RESEARCH PAPER

Hydrogel Technology in Oncology: From Sustained Drug Release to Tumor Responsive Therapeutics

Tanisha Goyal[1], Tarun Parashar[1*], Kanchan Singh[1] , Achal Tadas[2]
[1]School of Pharmacy and Research,
Dev Bhoomi Uttarakhand University, Dehradun, Uttarakhand – 248007
Email Id: parashar89tarun@gmail.com, ORCHID id: 0000-0002-8250-5859, Mobile no.: 8006939831.
[2]JBIT College of Pharmacy,
23 Milestone, NH-07, Chakrata road,
Shankarpur, Dehradun, Uttarakhnd, 248197, India.

ABSTRACT
Cancer is a complicated illness that poses a significant threat to world health. Traditional treatments such as immunotherapy, chemotherapy, and surgery have advanced, but problems such drug resistance, recurrence of cancer, and severe side effects still exist. Stimulus-responsive nanomedicines present a viable means of enhancing the effectiveness of cancer therapies while mitigating side effects. The high-water content of hydrogels makes them distinct from other types of nanocarriers, mechanically tunnelable characteristics, and responsiveness to both internal and external stimuli. Because of these properties, hydrogels are a good choice for targeted drug release in the tumor microenvironment (TME). The many biological, chemical, and physical stimulus-responsive mechanisms are covered in this review along with the advancements and difficulties that have been made in the use of hydrogels in management of cancer to date.
Keywords: Cancer, Hydrogels, Chemotherapy, Treatments.
How to cite this article: Goyal T, Parashar T, Singh K, Tadas A. Hydrogel Technology in Oncology: From Sustained Drug Release to Tumor Responsive Therapeutics. Int J Drug Deliv Technol. 2026;16(41s): 731-743. DOI: 10.25258/ijddt.16.41s.80

1. INTRODUCTION

Cancer is a disease that affects the entire ecosystem of the body by gradually disrupting immunological, metabolic, neuroendocrine, and perhaps microbial functions [1]. Cancer is aggressive and may impair the immune system [2]. Over half of individuals under 65 will develop cancer, but early detection and effective treatment save millions. Cancer's high death rates are a global health concern, with the United States reporting 1,958,310 new cases and 609,820 deaths in 2023 [3]. When healthy cells in one area of the body begin to proliferate uncontrolled, cancer results [4]. Cancer, a disorder characterized by abnormal cell proliferation, can be caused by genetic or epigenetic alterations in the body's cells. A subgroup of neoplasms is formed by this aberrant development when uncontrolled cell proliferation results in a lump or mass that may be dispersed widely. By 2025, estimates based on global demographics indicated that there would be a rise in the incidence of cancer, with an estimated 420 million new cases yearly. In 2018, around 18 million global cancer cases were reported, with 9.5 million cases involving males and 8.5 million involving women [5]. Cancer can be caused by a variety of processes that modify DNA, including mutations, errors in DNA replication, chromosomal recombination, epigenetic modifications, and exposure to environmental and hormonal stimuli. Oncogenes like ras and c-myc may become more active as a result of these alterations, whilst the activity of tumor suppressor genes like PTEN and P53 as well as apoptosis-related genes like Bax and Caspases may decrease. Additionally, within a 1-2 mm radius, cancer cells can diffusely take up nutrition and oxygen. After this, they start to produce different growth factors, which cause localized blood vessels to develop. Furthermore, cancer cells modify their rate of metabolism (anaerobic or aerobic) based on oxygen availability. Moreover, cancer cells have an important trait which is immune system evasion [6-7] Conventional therapies like radiotherapy, chemotherapy, and surgery have been applied extensively. On the other hand, current developments include radionics, stem cell therapy, chemo dynamic treatment, sonodynamic therapy, ablation therapy, targeted therapy, nanoparticles, ferroptosis-based therapy, and natural antioxidants. Creating secure and efficient cancer nanomedicines is the main goal of current oncology techniques [8]. By influencing disease's bioelectrical characteristics, bioelectronic medicine employs the body's electrical communication networks to treat conditions like cancer. This approach has transformed medicine by using neuromodulation to target specific diseases. Biomarker analysis provides point-of-care application, speed, and precision in tumour biomarker identification through the use of biosensors. Bioelectronic medicine is a new method to cancer detection and therapy that enhances patient outcomes and quality of life [9].

1.1. Cancer Proliferation and Spread

• Abnormal Cell Division: In accordance with their life

cycle, cells grow, divide, and replace damaged ones. But this process is hampered by cancer, which is brought on by DNA alterations. Mutations allow cells to proliferate unnecessarily and survive when they ought to die, leading to uncontrolled growth and the development of tumors.

• Tumor Formation: Not all tumors are malignant, yet they can still cause health issues. While malignant tumors spread to nearby tissues and may result in more serious problems, benign tumors stay localised.

• Metastasis: This is the process by which cancer cells travel through the lymphatic or circulatory systems. Metastatic malignancies are more advanced, more difficult to cure, and frequently have worse death rates [10]. Cancer is caused by the interaction of three different chemical types we consume from the outside, which interact with genetic variables.

These groupings are:

I. Physical Carcinogens: Ionising radiation, which includes radon, uranium, sunlight's UV rays, and radiation from sources that release X, beta, and gamma radiation.

II. Chemical Carcinogens: Substances that contain around 60 known powerful carcinogens or toxins that are obtained via smoking cigarettes or consuming tobacco products, including vinyl chloride, n-nitrosamines, cadmium, asbestos, benzene, benzidine, and nickel. These also include food and drinking water pollutants like arsenic. (aflatoxin).

III. Biological Carcinogens: Pathogens such as Merkel cell polyomavirus, Epstein-Barr virus (EBV), hepatitis B and C, helicobacter pylori, microstosoma species, Kaposi's sarcoma-associated herpesvirus (KSHV) and human papillomavirus (HPV) [5]. Furthermore, cancer is also brought on by aging. As people age, the common occurrence of cancer increases considerably. The most frequent cause of cancer is heredity, which can result in colon, ovarian, breast, prostate, and tumor-like skin cancers. High-temperature-formed chemicals also raise the risk for those who eat a lot of cooked meat. It is challenging to demonstrate that a chemical does not contribute to or is not linked to an increased risk of cancer [5].

1.2. Cancer Types

1. Carcinomas: These malignancies begin as solid tumors in the tissues or skin that cover the surfaces of internal organs and glands. Prostate cancer, colorectal cancer, breast cancer, and lung cancer, are a few examples.

2. Sarcomas: This kind of cancer starts in the connective and supporting tissues of the body, including muscles, cartilage, blood vessels, tendons, joints, nerves, and fat.

3. Leukemia: When healthy blood cells proliferate out of control, leukemia, a blood cancer, develops. Acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, and chronic lymphocytic leukemia, are all included.

4. Lymphoma: The lymphatic system, which aids in the defence against infection, is the origin of lymphomas. Both Hodgkin lymphoma and non-Hodgkin lymphoma fall under this category of malignancy.

5. CNS Cancer: These malignancies start in the tissues of the brain and spinal cord. They include meningiomas, spinal cord tumors, vestibular schwannomas, gliomas, primary CNS lymphomas, pituitary adenomas, and brain tumors.

6. Multiple Myeloma: The cancerous growth starts in plasma cells, which then gather in the bone marrow to create tumors within the bones. It is sometimes referred to as Kahler disease and plasma cell myeloma.

7. Melanoma: Cells that differentiate into melanocytes specialized cells that make melanin are the source of melanoma. Although they can sometimes arise in other pigmented tissues, such as the eye, melanomas usually first appear on the skin.

8. Other Tumor Types: Germ Cell Tumors start in the cells that develop into sperm or eggs. They may be benign or cancerous, and they can appear anywhere in the body [5].

