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HYBRID NANOGEL SYSTEMS' RECENT DEVELOPMENT: MANUFACTURING AND ANWENDUNG IN DRUG SIMULTANEOUS DELIVERY ASSOCIATED IMAGING APPROACH

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ABSTRACT

Researchers in pharmacy are paying increasingly close attention to nanogel particularly hybrid nanogels. Even numerous agents with differing physicochemical properties can be delivered together thanks to the special hybrid and compartmentalized structures. The unique hybrid and compartmentalized structures provide great potential for co-delivery of multiple agents even the multiple agents with different physicochemical properties. Otherwise, the hybrid nanogel encapsulating optical and magnetic resonance imaging contrast can be utilized in imaging technique for disease diagnosis. More importantly through nanogel-based multifunctional drug delivery systems the stimuli-responsive features might be easily employed for the design of targeted release of drug. This review summarizes the construction of diverse hybrid nanogels and multicompartment nanogels. The application in co-delivery of multiple agents and imaging agents for diagnosis as well as the application in the design of stimuli-responsive multifunctional nanogels as drug delivery are also reviewed and discussed. The future prospects in the application of multifunctional nanogels will be also discussed in this review.

Keywords: Hybrid nanogel, Stimuli-responsive, co-delivery, Imaging technique.

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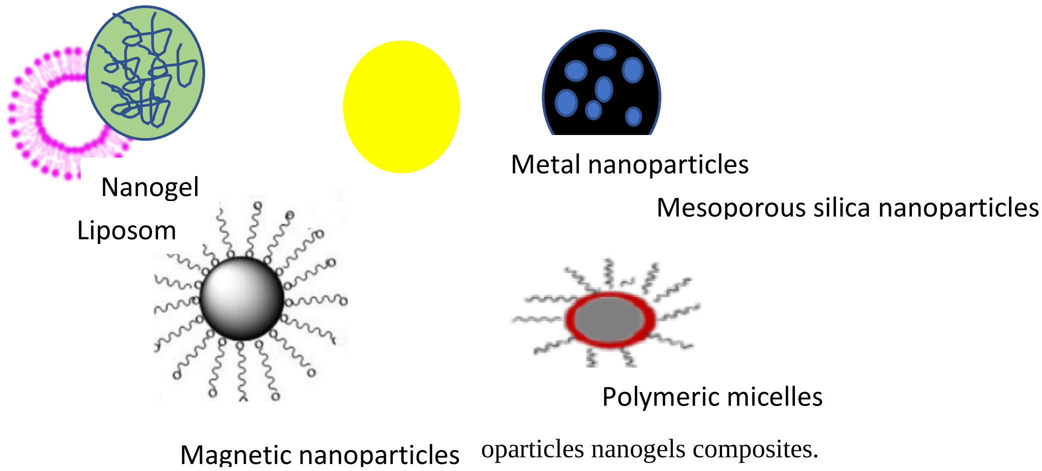
INTRODUCTION

Nanotechnology has revolutionized various fields, offering unprecedented opportunities for the development of advanced materials with unique properties and applications. Among these innovative materials, hybrid nanogels have emerged as a promising class of nanomaterials at the intersection of nanotechnology and polymer science **[1]**. These nanogels represent a fusion of nanoscale particles or structures within a hydrogel matrix, combining the advantages of both components to create versatile and multifunctional materials. Hybrid nanogels are characterized by their three-dimensional network of crosslinked polymer chains that form a highly hydrated structure. This structure can encapsulate and immobilize nanoparticles, organic molecules, or even biomolecules, resulting in a wide range of applications across various fields, including drug delivery, tissue engineering, diagnostics, and environmental remediation **[2]**. In this introductory exploration of hybrid nanogels, we will delve into their unique properties, fabrication methods, and diverse applications. We will also highlight the potential benefits they offer in addressing complex challenges in medicine, materials science, and environmental protection. As we navigate through the intricacies of hybrid nanogels, it becomes evident that these nanomaterials hold immense promise in shaping the future of nanotechnology and materials engineering **[3]**.

