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An Analysis of Smart Hydrogels

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ABSTRACT

As an emerging drug carrier, hydrogels have been widely used for tumour drug delivery. A hydrogel drug carrier can cause less severe side effects than systemic chemotherapy and can achieve sustained delivery of a drug at tumour sites. In addition, hydrogels have excellent biocompatibility and biodegradability and lower toxicity than nanoparticle carriers. Smart hydrogels can respond to stimuli in the environment (e.g., heat, pH, light, and ultrasound), enabling in situ gelation and controlled drug release, which greatly enhance the convenience and efficiency of drug delivery. Here, we summarize the different sizes of hydrogels used for cancer treatment and their related delivery routes, discuss the design strategies for stimuli-responsive hydrogels, and review the research concerning smart hydrogels reported in the past few years

Keywords: Hydrogels, tumour drug delivery system, stimuli responsive materials, biocompatability and biodegradability.

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INTRODUCTION

Apoptosis or the death of cells, and host carrier mortality are the outcomes of cancer, a fatal disease caused by the unchecked growth of abnormal cells in a particular region of the body. Historically, people have regarded cancer as one of the most terrifying illnesses. 9.6 million cancer-related deaths occurred globally in 2018. Currently, immunotherapy, radiation, chemotherapy, and surgery are the available cancer treatments. Chemotherapy has a limited therapeutic index, low therapeutic index, drug tolerance, adverse drug responses, and inadequate targeting, notwithstanding its potential efficacy in certain circumstances. Innovative drug delivery systems have been developed recently to lessen side effects and boost chemotherapy efficacy. One such technique is nanotechnology, which can induce selective drug accumulation in tumour tissue by passive and active targeting route. Even though there are many advantages to using nanoparticles for targeted distribution, some of them have drawbacks such as burst release, poor adherence, and irreversible deformation. not fit for continuous management. One is thinking of cancer the second-deadliest sickness in the world, with a substantial percentage of deaths worldwide. Ten deaths were related to cancer million fatalities worldwide in 2020. In contrast to the quickly growing worldwide population, a decline in the mortality toll practically from earlier years. In 2018, the death rate was 9.6%. million, down from 7.6 million in 2007. 14.1 million in 2012.There will likely be 19.3 million new instances of cancer by 2025. Approximately one in eight men and one in ten women experience some form of mental illness, per credible statistical studies. because of these illnesses. Two plants used as medicines and their byproducts have always been crucial to the field of medicine formation of different illnesses. Three Various Types of In the regulated administration of pharmaceuticals, nanocarriers are utilized as 0-d material, 1-d material, and cancer treatment are some of the primary liposomesmicelles, mesoporous, 2-d substance, polymeric nanoparticles, hydrogels, and dendrimers. The hydrogels a new medication delivery method, have been regularly used to medicines tumours. Four The negative effects of a hydrogel drug carrier are effects compared to systemic chemotherapy and has the ability to transport medications to prolonged lengths of time in tumour regions. In addition, hydrogels are more readily biodegradable, less harmful to biocompatible. Smart hydrogels enable in situ gelation and regulated drug release by responding to environmental cues like heat, pH, light, and ultrasound. release, greatly enhancing the practicality and effectiveness the administration of drugs[5]. Three-dimensional (3D) hydrogel structure composed of the first ever hydrophilic polymer physiologically by Lim and Wichterle in 1960. Wichterle and in 1960, Lim coined this phrase for the first time in biology.10 In the previous several decades, the quantity of references released with the subject "hydrogels" has increased at a sounding pace, with almost 5000 papers released in 2010. almost five times as many papers on "nano-technology," which has also recently gained popularity, were published in that year. year with reference to "nano-technology," which has also lately. The four qualities that make hydrogels appealing are their regulated drug release, drug-loading capacity, biocompatibility, and biodegradability. Biocompatibility is the ability to since there is no discernible cellular or after being implanted, the body does not experience systemic toxicity. enhance the immune system. In addition, a lot of natural materials utilized to make hydrogels, including natural and synthetic polymers treatment for cancer is biodegradable. novel methods for delivering drugs pharmaceutical devices with non-destructive surface analysis (NDDS) studied and developed a great deal in the last few years. With the use of hydrogel compositions, numerous physical manifestations, such as slabs and nanoparticles, films and coatings. Given the existence of hydrophilic moieties in Being hydrophilic polymers, hydrogels are the materials that have their ability to create a three-dimensional network structure soak up a lot of water. A broad variety of hydrogels[(1) (6)(7)(8)].

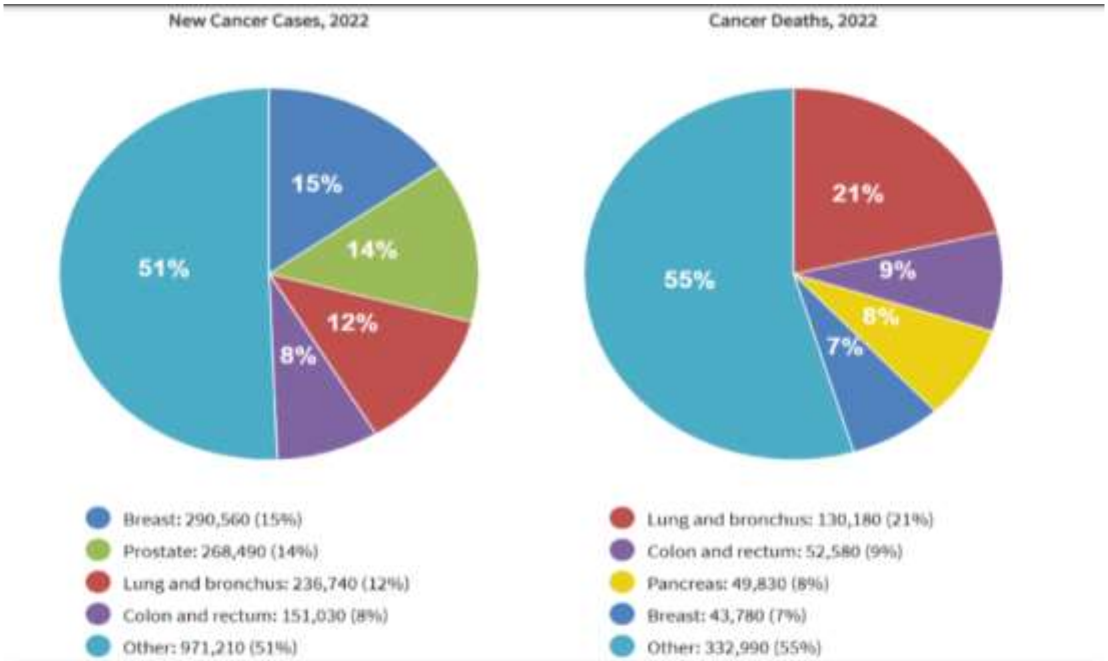

Figure 1: Common types of cancer

WHAT IS CANCER

- A group or lump of tissue is called a tumour.
- Benign tumours do not infiltrate or spread throughout adjacent tissues. Certain conditions, such benign brain tumours, might have fatal consequences or cause severe symptoms.
- Malignant tumours have the ability to metastasize, or spread into, neighbouring tissues and organs. This process allows the tumours to grow into new locations throughout the body. There are cancer cells in malignant tumours.
- Cancer is a disorder when certain body cells proliferate out of control and invade other bodily areas.
- Since the term "cancer" is so wide, there are over 100 distinct forms of cancer, each with its own set of risk factors and causes.
- In their lifetime, one in two men and one in three women will receive a cancer diagnosis, according to the American Cancer Society.

