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A COMPREHENSIVE GUIDE TO HYDROGEL-BASED CONTROLLED DRUG DELIVERY FOR CANCER TREATMENT

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ABSTRACT: Common kinds of chemotherapy may cause harm to normal cells and tissues. Localised chemotherapy, unlike systemic chemotherapy, can lessen side effects by providing a consistent supply of chemotherapeutic chemicals directly to the tumour location. This emphasises the importance of controlled-release biodegradable hydrogels as chemotherapeutic drug delivery systems. This study looks at employing hydrogels as drug delivery methods for HCC, including thermosensitive, pH-sensitive, photosensitive, dual-sensitive, and glutathione-responsive hydrogels. Hydrogel-based drug delivery systems outperform traditional systemic chemotherapy in cancer treatment. Cancer immunotherapy has emerged as the new paradigm for cancer treatment. The development and discovery of new therapeutic molecules has increased the use of immunotherapy in clinical studies. This article discusses the current state of functional hydrogels for effective cancer immunotherapy. First, we will discuss the fundamental principles of cancer immunotherapy and the benefits of employing hydrogels to implement these mechanisms. Finally, we briefly explore the existing issues and potential applications of hydrogels for effective cancer immunotherapy.

INTRODUCTION: Cancer is a deadly disease produced by the unregulated proliferation of aberrant cells in a specific area of the body, resulting in cell damage or death (apoptosis) and death of the host carrier. Cancer has traditionally been considered one of the scariest diseases. In 2018, 9.6 million people died from cancer throughout the world. Currently available cancer therapies include surgery, chemotherapy, radiation, and immunotherapy. Although chemotherapy may be successful in some cases, its general usage is limited because of adverse drug responses, low therapeutic index, drug tolerance, and inadequate targeting.

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To increase chemotherapy efficacy and decrease side effects, various innovative drug delivery techniques have been developed in recent years, including nanotechnology, which can produce selective drug accumulation in tumor tissue *via* passive and active targeting routes. Although nanoparticles have several benefits for targeted distribution, some suffer from burst release, poor adhesion, and permanent deformation, making them unsuitable for long-term administration. Cancer is considered the world's second deadliest illness, accounting for a significant portion of global mortality.

Cancer caused 10 million deaths globally in 2020. In comparison to the rapidly rising global population, the death toll rate has reduced pragmatically from prior years. The death rate in 2018 was 9.6 million, compared to 7.6 million in 2007 [1]. In 2012, 14.1 million new cancer cases and 8.2 million cancer-related deaths were recorded

globally. By 2025, new cancer cases are estimated to total 19.3 million. According to reliable statistical research, one in every eight males and one in every ten women suffer from these disorders [2]. Medicinal plants and their derivatives have traditionally played an important role in medication development of various diseases [3]. Different ypes of nanocarries are used as controlled delivery vehi\cles in the cancer treatment, some of the main are-0-d material, 1- d material, 2-d material, mesoporous, iposomes, micelle, dendrimer, polymeric nanoparticles, and hydrogels. Hydrogels, a new drug carrier, have been routinely employed to deliver tumor drugs [4].

A hydrogel drug carrier has fewer adverse effects than systemic chemotherapy and can deliver drugs to tumor areas for longer periods. Furthermore, hydrogels are more biocompatible, biodegradable, and less toxic than nanoparticle carriers. Smart hydrogels may respond to environmental stimuli (such as heat, pH, light, and ultrasound), allowing for in situ gelation and controlled drug release, significantly improving the convenience and efficiency of drug administration [5]. Hydrogel is a three-dimensional (3D) structure made out of hydrophilic polymers that was first used physiologically by Wichterle and Lim in 1960. Wichterle and Lim used this term for the first time in biology in 1960.10 During the last few decades, the number of references published under the topic "hydrogels" has soared at a tremendous rate, with nearly 5000 papers published in 2010, approximately five times the number of papers published that year related to "nano-technology," which has also recently become a hot topic.

