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Review Article

Recent Advances in Smart Hydrogel for Drug Delivery in Cancer Therapeutics

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ABSTRACT

Cancer has been listed as the world's second-leading cause of death. Even with the significant progress made in recent years, advanced stages of the disease are still incurable. Conventional treatment options, such as surgery, chemotherapy and radiotherapy, have several inherent drawbacks that result in severe side effects and poor therapeutic efficacy. These drawbacks include their limited applicability, low bioavailability, multidrug resistance and high recurrence. Three-dimensional networks of natural or synthetic polymers, known as hydrogels, have special qualities like biocompatibility, elasticity, porosity, permeability, softness and similarity to soft biological tissues. By enabling controlled drug release and lowering non-targeted exposure, hydrogel-based drug delivery systems have demonstrated improved results in minimizing side effects in recent times. Smart hydrogels that may react to environmental stimuli, such as changes in pH, redox, enzyme levels, temperature, light, shear/strain and so on, to alter their structure and properties. The present review highlights the basics of hydrogels and recent developments in their applications for targeted delivery of anticancer medications.

Keywords Cancer therapeutics, Hydrogel, Smart hydrogel, Stimuli-responsive hydrogel.

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INTRODUCTION

The second deadliest disease in the world is cancer. Global cancer statistics show that in 2020, there were 10 million deaths caused by cancer and 19.3 million additional instances.[1] According to cancer facts and statistics, it is estimated that in 2023, there will be over 609,820 cancer-related fatalities in the US, or nearly 1,670 deaths every day. Cancers of the lungs, prostate and colon in men and the breast, colon and lungs in women account for a greater proportion of fatalities.[2] When risk factors like smoking, being overweight, aging, not following a healthy diet and a growing population are ignored, mortality and morbidity rates from cancer have been continuously increasing. Authorized statistical research indicates that 1 in 8 males and 1 in 10 women have been diagnosed with this disease.[3,4] According to WHO forecasts, there will be more than 10 million new instances of cancer reported annually and 13.1 million deaths worldwide from cancer by 2030.

Conventional cancer therapies typically include surgery, precision medicine, targeted therapy, immunotherapy, radiation therapy; chemotherapy, hormone therapy and stem cell transplantation.[5] The type of cancer, its stage of development, potential side effects and the patient's overall condition significantly affect the treatment approaches for cancer. One of the most important cancer treatment strategies is chemotherapy, which mainly kills cancer cells by using toxic chemicals locally or systemically to extend patient life, inhibit the progression of the disease, can provide palliative care by reducing certain cancer symptoms.[6,7] Chemotherapy damages the human body significantly while often not being able to eradicate cancer cells.[8] The most significant adverse effects of traditional chemotherapy include non-selectivity, Multidrug Resistance (MDR), insolubility of some anticancer medications and systemic toxicity (nausea, vomiting, skin rash, neuropathy, hair loss, low blood cell counts and lack of appetite).[9,10] Among the most common and effective cancer treatment techniques is radiation therapy, which typically uses high radiation doses to destroy cancerous cells.[11] To cause cancer cell death, internal Radioisotope Treatment (RIT) introduces therapeutic radioisotope compounds into tumoral tissues using a non-invasive approach. External Beam Radiation Treatment (EBRT) is a treatment that uses external beams of protons, electrons, or high-energy X-rays to directly target and destroy tumors.[12] By interfering with the DNA self-repair mechanism of cancer cells, this approach effectively eliminates them with minimum damage to healthy tissues.[13,14] Current conventional treatment of cancer is schematically depicted in Figure 1.

Traditional cancer treatments involve surgery that removes the cancer physically, chemotherapy that delivers antitumor drugs

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systemically and radiotherapy which uses ionizing charged ionizing radiation and beams to kill cancer cells. Current therapies are typically associated with severe side effects such as limited targeting, low tolerance and ineffectiveness, which significantly damage nourishing cells while destroying cancer cells.[15] It has been found that high radiation dosages can damage patients' peritumoral normal tissues permanently and have several kinds of additional adverse effects.[16] The main limitation of radiation therapy is its non-targetability, which can result in a variety of negative implications like fatigue, vomiting, nausea and hair loss.[17,18] Antitumor medications are highly toxic to the liver, kidneys, or haematological system because they are particularly harmful to cells that multiply quickly or are involved in the process of metabolism and elimination of drugs.[19] The issues that cause treatment failure are cancer metastasis and recurrence because currently recommended treatment modalities such as chemotherapy, radiation therapy, surgery, etc., are not sufficiently effective.[20]

HYDROGEL

The first hydrogel material appeared in literature in 1960. A biocompatible hydrogel made of Polyhydroxy Ethyl Methacrylate (PHEMA) was described by Wichterle and Lim and applied to applications involving permanent contact with human tissues.[21] A gel that swells when exposed to water or aqueous solutions is referred to as "hydrogel".[22] In hydrogels, hydrophilic macromolecules are arranged in three-dimensional polymeric networks that possess superior swelling, elastic and absorbent properties. Hydrogels possess numerous potential applications in the biomedical and pharmaceutical sectors due to their unique features, which include being soft, flexible, porous, biocompatible and similar to live tissue.[23,24] Hydrophilic polymer chains absorb an immense amount of water to create hydrogels.[25] Hydrogels with hydrophilic groups (-OH, -CONH-, -$CONH_2$- and -SO_3H) in their structure are more likely to absorb water. The 90% water content provides a physiologically appropriate environment for the cargo.[26] Transverse connections of monomeric or polymeric networks, as well as covalent and noncovalent interactions, are used to prepare hydrogels. The gelation mechanism of hydrogels forms a branched three-dimensional network structure through macromolecular polymerization. The primary function of functional groups joined to the backbone of polymers is to facilitate the absorption of water, whereas polymeric chains are resistant to dissolving in aqueous solutions because of cross-links that exist between them. Hydrogels are a great option for biomedical applications because of their unique characteristics, which include their hydrophilic activity, soft tissue-like water content, ductility and sensitivity to physiological changes.[27,28]

