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Review Article

A Review on Self Assembling Cyclodextrin Hydrogels

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ABSTRACT

Cyclodextrin (CD)-based self-assembling hydrogels have gained significant devotion in biomedical, pharmaceutical, and material science due to their unique ability to form stable supramolecular structures through host–guest interactions. The hydrophilic exterior and hydrophobic cavity of CDs enable the encapsulation of various guest molecules, leading to stimuli-responsive, biocompatible, and tunable hydrogels. Because of their porous nature, hydrogels are used extensively in the biomedical and material sciences. Cyclodextrin (CD), a naturally occurring oligosaccharide, has demonstrated exceptional potential for use in the production and use of hydrogels. CD may be added to hydrogels to create networks that are physically or chemically cross-linked. Additionally, CD is a perfect carrier for delivering active substances into target tissues due to its distinctive cavity shape. This review outlines practical techniques for creating hydrogels that include CDs. The possible biological uses of hydrogels containing CD are also examined. It is addressed how CD-containing hydrogels leak and degrade under various circumstances. Lastly, a presentation of the present issues and potential avenues for further study on hydrogels containing CD is made.

INTRODUCTION

Hydrogels are 3-D networks of hydrophilic polymers that can absorb a lot of water without losing their structure because of chemical & physical cross-linking. Among the wide array of hydrogel systems, self-assembling hydrogels have gained significant interest due to their reversible, non-covalent interactions and their responsiveness to environmental stimuli like pH, temperature, or ionic strength [1,2]. Cyclodextrins (CDs)—cyclic oligosaccharides composed of α-(1→4)-linked glucopyranose units—have emerged as promising building blocks in the growth of self-assembling hydrogels. Their unique toroidal structure, which features a hydrophobic internal cavity &

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hydrophilic outer surface, allows for the creation of inclusion complexes with a wide variety of hydrophobic guest molecules. This host–guest collaboration is the fundamental driving force behind the self-assembly of CD-based hydrogels [3,4].CD-based hydrogels benefit from several advantages are: a) They are biocompatible, biodegradable, and non-toxic, which makes them suitable for biomedical and pharmaceutical applications [5]. b) Their modular design allows fine-tuning of mechanical and physicochemical properties by fluctuating the type of CD, the guest molecule, or the method of cross-linking [6]. c)They offer stimuli-responsive behavior, such as sol-gel transition upon pH or temperature change, which is critical for controlled drug release, tissue scaffolding, and smart therapeutic systems [7]. Over the past decade, research into supramolecular hydrogels based on CD inclusion complexes has expanded, showing promising results in various domains such as drug delivery, biosensing, regenerative medicine, and environmental remediation [8,9]. However, challenges related to mechanical robustness, scalability, and long-term stability remain and are currently being addressed through hybrid systems and novel cross-linking strategies. Hydrogels can be used as macromolecular platforms for implant coatings, wound healing dressings & drug delivery [10,11]. For hydrogel systems, earlier research created localized, regulated drug release systems [12,13]. Using non-covalent techniques to encapsulate drug molecules within hydrogel or creating unstable chemical bonds to covalently link drug molecules to hydrogel matrix are common approaches for drug loading. The manufacturing procedure and the drug loading quantity are unsatisfactory, despite the hydrogel's ability to efficiently regulate the release duration when the drug is loaded using a covalent technique [14,15]. This review aims to comprehensively discuss the fundamentals of cyclodextrins, mechanisms of self-assembly, preparation methods, characterization techniques, and applications of CD-based self-assembling hydrogels, while also providing insights into their current limitations and future prospects.

Fundamentals Of Cyclodextrins

CDs are a group of naturally occurring, cyclic oligosaccharides formed from starch via enzymatic degradation using cyclodextrin glycosyltransferase (CGTase) [16]. These macrocyclic molecules are composed of α-(1→4)-linked D-glucopyranose units, which form a toroidal (truncated cone-like) structure with a hydrophilic exterior & a relatively hydrophobic internal cavity [17]. This unique amphiphilic structure enables cyclodextrins to form host–guest inclusion complexes with a wide variation of hydrophobic particles. This property forms the basis of their applications in drug delivery, environmental remediation, supramolecular chemistry, and hydrogel formation [18].