FABRICATION

Nanoparticle

Pharmaceutical researchers have been interested in a variety of nanoparticles because they provide a method to overcome therapeutic limitations **[4]**. However, due to factors including poor drug loading, unstable characteristics, and burst drug release, nanoparticles are far from ideal. Therefore, new nanoparticle composite techniques have been proposed that mix nanoparticles with different structures. A superior functionality may be endowed, and each component's synergistic properties may be improved by the novel structural combination **[5]**. On the basis of these encouraging visions, numerous fresh attempts on hybrid NPs have been made. Nanogels have been widely chosen to create gel because of their exceptional properties, such as their ease of mixing with pharmacological agents (hydrophilic drugs, proteins). Multi-responsive nanogels can potentially be used to act as a depot for prolonged and controlled medication delivery.



oparticles nanogels composites.

Polymeric NP

Polymeric NPs made by specific modification to effectively carry drugs, genes, or other substances in order to increase chemotherapeutic efficacy and decrease systemic toxicity. A different method made of cross-linked hybrid nanogels based on cyclodextrin has been demonstrated to be a potential drug delivery mechanism **[6,7]**. The quercetin-PAE nanogels were then given the spherical morphology by being PEGylated with a covering. By adjusting the concentration of the feed reactant, the hybrid nanogel size could be precisely controlled, and as the concentration rose, so did the particle size.

Metal Nanoparticle

Metal nanoparticle (NP)-hydrogel nanocomposites are a specific type of nanocomposite material that combines metal nanoparticles with hydrogels **[8]**. In this case, the nanoparticles are made of metals or metal alloys. These nanocomposites offer a unique combination of properties and have a wide range of potential applications in various fields. The metal nanoparticles used in these nanocomposites are typically on the nanometer scale, with dimensions ranging from 1 to 100 nanometers **[9]**. Common metal nanoparticles used include gold (Au), silver (Ag), platinum (Pt), palladium (Pd), and others. These metal nanoparticles can exhibit unique optical, electrical, and catalytic properties due to their small size and high surface area-to-volume ratio. Hydrogels are water-absorbing, three-dimensional networks of hydrophilic polymer chains. They have a high-water content and are known for their soft and gel-like insistency. Hydrogels are biocompatible and can retain water or aqueous solutions within their structure **[10]**. Metal nanoparticle-hydrogel nanocomposites are created by incorporating metal nanoparticles into the hydrogel matrix. This integration results in materials with combination of properties and functionalities, including: Enhanced Electrical Conductivity: Metal nanoparticles, especially those made of noble metals like gold and silver, can impart electrical conductivity to the hydrogel. This is valuable for applications such as flexible electronics, sensors, and conductive biomaterials. Some metal nanoparticles have catalytic properties, and when embedded in a hydrogel, they can catalyze specific reactions **[11]**. This makes them useful for applications like environmental remediation and catalytic reactors. Noble metal nanoparticles, such as gold and silver, exhibit unique optical properties like surface plasmon resonance (SPR) **[12]**. These optical properties can be tuned by controlling the size and shape of the nanoparticles and can be utilized in sensors, imaging, and drug delivery applications. Metal nanoparticle-hydrogel nanocomposites can be used for controlled drug delivery **[13]**. Drugs or therapeutic agents can be loaded onto or into the nanoparticles, and the hydrogel matrix can control the release rate, offering a sustained and targeted delivery mechanism. The combination of metal nanoparticles and hydrogels can create responsive materials for sensing and detection applications. Changes in the properties of the nanocomposite, such as electrical conductivity or optical response, can be used to detect specific analytes or environmental conditions **[14, 15]**. Metal nanoparticle-hydrogel nanocomposites are versatile materials with applications in fields such as biomedicine, electronics, environmental science, and materials engineering. The choice of metal nanoparticles and hydrogel composition can be tailored to specific applications, allowing for the development of materials with tailored properties and functions.

