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From Concepts to Applications: A Comprehensive Review of Hydrogels

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A B S T R A C T

Hydrogels have emerged as promising biomaterials for use in drug delivery systems. This is because of their special capacity for regulated release, biodegradability, and biocompatibility. An overview of the most recent advancements in hydrogel-based drug delivery systems is given in this paper, with particular attention to their synthesis, design, and uses. There is also discussion of the basic characteristics of hydrogels. We outline many classification schemes for hydrogels according to their ionic charge, responsiveness, crosslinking technique, and place of origin, as well as samples and salient features. The design considerations for hydrogels in drug delivery are also examined in this review, with a focus on the importance of mechanical qualities, biocompatibility, biodegradability, and stimuli responsiveness. Highlighted are recent developments in smart hydrogels, nanocomposite hydrogels, 3D-printed hydrogels, and injectable hydrogels, as well as their possible uses in tissue engineering, regenerative medicine, oral, transdermal, ophthalmic, and cancer therapy.We address the challenges and limitations of hydrogel-based drug delivery systems, including scale-up and manufacturing issues, regulatory concerns, and long-term biocompatibility issues. Finally, the review concludes by discussing future perspectives and emerging trends in this area, including the possibilities for personalized medicine and the integration of hydrogels with technologies such as artificial intelligence and nanotechnology.

Keywords: Hydrogels, Drug delivery, Biocompatibility, Stimuli-responsive, Nanocomposite, 3D printing, Personalized medicine

1. INTRODUCTION

Hydrogels are polymers that are arranged in three-dimensional networks. They have special molecular structure and physical-chemical features. contain a large amount of water, are soft, and can be easily shaped. These qualities make them suitable for many biomedical applications, as they are compatible with living tissues (1). The water absorption capacity is typically about 10-20 times their dry weight. Some superabsorbent hydrogels capable of absorbing up to 1000 times their original weight (2,3). The ability of hydrogels to absorb water comes from hydrophilic functional groups such as hydroxyl (-OH), carboxyl (-COOH), amine (-NH_2), amide (-$CONH_2$), and sulfonic acid (-SO_3H) groups. Hydrogen bonding allows the network to expand significantly while keeping its structure intact (3). Hydrogels usually have low elastic moduli, ranging from 100 to 100 kPa. They also have high extensibility and flexibility similar to tissue. Recent advancements have produced high-strength hydrogels with compressive moduli that can reach up to 43 MPa. This shows the potential for improving mechanical properties through innovative design strategies (4–6). Their low protein adsorption characteristics and minimal immune response make them particularly suitable for use in biomedical applications. The structural similarity to the extracellular matrix (ECM) facilitates cellular interactions and tissue integration (3,7). Their role in biomedicine is gaining attention. They improve the precision of drug delivery, support tissue engineering, and assist diagnostic techniques. This shows their importance in modern medicine (8). Conductive hydrogels possess useful features. They conduct electricity and can imitate the characteristics of natural tissues. This makes them suitable for applications in regenerative medicine and drug delivery, among other fields (9). Graphene-based hydrogels take advantage of their strong mechanical and optical properties for photo thermal applications, further increasing their usefulness in targeted, non-invasive biomedical strategies (10). Bacterial cellulose-based hydrogels are effective materials for wound dressings, tissue engineering, and drug delivery (11)**.** Metallic nanocomposite hydrogels provide antimicrobial benefits and support new developments in drug delivery systems (12)**.** These properties show how hydrogels contribute to progress in biomedicine and better healthcare standards (13).Hydrogels play important role in drug delivery systems due to their unique characteristics. They are biocompatible, biodegradable also possess adjustable mechanical properties and respond to different stimuli (14). These 3D polymer networks can encapsulate different therapeutic agents and allow controlled drug release. This makes them ideal for many biomedical applications (15). Polymer-based hydrogels are hydrophilic in nature and hold large amounts of water. It is important to study physical and chemical properties and compatibility of hydrogels with biological tissues. These features allow for effective control of drug release in response to specific triggers, such as pH, temperature, or the presence of enzymes. This responsiveness aids in focused drug delivery, which may lower systemic toxicity and improve treatment accuracy(16). Hydrogels are also used for transdermal drug delivery. It can avoid degradation of drug in the digestive system and first-pass metabolism in the liver (17). Polyethylene glycol (PEG)-based hydrogels have gained attention for their role in bone regeneration.

Hydrogel act as effective carriers due to their good compatibility with biological tissues and ability to retain water (18). This review aims to provide an overview of the latest developments in hydrogel-based drug delivery systems and their role in improving therapeutic outcomes. This review focuses on different types of hydrogels, their properties, and their design for controlled, sustained, and targeted drug release. The main objective of this review is to summarize recent research on hydrogel synthesis, highlight their applications in areas such as cancer therapy, wound healing, and tissue engineering, and discuss innovative approaches such as smart and stimuli-responsive hydrogels. This review also aims to identify the challenges and future directions for making hydrogel systems more effective and clinically applicable.

2. FUNDAMENTALS OF HYDROGELS

Hydrogels can be categorized in various ways. Each classification method highlights specific characteristics and potential applications. Grasping these classification systems is essential for selecting the appropriate hydrogel types for particular drug delivery purposes (19,20).

