

HYDROGEL BASED CONTROLLED DRUG DELIVERY SYSTEM FOR CANCER TREATMENT

Jaydatta Jagannath Chorge, Patil Hanumant, Vikas Chavan

Gajanan Maharaj College of Pharmacy, Chh.Sambhajinagar

Jaydattachorge912002@gmail.com

Mr. Tejas More, (M.Pharm) Department of pharmaceutical Chemistry, Gajanan Maharaj

College Of Pharmacy Chh.Sambhajinagar

Dr. Kavita Kulkarni (Phd.Mpharm), Department of Quality Assurance

Gajanan Maharaj College Of Pharmacy, Chh.Sambhajinagar.

ABSTRACT

Hydrogels have gained significant attention in various medical applications, including wound care, burn treatment, dressings, contact lenses, and tissue engineering. Recently, their potential in localized cancer therapy has also been investigated extensively. This chapter focuses on the use of injectable hydrogel systems specifically designed for direct application at tumor sites.

We begin by outlining the fundamental properties of hydrogels and categorizing them based on their triggering mechanisms. These classifications include pH-sensitive, temperature-responsive, magnetically responsive, light-activated, and ultrasound-responsive hydrogels. Each category is examined in detail to understand its unique characteristics and applications.

Furthermore, we delve into the design principles and operational mechanisms of various stimulus-responsive hydrogels, highlighting notable research examples. By exploring these innovative hydrogel systems, we aim to shed light on their promising role in enhancing localized cancer treatment.

INTRODUCTION

The Urgent Challenge of Cancer and Innovative Hydrogel Solutions

Cancer remains one of the most critical global health issues, profoundly affecting the well-being of individuals worldwide. In 2012, there were 14.1 million new cases and 8.2 million cancer-related deaths reported globally. Projections suggest that

by 2025, new cancer cases could surge to 19.3 million. According to authoritative statistics, approximately 1 in 8 men and 1 in 10 women will face a cancer diagnosis in their lifetime, highlighting the urgent need to address this major clinical challenge.

The World Health Organization reports that cancer is a leading cause of death worldwide, accounting for about 9.6 million deaths in 2018—approximately 1 in 6 deaths globally. Beyond its mortality impact, cancer significantly diminishes quality of life and life expectancy.

Researchers are actively exploring strategies to mitigate the adverse effects of chemotherapy while enhancing treatment efficacy. Recent clinical trials have begun investigating targeted therapeutic approaches utilizing drug-loaded nanoparticles. However, these nanoparticles often accumulate in healthy tissues, leading to undesirable side effects and complicating targeted therapy.

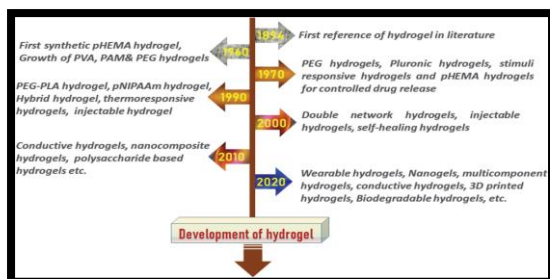
This challenge has prompted a shift towards developing novel drug delivery systems for breast cancer, with local drug delivery emerging as an effective strategy for tumor eradication while minimizing systemic side effects. Hydrogel-based drug delivery systems have shown promise in this regard,

facilitating controlled drug release and reducing non-targeted exposure. Hydrogels are three-dimensional polymer networks—either natural or synthetic—that exhibit unique properties such as softness, flexibility, porosity, permeability, biocompatibility, and similarity to soft tissues.

Moreover, the ability of certain polymers to respond to stimuli—such as pH, temperature, enzymes, and light—allows for the creation of smart or stimuli-responsive hydrogels. This paper focuses on various stimuli-responsive hydrogels tailored for breast cancer treatment.

In summary, hydrogel systems offer numerous advantages: they exhibit minimal side effects, enable easy administration, achieve high local drug concentrations, provide sustained release, and are minimally invasive. These features present significant potential for advancing cancer treatment. This review aims to highlight various hydrogel systems effective in targeting cancer and to summarize their key benefits, providing insights for more precise, efficient, and personalized cancer therapies.

HISTROY



The 1990s marked a significant period for the development of thermo-responsive hydrogels, particularly those made from polymers like polyvinyl alcohol (PVA),

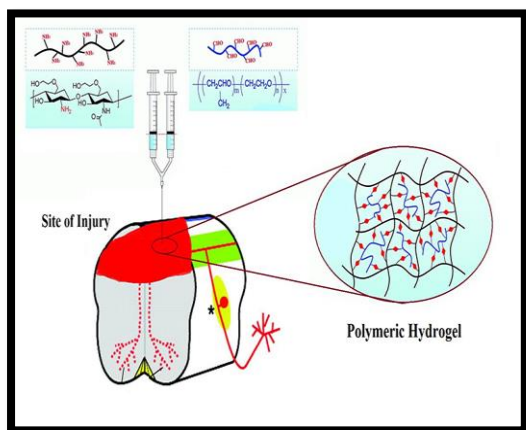
poly(N-isopropylacrylamide), and polyethylene glycol (PEG). Researchers focused on harnessing these materials for on-off release mechanisms, particularly below their lower critical solution temperature (LCST). A notable milestone was reached in 1999 when Elisseff et al. demonstrated the potential of injectable hydrogels for targeted drug delivery, using cartilage as a model system.