Inorganic Nanoparticle

In addition to metal nanoparticle-hydrogel nanocomposites, there are various other inorganic nanoparticle-hydrogel nanocomposites that combine different types of inorganic nanoparticles with hydrogels **[16]**. These nanocomposites offer a wide range of properties and functionalities for various applications. Silica nanoparticles (SiO2 NPs) are commonly used in combination with hydrogels. Silica NPs can reinforce the hydrogel matrix, improve mechanical strength, and provide a stable structure. These nanocomposites find applications in tissue engineering, wound healing, and drug delivery **[17]**. Carbon nanotubes (CNTs) are cylindrical carbon structures with excellent mechanical, electrical, and thermal properties. When incorporated into hydrogels, CNTs can enhance the mechanical strength, electrical conductivity, and stability of the hydrogel. They are used in applications such as tissue scaffolds, biosensors, and neural interfaces. Graphene oxide is a derivative of graphene with oxygen-containing functional groups **[18]**. GO can be dispersed in hydrogels to improve mechanical properties and provide a large surface area for drug loading. GO-hydrogel nanocomposites are used in drug delivery, tissue engineering, and wound healing. Iron oxide nanoparticles (e.g., magnetite or maghemite) are often used in hydrogels for magnetic targeting and drug delivery **[19]**. These nanocomposites can be guided to specific locations using external magnetic fields, making them useful for cancer therapy and imaging. TiO2 nanoparticles are known for their photocatalytic properties. When incorporated into hydrogels, they can be used for environmental applications, such as water purification and pollutant degradation under UV light. Lanthanide-based nanoparticles, such as upconversion nanoparticles, can be integrated into hydrogels for bioimaging and sensing applications **[20]**. These nanocomposites are capable of converting lower-energy excitation into higher-energy emission, enabling deep tissue imaging. Cerium oxide nanoparticles have antioxidant properties and are used in hydrogels for wound healing and tissue repair. They can scavenge reactive oxygen species (ROS) and promote tissue regeneration **[21]**. ZnO nanoparticles are known for their antimicrobial and UV-blocking properties. When combined with hydrogels, they can create wound dressings and skincare products with enhanced antibacterial and sunblocking capabilities. These are just a few examples of inorganic nanoparticle-hydrogel nanocomposites, and the possibilities are extensive **[22,23]**. The choice of inorganic nanoparticles and hydrogel components can be tailored to specific applications, allowing for the development of materials with customized properties and functions in fields ranging from biomedicine to environmental science and beyond **[24, 25]**.

Multicompartment Nanogels

Multicompartment nanogels are complex nanostructures that consist of multiple compartments or domains within a single hydrogel particle. These compartments can vary in size, shape, composition, and functionality, allowing for a wide range of applications across different fields, including drug delivery, nanomedicine, and materials science. Multicompartment nanogels can incorporate different types of materials or nanoparticles into distinct compartments. This allows for multifunctionality, where each compartment serves a specific purpose or carries out different tasks. For example, one compartment may encapsulate a drug, while another compartment contains a contrast agent for imaging **[26]**.

Controlled Release: The separate compartments in multicompartment nanogels can be designed to release their contents at different rates or under specific conditions. This controlled release profile is valuable for drug delivery applications, where it can provide a sustained or sequential release of therapeutic agents **[27].** Combination Therapies: Multicompartment nanogels can enable combination therapies by encapsulating multiple drugs or therapeutic agents within different compartments. This is particularly beneficial for treating complex diseases or targeting multiple aspects of a medical condition simultaneously **[28]**. Targeted Delivery: By incorporating targeting ligands or nanoparticles into specific compartments, multicompartment nanogels can enhance the targeted delivery of drugs or imaging agents to specific tissues or cells. This improves the therapeutic efficacy and reduces side effects **[29]**. Diagnostic Imaging: Some multicompartment nanogels are designed for diagnostic purposes, incorporating contrast agents in one compartment to enable imaging while simultaneously carrying therapeutic agents in other compartments for treatment guidance **[30]**. Responsive Behavior: Multicompartment nanogels can be engineered to respond to external stimuli such as pH, temperature, or specific biomarkers. This responsiveness can trigger the release of contents from particular compartments when needed **[31]**.