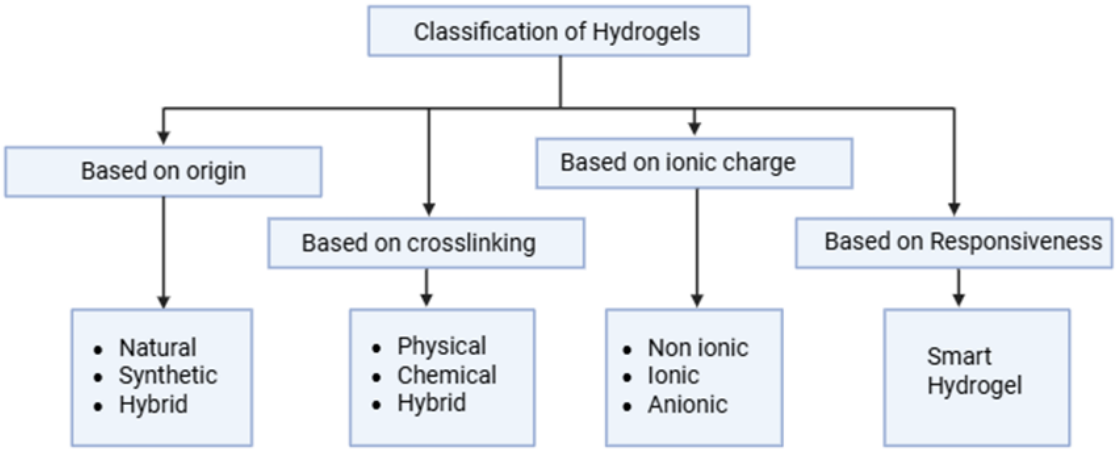

Fig. 1: Classification of Hydrogels

2.1.1 Classification by Origin

Natural Hydrogels are made from naturally occurring polymers like alginate, chitosan, hyaluronic acid, gelatin, collagen, and fibrin. These materials are biocompatible and biodegradable in nature. Because of batch to batch variability they may not be mechanically strong as synthetic hydrogels (7).Synthetic hydrogels are made up of synthetic polymers such as polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyacrylic acid, and poly(2-hydroxyethyl methacrylate) (PHEMA). Polymer improves uniformity, and mechanical durability. But use of synthetic polymer may cause of loss of certain natural biological functions (2). Combine natural and synthetic components become advantageous for both systems. This approach provides adjustable properties while ensuring biocompatibility (19).

2.1.2. Classification by Crosslinking Mechanism

Physical Hydrogels are formed by non-covalent interactions like hydrogen bonding, electrostatic interactions, hydrophobic associations, and chain entanglements. With the change in environment these systems reversibly switch between liquid and gel states. Usually they are mechanically weaker but provide more reversibility (19,20). Chemical Hydrogels creates covalent crosslinking between polymer chains, forms permanent networks that do not dissolve in water. These hydrogels show better mechanical properties and stability, but they do not have the reversibility of physical gels (19). Hybrid Hydrogels incorporate both physical and chemical crosslinking methods at the same time. This combines the benefits of both approaches (19,20).

2.1.3. Classification by Responsiveness

Conventional hydrogels display properties that remain relatively stable regardless of external conditions. Smart or stimuli-responsive hydrogels experience significant changes in their properties when exposed to external stimuli, including pH, temperature, light, electric fields, ionic strength, or biological molecules. These types of materials facilitate controlled and targeted drug release applications (19,20)**.**

2.2.4. Classification by Ionic Charge

Neutral (Non-ionic) Hydrogels contain no ionisable groups and maintain consistent properties across different pH ranges. Ionic Hydrogels include anionic (negatively charged), cationic (positively charged), and amphoteric (containing both acidic and basic groups) systems. Zwitterion Hydrogels possess both cationic and anionic functionality within each repeating unit. They often show excellent biocompatibility (19,21).

2.3. Synthesis of Hydrogel

It involves different approaches that can be grouped into physical and chemical crosslinking methods. The choice of synthesis method greatly affects the final properties, structure, and performance of the resulting hydrogel (21,22).Physical crosslinking method based on non-covalent interactions to create a three-dimensional network structure. These methods have several advantages, such as allowing for mild processing conditions, and not using potentially toxic crosslinking agents. Crystallization-Based Gelation involves forming crystalline regions that serve as physical crosslinks. This is commonly seen in poly(vinyl alcohol) systems through freeze-thaw cycles. Hydrogen Bonding uses intermolecular hydrogen bonding between polymer chains, which is often improved by the presence of complementary functional groups. Electrostatic Interactions involve ionic complexation between oppositely charged polymers or the interaction of charged polymers with multivalent ions, such as in alginate-calcium systems (21,23). Chemical crosslinking forms covalent bonds between polymer chains. This process creates permanent network structures with improved mechanical properties (19,22,24). Bifunctional or multifunctional small molecules act as crosslinking agents. Common crosslinkers include glutaraldehyde, glyoxal, N,N'-methylenebisacrylamide (MBA), and ethylene glycol dimethacrylate (EGDMA) (19,22,24). Polymer–polymer Crosslinking method involves direct covalent bonding between functionalized polymer chains, which eliminate requirement of external crosslinking agents (24).Radiation-induced crosslinking is a modern synthesis technique that offers unique benefits for preparing hydrogels (25,26).Gamma radiation synthesis method employs high-energy gamma rays (usually from Cobalt-60 sources) to induce crosslinking through free radical mechanisms (25,26).Electron Beam and UV Radiation are alternative radiation methods provide similar benefits but differ in penetration depths and processing characteristics (26).Microfluidic synthesis technique allows for precise control over hydrogel size, shape, and composition. This method is useful for making uniform microparticles and complex shapes. Advanced 3D Printing method enables the creation of complex, patient-specific hydrogel structures with controlled architecture and distribution of components. Template directed synthesis is a new approach which employs sacrificial templates to form hydrogels with specific porosity, morphology, or internal structure (19,27).