TO REDUCE YOUR RISK OF DEVELOPING CANCER

- Avoid using any kind of tobacco, such as chewing tobacco, cigars, or cigarettes. Retain a healthy weight. Consume a balanced diet by restricting or staying away from processed, red, and processed meat as well as whole grains, fruits, and vegetables.
- Engage in frequent physical activity to get moving. The NCI suggests 150–300 minutes of moderate activity or at least 75–150 minutes of intense activity per week. Avoiding alcohol

is recommended. If you do choose to drink, try not to exceed one drink for women or two for men every day.

- Use broad-brimmed hats, sunglasses, sunscreen, and clothing to protect your skin from the sun. Refrain from the sun between the hours of 10 a.m. and 4 p.m. Understand who you are, your medical history, and your risks. Share this information with your healthcare team. Obtain routine examinations and tests for cancer.

What Are Cancer Screening Tests

Screening entails examining your body for cancer before any symptoms appear. Regular screenings can detect malignancies early, when therapy has the best chance of being effective. These are some of the main showings.

- Breast cancer screening
- Cervical cancer screening
- Colorectal screening
- Lung cancer screening
- Skin cancer screening

WHAT VACCINES HELP REDUCE CANCER RISK

- Human papillomavirus, or HPV, is a sexually transmitted infection that is associated with a number of malignancies. The strains of HPV that most frequently result in these cancers are protected against by the HPV vaccination. Though it doesn't cure current illnesses or infections, HPV immunization helps prevent new HPV infections. The HPV vaccine, then, functions best when administered prior to any HPV exposure. Standard cervical cancer screening procedures, such as Pap and HPV testing, are not replaced by the HPV vaccination.
- The hepatitis B virus (HBV) is the cause of hepatitis B, a liver illness. It can range in intensity from an acute, short-term illness that goes away in a few weeks serious long-term condition called a chronic one that can cause liver cancer or disease. All age groups can receive the hepatitis B vaccination to protect against HBV infection.

METHODS TO PRODUCE HYDROGEL

Cross-linked networks of synthetic polymers such as polyethylene oxide (PEO), polyvinyl pyrrolidone (PVP), polylactic acid (PLA), polyacrylic acid (PAA) (Onuki et al., 2008), polymethacrylate (PMA), polyethylene glycol (PEG) or natural biopolymers such as alginate, chitosan, carrageenan, hyaluronan, and carboxymethyl cellulose (CMC) have been reported. The various preparation techniques adopted are physical crosslinking, chemical cross-linking grafting polymerization, and radiation cross-linking. Such modifications can improve the mechanical properties and viscoelasticity for applications in biomedical and pharmaceutical fields. The general procedures for making chemical and physical gels are listed below.

Physical Cross-Linking

Physical or reversible gels have gained popularity because of their advantage of not requiring cross-linking agents and their relative simplicity of manufacture. The integrity of the materials to be ensnared (such as cells, proteins, etc.) is impacted by these agents, and their clearance prior to application is required. A lot of research is presently being done in this field, especially in the food business, on the development of a wide variety of gel textures through careful selection of hydrocolloid type, concentration, and ph. The different techniques described in the literature to produce hydrogels that are physically cross-linked are:

- Heating/cooling a polymer solution
- Ionic interaction
- Complex coacervation
- H-bonding
- Maturation (heat induced aggregation)
- Freeze-thawing

Chemical Cross -Linkers

The cross-linking agent that is used to bind two polymer chains together or the grafting of monomers onto the polymer backbone are the two methods of chemical cross-linking. By reacting with cross-linkers like aldehyde (e.g., glutaraldehyde, adipic acid dihydrazone), functional groups of both natural and synthetic polymers (e.g., OH, COOH, and NH2) can interlink. To produce chemically cross-linked persistent hydrogels, several techniques have been documented in the literature. In addition to other chemical cross-linking techniques, chemically cross-linked permanent hydrogels can also be produced by hydrophobic interactions (Hennink & Nostrum, 2002) and IPN (polymerize a monomer within another solid polymer to form interpenetrating network structure) (2003). The latter technique incorporates a polar hydrophilic group by hydrolysis or oxidation. To create chemically cross-linked permanent hydrogels, other techniques include hydrophobic interactions (Hennink & Nostrum, 2002) and IPN (polymerize a monomer within another solid polymer to form interpenetrating network structure), which incorporate a polar hydrophilic group by hydrolysis or oxidation followed by covalent cross-linking. The main chemical processes (e.g., crosslinker, grafting, radiation in solid and/or aqueous state) that are utilized to create hydrogels from various natural polymers are reviewed in the section that follows Chemical cross-liners

Grafting

The polymerization of a monomer on the backbone of a premade polymer is known as grafting. High energy radiation therapy or the use of chemical reagents both activate the polymer chains. Branching and subsequent cross-linking are caused by the expansion of functional monomers on activated macroradicals.

- Chemical grafting
- Radiation grafting

Radiation Cross-Linking

In order to maintain the biocompatibility of the biopolymer, radiation cross-linking is a commonly utilized process that doesn't require the addition of chemical additives. It is also a cost-effective method to change biopolymers with their final use notably in biomedical applications because the modification and sterilization can be completed in a single phase. The key component of the approach is the generation of free radicals in the polymer after it is exposed to a high energy source, such as an electron, gamma, or x-ray. The polymer environment (i.e., diluted solution, concentrated solution, solid state) will determine the influence of radiation, either direct or indirect.