Multicompartment nanogels are often made from biocompatible materials, making them suitable for various biomedical applications. They can be used in vivo for drug delivery or imaging, among other uses **[32]**. Materials Diversity: The compartments within multicompartment nanogels can be composed of different materials, including polymers, lipids, or inorganic nanoparticles, depending on the desired properties and functions **[33]**. Tissue Engineering: Multicompartment nanogels can be used in tissue engineering to create scaffolds with multiple compartments that mimic the complexity of native tissues. This is useful for regenerative medicine applications.

Theragnostic: The combination of diagnostic and therapeutic capabilities in a single nanogel structure is often referred to as theragnostic. Multicompartment nanogels have great potential in theragnostic applications by combining imaging and therapy within a single platform **[34-37]**.

MULTIPLE STIMULI RESPONSIVE HYBRID NANOGEL

These nanogels are designed to respond to specific external stimuli, such as changes in pH, temperature, light, or the presence of biomolecules. The ability to trigger controlled changes in these nanogels' properties or behavior in response to environmental cues makes them valuable for a wide range of applications **[38, 39]**.

pH Responsive

pH-responsive nanogels can undergo volumetric changes in response to changes in pH. They are particularly useful for drug delivery applications because pH levels can vary significantly within the body. For example, some nanogels expand in acidic environments (e.g., tumor microenvironments) and release drugs selectively in these regions **[40]**.

Temperature Responsive

Temperature-responsive nanogels undergo reversible changes in volume or structure as the temperature changes. They are often used in applications like controlled drug release and tissue engineering. Common temperature-responsive polymers include poly(N-isopropylacrylamide) (PNIPAM) and its derivatives **[41]**.

Light-responsive Hybrid Nanogel Systems

Nanogels can change their properties or release cargo in response to exposure to specific wavelengths of light. Light can be used as a remote trigger for controlled drug delivery, photothermal therapy, and other applications. Light-responsive nanogels often incorporate photoactive components like azobenzene or photothermal agents like gold nanoparticles **[42]**.

Biological Stimuli-Responsive Nanogels

Some nanogels respond to biological cues such as enzymes, antibodies, or specific molecules. These systems are used for targeted drug delivery and diagnostics. For example, enzyme-responsive nanogels can release drugs in response to the presence of disease-specific enzymes **[43]**.

APPLICATION OF HYBRID NANOGEL

Co-delivery Nanocomposites

Due to their various release mechanisms, two medicines' release kinetics showed differing regulated features. Because of the combined actions of micelles and nanogels, the release of CFX was sustained over a lengthy period of time while the release of TMD was short-term. The drug release was also significantly influenced by the pH and temperature of the environment **[44, 45]**. The finding was that the hybrid nanogels that had been created had a thermal response to body temperature. Thus, following injection into a tumor location, transformed into a gel, at which point the medicines were gradually released. In July 2015, a patent for a nanogel composite was also approved **[46]**.