Table 1. Classification of Hydrogels

Classification Basis	Type	Representative Examples	Key Characteristics	Drug Delivery Advantages	Reference
ORIGIN	Natural	Alginate, Chitosan, Collagen, Hyaluronic acid, Gelatin, Pectin	Biocompatible, biodegradable, inherent bioactivity, batch variability	Low toxicity, cell recognition, ECM mimicry, enzymatic degradation	(16,28)
	Synthetic	Poly(acrylic acid) (PAA), Poly(N-isopropylacrylamide) (PNIPAM), Polyethylene glycol (PEG), Poly(vinyl alcohol) (PVA)	Tunable properties, reproducible, precise control, high mechanical strength	Controlled release kinetics, scalable production, customizable functionality	(20,24)
	Hybrid/Semi-synthetic	Alginate-PEG, Chitosan-PVA, Collagen-PEG, Dextran-PNIPAM	Combines natural biocompatibility with synthetic tunability	Enhanced mechanical properties with biocompatibility, optimized drug release	(16,28)
CROSSLINKING MECHANISM	Physical/Reversible	Hydrogen bonding (Gelatin), Ionic interactions (Alginate-Ca^{2+}), Hydrophobic associations, Chain entanglements	Thermoreversible, mild formation conditions, injectable, self-healing	Easy processing, in situ gelation, minimal cytotoxicity, thermoresponsive release	(20,24)
	Chemical/Permanent	Covalent crosslinking via glutaraldehyde, N,N'-methylenebisacrylamide (MBA), Photo-crosslinking,	Permanent networks, high mechanical stability, controlled degradation	Sustained drug release, structural integrity, predictable kinetics	(24,29)

Classification Basis	Type	Representative Examples	Key Characteristics	Drug Delivery Advantages	Reference
		Click chemistry			
	Enzymatic	Transglutaminase-mediated (Gelatin-Chitosan), Horseradish peroxidase (Tyramine-modified polymers)	Mild conditions, substrate specificity, biocompatible, in situ formation	Biocompatible crosslinking, controlled gelation kinetics, cell-friendly environment	(20)
STIMULI-RESPONSIVENESS	pH-Responsive	Poly(acrylic acid), Guar gum succinate, Chitosan derivatives, Kappa-carrageenan/PVA	pH-triggered swelling/deswelling, ionizable groups (-COOH, -NH_2)	Site-specific release (gastric vs intestinal), tumor targeting (acidic microenvironment)	(30,31)
	Temperature-Responsive	PNIPAM, Pluronic F127, PLGA-PEG-PLGA triblock copolymers	LCST ~32°C, sol-gel transition	Injectable systems, body temperature triggered gelation, hyperthermia-activated release	(31,32)
	Light-Responsive	Azobenzene-containing polymers, o-nitrobenzyl derivatives, Spiropyran-modified hydrogels	Photoisomerization, photodegradation, reversible/irreversible changes	Spatiotemporal control, on-demand release, non-invasive activation, precise dosing	(33)
	Dual/Multi-Responsive	Chitosan-PNIPAM-itaconic acid, Lysine-modified PVCL	Multiple stimuli sensitivity, enhanced targeting specificity	Tumor-specific release (pH + temperature), enhanced therapeutic efficacy	(31,32)
	Magnetic-Responsive	Magnetite nanoparticles/poly(acrylamide) composites	Magnetic field-induced pore opening, remote activation	External control, deep tissue targeting, pulsatile release	(30)
	Enzyme-Responsive	MMP-cleavable peptides, Hyaluronidase-sensitive HA	Substrate-specific degradation, biological trigger recognition	Disease-specific activation, targeted degradation, biological responsiveness	(30)
IONIC CHARGE	Nonionic	PEG hydrogels, PNIPAM, PVA	No ionizable groups, pH-independent swelling	Stable drug release across pH range, reduced protein adsorption	(28,30)
	Anionic	PAA, Alginate, Carboxy methylcellulose	Negatively charged, pH-sensitive (basic conditions)	Cationic drug loading, gastric protection, intestinal release	(20)
	Cationic	Chitosan, PDMAEMA, Quaternized polymers	Positively charged, pH-sensitive (acidic conditions)	Anionic drug encapsulation, mucoadhesive properties, antimicrobial activity	(24)

Classification Basis	Type	Representative Examples	Key Characteristics	Drug Delivery Advantages	Reference
	Amphoteric/Zwitterionic	Containing both acidic and basic groups	pH-dependent charge switching, protein resistance	Reduced biofouling, biocompatible, dual drug loading	(28)