Hydrogels' appeal stems from four properties: biocompatibility, biodegradability, drug-loading ability, and controlled drug release. Biocompatibility means that the hydrogel does not produce noticeable cellular or systemic toxicity in the body after being implanted, nor does it stimulate immune activity. Furthermore, many natural polymers and synthetic polymers used to create hydrogels for cancer therapy are biodegradable. Novel drug delivery systems (NDDS) are a type of pharmaceutical device that has undergone much study and development in recent years. Hydrogel formulations allow for the creation of a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. Because hydrophilic moieties exist in hydrogels, which are hydrophilic polymers, the materials have a three-dimensional network structure, allowing them to absorb large volumes of water. Hydrogels have a wide range of applications for cancer therapy- Hydrogels are commonly utilized in cancer radiation, chemotherapy, immunotherapy, hyperthermia, photodynamic treatment, and photo-thermal therapy because of their high biocompatibility, biodegradability, drug loading, and controlled release properties.

Hydrogels: Van Bemmelen was the first to coin the term "hydrogel" in 1884. Wichterle and Lim introduced cross-linked hydroxyethyl methacrylate (HEMA) hydrogels in 1960 as a form of hydrophobic gel intended for biological applications. Some research has been conducted on hydrogels in regenerative medicine, medication delivery, tissue engineering, and agricultural applications [6]. Hydrogels are classified into three sizes: macroscopic, micro-gels (0.5-10 μm), and nanogels (<200 nm). Diverse sizes and architectures dictate the diverse activities of the hydrogels, as well as the delivery channel by which they are delivered for cancer therapy. There are two types of hydrogels: synthetic and natural. Natural and manmade polymers are excellent drug-delivery polymers for target tissues. Polymeric nanoparticles remain in the bloodstream for an extended period before being removed, allowing them to reach the targeted tumor. They must be non-toxic, biocompatible, and biodegradable.

Natural polymers such as starch, chitosan, alginate, hyaluronic acid, silk, gelatin, collagen, fibrin, and glycosaminoglycans have piqued researchers' attention due to their abundance, nontoxicity, biocompatibility, and biodegradability. Cellulose is an abundant natural polysaccharide that is commonly utilized as a hydrogel due to its great biocompatibility and biodegradability. Cytokines, anticancer vaccines, checkpoint inhibitors, and CAR-T cells are the most widely utilized cancer immunotherapy drugs. One common feature of these medicines is that they target immune cells independent of their location or the presence of tumor cells. Systemic administration of such medicines, particularly checkpoint inhibitors, frequently leads to immune-related adverse events

(irADs). Local administration considerably reduces the danger of irADs while ensuring that agents are targeted and effective in achieving the necessary degree of anti-cancer immunity [7]. Polyethylene glycol (PEG) is a common building element for biomaterials used in biomedical engineering, including tissue regeneration and medication delivery. PEG-based biomaterials have several notable advantages, including biocompatibility, no immune response stimulation, and high-water solubility [8]. Chitosan is a natural polysaccharide generated from chitin. When utilized as a carrier, chitosan improves its solubility in water. Due to its muco-adhesive cationic nature, it can keep therapeutic materials at the tumour site, allowing for regulated medication administration. It is widely recognized for its regulated non-immunogenicity, biodegradability, and availability. Dextran is another essential polysaccharide that is often transformed into enzymatically biodegradable reactions and is pH sensitive.

Because of their flowability, injectability, biocompatibility, and network-like structure, xyloglucan and collagen structures can also be employed for local medicinal drug administration. Gelatin is a highly biodegradable and biocompatible biopolymer protein that occurs naturally and has thermo-reversible properties. Gelatin in an aqueous solution hardens at temperatures below 25°C owing to the creation of triple helices and stiff three-dimensional networks, and it returns to liquid at temperatures over 30°C due to conformational shifts from a helix to a more flexible coil. When coupled with other polymers, gelatin produces thermal gelation close to body temperature, making it an efficient drug delivery agent. Some of the common hydrogel are classified in the **Table 1** [9]. To far, an outstanding library of drug delivery vehicles has been produced with diverse sizes, topologies, and surface physicochemical features, as well as targeting techniques.

TABLE 1: CLASSIFICATION OF SOME COMMON HYDROGELS

Source	Natural hydrogel	Collagen, chitoson,hyaluronic acid, gelatin.
	synthetic hydrogel	Polyethylene glycol (PEG), N-isopropyl acrylamide (PNIPAM), Poloxamer.
Crosslinking method	Physically crosslinked	Hydrogen bonding, Ionic interactions, hydrophobic interactions.
	Chemically crosslinked	Glutaraldehyde, epichlorohydrin, adipic dihydrazide, and polyaldehydes.
Response to environment stimuli	Environmentally sensitive hydrogels	Temperature sensitive, Electric-field sensitive, pH sensitive, Light sensitive.