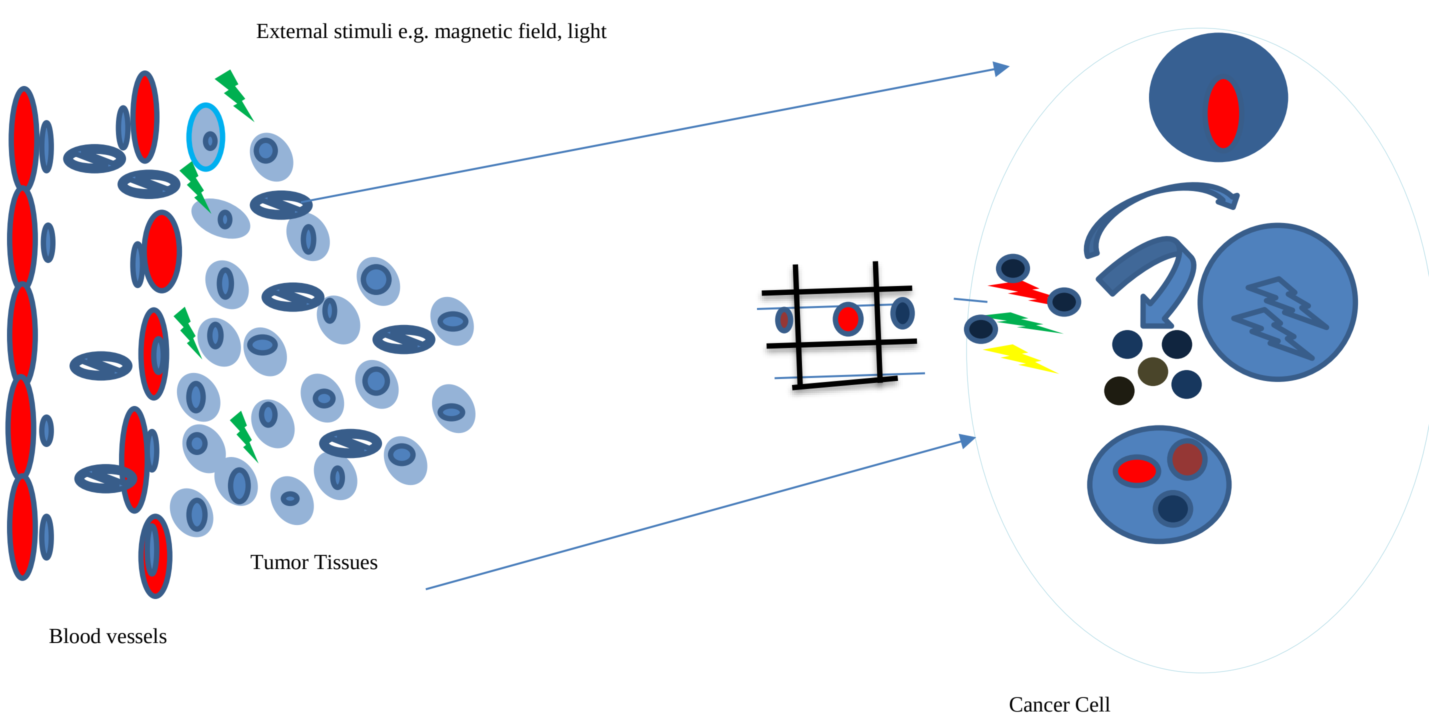


Fig 2. Hybrid nanogels respond to various stimuli.

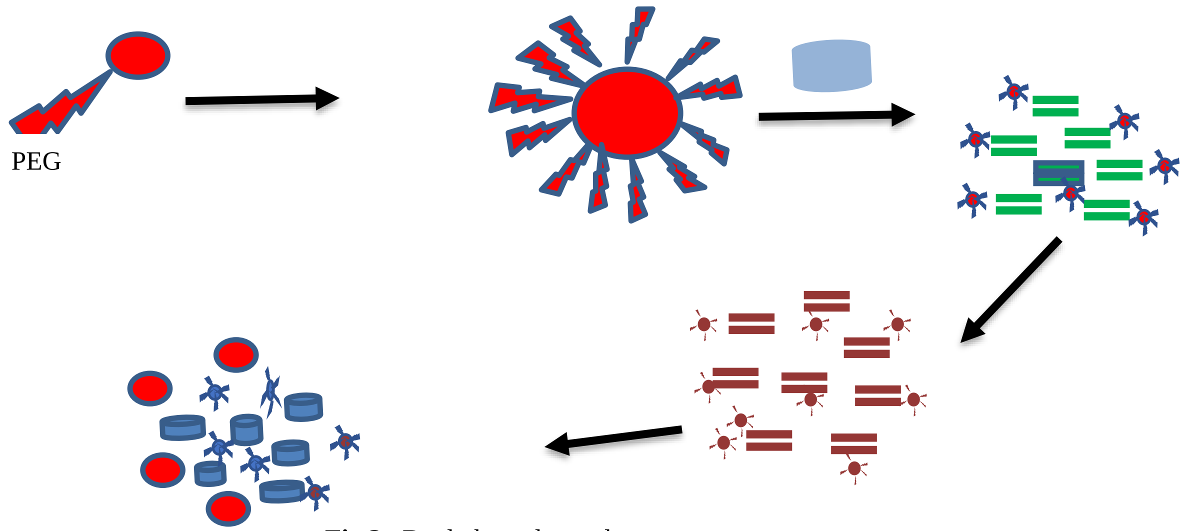


Fig 3. Dual phase drug release process.