Entering the 21st century, advancements in physio-chemical techniques and structural modifications led to enhanced mechanical properties of hydrogels. Innovative approaches included incorporating various crosslinkers, altering the polymer network architecture, and combining natural and synthetic polymers. A groundbreaking development occurred in 2003 with Gong et al.'s introduction of double-network hydrogels, which exhibited exceptional mechanical strength (17.2 MPa compression stress and 92% strain) through a two-step polymerization process involving poly(2-acrylamido-2-methylpropanesulfonic acid) and polyacrylamide (PAM).

The evolution of hydrophilic and hydrophobic polymer synthesis has facilitated the creation of biocompatible hydrogels suitable for diverse biomedical applications, including bone implants, biosensors, contact lenses, and tissue engineering. Recently, hydrogel research has rapidly expanded, focusing on innovative forms such as wearable hydrogel patches, conductive hydrogels, injectable variants, self-healing designs, multi-component structures, and biodegradable options.

The rise in hydrogel research is evident in the exponential increase in publications over the last two decades, as illustrated by a search on PubMed® for the term "hydrogel" in peer-reviewed papers, underscoring their growing significance in the biomedical field.

HYDROGEL



Definition

Hydrogels are soft materials composed of cross-linked polymers that can absorb and retain large amounts of water, forming a gel-like consistency.

Properties

- Molding: Hydrogels can be shaped into various forms.
- Stimuli Response: They can change their properties in response to external stimuli such as temperature, pH, light, and ultrasound.

Uses

Hydrogels are employed in a variety of applications, including:

- Drug Delivery: Facilitating controlled release of medications.

- Tissue Engineering: Serving as scaffolds for cell growth and tissue regeneration.
- Wound Healing: Promoting moisture retention and healing.
- Contact Lenses: Providing comfort and hydration.
- Hygienic Products: Used in diapers and feminine hygiene products.
- Diagnostic Devices: Involved in biosensors and other medical devices.

Classification of Hydrogels

1) Based on Source of Origin

- Natural Polymers: Derived from biological sources (e.g., chitosan, alginate, collagen), these hydrogels are biodegradable and biocompatible, making them suitable for applications like drug delivery, wound healing, and tissue engineering.

- Synthetic Polymers: Man-made hydrogels (e.g., polyethylene glycol, polyacrylamide) are more chemically stable and can be easily modified for specific uses.

- Hybrid Polymers: A blend of natural and synthetic polymers, offering improved properties over each type individually.

2) Based on Composition

- Homopolymer Hydrogels: Made from a single monomer, these hydrogels' properties are determined by the specific monomer used.

- Copolymer Hydrogels: Formed from two types of monomers, with one typically responsible for water absorption and gel formation.

- Interpenetrating Polymer Networks (IPNs): Composed of two or more intertwined polymer networks, where one is crosslinked in the presence of another.

3) Based on Crosslinking

- Physical Crosslinking: These hydrogels are formed via non-covalent interactions (e.g., hydrogen bonds, ionic interactions, or environmental triggers like pH or temperature) without the need for chemical crosslinking agents.

- Chemical Crosslinking: Covalent bonds between polymer chains are formed through chemical reactions, such as Schiff base formation, radical polymerization, or enzymatic reactions, resulting in highly stable hydrogels.

4) Based on Ionic Charge

- Ionic Hydrogels: Contain charged groups (e.g., anionic carboxyl or cationic amines) which influence swelling behavior and response to pH changes.

- Non-Ionic Hydrogels: Lack charged groups, typically resulting in more neutral swelling properties.

- Ampholytic Hydrogels: Contain both positive and negative charges, contributing to unique swelling and interaction properties.

5) Based on Physical State-

-Solid Hydrogels: These have a strong crosslinked structure and are designed to mimic biological tissues, often used in tissue engineering.

- Liquid Hydrogels: These are typically injectable and may solidify in response to

stimuli such as pH or temperature, useful in drug delivery applications.

- Semi-Solid Hydrogels: These are adhesive and are often used in mucoadhesive formulations for localized drug delivery in areas like the mouth or nasal passages.

6) Based on Stimuli Responsiveness

- Physical Stimuli-Responsive Hydrogels: React to changes in temperature, light, or pressure.

- Chemical Stimuli-Responsive Hydrogels: Respond to chemical triggers such as pH, glucose levels, or other environmental chemicals.

- Biological Stimuli-Responsive Hydrogels: Respond to biological signals such as enzymes or antigens, making them useful for targeted drug delivery or tissue-specific applications.

Properties of Hydrogels

Hydrogels exhibit unique properties that make them suitable for a variety of applications:

1. Swelling Characteristics

- Hydrogels can absorb water and swell when placed in an aqueous environment, closely mimicking natural tissues.