Hydrogels are a novel class of drug carriers with numerous positive attributes that could revolutionize cancer treatment approaches. First of all, hydrogels are excellent at delivering drugs and releasing them under precise control. Therefore, an integrated cancer therapy sequence can be made possible by loading hydrogels with a range of pharmaceutical agents, including immunosuppressants, radionuclides and chemotherapeutic drugs, to cause a series of events that involve multiple therapeutic modalities.[29] Because of its high drug loading, sustained drug release, controllability, biocompatibility and sensitivity to particular stimuli, hydrogel-based therapy is emerging as a potentially effective cancer treatment choice. Hydrogels are an effective way to engage in cancer treatment delivery because they can control drug loading and release with long-lasting effects.[30] The hydrogel carrier enables multiple medications to work together to create synergistic anticancer effects at low dosages and high drug loading, while also allowing the administration of drugs directly into the tumor site.[31] Hydrogel-based targeted delivery of anticancer drugs to tumor locations is becoming more popular as a way to minimize drug toxicity in the tumor region.[32,33] In recent years, multiple formulations based on hydrogel have been designed for the diagnosis, treatment and prevention of cancer; some of these have even enrolled in clinical studies. It was suggested that hydrogel have potential applications as medication transporters in cancer treatments because they have been effectively employed in several biomedical applications.

Hydrogels are categorized based on many factors such as their physical characteristics, degree of swelling, process of manufacturing, origin, ionic charges, sources, biodegradation rate and noticeable types of cross-linking.[34] Based on the sources of their constituent parts, hydrogels are classified into two categories i.e. natural and synthetic[35] Three synthetic hydrogels that are frequently utilized are poly (ethylene glycol), poly (vinyl alcohol) and Polyhydroxy Ethyl Methacrylate (PHEMA) (PEG). Polysaccharides (like hyaluronic acid and alginate), proteins (like collagen and gelatine) and DNA are examples of natural hydrogels. Anionic, cationic and neutral hydrogels are the three categories of hydrogels classified according to their network charge. The polymer's charge determines the charge of the entire network.[36,37] There are three groups of hydrogels based on the polymeric compositions. Hydrogels are made of homopolymers, which consist of a single species of monomer. Copolymeric hydrogels consist of two or more monomer species, one of which is hydrophilic in nature. Multipolymeric hydrogels consist of two distinct but connected polymer chains.[38] Homopolymer: consists of a single species of monomer. Depending on the type of cross-linking junctions, hydrogels can be categorized as chemically or physically cross-linked. Physical hydrogels are produced at the molecular level through interactions between noncovalent bonds. Hydrogels that have been chemically cross-linked are created by irreversible covalent cross-linking interactions. Chemical cross-linking interactions bring the direct contact of linear or branched polymers, which gives them extremely high mechanical strength.[39-41] Chemically cross-linked hydrogels are created by irreversible covalent cross-linking

interactions. Hydrogel swelling in aqueous solutions is controlled by networks of polymeric molecules with functional groups. Physical hydrogels are produced at the molecular level through interactions between noncovalent bonds.

SMART HYDROGELS

The term 'smart' or 'intelligent' was created to describe these hydrogels in the way that they sense a stimulus and react by changing their chemical or physical behavior, which causes the drug that is trapped to release. Transporting therapeutic agents to an affected area and releasing their contents in responds to internal or external stimuli (e.g., pH, enzymes, redox, temperature and light) is known as a stimuli-sensitive drug delivery system.[42] Smart hydrogels are multifunctional materials that can be created from a single or combination of polymers.[43] The hydrophilic groups (-NH_2, -OH, -COOH, -SO_3H, etc.,) present on the polymer chains, together with capillary action and osmotic pressure, are responsible for hydrogels' high-water absorption capacity.[44] In terms of smart hydrogel therapeutic systems, diffusion, matrix breakdown and material shrinking or swelling all influence the active ingredient's release. Smart hydrogels can exhibit temperature, photoelectricity and pH impacts, which can modify the hydrogel's characteristics to enable sustained and controlled drug release. By achieving dual controllability over both time and location across the drug delivery process, this smart hydrogel platform improves the effectiveness of treating oral tumors while lowering adverse effects.[45,46] Due to their ability to precisely control individual reactions, these smart hydrogels that are multi-responsive offer a competitive advantage in targeted medication administration.[47-49] The therapeutic effectiveness of the pharmaceuticals is increased while fewer adverse effects are done to healthy tissues due to the responsive hydrogels' potential to recognize changes in tumor tissue and release medications in response.[50]