- Aqueous state radiation
- Radiation in paste
- Solid state radiation
- Cross-linking in solid state.[2][10]

MECHANISM OF HYDRODEL FORMATION

Hydrogels are formed by using polymers, which are materials made of carbohydrates. These polymers are commonly used because they have easy-to-change functional groups and are easily accessible. Biocompatibility and other characteristics are important considerations when designing hydrogels for specific applications. This can be achieved by choosing the right type of monomer or polymer and the appropriate hydrogel formation reactions. Hydrogels are created using two methods: chemical crosslinking and physical crosslinking.

Chemical Cross-Linking

Chemical cross-linkable hydrogels are a kind of hydrogel that can change from a liquid to a solid by forming strong bonds. This technique is also applied in in situ hydrogel systems. In this process, different reactions like light-induced polymerization, enzyme reactions, and click chemistry are used. In this part, we will talk about how reactions are used to create hydrogels. Various methods for making these hydrogels will be explained. Scientists have been interested in hydrogels made through chemical crosslinking due to their strong mechanical properties.

Optical Polymerization

This method uses light to initiate the reaction between molecules, resulting in the formation of a strong bond without the use of harmful chemicals or excessive energy. It is a convenient and efficient way to create crosslinked polymers without the need for additional materials or complex procedures. Reaction. This technique involves using water-loving polymers with molecules that react to light. When the polymer solution is hit by UV or visible light, it creates an optical decomposition initiator and free radicals, leading to the polymerization process. This results in the formation of crosslinked polymers. Typically, these materials contain acrylates and methacrylate's that are activated by light to form a polymer. The speed of the solidifying process can be managed, and the resulting substance can be utilized. Therapeutic substances like proteins and medications are released using this technique. It is a highly effective method for turning a single molecule into a larger compound with the help of light. Optical polymerization makes the hydrogel stronger and helps cells disappear as the gel forms, making it useful for medical treatments. This technique also forms a porous structure. The hydrogel can be easily structured using optical polymerization at body temperature and pH, whether inside or outside the body. In the medical field, when making hydrogels, it's important to use a safe optical primer and the right kind of light from a light source. This light helps the hydrogel gel up by using UV radiation to trigger a reaction in the vinyl groups.

Enzymatic Reactions

Enzymes help reactions happen in living things. Because of this, many people are interested in using enzymes for cell-related tasks. Enzymatic reactions need just right conditions like the right pH, temperature, and biological environment to crosslink effectively. One key benefit of using this technique to create hydrogels is the unique enzyme substrate that can stop harmful substances from getting in due to side reactions. Enzymes like horseradish peroxidase (HPR) that have been changed a bit, as well as tyrosinases, are used to help make hydrogel systems for tissue engineering. HPR is an enzyme that is strong and easy to purify, making it useful for creating hydrogels in this process. Because of this, it is used in different medical treatments like releasing drugs. The HPR-H2O2 enzyme water system is commonly used in creating natural hydrogels like chitosan, hyaluronic acid, and dextran for tissue reconstruction and repair through tissue engineering. In a study conducted by Kurosawa and colleagues, hydrogels were made by combining water and gelatin. In this research, hyaluronic acid was modified with tyramine and tagged with a fluorescent label called amino fluorescein for enzymatic reactions and to produce therapeutic proteins. The time it takes for the gel to form under the skin was decreased, making it a good method to create hydrogels using enzyme reactions that can link molecules together because it is selective and works well with cells.

Click Reaction

A reaction called click chemistry, defined by Sharples and others, involves specific types of reactions that occur quickly and efficiently with the help of a catalyst. These reactions have great biological properties and are effective. Good reaction conditions that are favorable are essential for the synthesis and activation of polymers. Click chemistry is important in this process and is a useful and adaptable way to add functions to polymers. Click chemistry is a method that uses molecules to create hydrogels, nanogels, and microgels because of the advantages it offers. It has been used for tissue engineering and delivering drugs. Click chemistry is a new method for linking polysaccharides in hydraulic chemicals. Click reactions involve many different reactions, such as copper (I) reactions (aided by alkyne amide complexes), catalytic reactions using alkyne amides, and silicosterone reaction with disaccharide (DA), including the intergroup reaction of alkynes. Click chemistry is commonly associated with compounds like alkynes and azides because of their effectiveness in the body's natural conditions and their ability to specifically target certain molecules. The reaction occurs without a catalyst or primer and helps control the degree of reaction using side products that can be reversed through heat. This process also maintains the biocompatibility of the material. Researchers created starch-based hydrogels by combining thiol and allyl groups of starch using click reaction for use in biomedical and tissue engineering purposes. The hydrogel that was produced exhibited positive swelling and biodegradability.

Physical Crosslinking

Physical Crosslinking Hydrogels can be created by changing the forces within the molecules. This includes hydrogen bonding, hydrophobic interaction, and electrostatic ionic force. To avoid making the crosslinker more toxic in the chemical process, this method allows for the creation of hydrogel using easy and safe steps. Different techniques can be used to physically cross-link materials, such as ionic methods, temperature-dependent methods, and PH dependent methods for cross-linking

Ionic Crosslinking

Ionic crosslinking is a type of physical method used for crosslinking. This reaction occurs without the involvement of any chemicals. creating a strong connection between the polymer chains by using an ion crosslinking agent to make a gel. This technique helps to make the material very strong. Hydrogels are made from alginate, which is a natural substance. When alginate comes into contact with certain substances like calcium, it can turn into a gel. These ions help the gluronic acid groups in the alginate chain bond together, creating ionic bonds within the polymer chain. Hydrogen alginate is often used as an ECM. Lately, scientists have been studying this in more detail. By adjusting factors like the size of molecules and the amount of alginate used, we can enhance the time it takes for gels to form, strengthen their physical characteristics, and make them more compatible with living tissues. By adjusting the amounts of sodium alginate and calcium in the hydrogel mixture, it can be made suitable for injecting into the body as a biomaterial and for growing cells in a lab setting. Some other natural materials can also be used for this purpose. Chitosan is a substance that can link ions together, and it has been used in things like releasing medication.

