"Injectable Thermosensitive Hydrogels For Therapy of Cancer"

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1. Abstract

Injectable thermosensitive hydrogels have emerged as a cutting-edge strategy in cancer treatment, enabling localized and prolonged delivery of therapeutic agents directly to the tumour site. These smart materials undergo a reversible sol–gel transition at physiological temperature, shifting from a liquid to a gel state, which facilitates minimally invasive administration and sustained drug release. By concentrating therapy at the diseased site, they enhance treatment efficacy, limit systemic toxicity, and protect surrounding healthy tissues. Moreover, their design can be tailored to respond to multiple stimuli, such as temperature or pH, thereby broadening their therapeutic scope. This review summarizes recent advancements in injectable thermosensitive hydrogels, with emphasis on their structural design, mechanisms of action, and potential clinical applications. It also discusses current challenges and future perspectives for translating these systems into effective and patient-friendly cancer therapies.

***2. keywords* :**

Injectable thermosensitive hydrogels; Cancer therapy; Localized drug delivery; Controlled release; Targeted therapy; Biocompatibility; Sustained release; Thermoresponsive polymers

3.

4. Introduction

4.1. Cancer -

Cancer is a complex and multifactorial disease that originates from the uncontrolled growth and division of abnormal cells. These malignant cells can infiltrate surrounding tissues and, through metastasis, spread to distant organs. Because it can arise in nearly any tissue, cancer remains one of the foremost causes of death worldwide. Advancing knowledge of its biological mechanisms and developing innovative therapeutic approaches are essential steps toward improving treatment outcomes.

Cancer develops when mutations occur in a cell's DNA, disturbing the normal processes of growth and division. Such mutations can result from inherited genetic predispositions, exposure to environmental carcinogens, or random errors during DNA replication. Once these altered cells begin to proliferate uncontrollably, they can invade surrounding tissues and eventually spread to distant organs through the bloodstream or lymphatic system.

The impact of cancer extends well beyond physical health, often affecting emotional well-being, social relationships, and overall quality of life. Treatment strategies are determined by the type and stage of cancer and may include surgery, chemotherapy, radiation therapy, or a combination of these approaches. In recent years, significant advances in research have led to the development of targeted therapies and immunotherapies, offering new avenues of treatment and renewed hope for patients battling this disease.

Despite major advances, cancer continues to be a serious global challenge, making ongoing research vital for improving treatment outcomes and moving closer to a cure. Early detection, preventive strategies, and comprehensive supportive care play a crucial role in managing the disease. Continued efforts in these areas are essential to lessen the overall impact of cancer on both individuals and society.

4.2. **Types of Cancer -**

Cancer can be classified according to the type of cell in which it originates. The major categories include:

1. **Carcinomas**

Origin: Epithelial cells lining the skin, glands, and internal organs.

Examples: Lung cancer, breast cancer, prostate cancer, colon cancer.

2. **Sarcomas**

Origin: Connective and supportive tissues, including bone, cartilage, fat, muscle, and blood vessels.

Examples: Osteosarcoma (bone), Liposarcoma (fat), Angiosarcoma (blood vessels).

3. **Leukaemia's**

Origin: Blood-forming tissues, particularly the bone marrow.

Examples: Acute lymphoblastic leukaemia (ALL), Chronic myeloid leukaemia (CML).

4. **Lymphomas**

Origin: Immune system cells, mainly lymphocytes in lymph nodes and lymphatic tissue.

Examples: Hodgkin lymphoma, non-Hodgkin lymphoma.

5. **Myelomas**

Origin: Plasma cells within the bone marrow.

Example: Multiple myeloma.

6. **Central Nervous System (CNS) Cancers**

Origin: Brain and spinal cord cells.

Examples: Gliomas, Astrocytomas, Medulloblastomas.

7. **Germ Cell Tumours**

Origin: Reproductive cells that develop into sperm or eggs.

Examples: Testicular cancer, Ovarian germ cell tumour.

8. **Blastomas (primarily pediatric cancers)**

Origin: Immature precursor cells, also called blasts.

Examples: Neuroblastoma, Retinoblastoma, Nephroblastoma (Wilms tumour).

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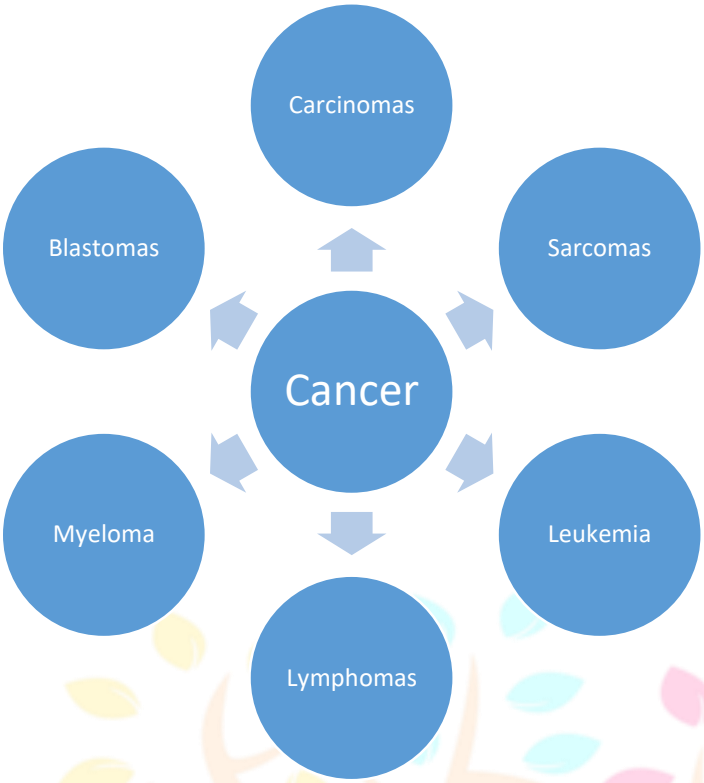

Fig. 1 Types of Cancer

5. Hydrogels -

Hydrogels are increasingly recognized as valuable platforms in cancer therapy due to their distinctive properties. They combine excellent biocompatibility and biodegradability with a strong ability to encapsulate therapeutic agents for controlled and prolonged release. These characteristics make them suitable for integration into multiple treatment approaches, such as chemotherapy, radiotherapy, immunotherapy, hyperthermia, photothermal therapy, and photodynamic therapy, where they enhance precision, reduce side effects, and improve overall therapeutic outcomes.