- The degree of swelling is influenced by the cross-linking ratio: higher cross-linking results in tighter structures and reduced swelling.

- Chemical structure plays a role: hydrophilic groups lead to higher swelling compared to hydrophobic groups.

2. Dynamics of Swelling

- Swelling kinetics can be categorized as:

- Diffusion-Controlled (Fickian): Water enters faster than the polymer chains can relax.

- Relaxation-Controlled (Non-Fickian): Swelling is more dependent on the polymer's relaxation dynamics.

3. Mechanical Properties

- Mechanical integrity is crucial for applications like drug delivery systems.

- The degree of cross-linking affects the mechanical strength; however, higher cross-linking can lead to brittleness.

- Copolymerization can enhance mechanical properties through the addition of co-monomers that promote hydrogen bonding.

4. Cytotoxicity and In Vivo Toxicity

- Cytotoxicity tests evaluate the safety of hydrogels through methods like extract dilution, direct contact, and agar diffusion assays.

- Issues arise from unreacted monomers and initiators that can leach into the surrounding environment.

- Strategies to mitigate toxicity include optimizing polymerization kinetics and extensive washing, as well as using techniques like gamma irradiation or thermal cycling to eliminate initiators.

Materials Used in Hydrogel Preparation

Various polymers can be utilized in hydrogel systems, including:

- Cellulose Derivatives: Natural polymers that provide biocompatibility.

- Natural Gums: Like xanthan gum, often used for their thickening properties.

- Polyacrylates: Synthetic polymers that exhibit excellent swelling behavior.

- Gelatin A natural polymer derived from collagen, commonly used in biomedical applications.

HYDROGEL ADVANTAGES AND DISADVANTAGES

- Advantages:

- Biocompatibility: Mimic natural tissues, minimizing immune response.

- Drug Delivery: Low toxicity, capable of swelling and releasing drugs over time.

- Shape Adaptability: Easily adaptable to various body cavities and shapes.

- Wound Healing: Create moist environments conducive to healing and localized drug delivery.

- Disadvantages:

- Mechanical Strength: Low strength, limiting their use in certain clinical settings.

- Weak Adhesion: Poor adhesion to tissues can hinder application.

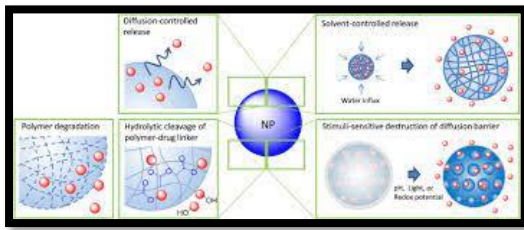
- Toxicity: Potential for toxic byproducts after crosslinking reactions.

- Encapsulation and Leakage: Inefficient drug encapsulation and potential for cargo leakage.

- Controllability: Difficulty in controlling drug release dynamics and responsiveness.

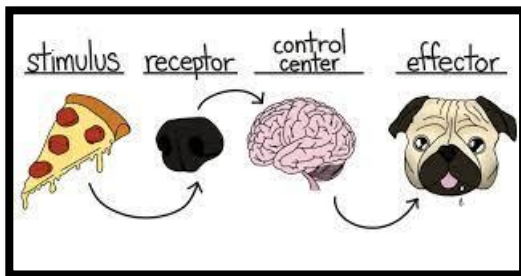
APPLICATION OF HYDROGEL FOR CANCER TREATMENT

1. Controlled Drug Release



Hydrogels can be engineered to release therapeutic agents in a controlled and precise manner. This capability allows for a sustained release of drugs, which can minimize the total dosage required while enhancing treatment efficacy. By tailoring the hydrogel's properties, researchers can achieve a release profile that matches the patient's needs, ensuring optimal drug concentration at the tumor site over time.

2. Response to Environmental Stimuli



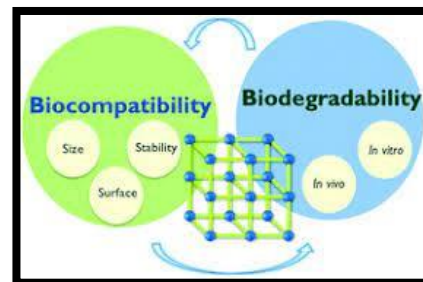
Hydrogels can be designed to respond to various environmental stimuli, such as heat, pH, light, and ultrasound. This feature enables in situ gelation—the hydrogel can transform from a liquid to a gel at the tumor site upon exposure to specific triggers, facilitating localized drug delivery. For example, pH-sensitive hydrogels can release drugs in response to the acidic microenvironment commonly found in tumors, providing a targeted treatment approach.