Cyclodextrins (CDs) are classified based on number of D-glucopyranose units forming their cyclic structure. The most common naturally occurring CDs are:

a) α-Cyclodextrin (α-CD): having six units of glucose

b) β-Cyclodextrin (β-CD): having seven units of glucose

c) γ-Cyclodextrin (γ-CD): having eight units of glucose

By using cyclodextrin glycosyltransferase (CGTase), these macrocycles are enzymatically generated from starch [19]. The amount of units of glucose determines the cavity size, binding ability, and aqueous solubility, all of which directly

impact their utility in host–guest chemistry and hydrogel applications [20].

a) α-Cyclodextrin (α-CD): having six units of glucose

α-CD is the smallest natural cyclodextrin, composed of six D-glucopyranose units linked via α-(1→4) glycosidic bonds, forming a cyclic oligosaccharide [21]. Its structure results in a relatively narrow hydrophobic cavity with a diameter of approximately 0.47–0.53 nm, making it suitable for hosting small hydrophobic guest molecules such as aliphatic chains, linear polymers, and short-chain fatty acids [22]. Due to its high aqueous solubility compared to β-CD, α-CD is especially useful in pharmaceutical and food applications where rapid dissolution is important [23]. In hydrogel systems, it is commonly used to form channel-type inclusion complexes with polyethylene glycol (PEG) or polypropylene glycol (PPG). These complexes allow for linear threading of polymers through the CD cavity, which is essential in pseudorotaxane and polyrotaxane-based self-assembling hydrogels [24].

Applications of α-CD in Hydrogels: Acts as a physical cross-linker by forming inclusion complexes with polymers. Enables reversible self-assembly driven by host–guest interactions. Provides stimuli-responsive behavior (e.g., temperature, ionic strength) when included in supramolecular systems [25]. In biomedical applications, α-CD is considered non-toxic & biodegradable, and it has been explored for oral drug delivery, gene carriers, and mucoadhesive hydrogel formulations [26].

b) β-Cyclodextrin (β-CD): having seven units of glucose

β-CD consists of seven D-glucopyranose units connected by α-(1→4) glycosidic bonds, forming a toroidal (truncated cone) structure with a moderate-sized hydrophobic cavity. Among the natural cyclodextrins, β-CD is studied extensively and used widely, largely because of their optimal cavity size for many pharmaceutical molecules and its commercial availability [27]. Despite its utility, β-CD has relatively low aqueous solubility, which limits its direct application in some biomedical systems. However, this can be overcome through chemical modifications (e.g., hydroxypropylation or methylation), enhancing its solubility and biocompatibility [28]. Inclusion Complexation Behavior: The β-CD's cavity size of is ideal for the inclusion of aromatic molecules, steroidal compounds, fatty acids, and various hydrophobic drug molecules [29]. The host–guest complex creation is governed by non-covalent interactions like hydrophobic forces, van der Waals interactions & hydrogen bonding [30].

Applications of β-CD in Hydrogel Systems β-CD plays a critical role in progress of self-assembling supramolecular hydrogels by:

Acting as a host molecule to bind guest-functionalized polymers (e.g., adamantane, azobenzene, or ferrocene-modified moieties). Serving as a physical cross-linker to create reversible and stimuli-responsive gel networks. Providing encapsulation sites for drugs, improving stability, solubility, and sustained release characteristics [31]. It has been utilized in hydrogels for applications in drug delivery, wound dressing, 3-D cell culture scaffolds & biosensors [32].

c) γ-Cyclodextrin (γ-CD): having eight units of glucose

γ-CD consists of eight D-glucopyranose units linked by α-(1→4) glycosidic bonds, forming the

largest natural cyclodextrin in terms of internal cavity size. Its wide hydrophobic cavity (~0.75–0.83nm in diameter) allows it to encapsulate larger and bulkier guest molecules, including macromolecules, polymers, and multi-ring systems, which may not fit into α- or β-CD [33]. γ-CD's excellent aqueous solubility makes it especially attractive for biomedical and pharmaceutical applications. It also exhibits low toxicity and rapid renal clearance, favoring its use in parenteral and oral drug delivery systems [34]. Inclusion Complexation and Molecular Behavior: The host–guest complexation is governed by hydrophobic interactions, size-fit complementarity, and sometimes multivalent binding, making γ-CD particularly effective in multicomponent self-assembling systems [35]. Due to its larger cavity, γ-CD can accommodate: Large hydrophobic drugs (e.g., curcumin, paclitaxel), polycyclic and aromatic compounds, polymer segments and peptide chains.