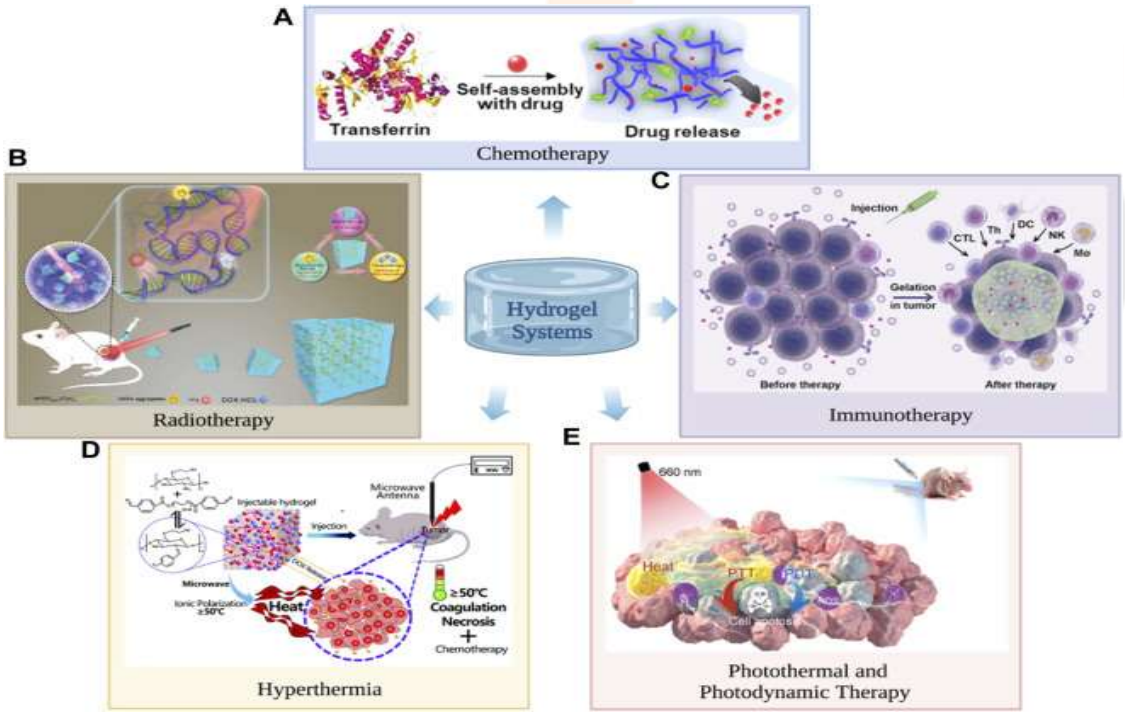

Fig. 2 Hydrogel can be used in Multiple Treatments for Cancer

5.1. Role Of Hydrogels In Cancer Treatement

1. **Chemotherapy**
Chemotherapy plays an important role in cancer treatment and is frequently used alongside surgery or in combination with other therapies to eliminate cancer cells. However, commonly used chemotherapeutic drugs face several challenges, including severe side effects, limited drug tolerance, and lack of precise targeting. As a result, chemotherapy may fail to completely destroy cancer cells while also causing significant damage to healthy tissues and overall well-being.

2. **Radiation Therapy**

Radiation therapy involves the use of high doses of radiation, often exceeding 60 Gy, to destroy cancer cells and shrink tumour's. Modern approaches have shifted from broad exposure to highly precise, targeted techniques that maximize cancer cell eradication while minimizing damage to surrounding healthy tissues. By disrupting the DNA repair mechanisms of malignant cells, targeted radiation enhances treatment effectiveness and improves therapeutic outcomes.

3. **Immunotherapy**
Cancer frequently arises in a highly complex and protective microenvironment that can reduce the success of conventional treatments such as chemotherapy and radiation. Immunotherapy seeks to overcome this limitation by activating and strengthening the body's natural immune defences to detect and eliminate cancer cells, representing a powerful and promising strategy for managing treatment-resistant tumours.

4. **Hyperthermia**
Hyperthermia treatment exploits the unique characteristics of the cancer microenvironment to selectively induce cancer cell death or apoptosis, leaving normal tissues largely unharmed. Heat can destabilize lysosomes within cancer cells, disrupt mitochondrial function, reduce oxygen uptake, and create hypoxic conditions that make cancer cells more vulnerable to treatment.

5. **Photothermal and Photodynamic Therapy**

Photothermal therapy (PTT) provides deep tissue penetration, non-invasive tumour ablation, and minimal chemoresistance, while photodynamic therapy (PDT) offers precise targeting, low invasiveness, and minimal side effects. Both therapies have become valuable options in cancer treatment, demonstrating significant therapeutic potential.

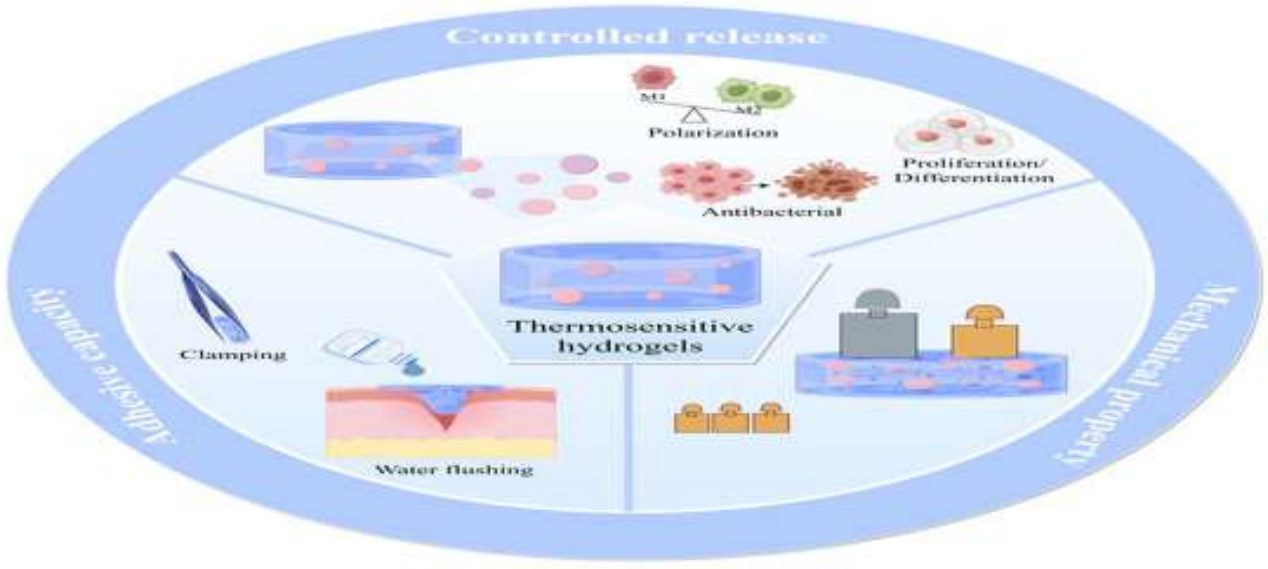

Fig. 3 Thermosensitive Hydrogels

6. **Thermosensitive Hydrogels -**
Thermosensitive hydrogels are a type of hydrogel that responds to temperature changes by undergoing a reversible phase transition between liquid and gel states. This property allows them to serve as efficient carriers for drugs, enabling controlled and localized delivery in response to body temperature, thereby enhancing the effectiveness of cancer therapies while reducing side effects.

a. Properties

1. **Thermoresponsiveness:** These hydrogels can change their physical state in response to temperature variations, transitioning between liquid and gel forms.