3. Reduced Side Effects



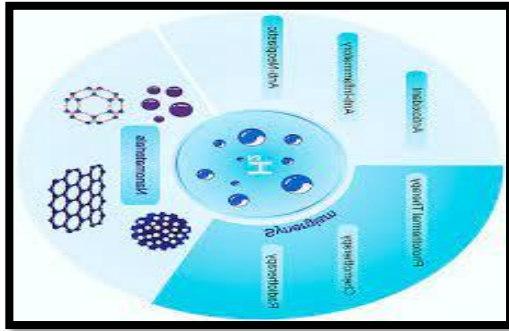
Compared to traditional systemic chemotherapy, hydrogels can significantly reduce side effects. By localizing drug delivery directly to the tumor site, they minimize the exposure of healthy tissues to cytotoxic agents. This targeted approach helps mitigate common chemotherapy side effects, such as nausea, fatigue, and immune suppression, improving the patient's quality of life during treatment.

4. Improved Biocompatibility and Biodegradability



Hydrogels are often made from biocompatible and biodegradable materials, ensuring that they are safe for use in the human body. Unlike some nanoparticle carriers, hydrogels typically exhibit lower toxicity, reducing the risk of adverse reactions. Their ability to degrade naturally over time also means that they can be safely absorbed or eliminated by the body, eliminating the need for invasive removal procedures.

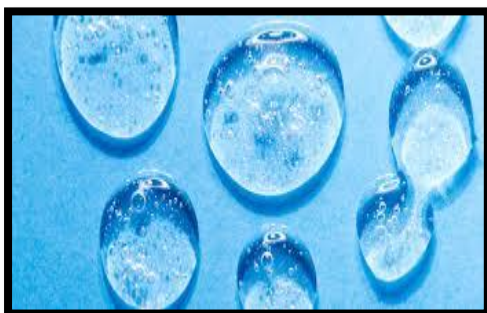
5. Combination Therapies



Hydrogels can serve as versatile platforms for combination therapies, integrating multiple treatment modalities such as chemotherapy, radiotherapy, and immunotherapy. This multifaceted approach can enhance therapeutic efficacy by simultaneously targeting different aspects of tumor biology. For instance, hydrogels can be loaded with both chemotherapeutic agents and immunomodulators, promoting a synergistic effect that improves overall treatment outcomes.

In summary, the unique properties of hydrogels make them highly valuable in cancer treatment, offering controlled drug release, responsiveness to stimuli, reduced side effects, improved biocompatibility, and the potential for combination therapies.

OVERVIEW OF HYDROGELS



Hydrogels are three-dimensional (3D) crosslinked networks composed of natural or synthetic polymers capable of absorbing and retaining significant amounts of water.

These polymers are hydrophilic, containing functional groups such as hydroxyl (-OH), carboxyl (-COOH), amide (-CONH-), primary amide (-CONH₂), and sulfonic groups (-SO₃H), which enable physical and chemical crosslinking. Hydrogels exhibit viscoelastic properties, meaning they possess both liquid-like (viscous) and solid (elastic) components, which allows them to mimic the mechanical properties of natural tissues.

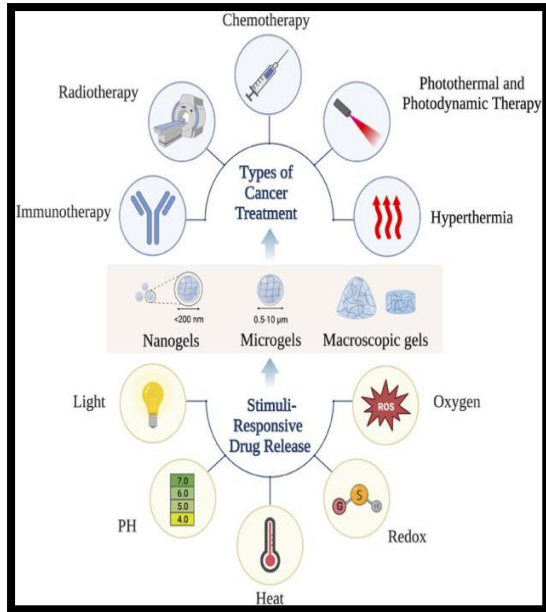
Key Properties of Hydrogels:

- Crosslinking and Functionalization: Hydrogels can be tailored by altering polymer composition, crosslinking types (chemical or physical), and synthesis methods. These factors influence properties such as swelling behavior, pore size, and viscoelasticity.

- Polymer Composition: Hydrogels may be made from either large polymeric chains synthesized from monomers or preformed polymers modified through mixing or chemical treatments.

HYDROGEL IS USED IN THE THERAPY OF CANCER

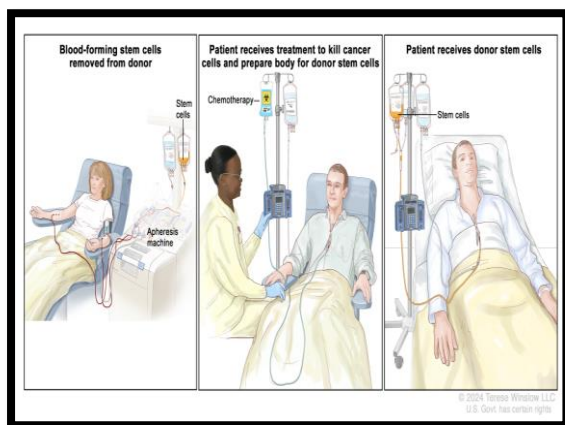
- 1) Chemotherapy
- 2) Radiotherapy
- 3) Immunotherapy
- 4) Hyperthermia
- 5) Photodynamic therapy and photothermal therapy



