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DRUG DELIVERY BASED ON HYDROGEL FOR THE TREATMENT OF CANCER

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Abstract
This highlights the significance of controlled releasing biodegradable hydrogels as chemotherapeutic drug delivery systems. This study examines the use of hydrogels as drug delivery methods for HCC (Hepatocellular carcinoma), including thermo sensitive, pH-sensitive, photosensitive, dual sensitive, and glutathione responsive hydrogels. Localized chemotherapy, as opposed to systemic chemotherapy, can reduce side effects by delivering a steady supply of chemotherapeutic chemicals directly to the tumor location. Hydrogels have been used for wounds, burns, dressings, contact lenses, tissue engineering applications, and more. Finally, hydrogel can intelligently respond to environmental changes according to internal and external environmental stimuli, allowing for remote control and on-demand release of the anti-cancer active substance. This significantly improves drug targeting, lowering dosages and increasing treatment efficacy.
Keywords: Hydrogels, Controlled release, drug delivery system, Macroscopic design, microgels and nano gels, release mechanism, Drug diffusion coefficient, Applications.

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INTRODUCTION

Cancer immunotherapy is a promising approach to treating various types of cancer by using the body's immune system to detect and destroy cancerous cells [1]. Unlike traditional therapeutic methods like radiation therapy and chemotherapy, which target cancer cells directly, immunotherapy works by enhancing the immune response targeted at tumours, potentially reducing side effects and producing longer-lasting effects compared to traditional treatments [2]. However, there are still issues that restrict immunotherapy's broad effectiveness and applicability, even in spite of its amazing success in certain situations. The requirement for novel drug delivery methods that can efficiently transport immunotherapeutic drugs to the tumour site while reducing systemic toxicity and off-target effects is one such difficulty [3]. Due to problems such low bioavailability, quick excretion from the body, and incapacity to enter the tumour microenvironment, traditional drug delivery techniques frequently fall short of the intended therapeutic results [4].

THE BASICS OF HYDROGELS

Because of their exceptional qualities and capacity to encapsulate medicinal molecules for regulated release, hydrogels have demonstrated their versatility as materials in the field of drug delivery. Three-dimensional networks of hydrophilic polymer chains make up hydrogels, which are renowned for their exceptional capacity to absorb and hold large volumes of water. This characteristic gives depending on the specific polymers and crosslinking agents used in their creation, ranging from densely packed structures to sparsely connected matrices. Hydrogels' porosity, mechanical strength, and swelling behavior can all be altered to suit a range of uses, including medication delivery. One essential property that allows hydrogels to encapsulate and release therapeutic chemicals under controlled conditions is their ability to swell and assimilate Because of water.

Types of Hydrogels Used in Drug Delivery

Numerous hydrogels with unique qualities and benefits have been studied for drug delivery applications. Among the most popular hydrogel varieties for drug administration are natural, synthetic, and hybrid hydrogels; each has unique advantages based on its intended purpose. Natural hydrogels are typically composed of proteins (like collagen and gelatin) or polysaccharides (chitosan, hyaluronic acid, and alginate). These hydrogels are appropriate foliker applications where a low foreign body response is needed because they are biocompatible and frequently show good biodegradability. Applications for hydrogels in tissue engineering and regenerative medicine benefit from their great biological system adaptability. Enhance interactions with biological systems by adding motifs to bioactive compounds or natural hydrogels. On the other hand, artificial polymers like polyethylene glycol (PEG) and poly (N-isopropylacrylamide) are used to create synthetic hydrogels. either poly(vinyl alcohol) (PVA) or PNIPAAm). By precisely controlling their mechanical and chemical characteristics, these artificial hydrogels enable researchers to modify their behavior for certain drug delivery applications.