2. **Reversibility:** The phase change is reversible, allowing the hydrogel to revert to its original state as the temperature shifts.

3. **Tunable Phase Transition Temperature:** The temperature at which the hydrogel undergoes a phase change can be adjusted by modifying its chemical composition.

4. **Biocompatibility:** Thermosensitive hydrogels can be engineered to be biocompatible

7. Thermosensitive Hydrogels for Cancer Therapy -

Thermosensitive hydrogels are emerging as promising platforms in cancer therapy due to their unique physicochemical properties. These systems undergo a temperature-responsive sol–gel transition, enabling controlled and site-specific drug release at the tumour location. This localized delivery minimizes systemic toxicity while enhancing therapeutic efficiency. In addition, their ability to provide sustained release of anticancer agents contributes to improved long-term treatment outcomes. The potential of thermosensitive hydrogels to selectively target tumour cells and adapt to the tumour microenvironment highlights their relevance in precision medicine. Collectively, they offer key advantages—including enhanced drug delivery, reduced side effects, and superior therapeutic performance—and ongoing research is likely to further expand their role in the future of cancer treatment.

8. Injectable Thermosensitive Hydrogels

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Injectable thermosensitive hydrogels represent a next-generation drug delivery system designed to respond to temperature variations through a sol–gel phase transition. This property enables precise, localized, and sustained release of therapeutic agents at the intended site of action. Formulated to be both biocompatible and biodegradable, these hydrogels can be administered in liquid form and subsequently transform into a gel upon reaching physiological temperature. Their ability to provide targeted delivery not only enhances therapeutic effectiveness but also minimizes systemic toxicity, making them highly valuable in cancer therapy and other biomedical application.

7.1 Classification of Injectable Thermosensitive Hydrogels –

Injectable thermosensitive hydrogels can be classified based on their composition, properties, and applications:

1. **Based on Composition**
   - **Polymer-based hydrogels:** Prepared from synthetic or natural polymers, such as poly(N-isopropylacrylamide) (PNIPAM) or poly(ethylene glycol) (PEG).
   - **Polysaccharide-based hydrogels:** Derived from natural polysaccharides like hyaluronic acid or alginate, offering excellent biocompatibility.
2. **Based on Properties**
   - **Thermoresponsive hydrogels:** Capable of undergoing a reversible phase transition when exposed to temperature changes.
   - **Biodegradable hydrogels:** Designed to degrade naturally over time, thereby eliminating the need for surgical removal after treatment.
3. **Based on Applications**
   - **Cancer therapy:** Used for localized and sustained delivery of chemotherapeutic agents, reducing systemic side effects.
   - **Tissue engineering:** Serve as scaffolds to support tissue regeneration and repair in regenerative medicine.

9. Aim -

- Develop a localized, patient-friendly cancer therapy
- Achieve controlled and prolonged drug delivery
- Target tumour cells while sparing healthy tissues
- Reduce systemic toxicity of chemotherapy
- Enable co-delivery of chemo, gene or immunotherapy
- Ensure safe, biodegradable formulation
- Improve comfort and treatment adherence.

10. Objectives –

- Design sol-gel transition hydrogel formulations
- Provide sustained drug release at tumour site
- Improve tumour-specific drug accumulation
- Lower off-target drug exposure
- Integrate multifunctional therapeutic strategies
- Test for safety, stability, biodegradability
- Evaluate long-term clinical effectiveness. [8]

11. Needs -

- To reduce systemic side effects of conventional chemotherapy.
- To provide localized and minimally invasive drug delivery.
- To improve patient compliance and comfort.
- To effectively target the tumour microenvironment for enhanced treatment outcomes. [9]

12. Scope -

- Development of advanced thermosensitive hydrogel-based drug delivery systems.
- Application in solid tumour's where local therapy is most beneficial.
- Incorporation of multimodal therapies (chemotherapy, immunotherapy, gene therapy, photothermal therapy).
- Potential translation into personalized and clinical cancer treatment.[10]

13. Physicochemical Properties, Pre-clinical studies and Clinical Trials -

Injectable thermosensitive hydrogels are emerging as an innovative platform for cancer treatment due to their unique physicochemical properties. These hydrogels are typically formulated using biocompatible polymers, including poly(N-isopropylacrylamide) (PNIPAM), poloxamers, or poly(ethylene glycol)-based copolymers. At room temperature, these materials exist in a sol (liquid) state but transition to a gel state at physiological temperature (37 °C). This thermoresponsive characteristic facilitates minimally invasive injection, followed by in situ gelation at the tumor site, thereby ensuring localized and sustained drug delivery. Additionally, the biodegradability, porosity, swelling capacity, and mechanical strength of these hydrogels can be customized to optimize drug loading, release profiles, and interactions with the tumour microenvironment, ultimately enhancing therapeutic efficacy.

Preclinical studies have extensively explored thermosensitive hydrogels as carriers for chemotherapeutic drugs (such as doxorubicin and paclitaxel), immune modulators, and nucleic acids. Results from animal models indicate that these hydrogels improve drug accumulation within tumour's, extend retention at the tumour site, and minimize systemic toxicity when compared with free drug administration. In addition, multifunctional hydrogel systems that integrate photothermal agents or gene therapy components have demonstrated synergistic effects, leading to more effective tumour regression.

In the clinical setting, research has progressed to early-phase trials. For example, formulations such as OncoGel® (a paclitaxel-loaded thermosensitive hydrogel based on ReGel™ polymer) underwent phase I and II clinical studies, demonstrating safety and local tolerability in patients with esophageal and brain cancers, although further development faced challenges with large-scale efficacy outcomes. Ongoing investigations are focused on optimizing hydrogel formulations to improve stability, reproducibility, and scalability for translation into human use. These studies highlight the potential of thermosensitive hydrogels as an advanced localized therapy for solid tumour's, though more comprehensive clinical validation is required for widespread adoption. [11]