Hydrogels in Cancer Chemotherapy

Hydrogels, with their versatile properties, have shown significant potential in enhancing cancer therapies like chemotherapy, radiotherapy, immunotherapy, hyperthermia, photodynamic therapy, and photothermal therapy. Here's a detailed overview of how hydrogels contribute to these treatments:

1. Chemotherapy



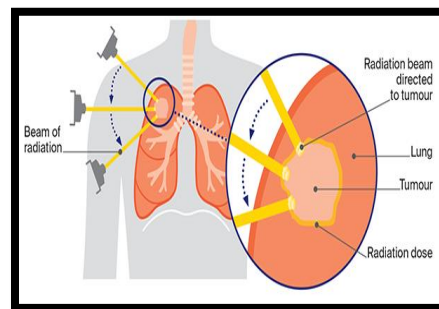
Chemotherapy is a common cancer treatment, often used alongside surgery or other therapies to kill cancer cells. However, chemotherapeutic drugs frequently have drawbacks, including

serious side effects, poor targeting, and the inability to completely eliminate cancer cells while causing harm to the body. Hydrogels, as drug carriers, offer controlled drug release, reducing adverse effects and improving targeting.

- **Controlled Drug Release:** Hydrogels can encapsulate chemotherapy drugs and release them in a controlled manner, minimizing systemic toxicity. Hydrogels, formed by crosslinking in aqueous solutions, reduce the risks of drug denaturation or aggregation, improving the stability of anti-cancer drugs in vivo.

- **Responsive Hydrogels:** Stimuli-responsive hydrogels can release drugs in response to environmental changes (e.g., temperature, pH). For example, Lee et al. (2021) developed a temperature- and pH-responsive hydrogel, which demonstrated high efficacy in releasing anticancer drugs and killing cancer cells.

2. Radiotherapy

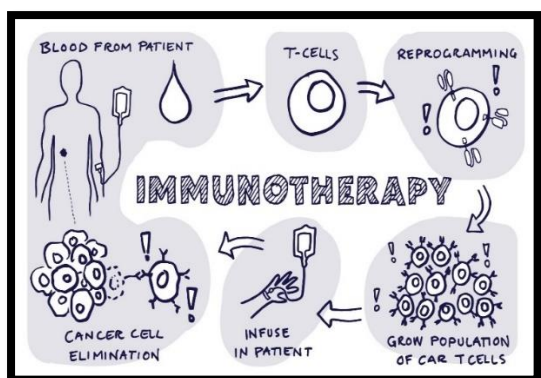


Radiotherapy, which uses high doses of radiation to kill cancer cells, has evolved into a more precise treatment, targeting tumors while minimizing damage to healthy tissues. Hydrogels have enhanced the effectiveness of radiotherapy by overcoming some limitations, such as the self-repair ability of cancer cells and radiation resistance.

- Shape Adaptability and Responsive Nature: Hydrogels can be loaded with radionuclides, chemotherapeutic drugs, and radiosensitizers to enhance radiation's effectiveness.

- Example: Wang et al. (2021) created an injectable hydrogel that consistently releases Endostatin (ES) and improves tumor oxygenation, thereby enhancing radiation sensitivity. Zhang et al. (2021a) also developed a multifunctional hydrogel with gold nanoparticle aggregates (GNPs), doxorubicin, and iodine-131 (131I) that serves as a synergistic platform for cancer therapy.

3. Immunotherapy



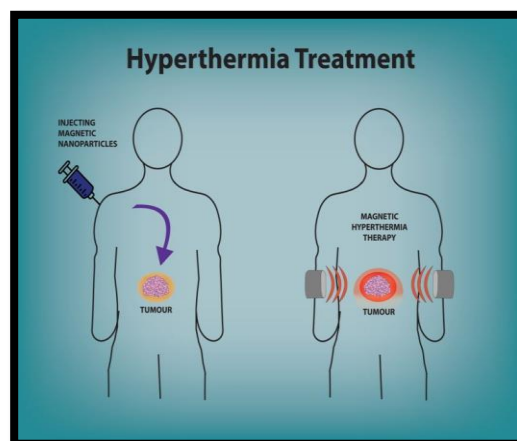
Immunotherapy harnesses the body's immune system to fight cancer. It is particularly effective at preventing metastasis and recurrence. However, immunotherapy's efficacy is limited by factors such as the inability of immune checkpoint blockers (ICBs) to penetrate solid tumors and low T-cell infiltration. Hydrogels provide solutions to these challenges by facilitating the local and sustained delivery of immunotherapy drugs.

- Enhanced Drug Penetration and Release: Hydrogels can carry immune checkpoint blockers and other drugs that enhance T-cell

infiltration, allowing for a more targeted and prolonged response. Hydrogels also enable sequential drug release, triggering cascades of immune responses.