Applications of γ-CD in Hydrogel Systems

γ-CD plays a unique role in forming soft, flexible, and highly swollen hydrogels due to its large cavity and high solubility. Applications include: Supramolecular hydrogels formed via interactions with bulky guests or multi-arm polymers, Drug encapsulation and sustained release, especially for poorly water-soluble drugs, Tissue engineering scaffolds, where high swelling and low toxicity are advantageous. Gene and protein delivery systems, through encapsulation and protection mechanisms. In combination with responsive guest molecules (e.g., redox-sensitive or photo-cleavable compounds), γ-CD enables intelligent and reversible self-assembly, ideal for controlled release applications [36].

Structural Configuration

Cyclodextrins possess a unique truncated cone (torus)-shaped structure with the following characteristics: a) Hydrophilic exterior- Because hydroxyl groups are present at rim. The thin rim is where the primary hydroxyl groups are situated at C6. The broader rim contains secondary hydroxyl groups at C2 & C3. b) Hydrophobic interior cavity- Formed by the inward-facing H-atoms and ether-like oxygen bridges. This amphiphilic structure allows CDs to encapsulate hydrophobic particles in their cavity while remaining soluble in aqueous environments—a key property for supramolecular self-assembly [37].

Table 1: Comparison of Cyclodextrins

Cyclodextrin	No. of Glucose Units	Cavity Diameter (nm)	Cavity Volume (nm³)	Water Solubility (g/100 mL at 25°C)
α-CD	6	0.47–0.53	~174	~14.5
β-CD	7	0.60–0.65	~262	~1.85
γ-CD	8	0.75–0.83	~427	~23.2

Among them, β-CD is studied widely because of its ideal cavity size for many drugs & low costs. However, its poor solubility often requires chemical modification for biomedical use [38].

Functional Behaviour in Self-Assembling Systems

In hydrogel systems, the cavity size and chemical environment of each CD type determine: The range of guest molecules it can encapsulate. The inclusion complex's stability, degree and type of self-assembly or cross-linking. For instance: α-CD is suitable for linear polymer threads (e.g., PEG), β-CD forms stable complexes with aromatic or

steroid-like structures and γ-CD accommodates larger or bulkier molecules due to its wider cavity [39].

Mechanism Of Self-Assembly in Cyclodextrin Hydrogels

Host–Guest Inclusion Complexation: At the heart of cyclodextrin (CD)-based hydrogel self-assembly lies the host–guest inclusion complexation mechanism. This non-covalent molecular recognition process enables CDs to encapsulate hydrophobic guest molecules within their internal cavity, forming reversible, dynamic complexes in aqueous environments. These interactions serve as physical cross-links in hydrogel networks, enabling soft, stimuli-responsive & self-healing materials [40]. The self-assembly of cyclodextrin-based hydrogels is driven by non-covalent interactions, particularly host–guest inclusion complexation between CDs & suitable guest particles. This supramolecular chemistry approach enables the creation of physically cross-linked networks that are reversible, stimuli-responsive, and biocompatible, making them highly attractive for biomedical and material science applications [41].

Structural Basis

Cyclodextrins are perfect hosts for a variety of hydrophobic or amphiphilic compounds because of their hydrophilic outer surface & hydrophobic internal cavity. The interior cavity size varies among CD types: α-CD: ~0.5 nm (suitable for linear chains like PEG), β-CD: ~0.6 nm (ideal for aromatic and steroidal molecules), γ-CD: ~0.8 nm (fits bulky or macromolecular guests). These cavities accommodate guest molecules via: Hydrophobic interactions, Van der Waals forces and Hydrogen bonding. No covalent bonds are formed, which ensures reversibility and tunability of the gel network [42].

Common Guest Molecules: Guest molecules are often introduced as functional groups on polymer backbones or as small molecules that interact with CD-modified polymers.

Table 2: Common guest moieties include

Guest Molecule	CD Type	Affinity Constant (Ka, M^{-1})	Function
Adamantane	β-CD	~10^4–10^5	Strong binding, gel crosslinking
Azobenzene	α-/β-CD	~10^3 (trans), ~10 (cis)	Photo-responsive switching
Ferrocene	β-CD	~10^3–10^4	Redox-responsive gel behaviour
PEG (polymer)	α-CD	Variable	Pseudopolyrotaxane threading

The reversible complexation/dissociation of these pairs allows for stimuli-responsive behaviour, such as sol–gel transitions triggered by light, pH, redox, or temperature [43].