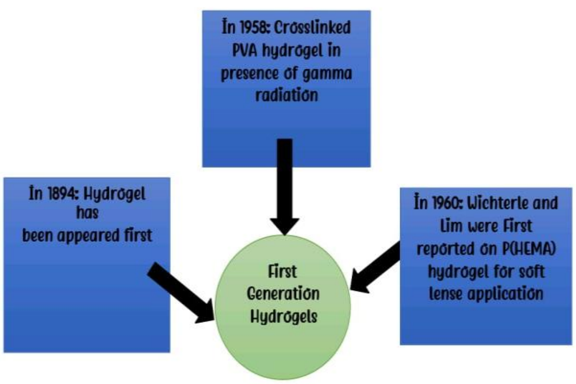

Figure 1: Importance events of hydrogel research

Classifications of Hydrogels

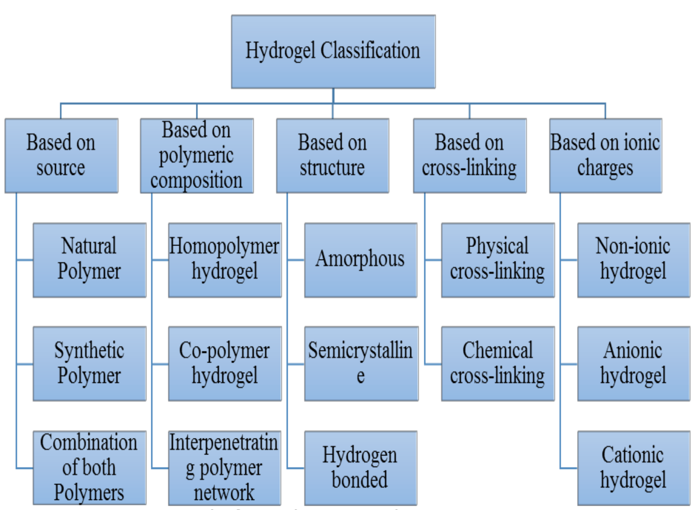

Fig: 2 Classification of hydrogels

Based on source

It is possible to produce Hydrogel by using either natural or synthetic and a combination of both polymers.

Natural Polymer	Synthetic Polymer	Combination of both Polymers
Anionic polymers Alginic acid, pectin	PEG-PLGA-PEG	Collagen-PEG
Cationic polymers Chitosan, Polylysine	PEG-PLA-PEG	Collagen-hydroxyethyl methacrylate
Amphipathic polymers Collagen, Fibrin	PEG-PCL-PEG	Alginate-Poly (sodium acrylate-co-acrylamide)
Neutral polymers Dextran, Agarose	PLA-PEG-PLA	Collagen-g-poly (acrylic acid)

Depending on the polymeric composition approach three categories of compositions exist:

I. Hydrogel homopolymer:

They are made up of a single ydrophilic monomer. Their backbone is usually composed of crosslinks. Homopolymer hydrogel can be prepared in a variety of way. [5].

II. Co-polymer hydrogel

III. Composed of two or more co-monomer species, it requires at least one hydrophilic monomer to expand. Packed with a stimulus-feeling quality, hydrogels are in high demand and are frequently used as smart materials for transducers, actuators, and optical biosensors [6].

IV. Interpenetrating polymer network:

An interpenetrating polymer network is made up of two polymers that are crosslinked between molecules that are similar to one another but do not form a covalent bond. The interpenetrating polymer network is improved by applications that provide medication continuously over a long period of time [7].

Based on structure

(I) **Amorphous**: Macromolecular chains are arranged randomly;

(II) **Semicrystalline**: They are distinguished by their dense, ordered sections of macromolecular chains;

(III) **Hydrogen Bonded**: They have a well-known three-dimensional (3D) structure; and 3.4 **based on cross linking**: Hydrogels are divided into two groups according to the types of cross linking: chemical and physical cross linking [8]

Ionic charge-based Ionic charge-based hydrogels come in three varieties:

Hydrogels that are non-ionic hydrogel, Anionic hydrogel, cationic hydrogel.

Hydrogels can be released as needed and react intelligently to changes in the internal and external environment.

As previously stated, the secret to effectively delivering active medications to their intended targets, minimising adverse effects, and optimising their effectiveness is the development of responsive hydrogels. Anti-cancer active ingredients can be remotely controlled and released on demand thanks to hydrogel materials' intelligent response to environmental changes based on internal and external stimuli, including light (particularly near-infrared light), pH, temperature, redox potential, and magnetism.