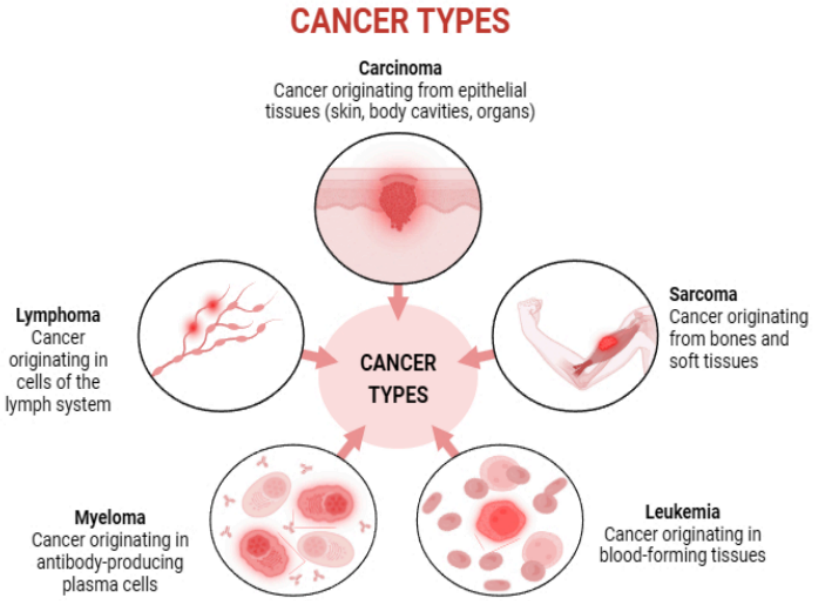

Fig. 1. shows various types of cancer

1.3. Cancer Symptoms & Signs

Early Symptoms of Cancer:

- Regular coughing or blood in the saliva
- Bowel movements or blood in the stool
- Inexplicable anaemia
- Urination changes
- Weight loss
- Stomach discomfort and nausea
- Pain in bones

Later Symptoms:

- An observable variation of a mole's or wart's size, colour, shape, or thickness.
- Heartburn or trouble swallowing
- Sore throat
- Dry mouth
- A tumor or thickening in the testicles or breast
- Fatigue
- Fever
- Aches in the limbs and other body regions [5].

1.4. Risk Factors of Cancer

Several variables affect a person's likelihood of acquiring cancer, and it's important to recognize these risk factors. The following are a few typical risk factors that might raise your chance of getting cancer:

• **Tobacco Use:** Using tobacco products and smoking raises the risk of cancer.

• **Heavy Alcohol Use:** Drinking too much alcohol increases your chance of developing several malignancies.

• Insufficient Exercise: Living a sedentary lifestyle raises the risk of cancer.

• **Air Pollution Exposure:** Prolonged exposure to air pollution may increase the risk of lung cancer.

• Radiation Exposure: Radiation exposure from medical or occupational sources can raise the risk of cancer.

• **Unprotected UV Light Exposure:** Skin cancer has been related to prolonged exposure to sunshine and tanning salons.

1.5. Cancer diagnosis

1. Lab tests evaluate chemicals that cause cancer in the body, such as abnormal amounts of compounds that cause cancer. These tests include testing on urine, blood, and other bodily fluids.

2. To identify tumors, imaging tests provide images of the inside of the body. These diagnostic procedures might involve positron emission tomography (PET), ultrasound, bone scans, computerized tomography (CT), X-rays, and magnetic resonance imaging (MRI).

i. CT scan: This scan creates three-dimensional (3D) pictures of organs from various angles using X-ray equipment connected to computers. To improve the pictures, a contrast agent may be given prior to the scan. A machine shaped like a doughnut is used to do the scan, and it rotates around the body.

ii. MRI: This scan produces finely detailed pictures of bodily organs in slices using radio waves and a strong magnet. An MRI may need the administration of a contrast substance beforehand, much like a CT scan. A loud pounding noise and rhythmic pulses are produced during the scan, which is carried out in a round chamber equipment.

iii. Nuclear Scan: Also referred to as a radionuclide scan, this examination produces pictures of bodily organs by using radioactive material. The patient receives a little injection of a tracer, which is a radioactive substance. The substance enters the bones through the circulation and accumulates there. The radioactivity is then measured by the scanner to provide pictures of the bones or organs.

iv. Bone Scan: This scan is used for injury or any bone abnormalities. A small amount of radioactive material is introduced into the patient's vein before to the scan. A specialised scanner may detect abnormal locations in the bones where the material accumulates after passing through the blood and identifying them as "hot spots".

v. PET Scan: As the cancer cells need more glucose than healthy cells, this scan employs a radioactive glucose substance to provide 3D pictures of bodily organs.

vi. Ultrasound: Computers employ high-energy sound waves to create tissue echoes, which are then used to produce pictures of bodily parts. The transducer, an ultrasonic tool, is gently pushed across the skin to produce an image that is referred to as a sonogram.

vii. X-rays: Images of bodily organs are produced using low radiation dosages. The patient must remain still and hold their breath for one to two seconds while the X-ray beam is focused on the desired body location.

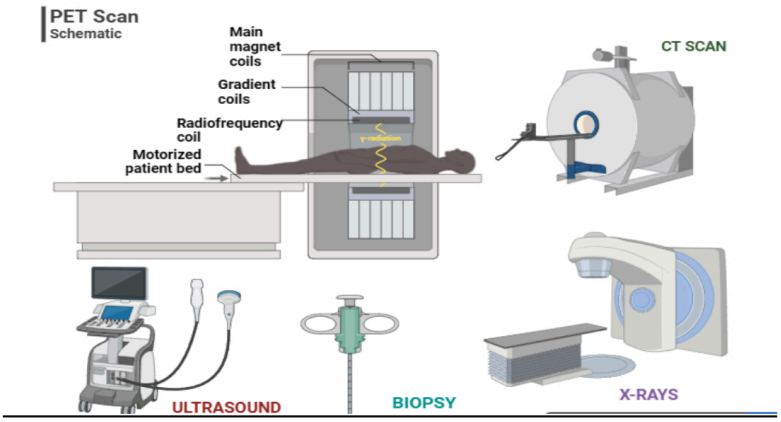

Fig. 2. shows different techniques of cancer detection

3. A biopsy is a process used to identify cancer by taking a tissue sample from the patient's body. A pathologist uses a

microscope to analyse the tissue, documenting the findings in a pathology report. A biopsy sample can be obtained in a number of ways:

i. With Needle: This technique is used for a number of biopsies, including spinal taps, bone marrow aspirations, and biopsies of the prostate, liver, and breast. It involves taking a needleful of fluid or tissue from the body.

ii. Endoscopy: This technique uses a narrow, illuminated tube called an endoscope to inspect internal body parts through naturally occurring openings in the body like the mouth or anus. During the examination, if the physician finds any abnormal tissue, they remove it.

iii. Through Surgery: Excisional (removal of the complete abnormal cell region together with some normal cells) or incisional (removal of a small portion of an abnormal area) surgical methods can be used to eliminate abnormal cells. Before biopsies, patients are given anaesthesia and sedatives to help them rest [5].

1.6. Cancer Treatment

1. Surgery
2. Radiotherapy
3. Chemotherapy
4. Bone marrow transplant
5. Immunotherapy
6. Targeted therapy
7. Hormone therapy
8. Cryosurgery
9. Photodynamic therapy
10. Peripheral stem cell transplant [11].