Mechanism in Hydrogel Networks

In a typical CD-based supramolecular hydrogel: CD moieties (hosts) are grafted onto one polymer chain. Guest moieties (e.g., adamantane) are attached to a second polymer. Upon mixing in water, host–guest complexes form spontaneously. These interactions act as non-covalent cross-links, resulting in a three-dimensional hydrogel network. This mechanism provides: Dynamic bonding → self-healing behavior, Shear-thinning properties → injectability, Biocompatibility and modularity → biomedical adaptability [34]

Advantages of Host–Guest Complexation in Hydrogels: Reversible and tunable interaction strength, Enables smart material design (e.g., drug

release on-demand), Mild conditions for gelation (aqueous, ambient temperature), Compatible with biopolymers, peptides, and therapeutic agents.

Types of Self-Assembling Systems

Self-assembling cyclodextrin (CD) hydrogels can be categorized based on the structural configuration and interaction mode between the cyclodextrin molecules and their guest counterparts [35]. These systems rely on non-covalent host–guest inclusion complexation, allowing for the formation of reversible, dynamic networks with tunable physicochemical properties. Depending on how CDs and guest molecules are organized, three main self-assembly strategies are identified:

A. Linear Self-Assembly (Pseudopolyrotaxane Structures)

In this system, CDs are threaded onto linear polymer chains (typically polyethylene glycol, PEG), forming pseudopolyrotaxanes [36]. The CDs can spontaneously align along the polymer chain through hydrophobic interactions and hydrogen bonding. Mechanism: CDs slide onto the polymer like beads on a string. Cross-linking: Additional stabilization can occur through crystallization of CD columns or further modification. Common pairs: α-CD + PEG.

Applications:

Injectable and thermoresponsive hydrogels, Controlled drug delivery systems, Molecular entrapment and release platforms.

B. Network Self-Assembly (Multicomponent Host–Guest Systems)

This design involves CDs and guest molecules tethered onto separate polymer backbones, which assemble into 3D networks through multiple host–guest interactions. Each interaction serves as a physical cross-link, generating a robust and flexible gel structure [37]. Host polymer: CD-functionalized (e.g., β-CD-grafted chitosan), Guest polymer: Hydrophobic moieties like adamantane, azobenzene, or ferrocene, Complexation: Intermolecular cross-linking forms the gel.

Applications: High modularity (independent tuning of host and guest polymers), Stimuli responsiveness (light, redox, pH) [38], Improved mechanical integrity and biocompatibility.

C. Multivalent and Branched Self-Assembly

Here, multi-armed or branched polymers are modified with multiple CD or guest units, leading to high-density, multivalent interactions [39]. This increases the cross-link density, resulting in stronger, more elastic, and more stable hydrogels. Polymeric architecture: Dendrimers, star-shaped PEGs, or comb-like structures. Functionalization: Each arm contains CD or guest moieties. Self-assembly: Dense host–guest interactions produce robust hydrogels [40]

Applications: Tissue engineering scaffolds, Injectable gels for drug or cell delivery, Biodegradable wound dressings

Table 3: Comparison of Self-Assembly Types

Type	Key Interaction	Typical CD Used	Advantages	Applications
Linear (Pseudopolyrotaxane)	Threading of CD onto polymer	α-CD	Simple assembly, thermoresponsive	Drug delivery, injectable gels

Network (Binary host–guest)	CD on one polymer, guest on another	β-CD	Modular, reversible, stimuli-responsive	Tissue scaffolds, biosensors
Multivalent/Branched	Multi-arm polymer with CD or guest	β-/γ-CD	Stronger, tunable mechanics	3D culture, wound healing, protein delivery

Stimuli-Responsive Behaviour

Due to reversible nature of host–guest interactions, CD-based hydrogels can respond to various external stimuli: pH- Protonation/deprotonation affects guest solubility and complexation [41]. Temperature: Thermosensitive polymers like PNIPAM can be incorporated. Light: Azobenzene derivatives undergo trans–cis isomerization, altering binding affinity with CDs. Redox: Ferrocene oxidizes to ferrocenium, which disrupts CD binding [42]. These properties make self-assembling CD hydrogels ideal for controlled drug release, on-demand gelation, and smart materials.