Some important properties of hydrogel are summerised below:

Swelling Properties: All polymer chains in hydrogels are physically or chemically bonded to one another and are thus treated as a single molecule, regardless of size. As a result, there is no idea of molecular weight for hydrogels, which are sometimes referred to as infinitely huge molecules or super macromolecules.

One of the factors influencing water absorption capacity is the degree of cross-linking and the type of cross-linking agent utilised. A modest change in environmental circumstances can cause rapid and reversible alterations in a hydrogel. The amount of aqueous medium incorporated in a hydrogel is measured gravimetrically and represented as a swelling ratio.

$$\text{Swelling Ratio} = Ws - Wd/Wd$$

Where, Ws is the weight of the hydrogel in its swollen condition, and Wd is the weight of the hydrogel when dry.

Mechnical Properties: Hydrogel mechanical characteristics are critical for pharmaceutical and biological applications. The examination of mechanical properties is critical in a variety of biomedical applications, including ligament and tendon restoration, wound dressing material, and drug matrix development.

Hydrogel Inhomogeneity: It affects drug delivery, tissue engineering, and cartilage replacement materials. Hydrogels should have mechanical qualities that allow them to keep their physical texture while delivering therapeutic moieties for a set amount of time. By varying the degree of crosslinking, the desired mechanical characteristic of the hydrogel may be obtained. An increase in the

degree of crosslinking results in a stronger hydrogel, which reduces the percentage elongation of the hydrogels and forms a brittle structure.

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It was discovered that the scattering intensity from gels is always greater than that of the polymer solution. The gel's homogeneity grows with the cross-linking network across the gel polymer, but decreases with the gel's ionisation degree.

Biocompatible Properties: In order to be used in the biomedical area, hydrogels must be biocompatible and non-toxic. Most polymers used for this purpose need to pass cytotoxicity and in-vivo toxicity studies. Biocompatibility refers to a material's capacity to respond appropriately to a host in a certain application. Biocompatibility studies include two parameters: biosafety and bio-functionality.

A. Biosafety refers to the proper host response, both systemic and local, and the lack of cytotoxicity, mutagenesis, and/or carcinogenesis.

B. Biofunctionality refers to a material's capacity to accomplish the precise purpose for which it is intended. This term is very important in tissue engineering since the nature of tissue constructs is to constantly interact with the body throughout the healing and cellular regeneration processes, as well as scaffold degradation. Furthermore, initiators, organic solvents, stabilisers, emulsifiers, unreacted monomers, and cross-linkers employed in polymerization and hydrogel synthesis might be harmful to host cells if they leak into tissues or encapsulated cells. To eliminate dangerous substances from premade gels, a variety of purification techniques should be used, such as solvent washing or dialysis [10].

Hydrogel-based systems provide benefits over traditional immunotherapy approaches, such as systemic toxicity and limited effectiveness, prompting researchers to create local sustained release platforms for immunotherapeutic drugs. However, numerous crucial issues must be addressed before converting these experimental findings to clinical applications. First, the pharmacokinetics of therapeutic drugs are generally easy to detect and explain in experimental settings, but biological interactions in vivo, particularly in humans, make real-life study highly challenging. Furthermore, while animal models can be used to assess the short-term biocompatibility of hydrogels, they do not guarantee the same organ biocompatibility in humans.

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Before being used in clinical settings, novel hydrogels must be thoroughly tested under controlled laboratory circumstances. Advancements in cancer immunotherapy have led to a growing need for patient-specific immunotherapies. Such an upsurge in patient demand may imply that immunotherapy is becoming more widely accepted and approved as a new cancer treatment. Nonetheless, this highlights the necessity for more exact control over the properties of medicinal medicines. There are now two primary hydrogel-based anti-cancer nanomedicines in use in clinics **Table 2.**