Temperature Dependent Methods

Temperature plays a crucial role in creating hydrogen through physical crosslinking. Hydrogels that are sensitive to temperature turn into a liquid when it's cold and become a gel at body temperature. Water-soluble polymers can turn into a gel when the temperature changes. These gels, known as hydrogels, are commonly used in tissue engineering. These hydrogels can form without the use of any chemicals. The point at which they turn into a gel can be changed to a different level. The temperature is kept close to normal body temperature when injecting polymers into the body, allowing them to solidify. Natural and synthetic polymers are both used for this process. Natural polymers like cellulose, chitosan, and gelatin derivatives, along with synthetic polymers such as poly-isopropyl acrylamide (PNIPAAM) and pluxamer, are commonly used in various applications. Scientists have focused on studying how PNIPAAM copolymers can help with releasing chondrocytes and growth factors in tissue engineering. Additionally, poloxamers have been experimented with for lung tissue engineering purposes. Scientists have enhanced the strength of poloxamer by physically gelling it with a crosslinking agent, in order to better trap cells. Researchers are interested in a special type of gel made from hyaluronic acid that can change with body temperature. This gel is safe for the body and reacts well to changes in temperature.

pH Dependent Methods

pH-dependent techniques: Hydrogel stimulation should be used since each part of the body is connected to a particular pH level. pH-sensitive hydrogels are commonly used in research because they react to different stimuli. They are especially popular among scientists for their ability to adapt to changes in pH levels. pH-sensitive hydrogels change size depending on the pH level of their environment. These hydrogels have acidic groups that can become charged at certain pH levels. pH-sensitive hydrogels are commonly used in medical field for tasks like controlling drug release and making heart valves, because they can react to changes in pH levels. In certain situations, like when releasing medication, hydrogels may experience varying temperatures inside the body due to environmental changes. In order to learn how pH-sensitive hydrogels are created, researchers need to make changes in temperature, according to a study conducted by Hu et al. Carboxymethyl chitosan was combined with a special acid crosslinking agent in the best conditions to create hydrogels that can sense changes in pH levels. Carboxymethyl chitosan is safe to use and does not harm the environment. Biodegradable materials are substances that can break down naturally and are commonly used in the field of medicine.

TYPES OF HYDROGELS

There are two types of hydrogels: natural hydrogels and synthetic hydrogels. These categories are based on the type of polymer used to make the hydrogel. Polymers that have been hydrogenated, whether they are natural or man-made, are seen as important ingredients for medical uses. Both natural and synthetic polymers are utilized in creating hydrogels. The hydrogel needs to be friendly to the body, able to break down naturally, and in certain cases, should work well with blood when it comes into contact with it.

Natural Hydrogels

Natural hydrogels are gels made from polymers sourced from nature. They are used for various applications. Using natural polymers to create hydrogels has benefits like being safe for the body, easy to break down, and not harmful. The decision to use natural polymers in making hydrogels relies on various factors. One reason for using biomaterials is to make sure they are safe for the body and can break down naturally. For instance, when using hydrogels to release substances slowly, it is important that they are compatible with the body and can be broken down easily. Polysaccharides and proteins are types of natural polymers that are commonly used to transport substances for release. The testing inside the body of these materials demonstrated that they are safe for use in living organisms. Polysaccharides are the best choice for use because they are safe for the body, break down easily, last a long time, and are not harmful. Natural hydrogels are often used in medical treatments. Different materials like alginate, collagen, gelatin, and fibrin can be used for various purposes. For instance, alginate has been used to help restore normal heart function in people who have had a heart attack. Collagen is also used as a substitute for vascular bundles. Gelatin is suitable for creating fake structures. Fibrin is helpful for making new tissues and sticking things together, as well as preventing blood from clotting during surgery

Synthetic Hydrogels

Synthetic hydrogels are made from synthetic materials like polyamides or polyethylene glycol (PEG). Lately, man-made polymers have started to be used instead of natural polymers in making hydrogels because they last longer, are stronger, and can soak up more water. Synthetic polymers are commonly used in making hydrogels for different medical purposes. These polymers repel water and have strong mechanical properties. Chemicals are more effective than natural polymers. Some examples of these polymers are polyacrylamide and its related compounds, polyvinyl alcohol, and PEG. PEG is widely used as one of the most popular polymers. Synthetic hydrogenation is commonly used in different medical purposes like controlling drug release, creating tissue structures, making bone replacements, and producing wound coverings. This material is applied in various medical treatments. PEG is commonly used in various applications because it is safe for the body, does not cause an immune response, and does not easily attract proteins. PEG can also create solid substances on its own. Network structures can be enhanced by incorporating factor groups, which helps to improve crosslinking within the network.

PROPERTIES OF HYDROGELS

Hydrogels are special types of network polymers that can soak up and hold onto water. This helps in forming the structure of the hydrogen network. Property of the material makes the hydrogel expand

Swelling of Hydrogels

When a hydrogel swells, we can calculate its equilibrium swelling using a specific formula. The swelling ratio of hydrogels can be calculated by using the formula: swelling ratio = (weight of swollen hydrogels - weight of dried hydrogels) / weight of dried hydrogels. Just make sure to measure the weights of the hydrogels accurately before and after freeze-drying. In typical hydrogel setups, the drug is released by the hydrogel swelling or shrinking and the drug moving through the polymer network. A hydrogel can change its swelling, structure, strength, or permeability in response to different triggers, making it known as a stimulus-responsive hydrogel or a biologically sensitive hydrogel. These agents are useful in changing how drug agents are released from hydrogels to control the release of drugs. we can see how much the adipic acid dehydrated / polyglutamic acid and hyaluronic acid swell with hydrogen. Both substances swell a lot, with the highest swelling rate being very high. Research indicates that when the amount of solid material was 1% in weight, the hydrogel dissolved in a phosphate buffer salt solution. Xiobin and colleagues created a thick gel that can hold a lot of liquid by mixing hyaluronic acid and polyglutamic acid together. This gel can be injected into the body to control how proteins are released. As more polymer was added, the swelling went down because there were more crosslinks forming in the structure. Their study found that the amount of hydrogel swelling can be influenced by the NH2 / CHO molar ratio. Once the NH2 / CHO molar ratio reaches 1:2, the percentage of hydrogel swelling changes. The swelling rate of the hydrogel was double that of the 2:1 hydrogel. When the ratio was 1:3 NH2 / CHO, the rate was low. The hydrogel dissolved in phosphate buffer due to its cross-linking structure. One way to control the release of a substance is by using pH-sensitive polymers that can swell in different conditions. This method is known as the pH-sensitive polymer solution (PBS) 24 Researchers have utilized the swelling properties of pH-sensitive polymers to carefully release drug substances. The size of the polymer molecules and the connections between them play a key role in this process. Controlling the release rate of drugs and oxygen permeability are key factors in how swelling works. Hydrogels can expand in biological settings and hold onto substances. A lot of water is held together by links between the chains in the structure, which stops it from breaking down and keeps the network's size the same. The hydrogel's characteristics can be greatly influenced by things like temperature, pH, and ion concentration, which may lead to it shrinking or expanding. Moving the hydrogel from one phase to another helps release the drug. The drug is mainly released when the hydrogel swells, and the release can be controlled by adding PEG to the PNIPAAM, affecting either inflation, diffusion, or both. A polymer system was used to enhance the copolymer's ability to swell