pH-responsive hydrogel

The term "pH-responsive hydrogel" refers to a hydrogel composition that reacts to changes in environmental pH. Ionic pendant groups in polymeric hydrogels that can provide or take protons in response to pH shifts in the surrounding environment have been described by Patel and Mequanint.[51] Polymers can be added to the pH-responsive hydrogel system to form an interpenetrating network that will improve the system's mechanical properties, rheological behaviour and sensitivity to reversible pH-induced swelling and de-swelling.[52] Among these, the two most significant factors for regulating the characteristics of pH-responsive hydrogels are pH and the type of pendant groups. Due to the protonation of amino/imine groups, cationic hydrogels such as chitosan and poly (ethylene imine)[53] swell in low pH (acidic medium). In conditions with a higher pH (basic medium), anionic hydrogels such as carboxymethyl chitosan swell because of ionization of the acidic groups. Hydrogels that respond to variations in pH are produced by polymers that react to changes in pH and have Proton-accepting and proton-releasing ionizable functional groups.[54,55] Drugs distributed inside the extracellular framework of tumorous tissues are more effectively delivered by cationic hydrogels and the administration of drugs within tumor cells is better delivered by anionic hydrogels.[56,57] By creating polyelectrolyte complexes between cationic (like chitosan) and anionic (like alginate and dextran) polymers, pH-sensitive hydrogels can also be formed without the need for chemical cross-linkers.[58,59] Several mechanisms, including destabilization, dissociation and modification of the drug/vehicle partition coefficient, lead to conformational modifications in pH-sensitive polymers.

Yuan Fen Liu *et al.*, developed a pH-responsive injectable OE peptide hydrogel that can be used as a carrier material for the anticancer medications Paclitaxel (PTX) and Gemcitabine (GEM) that has the ability to release drugs at the tumour site concurrently to produce the anticancer activity. GEM is a difluorinated nucleoside antimetabolite drug that dissolves in water. Its short half-life and requirement for constant high dosages make it extremely risky, but when used alone, it is remarkably excellent for a broad variety of solid tumours.[60] PTX is a diterpene alkaloid drug that is very lipid-soluble. Despite having additional issues, such as low absorption, it is less harmful than certain other anticancer treatments.[61] PTX and GEM together are frequently used in cancer treatment to minimize adverse effects and increase efficacy, after figuring out the OE polypeptide's ideal gelation concentration. The authors carried out an *in vitro* release study for seven days to demonstrate its pH sensitivity. PTX was released from the OE hydrogel at pH values 5.8 and 7.4 at rates of 96.90% and 38.98%, respectively. GEM's release from the OE hydrogel was 99.99% and 99.63% in three days with pH values of 5.8 and 7.4.[62]

Hyaluronic Acid (HA) and Fluorescein Isothiocyanate (FITC) were combined to create a Mesoporous Silica Nanocomposite (MSN) by Chen and Liu (2016). Through sensitive interactions (hydrogen bonds) between HA, these MSN may self-assemble into hydrogels enveloping tumour tissue. Because of its controlled release properties and drug loading in the FITC-HA-MSN nanoconjugate, Doxorubicin (DOX) was selected as the model drug. To prevent a recurrence, the hydrogel can provide several kinds of anti-tumour medications within and surrounding tumor tissue. It can also pinpoint the exact position of tumour and remain in the microenvironment for an extended period. Under physiologically simulated conditions, an investigation was conducted on the precise nature of Dox's controlled-release from the FITC-HAMSN nanoconjugate. The release of FITCHA-MSN nanocarriers will occur from the progressive degradation of the HA hydrogel network by HAase, an enzyme that is commonly found in tumor tissue. Based on cytotoxicity studies, FITCHA-MSN nanohydrogels containing Doxorubicin

(DOX) exhibited higher cytotoxicity towards tumor cells while exhibiting less toxicity towards normal cells.[63]

Temperature responsive hydrogel

Thermosensitive or temperature-sensitive hydrogels are hydrogels that react to variations in temperature. Additionally, there are several notable advantages that temperature-responsive hydrogels provide, including easy handling, gradual drug release and simplicity in combining multiple therapies.[64] Thermoresponsive hydrogels exhibit gelling behaviour that can only be influenced by temperature changes, independent of any other external stimuli. The phrase "sol-gel transition" refers to the phenomenon where a solution converts into a gel. A solidification and separation from solution are observed in certain hydrogels at higher temperatures. The Lower Critical Solution Temperature (LCST) is an indication of this threshold. The polymers are soluble below the LCST Gel formation results from their increasing hydrophobicity and insoluble nature above the LCST. In contrast, the Upper Critical Solution Temperature (UCST) of hydrogels formed during the cooling of a polymer solution. Several methods may be employed in experiments to check the sol-gel transition of thermosensitive hydrogels, including spectroscopy,[65] Differential Scanning Calorimetry (DSC)[66] and rheology.[67] With its enormous potential for application in cancer therapy. Nowadays, among the most desired types of responsive hydrogels is temperature-sensitive hydrogel.[68,69]