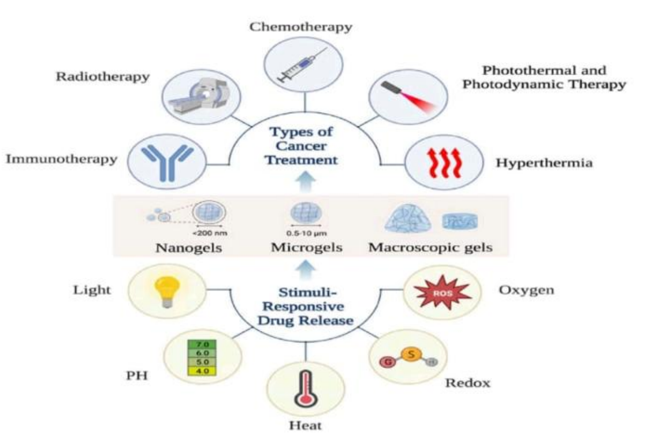

Figure: 3 Graph abstract

HYDROGELS THAT ARE PHOTOSENSITIVE

One of the hottest topics in cancer chemotherapy is the logical design of light-stimulating hydrogel-like medications, particularly those that respond to near-infrared light. The non-invasive stimulation of light allows lightresponsive hydrogels to regulate the in situ polymerisation ofhydrogels and precisely time and space the release of anti-cancer drugs (Buwalda et al., 2017)

PH-responsive hydrogels

PH-responsive hydrogels are also a research hotspot in cancer therapy. According to Minchinton and Tannock (2006), normal tissue has a slightly alkaline pH of approximately 7.4, while the extracellular environment (pH of 5.8 to 7.2) and intracellular endosomes (pH of approximately 5.5) of cancer tissue are acidic. As a result, designing a hydrogel that releases anti-cancer drugs only in a specific acidic environment can improve therapeutic efficacy and enhance drug targeting while also reducing drug release in normal bodily tissues and reducing systemic side effects. Raza et One of the easiest irritants to regulate is temperature (Zhang et al., 2022d). Significant benefits are also provided by temperature-responsive hydrogels in terms of multitherapy combinations, convenience of use, precise control, and gradual drug release (Shen et al., 2022). Because of their significant potential for use in cancer therapy, temperature-sensitive hydrogels have emerged as one of the most sought-after responsive hydrogels in recent years (Li et al., 2022b; He et al., 2022). An in situ forming system is the injectable temperature-responsive hydrogel. The hydrogel gels quickly after injection and stays in solution at room temperature since the in vivo temperature is higher than the low critical solution temperature (LCST) (Zhao et al., 2022)

Hydrogels are useful in a variety of cancer treatments.

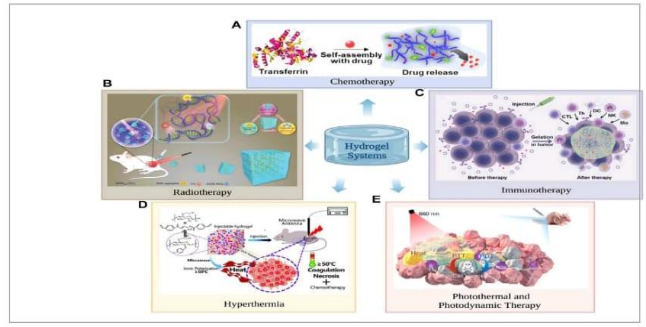

Figure: 4 Hydrogels can be used in cancer chemotherapy

The use of Chemotherapy

Chemotherapy has a particular impact on cancer treatment and is frequently used to destroy cancer cells in conjunction with other therapies or as an adjuvant surgical treatment. But currently, widely used chemotherapeutic medications in clinical settings share the same issues such severe side effects, inadequate drug tolerance, and inadequate targeting. Chemotherapy frequently damages the human body while failing to eradicate cancer cells entirely (Meng et al., 2022b) [9]

Radiation treatment

One of the most common and efficient ways to treat cancer is radiation therapy, which typically uses high doses of radiation (>60 Gy) to destroy disease cells and reduce cancer (Prabhu et al., 2021). Nowadays, radiation therapy is more accurately targeted than it was previously. This makes it possible to effectively destroy cancer cells while interfering with their ability to repair their DNA and minimising harm to healthy tissue (Lu et al., 2022; Moghaddasi et al., 2022).