TABLE 2: COMMON HYDROGEL-BASED ANTI-CANCER NANOMEDICINES IN USE IN CLINICS

Type of Cancer	Hydrogel-based clinical products	Anti-cancer drugs	Delivery system	Company name	Approval year
Breast cancer & Ovarian cancer	Genexol-PM®	Paclitaxel	Micelle polymer	Samyang	2009
Esophageal cancer	Oncogel™	Paclitaxel	Thermal Sensitive ReGel polymer	Diatos	2007

Benefits of Hydrogels in Drug Delivery: Hydrogels have been defined in a variety of ways throughout the years, but they are most commonly described as a cross-linked polymeric network generated by the conjugation or reactivity of one or more monomers and exhibiting water-swollen properties. Though hydrogels are three-dimensional networks, they have the potential for water absorption due to the presence of hydrophilic capabilities that may fill the gap between macromolecules and have a higher affinity for biological fluids.

Hydrogel-based advanced dressings have been demonstrated to be extremely successful in wound healing because of their moisture-retaining properties at the application site, which prevent fluids from spreading to adjacent healthy skin regions. Commercially available hydrogels include DermaFilm®, Condress®, Kaltostat®, and Sofargen®. Hydrogels are being used for drug delivery due to their unique physical features. Controlling cross-link density in the gel matrix and hydrogel affinity for the aqueous environment can help to fine-tune their extremely porous structure. This permits medications to be placed into their gel matrix and subsequently released in an amount determined by the diffusion coefficient of small molecules or macromolecules. Because of their pharmacokinetic features, hydrogels can be employed for drug administration with the primary goal of maintaining a high local concentration of the drug in the surrounding tissues for a longer length of time, as well as for systemic distribution. Hydrogels are biocompatible and can be employed in the peritoneum and other parts of the body.

The high water content of hydrogels, along with their physical resemblance to the natural extracellular matrix and mechanical qualities, promotes biocompatibility. It is possible to create biodegradable or dissolvable hydrogels by environmental, hydrolytic, or enzymatic means, albeit this may not be desired depending on the timing and location of the drug delivery device. Hydrogels, on the other hand, are somewhat malleable and may be shaped to fit any surface. Some hydrogels' muco- or bio-adhesive properties might be useful when applying them to non-horizontal surfaces or immobilizing them at the application site. Hydrogels' effectiveness in biomedical applications led to the hypothesis that they may be employed for medication delivery in cancer therapy. Local medication delivery may be particularly effective in situations of nonsquamous or incompletely excised tumors, although most cancer therapy research focuses on systemic and oral administration.

In this context, the in situ application of hydrogels, particularly stimuli-responsive hydrogels, to the tumor site/cavity has already been proposed as a way to increase local sustained drug release while decreasing off-target effects and overall exposure. The use of different injectable hydrogel-based drug delivery systems, such as thermosensitive, pH-sensitive, photosensitive, dual-sensitive, and active targeting hydrogels, to deliver chemotherapeutics to tumours. Injectable hydrogel systems provide certain advantages over systemic chemotherapy, including lower toxicity in normal tissues, localised and prolonged drug administration in the tumour region, more effective cell death, and tumour growth suppression. The efficacy of these hydrogels for localised chemotherapy has been thoroughly investigated in highly structured and regulated *in-vitro* settings. Proof-of-principle studies on their action in numerous rodent cancer models are also promising.

However, much of the *in-vivo* investigations to date have focused on hydrogels in subcutaneous ectopic tumour models. The benefits of ectopic tumour models include simplicity of monitoring tumour growth and, because the majority are subcutaneous, direct placement of hydrogel near or into the tumour mass is simple. One important disadvantage of ectopic tumour models is the lack of a tumor-specific microenvironment. Although this represents the field's natural development from *in-*

vitro to preclinical *in-vivo* models, more testing in orthotopic tumour models that more properly depict the tumour environment within a specific tissue and/or organ is necessary. Such investigations will offer the requisite validation of the hydrogels as local chemotherapy treatment alternatives, paving the path for clinical research in humans that may begin to address the efficacy of these drug delivery platforms for local chemotherapy and cancer treatment [11].