- Example: Jin et al. (2018) designed a hybrid hydrogel for melanoma therapy that effectively reshapes the tumor microenvironment and boosts immune responses. Similarly, Dai et al. (2020) developed a hydrogel system that strengthens both innate and adaptive immune responses in melanoma and hepatocellular carcinoma treatments.

4. Hyperthermia



Hyperthermia therapy raises the temperature of cancerous tissues to damage and kill cancer cells. Hydrogels, especially those with responsive properties, can be used to deliver heat-sensitive agents or nanoparticles to tumors. These hydrogels can release therapeutic agents upon heating or directly aid in the localized increase in temperature necessary for treatment.

5. Photodynamic Therapy (PDT) and Photothermal Therapy (PTT)

Hydrogels are also employed in photodynamic and photothermal therapies, where light or heat is used to destroy cancer

cells. These therapies often require photosensitizers or nanoparticles, which can be encapsulated in hydrogels. The hydrogel matrix ensures controlled and sustained delivery of these agents, increasing the precision and efficiency of the treatment.

The development of thermogels—hydrogels responsive to temperature—addresses this by allowing for localized heat application and sustained, controlled drug release. Thermogels can carry multiple cancer treatments such as chemotherapeutics, radionuclides, and immunosuppressants, enabling a comprehensive therapeutic approach. For example, Chen et al. (2021b) developed an injectable thermogel combining hyperthermia with immunotherapy, enhancing immune cell activity and reducing cancer recurrence

- Example: The combination of photosensitizers with hydrogels enhances the localization and effectiveness of both PDT and PTT, minimizing side effects and improving patient outcomes.

6. Photothermal and Photodynamic Therapy

Photothermal Therapy (PTT) and Photodynamic Therapy (PDT) have emerged as promising non-invasive cancer treatment options. PTT uses heat generated from light absorption to ablate cancer tissues, while PDT generates reactive oxygen species (ROS) through light-activated photosensitizers to destroy cancer cells.

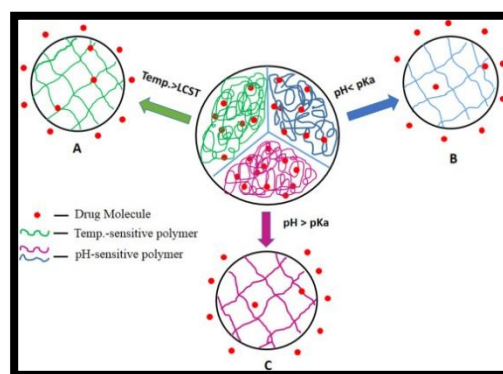
Traditional photothermal agents often suffer from low biocompatibility and poor targeting, causing adverse effects.

Hydrogels, however, offer a solution by enhancing biocompatibility, stability, and targeted delivery of phototherapeutic agents. Su et al. (2021) developed a hydrogel with excellent photothermal effects, enabling cancer eradication without damaging surrounding tissues.

PDT is limited by poor tissue penetration due to the short wavelengths of light needed to activate photosensitizers. Innovative hydrogels, such as those developed by Shu et al. (2021), address this by enabling sustained light harvesting from ultraviolet (UV), visible, and near-infrared (NIR) light, extending the therapeutic effects even after the external light source is removed.

Combining PTT and PDT into dual phototherapy offers enhanced treatment efficiency by overcoming the limitations of single therapies. Injectable hydrogels with dual phototherapeutic agents facilitate both thermal and oxidative cancer cell destruction, offering great potential for clinical applications.

HYDROGELS FOR BREAST CANCER THERAPY



Hydrogels are becoming a key tool in breast cancer treatment due to their ability to control drug release, improve targeting, and reduce side effects. Breast cancer, the most common cancer in women, presents

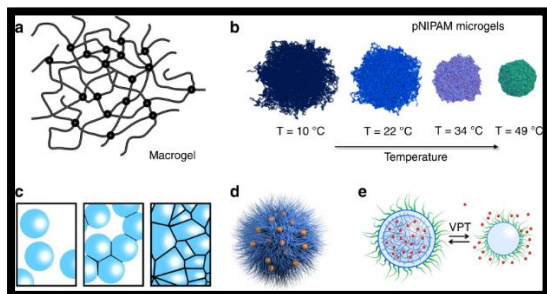
challenges such as relapse and drug resistance. Smart hydrogels can encapsulate cytotoxic drugs, releasing them in a controlled manner directly at the tumor site, thereby reducing systemic toxicity .

pH-sensitive hydrogels are particularly effective for targeting the acidic microenvironment of tumors, ensuring that drugs are released only in cancerous areas. This targeted approach minimizes side effects and increases drug efficacy . The ability of hydrogels to be delivered through various routes, including intravenous and in situ injections, enhances their versatility and effectiveness in breast cancer treatment. By incorporating smart delivery mechanisms like pH- and temperature-responsiveness, hydrogels offer an advanced, customizable approach to treating complex cancers like breast cancer, improving patient outcomes while minimizing adverse reactions.