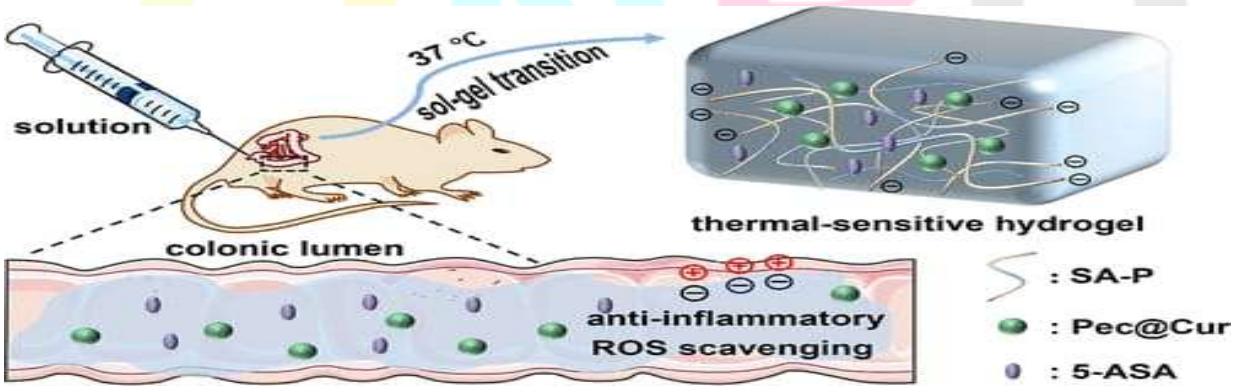

Fig. 4 Preclinical and Clinical Trials Studies

14. Mechanism of Action –

The mechanism of action of injectable thermosensitive hydrogels in cancer therapy is based on their ability to undergo a sol–gel transition in response to physiological temperature. At room temperature, the hydrogel exists in a liquid sol form, allowing it to be injected minimally invasively into the tumour site. Upon exposure to body temperature (≈37 °C), the polymer chains undergo conformational changes that lead to gelation, forming a semi-solid matrix in situ. This gel serves as a localized drug depot,

encapsulating chemotherapeutics, immunomodulators, or genetic materials. Drugs are then released in a controlled and sustained manner through diffusion, hydrogel swelling, or gradual polymer degradation. This localized release ensures a high concentration of drug at the tumour site, improving therapeutic efficacy, while significantly reducing systemic distribution and adverse effects associated with conventional chemotherapy. Furthermore, thermosensitive hydrogels can be engineered to respond to the tumour microenvironment (e.g., pH, enzymes, hypoxia), enhancing selective drug release. Multifunctional designs may also incorporate photothermal or immunotherapeutic agents, where the hydrogel matrix not only delivers the drug but also synergizes with external stimuli (light, heat) to induce tumour cell apoptosis. Overall, their mechanism integrates site-specific gelation, controlled release, and tumour-targeted activity, making them highly effective carriers for advanced cancer therapy. [12]

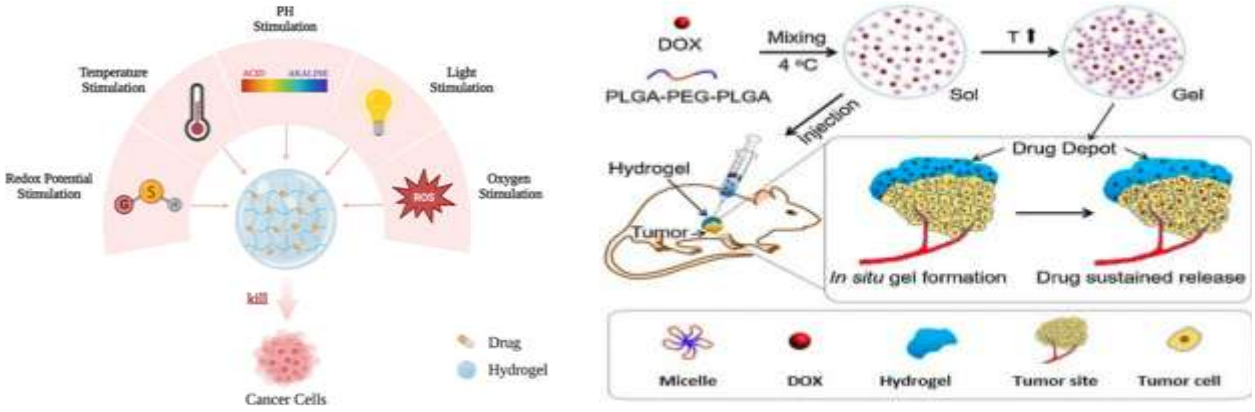

Fig. 5 Mechanism of Action

15. Types of Drug Delivery Systems Based on Injectable Thermosensitive Hydrogels in Cancer Therapy -

1. Chemotherapeutic Drug Delivery Systems

Encapsulation of drugs like doxorubicin, paclitaxel, and cisplatin.

Ensures sustained and localized release, improving tumour targeting while minimizing systemic toxicity.

2. Protein and Peptide Delivery Systems

Delivery of therapeutic proteins, antibodies, or cytokines for tumour immune modulation.

Maintains protein stability and allows controlled release in the tumour microenvironment.

3. Gene Delivery Systems

Hydrogels act as carriers for DNA, siRNA, or miRNA, protecting nucleic acids from degradation.

Enables localized gene therapy and silencing of oncogenic pathways.

4. Immunotherapy Delivery Systems

Hydrogel matrices are loaded with immune checkpoint inhibitors, vaccines, or adjuvants.

Enhances localized immune response while limiting systemic side effects.

5. Combination / Multifunctional Delivery Systems

Co-delivery of chemotherapy with immunotherapy, radiotherapy, or photothermal/photodynamic therapy.

Produces synergistic therapeutic outcomes and overcomes tumour resistance.

6. Stimuli-Responsive Delivery Systems

Hydrogels designed to respond not only to temperature, but also to pH, enzymes, hypoxia, or redox conditions in tumour's.

Enables on-demand, smart drug release specifically at the tumour site. [13]

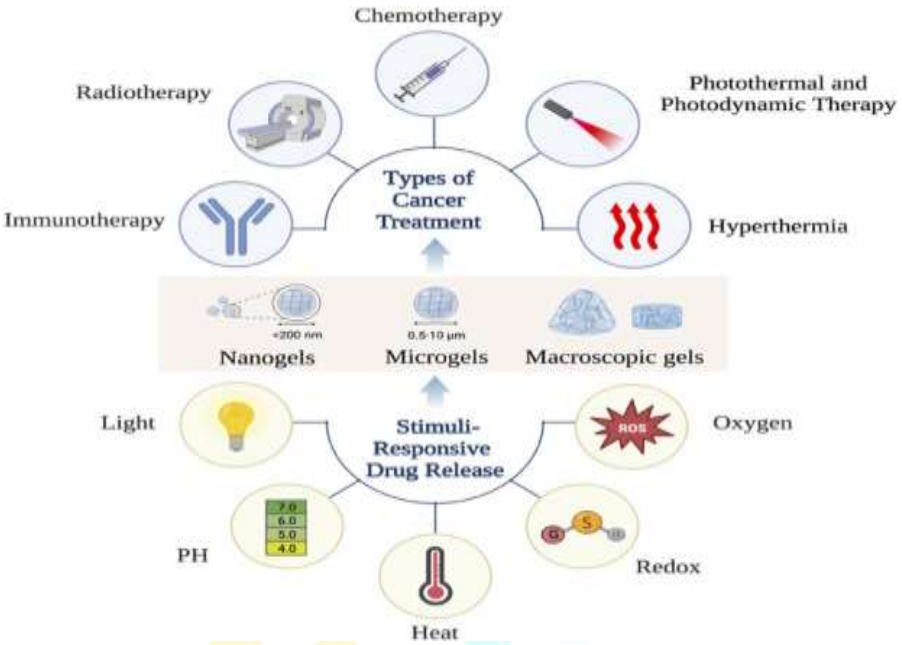

Fig. 6 Types of Cancer Treatments

16. Advantages -

- Localized Drug Delivery
- Controlled Release
- Targeted Therapy
- Biocompatibility
- Simple Administration
- Improved Patient Compliance
- Enhanced Therapeutic Efficacy [14]