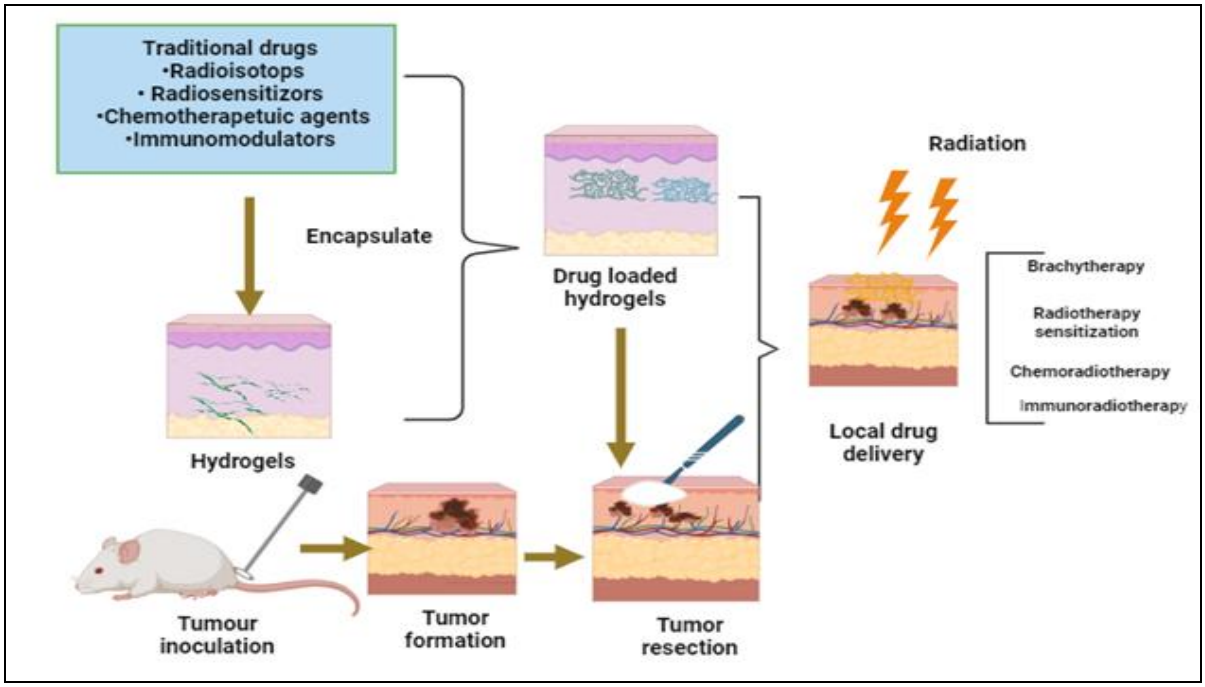

FIG. 1: A SCHEMATIC ILLUSTRATION OF THE USE OF HYDROGEL-BASED LOCAL MEDICATION DELIVERY DEVICES FOR POSTOPERATIVE RADIOTHERAPY

The hydrogel-based medication delivery methods offer distinct benefits in postoperative radiotherapy. Traditional medication formulations (such as radioisotopes, radio-sensitizers, chemotherapeutic medicines, or immune-modulators) were studied by encapsulating them in hydrogels and combining them with postoperative radiation to prevent tumor reoccurrence **Fig. 1**. This local drug delivery strategy avoids the nonspecific dispersion of standard medications, sensitizes radiation, and allows for the combination of several treatment options [12]. Hydrogels can be used in the cancer treatment as Radiotherapy, Immunotherapy, hyperthermia, photothermal and photodynamic therapies. Postoperative concurrent chemo-radiotherapy, which administers chemotherapeutics and radiotherapy after surgery, is now the standard treatment for solid tumors such as lung, esophageal, gastrointestinal, and brain cancers. Radiotherapy exposes normal tissues to radiation as well. Radioactive necrosis occurs when the radiation exposure surpasses the normal tissue's maximal tolerance threshold. Traditional chemotherapeutic drugs have been shown to make radiation more effective in solid tumors, however, their nonspecific tissue distribution causes significant harm to other tissues and organs. Hydrogel has been widely used in postoperative chemoradiotherapy due to its unique properties, including intraoperative delivery, prolonged drug release, and high drug loading. Doxorubicin (DOX), a broad-spectrum anticancer medication, can efficiently limit the production of RNA and DNA, hence eliminating tumour cells. However, doxorubicin's harmful side effects, including as myelosuppression and cardiac damage, severely limit its utilization in clinical settings. In order to reduce DOX toxicity, smart hydrogels were used. Researchers used a thermos-responsive hydrogel (PEG-PLGA-PEG) to co-deliver 131I as a radioactive source and DOX/PECT micelles as a chemotherapeutic to accomplish combination chemoradiotherapy [12]. Smart hydrogel-based medication delivery devices for oral tumors may be regulated using stimulation variables. By inserting hydrogels in the afflicted region of oral cancer, related stimuli are used to regulate the local targeted transmission of medications and other

bioactive molecules, as illustrated in **Fig. 2**. The four most prevalent environmentally sensitive hydrogels are described below thermosensitive hydrogels, photosensitive hydrogels, enzyme-responsive hydrogels, and pH-sensitive hydrogels [13].