Advantages of CD-Based Self-Assembly: Mild preparation conditions (aqueous, room temperature), Injectability and self-healing properties, Biocompatibility and biodegradability, Tunable mechanical and physicochemical characteristics, Versatility in incorporating diverse bioactive molecules.

Preparation Methods: The preparation of cyclodextrin-based self-assembling hydrogels relies primarily on formation of non-covalent host–guest inclusion complexes between CD units & their complementary guest molecules. Unlike covalently cross-linked hydrogels, these systems are constructed via reversible physical interactions under mild, aqueous conditions, often at physiological temperature and pH [43].

General Procedure The overall hydrogel formation process typically involves the following steps:

Synthesis or Functionalization of CD and Guest Components: CDs (α-, β-, or γ-CD) may be grafted onto polymer backbones (e.g., PEG, chitosan, hyaluronic acid) [44]. Guest molecules (e.g., adamantane, azobenzene, ferrocene) are chemically conjugated to complementary polymers or monomers.

Mixing in Aqueous Solution: The host and guest components are dissolved in water or buffer (e.g., PBS) and mixed under gentle stirring. Supramolecular inclusion complexes form spontaneously, leading to gelation [45].

Gelation Time and Conditions: Gelation typically occurs within seconds to minutes at room or body temperature. The mechanical strength & amount of gelation can be tuned by adjusting CD/guest ratios, polymer concentration, molecular weight, and solution pH [46].

Characterization and Application: The formed hydrogel is characterized by techniques such as rheology, FTIR, NMR, and SEM & applied in drug delivery, tissue engineering, or other areas [47].

Specific Preparation Strategies

Pseudopolyrotaxane-Based Hydrogel (Threading Method)

Materials: α-CD + PEG, Process: α-CD molecules spontaneously thread onto PEG chains, forming supramolecular pseudopolyrotaxanes, Stabilization: Can be enhanced by hydrogen bonding or crystallization of CD columns [48].

Binary Host–Guest Complexation (Modular Mixing) Materials: β-CD-functionalized polymer + adamantane-modified polymer, Process: Two aqueous solutions are mixed, forming a hydrogel via multiple host–guest cross-links. Advantage: Customizable and reversible system [49].

Self-Assembly via Multivalent Interactions Materials: Multi-arm polymers (e.g., 4-arm PEG) with CD or guest ends**,** Process: Mixed with complementary multi-valent counterparts to form highly cross-linked, mechanically tunable gels. Application: Suitable for injectable and shape-adaptable hydrogels [50].

Table 4: Factors Affecting Hydrogel Formation

Parameter	Effect on Hydrogel
CD type (α, β, γ)	Determines guest size compatibility and cavity interaction strength
Polymer molecular weight	Affects gel stiffness and viscoelasticity
Host–guest ratio	Controls network density and gel strength
pH and ionic strength	Can modulate host–guest interaction and gelation behavior
Temperature	Influences thermoresponsive behavior (especially with PNIPAM)

Properties And Characterization

Cyclodextrin-based self-assembling hydrogels exhibit unique physicochemical and mechanical properties owing to their non-covalent host–guest interactions [51]. These properties determine their performance, stability, biocompatibility, and applicability in drug delivery, tissue engineering, and smart materials. Accurate characterization of these hydrogels is essential for understanding their structure–function relationships and optimizing their use in biomedical and industrial settings [52].

Key Properties

Reversibility and Stimuli-Responsiveness: The supramolecular nature of CD hydrogels allows reversible gelation, making them self-healing and injectable. These hydrogels react to several stimuli, including: Temperature, pH, Redox conditions, Light. Example: Azobenzene-modified guest molecules undergo *trans–cis* isomerization upon light exposure, weakening or disrupting the host–guest complex with β-CD [53].

Mechanical Strength and Elasticity: It is possible to adjust mechanical properties by: Polymer concentration, Degree of crosslinking, Host–guest binding affinity, Multivalent systems or use of high-molecular-weight polymers enhance gel stiffness, elasticity, and resilience [54].

Shear-Thinning & Self-Healing Behavior: Under shear, the non-covalent bonds break temporarily, allowing the gel to flow (injectability).When the shear is removed, the host–guest bonds re-form, restoring the original structure.