Immunotherapy

Immunotherapy is one of the most promising strategies to maximise the therapeutic effects of traditional cancer therapy, which has been widely used to treat various malignancies (Bader et al., 2020; Zhang and Zhang, 2020). However, the immune checkpoint blockers commonly used in clinical practice are primarily monoclonal antibodies with large molecular weights, which have difficulty penetrating and easily accumulate in solid cancer (Liu et al., 2019a). [10]

Hyperthermia

Treatment of hyperthermia can benefit from the highly heterogeneous nature of the cancer microenvironment to induce apoptosis or death of cancer cells while leaving healthy tissue largely intact; heat can destabilise cytoplasmic lysosomes in cancer cells, disrupt mitochondria, limit oxygen uptake capacity, and make cancer tissue hypoxic, which further enhances the responsiveness of cancer cells to heat (Long et al., 2022). Scholars both domestically and internationally have frequently observed the synergy between hyperthermia and other therapies.

6. MECHANISM OF RELEASE

Drug delivery system with diffusion control

Concepts from volume, hydrodynamics, or obstruction are used to calculate controlled-release drug diffusivities. Polymer hydrogel membranes and reservoir systems are the two groups into which diffusion types are divided. While the medication is widely available. The polymeric membrane in a reservoir covers the drug core across the polymeric network in a matrix system. Drug diffusion is mostly caused by the crosslinked network's mesh size, which is determined by a number of factors such as composition, gel structure, crosslinking density, and external stimuli. When the hydrogel is inflated, the mesh size of the polymeric network can vary from 50 to 100 nm, which is much bigger than the drug molecules. Consequently, diffusion continues in the expanded condition. Fick's law of diffusion is commonly used in diffusion controlled release models with constant or variable coefficients of diffusion [11]

7. APPLICATIONS

Hydrogel-based devices provide an extremely controlled release mechanism. Hydrogels are an excellent bio-adhesive material that is suitable for transdermal, oral, subcutaneous, and ocular medication delivery due to their biochemical properties [12].

Delivery via subcutaneous means

One of the greatest methods to assess a drug's effectiveness and predict if a mouse will experience a harmful reaction in vivo is by administering subcutaneous injections. Hydrogels have an immune-privileged impact since they are placed in the vascularized subcutaneous area.The foreign particle should just be minimally irritated. Polyethylene hydrogels have been shown to have negligible cytotoxicity in mice models 60 days following injection. Results from alginate, pectin, chitosan, polyacrylamide, and gelatin hydrogels were comparable. Chitosan material is preferred since it doesn't trigger inflammation or immunogenicity [13].

Drug administration by mouth

The body administers therapeutic medications orally to the stomach, colon, small intestine, or oral cavity using a controlled drug delivery system. Clinicians specifically target this unique tissue system when administering medications to the gastrointestinal tract. When variables are modifiable and this is the most practical delivery method, and patient compliance is assured. Oral hydrogels must provide bioavailability according to the medium's characteristics, including pH variations along the digestive system. The controlled drug delivery system is enhanced by chitosan and chitosan-based hydrogels' mucoadhesive and pH-sensitive properties. With levels ranging from 1 to 7.5, the GI system experiences significant pH fluctuation.The gels' mucoadhesive properties make them advantageous for oral administration. The primary advantages of employing thiolated polysaccharides in gel compositions have been found to be their mucoadhesive and in-situ gelling properties [14].

CONCLUSION

Hydrogels offer special benefits like improved stability, controlled release, and targeted delivery of vaccine components, which can improve vaccine efficacy, durability, and administration. Their use in vaccine development is a significant advancement with the potential to completely transform vaccination strategies. Numerous innovative delivery systems have been made possible by the steadily growing interest in functional polymers, especially in cancer immunotherapy. We have particularly examined the state of hydrogels in the delivery of different immunotherapeutic drugs in this review. Hydrogels are a perfect material for biomedical applications because of their low toxicity, biocompatibility, and biodegradability.

AUTHOR CONTRIBUTIONS

All authors are contributed equally

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The Authors have no Conflicts of Interest to Declare.

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