17. Limitation –

- Narrow gelation temperature window and gelation kinetics
- Poor mechanical strength and fast erosion in vivo
- Burst release of drugs or poor release of macromolecules
- Limited drug loading capacity and compatibility issues
- Difficulty in controlling degradation rate and by-products
- Tumour microenvironment barriers (high pressure, dense ECM) limiting penetration
- Heterogeneity across patients and tumour sites affects efficacy
- Lack of real-time monitoring of gel placement and drug release
- Challenges in sterilization, large-scale manufacturing, and reproducibility
- Limited clinical translation and safety data compared to preclinical studies

18. Challenges -

- Scalability and Reproducibility
- Regulatory Hurdles

- Tumour Heterogeneity

- Limited Penetration

- Biocompatibility and Biodegradability

- Controlled Release

- Administration and Distribution

- Toxicity and Side Effects

- Cost and Complexity [15]

19. Applications -

1. Localized chemotherapy delivery – sustained release of anticancer drugs directly at the tumour site to minimize systemic toxicity.

2. Post-surgical tumour recurrence prevention – filling irregular tumour resection cavities with drug-loaded hydrogels to kill residual cancer cells.

3. Photothermal and photodynamic therapy support – incorporation of photothermal agents or photosensitizers for light-triggered tumour ablation.

4. Radiotherapy enhancement – as carriers of radiosensitizers to improve local tumour control.

5. Immunotherapy delivery – local release of cytokines, immune checkpoint inhibitors, or vaccines to modulate the tumour immune microenvironment.

6. Gene and nucleic acid delivery – delivery of siRNA, miRNA, or plasmids for targeted gene therapy in tumour's.

7. Combination therapy platforms – co-loading of multiple agents (e.g., chemo + immuno + photo agents) for synergistic anti-tumor effects.

8. Theranostic applications – integration with imaging agents or nanoparticles for real-time monitoring and therapy. [16]

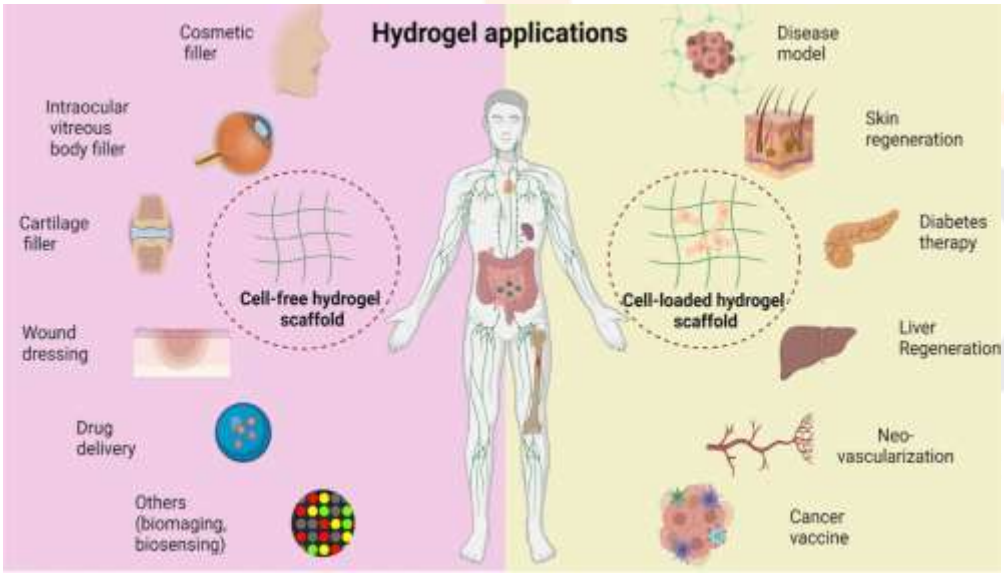

Fig. 7 Application of Hydrogels

19. Materials -

19.1. Polymers : -

1. PNIPAM (Poly(N-isopropylacrylamide)): A thermosensitive polymer that exhibits a phase transition at around 32°C, making it suitable for injectable hydrogel applications. PNIPAM is hydrophilic below its lower critical solution temperature (LCST) and becomes hydrophobic above it, allowing for controlled release of therapeutic agents.

2. PEG (Polyethylene Glycol): PEG is a biocompatible and highly hydrophilic polymer that is often incorporated into thermosensitive hydrogels to modify their physicochemical properties. The addition of PEG enhances the overall stability and biocompatibility of the hydrogel, reducing the risk of immune reactions and making it well-suited for biomedical applications. Moreover, PEG can help fine-tune the thermosensitive behaviour of hydrogels, improving their performance in controlled drug delivery systems for cancer therapy.

3. PLA (Polylactic Acid): A biodegradable and biocompatible polymer that can be used to form thermosensitive hydrogels. PLA can be degraded by hydrolysis, making it suitable for applications where biodegradability is desired.

4. Poly(lactic-co-glycolic acid) (PLGA): PLGA is a biodegradable and biocompatible polymer widely used in the design of thermosensitive hydrogels. One of its key advantages is the ability to tailor its degradation rate by adjusting the ratio of lactic acid to glycolic acid, allowing precise control over drug release kinetics. This makes PLGA-based hydrogels particularly suitable for controlled and sustained delivery of therapeutic agents in cancer therapy and other biomedical applications.

19.2. Cross-linkers : -

1. Glutaraldehyde: A chemical cross-linker that can be used to form covalent bonds between polymer chains, enhancing the mechanical strength of hydrogels. Glutaraldehyde can be used to cross-link polymers with amine groups, forming stable and durable hydrogels.

2. Genipin: A natural cross-linker that can be used to form hydrogels with improved biocompatibility and mechanical properties. Genipin can cross-link polymers with amine groups, forming stable and biocompatible hydrogels.

19.3. Solvents : -

1. Water: A common solvent used to dissolve polymers and therapeutic agents for hydrogel formation.

2. Phosphate-buffered saline (PBS): A biocompatible solvent that can be used to simulate physiological conditions for hydrogel testing**.**

3. Dimethyl sulfoxide (DMSO): A polar solvent that can be used to dissolve hydrophobic therapeutic agents and polymers.

19.4 Therapeutic Agents : -

1. Doxorubicin: A chemotherapeutic agent that can be loaded into thermosensitive hydrogels for localized cancer treatment. Doxorubicin can be released in a controlled manner, reducing systemic side effects and improving treatment efficacy.