3. HYDROGEL DESIGN CONSIDERATIONS FOR DRUG DELIVERY

The design of hydrogels for drug delivery requires careful consideration of several interconnected factors. These factors collectively influence the performance, safety, and effectiveness of the delivery system. Biocompatibility is a important requirement for any hydrogel used in drug delivery. It involves multiple aspects of evalution and optimization of biological compatibility (30) Hydrogels must decreases immune reactions of drug to ensure safe and effective drug delivery. Natural hydrogels usually have better biocompatibility because of their similarity. Synthetic hydrogels may need surface modification or addition of bioactive molecules to achieve optimal biocompatibility (34–36). Recent developments in hydrogel design focus on immunomodulating hydrogels that actively manage immune responses. These systems can be designed to recruit specific immune cells, like dendritic cells for cancer treatment, while preventing undesirable inflammatory responses (20,35). Avoiding cytotoxic effects is crucial for successful drug delivery applications. Potential sources of toxicity include unreacted monomers, crosslinking agents, initiators, and degradation products. For example, commonly used photoinitiators like Irgacure can reduce cell viability, even at low concentrations. Therefore, purifying hydrogels through dialysis or thorough washing is often necessary to remove harmful residues (36,37). The design should include features that encourage positive cellular interactions, such as suitable mechanical properties, surface chemistry, and the presence of cell adhesion sites. Hydrogels that mimic the water content (70-90%) and mechanical properties of target tissues show better biocompatibility and integration (36,37). The degradation rate must be adjusted to match the desired drug release profile and application needs. Key factors that influence degradation are crosslinking density, and seversl environmental factors such as pH, temperature and ionic strength (38). Enzyme-responsive hydrogels provide excellent specificity for targeted drug delivery. For instance, hydrogels that can be cleaved by matrix metalloproteinases (MMP) can release drugs specifically in tumors, where MMPs are overexpressed. Likewise, hydrogels that are sensitive to colonic bacteria-specific enzymes allow for targeted drug delivery in the colon (38,39). Performance of hydrogels is affected by their mechanical properties. It influences drug release rates, tissue integration and patient comfort. Hydrogels show a unique viscoelastic nature that combines both elastic and viscous properties. It should enable controlled deformation, which helps in releasing the drug when needed (15,40,41). Recent advancements have produced hydrogels with remarkable mechanical properties. These enhanced properties are achieved through innovative crosslinking techniques such as double-network designs and the integration of sacrificial . Compressive properties are significant for load-bearing applications and injectable hydrogels. It must keep their structure under physiological pressures. Sacrificial weak bonds systems use a densely crosslinked polyelectrolyte network combined with a loosely crosslinked network. Breakdown of weak bonds absorbs energy and stops cracks from spreading (15,41).

Table 2. Degradation and release mechanism of hydrogels

Hydrogel Type		Examples	Degradation Characteristics	Drug Release Mechanism	Clinical Applications	Reference
Natural Hydrogels	Alginate	Ca^{2+}-crosslinked alginate	Ionic dissolution, enzymatic (alginate lyase)	Diffusion-controlled, pH-responsive	Oral, wound healing	(42)
	Chitosan	TPP-crosslinked chitosan	Enzymatic (chitinase, lysozyme)	pH-responsive swelling/deswelling	Oral, antimicrobial delivery	(41)
	Gelatin	Thermally-crosslinked gelatin	Thermal melting, enzymatic (collagenase)	Temperature-triggered release	Injectable, tissue engineering	(2)
Synthetic Hydrogels	Hyaluronic Acid	EDC/NHS crosslinked HA	Enzymatic (hyaluronidase)	Enzyme-responsive degradation	Ocular, joint injection	(3)
	PNIPAM	Thermosensitive PNIPAM	Hydrolytic degradation of crosslinks	Temperature-responsive (LCST ~32°C)	Injectable, hyperthermia therapy	(3,43)
	PAA (Poly(acrylic acid))	Chemically crosslinked PAA	Hydrolysis of ester bonds	pH-responsive swelling	Oral, colon targeting	(44)
	PVA	Physically	Crystalline domain dissolution	Physical dissolution	Transdermal,	(41)

Hydrogel Type		Examples	Degradation Characteristics	Drug Release Mechanism	Clinical Applications	Reference
		crosslinked PVA			contact lenses	
	PEG-based	Photo-crosslinked PEG	Photodegradable linkers, hydrolysis	Light-responsive, diffusion-controlled	On-demand release, tissue engineering	(45)
Hybrid / Composite Hydrogels	PAM/Gelatin	Dual-crosslinked PAM/Gel	Combination of physical/chemical	Dual-responsive (pH/temperature)	Dual drug delivery, wound healing	(11)
	Chitosan-PVA	Blended CS-PVA	Sequential degradation	pH-responsive with sustained release	Transdermal, controlled release	(2)
	Alginate-PEG	Covalently linked Alg-PEG	Dual degradation pathways	Enhanced mechanical stability	Injectable, cell delivery	(42)
Tough / Reinforced Hydrogels	Double Network	PAMPS/PAAm DN	Sacrificial bond mechanism	Mechanically-triggered release	Load-bearing applications	(44)
	Nanocomposite	Clay-reinforced PNIPAM	Clay-polymer network breakdown	Mechanical stress-responsive	Injectable, high-strength applications	(44)
	IPN (Interpenetrating Network)	Gelatin/PAM IPN	Independent network degradation	Sequential drug release	Multi-drug delivery systems	(11)
Stimuli-Responsive Hydrogels	pH-responsive	Chitosan-itaconic acid	pH-triggered network breakdown	Site-specific release (gastric vs intestinal)	Oral, colon targeting	(3)
	Temperature-responsive	PLGA-PEG-PLGA	Sol-gel transition reversibility	Injectable, body temperature gelation	Localized injection, cancer therapy	(3)
	Light-responsive	Azobenzene-modified	Photoisomerization/photocleavage	Spatiotemporal controlled release	On-demand therapy, precise dosing	(3)
Relationship To Drug Release	High Modulus (>100 kPa)	Synthetic, tough hydrogels	Slower degradation	Sustained release (weeks–months)	Long-term therapy	(45)
	Medium Modulus (10–100 kPa)	Natural, hybrid hydrogels	Moderate degradation	Controlled release (days–weeks)	Most drug delivery applications	(46)
	Low Modulus (<10 kPa)	Soft, injectable hydrogels	Rapid degradation	Burst/immediate release (hours–days)	Acute therapy, injections	(3,46)

Advanced hydrogel systems can deliver multiple drugs simultaneously with independent release profiles. It is possible by using different strategies such as compartmentalized systems, layered hydrogels or differential loading (47). The successful design of hydrogel drug delivery systems requires integrated consideration of all design parameters. Biocompatibility must be maintained while achieving desired mechanical properties and release kinetics. Stimuli-responsiveness should complement rather than compromise other design requirements (36,37). Recent advances in computational modelling and machine learning are enabling more sophisticated design optimization, predicting optimal formulations based on desired performance criteria. This integrated approach promises to accelerate the development of next-generation hydrogel drug delivery systems with unprecedented precision and therapeutic efficacy (47)

4. Recent Advances in Hydrogel-Based Drug Delivery Systems

Hydrogel-based drug delivery systems have made significant dvelopment in recent years. This progress from improvements in materials science, nanotechnology, and manufacturing techniques. Each advancement helps overcome the limits of traditional drug delivery methods and supports more effective treatment strategies (15,48).