Wu *et al*., (2014) developed cisplatin containing thermosensitive hydrogel (PEG-PCL-PEG/DDP, PECE/DDP) and Paclitaxel-loaded polymeric micelles are combined to provide an *in situ* gel-based dual drug delivery system (PEG-PCL-PEG/DDP+MPEG-PCL/PTX, abbreviated as PDMP). For the lung cancer therapy, PTX and cisplatin (DDP) are both commonly used chemotherapeutic drugs. Monomethoxy Poly (Ethylene Glycol)-Poly(ε-Caprolactone) (MPEG-PCL), an amphiphilic copolymer, indicates potential and has been employed as a vehicle for anti-tumor administration of drugs. To increase the Permeability and Retention (EPR), The use of MPEG-PCL copolymers as drug delivery systems has been extensively employed to improve the therapeutic efficacy of hydrophobic drugs by overcoming their insoluble nature.[70,71] PDMP, a hydrogel composite that was formed *in situ* showed DDP-loaded PECE hydrogel with MPEG-PCL/PTX micelles. When subjected to body temperature, PDMP transforms into a stationary hydrogel from a solution state, indicating that it could be a useful drug reservoir for orthotropic lung cancer treatment. The rheological assay was additionally performed to check the thermosensitivity of the PDMP hydrogel composite. The xenografted lung cancer model has been employed in *in vivo* research to assess the PDMP's anti-tumor activity. The findings indicated that PDMP is useful in preventing growth of tumour and extending the period of tumor-bearing BALB/c nude mice survive.[72]

Fong *et al*., synthesized the conjugated Graphene Oxide (GO)/Folic Acid (FA) (GOFA) for the specific delivery of the anticancer medication doxorubicin by utilizing the pH-sensitive drug release properties of GO following intracellular absorption. Doxorubicin is an effective anthracycline antibiotic for treating different types of cancers. It works mostly on DNA by inhibiting the transcription and replication processes.[73,74] Further, injectable *in situ* thermosensitive Hyaluronic Acid-Chitosan-g-Poly (N-isopropyl acrylamide) (HACPN) hydrogel is used to encapsulate GOFA-DOX. As an injected hydrogel drug delivery vehicle, the HACPN hydrogel is more suitable.[75] HACPN hydrogel could readily fulfill one of the main requirements of intratumoral dispersion using *in situ* depot-forming systems, especially in local delivery.[76] At 25°C, the HACPN solution flowed freely; at 37°C, it gelled.[77] Drugs can be continually released by the gelled HACPN to release DOX inside the tumor. The MTT tests proved that GOFA-DOX/HACPN's cytotoxicity on MCF-7 cells was time and dose-dependent. According to *in vivo* anti-tumour tests, Intratumor administration of GOFA DOX/HACPN is an effective and safe drug delivery strategy for breast cancer.[78]

Light responsive hydrogel

Photoresponsive polymers are unique types of polymers that show reversible modifications in conformation and structure in reaction to light and dark.[79] Researchers are very interested in light stimulation as one of the main external stimuli for "smart" hydrogels.[80] It provides an option of reversible, remote applications with extremely fine control over spatiotemporal characteristics and intensity.[81,82] Photosensitive moieties are incorporated into the polymer structure to produce light-responsive hydrogels. depending on the Photosensitizer (PS) used the response may be reversible or irreversible.[83] Some examples of photo-responsive agents are reduced graphene oxide,[84] indo-cyanine green,[85] gold nanoparticles,[86] iron oxide[87] and black phosphorus quantum dots.[88] Hydrogels with photosensitive groups are susceptible to cleavage, isomerization, or dimerization in response to light. The hydrogel structure may additionally undergo partial or total decrosslinking, degradation, swelling, or shrinking. The hydrogel's drug release phenomenon can be regulated at specific locations to prevent systemic exposure by using light. When exposed to light, light-responsive hydrogels can absorb it and produce a lot of heat around the cancer location, which can kill cancer cells in concert with medications delivered in a synergistic manner.[89,90]

Kang *et al*., created DNA cross-linked hydrogel in which complementary DNAs (cDNAs), which reacts differently when exposed to different wavelengths of light, can be hybridized by adding photosensitive azobenzene molecules to DNA strands as crosslinkers. By leveraging the photo-induced reversible sol-gel transitions, the hydrogel was employed for precisely encapsulate and release gold nanoparticles, fluorescein, horseradish peroxidase and chemotherapeutic drugs like doxorubicin. At 450

nm, doxorubicin was incorporated within the hydrogel and at 350 nm, photons discharged it. According to *in vitro* release data, doxorubicin had a net drug release rate of 65% with a sustained therapeutic effect after 10 min. This suggested that the hydrogel system could offer an effective delivery mechanism for anti-tumor drugs in targeted therapy.[91]

Mingyu Yang *et al.*, developed HA-dopamine-based sodium Selenite (Se)-directed cross-linked hydrogels loaded with Indocyanine Green (ICG), a photothermal agent, for the purpose of targeted breast cancer therapy. Dopamine and HA were covalently bound to produce the HD conjugate with the generation of an amide link through the coupling of NHS and EDC HCl.[92] Se was employed as a pH modulator, coordinating intermediary and antitumor agent in gel crosslinking. She can provide an alkaline pH, work with the functional groups of HD to promote the polymerization of dopamine (in the HD conjugate) and destroy cancer cells by pro-oxidant actions. The covalent connection of the dopamine group and the way that selenium interacts with the functional groups of HD were used to create the HD/Se gel. With significant temperature increases, the hydrogel-entrapped ICG demonstrated good photothermal effectiveness. ICG's photothermal effect paired with Se's pro-oxidant activity significantly inhibits tumor growth without hurting health. In MDA-MB-231 cells, the combined anticancer effects of Se and ICG were examined in the absence or presence of NIR laser irradiation. MDA-MB-231 cells was also used to assess Se's antiproliferative properties. The multifunctional cross-linked HD/Se/ICG gel system is a suitable and safe option for breast cancer locoregional therapy.[93]