2. Cisplatin: A chemotherapeutic agent that can be loaded into thermosensitive hydrogels for localized cancer treatment. Cisplatin can be released in a controlled manner, reducing systemic side effects and improving treatment efficacy.

19.5 Other Materials : -

1. Nanoparticles: Nanoparticles can be used to enhance the delivery and efficacy of therapeutic agents. Nanoparticles can be loaded into thermosensitive hydrogels, allowing for controlled release and targeted delivery.

2. Micelles: Micelles can be used to solubilize hydrophobic therapeutic agents, improving their delivery and efficacy. Micelles can be loaded into thermosensitive hydrogels, allowing for controlled release and targeted delivery. [17]

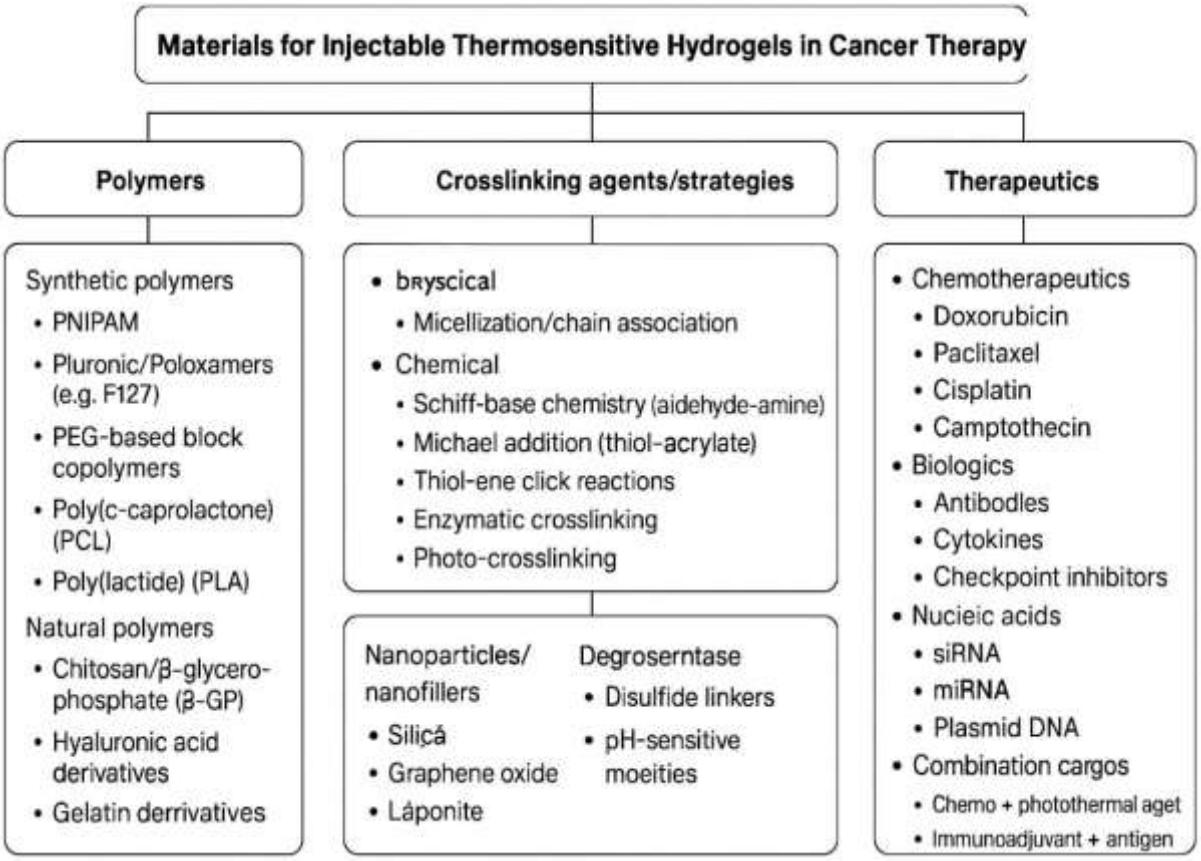

Fig. 8 Materials used in Injectable Thermosensitive Hydrogels

20. Methods -

1. Polymerization : -

The first step in preparing injectable thermosensitive hydrogels is polymerization. This involves mixing monomers, such as N-isopropylacrylamide (NIPAM), with initiators, such as ammonium persulfate, and allowing the polymerization reaction to proceed. The resulting polymer, such as poly(N-isopropylacrylamide) (PNIPAM), exhibits thermosensitive properties, meaning it undergoes a phase transition in response to changes in temperature.

2. Cross-Linking

Following polymerization, cross-linking is carried out to strengthen the hydrogel structure. This process entails the establishment of covalent bonds among polymer chains, resulting in the formation of a three-dimensional network. that enhances the stability and durability of the hydrogel. Chemical cross-linkers, such as glutaraldehyde, are often employed to achieve this interconnected structure, ensuring the hydrogel maintains its integrity during drug loading and release.

3. Hydrogel Preparation : -

Once the polymer has been synthesized and cross-linked, the hydrogel can be prepared. This involves dissolving the polymer in a solvent, such as water or phosphate-buffered saline (PBS), and allowing the polymer to form a gel-like structure. The resulting hydrogel can be designed to exhibit specific properties, such as thermosensitivity, biocompatibility, and biodegradability.

4. Synthesis Methods : -

There are several synthesis methods that can be used to prepare injectable thermosensitive hydrogels, including:

1. **Free Radical Polymerization:**
   This technique uses free radical initiators to polymerize monomers into long polymer chains. The resulting polymers can then be cross-linked to form a three-dimensional hydrogel network. Free radical polymerization is widely employed due to its simplicity, versatility, and ability to produce hydrogels with tunable mechanical and chemical properties suitable for biomedical applications.
2. **Click Chemistry:**
   Click chemistry involves highly efficient, specific chemical reactions to form polymers or cross-link polymer chains. This method allows precise control over the hydrogel's structure and functionality, enabling the creation of robust, biocompatible hydrogels with customizable properties for targeted drug delivery and other therapeutic applications.

5. Characterization Methods : -

After preparing the hydrogel, several characterization methods can be used to evaluate its properties, including:

1. Dynamic Light Scattering (DLS): This method involves measuring the size and distribution of polymer particles or hydrogel networks.

2. Rheology: This involves measuring the mechanical properties of hydrogels, such as storage and loss modulus, to assess stiffness, elasticity, and viscoelastic behavior for optimal performance in drug delivery.

3. Scanning Electron Microscopy (SEM): This method involves visualizing the morphology and structure of hydrogels.

6. Injectability Testing : -

Injectability testing is used to evaluate the ability of the hydrogel to be injected through a needle or syringe. This involves measuring the flow properties of the hydrogel and evaluating its ability to withstand shear stress.

