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Review

Hydrogel Systems for Clinical Research emerging trends in Therapeutics

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Abstract

This abstract summarizes current trends in hydrogel design and translational strategies that are advancing clinical research in therapeutics. It emphasizes responsive chemistries, device–drug combination pathways, and application niches with promising near-term clinical applications. Hydrogels are water-based polymer networks that can change their mechanical and transport properties. In the last ten years, they have quickly moved from research labs to real-world applications. Hydrogels are useful for several purposes: they can provide localized drug delivery, act as carriers for cells and genes, and serve as scaffolds for healing wounds and regenerating tissues. They are also effective in transdermal microneedle systems, which allow for painless drug administration. Hydrogels are becoming important platforms in clinical settings, effectively connecting biologics, small molecules, and cell therapies. They are particularly useful for local treatments, chronic wound repair, osteoarticular injections, and minimally invasive vaccine delivery. Early strategic engagement on chemistry, manufacturing, and controls (CMC) as well as regulatory pathways for combination products, along with the design of imaging-enabled endpoints, will help accelerate first-in-human studies and enhance the therapeutic impact.

Keywords: Hydrogels, Injectable depot, Microneedles, Locoregional immunotherapy, Cell encapsulation, Clinical translation.

INTRODUCTION

Hydrogels have played a pivotal role in shaping modern drug delivery systems since their first biomedical application in the 1960s, when Wichterle and Lím introduced poly(2-hydroxyethyl methacrylate) (PHEMA) for use in contact lenses. The material's high water content, biocompatibility, and mechanical resemblance to soft tissues quickly established hydrogels as versatile candidates for controlled drug release. Early systems relied primarily on diffusion-controlled mechanisms to facilitate the release of small molecules from crosslinked synthetic matrices. (1)

By the 1980s and 1990s, the scope of hydrogels expanded significantly with the exploration of biodegradable and stimuli-responsive polymers, including polyvinyl alcohol, polyethylene glycol (PEG), alginate, and chitosan. These advancements introduced swelling- and erosion-controlled mechanisms, enabling more precise control over drug release and paving the way for targeted therapies. pH- and temperature-sensitive hydrogels, in particular, emerged as promising platforms for colon-specific and localized drug delivery, while applications in ocular, oral, and transdermal systems highlighted their versatility in clinical use.

The 1990s and 2000s marked the rise of "smart" or responsive hydrogels engineered to react to physiological cues such as pH, temperature, glucose concentration, and enzymatic activity. In situ gelling systems, capable of undergoing sol-to-gel transitions upon administration, gained traction as minimally invasive delivery platforms. Concurrently, research focused on peptide and protein delivery, cell encapsulation for tissue engineering, and the adoption of safer physical crosslinking techniques to reduce toxicity.

In the 2010s, hydrogel research advanced toward translational applications, bridging the gap between laboratory innovation and clinical deployment. This period saw the emergence of injectable and hybrid hydrogel systems that integrate nanoparticles, liposomes, and micelles to enhance stability, drug compatibility, and multi-stage release profiles. Regulatory frameworks also increasingly emphasized reproducibility and safety, particularly for PEG-based synthetic hydrogels.

Today, hydrogels stand at the forefront of drug delivery innovation, offering responsive, biocompatible, and customizable platforms that hold immense potential for improving therapeutic precision and patient outcomes.

Emerging Trends in Therapeutics (2020s–Present)

Injectable & Self-Healing Hydrogels

Shear-thinning, reversible networks enable needle delivery and structural recovery after injection. They are applied in cancer therapy, orthopedics and wound healing.

Host–Guest Supramolecular Systems:

Cyclodextrin–guest complexes and other affinity motifs enable programmable, reloadable release. They are modular and adaptable for both small molecules and biologics.

Nanoparticle–Hydrogel Hybrids:

Integrate hydrogel scaffolds with nanoparticles for dual-drug release, targeting, and theranostics, allowing for sequential or compartmentalized release.

Multi-Stimuli Responsive Hydrogels:

Integrate hydrogel scaffolds with nanoparticles to achieve sophisticated dual-drug release mechanisms that enhance targeting and theranostic capabilities. This approach facilitates both sequential and compartmentalized release, enabling precise therapeutic interventions and improved treatment outcomes.