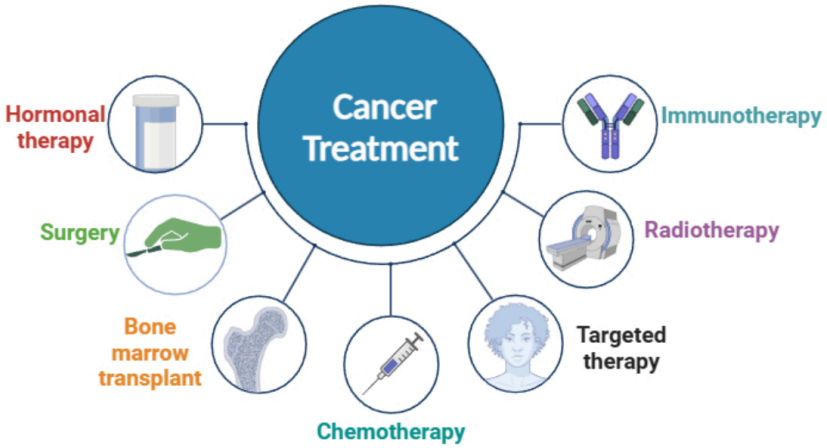

Fig. 3. Cancer Treatment Options

1) Surgery: Expert oncologists frequently employ this technique to remove a malignant tumor from the body along with any surrounding tissues. Tumor removal is the major purpose of this therapy for local malignancies.

2) Radiation Therapy: Radiation therapy uses high-energy particles or waves like protons, gamma rays, electron beams or X-rays to destroy cancer cells.

3) Chemotherapy: To destroy cancer cells, doctors employ medications and other substances in this procedure. Since chemotherapy enters the circulation and has the potential to impact the entire body, it can treat tumors that have spread.

4) Bone Marrow Transplant: A bone marrow transplant (BMT) replaces damaged bone marrow with healthy stem cells to treat malignancies, such as lymphoma, leukemia, immune deficiency diseases, aplastic anaemia, and certain solid tumor cancers.

5) Immunotherapy: It boosts the immune system's ability to fight diseases like cancer.

6) Targeted Therapy: The goal of this therapeutic approach is to target particular chemicals and substances that stimulate the growth and division of cancer cells. It provides a more accurate means of treating illness while minimising damage to healthy cells.

7) Hormone therapy: It can be used for malignancies like the prostate and breast that are susceptible to hormones. This course of medication prevents the growth-promoting natural hormones.

8) Cryosurgery: Cryosurgery, also known as cryotherapy, is a helpful treatment for premalignant and benign lesions. It's a quick process that allows treating several lesions in one visit. The degree of tissue loss may be predicted based on the length of freezing (freeze time), the amount of thawing time (time until the ice ball defrosts), and the halo diameter, or the perimeter of frozen tissue around the lesion. Cryo Tweezers and liquid nitrogen probes are two more cryosurgery techniques [12].

9) Photodynamic therapy (PDT): It has special benefits over traditional therapies. By combining photosensitising chemicals with light activation, cancer cells can be specifically and locally destroyed with less harm to the surrounding healthy tissues [13]. Reactive oxygen species (ROS), which have the ability to kill cancer cells, are produced when the photosensitiser is exposed to light in the presence of oxygen. PDT may be impeded by intrinsic multidrug resistance (MDR) pathways in cancer cells, as is the case with many other cancer therapies [14].

10) Peripheral stem cell transplant: A peripheral stem cell transplant (PBSCT) is a surgical technique in which healthy stem cells are used to replace a patient's damaged or sick blood-forming stem cells. PBSCTs are utilised in the

treatment of autoimmune diseases, blood problems, and certain cancers. Through this treatment, patients can safely undergo high doses of radiation therapy and chemotherapy, which can harm good cells in addition to destroying cancerous ones. Because these cells develop into several blood cell types, such as red blood cells, white blood cells, and platelets, PBSCTs restore the patient's capacity to make blood. PBSCT uses autologous or allogeneic stem cells which introduces a novel therapeutic approach for the treatment of both malignant and non-malignant diseases [15].

2. HYDROGELS

Hydrogels are large-volume, three-dimensional (3D) cross-linked molecular networks, usually composed of polymers. Covalent bonds or noncovalent interactions form the network of a hydrogel. Hydrophobic contacts, coordination interactions, hydrogen bonds, supramolecular interactions, electrostatic interactions, and physical entanglements are examples of noncovalent interactions. In order to create hydrogels with desirable qualities, a variety of synthetic and natural polymers, including polyacrylamide and poly(vinyl alcohol), as well as polypeptides, polysaccharides, and DNA, have been thoroughly investigated. Hydrogels possess a variety of physicochemical properties that can be effectively manipulated to meet the unique needs of applications in a variety of fields, including biomedicine, tissue engineering, biosensors, and environmental engineering. These properties include strength, adhesiveness, toughness, elasticity, conductivity, stretchability, antiadhesion, and shape-memory capability. Hydrogels' water-rich, three-dimensional network structure permits adequate diffusivity and offers a physiologically similar environment for the metabolism of cells and tissues. A variety of approaches may be used to create hydrogels, such as using a natural or synthetic polymer as the primary source, homopolymer, copolymer, or permeable networks. They can be biodegradable or biostable, and they can contain anionic and cationic chemical and physical cross-links [16]. Patients can avoid surgical implantation issues including pain and inflammation by using this kind of hydrogel, also known as injectable hydrogel, as hydrogels can be created at the appropriate site in the body based on biological parameters [17].

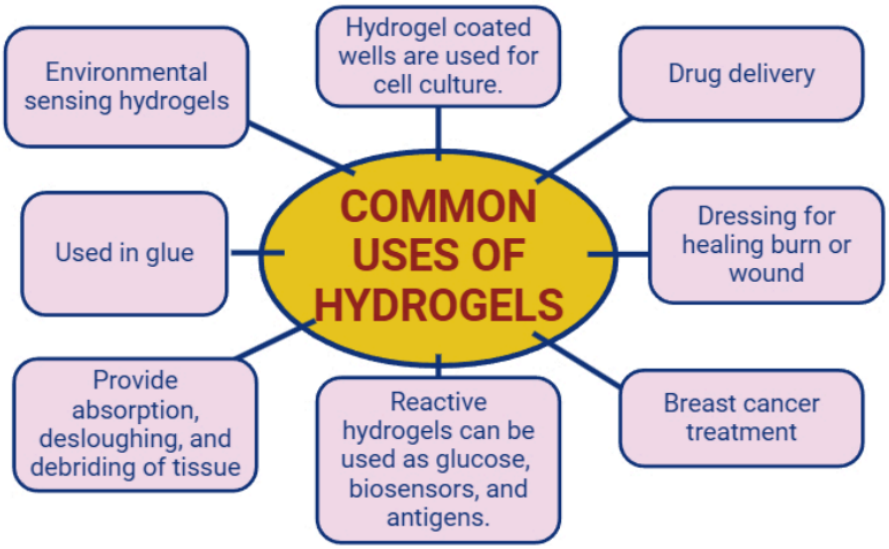

Fig. 4. Common uses of Hydrogels

2.1. Merits

1. Hydrogels are more elastic and stronger.
2. Hydrogels have a high degree of transparency and is easily adjustable.
3. They are more flexible than real tissue due to their high water content.
4. They are both biocompatible and biodegradable, and they can be injected.
5. Hydrogels may sense variations in temperature, pH, or metabolite concentration and respond to such changes by releasing their load.
6. Permits the prompt release of nutrients or medications [18].
7. Guard your cells [19].

2.2. Demerits

1. Expensive.
2. Non-adherent, requiring additional dressings for security, and uncomfortable to move around in.
3. Challenge to sterilize.
4. Less deposition in contact lenses might cause dehydration, red-eye responses, and hypoxia [18].
5. Poor mechanical potency.
6. May be difficult to manage.
7. Loading with nutrients and/or medicines is challenging [19].