Hydrogels possess unique advantages and limitations in biomedical applications, especially in drug delivery and cancer treatment. Below is a summary of the key points:

Hydrogel Size Variations

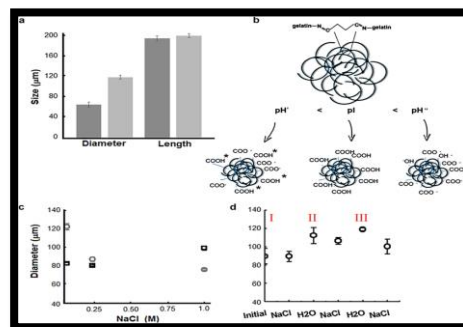
1) Macro gels



Larger than millimeters, capable of carrying substantial drug loads, suitable for

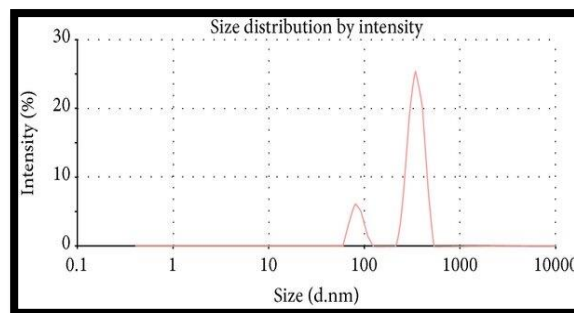
transepithelial delivery and internal placement.

2) Microgels



Sized between 0.5–10 µm, offering a large surface area for oral, pulmonary, and intrabony drug delivery.

3) Nanogels:

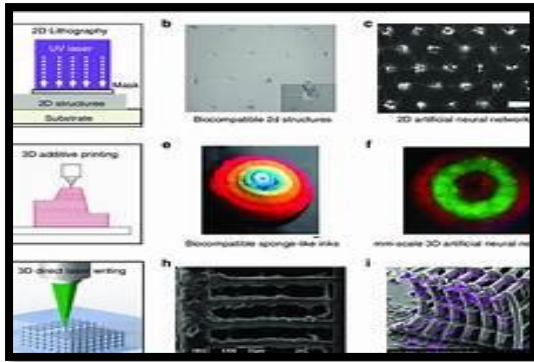


Nanoscale hydrophilic polymer particles ideal for systemic drug administration.

Smart, Responsive Hydrogels

Hydrogels can intelligently respond to both internal (pH, redox potential) and external stimuli (light, temperature, magnetism), enabling controlled, on-demand drug release.

1) Photosensitive Hydrogels

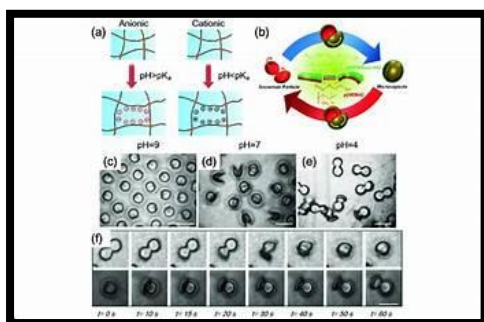


Light-responsive hydrogels can be activated by non-invasive light sources (such as near-infrared light), allowing precise spatiotemporal control of drug release and cancer treatment. They also possess high photothermal conversion efficiency, generating heat to synergize with drug action.

- Examples:

- Near-infrared systems like methylcellulose hydrogels loaded with the photothermal agent IR820 for oral cancer treatment.
- Photosensitive hydrogels combining protoporphyrin IX with nanoparticles, facilitating photodynamic and chemodynamic therapies.

2) pH-responsive Hydrogels



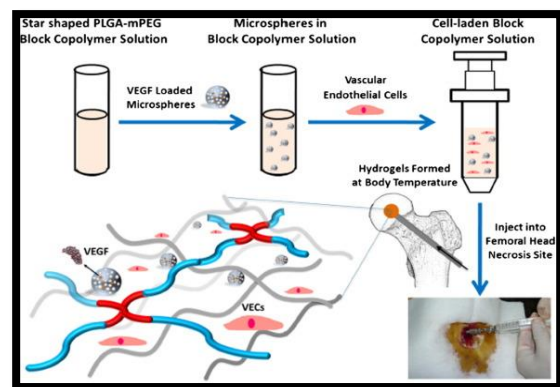
These hydrogels take advantage of the acidic tumor microenvironment to release drugs specifically in cancerous tissues, enhancing targeting and minimizing side

effects. The differences in pH between normal and cancerous tissues allow for selective drug delivery.

- Examples:

- PTX/fer-8 hydrogels for sustained paclitaxel release in HepG2 cells.
- Schiff base bonding hydrogels delivering doxorubicin with enhanced therapeutic efficacy.

3) Thermosensitive Hydrogels



Temperature-sensitive hydrogels form gels in response to body heat and are widely used in cancer therapies for controlled and prolonged drug release. These hydrogels are especially useful for local administration and can be loaded with various therapeutic agents for multi-modal treatments.

- Examples:

- Poly(γ -ethyl-L-glutamate)-based hydrogels for combined chemotherapy and immunotherapy with sustained drug release.