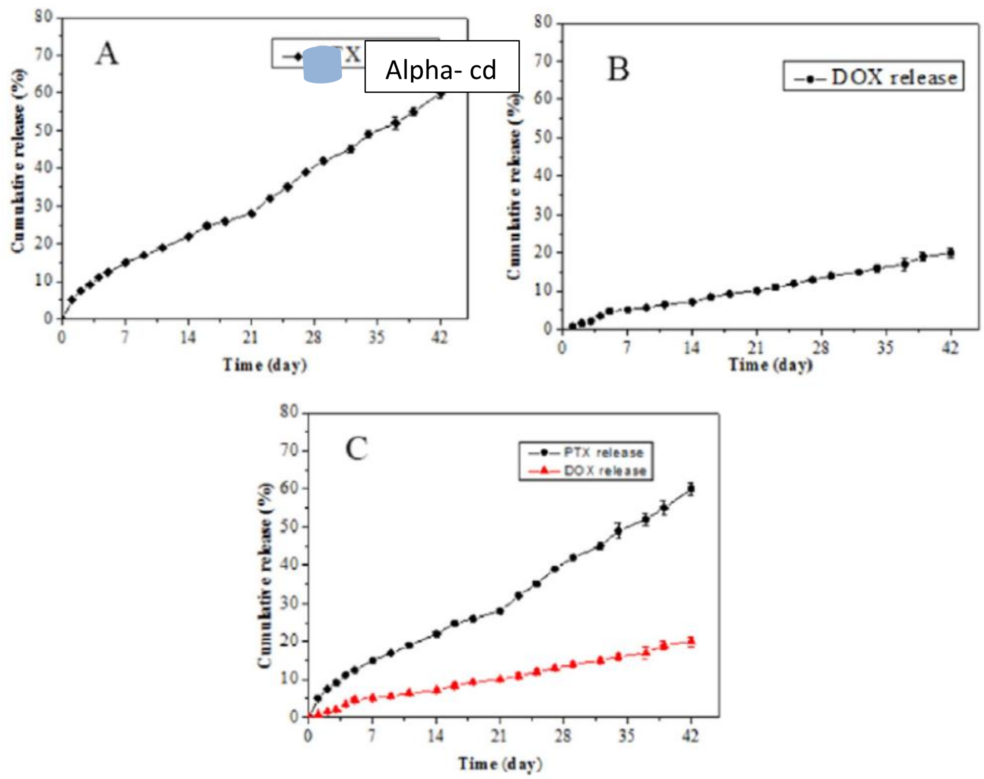


Fig. 4. PTX or DOX release profiles.

Hydrogel-prodrug Nanocomposites for Combined Delivery

This innovative strategy combines prodrugs, hydrogels, and nanocomposite materials to achieve controlled and targeted drug release for therapeutic purposes. Prodrugs are inactive or less active forms of a drug that are designed to undergo a specific chemical transformation in the body to become the active drug **[47]**. This modification can improve drug solubility, stability, or target-specific delivery. In the context of prodrug-hydrogel nanocomposites, prodrugs are often incorporated to enhance the loading and release of therapeutic agents. Hydrogels are three-dimensional networks of hydrophilic polymers that can absorb and retain a significant amount of water. They are highly biocompatible and can be tailored to have specific properties, such as swelling, mechanical strength, and degradation rates. Hydrogels provide a stable matrix for drug incorporation and controlled release. Nanocomposites are materials that incorporate nanoparticles into a matrix, often to enhance specific properties. In the context of prodrug-hydrogel systems, nanoparticles can be loaded with drugs or therapeutic agents, improving drug encapsulation efficiency and controlled release characteristics **[48]**. The integration of these components in prodrug-hydrogel nanocomposites involves several steps:

Prodrug design: Prodrugs are carefully designed to have the desired pharmacokinetic properties and chemical transformations that will lead to the release of the active drug once inside the body.