2.3. Hydrogel technical features

The following qualities are desired in the perfect hydrogel material:

1. The maximum saline absorption capability.

2. An absorption rate adapted to the demands of a certain application.
3. Very low solubility and monomer residue.
4. Maximum durability and stability in cases of swell and storage.
5. Odorless, colourless, and non-toxic [18].
6. The maximum absorption under load (AUL).
7. Affordable
8. pH: the neutrality in water after swelling.
9. Photostability
10. Re-wetting capability [19].

2.4. Characteristics of Hydrogels

1. High Water Content: Hydrogels can absorb and hold onto high water content often more than 90% of their weight
2. Soft and Flexible: They resemble natural tissues due to their soft, gel-like nature.
3. Biocompatibility: Many hydrogels can be used in medical applications without causing adverse reactions.
4. Mechanical qualities: Hydrogels, based on their composition and structure, exhibit a wide range of mechanical properties, ranging from extremely soft to robust.
5. Stimuli-Responsive: Certain hydrogels can react to changes in their surroundings, such as pH, ionic strength, or temperature, by modifying their characteristics.
6. Permeability: Hydrogels, being permeable to small molecules, enable the controlled release of drugs or nutrients.
7. Swelling Behaviour: They can expand considerably when exposed to water, which is advantageous for products like contact lenses and wound dressings.
8. Transparency: A lot of hydrogels may be used in optical applications, including contact lenses since they are transparent.
9. Self-Healing: Some hydrogels have self-healing properties, allowing them to repair themselves after damage.
10. Adhesiveness: Medical adhesives and wound care solutions benefit from the ability of certain hydrogels to stick to biological tissues.
11. Environmental Sensitivity: Hydrogels are designed to respond to specific environmental triggers, such as magnetic fields or light, which can be used in smart drug delivery systems.
12. Biodegradability: A lot of hydrogels may naturally decompose in the environment or body without harming anyone [20].

2.5. Classification of hydrogels

1. Based on Origin

• **Natural Hydrogels:** These hydrogels are made of organic ingredients such collagen, hyaluronic acid, lysozyme, alginate, and gelatin and have high cell adhesion properties. They are also biodegradable and biocompatible.
• **Synthetic Hydrogels:** Made up of synthetic polymers such as polyacrylamide and polyethylene glycol. Polyethylene glycol-based hydrogels are frequently used in biomedical applications due to their low immunogenicity, non-toxicity, and compatibility.
• **Hybrid hydrogels:** Hybrid hydrogels combine synthetic and natural polymer hydrogels, combining biopolymers like dextran, collagen, and chitosan with synthetic polymers like poly (N-isopropylacrylamide) and polyvinyl alcohol.

2. Based on Polymer Composition

• **Homopolymeric hydrogels:** Homopolymeric hydrogels are composed of a single monomer, with the cross- linked skeleton influenced by the type of monomer and the polymerization method. Copolymeric hydrogels: Copolymeric hydrogels consist of multiple monomer species and a hydrophilic component, which are arranged in block, random, or alternate sequences within the polymer network.
• **Semi-Interpenetrating Networks (semi-IPNs):** These networks are made up of two types of polymer networks: branching and cross-linking.
• **Interpenetrating Polymer Networks (IPNs):** Made up of two or more non-covalently linked interlaced polymer networks.

3. Based on Cross-Linking Method

• **Physically Cross-Linked Hydrogels:** Produced by hydrogen bonds, crystallization, ionic interactions, or other physical processes.
• **Chemically Cross-Linked Hydrogels:** They are made up of polymer chains that are covalently bonded.

4. Based on Response to Stimuli

• **pH-Sensitive Hydrogels:** These hydrogels alter size in reaction to pH variations.
• **Temperature-Sensitive Hydrogels:** These gels react to temperature variations by often expanding at low temperatures and contracting at high ones.
• **Light-sensitive hydrogels:** When exposed to light, these materials alter.
• **Magnetic-Sensitive Hydrogels:** Hydrogels that are magnetically sensitive react to magnetic fields [21-23].

5. Based on biodegradability

• **Biodegradable hydrogels:** Natural polymers like Chitosan, fibrin, and agar, and synthetic polymers like poly (aldehyde guluronate), polyanhydrides, and N-isopropyl acrylamide, are all biodegradable.
• **Non-biodegradable hydrogels:** They are typically prepared using vinylated monomers or macromers like 2-hydroxyl ethyl methacrylate, methoxyl poly (ethylene glycol), 2-hydroxyl propyl methacrylate, and acryl amide.

6. Based on configuration

• Crystalline
• Amorphous (non-crystalline).
• Semi-crystalline: A complicated blend of amorphous and crystalline phases [18].

2.6. Techniques for Hydrogel Preparation

1. Physical Cross-Linking

Freeze-Thaw:
• **Procedure:** This entails periodically thawing and freezing a polymer solution. Water crystallises during freezing and melts when it thaws, leaving a network that is physically connected.
• **Applications:** Often applied to polyvinyl alcohol (PVA) hydrogels, which are used in the biomedical industry for wound healing and drug delivery systems.
Ionic Interaction:
• **Process:** Polymers with ionic groups (e.g., alginate) form hydrogels in the presence of multivalent counter-ions (e.g., calcium ions). The ionic bonds between the polymer chains create a gel network.
• **Applications:** Often utilised in the food business (for example, in alginate gels) and in biomedical settings to release drugs under regulated conditions.
Hydrogen Bonding:
• **Process:** Hydrogels are formed through hydrogen bonds between polymer chains. This method is often used with natural polymers like gelatin and agarose.
• **Applications:** Used as scaffolds for cell culture and in tissue engineering.

2. Chemical Cross-Linking
Free Radical Polymerization:
• **Process:** To form a cross-linked network, monomers with double bonds (e.g., acrylamide) polymerize in the presence of initiators (e.g., ammonium persulfate).
• **Applications:** Produce hydrogels for applications such as contact lenses and superabsorbent materials.
Radiation Cross-Linking:
• **Process:** Cross-linking in polymers is initiated by high-energy radiation, such as gamma rays and electron beams. This method does not require any chemical initiators.
• **Applications:** Used for sterilizing and cross-linking hydrogels in medical devices and wound dressings.

Enzymatic Cross-Linking:
• **Process**: Enzymes such as transglutaminase catalyze the formation of covalent bonds between polymer chains. This method is often used with proteins and polysaccharides.
• **Applications:** Used in the food industry and for creating biocompatible hydrogels for medical applications.

3. Hybrid Methods
Interpenetrating Polymer Networks (IPNs):
• **Process:** Two or more polymer networks are independently synthesized and then interlaced without the formation of covalent bonds. This creates a network with enhanced mechanical properties.
• **Applications:** Used as biomaterials for tissue engineering and in drug delivery systems.
Solution Polymerization:
• **Process:** Monomers are polymerized in a solvent, and the resulting hydrogel is precipitated out. This method involves various functional groups.
• **Applications:** Used for creating hydrogels with specific chemical functionalities for targeted applications.
4. Emulsion Polymerization
Inverse Emulsion Polymerization:
• **Process:** Monomers are polymerized in an oil-in-water emulsion, resulting in hydrogel particles. The particle size can be controlled using this technique.
• **Applications:** Used in the formation of hydrogel microspheres for use in cosmetic and drug delivery applications.
Suspension Polymerization:
• **Process:** Monomers are dispersed in a continuous phase and polymerized to form hydrogel beads. This method is suitable for producing uniform hydrogel particles.
• **Applications:** Used in water treatment and as carriers for immobilized enzymes.