Dual-Network & Tough Hydrogels:

Integrate hydrogel scaffolds with nanoparticles to achieve sophisticated dual-drug release mechanisms that enhance targeting and theranostic capabilities. This approach facilitates both sequential and compartmentalized release, enabling precise therapeutic interventions and improved treatment outcomes.

Bioactive & Cell-Instructive Hydrogels:

Incorporate adhesion ligands, protease-cleavable sites, and growth factor binding domains to support regenerative medicine, stem cell therapy, and immunotherapy.

Clinical Translation & Personalization:

Emphasize the importance of scalable manufacturing techniques alongside the development of personalized formulations that directly cater to individual patient needs. Transition towards the realm of precision medicine, where the release mechanisms of hydrogels are meticulously tailored to align with the unique biological characteristics of each patient. (2)

METHODS

There are several key methods for designing, synthesizing, and applying hydrogels in clinical therapeutics. These include various cross-linking techniques, approaches to introduce stimuli responsiveness, mechanisms for drug loading and release, and strategies to mimic natural systems for improved performance.

Hydrogel formulation methods

Chemical Cross-Linking

Chemical hydrogels are created through covalent bonds formed between polymer chains using cross-linking agents. Common methods for producing these hydrogels include free-radical polymerization, irradiation (such as using gamma rays for PVA-based gels), and chemical reactions that introduce functional groups to establish a stable three-dimensional network. Typically, chemical hydrogels exhibit greater mechanical strength and stability.

PROCEDURE

1. **Polymer Solution Preparation:**
   - Dissolve the chosen polymer (e.g., PVA, chitosan, alginate) in water or an appropriate buffer. Adjust the concentration for desired gel strength.
2. **Add Cross-Linking Agent**
   - Add a small-molecule cross-linker, such as glutaraldehyde or glyoxal, or functionalized polymers for polymer-polymer cross-linking.
   - The cross-linker should have at least two reactive groups capable of forming covalent bonds, such as aldehyde groups that facilitate Schiff base formation with amine groups on polymers. [3]
3. **Initiate Cross-Linking Reaction**
   - Mix the components thoroughly under appropriate conditions, which include temperature (typically room temperature to around 50 °C), pH (often mildly acidic for Schiff base reactions), and reaction time (ranging from minutes to hours).
   - For photo cross-linking, expose the solution containing photosensitive groups to UV or visible light for a duration of seconds to minutes.
   - For enzymatic cross-linking, add the enzyme (e.g., transglutaminase) along with the relevant substrates under physiological conditions, allowing for a reaction time of minutes to hours.
4. **Gelation Monitoring**
   - Check for gel formation either visually or using spectroscopic methods to confirm the formation of the hydrogel network.
5. **Purification**
   - Wash the hydrogel thoroughly with water or buffer to remove unreacted cross-linkers, monomers, or initiators, reducing toxicity.
6. **Shaping and Drying**
   - Mold the hydrogel into preferred shapes (films, beads, sheets) before employing drying methods, such as freeze-drying or air drying, for use or storage.

Physical Cross-Linking

Physical hydrogels rely on non-covalent interactions such as hydrogen bonding, ionic interactions, and secondary bonding (e.g., thermal gelation in agarose and electrostatic blending of oppositely charged polymers). These networks are reversible and typically more biocompatible, though generally less mechanically robust.

PROCEDURE

1. **Ionic / metal-ion complexation**
- Ca^{2+} crosslinked alginate and its Sr^{2+}/Ba^{2+} variants exhibit fast gelation and enable easy in-situ formation, making them injectable.
- The mesh size and choice of ions can tune the swelling and diffusion-controlled release properties.
- These materials are widely used for wound dressings and for encapsulating cells and therapeutics.
2. **Hydrogen bonding & dipole interactions**
- Reversible hydrogen-bond networks create self-healing, shear-thinning gels, where the dynamics of the bonds determine the rate at which payloads diffuse or are released under stress. This property makes them ideal for shear-sensitive injectable systems.(2)
3. **Hydrophobic association / micelle-driven networks**
- Amphiphilic polymers create hydrophobic areas or micelles that serve as physical connections.
- These are helpful for carrying and slowly releasing hydrophobic drugs. The release depends on how stable the micelles are and how quickly the polymers can exchange. [4]
4. **Host–guest supramolecular crosslinks**
   - Highly tunable and reversible inclusion complexes enable precise and modular binding of drugs or drug-containing guests; the kinetics of association and dissociation govern the release. This method is excellent for on-demand and localized release.