Mechanical Properties

Injectable chemical hydrogels are stronger and last longer than physical hydrogels. However, they often use harmful crosslinking agents. Preparation may harm biocompatibility, but hydrogels form physical-chemical interactions that eliminate the need for toxic initiators. The characteristics of hydrogels are crucial for designing hydrogels for medical use. In tissue engineering, the strength and flexibility of hydrogels are key factors to consider. The characteristics of scaffolds, both big and small, are crucial for controlling how cells behave. The way cells and the environment they're in interact can influence cell shape. Cells are influenced by the stiffness of their environment. For instance, the stiffness of the extracellular matrix can impact adult human skin fibroblasts. Cells can also be affected when they are exposed to different conditions. Tougher surfaces make the cell membrane more rigid and help the cell's structure. Also, cells grow faster on harder surfaces. Hydrogel biomaterials have different mechanical properties when compared to softer substrates. Scientists use time independent and time-dependent viscoelastic theories to study and understand these properties. The composition of the hydrogel and the effective crosslinking ratio can be evaluated. PNIPAAM hydrogel made using the free radical polymerization method is not very strong, so regular mechanical tests can't be used to figure out how strong it is. Several factors can impact how strong hydrogels are, such as how much monomer is used at the start, the level of crosslinking agent, the temperature during polymerization, how much the hydrogel has swelled, and how the measurements are taken. This can make it tricky to accurately compare any mechanical attribute. - Reza Abdollahi Researchers utilized graphene oxide to improve the strength of PAA bonded with amylose. They think that graphene oxide can effectively enhance the tensile strength of the material.

BIOLOGICAL PROPERTIES

Biological characteristics: Important features of injectable hydrogels for different medical uses include being safe for the body and not harmful, having strong enough properties, being easy to inject, and staying stable. The hydrogel needs to have the right mechanical and biological properties which should be like the tissue it is replaced with. In many research studies, Zhao and colleagues have attempted to create the best mechanical and biological characteristics by mixing different materials. The gelatin methacrylate fibers were connected with UV light after being made using linking and electro spinning techniques. The findings indicated that altering the exposure time can modify the physical and biological characteristics of electrospun hydrogel. This helps in creating a hydrogel that mimics real bone tissue. It is crucial to create a hydroxyapatite / carbon nanotube / HA CNT composite that has great mechanical and biological qualities for making bone substitutes. The unique design of the composite not only improves the flow of body fluids but also enhances has a bumpy and damp surface that cells like to stick to and grow on. This makes the HA / CNT composite great for both biology and mechanics. Bone replacement applications and tissue scaffold preparation can greatly benefit from the use of this material. Expanding cells in biological substances is a crucial part of basic biological processes. Osteoblasts have certain characteristics. Before using an injectable hydrogel, it is important to check if it is safe for the cells to grow and change. Natural hydrogels are able to interact with cells in the body without causing any harm or triggering immune responses. This is because the components of natural hydrogels closely resemble those found in the extracellular matrix, making them compatible with the body. When creating artificial hydrogels, it is important to make sure that the hydrogel's structure works well with cells, tissues, and body fluids. The hydrogel should also be safe for the body, meaning it should not be toxic, cancer-causing, or lead to long-term physiological or inflammatory responses after it breaks down.

APPLICATIONS OF HYDROGEL IN MEDCINE

Tissue Engineering

the attention of researchers for their potential use in tissue engineering within the field of medicine. Hydrogels made from natural or synthetic polymers are being widely studied for tissue engineering and regenerative medicine. Different types of hydrogels have been tested for these applications. Repair damaged bone-to-bone connections or joint cartilage with the help of alginate, a substance made from brown seaweed and certain bacteria. One special thing about alginate is that it can connect with other molecules like Ca2+ at room temperature, which helps in different biotechnical processes like molding, spraying, or 3D printing.

PHYSICAL HYDROGELS

Physical hydrogels are known for being biocompatible, safe, and affordable. One type of physical hydrogel is alginate. Hydrogel is good for helping chondrocytes grow and multiply while also keeping their chondrogenic features. Once chondrocytes are added to it, they can thrive. Within 21 to 28 days, the body produces type II collagen and the advanced cartilage gene. Alginate is also involved in this process. Primary bone cells, such as chemical stem cells (MSCS), are used for bone regeneration. When encapsulated, MSCS can create collagen ECM that merges with the bone. Host tissue is the second most common natural material that comes from things like oyster shells, insects, fungi, and marine waste. Chitosan is a great material for tissue engineering because it is biocompatible and biodegradable. When chitosan is made through enzymatic grafting, it can help chondrocytes grow and multiply. Stem cells help to keep their chondrogenic characteristics and shape and boost the production of extracellular matrix in a lab setting. The extracellular matrix is known as a substance made by cells to provide support. Neutral materials provide a strong support for cells to grow on. These materials are more compatible with the body and can be used in various ways because of their effective properties. Alexander and his colleagues successfully utilized tissue engineering to replace an artificial hip joint 36. Specialists create injection hydrogels that are sensitive to temperature for use in tissue engineering. They mix PEG and PNIPAAM to make these hydrogels. They think that hydrogels made with PNIPAAM have weak strength and low resistance to pressure. Because PNIPAAM polymer is sensitive to temperature, it is a good choice for creating a biological material that can be injected to help regenerate or replace soft tissue. Hydrogels created from natural substances are commonly used in tissue engineering as support structures. They mimic the structure of body tissues and give chemical signals to help cells grow and change. Optical crosslinking is commonly used to create polymer scaffolds for tissue engineering because of their effectiveness. Hydrogels can cure quickly under natural conditions and at normal body temperatures. They have special control over how they solidify, making it possible to create scaffolds in different shapes. When using hydrogels for medical purposes and building tissues, it's important for them to have strong mechanical properties. Characteristics are comparable to those of actual tissue.