5. Grafting
Grafting Onto:
• **Process:** Preformed polymer chains are grafted with monomers to form hydrogels. This method allows for the modification of existing polymers.
• **Applications:** Used to improve the characteristics of hydrogels for certain uses, including enhancing biocompatibility.
Grafting From:
• **Process:** Monomers are polymerized from the surface of a preformed polymer. This method is used to create hydrogels with a high degree of functionalization.
• **Applications:** Used in the development of responsive hydrogels for sensors and actuators.

6. Template Polymerization
Molecular Imprinting:
• **Process:** A template molecule is present during the polymerisation of functional monomers and is subsequently eliminated to provide certain binding sites. This method creates hydrogels with high selectivity for the template molecule.
• **Applications:** Used in biosensors and separation processes.

7. Sol-Gel Process
Sol-Gel Transition:
• **Process:** A sol (colloidal solution) undergoes gelation to form a hydrogel network. This method is often used with silica-based materials.
• **Applications:** Used in the creation of hybrid organic-inorganic hydrogels for biomedical and environmental applications.

8. Electrospinning
Electrospun Fibers:
• **Process:** Polymers are electrospun into nanofibers, which are cross-linked to produce hydrogels. This method is used for the formation of hydrogels with a high surface area.
• **Applications:** Used in tissue engineering scaffolds, filtration membranes, and wound dressings [23-25].

2.7. Hydrogels For Biomedical Applications
Hydrogels have unique properties that are useful in many biomedical applications is depicted in Table 1 [32], such as

in vivo tissue scaffolds, high-end drug delivery systems, external dressings, and inexpensive medical supplies.

1. Medical dressing: Medical dressings collect fluid from wound exudate, act as a barrier to protect wounds, and encourage wound healing is shown in Fig.5. Hydrogel dressings efficiently absorb fluids and produce a moist environment for tissue regeneration because of their high flexibility and biocompatibility. Hydrogel dressings are a great option for medical dressings as their elastic properties may also aid avoid subsequent harm brought on by wound adhesion [26].

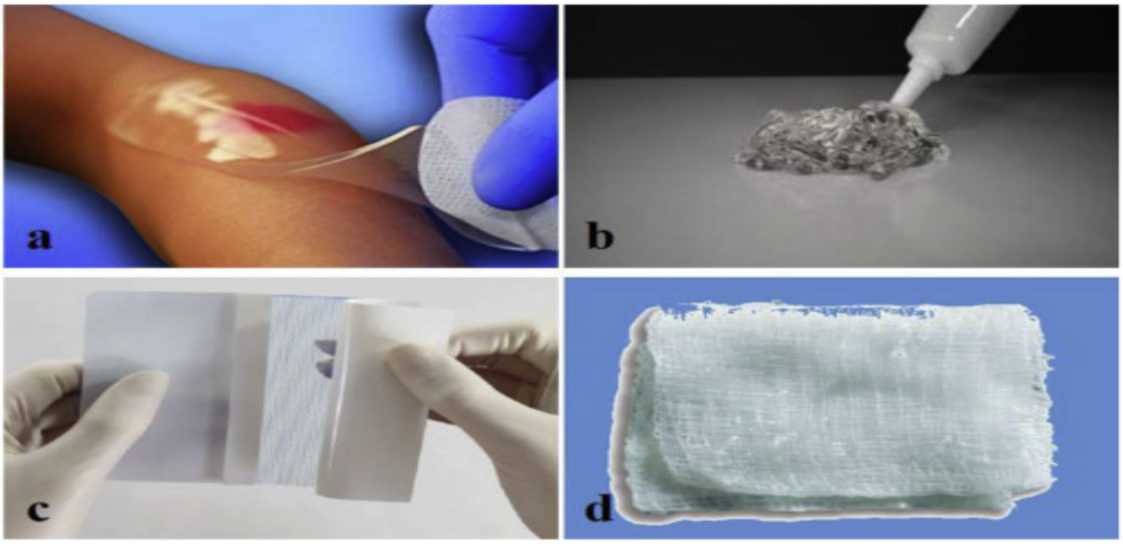

Fig. 5. Different forms of hydrogel wound dressings available in the market.
(a) Neoheal® hydrogel sheet used for wound dressing, (b) Amorphous gel that can be used for necrotic wounds and burns, (c) Hydrogel film, and (d) Hydrogel-impregnated gauze.

2. Drug Delivery System:

Drug delivery systems are specialized technologies intended for the controlled release and targeted delivery of medicinal substances as shown in Fig.6. Drugs can be stored in hydrogels, which can also regulate the rate of drug release and expedite the release process. They can be used to modify the strength and hardness of formulations, cover up the smell of medicines, and encourage decomposition [26].

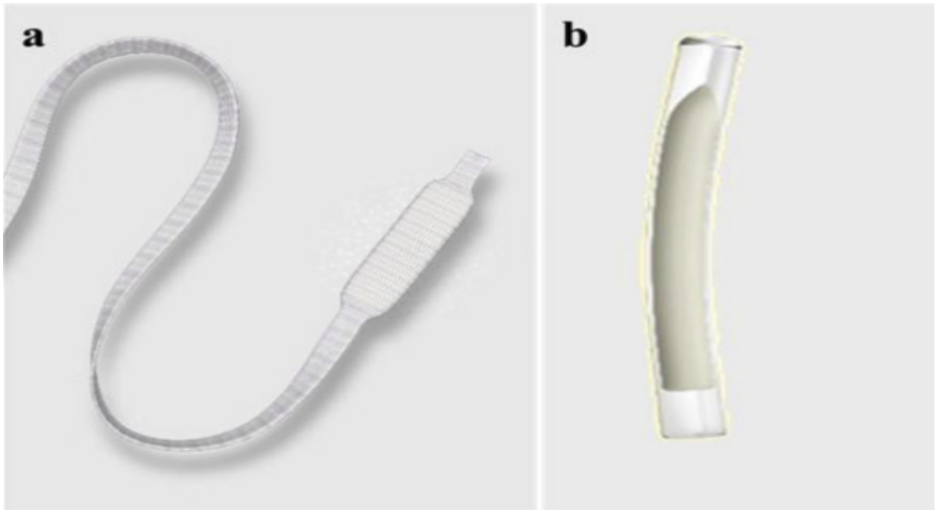

Fig. 6. Hydrogel implant for medication delivery that is available commercially: (a) The hydrogel-based product Cervidil®, containing 10 mg of dinoprostone; and (b) SUPPRELIN® LA, a subcutaneous implant.

3. Pulp Regeneration:

Pulp regeneration involves cultivating pulp stem cells in vitro and transplanting them onto a biocompatible, absorbable, and degradable scaffold to create pulp-dentin complexes and pulp-like tissues. This is done by applying tissue engineering concepts. The goal of this procedure is to restore the physiological function of injured pulp tissue. Hydrogels, which can be molded into injectable forms, can fill the pulp chamber and root canal before gelation. The gel produced after gelation is ideal for pulp regeneration research due to its tight cling to tissue and even cell distribution. This could help address foreign cells in pulp

regeneration that struggle to swell into the root canal scaffold [27].

4. Tissue Engineering:
Tissue Engineering (TE) is a crucial technique for in vivo tissue regeneration, where patient cells are mixed with a polymer in vitro to prepare for implantation. The hydrogels act as a natural extracellular matrix, encouraging tissue regeneration and cell proliferation. The pseudo-extracellular matrix aims to restore damaged or absent tissue by stabilizing structure and forming cell connections. Tissue engineering has great potential to regenerate failing tissue, but full replacement requires a healthy substitute [28].

5. Biosensor:
Biosensors combine physical and synthetic sensors to detect and report biophysical properties of a system, or provide valuable biochemical data. They are necessary for many different applications, including environmental monitoring, home diagnostics, and care testing. The bio component, made up of chemicals, antibodies, live cells, or tissues, is unique to each analyte. Hydrogels are employed in inhydrogel-based sensors as well as biosensors to protect components from natural atoms or cells [28].