4.1. Smart Hydrogels

Smart hydrogels also known as stimuli-responsive hydrogels. They respond dynamically to environmental changes. These materials can alter their properties in response to specific stimuli, allowing precise control over drug release and targeting. Their ability to react to physiological condition makes them particularly useful for solving complex medical challenges (42).

4.1.1. pH-Responsive Hydrogels

pH-responsive hydrogels exploit the natural pH variations throughout the human body to achieve site-specific drug delivery. It offers great potential for focused therapeutic interventions. Ionizable functional groups that response to local pH changes. It undergoes protonation or deprotonation and resulting in swelling or deswelling behaviours that control drug release. The pH difference from the acidic environment of the stomach (pH 1.2-3.0) to the neutral-to-alkaline conditions in the small intestine (pH 6.8-7.4) is ideal for oral drug delivery. It also supports targeted cancer treatment as tumour tissues (pH 6.0-6.8) are more acidic than normal tissues (pH 7.4) (47,49). Recent advancements in pH-responsive systems have shown great precision in controlling drug release. New formulations using carboxyl and amino groups have achieved almost complete drug release (93%) at physiological pH, while releasing very little under acidic conditions. We now understand that drug release can occur through swelling-induced changes in mesh size and drug diffusion, as well as through the disruption of ionic interactions between the drug and polymer (47,49).The versatility of pH-responsive hydrogels extends to combination therapy approaches, where dual-drug delivery systems can simultaneously release multiple therapeutic agents that work well together. Liu's pioneering work on pH-responsive peptide nanogels showed the simultaneous release of gemcitabine and paclitaxel specifically within tumor microenvironments. This method boosts anti-tumor effectiveness while reducing the chances of drug resistance. This represents a significant step forward in tackling the complex issue of cancer drug resistance through coordinated multi-drug delivery strategies (47,50).

4.1.2. Temperature-Responsive Hydrogels

Temperature-responsive hydrogels use thermal changes to control drug release. Poly(N-isopropylacrylamide) (PNIPAM) is the classic thermosensitive polymer because of its lower critical solution temperature (LCST) near body conditions. These systems undergo large volume phase changes at certain temperatures. This allows for precise control over drug release through temperature-triggered swelling or shrinking. The LCST phenomenon lets these hydrogels be injectable solutions at room temperature while quickly solidifying upon injection at body temperature, forming local drug depots for sustained delivery (51,52). Recent innovations in temperature-responsive systems focus on improving response times and broadening therapeutic uses. The combination of melamine functionalized PNIPAM copolymers has produced dual pH and temperature-responsive systems. Thus system can release nearly 100% of drugs for both hydrophilic (5-fluorouracil) and hydrophobic (ibuprofen) under specific conditions (pH 4.0, 45°C). These developments reveal the potential for creating flexible platforms that can deliver diverse drug classes with customized release profiles (53). Temperature-responsive hydrogels are very beneficial in ocular drug delivery. Innovative approch of thermosensitive hydrogel systems with furan and maleimide groups for intravitreal injection achieve immediate sol-gel changes when exposed to body temperature. These systems showed sustained release for 13-35 days for various therapeutic agents (51). These hydrogels have also shown promise in cancer treatment. PNIPAM-based systems allow for targeted delivery of anti-cancer agents using localized heat. Their temperature sensitivity near body conditions enables precise timing and location control of drug release, minimizing overall exposure while maximizing effectiveness at target sites (51,54).