Wound Dressing

Wound Dressing: MC methylcellulose hydrogels with silver oxide particles were created by Min Hee Kim and his team for use as wound dressings. This experiment utilized Sprague four week-old field mice. The experiment was conducted in controlled conditions with regulated temperature, humidity, and other factors. The examination of the tissue samples revealed that using MC hydrogel with silver oxide nanoparticles on the wound helped it heal better compared to not using any treatment. Researchers found that using MC hydrogel on burn wounds can help them heal faster. They also looked at how burn wounds are treated with this hydrogel. Study the tissue that has not been treated. Use biological dyes to assess particles on days 1, 3, 7, 14, and 21. The findings indicated that hydrogels without silver nanoparticles led to inflammation and tissue necrosis, whereas hydrogels with silver nanoparticles did not cause inflammation or necrosis. Dressings made of hydrogel can soak up water many times their weight when dry. This helps to absorb fluids from wounds and lower the temperature at the wound area, creating a moist environment that promotes healing. Current wound dressings have drawbacks like not being able to kill bacteria, not allowing enough oxygen and water to pass through, and having weak structure. To solve these issues, Hassan Namazi and his team created a special gel with antibiotics. They made this gel by mixing mesoporous silica with other materials. Carboxy methylcellulose was used as a carrier for nanoparticles. Antibacterial drugs like tetracycline and methylene blue were added to the system and released at different rates. Tetracycline is a type of strong medicine that can be used to help treat skin infections, acne, and wounds on the body. Tetracycline worked well for treating bacterial skin infections when applied on the skin. Methylene blue is a type of dye that can kill germs and is used in people to treat poisoning, kidney stones, methemoglobin, and cyanide. Moreover, it is commonly used as a substance that reacts to light in photodynamic therapy, a new method to combat bacteria that are resistant to antibiotics.

Drug Release

Abdullahi and colleagues were able to create a hydrogel containing fluoxetine using ultrasound. Researchers demonstrated how the drug is slowly released in a model of the human body. They think that the way the drug is released from the hydrogel depends on different things. pH is a crucial factor in drug release, along with the hydrogel's makeup, shape, how it's made, the medication type, and the environment. In a different test, Ganji and his team were able to gradually release pyridostigmine bromide by using a special injectable hydrogel that reacts to changes in temperature. Researchers observed a darker solution when glycerol phosphate salt was added to the chitosan solution during in vitro experiments. Researchers observed how the cloudiness of chitosan and chitosan/glycerol phosphate solutions changed when they contained 8% salt by weight/volume. In a chitosan solution, the cloudiness of the solution stayed the same at 37° C. This means that chitosan solution without glycerol does not change much over time. Phosphate salt does not change with temperature and stays the same for a long time at 37°C. But, when added to chitosan/glycerol phosphate solution, a small increase in cloudiness was seen over time at 37°C. After 9 minutes, the darkness suddenly got darker. The point where the darkness suddenly gets darker is called the point of gel formation. This test proved that when glycerol phosphate salt was added to the chitosan solution, it made the solution less stable at 37° C. It also caused the solution to turn into a gel instead of staying a liquid. [3][11][12][13][14][15]

HYDROGELS CAN BE USED IN MULTIPLE TREATMENTS FOR CANCER

Chemotherapy

Chemotherapy is a helpful treatment for cancer and is often used alongside surgery or other treatments to kill cancer cells. Chemotherapy drugs commonly used in medical treatment have similar issues, like harsh side effects, low tolerance, and difficulty targeting specific areas. Sometimes, chemotherapy may not be able to completely eliminate the disease. Cancer cells are targeted by hydrogels, a great new drug carrier, while also causing harm to the human body, according to. Hydrogels can control how drugs are stored and released. Hydrogels can effectively help deliver cancer drugs and can have lasting effects. They are typically made by linking polymers together in water, which helps lower the chances of risks. The breaking down and clumping together of anti-cancer drugs can happen when they come into contact with organic solvents. Hydrogels are great because they are safe for the body and can break down naturally, which helps to lower the bad effects of chemotherapy. Hydrogels have great properties that help them work well in the body and make it easier for active drugs to be added to them. Making hydrogels that can react to changes in the body is important. The main goal is to effectively deliver drugs to their specific targets, which helps to decrease side effects and make the drugs work better. Lee and his team have been working on this. In 2021, as a specialist content writer, I will rewrite the following text in a more simple and clear way.

Radiation therapy

Radiation therapy is a common and effective way to treat cancer by using high doses of radiation to kill cancer cells and reduce tumour size. Radiation therapy has changed from using radiation everywhere to focusing on specific areas. This helps kill cancer cells effectively by stopping them from repairing their own DNA. Radiotherapy can cause less harm to healthy tissue. But the healing abilities of DNA can interfere with the effectiveness of this treatment. Cancer cells can become more resistant to radiation after being exposed to low oxygen levels, and the amount of radiation given to them may not be evenly spread out when implanted locally. This makes the treatment or remission process less effective. Early stage cancers may be detected using this method, but it is not certain if it works for cancers in later stages or that have spread to other parts of the body. Some hydrogels have multiple networks and a porous structure. Structures can change their shape and react to different triggers inside and outside the body. They can carry precise amounts of radionuclides to target cancer cells effectively.

Immunotherapy

Since cancer has very complicated surroundings, the usual treatments like radiation and chemo don't always work well (Chen and Mellman, 2013; Chen et al., 2018). Immunotherapy techniques can help stop cancer from spreading and coming back by boosting the body's immune system. This is why immunotherapy is so important in fighting cancer. One very helpful way to make traditional cancer treatments work better is by combining them with other treatments. This method has been used a lot to treat different types of cancer. But the immune checkpoint blockers that are often used in hospitals are mostly large molecules called monoclonal antibodies. These antibodies have trouble getting into and building up in solid cancer cells

Hyperthermia

Hyperthermia treatment uses the differences in cancer cells and healthy tissue to kill cancer cells without harming healthy tissue. Heat can make cancer cells' lysosomes unstable, affect their mitochondria, reduce their ability to take in oxygen, and create a low oxygen environment in cancer tissue. This makes cancer cells more sensitive to heat. Researchers from around the world have recognized the positive effects of combining hyperthermia with other treatments. Hyperthermia has the ability to enhance the effectiveness of other therapies. Immunotherapy works well when combined with hyperthermia. Hyperthermia raises the temperature near the cancer, which helps widen blood vessels and speed up blood flow. This helps boost the immune response and makes treatment more effective. Immune cells are more likely to move into the body when hyperthermia is applied, as shown in studies by Dias et al. (2022) and Sengedorj et al. (2022). Additionally, hyperthermia can work together with radiotherapy and chemotherapy to boost their effectiveness. Cancer cells have a hard time keeping things balanced and keeping their cell walls strong when the temperature is high. This can mess up how DNA and proteins work in the cells. Some cancer cells can be tough and not respond well to radiation and chemotherapy drugs (Minaei et al., 2022; Zeng et al., 2022). Certain methods like radiofrequency ablation and microwave ablation are used to treat cancer directly where it is located. Many people are interested in using focused energy ultrasound treatment to treat cancer that cannot be removed through surgery

Photo thermal and photodynamic therapy

Photo thermal therapy (PTT) can penetrate tissues deeply, destroy cancer cells without surgery, and have little resistance to chemotherapy, according to . Photodynamic therapy (PDT) is good because it can target well, has few side effects, is not very invasive, and works really well to cure. Dynamic therapy is a popular cancer treatment that includes using photo thermal agents. These agents, like organic reagents and inorganic nanoparticles, are commonly used but have some drawbacks. They may not be biocompatible and can accumulate in the body in non-specific ways, which can lead to unintended effects. Common side effects in regular tissues and organs can be anticipated.