Swelling Behavior: CD hydrogels exhibit high water uptake due to their hydrophilic nature. The degree of swelling depends on crosslink density and external circumstances like pH & ionic strength.

Biocompatibility and Biodegradability: CDs are inherently non-toxic and biocompatible. When combined with biodegradable polymers (e.g., chitosan, hyaluronic acid), the hydrogels become suitable for in vivo applications [55,56].

Characterization Techniques

Rheological Analysis

Measures storage (G′) and loss (G″) moduli to assess viscoelastic properties. Determines gelation time, mechanical strength, and self-healing capability. Example: Time sweep and strain sweep tests can reveal gel robustness and recovery under deformation [57].

Fourier Transform Infrared Spectroscopy (FTIR)

Confirms the formation of host–guest complexes by identifying characteristic vibrational shifts in CD and guest molecules. Example: Shifts in hydroxyl stretching or carbonyl bands indicate complexation [58].

Nuclear Magnetic Resonance (NMR) Spectroscopy

^{1}H NMR & 2D NOESY are used to verify inclusion complexation and molecular interactions between CDs and guest moieties [59]. Inclusion leads to upfield or downfield shifts in guest molecule protons**.**

Scanning Electron Microscopy (SEM)

Reveals microstructure & morphology of freeze-dried hydrogels. Helps assess pore size, network density, and porosity, which influence drug release and tissue ingrowth [60].

Swelling and Degradation Studies

Gravimetric methods track hydrogel weight change over time in aqueous environments. Biodegradation can be tested in enzyme-containing buffers (e.g., lysozyme for chitosan-based hydrogels).

Drug Loading and Release Profiling

UV–Vis or HPLC is used to quantify drug encapsulation efficiency and release kinetics. Release profiles are evaluated under physiological or triggered conditions to mimic target environments [61].

Applications Of Cyclodextrins

The exact potential of the CDs in the sector of pharmaceutical applications is because of their capability to affect several properties influencing the behavior and therapeutic outcomes of drugs. Cyclodextrins are typically employed to improve the solubility, permeability, stability as well as adverse effects including irritation. Generally, most of these applications are associated to their capability to form inclusion complexes [62].

Solubility and dissolution enhancement: The most extensive use of the CDs is to improve the solubility of drug in aqueous solutions. An increase in solubility also aids in improving bioavailability and hence therapeutic efficiency. Cyclodextrins have the capability to form the inclusion complexes, which increases the solubility and dissolution of drug molecules in the solid state [63]. Even though solubilization effects of all the CD molecules can be found throughout the literature, methylated CDs have the greatest potential of increasing the solubility as they decrease the crystallinity of drugs, which also increases the dissolution [64]. Although the influences of the CD complexation on it are extremely empirical, yet a number of historical findings permit several inferences: Firstly, the poorer the water solubility of the drug, the superior the solubility enhancement through the CD complexation. Secondly, compared to derivatives with greater molar substitutions, derivatization of CDs with less molar substitution provides improved solubilization. Thirdly, the charge closeness to the cavity is the only factor that affects the CDs' propensity to dissolve. The ability improves with increasing closeness. Finally, by adding different group polymers, it is possible to

enhance complexation and subsequently solubilization.

Permeability across biological membrane: Surprisingly, permeability across biological membranes may be influenced by a number of parameters, including the partition coefficient, molecular weight, and molecule shape. In CD complexation, the free drug has the ability to pass through biological membranes, however CDs do not contribute to the increased penetration of hydrophilic medicines [64]. The medication formulation and the barrier are now the only factors influencing delivery across biological membranes. Cyclodextrins can influence delivery across water diffusion layer-controlled barriers, although their effects across lipophilic membranes are restricted. The addition of hydrophobic cyclodextrins, which easily penetrate the mucosa, is the lone exception to this barrier [65].

Higher photo- and thermal stability: Their impact on the chemical stability of medications is another significant characteristic of these excipients. When creating a pharmacological formulation, stability characteristics and the variables influencing them should be considered. Then, the proper stability enhancers should be included in accordance with the specifications. CDs are fine known for their capacity to enhance general stability by mitigating the effects of oxygen, light, and temperature [66,67]. A product's degradation in the presence of light can have a number of negative consequences. The creation of a compound between CD & vitamin E was discovered to increase photo stability. Studies are necessary to determine the extent to which any preparation can be shielded against excipient-mediated degradation in addition to the protective impact of CD stability [68].