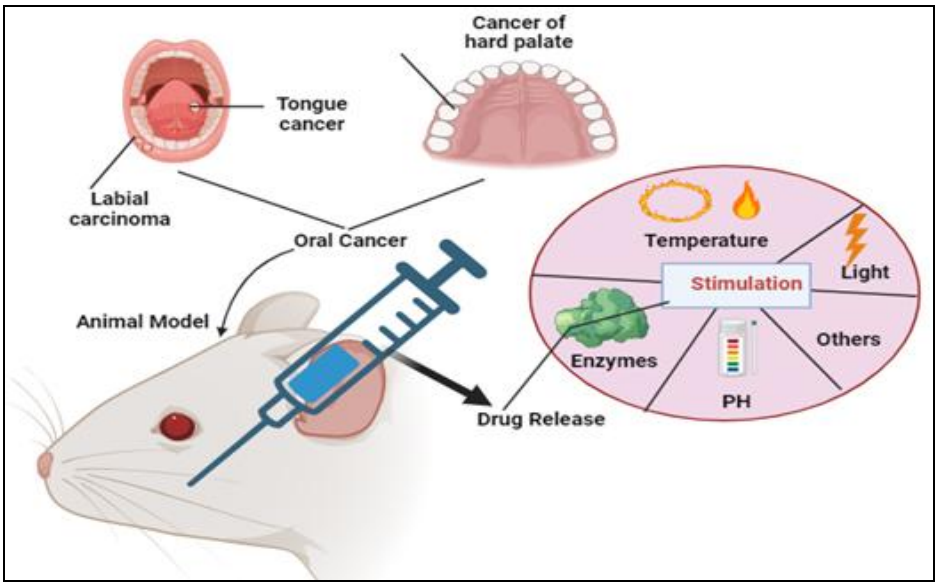

FIG. 2: A SMART HYDROGEL-BASED MEDICATION DELIVERY DEVICE FOR ORAL CANCER TREATMENT

Hydrogel-based drug delivery techniques treating tumours include thermosensitive, pH-sensitive, photosensitive, dual-sensitive, and glutathione-sensitive hydrogels. Injectable hydrogel systems provide several advantages, including decreased toxicity to normal tissues, localised and extended drug distribution in the tumour site, more effective cell killing, and tumour growth inhibition. The efficiency of these hydrogels for localised chemotherapy has been extensively studied in highly organised and regulated in vitro environments. Because most ectopic tumour models are subcutaneous, direct implantation of a hydrogel near or within the tumour mass is straightforward, and ectopic tumour development may be tracked with reasonable ease [14].