Hydrogel materials have multiple sizes and multiple delivery routes

Macrogels

Macrogols are big hydrogels that are larger than millimetres. People find microgels interesting because they can hold a lot of medicine, stay strong, and react easily to stimuli. Macrogols are known for their ability to quickly respond to a stimulus. But because they are big in size, it can be tricky to use them for treatment. So, they work better when delivered directly to the affected area, like through trans- methods. In Lima et al.'s study from 2020, they mentioned that dermal administration, direct injection, or applying medication directly to the surface of the surgical cavity are common methods. These methods are often used for treating malignant cancers with complicated anatomical structures like mesothelioma. When cancers like lipoma, stage Iva thymoma, disseminated ovarian cancer, and colorectal cancer spread to the peritoneum, surgeons find it very hard to remove them completely with surgery. Chemotherapy given after surgery may not work well because the drugs have trouble reaching the remaining cancer cells in the body, making it less effective (Motohara et al., 2019). During surgery, high-performing gels are injected or sprayed directly onto the cancer tissue, effectively killing cancer cells and reducing harm to normal tissues. This improves the accuracy and effectiveness of treatment. Norouzi and colleagues (2016) conducted research on a surface filled hydrogel (SFH) that can do the same thing. Majumder and his team (2021) also found this type of hydrogel to be effective. Wrapping tiny particles of microRNA with cancer-fighting abilities.

Microgels

Microgels are small hydrogels that are between 0.5 and 10 micrometres in size and have a bigger surface area than larger hydrogels. They can lower the amount of water-rejecting medicine and manage how it is let out. Microgels are useful for releasing water-hating drugs well. However, they are usually avoided for injecting into blood vessels due to the risk of substances in tiny sizes being easily impacted. A study by Lima and his team in 2020 discovered that macrophages in blood vessels play a key role in phagocytosis. This process is crucial for battling gastrointestinal cancer, lung cancer, and hepatocellular carcinoma. Researchers are investigating how tiny gel particles can help transport medicine through the mouth or lungs. Methods like delivery and TACE could be helpful in delivering cancer-fighting drugs. When a small gel containing medication is taken by mouth, the medicine can go straight to the specific area needing treatment. The medicine can easily enter the cells of stomach cancer and start working fast. Thanks to small gels, the medicine can pass through the gut lining easily and remain effective. Lin and his team found that the treatment's benefits lasted for a long time. In 2018, Minhas and his group created a unique pectin hydrogel that can handle heat and is designed for the colon. This hydrogel is able to deliver 5-fluorouracil (5-FU) to effectively treat colon cancer. The hydrogel is formed by combining methacrylic acid (MAA), ethylene glycol Di methacrylate (EGDMA), and pectin through a process called cross-linking polymerization.

Nanogels

Experts believe that using small engineered materials and medications can be beneficial in treating cancer by mixing various treatments. This innovative approach is significant in the field of cancer treatment. Nevertheless, some of these small materials face challenges in passing through the blood-brain barrier, which can hinder the delivery of drugs that focus on tumors. Nanogels are unique because they have a large surface area and interesting features like nanomaterials. They are also stable and can mix with water, similar to 3D cross-linked materials. Nanogels are strong like parts of our body and can stay intact for a long time without causing any harm. Tiny nanogels smaller than 200 nm are very useful. These small gels can hold many drugs due to their large surface area. They can travel through the blood-brain barrier and attach to specific areas to locate cancer cells. In 2019, Wu and his team found that nanogels are great for carrying drugs. In 2016, Shatsberg and their team created a tiny gel that can transport medicine. They used polyglycerol and placed miR-34a inside. Doctors discovered that a special gel known as nanogel can be used to treat a type of brain cancer called Glioblastoma multiforme (GBM). Researchers found that a particular substance can help reduce the growth of ovarian cancer cells in laboratory experiments. In previous studies, scientists successfully used a tiny gel made of poly (Nisopropylmethacrylamide) (PNIPMAm) to hold epidermal growth factor receptor (EGFR) siRNA and stop the growth of GBM cells when tested on cells and animals. This gel is created by combining pollutant and poly (deca-4,6-diynedioic acid) (PDDA) using a method called crosslinking.

Hydrogels can intelligently respond to internal and external environmental changes and be released on demand

Photosensitive hydrogels

Designing medications that behave similarly to hydrogels and respond to light, especially near-infrared light, is a popular area of research in battling cancer. Using light to turn on these medications is a gentle approach. Gels can help in making hydrogels and causing the release of anti-cancer medications at specific times and locations. Experts commonly use special hydrogels that respond to light for this purpose. These hydrogels effectively convert light into heat, which can assist in eliminating cancer cells when combined with medications and illuminated. In 2021, Wu and colleagues developed a novel technique that reacts to near-infrared light. Researchers used a substance called methylcellulose to create a structure and added various substances to it. They are now using a combination of IR820 photothermal agent and silica nanoparticles to assist individuals with oral cancer. These small particles contain the anti-cancer medication doxorubicin (DOX) and are able to release it in a specific manner. When IR820 is exposed to near-infrared light, it teams up with DOX to produce a powerful effect through both heating and chemical reactions. In 2022, Ding and his team discovered a method to destroy cancer cells permanently by using a special alginate hydrogel. This hydrogel contains special nanoparticles that can effectively treat cancer by using light therapy in the cancer area. In 2021, Azadikhah and his group worked together

PH-responsive hydrogels

Researchers are studying hydrogels that can respond to pH levels in cancer treatment. These hydrogels react to the acidity in the environment around cancer cells and inside the cells themselves. Cancer cells are more acidic than healthy cells, which are slightly alkaline. Experts have found that by utilizing varying pH levels, they can develop a special gel that will only release cancer-fighting medications in acidic conditions. Research conducted by al. (2019) emphasized the significance of drug delivery methods that can pinpoint specific areas of the body, making treatments more effective while reducing side effects in other areas. In 2019, scientists made a unique gel named PTX/FER-8 that can detect pH levels. This gel has a peptide called FER-8 and can hold paclitaxel, a certain medicine. FER-8 hydrogels form when lysine (K), phenylalanine (F), arginine (R), and glutamic acid (E) come together through dehydration condensation. Qu et al. found that the system increased the PTX drug levels in HepG2 cancer cells and kept working for 96 hours, effectively stopping the cancer cells from growing. In 2017, a group of researchers developed a hydrogel drug delivery system by combining N-carboxyethyl chitosan (CEC) with Di benzaldehyde-terminated polyethylene glycol (PEGDA) through a special bonding reaction. The active drug in the system is Doxorubicin (Dox). pH-responsive hydrogels have been found to target well, work effectively in treatment, and cause fewer side effects. A study by Liu and their team in 2022 showed that responsive hydrogels could be a good option for treating cancer. Researchers developed a special gel with gemcitabine (GEM) and paclitaxel (PTX). This gel is made of amino acids and works well with different pH levels. It can be used with different drug combinations for treatment.