Dual responsive hydrogel

Due to their many potential applications and capabilities, pH- and temperature-sensitive hydrogels are prominent instances of dual-responsive hydrogels. A highly injectable system that undergoes a sol-to-gel conversion *in situ* responds to body temperature and facilitates the release of drugs at a certain tumor pH is very desirable in an environment of cancer.[94]

Singh *et al.*, created temperature- and pH-triggered PNIPAM smart Nanogel systems (NPs) that were loaded with Anastrozole (ANST) using a solvent evaporation technique for pH and temperature-sensitive delivery of drugs. The solvent evaporation technique was used to prepare the blank and the ANST-loaded nanocarrier (ANST).[95] 50 mg of Poly-N-isopropyl acrylamide and 5 mg of ANST usually dissolved in 2 mL of acetone. The drug and polymer solution were added dropwise to an aqueous solution containing 0.2% D-α-Tocopheryl Polyethylene glycol 1000 Succinate (TPGS) or Tween-80 in order to form an organic phase in O/W emulsion. The mixture was then sonicated using a pulse mode with an energy output of 30% magnitude.[96] The formulation exhibited a significantly faster release of ANST at pH 5.0 compared to pH 7.4, potentially indicating optimal release within the microenvironment of the tumor. *In vitro* cytotoxicity demonstrated that the NPs beat free ANST in terms of cell uptake and anti-tumor activities on MCF-7 cells.[97]

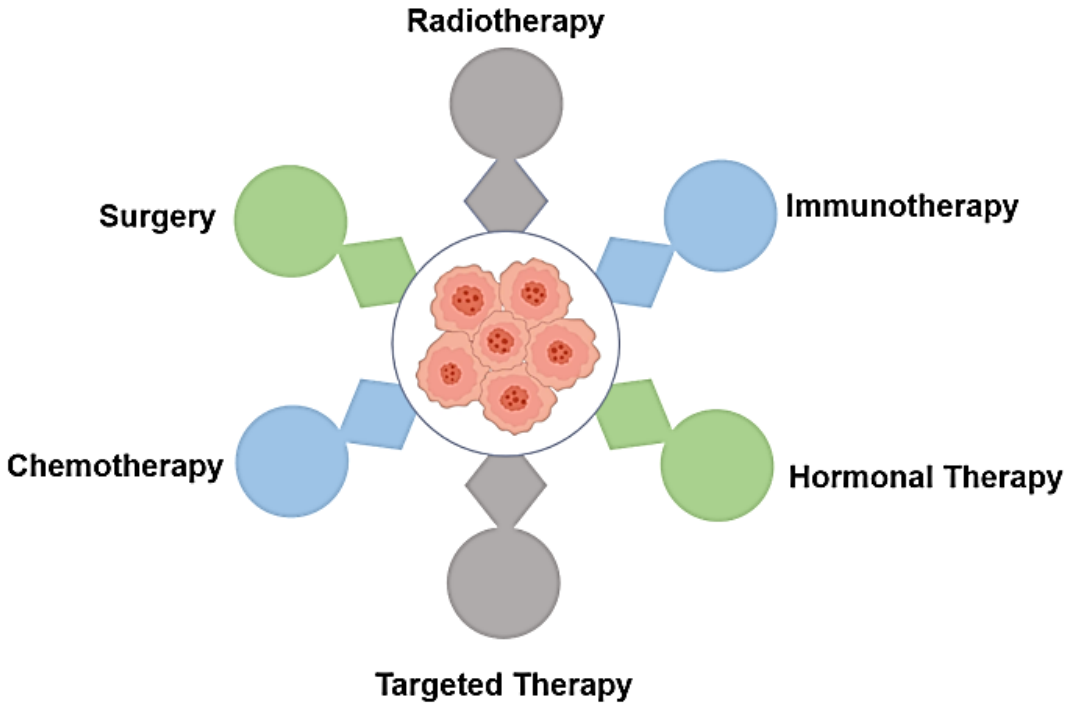

Figure 1: Current conventional treatment of cancer.

Marziyeh Fathi *et al.*, prepared Chitosan/poly(N-isopropyl acrylamide-co-itaconic acid) dual thermo-and pH-sensitive injectable hydrogels for doxorubicin administration in breast cancer. At 37°C and 40°C, chitosan solutions with pH values of 5.5 and 7.4 were combined with synthetic poly (Nisopropylacrylamide-co-itaconic acid) (PNIAAm-co-IA) to create hydrogels. When DOX was incorporated in the hydrogel combination, its presence was verified by the FT-IR spectra. The overall release of DOX was assessed *in vitro* at various temperatures and pH levels. At pH 5.5, DOX was released more quickly than at pH 7.4, possibly because the hydrogel swelled more quickly in an acidic solution. The release concentration at 37°C was greater than at 40°C at pH 5.5, resulting in sustained drug release at pH 5.5 at 40°C. The study evaluated the hydrogels' cytotoxicity using an MTT assay. According to cytotoxicity tests, MCF-7 cells treated with hydrogel leachates maintained a viability level above 90%. The study proposed the use of an engineered smart copolymer in natural-based hydrogels to develop hydrogels with improved environmental responses for breast cancer therapy.[98]