7. Stability Testing : -

Stability testing is used to evaluate the stability and degradation of hydrogels over time. This involves measuring the weight loss, mechanical properties, and morphology of the hydrogel over time.

8. In Vitro and In Vivo Testing : -

Finally, in vitro and in vivo testing can be used to evaluate the biocompatibility, efficacy, and safety of hydrogels. This involves testing the hydrogel in cell culture or animal models to evaluate its performance and potential side effects. [18]

9. Sterilization Methods : -

Sterilization is a crucial step in preparing injectable thermosensitive hydrogels to eliminate microorganisms and prevent contamination. The process typically includes preparation, sterilization, and verification. Preparation ensures the hydrogel is clean and free of visible contaminants. Sterilization can be performed using methods such as autoclaving, gamma irradiation, ethylene oxide, filtration, or ultraviolet (UV) light. For instance, autoclaving exposes the hydrogel to high-pressure steam at 121 °C for 15–30 minutes, while gamma irradiation uses ionizing radiation (10–50 kGy). Verification involves confirming sterility after treatment to ensure the hydrogel is safe for clinical use..

10. Drug Loading and Release in Thermosensitive Hydrogels -

Thermosensitive hydrogels are effective drug delivery systems due to their ability to undergo phase transitions with temperature changes. Drugs can be incorporated via physical encapsulation, where they are trapped within the hydrogel during gelation, or chemical conjugation, where they are covalently bound to the hydrogel network. Drug release can occur through diffusion**,** hydrogel degradation, or stimuli-responsive mechanisms triggered by temperature. Designing hydrogels for optimal drug delivery requires careful consideration of composition, crosslinking density, and degradation rates to achieve effective and sustained therapeutic outcomes.

11. Packaging and Storage of Thermosensitive Hydrogels -

Thermosensitive hydrogels require careful packaging and storage to maintain their stability, efficacy, and sterility. The packaging material should be compatible with the hydrogel and protect it from environmental factors such as moisture, light, and temperature fluctuations. Storage conditions should be controlled to prevent degradation or premature gelation. This includes storing the hydrogel at a consistent temperature, minimizing light exposure, and maintaining humidity control. Proper packaging and storage are crucial for ensuring the quality and performance of thermosensitive hydrogels. [21]

12. Regulation of Thermosensitive Hydrogels -

Thermosensitive hydrogels are subject to regulatory oversight to ensure their safety and efficacy for biomedical applications. Regulatory agencies evaluate these hydrogels based on their intended use, manufacturing process, and performance characteristics. Key regulatory considerations include biocompatibility, sterility, and controlled manufacturing processes. Thermosensitive hydrogels must comply with regulatory requirements for labelling and packaging. The regulatory pathway for these hydrogels may involve 510(k) clearance, PMA approval, or IDE approval, depending on the device's risk classification and substantial equivalence to existing devices. [22]

21. Evaluation of Thermosensitive Hydrogels -

Thermosensitive hydrogels require comprehensive evaluation to ensure their quality, safety, and efficacy for biomedical applications. The evaluation process involves assessing their physical, chemical, and biological properties.

Evaluation Parameters : -

21.1 Thermoresponsive behaviour : -

Determine the lower critical solution temperature (LCST) or upper critical solution temperature (UCST).

1. Differential Scanning Calorimetry (DSC): Measure the heat flow associated with phase transitions.

- Prepare hydrogel samples.
- Run DSC experiment.
- Analyse thermogram.

2. Dynamic Light Scattering (DLS): Determine the hydrodynamic size and size distribution.

- Prepare hydrogel samples.
- Run DLS experiment.
- Analyse size distribution.

21.2 Mechanical Properties : -

Evaluate the hydrogel's mechanical strength, elasticity, and durability.

1. Dynamic Mechanical Analysis (DMA): Evaluate the hydrogel's viscoelastic properties.

- Prepare hydrogel samples.
- Run DMA experiment.
- Analyse storage modulus (G') and loss modulus (G").

2. Rheometry: Assess the hydrogel's rheological properties.

- Prepare hydrogel samples.
- Run rheometry experiment.
- Analyse viscosity and shear stress.

21.3 Biocompatibility : -

Assess the hydrogel's biocompatibility through in vitro and in vivo studies

1. **In Vitro Cytotoxicity Tests:** Assess cell viability using MTT assay or Live/Dead assay.
   - Prepare hydrogel extracts.
   - Culture cells with extracts.
   - Analyse cell viability.
2. **In Vivo Studies:** Evaluate biocompatibility in animal models.
   - Implant hydrogels in animals.
   - Monitor animal response.
   - Analyse tissue response.

21.4 Degradation Profile : -

Study the hydrogel's degradation rate and mechanism.

1. **Gel Permeation Chromatography (GPC):** Determine molecular weight changes.
   - Prepare hydrogel samples.

- Run GPC experiment.

- Analyse molecular weight distribution.

2. **Spectroscopy:** Study degradation mechanisms using techniques like FTIR or NMR.

- Prepare hydrogel samples.

- Run spectroscopy experiment.

- Analyse spectral changes. [23]