Thermosensitive hydrogel

According to Zhang and colleagues (2022d), managing temperature can be easy but sometimes annoying. Temperature-responsive hydrogels have advantages like being easy to control, simple to use, and changing slowly. They also make it easier to release drugs and combine multiple therapies (Shen et al., 2022). Recently, temperature-sensitive hydrogels have become very popular among researchers. They have shown great potential for cancer treatment. When these hydrogels are injected into the body, they turn into a gel at the injection site. This happens because the body's temperature is higher than the critical temperature for the hydrogel. This allows the gel to form quickly and stay in liquid form at room temperature. Temperature-sensitive hydrogels that can be injected into the body are able to carry different things such as cancer drugs, genetic material, healing agents, light therapy drugs, immune system suppressors, and radioactive particles all at once. These things can be given directly to a specific spot in the body using these gels. The gel can be used to aim at certain sick tissues, organs, or hollow spaces in the body. It can also be put under the skin. When it becomes a gel in the body, the hydrogel can effectively release medicine. Khan and his team figured out how to carefully and controlled release a substance over a long time (2019). In 2018, Lv and his team looked into this process too. They made a new gel that reacts to temperature by mixing various materials. This gel could store drugs such as DOX, IL-2, and IFN-γ and let them out when necessary. Using chemotherapy alongside immunotherapy to develop a new way of treating diseases.

Redox-responsive hydrogels

Found that high levels of glutathione in cells can cause the release of drugs from redox sensitive hydrogels by creating a reducing environment. Researchers showed that cancer cells have four times more glutathione compared to regular cells. Additionally, the level of glutathione inside the cells is much higher than outside the cells. As a result, redox-responsive hydrogels have the benefits of regular hydrogels and can target specific areas when releasing medication, effectively destroying cancer cells and minimizing harm to healthy cells. Krisch and his team created a redox-responsive nanogel using thiol-functionalized aspartate and added fluores- to it. The research used cent dextran as a sample drug. It found that the nanogel will break down in cancer cells' environment and release the drug as needed. Additionally, a naturally glowing photoclick component can be added to redox-responsive hydrogels to create a smart delivery system for cancer treatment that is safe and effective. Li and colleagues (2016) created a way to track and target things effectively using fluorescence. Researchers developed special hyaluronic acid nanogels loaded with cytochrome c to deliver it directly to cells that are activated by CD44. This helps speed up the process of cancer cell death and prevents cancer from coming back. Using confocal microscopy, it was found that cancer cells effectively and accurately took in HA-NGs, while normal cells rarely did. Tests were conducted both in the lab and with live animals. Experiments showed that the special hydrogel that responds to redox can find and destroy cancer cells without causing many side effects in the body.

Oxygen-sensitive hydrogels

Reactive oxygen species (ROS) are found in the surroundings of various solid cancers and leftover cancers after surgery, helping cancer to grow and spread to other parts of the body (Zhang et al., 2021b). Hence, researchers around the world are starting to focus more on using oxygen-sensitive treatments for cancer. This method is becoming popular because it is proving to be effective in fighting cancer. Hydrogels that are sensitive to oxygen could be really useful in treating cancer because they are very stable, can carry a lot of medicine, can change their surface, and react well to changes in their environment. Zhang and colleagues (2022e) created a hydrogel that reacts to ROS using a material called poly (deca-4,6-diynedioic acid) (PDDA). The hydrogel proved to be flexible enough to continuously release both photosensitizers and immune checkpoint blocking (ICB) antibodies, leading to effective treatment. Chen and his team have discovered that combining photodynamic therapy with ICB therapy can work well together in treating certain types of cancers that are hard to treat. This combination has a lot of promise for treating cancers that don't respond well to immune therapy. In 2022, researchers created a special hydrogel that can react to changes in temperature and ROS levels. This hydrogel is made using BCNU, TMZ, and poly (lactic-co-glycolic) acid nanoparticles. It helps stop glioma from coming back after surgery. But as the cancer gets bigger, the unusual blood vessels in the cancer may not give enough oxygen, leading to less ROS (Zou et al., 2020). To improve the effectiveness of oxygen-sensitive anticancer treatments and reverse cancer hypoxia, Zhou et al. (2022c) came up with a clever design involving a biguanide. Altered chitosan, known as Bi-Ch, has been proven to effectively stop abnormal cancer cell energy production and help change the low-oxygen environment in cancer cells. Bi-Ch has been proven to increase the amount of doxorubicin in cancer cells, which significantly boosts the effectiveness of chemotherapy and photodynamic therapy that are sensitive to oxygen. This makes Bi-Ch a very hopeful option for treatment. Zhou and colleagues found that certain substances can slow down the growth and spread of cancer cells. In another study, Zhang and his team discovered a link between ROS and cancer. A new type of hydrogel was created using tegafur -protoporphyrin IX heterodimers, chitosan, and silk sericin. When the hydrogel was injected into a tumor, it caused the tumor to change. A drug reservoir is placed inside the cancer to slowly and accurately release the drug, bypassing different obstacles in the body.[4][5][16][17][18][19][20]

CONCLUSION

Hydrogel materials, known for their exceptional biocompatibility and biodegradability, serve as innovative drug carriers in cancer treatment, offering three significant benefits. Firstly, these materials function as precise and controlled drug delivery systems, enabling the continuous and sequential release of various therapeutic agents, including chemotherapeutics, radionuclides, immunosuppressants, hyperthermia agents, and phototherapy agents. They are extensively utilized in cancer therapies such as radiotherapy, chemotherapy, immunotherapy, hyperthermia, photodynamic therapy, and photo thermal therapy. Secondly, hydrogels come in various sizes and can be administered through multiple delivery routes, allowing for targeted treatment of different cancer types and locations. This capability enhances drug targeting, reduces the required dosage, and improves overall treatment efficacy. Lastly, hydrogels can intelligently respond to changes in their environment, allowing for the remote control and on-demand release of anti-cancer agents based on internal and external stimuli. With these advantages, hydrogel materials have emerged as a promising solution in cancer treatment, offering hope for improved survival rates and enhanced quality of life for cancer patients.

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