Mohadese Mahdian *et al.*, synthesized a NIR/pH dual-responsive hydrogel for drug delivery of Curcumin (CU) as a model antitumour drug. Chitosan NCs and PDA NPs, a dual stimuli-responsive hydrogel was created that was then used as a drug carrier to deliver the antitumour drug CUR. First, chitosan nanocapsules were used to initially encapsulate the CUR and then integrated into hydrogel, which responded to changes in pH and exposure to NIR light, respectively. Through the use of TEM, FT-IR and DLS methods, The CUR was encapsulated inside CURNCs was examined. The Polydopamine Nanoparticles (PDA NPs)-containing glucose-cross-linked gelatin hydrogel (referred to as GGPDNCs) was used to protect the CUR-loaded Chitosan Nanocapsules (CURNCs). At two different pH levels and two temperatures, 37°C and 50°C, an examination was conducted on the CUR release from GGPDNCs-hydrogel. Based on the results, Temperature-dependent CUR release maximized at 50°C and pH 5.0. Cell viability was examined *in vitro* through the MTT assay, shown the cytotoxic effect of CURNCs on CT26 cells. The proposed hydrogel offers excellent pH and temperature-controlled release profile along with loading efficiency that is similar to certain recently developed curcumin delivery technologies.[53]

Magnetic responsive hydrogel

Magnetic-responsive hydrogels are widely used stimulus-responsive hydrogels that have received a lot of for remote-controlled drug delivery.[99] Magnetically responsive hydrogels are generally produced by combining magnetically sensitive materials with hydrogel networks.[100] Composite materials with biocompatibility, biodegradation and magnetic responsiveness are used to create magnetic hydrogels. To develop magnetic hydrogels for use in biomedical applications, as well as various magnetic nanoparticles including transition metal ferrites ($CoFe_2O_4$, $MnFe_2O_4$ and iron oxide (Fe_3O_4, γ-Fe_2O_3)[101,102] and Transition metal alloys (FePt) can be utilized as magnetically responsive elements in hydrogels. Typically, magnetic hydrogels are composed of a hydrogel matrix combined with a magnetic element that is integrated into the matrix. The superior penetration to deep organs and minimum interference of magnetic-field-sensitive hydrogels are two key benefits that have gained particular interest.[103] The intrinsic non-responsive hydrogels become responsive to external magnetic stimuli through the addition of magnetic inclusions, allowing them to be remotely and tunablely magnetically operated to move, deform and transform in response to magnetic fields.

Wu *et al.*, prepared created an inclusion complex between a-Cyclodextrin (a-CD) and Using PEGylated Iron Oxide (Fe_3O_4) nanoparticles, an injectable magnetic hydrogel with shear thinning has been developed. PEGylated Fe_3O_4 nanoparticles were coated with a-CD partly inclusion complexes to create a self-assembling Magnetic Supramolecular Hydrogel (MSH) that is suitable for controlled thermoreversible gel-sol transition and shear thinning injection. In addition, the lipid layer of Magnetic Nanoparticles (MNPs) may be colored by hydrophobic compounds like PTX using biocompatible supramolecular hydrogels. Extended anticancer drug concentration can be obtained due to the dual structure of MSH, which allows for distinct release processes from a single sample containing multiple drug molecules MNP-mediated generation of heat during gel-sol has the potential to damage cancer cells and start the release of anti-cancer drugs. Experiments conducted *in vivo* on animal models containing tumors have demonstrated that MSH possesses the reliable ability to eradicate tumors in concert and to completely inhibit the local recurrence of breast cancer on surgical excision.[104]

Electric responsive hydrogel

Hydrogels that are sensitive to electrical fields can undergo alterations in their properties such as expansion, contraction, deformation, or deterioration. Electrically conductive polymers are a promising strategy for on-demand DDSs because they can be reduced or oxidized to release integrated small molecules.[105] Another strategy to formulate electricity-sensitive hydrogels is to incorporate conductive inorganic nanomaterials such as carbon nanotubes, graphene and their derivatives, which not only improve the hydrogels' mechanical properties and electrical conductivity, but also facilitate drug release when triggered by an electric field.

Yao *et al.*, developed a unique self-driven Triboelectric Nanogenerator (TENG)-stimulated Catalytic (TENG-Cat) system designed after the electrical preorganization effect observed in natural enzymes. a human self-driven TENG as the electric field stimulator, a nanozyme and a conductive hydrogel made of poly(2,3-dihydrothieno-1,4-dioxin):poly(styrene sulfonate), which could be injected into the tumor tissue to provide electric pulses, generate ROS and increase local accumulation of the

loading nanozyme. Particularly, the self-driven wearable TENG was very biosafe, capable of producing electric pulses while moving and capable of altering electric fields in a flexible manner. An *in vivo* research on mice with extremely aggressive 4T1 breast cancer revealed that the designed TENG-Cat system significantly inhibited the tumor. The smart electric stimuli responsive system's superior antitumor efficacy reveals a new therapeutic mode for self-driven at-home local antitumor therapy.