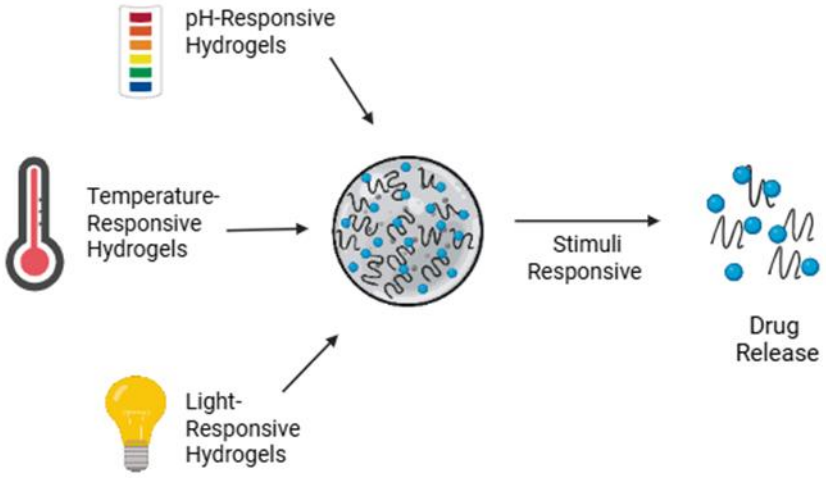

Fig. 2: Smart Hydrogels

4.1.3. Light-Responsive Hydrogels

Light-responsive hydrogels offer better control in drug delivery. They provide non-invasive and focused treatment through light stimulation. These systems feature photosensitive components that change structure when exposed to light. It allow accurate control over drug release by adjusting light conditions like intensity, wavelength, exposure time, and beam size. The key mechanisms for light-responsive drug delivery include three main pathways. Photoisomerization systems that change shape reversibly, photochemical systems that involve breaking or forming bonds, and photothermal systems that convert light to heat for drug release (55,56). The development of light-responsive systems has moved from early ultraviolet (UV) activated platforms to more advanced near-infrared (NIR) responsive systems. UV systems are mostly restricted to in vitro use due to their potential for cellular harm and limited tissue penetration. NIR systems have changed the field by enabling deep tissue penetration and safer in vivo applications It makes them more viable for clinical use (55,57). Recent advancements in photosensitizer technology have greatly increased the versatility of light-responsive hydrogels. The integration of upconversion nanoparticles (UCNPs) and two-photon excitation systems allows for using NIR light to trigger responses that normally need UV light. It combines the precision of UV systems with the safety and depth advantages of NIR light. This creates new way for treating deep-seated conditions while maintaining precise control over drug release (55,58). The clinical uses of light-responsive hydrogels cover a wide range of therapeutic areas. In cancer therapy photocleavable hydrogels allow for precise targeting of tumors while limiting systemic exposure to harmful chemotherapy drugs. The ability to repeatedly trigger drug release with controlled light exposure gives unprecedented flexibility in treatment plans (55,59).

4.2. Nanocomposite Hydrogels

Nanocomposite hydrogels combine nanotechnology and hydrogel science. Merging the best features of both to create multifunctional drug delivery platforms improves their performance. These hybrid systems incorporate various nanoparticles within hydrogel matrices to achieve properties that neither could accomplish alone. This includes better mechanical strength, greater drug loading capacity, responsive behaviors to stimuli, and the ability to deliver drugs while also providing imaging (60–62).The design flexibility of nanocomposite hydrogels allows for the use of various nanoparticle types. Carbon-based nanoparticles like carbon nanotubes (CNTs) and graphene are biocompatible and enhance mechanical, electrical, and thermal qualities. These materials are especially useful in applications needing electrical conductivity, such as nerve tissue engineering and heart-related applications where electrical signaling is crucial (60,62). Recent developments in nanocomposite hydrogels have aimed at achieving synergistic effects between nanoparticles and polymer matrices. Thiol-functionalized gold nanoparticles can form chemical bonds with polymer networks which improves mechanical properties. These enhanced interactions affect not only mechanical strength but also drug release rates and biological reactions (61). Nowadays nanocomposite hydrogels have widely used in drug deliver. It shows potential in cancer treatment, wound healing and tissue engineering. In oncology they enable combination therapies that merge chemotherapy, photothermal therapy, and photodynamic therapy in single platforms. Through targeted delivery of multiple therapeutic agents with separate release profiles helps solve the complex problem of cancer treatment (62).Metallic nanoparticles such as gold and silver offer unique optical, antimicrobial, and catalytic properties. Gold nanoparticles enhance imaging and allow for photothermal therapy. Silver nanoparticles provide strong antimicrobial action for wound healing. Incorporating these metallic nanoparticles into hydrogel networks creates multifunctional platforms (63,64).

4.3. 3D-Printed Hydrogels

3D printing technology has transformed hydrogel drug delivery. It enable creation of complex, customized therapeutic devices with precise control over structure, composition, and drug distribution. Merging 3D printing with hydrogel science has created new way for building advanced drug delivery systems previously impossible to produce through traditional methods (65,66). Polypills created with 3D-printed hydrogel systems are highly beneficial. These devices can combine multiple drugs with various release profiles into a single dosage form. This approach addresses the complex medication regimens often needed for chronic conditions. Integration of immediate-release and extended-release within single devices improves patient. It is particularly important for elderly patients managing multiple health issues(66). Recent advancements in 3D printing materials has widened the range of polymers that can be used in hydrogel drug delivery. For crating drug loading filaments biocompatible polymers such as polylactic acid (PLA), polycaprolactone (PCL), and polyvinyl alcohol (PVA) have been used effectively. Compatibility of this material with various drugs supports versatile platform development for many therapeutic applications (67,68). The personalized medicine applications of 3D-printed hydrogels can encompass complex patient-specific requirements.. By using this technology it is possible to create devices with custom shapes based on individual drug processing rates. This level of customization marks a significant advancement toward truly personalized treatment approaches (69,70). The clinical application of three-dimensional (3D) printed hydrogel systems has demonstrated significant potential in pediatric and geriatric populations. It has capacity to develop age-appropriate formulations with precise dosing and acceptable palatability addresses. Capability for on-demand manufacturing facilitates the production of medications with limited shelf life or patient-specific requirements. By this way it become viable alternatives to conventional compounding pharmacy practices (69).