6. Hydrogels in Contact lenses:
Hydrogels, made from polyvinyl alcohol (PVA), are used in artificial contact lenses to maintain eye health and whiteness by allowing oxygen to pass through. These hydrogels can be altered for ophthalmic and corneal replacement applications. Hyaluronic acid (HA)-treated hydrogels are effective in contact lens applications due to their biocompatibility and hydrophilic properties. However, high molecular weight HA may cause transparency issues. Hydrogels treated with HA exhibit lower lysozyme absorption and water contact angles compared to UV light-treated hydrogels [28].

7. Cardiac Repair:
Myocardial infarction is a significant health risk, causing necrosis and scarring of myocardial cells, leading to heart failure. Direct heart transplantation is influenced by donor numbers and rejection reactions, with a low success rate. Cell transplantation is a more effective treatment, but its low retention and survival rate limit its widespread clinical application. Hydrogels, three-dimensional polymer networks with high water content, can be used for cell transplantation, tissue regeneration, and cell survival. They have biocompatibility, low immunogenicity, high permeability, and tunable mechanical properties. Injectable hydrogels offer a better environment for transplanted cells and are crucial in cardiac tissue engineering. They can be infused into the myocardium via catheter for minimally invasive treatment [29].

8. Neural Tissue Repair:
Peripheral nerve injury (PNI) is a severe condition causing loss of motor, sensory, and autonomic functions, disrupting axonal continuity, distal nerve fibre degeneration, and neuronal death. Traditional surgical treatments like autologous nerves and synthetic biomaterials are limited due to their supply and size mismatch. To address this issue, tissue scaffolds can be used as carriers for nerve cell proliferation and platforms for neuro- pharmaceutical distribution. Natural polymer hydrogels, which mimic human nerve tissue, have become popular medicinal materials for brain tissue healing due to their mechanical characteristics and ability to stimulate nerve cell growth. Bioactive substances can be used to create a hydrogel neural tissue scaffold that can release drugs slowly. Additionally, natural polymer hydrogels can be used as a substrate for cell culture to treat peripheral nerve injury by promoting nerve axon development, orienting cells, and filling in injured neural gaps [30].

9. Bone Tissue Repair:
Bone self-recuperating is crucial for healing and recovery, but traditional methods like autografts, allografts, and xenografts have limitations. Hydrogels, which sense external physicochemical stimuli like light, pH, temperature, and magnetic fields, can improve their properties like injectability, self-healing, and shape memory. These hydrogels can treat bone tissue damage, facilitate functional restoration, and implant active cells and cell growth factors into damaged tissues [28].

Table 1 Hydrogels and their biomedical applications [32].

Application	Hydrogel	Application
Wound healing	Methacrylate, nanofiller-enhanced	Dressing, cream
Dental	Peptide and collagen-based	Implant, dressing, cream
Drug and Vaccine Delivery	Stimuli-responsive, nanofiller enhanced, peptide-based, collagen-based, molecularly imprinted polymer (MIP) based	Implant, dressing, contact lenses, soft-gel capsules
Ophthalmic	Methacrylate, gelatin	Microemulsion eye drops, contact lenses
Orthopaedic	Collagen, nanofiller enhanced, methacrylate	Implants, microgel
Cardiac	Nanofiller-enhanced, gelatin, stimuli-responsive, self-oscillating	Bio-actuator, implant
Organ Culture	Gelatin, collagen, peptide, stimuli responsive	Scaffold
Plastic surgery	Hyaluronic acid (HA), stimuli-responsive, methacrylate	Trans-dermal implant

Cosmetics	HA, stimuli-responsive, methacrylate	Cream, dressing
Diapers/ Sanitary Pad	Methacrylate	Pads, Diapers
Medical Devices	HA, stimuli-responsive	Robotic dispensers
Agricultural	Methacrylate	Powder
Nutraceutical	Peptide	Micro-particles

10. Rehabilitation of Spinal Cord Injury:

Spinal cord injury (SCI) is a condition causing temporary or permanent changes in the spinal cord's function, often resulting in severe symptoms like persistent pain and tetraplegia. While mesenchymal stem cell (MSC) transplantation is a viable treatment option, its survival rate is low. Hydrogel materials, being biocompatible and biodegradable, are often used in tissue engineering to reduce inflammation at the lesion site, load MSCs for repair, and create an environment conducive to tissue regeneration when paired with MSCs [28].

11. Osteoarthritis Cartilage Damage Repair:

Osteoarthritis is a degenerative condition that damages cartilage tissue due to long-term inflammation caused by the immune system and other processes. To restore cartilage tissue, tissue engineering using biological scaffolds, seed cells, and growth factors is a viable approach. However, inflammation and inadequate support after seed cell transplantation can lead to widespread cell death, making it unsuitable for cartilage regeneration. Hyaluronic acid hydrogels, which are essential in connective, epithelial, and neural tissues, are often used in osteoarthritis cartilage regeneration due to their minimal immunogenicity, strong biocompatibility, and biodegradability. These hydrogels are essential for supporting cell growth, differentiation, and facilitating cellular nutrient flow while remaining biocompatible and bioresorbable [33].

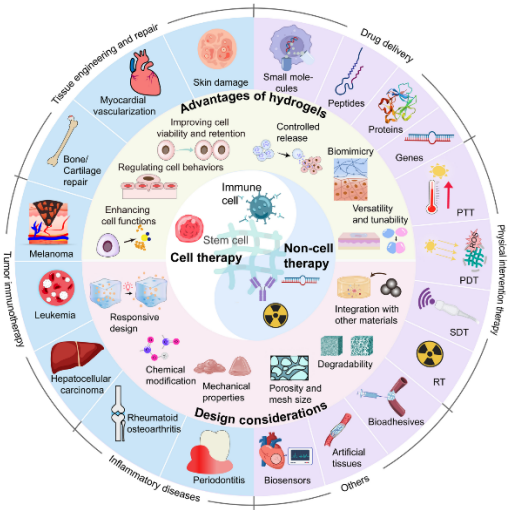

Fig. 7. Schematic representation of hydrogel uses in cell and non-cell therapies [34]

2.8. Hydrogels in Cancer Therapy

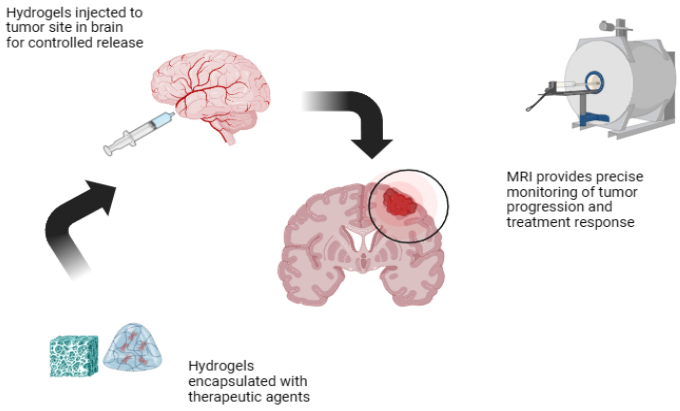

Fig. 8. shows how therapeutic drugs are applied using hydrogel to treat brain tumors.

Drug Delivery:

- Increased bioavailability and solubility of the medication.
- Long-term release of medicinal substances, lowering

dosage requirements.
• Targeted delivery to tumor sites, minimizing systemic toxicity.
Examples:
Liposomal hydrogels as a chemotherapeutic agent pH-sensitive hydrogels for acid-responsive drug release Thermoresponsive hydrogels for in situ gelation

1) Immunotherapy:
• Establishing a milieu that stimulates the immune system.
• Synergistic effects by combination with other treatments.
• Delivery of adjuvants and immune checkpoint inhibitors.