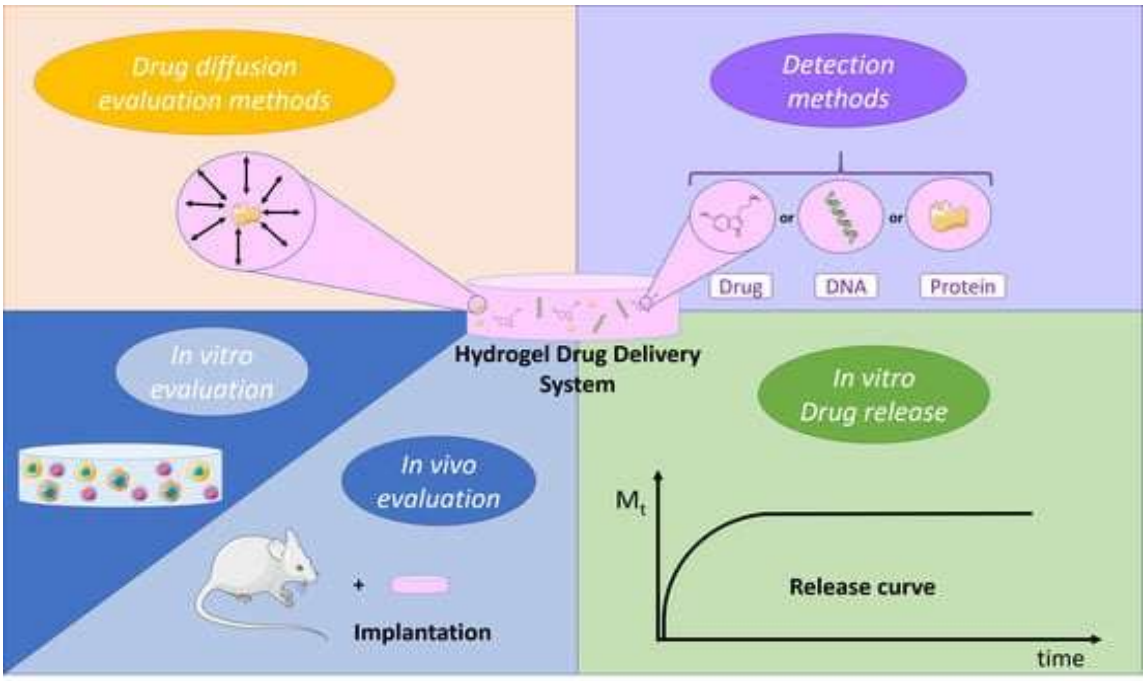

Fig. 9 Evaluation Parameters of Thermosensitive Hydrogels

22. Results and Discussion -

Extensive review on injectable thermosensitive hydrogels has established their potential as localized drug delivery systems for cancer therapy. The fundamental outcome reported in multiple studies is their ability to undergo a reversible sol–gel transition in response to temperature, remaining in a fluid state at room temperature and transforming into a gel upon exposure to body temperature. This property facilitates minimally invasive administration through conventional syringes while ensuring rapid depot formation at the tumour site. The in situ formed hydrogel acts as a drug reservoir, prolonging residence time and providing sustained release of therapeutic agents. Materials such as poly(N-isopropylacrylamide) (PNIPAM), Pluronic®-based copolymers, chitosan/β-glycerophosphate systems, and poly(organophosphazenes) have consistently demonstrated gelation in the physiological range of 30–37 °C, confirming their suitability for clinical applications.

Evaluation of gelation temperature and gelation time is a critical parameter in determining therapeutic applicability. Hydrogels must gel rapidly once injected into the tumour microenvironment to prevent drug leakage and ensure localized action. Rheological studies confirm that properly designed formulations achieve sol–gel transition within minutes under physiological conditions. Alongside gelation behaviour, injectability is another essential evaluation parameter. Syringeability tests, usually quantified as extrusion force through fine-gauge needles, demonstrate that formulations with lower viscosity at ambient temperature are easier to inject while still forming strong gels at body temperature. An optimal balance between low viscosity for administration and high mechanical stability after gelation is consistently highlighted in the literature.

The mechanical strength of the hydrogel, often assessed by rheological parameters such as storage modulus and loss modulus, directly influences depot stability. Stronger gels resist physiological shear forces and retain the drug depot at the target site, whereas weaker formulations may degrade prematurely, leading to uncontrolled drug release. Closely related to mechanical performance are the swelling and degradation properties of hydrogels. Swelling behaviour affects drug release kinetics, while degradation rate determines the duration of therapeutic activity. In vitro degradation studies using enzymatic and hydrolytic conditions have shown that degradation profiles can be tuned from days to months depending on polymer structure and crosslinking density.

Another crucial evaluation parameter is drug loading and release profile. Effective hydrogels achieve high encapsulation efficiency and predictable release behaviour. Most studies report biphasic release kinetics, with an initial burst release followed by prolonged,

near zero-order release. This release pattern ensures immediate therapeutic action along with long-term tumour suppression. Hydrophobic drugs such as paclitaxel or doxorubicin show particularly favourable release profiles due to their affinity for hydrophobic domains within the polymer matrix, while hydrophilic molecules often require chemical or ionic modifications to reduce premature leakage.

The in vitro biocompatibility and cytotoxicity of hydrogel formulations are evaluated through cell-based assays. Typically, blank hydrogels without drug loading exhibit minimal cytotoxic effects on normal cells, confirming material safety, while drug-loaded formulations retain their anticancer efficacy. Complementing in vitro testing, in vivo biocompatibility is usually assessed through histological studies, which often reveal only mild, transient inflammation at the injection site that resolves as the hydrogel degrades. This suggests a generally favourable safety profile, although long-term studies are still limited.

In vivo antitumour efficacy is a defining parameter in hydrogel evaluation. Preclinical studies in murine and xenograft tumour models consistently demonstrate that hydrogel-mediated local delivery of chemotherapeutics results in greater tumour volume reduction, delayed tumour recurrence, and improved survival compared to equivalent systemic doses. Importantly, local hydrogel delivery also minimizes systemic exposure and associated toxicities, as evidenced by reduced alterations in liver and kidney function markers. Pharmacokinetic and biodistribution studies further confirm higher local drug concentrations and sustained exposure at the tumour site, alongside reduced systemic circulation levels.

Recent investigations have expanded the scope of thermosensitive hydrogels by integrating multifunctional evaluation endpoints, including their ability to deliver combination therapies. Studies with dual-loaded hydrogels containing chemotherapeutics and immunomodulators have shown synergistic tumour suppression and systemic immune activation. Similarly, incorporation of photothermal agents or gene therapy vectors has been evaluated for combined chemo-photothermal or gene-enhanced therapies, with promising results in tumour regression and metastasis control. Evaluation of such multifunctional systems often incorporates advanced imaging modalities, such as fluorescence and MRI, to monitor depot stability and release dynamics in real time.

Overall, the results of preclinical evaluations strongly support the application of injectable thermosensitive hydrogels for cancer therapy. Their performance across critical parameters such as gelation behaviour, injectability, mechanical strength, degradation, drug loading efficiency, release kinetics, and in vivo antitumour efficacy highlights their therapeutic potential. However, the discussion of these results also underscores significant challenges. Tumour heterogeneity, variable interstitial pressures, and dense extracellular matrices can influence hydrogel distribution and drug penetration. Furthermore, reproducibility of formulations, scalability of production, and sterilization compatibility remain important barriers to clinical translation.

In conclusion, the evaluation parameters collectively indicate that injectable thermosensitive hydrogels represent a highly promising strategy for localized cancer therapy. They provide sustained release, enhanced local bioavailability, and reduced systemic toxicity, with additional potential for multimodal and image-guided therapeutic applications. Future research should prioritize long-term safety studies, standardized evaluation protocols, and translational studies in clinically relevant models to accelerate the movement of these hydrogels from bench to bedside.

23. Conclusion -

Injectable thermosensitive hydrogels have emerged as a powerful and innovative tool in modern cancer therapy. Their ability to undergo a temperature-triggered sol–gel transition enables localized and sustained release of therapeutic agents, including chemotherapeutics, immunotherapies, and other targeted molecules. This minimally invasive delivery system not only improves patient comfort but also reduces treatment-related complications. By ensuring high drug concentrations at the tumour site while limiting systemic exposure, these hydrogels significantly enhance therapeutic outcomes and reduce toxicity. Ongoing research is vital to further optimize their design, stability, and multifunctionality, ultimately advancing their clinical translation as a next-generation platform for effective and patient-friendly cancer treatment.

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