Polyelectrolyte complexation / electrostatic assembly

- Polymers with opposite charges, such as chitosan and alginate, form complexes that determine network porosity and allow for ionic-strength and pH-dependent release.
- These properties make them useful for oral, mucosal, and topical delivery systems.

5. **Physical crystallization / chain entanglement (thermal gelation, freeze–thaw PVA, protein β-sheets)**
   - Reversible crystallites or entanglements enhance networks; thermal responsiveness or enzymatic degradation can trigger release.
   - They are often used for mechanically robust scaffolds.
6. **Nanoparticle or colloid-bridged gels**
   - Nanoparticles (silica, lipid, polymeric) function as crosslinking junctions or drug depots within a hydrogel; release mechanisms arise from nanoparticle desorption/diffusion or hydrogel weakening.
   - This hybrid approach enhances loading capacity and multi-modal release.
7. **π–π stacking and aromatic interactions, peptide/protein self-assembly**
   - Utilized for the development of bioactive peptide gels, these innovative materials facilitate the release of therapeutic cargo through the dynamic exchange or degradation of supramolecular assemblies.

Novel trends

Recent advancements in hydrogel science have led to several new trends, particularly in biomedical and therapeutic applications. These trends focus on smart materials, advanced cross-linking techniques, composite formulations, and multifunctionality to meet complex medical needs. [5]

1. **Smart and Stimuli-Responsive Hydrogels**

These utilize physical (temperature, electric/magnetic fields), chemical (pH, ionic strengths, glucose), or biological triggers (enzymes, antigens) within the polymer network by incorporating functi onal pendant groups (e.g., carboxyl, amino, boronic acid).

Recent advances in hydrogel science have led to novel trends, particularly in biomedical and therapeutic applications. These trends highlight the importance of smart materials, advanced cross-linking techniques, composite formulations, and multifunctionality to meet complex medical needs.

2. **Advanced Cross-Linking and Hybrid Networks**

Novel cross-linking methods, including enzyme-mediated dual-network formation and ruthenium-catalyzed photo-crosslinking, enable tunable mechanical and functional properties for clinical use. Interpenetrating and double-network hydrogels are being engineered to better mimic natural tissues and enhance strength, resilience, and biocompatibility.

3. **Functional Composite and Bioactive Hydrogels:**

The emphasis is on composite hydrogels that integrate both natural and synthetic polymers, which are enhanced with nanoparticles for purposes such as antimicrobial action, cancer treatment, or wound healing. Examples of these hydrogels include iron delivery systems that utilize cyclodextrin complexes, cannabidiol-loaded composite wound dressings, and photodynamic therapy hydrogels that incorporate embedded sensitizers and metal ions.

4. **3D Printing and Topological Design:**

Novel approaches utilize 3D printing and network topology optimization to manage viscoelasticity, degradation, and release profiles in personalized and regenerative medicine. Computational modeling aids in designing advanced hydrogel networks for predictable mechanical and therapeutic outcomes.

5. **Biomedical and Clinical Application Innovations:**

Recent studies highlight wound dressings for rapid healing and infection resistance, photo-responsive cancer therapies, and injectable hydrogels for tissue regeneration. Many hydrogels are validated in animal models for localized chemotherapy, regenerative implants, and smart oral drug delivery.

CONCLUSION

Hydrogel systems have rapidly emerged as versatile and innovative platforms in the realm of clinical research, presenting a range of unique advantages such as exceptional biocompatibility, customizable mechanical properties, and the capacity for controlled drug release. Current trends underscore their expanding influence in areas such as targeted drug delivery, tissue engineering, regenerative medicine, and personalized therapeutics, where precision and effectiveness are paramount. Recent advancements in smart, stimuli-responsive, and bioactive hydrogels are facilitating a seamless transition from laboratory discovery to clinical implementation, showcasing their potential to address complex medical challenges. Despite the hurdles of large-scale production, navigating regulatory approvals, and ensuring long-term safety, hydrogel-based therapeutics offer immense promise for revolutionizing future healthcare. By enabling more effective, patient-centered treatments, these innovative systems are poised to significantly enhance therapeutic outcomes and improve the quality of life for patients. [6]

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