2) Radiotherapy:
• Radiosensitizers based on hydrogen for improved tumor response.
• Defence against radiation harm to healthy tissues.

3) Phototherapy and Hyperthermia:
• Hydrogels that are heat-sensitive for localised temperature increase.
• Hydrogels that react to light for photodynamic and photothermal treatment.

2.9. Specific Examples of Hydrogel-Based Cancer Treatments

Fig. 9 and Fig. 10 show different hydrogel based formulations and translational hydrogels [38,39]

1. Thermoresponsive hydrogels: When exposed to temperature changes, they gel in situ at the tumor site by passing through a sol-gel transition [30].

2. pH-sensitive hydrogels: Improve medication effectiveness and lessen systemic toxicity by releasing medications in the acidic tumor microenvironment [35].

3. Injectable hydrogels: Offer a less invasive method that is simple to apply to tumors [36].

4. Hydrogen-based scaffolds: Can be used for tissue engineering to create artificial tumor models for drug screening and development [37].

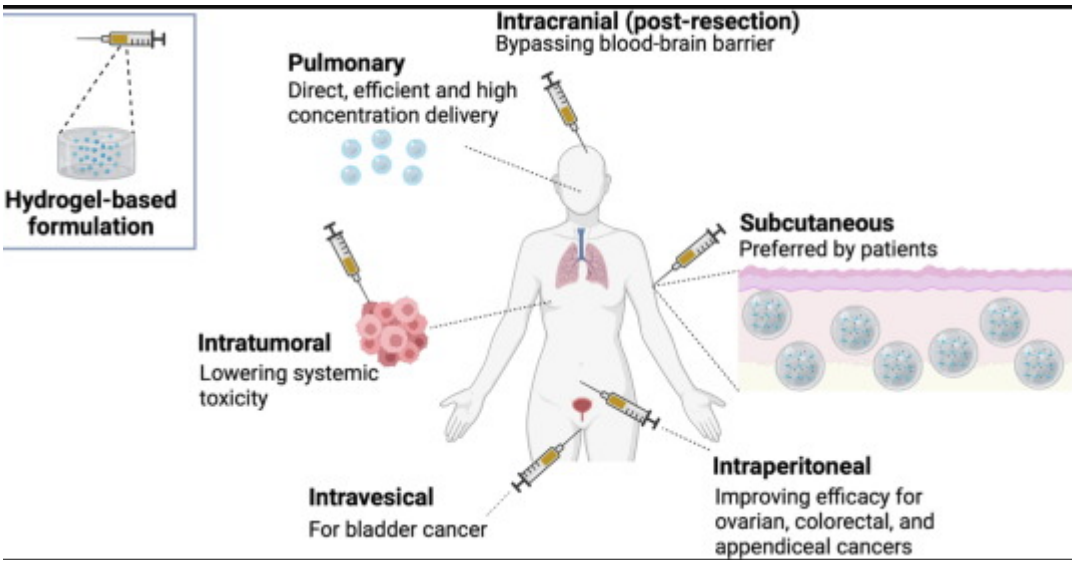

Fig. 9. shows different Hydrogel based formulations

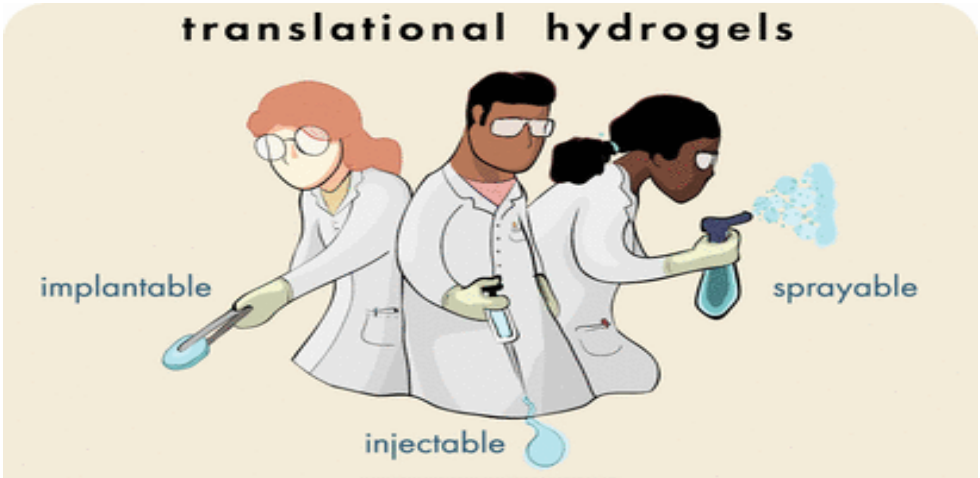

Fig. 10. illustrates several varieties of translational hydrogels

2.10. Challenges and Future Directions

Hydrogel-based cancer therapeutics have potential, but

they also confront challenges like:
• The manufacture of hydrogels that are reproducible and scalable.
• Kinetics of biodegradation and stability in vivo.
• The body's reaction to the hydrogel's ingredients.
• A smooth transition from the bench to the bedside.

Future studies ought to concentrate on:
• Creating hydrogels with sophisticated and intelligent functionality [40].
• Hydrogels can be used in conjunction with other nanomaterials for synergistic effects.
• Exploring the application of hydrogels in cancer vaccines and immunotherapy.
• Resolving obstacles related to regulations for clinical translation.

3. CONCLUSION

Controlled drug delivery systems based on hydrogels have enormous potential to improve cancer treatment outcomes while minimizing side effects. Hydrogels are perfect for targeted drug release in the tumor microenvironment because of their high water content and ability to respond to both internal and external stimuli. They provide benefits such as long-term release of therapeutic agents, increased bioavailability and targeted
delivery. Hydrogels have found application in diverse biomedical fields such as wound dressings, medication delivery, tissue engineering, and regenerative medicine. Hydrogels are essential for drug delivery, immunotherapy, radiation, and phototherapy in the context of cancer therapy. Specific examples include thermoresponsive hydrogels, pH-sensitive hydrogels, injectable hydrogels, and hydrogen-based scaffolds for tissue engineering. To ensure the successful clinical translation of hydrogel- based cancer therapeutics, addressing challenges such as reproducibility, scalability, biodegradation kinetics, and regulatory hurdles is imperative. Future research should focus on developing advanced hydrogels with intelligent functionality, exploring synergistic effects with other nanomaterials, and investigating applications in cancer vaccines and immunotherapy. In conclusion, controlled drug delivery systems based on hydrogels present a viable option for enhancing the effectiveness of cancer treatments. Continued research and development in this field have the potential to revolutionize cancer by providing more effective and targeted treatments for patients.