4.4. Injectable Hydrogels

Injectable hydrogels is a unique method for minimally invasive drug delivery. They combine the ease of liquid formulations with the long-term release benefits of solid matrices through gelation processes that occur in the body. These systems start as low-viscosity solutions for preparation and injection. Once exposed to physiological conditions, they quickly turn into semi-solid gels. This transformation creates localized drug depots with controlled release. The development of injectable hydrogels meets important clinical needs for accurate drug targeting while reducing pain and the complexity of procedures (71,72,73).The main principle behind injectable hydrogel systems is gelation under certain physiological conditions. Temperature-triggered gelation is the most common method. Triblock copolymers like poly(lactide-co-glycolide)-block-poly(ethylene glycol)-block-poly(lactide-co-glycolide) (PLGA-PEG-PLGA) change from liquid to gel near body temperature. These systems stay stable as injectable solutions at room temperature but solidify quickly when warmed to 37°C, creating drug depots in place with predictable gelation timing (71,72,74). pH-dependent gelation is another method for injectable hydrogel systems. It useful for targeting tissues with unique pH levels. The ability to change due to pH allows the creation of forces between polymer segments. It leads to reversible crosslinks and controllable release rates. The varying pH in chronic wounds, which ranges from 5.4 to 8.9 depending on the location and level of damage, offers potential for pH-responsive injectable systems in treating wounds (74).Recent progress in injectable hydrogel formulation has focused on improving flow properties for better injection and ensure quick gelation after administration. During injection shear-thinning enables smooth flow through small needles. This feature reduces the force needed for injection and lessens patient discomfort. Thixotropic recovery allows the structure to reform rapidly after the force is removed. These improvements are vital for applications that require injection through small catheters or into tight spaces (73,75). The clinical applications of injectable hydrogel systems cover different therapeutic fields. They are succesfully used in cancer treatment, pain management, and tissue engineering. Hydrogel systems also supports combination therapy where multiple treatment methods are combined into one platform. Hybrid hydrogel systems can include both chemotherapy agents and photosensitizers used for combined chemotherapy and photodynamic therapy. Systems that include both drugs and growth factors enable simultaneous treatment and tissue healing. These multifunctional strategies meet the complex needs of modern treatments. Also it offers convenience and precision of minimally invasive delivery (71,76).

5. APPLICATIONS OF HYDROGELS IN DRUG DELIVERY

Hydrogel-based systems for oral drug delivery provide an effective way of drug delivery. Recent advancement in oral hydrogel delivery protects drugs from gastric degradation and allows targeted release in the intestines. This is especially true for sensitive biologics, proteind and peptides that can degrade in harsh conditions. Their stimuli-responsive features allow for targeted release in specific areas of the digestive tract (77). Hydrogel basaed transdermal drug delivery is a non-invasive and avoid first-pass liver metabolism and gastrointestinal irritation and allow for sustained release of drugs. When applied to the skin, these systems form semi-occlusive layers that concentrate drugs within polymer matrices and facilitate controlled absorption through the skin barrier. Hydrogels can carry a higher drug load than alternatives like liposomes and nanoparticles.It allows for effective transdermal transport with controlled release and minimal degradation (78,79). Hydrogel-based systems for delivering drugs to the eye pass barriers of the eye. These barrier include various tissue barriers, quick clearance mechanisms, and the need to maintain steady drug concentrations. The eye's defense systems, such as blinking, tear drainage, and corneal barriers, often lead to poor bioavailability and rapid loss of conventional eye drop treatments (79,80).Stimuli-responsive hydrogel systems allowing liquid-to-gel transitions upon contact with the eye. This greatly increases how long the drug stays in place and improves comfort for patients. These smart hydrogels respond to changes in temperature, pH, or ionic strength. These gels that enable prolonged drug release and reduce frequency of drug application (80). Recent developmemt in ocular hydrogel formulations have been particularly successful in treating diseases affecting the back part of the eye. Hydrogel systems can overcome ocular barriers thus maintain sustaine drug release. Combining hydrogels with nanoparticles, liposomes, and dendrimers has shown promise in improving drug stability and targeting specific eye tissues (81).Hydrogels are widely used in cancer treatments. They offer targeted local treatment while minimizing systemic toxicity and keeping high drug concentrations at the tumor site. Hydrogels address the challenge of drug resistance and enhances overall treatment effectiveness. Multifunctional

hydrogels integrate chemotherapy, photothermal therapy, photodynamic therapy, and immunotherapy into cohesive systems that provide treatment and diagnostic imaging. These advanced platforms include diagnostic agents like magnetic nanoparticles, fluorescent dyes, and radiolabeled isotopes, improving tumor visualization and allowing real-time monitoring during treatment. (82,83).The development of thermosensitive and pH-responsive hydrogel systems from polypeptides, PLGA and chitosan derivatives has made it possible to achieve injectable gelation that targets tumor environments. These systems can maintain therapeutic levels of anticancer agents like doxorubicin, paclitaxel, and docetaxel. It minimizes off-target effects typical of standard chemotherapy (84). Hydrogels play key roles in regenerative medicine. They provide scaffolds for cell organization, act as drug depots and provide matrices for cell encapsulation and transplantation. Recent applicaton of hydrogels in bone regeneration shows ideal conditions for healing through cell therapy. Studies have shown positive results in enhancing bone density, aiding fracture healing, managing long bone defects, and addressing cartilage injuries and osteoarthritis. Hydrogels are significantly used in Wound healing. Both natural and synthetic polymer systems help with skin regeneration and tissue repair. Alginate-based hydrogels combined with collagen, chitosan, and gelatin have improved skin healing. Synthetic polymers like poly(vinyl alcohol), poly(ethylene glycol), and polylactic acid support cell attachment and growth in skin regeneration efforts (85,86).