Improved drug safety: When CDs improve the medications' solubility, dissolution & bioavailability [69], It lowers the possibility of harmful effects by ensuring that the medication will have the necessary residence duration in body & not remain longer [70]. An investigation into the combination of CD with the antiviral medication ganciclovir revealed that the drug's efficacy was greatly increased and its adverse effects were lessened. Similarly, CDs can lessen discomfort brought on by ophthalmic and injectable medications [71].

Control of drug release: CDs with acyl and ethyl groups may extend the duration of medication release [72]. Using the GIT's epithelial surface, where per-Obutanoyl β-CD is recognized for its mucoadhesive properties, is one way to regulate medication release. Because of their ability to form gels, HP-β-CDs are used to prolong medication release. Osmotic pumps are commonly used in controlled medication delivery systems because they are special and offer a consistent drug concentration in the systemic circulation [73]. Combining the CD conjugates with the appropriate release formulations allows for the development of more complex prolonged delivery systems. The grouping of ketoprofen with β-CD produced this action & adding this preparation to CD conjugates produced a repeated release profile [74].

Challenges And Future Perspectives

Despite the significant improvement and promising applications of self-assembling cyclodextrin (CD) hydrogels, several scientific and translational challenges remain that limit their widespread clinical and industrial use.

Challenges

Limited Mechanical Strength: While supramolecular CD hydrogels exhibit excellent self-healing and injectability, they often hurt from weak mechanical properties, restricting their

utility in load-bearing biomedical applications (e.g., cartilage or bone repair) [75].

Host–Guest Binding Specificity: The success of hydrogel formation depends heavily on the affinity and selectivity of host–guest interactions. Designing guest molecules with optimal binding constants that are stable under physiological conditions is complex.

Scale-Up and Reproducibility: Manufacturing supramolecular CD hydrogels at commercial scale with consistent physicochemical properties and performance remains a technical hurdle due to batch-to-batch variability.

In Vivo Stability and Degradation: Although CDs are generally biocompatible, the in vivo behavior (e.g., degradation rate, immune response, renal clearance) of the hydrogel network needs comprehensive evaluation, particularly for long-term applications [76].

Controlled Release Precision: Achieving precise and sustained release of therapeutics from CD hydrogels is challenging due to the dynamic & reversible nature of host–guest interactions, especially when influenced by complex biological environments.

Future Perspectives

Multifunctional and Responsive Hydrogels: Formation of multi-stimuli-responsive hydrogels (e.g., pH/redox/light dual-responsive systems) could lead to advanced smart materials for on-demand drug delivery and bio-sensing.

Hybrid and Composite Systems: Integration of CD-based supramolecular hydrogels with nanoparticles, biopolymers, or 3D-printed scaffolds may enhance their mechanical, electrical, and biological functionalities [77].

Clinical Translation: More in vivo studies, toxicological profiling, and regulatory standardization are essential to validate the safety & efficacy of CD hydrogels in humans, especially for injectable implants, regenerative medicine, and topical formulations.

Synthetic Innovation: Advances in synthetic chemistry may allow the creation of highly selective and tunable CD derivatives with enhanced inclusion properties, paving the way for new biomedical applications [78].

Sustainable Materials: Use of green chemistry and biodegradable polymers in CD hydrogel preparation can lead to more eco-friendly and sustainable solutions, particularly for environmental or agricultural applications.

CONCLUSION

Self-assembling cyclodextrin (CD) hydrogels represent a dynamic and versatile class of supramolecular biomaterials driven by host–guest inclusion complexation. Their modular design, biocompatibility, reversible cross-linking, and stimuli-responsiveness offer tremendous potential across a broad range of biomedical, pharmaceutical & material science applications. Through various preparation methods—such as pseudopolyrotaxane formation and multivalent network assembly—these hydrogels can be tailored for applications including tissue engineering, drug delivery, wound healing & responsive biosensors. However, challenges such as limited mechanical strength, binding specificity, and scalability must be addressed to fully understand their clinical and commercial potential. Future advancements in polymer chemistry, nanotechnology, and biomaterials engineering are expected to overcome current limitations and expand the utility of CD hydrogels as next-generation smart materials.

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