Acknowledgment
School of Pharmacy and Research, Dev Bhoomi Uttarakhand University, Dehradun, Uttarakhand – 248007

Credit authorship contribution statement
Tanisha Goyal - Writing - original draft - Conceptualization.
Dr. Tarun Parashar – Writing - review, visualization, editing, investigation.
Ms. Kanchan Singh – Writing - review, visualization

Declaration of competing interest
The author declares that they have no known competing interest

Data availability
None

REFERENCES

1. Kroemer G, Chan TA, Eggermont AMM, Galluzzi L. Immunosurveillance in clinical cancer management. CA Cancer J Clin. 2024 Mar-Apr;74(2):187-202. doi: 10.3322/caac.21818. Epub 2023 Oct 25. PMID: 37880100; PMCID: PMC10939974.
2. Sharath NS, Misra R, Ghosh J. Application of hydrogel-based drug delivery system for pancreatic cancer. Recent Advances in Nanocarriers for Pancreatic Cancer Therapy. 2024;73–93. doi:10.1016/b978-0-443- 19142-8.00011-5
3. Dolati M, Ghaffari M, Norouzi M, Coactive chemoradiotherapy using polysaccharides- and synthetic polymers-based hydrogels for cancer treatment: A review. Carbohydrate Polymer Technologies and Applications. 2024;7:100463. doi:10.1016/j.carpta.2024.100463.
4. Tan S, Li D, Zhu X. Cancer immunotherapy: Pros, cons and beyond. Biomedicine and Pharmacotherapy. 2020;124:109821. doi:10.1016/j.biopha.2020.109821.
5. Saini A, Gupta N, Sharma N, Cancer causes and treatments. Int J Pharm Sci Res. 2020;11(7):3121-3134. doi:10.13040/ijpsr.0975-8232.11(7).3121-34.
6. Jaymand M. Hydrogel-based drug delivery systems for synergistic chemo/hyperthermia therapy of cancer: A comprehensive review. J Drug Deliv Sci Technol. 2024;95:105581. doi:10.1016/j.jddst.2024.105581.
7. Lassche G, Crezee J, Van Herpen C. Whole-body hyperthermia in combination with systemic therapy in advanced solid malignancies. Crit Rev Oncol Hematol. 2019;139:67-74. doi:10.1016/j.critrevonc.2019.04.023.
8. Debela DT, Muzazu SG, Heraro KD, New approaches and procedures for cancer treatment: Current perspectives. SAGE Open Med. 2021;9:20503121211034366. doi:10.1177/20503121211034366.
9. Shinde PR, Patel V. Core concept of bioelectronic medicine and their theranostic application in cancer: Bioelectronic medicine for theranostic application in cancer. Int J Pharm Sci Nanotechnol. 2022;15(4):6095- 6103. doi:10.37285/ijpsn.2022.15.4.10.
10. Teplyuk NM, Mollenhauer B, Gabriely G, MicroRNAs in cerebrospinal fluid identify glioblastoma and metastatic brain cancers and reflect disease activity. Neuro Oncol. 2012;14(6):689-700. doi:10.1093/neuonc/nos074.
11. Tewari M. Cancer and its treatment: An overview. Int J Adv Res. 2022;10(3):950–956. doi:10.21474/ijar01/14476.

12. Usatine RP, Stulberg DL. Cryosurgery. In: Dermatologic Procedures in Office Practice. 2024:167. doi:10.1016/C2024-0323930628.
13. Truong DH, Nguyen TQ, Dao TT, Nanoparticles as carriers of photosensitizers to improve photodynamic therapy in cancer. Pharm Dev Technol. 2024;29(3):221–235. doi:10.1080/10837450.2024.2322570.
14. Huang Z, Xu H, Meyers AD, Photodynamic therapy of cancer—Challenges of multidrug resistance. J Innov Opt Health Sci. 2015;8(1):1530002. doi:10.1142/s1793545815300025.
15. Lie AK, To LB. Peripheral blood stem cells: Transplantation and beyond. Oncologist. 1997;2(1):40–49. doi:10.1634/theoncologist.2-1-40.
16. Yang D. Recent advances in hydrogels. Chem Mater. 2022;34(5):1987–1989. doi:10.1021/acs.chemmater.2c00188.
17. Chamkouri H, Chamkouri M. A review of hydrogels, their properties and applications in medicine. Am J Biomed Sci Res. 2021;11(6):485–493.
18. Malpure PS, Mote MS, Chavan YG, A review on-hydrogel. Am J PharmTech Res. 2018;8(3):42–60.
19. Nagam SP, Venkateswarlu B, Divya Rani B, A comprehensive review on hydrogels. Int J Curr Pharm Res. 2016;8(1):19–23. Available from: https://journals.innovareacademics.in/index.php/ijcpr/article/view/10608
20. Bashir S, Teo YY, Naeem S, Fundamental concepts of hydrogels: Synthesis, properties, and their applications. Polymers (Basel). 2020;12(11):2702. doi:10.3390/polym12112702.
21. Sikarwar U, Khasherao BY, Sandhu D. A review on hydrogel: Classification, preparation techniques and applications. Pharma Innov. 2022;11(7):1172–1179. doi:10.22271/tpi.2022.v11.i7o.13944
22. Bustamante-Torres M, et al. Hydrogels classification according to the physical or chemical interactions and as stimuli-sensitive materials. Gels. 2021;7(4):182. doi:10.3390/gels7040182
23. Kaith BS, et al. Hydrogels: Synthesis, classification, properties and potential applications—A brief review. J Polym Environ. 2021;29:3827–3841. doi:10.1007/s10924-021-02184-5
24. Tang Y, et al. Advances in preparation and application of antibacterial hydrogels. J Nanobiotechnol. 2023;21:300. doi:10.1186/s12951-023-02025-8.
25. Maleki B, et al. Perspective chapter: Introduction to hydrogels – definition, classifications, applications and methods of preparation. In: IntechOpen; 2024. doi:10.5772/intechopen.1005061
26. Aswathy S, Narendrakumar U, Manjubala I. Commercial hydrogels for biomedical applications. Heliyon. 2020;6(4):e03719. doi:10.1016/j.heliyon.2020.e03719
27. Ye S, Wei B, Zeng L. Advances on hydrogels for oral science research. Gels. 2022;8(5):302. doi:10.3390/gels8050302
28. Ahmad Z, et al. Versatility of hydrogels: From synthetic strategies, classification, and properties to biomedical applications. Gels. 2022;8:167. doi:10.3390/gels8030167
29. Sun X, Nunes SS. Overview of hydrogel-based strategies for application in cardiac tissue regeneration. Biomed Mater. 2015;10(3):034005. doi:10.1088/1748-6041/10/3/034005
30. Zhang K, Xue K, Loh XJ. Thermo-responsive hydrogels: From recent progress to biomedical applications. Gels. 2021;7(3):77. doi:10.3390/gels7030077
31. Liu Y, et al. Engineered hydrogels for peripheral nerve repair. Mater Today Bio. 2023;20:100668. doi:10.1016/j.mtbio.2023.100668
32. Sameer J, Komal V, Shree RS. Advanced hydrogels for biomedical applications. Biomed J Sci Tech Res. 2018;5(1):BJSTR.MS.ID.001144. doi:10.26717/BJSTR.2018.05.001144
33. Gan X, et al. Applications of hydrogels in osteoarthritis treatment. Biomedicines. 2024;12(4):923. doi:10.3390/biomedicines12040923
34. Lu P, et al. Harnessing the potential of hydrogels for advanced therapeutic applications: current achievements and future directions. Signal Transduct Target Ther. 2024;9:166. doi:10.1038/s41392-024-01852-x
35. Xie Y, et al. Recent progress of hydrogel-based local drug delivery systems for postoperative radiotherapy. Front Oncol. 2023;13:1027254. doi:10.3389/fonc.2023.1027254
36. Mohammadi M, et al. Hybrid in situ-forming injectable hydrogels for local cancer therapy. Int J Pharm. 2022;616:121534. doi:10.1016/j.ijpharm.2022.121534
37. Gebeyehu A, et al. Polysaccharide hydrogel based 3D printed tumor models for chemotherapeutic drug screening. Sci Rep. 2021;11:372. doi:10.1038/s41598-020-79325-8
38. Erfani A, Diaz AE, Doyle PS. Hydrogel-enabled, local administration and combinatorial delivery of immunotherapies for cancer treatment. Mater Today. 2023;65:227–243. doi:10.1016/j.mattod.2023.03.006
39. Correa S, et al. Translational applications of hydrogels. Chem Rev. 2021;121(18):11385–11457. doi:10.1021/acs.chemrev.0c01177
40. Zhou X, et al. Recent research progress on tumor-specific responsive hydrogels. J Mater Chem B. 2024. doi:10.1039/d4tb00656a.