6. CHALLENGES AND LIMITATIONS

Even though hydrogel-based drug delivery systems show great promise, several key challenges still affects their acceptance in clinical settings and commercial markets. These challenges involve technical, regulatory, and safety issues, requiring collaboration between universities, businesses, and regulatory bodies to tackle them (87).Scale up and manufacturing pose significant obstacles for hydrogel commercialization. Moving from small-scale lab synthesis to large-scale industrial production introduces various technical difficulties. The variability seen from one batch to another in hydrogel systems. This makes it tough to maintain consistent quality and performance as production. The complex delivery systems linked to many advanced hydrogel formulations, such as those that respond to stimuli or use multiple components, add to the challenges of large-scale production. It is main reason why only few commercial products have made it through clinical trials (87,88).The process for regulatory approval also difficult especially for complex hydrogel systems that include new materials or advanced features. The FDA requires detailed biocompatibility testing based on ISO 10993-1 standards, particularly for long-term implantable hydrogel devices. This testing focuses on factors like cytotoxicity, sensitization, irritation, and systemic toxicity. The lack of clear regulatory paths for some hydrogel categories such as those using nanomaterials or showing responsive behaviors adds uncertainty for manufacturers and delays market entry (89).Biocompatibility and long-term safety concern become important challenges, especially for implantable and injectable hydrogel systems. Natural polymer-based hydrogels usually have excellent biocompatibility but synthetic ones may raise concerns about cytotoxicity. After implantation assessing long-term biocompatibility is particularly difficult, as foreign body reactions, chronic inflammation, and fibrotic encapsulation can occur over time. The chances of hydrogel dehydration and stiffening in the body can change mechanical properties and biological responses, potentially affecting treatment effectiveness and safety (90,91). The mechanical limitation of many hydrogel systems such as load-bearing situations or when strong structural integrity limit their use. Typical hydrogels have relatively weak mechanical properties because of their high water content and low friction among polymer chains. Although new developments in double-network and nanocomposite hydrogels have resolved some mechanical issues. These solutions often make manufacturing and gaining regulatory approval more complex (88,92). Quality control and standardization challenges are exacerbated by the complex multi-component nature of advanced hydrogel systems. Addition of drugs into hydrogel matrices introduces more variables that need monitoring throughout production. It is remain difficult to finding analytical methods to characterize and evalution of these complex systems. The development of suitable analytical techniques for real-time monitoring and quality assessment of hydrogel products is still lag behind product development (93,94).

7. FUTURE PERSPECTIVES

The future of hydrogel-based drug delivery is being shaped by important technology advances. These changes promise to change how we approach treatments through better precision, personalization, and smart responsiveness. Artificial intelligence and machine learning are becoming key drivers of hydrogel innovation. They allow for data-driven design improvements and predictive modeling. This helps to shorten development timelines and improve treatment outcomes (95,96).AI techniques help understand complex links between polymer composition, crosslinking methods, and functional properties. Machine learning algorithms can analyze large datasets to predict swelling behavior, mechanical strength, biodegradability, and drug release rates. These computational tools are useful in discovery of new polymer combinations and crosslinking strategies (95,96).The combination of nanotechnology and hydrogel platforms is leading to multifunctional hybrid systems. These systems offer controlled drug release, diagnostic imaging, real-time monitoring, and targeted delivery. Nanocomposite hydrogels that include stimuli-responsive nanoparticles allow for advanced therapeutic strategies that react to several environmental triggers at once (97,98). Personalized medicine offers a major opportunity for future hydrogel uses. AI algorithms analyze patient-specific data, including genetic profiles, metabolic rates, and medical histories, to create custom therapeutic formulations. Adding biosensors to hydrogel matrices enables real-time monitoring of therapeutic responses, which allows for adjustments in drug release based on physiological feedback (96,99). New manufacturing technologies, such as 3D printing and automated synthesis platforms, are making it possible to produce personalized hydrogel therapeutics on demand. These advancements support the creation of sophisticated drug delivery devices that can be produced at the care site. This reduces costs and improves access to advanced treatments (97,100).

8. CONCLUSION

In recent years, hydrogels have emerged as significant tools in drug delivery. These materials characterized by their unique three-dimensional polymer structures. Their compatibility with biological systems, and customizable properties useful in revolutionizing therapeutic approaches across various medical disciplines. The evolution from basic delivery systems to sophisticated smart hydrogels underscores their potential to address intricate clinical challenges while improving patient outcomes and treatment efficacy. An in-depth examination of hydrogel basics reveals that their success is rooted in a meticulous balance of their physical and chemical attributes, including swelling behavior, mechanical properties, and rates of biodegradation. The classification systems include natural and synthetic origins, physical and chemical crosslinking, and responsive and conventional designs, useful in choosing and improving materials. New synthesis methods such as radiation-induced crosslinking and innovative 3D printing, expanded delivery systems. Recent advances in smart hydrogel technology show great potential for controlling drug release based on different stimuli. These smart systems use physiological signals to enable targeted treatment while reducing overall exposure. Addition of nanocomposite materials has also improved hydrogel functionality. The clinical use of hydrogel systems in oral, transdermal, ocular, cancer treatment, and tissue engineering has shown their therapeutic value and market potential. Products approved by the FDA such as Retisert and Ozurdex demonstrate successful clinical use. Ongoing clinical trials continue to expand the range of hydrogel-based treatments. Hydrogels are important in modern drug development because they can protects biologics, provide sustained release over long periods, and deliver localized therapy with fewer side effects. Despite these successes, hydrogel drug delivery systems face significant challenges that require collaborative research. Sometimes in production scale up is complicated when trying to ensure consistency and reliability. Regulatory pathways for multi-component, responsive systems still need further development to suit the specific traits and performance of these innovative products. Long-term studies on biocompatibility are essential for ensuring patient safety, especially for chronic applications that involve extended exposure of tissues. The future of hydrogel-based drug delivery involves the integration of new artificial intelligence and nanotechnology. These developments may speed up the creation of personalized treatment solutions. Machine learning can help predict the best hydrogel formulations, while nanotechnology can expand their capabilities beyond basic drug delivery to include real-time monitoring, adaptive release systems, and multiple therapeutic strategies. The combination of these technologies with hydrogel science marks a shift toward personalized medicine, where treatments are specifically designed to meet individual patient needs and real-time physiological changes. Hydrogels are beneficial in drug delivery. They offer incredible control over the release of drugs which improves their effectiveness and reduced toxicity. Development in these systems comes from collaboration among materials scientists, pharmaceutical researchers, clinicians, and regulatory bodies. This teamwork will likely result in even better therapeutic solutions, enhancing patient care and clinical outcomes in various medical fields.

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