Enzyme-responsive hydrogel

In the development of functional biomaterials, especially for creating drug delivery systems, the enzyme-responsive approach gained significant attention among the various stimulus-responsive nanocarriers. The enzyme-based approach is very biocompatible and with the help of enzyme-based detection techniques. Treatment can be selectively and effectively administered to tumor regions where enzyme expression is elevated. Enzyme-responsive hydrogels provide a flexible platform for targeted drug delivery, biosensing, tissue engineering and regenerative medicine by utilising particular enzyme-cleavable moieties present in their polymer network. An enzyme-specific substrate or a substrate that mimics an enzyme must be present in the matrix of an enzyme-responsive *in situ* hydrogel system for the enzymatic active centre to be accessible. Significant variations exist between the levels of several enzymes in malignant tumors and normal tissues.[106] The enzymatic reaction occurs after injection into the tumor site and the biomaterial properties subsequently change, which leads to enzyme-mediated cross-linking or cleavage, inducing gelation or drug release.[107]

Wei Li *et al.*, developed MMP-responsive *in situ* forming hydrogel loaded with doxorubicin-encapsulated biodegradable micelles for local chemotherapy of oral squamous cell carcinoma.

Matrix Metalloproteinase 2 (MMP-2) is overexpressed in several cancer forms, including OSCC. It has been observed that MMP-2 plays a critical role in cancer invasion, progression, recurrence and metastasis. By taking advantage of this enzymatic activity, MMP-responsive nanocarriers such as hydrogels and nanoparticles have emerged as viable delivery systems for targeted drugs in cancer therapy.[108] The study developed an MMP-2-responsive injectable Hyaluronic acid (HA) hydrogel for local chemotherapy of OSCC. The hydrogel was formed by loading DOX into an amphipathic PDLLA-PEG-PDLLA triblock copolymer, forming DOX/polymer micelles called NanoDOX. The hydrogel was then mixed with a hydrogel precursor solution of Acrylate-HA (HA-AC) and cross-linked by a peptide. The hydrogel drug depot was injected directly at the tumor site and the drug depot was continuously degraded by up-regulation of MMP-2 expression in OSCC. *In vitro* studies showed a sensitive MMP-2-responsive drug release profile and significant cytotoxicity against squamous cells. *In vivo* investigations showed that the hydrogel depot effectively degraded and released the loaded NanoDOX, inhibiting tumor growth and reducing drug side effects.

Su T. *et al.*, designed an enzyme-responsive hydrogel composed of Glucose Oxidase (GOx), an N-hydroxylamine-heparin conjugate and β-D-glucose. By using a Glucose Oxidase (GOx)-mediated redox initiation system. This technique enables the rapid synthesis of hydrogels in mild environments with remarkable flexibility in modifying the physical and chemical properties. The developed enzyme-responsive hydrogel targets cancer cells with heparanase overexpression and minimizes the deleterious effects of premature drug release on normal cells. It allows regulated drug release that is initiated by heparin-specific cleavage by heparanase. Cargo is delivered from the hydrogel in amounts determined by the environmental heparanase levels. As heparanase overexpression is a hallmark for cancer cells. The hydrogels that can target these cells and deliver drugs specifically to them, with minimal harm to healthy cells.

Glucose-responsive hydrogel

A glucose-responsive hydrogel responds to changes in glucose levels in the surrounding environment.[109] Hao *et al.*, developed a glucose-responsive hydrogel and near-infrared laser for the treatment of breast cancer. The hydrogel was created by adding iron dichloride tetrahydrate and polyvinylpyrrolidone to degas deionized water, followed by adding gallic acid and GAFe nanocomplexes. Different glucose concentrations were mixed with the components and subjected to gelation conditions, including incubation and 808 nm laser irradiation. GOx, a stable enzyme capable of generating H_2O_2 from glucose, showed peak catalytic activity at certain temperatures. When coupled with GA-Fe nano complexes, a cascade reaction was observed, resulting in extremely reactive •OH radicals. This reaction was glucose-dependent and temperature-sensitive, with the maximum efficiency at 45°C and using NIR photons. The cytotoxicity of the GOx-GA-Fe catalyst combination was tested on breast cancer cells (4T1 murine breast cancer cells, MCF-7, BT474, SK-BR-3 and MDA-MB-231 human breast cells) and it was discovered that it triggers oxidative stress and cell death, especially in the presence of glucose.[110]

Clinical data

Although pre-clinical studies have demonstrated the efficacy of hydrogels in the treatment of liver cancer, further study is needed to get hydrogel-based therapeutics into clinical trials.[111] The hydrogel material can improve the targeting of the loaded medicine to reduce the dose and improve treatment efficiency, which has a major clinical value in further increasing the survival rate and quality of life of patients with malignant cancer. Despite their rapid development and promising applications, hydrogel materials have numerous hurdles in cancer treatment and are still a long way from being clinically viable for direct use.

Currently, the following issues are typically encountered in clinical translation. Considering the advancement of hydrogel-based drug screening and delivery systems, critical technological challenges and practical flexibility remain important road blocks to their successful clinical implementation. Hydrogel immunological adverse effects, including as inflammation, local discomfort, fibrosis and indefinite long-term impact, continue to be a source of concern for extensive clinical translation. Although synthetic tumor models have the potential to be clinically applicable, significant efforts must to be made to mimic tumor heterogeneity and improve their capacity to keep tumor samples viable outside the body.

