stomach retention for at least three hours—except gamma-hydroxybutyrate and its byproducts.		
10	"Gastroretentive formulations containing protein or peptide"	This invention relates to the design of a floating system for drug delivery that delivers peptides and proteins to the upper GIT for a prolonged duration. It offers a simple and cost-effective manufacturing process to address the problem of continuous delivery in the stomach/intestinal tract.	2023	[108]
11	"Expandable gastro retentive dosage form"	There is an oral gastro-retentive delivery tool that quickly unfurls when it comes into contact with stomach juice. The device is set up in a collapsed position for oral intake, unfolding for a predefined amount of time to retain food in the stomach and finally contracting to fit through the remaining portion of the GIT.	2021	[114]
12	"Oral sustained release formulation of tofacitinib"	The current invention is related to tofacitinib oral sustained release formulations and pharmaceutically acceptable tofacitinib salts. The pharmacokinetic profiles of the formulations discussed here are desirable.	2023	[115]

Patents related to hydrogels

Hydrogels are considered to be the most advanced and responsive drug delivery system with many recent advancements. Table 3 outlines several patented formulations, each described accordingly.

CONCLUSION

Gastro-retentive hydrogels have great potential for controlled drug delivery in the gastrointestinal tract because they are sensitive to pH, temperature, swelling, and ultrasonic stimuli. These stimuli-responsive properties enable targeted release, prolonged residence times, and increased therapeutic efficacy. As technology advances, it seems that future developments in gastro-retentive hydrogels will be promising. Gastro-retentive hydrogels have a promising future in terms of innovation and advancement. Emerging technologies like smart polymers, biomimetic materials, and advanced manufacturing processes have the potential to drastically alter the drug delivery strategies used in gastroenterology.

Through the integration of novel stimuli-responsive mechanisms like enzymatic degradation, magnetic guidance, and microbiota modulation, the potential of gastro-retentive hydrogels to deliver personalized therapies that meet the unique needs of individual patients can be further optimized. By making full use of stimuli-responsive hydrogel technology, the delivery of gastro-retentive drugs has the potential to transform the treatment of gastrointestinal disorders and enhance patient quality of life on a global scale.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Mr. Gaurav Moriya (1st author): Data collection and paper writing, Dr. Rupa Mazumder (Corresponding author): Study the concept and design of the manuscript, Dr. Swarupanjali Padhi (3rd author): Review of literature and data interpretation, Dr. Rakhi Mishra (4th author): planning and conceptualization.

CONFLICTS OF INTERESTS

The author declares no conflict of interest.

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