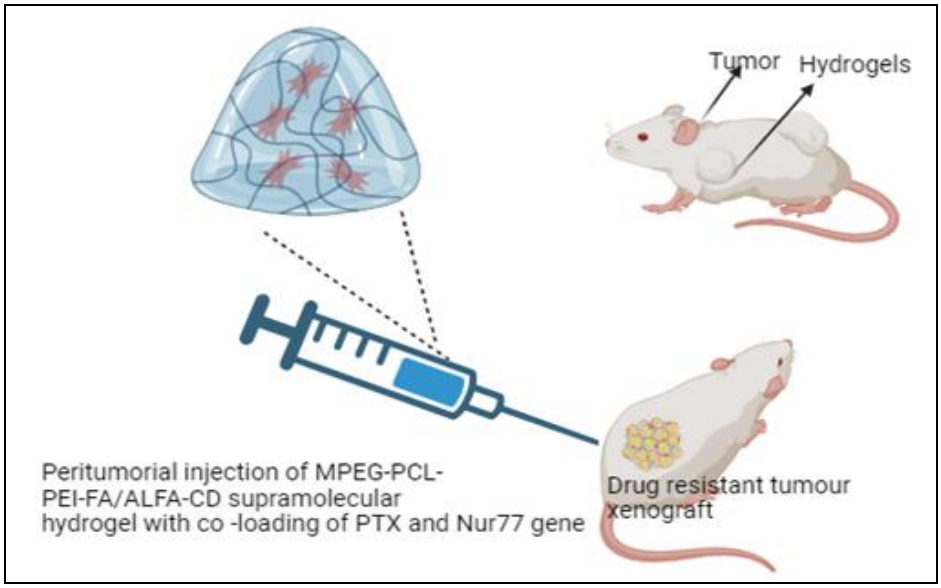

FIG. 3: HYDROGELS FOR THE DELIVERY OF CHEMOTHERAPEUTICS AND NUCLEIC ACIDS

Combining chemotherapy with gene therapy for cancer treatment requires therapeutic genes to overcome tumor angiogenesis and resistance to chemotherapeutic drugs, ultimately eliminating malignant lesions. 51, 52 To enable successful gene delivery, positively charged hydrogels create a

stable combination with negatively charged nucleic acids. Researchers presented a peritumoral-injected hydrogel made of α-cyclodextrin (α-CD) and a positively charged amphiphilic copolymer with a folic acid-targeting group **Fig. 3**. The hydrogel enabled 7-day codelivery of paclitaxel (PTX) and the B-cell lymphoma 2 (Bcl-2)-transformed gene Nur77 at the tumor site, thereby inhibiting the proliferation of drug-resistant tumor cells that overexpress folate receptors.

Hydrogels' electrostatic association with genes and delayed biodegradation ensure long-term release and high transgene expression in cells, improving gene therapy effectiveness significantly. Despite their various benefits, hydrogels do have certain limits. Several hydrogels are not suitable for load-bearing applications because to their poor tensile strength. These hydrogels prematurely disintegrate or flow away from a specific location. This limitation may be more relevant in many traditional drug delivery applications (for example, subcutaneous injection, in situ injection, and intratumoral injection). A more serious worry may be hydrogels' ability to distribute drugs. Drug loading into hydrogels can be limited in terms of quantity and homogeneity, especially for hydrophobic medicines. Most hydrogels' wide pore sizes and high water content cause payloads to be released quickly, also known as burst release. Colorectal and ovarian cancer are two deep tumours in the human body that appear to be challenging to cure with this strategy.

The similar issue exists with photo-crosslinking hydrogels for shallow visible light penetration. Even though many studies use subcutaneous tumours as an in vivo model, there are often important and complex anatomical structures (e.g., lymphatic systems, veins, arteries, and nerves) surrounding the tumour that can be eroded by carcinoma tissue and must be considered when developing a cancer treatment plan. There is also a scarcity of hydrogel-related studies on degradation and metabolism, immunological response, and biodistribution in the body among patients of various sexes and ages. As a result, hydrogel-based cancer therapy has a long way to go before it can be used in clinical settings [15]. Despite advancements in the use of hydrogels for postoperative radiation, problems remain.

In terms of clinical translation, hydrogels cannot totally replace conventional adjuvant therapy approaches [12]. The current hydrogel drug delivery system design is too complicated, posing a significant obstacle to product quality management. Hydrogels demonstrated regulated local drug release, however it was difficult to precisely control drug release behaviour per unit time. As a result, simplifying the hydrogel fabrication technique, as well as boosting the accuracy and rate of drug release, would presumably increase hydrogels' use prospects in postoperative irradiation.

CONCUSION: The hydrogel filled with nucleic acid pharmaceuticals efficiently regulates drug release and avoids nucleic acid breakdown, boosting the efficacy of melanoma immunotherapy. Hydrogels containing polypeptides, monoclonal antibodies, and other ingredients can also prolong medication retention in the body and efficiently trigger the immune system to attack tumour tissue, boosting the efficacy of melanoma immunotherapy. The utilisation of hydrogels to transport diverse medications is thus particularly appropriate for the present development of melanoma immunotherapy and has a wide range of applications. It is expected that as hydrogel research advances and immunotherapy improves, hydrogels will become a viable drug carrier, leading to new advancements in cancer treatment and encouraging future development.

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