CHALLENGES AND FUTURE PERSPECTIVE

Transitioning from experimentation to clinical settings is still riddled with challenges. As of right now, no hydrogel is being used to test cancer care standards. Investments of $10 million to $500 million may be necessary for the development of stimuli-responsive hydrogels based on natural polymer categories as "devices" and their products for therapeutic applications. As such, the current focus of research on stimuli-responsive "smart" hydrogels is on developing hydrogels that can react to various environmental stimuli. Research on bioinspired hydrogels that respond to many stimuli will be explored in the future. More effort should be placed into developing novel hydrogels that can dynamically change with minute changes, as well as determining the range of values for every hydrogel that responds to stimuli and produces the intended reaction. In the future, it may be possible to create intelligent injectable hydrogels by controlling drug release from hydrogels in response to extrinsic stimuli like light, magnetic fields, X-rays, ultrasound and microwaves, or intrinsic stimuli like acidic pH, ROS and enzymes in the tumor microenvironment. The potential to overcome current constraints and create next-generation hydrogels with better properties will be demonstrated by developments in materials science and nanotechnology.

CONCLUSION

Developing some innovative approaches is essential to achieving new and efficient cancer therapies, enhancing therapeutic results and lowering the systemic toxicity related to existing drugs. Stimulus-responsive hydrogels provide numerous novel prospects for precisely targeting the tumor location. With the help of hydrogels, anticancer medications can be safely administered to the tumor location in a sustained as well as controlled manner. At the site of the tumor, the release of medication can be regulated by leveraging the unique physiological properties of the tumor microenvironment. It is possible to control the rate and location of medication release can be managed by applying a magnetic field, light, or even small fluctuations in ionic strength. Smart hydrogel-based drug delivery systems, which facilitate site-specific drug delivery, enhance tumor accumulation, decrease off-target effects and provide personalized and precise therapeutic interventions, are poised to revolutionize cancer treatment due to ongoing advancements in material science, nanotechnology and biomedical engineering. When it comes to cancer treatment, *in situ* hydrogels in addition to serving as loading agents and drug carriers for unstable and poorly soluble pharmaceuticals, function as a localized depot for the eventual release of several treatments.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PEG-PCL-PEG: Poly(Ethylene Glycol)-Poly(ε-Caprolactone)-Poly(Ethylene Glycol); **DDP:** Cisplatin; **MPEG-PCL:** Monomethoxy Poly(Ethylene Glycol)-Poly(ε-Caprolactone); **PTX:** Paclitaxel; **EPR:** Enhanced Permeability and Retention; **DDS:** Drug Delivery Systems; **PDMP:** PEG-PCL-PEG/DDP+MPEG-PCL/PTX; **pH:** Potential of Hydrogen; **3D:** Three-Dimensional; **FDA:** Food and Drug Administration; **RBC:** Red Blood Cell; **JCR:** Journal of Controlled Release; **EPR:** Enhanced Permeability and Retention; **TEM:** Transmission Electron Microscopy; **SEM:** Scanning Electron Microscopy; **NMR:** Nuclear Magnetic Resonance; **FTIR:** Fourier Transform Infrared Spectroscopy; **UV-vis:** Ultraviolet-Visible Spectroscopy; **MRI:** Magnetic Resonance Imaging; **ROS:** Reactive Oxygen Species; **EDC:** 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; **NHS:** N-Hydroxysuccinimide; **PVA:** Polyvinyl Alcohol; **PCL:** Polycaprolactone; **PLGA:** Poly(lactic-co-glycolic acid); **HA:** Hyaluronic Acid; **PEG:** Polyethylene Glycol; **PNIPAM:** Poly(N-isopropylacrylamide); **GO:** Graphene Oxide; **DOX:** Doxorubicin; **HPMC:** Hydroxypropyl Methylcellulose; **LCST:** Lower Critical Solution Temperature; **UCST:** Upper Critical Solution Temperature; **EDC/NHS:** 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-Hydroxysuccinimide; **PHEMA:** Poly(2-hydroxyethyl methacrylate); **PVP:** Polyvinylpyrrolidone; **PEO:** Polyethylene Oxide; **PLA:** Polylactic Acid; **PLGA:** Poly(lactic-co-glycolic acid); **PCL:** Polycaprolactone; **PNIPAM:** Poly(N-isopropylacrylamide); **HEMA:** Hydroxyethyl Methacrylate; **NIPAAM:** N-Isopropylacrylamide; **PEGDA:** Polyethylene Glycol Diacrylate; **PAA:** Polyacrylic Acid; **PVA:** Polyvinyl Alcohol; **PCL:** Polycaprolactone; **HA:** Hyaluronic

Acid; **GO:** Graphene Oxide; **DOX:** Doxorubicin; **LCST:** Lower Critical Solution Temperature; **UCST:** Upper Critical Solution Temperature.

SUMMARY

Hydrogels can be used to safely administer anticancer medications to the tumor location in a sustained as well as controlled manner. The release of drug at the tumor site can be regulated according to the tumor microenvironment. The rate and location of drug release can be modulated in response to extrinsic stimuli like light, magnetic fields, X-rays, ultrasound and microwaves, or intrinsic stimuli like acidic pH, ROS and enzymes in the tumor microenvironment. Smart hydrogel-based drug delivery facilitates site-specific drug delivery, enhance tumor accumulation and decrease off-target effects. The current focus of research on smart hydrogels is on developing hydrogels that can respond to multiple environmental stimuli.

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