Hydrogel formulation: Hydrogels are formulated to encapsulate prodrugs and nanoparticles. The choice of hydrogel material and its properties (e.g., cross-linking density, degradation rate) can be tailored to the specific requirements of the drug delivery system.

Nanoparticle incorporation: Nanoparticles loaded with drugs or therapeutic agents are dispersed within the hydrogel matrix. These nanoparticles can be designed to release their cargo in response to specific stimuli, such as pH, temperature, or enzymatic activity **[49]**.

Segment-based Nanogels for Continuous Delivery

Multicompartment nanogels are a type of nanoscale drug delivery system that holds promise for co-delivery of multiple therapeutic agents. These nanogels consist of a three-dimensional network of cross-linked polymers that can encapsulate and release various bioactive compounds, such as drugs, genes, proteins, or imaging agents, in separate compartments or regions within the nanogel structure. Co-delivery, in this context, refers to the simultaneous delivery of multiple therapeutic agents to a target site, which can be particularly advantageous in various medical applications. Multicompartment nanogels allow for the precise compartmentalization of different therapeutic agents within the same delivery system **[51,52]**. Each compartment can be designed to release its payload independently, providing control over the release kinetics of individual agents. Co-delivery enables the administration of multiple therapeutic agents with complementary or synergistic mechanisms of action. This can lead to enhanced therapeutic efficacy, reduced side effects, and improved patient outcomes. Multicompartment nanogels can be used for combination therapy, where two or more therapeutic agents are delivered together to treat complex diseases. For example, in cancer treatment, co-delivery of chemotherapy drugs and targeted therapies can enhance tumor cell killing while minimizing damage to healthy tissues. The nanogel matrix can be engineered to provide controlled release of therapeutic agents over time. This allows for sustained and prolonged drug delivery, reducing the need for frequent dosing and improving patient compliance **[53]**.

Implications of Composite Nanogel Systems in Image Processing

Magnetic resonance imaging (MRI), which uses a variety of magnetic materials, and fluorescence imaging, which uses a variety of fluorescent agents, are the two most often utilized imaging modalities in medicine. Jie Yang and colleagues created a brand-new class of multifunctional hybrid nanogels that enclose a polypeptide monolayer that is pH- and temperature-sensitive on QDs. The successful integration of targeted tumor imaging and controlled medication delivery demonstrated the potential of these techniques. Additionally, the QD-polypeptide nanogels in their investigation displayed decreased in vitro cytotoxicity **[54]**. Similar to this, hybrid nanogels incorporating QDs have been developed for both gene delivery and stem cell engineering tracking **[55]**. In this study, magnetic Fe3O4 NPs were chemically trapped within porous poly (acrylic acid) nanogels to create hybrid Fe3O4-PAA nanogels, which have excellent drug loading capacities and sustained release characteristics.

CONCLUSION

One of the main areas of focus in the field of nanotechnology-based pharmacology has been the development of multifunctional nanogel delivery systems for the delivery of drugs, particularly co-delivery of numerous agents simultaneously. To prevent interactions between various agents, the construction offers a separate place for the several cargoes that have been enclosed. Additionally, the various release mechanisms brought on by the unique features of the various carriers or the various modifications on the various carriers can be used to manipulate consecutive independent release without any interference. Meanwhile, by fully utilizing beneficial characteristics of nanogels, drug release that is sustained and stimuli sensitive can be achieved. However, a number of issues have restricted the use of hybrid nanogels in therapeutic settings. The choice of the other component, unpredictable size and particle morphology, and a lack of pertinent clinical data about the efficacy and safety are some issues related to hybrid gel.

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