Hydrogels are versatile materials with growing potential in clinical applications, but their drawbacks must be addressed to fully realize their utility in drug delivery and cancer therapy.

4) Redox-Responsive Hydrogels

Redox-responsive hydrogels are highly effective in cancer treatment due to their ability to respond to the unique redox environments found in cancer cells. Cancer cells exhibit elevated levels of glutathione (GSH), a reducing agent, which is four times higher than in normal cells. This characteristic allows redox-responsive hydrogels to release drugs selectively in cancer cells while minimizing toxicity to normal cells.

Mechanism of Action

The high glutathione concentrations in cancer cells trigger the breakdown of redox-sensitive hydrogels, releasing the encapsulated drugs specifically at the tumor site. This makes them a promising tool for targeted drug delivery.

CONCLUSION

Hydrogels are versatile materials with a wide range of applications in drug delivery, tissue engineering, and more. Their unique properties, influenced by the choice of materials and preparation methods, make them suitable for many biomedical applications. Understanding their swelling dynamics, mechanical properties, and toxicity is crucial for the successful development of hydrogel-based systems.

This review highlights various materials, including hydrogels, that are being explored as drug delivery vehicles for cancer treatment. These materials show immense potential in enhancing therapeutic outcomes either as standalone therapies (monotherapies) or in combination with existing treatments (combination therapies). Despite some challenges in

clinical translation, promising new materials are under development, offering hope for more effective cancer treatments in the near future.

REFERENCE

1. Sung, H. et al. *Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin.* 71, 209–249 (2021).
2. Gotwals, P. et al. *Prospects for combining targeted and conventional cancer therapy with immunotherapy. Nat. Rev. Cancer* 17, 286–301 (2017).
3. Nam, J. et al. *Cancer nanomedicine for combination cancer immunotherapy. Nat. Rev. Mater.* 4, 398–414 (2019).
4. Riley, R. S., June, C. H., Langer, R., & Mitchell, M. J. *Delivery technologies for cancer immunotherapy. Nat. Rev. Drug Discov.* 18, 175–196 (2019).
5. Bangham, A. D., & Horne, R. W. *Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope. J. Mol. Biol.* 8, 660–IN610 (1964).
6. Folkman, J., & Long, D. M. *The use of silicone rubber as a carrier for prolonged drug therapy. J. Surg. Res.* 4, 139–142 (1964).
7. Leserman, L. D., Barbet, J., Kourilsky, F., & Weinstein, J. N. *Targeting to cells of fluorescent liposomes covalently coupled with monoclonal antibody or protein A. Nature* 288, 602–604 (1980).
8. Heath, T. D., Fraley, R. T., & Papahadjopoulos, D. *Antibody targeting of liposomes: cell specificity obtained by conjugation of F(ab')₂ to vesicle surface. Science* 210, 539–541 (1980).
9. Matsumura, Y., & Maeda, H. *A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumor tropic accumulation of proteins and the antitumor agent smancs. Cancer Res.* 46, 6387–6392 (1986).

10. Gerlowski, L. E., & Jain, R. K. *Microvascular permeability of normal and neoplastic tissues. Microvasc. Res.* 31, 288–305 (1986).
11. Nicolau, C., & Alving, C. R. *Demetrios Papahadjopoulos and liposomes: from art to science. J. Liposome Res.* 5, 627–634 (1995).
12. Weissig, V. et al. *DQAsomes: a novel potential drug and gene delivery system made from dequalinium™. Pharm. Res* 15, 334–337 (1998).
13. Amato, I. *Nanotechnologists seek biological niches. Cell* 123, 967–970 (2005).
14. U.S. National Library of Medicine. *Safety study of CALAA-01 to treat solid tumor cancers, https://clinicaltrials.gov/ct2/show/NCT00689065[https://clinicaltrials.gov/ct2/show/NCT00689065] (2013).*
15. Yamada, Y. et al. *MITO-Porter: A liposome-based carrier system for delivery of macromolecules into mitochondria via membrane fusion. Biochim. Biophys. Acta Biomembr.* 1778, 423–432 (2008).
16. Hu, C.-M. J. et al. *Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. Proc. Natl Acad. Sci.* 108, 10980–10985 (2011).
17. U.S. National Library of Medicine. *A study of BIND-014 given to patients with advanced or metastatic cancer, https://clinicaltrials.gov/ct2/show/NCT01300533[https://clinicaltrials.gov/ct2/show/NCT01300533] (2016).*
18. Yokoi, K. et al. *Serum biomarkers for personalization of nanotherapeutics-based therapy in different tumor and organ microenvironments. Cancer Lett.* 345, 48–55 (2014).
19. Yokoi, K. et al. *Capillary-wall collagen as a biophysical marker of nanotherapeutic permeability into the tumor microenvironment. Cancer Res.* 74, 4239–4246 (2014).
20. Miller, M. A. et al. *Predicting therapeutic nanomedicine efficacy using a companion magnetic resonance imaging nanoparticle. Sci. Transl. Med.* 7, 314ra183 (2015).