Hydrogel-Based Drug Delivery for Cancer Immunotherapy: Design, Advances, and Applications - A Comprehensive Review

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ABSTRACT

Hydrogels have attracted significant attention in the realm of vaccine development due to their unique attributes, which include compatibility with living tissues, a considerable water content, and modifiable physical traits. This article examines the utilisation of hydrogels in the process of vaccine development. Hydrogels function as adaptable vehicles for the transportation of vaccines, providing benefits including prolonged release, safeguarding against degradation of antigens, and precise administration to particular cells or tissues. The application of hydrogel matrices to encapsulate antigens and adjuvants has the potential to improve the stability, immunogenicity, and effectiveness of vaccines. Due to their distinctive attributes, they are exemplary contenders for drug delivery systems. Hydrogels are specifically engineered to facilitate the co-administration of therapeutic agents, including immune cells, cytokines, and monoclonal antibodies, with the aim of augmenting the therapeutic effectiveness of malignancy. Moreover, hydrogel-based vaccines can be administered via various routes, including injection, patches, or implants, providing flexibility and convenience in vaccination. Challenges such as formulation optimization, manufacturing scalability, and regulatory approval remain, but the continued research and development of hydrogel-based vaccines hold promise for improving vaccination strategies and addressing global health challenges.

KEYWORDS: Hydrogels, Vaccine development, Drug delivery, Immunotherapy, Cancer

INTRODUCTION

The utilization of cancer immunotherapy represents a hopeful strategy in combating diverse forms of cancer, harnessing the body's immune system to identify and eradicate cancerous cells [1]. In contrast to conventional therapeutic approaches like radiation therapy and chemotherapy, which target cancer cells directly, immunotherapy functions by augmenting the immune response directed at tumours. This may result in reduced adverse effects and longer-lasting responses in comparison to conventional treatments [2]. However, despite the remarkable success of immunotherapy in some cases, there are still challenges that limit its widespread efficacy and applicability. One such challenge is the need for innovative drug delivery systems that can effectively deliver immunotherapeutic agents to the tumor site while minimizing off-target effects and systemic toxicity[3]. Conventional drug delivery methods often fail to achieve the desired therapeutic outcomes due to issues such as poor bioavailability, rapid clearance from the body, and inability to penetrate the tumor microenvironment[4].

Hence, there arises a crucial necessity to devise sophisticated delivery platforms capable of overcoming these constraints and maximizing the effectiveness of cancer immunotherapy. Over the past few years, there has been a notable surge in interest surrounding hydrogel-based drug delivery systems, recognized as promising carriers for transporting therapeutics, including immunomodulatory agents, directly to the tumor site [5]. Hydrogels are three-dimensional networks formed by crosslinked polymer chains, known for their remarkable ability to swell and flexibly absorb and retain large amounts of water. Due to these unique properties, hydrogels are well-suited for drug delivery purposes, allowing them to encapsulate therapeutic agents and release them gradually under controlled conditions [6]. The objective of this research is to perform an exhaustive examination of hydrogel-based drug delivery systems utilised in cancer immunotherapy. The review will prioritise the elucidation of design principles, recent developments, and practical implementations of these systems [7]. Through a systematic examination of existing literature, our primary goal is to shed light on the potential of hydrogel-based delivery platforms in surmounting the challenges inherent in cancer immunotherapy and ultimately enhancing patient outcomes[8]. The study's objectives offer a detailed overview of cancer immunotherapy, elucidating its underlying principles, mechanisms of action, and current clinical utilization; second, to explore the imperative need for innovative drug delivery systems within the realm of cancer immunotherapy, emphasizing the shortcomings of conventional approaches while underlining

the prospective advantages afforded by hydrogel-based delivery systems; and third, to provide an introduction to the fundamental properties of hydrogels and their wide-ranging applications in drug delivery, encompassing their distinctive attributes, key design considerations, and recent advancements within the field[9]. Through this thorough investigation, our aim is to provide valuable contributions to the current understanding of hydrogel-based drug delivery for cancer immunotherapy, thereby encouraging further progress and innovation in this vital area of biomedical research [10].

FUNDAMENTALS OF HYDROGELS

Hydrogels have showcased their versatility as materials in the field of drug delivery owing to their remarkable properties and ability to encapsulate therapeutic substances for controlled release[11]. Hydrogels consist of three-dimensional networks made up of chains of hydrophilic polymers, known for their remarkable ability to absorb and retain significant amounts of water. This property differentiates them from alternative polymers and imparts them with a gel-like consistency [12]. Hydrogel structures exhibit considerable diversity, spanning from sparsely interconnected matrices to tightly packed structures, contingent upon the particular polymers and crosslinking agents employed during their fabrication. One can modify the swelling behaviour, mechanical strength, and porosity of hydrogels to accommodate a variety of applications, including drug delivery. The capacity of hydrogels to swell and incorporate water is a critical characteristic that enables them to encapsulate and discharge therapeutic agents under controlled conditions [13]. Hydrogels have showcased their adaptability as substances in the realm of drug delivery owing to their remarkable attributes and ability to encapsulate therapeutic compounds for controlled release [14]. Another key feature of hydrogels is its biocompatibility, i.e. its ability to interact with biological systems without causing adverse reactions. Biocompatible hydrogels are well tolerated by surrounding tissues, are not immune and are not toxic, making them suitable for various biomedical applications such as drug delivery and tissue engineering [15, 2]. Hydrogel biocompatibility is influenced by several factors, including its chemical composition, residual monomers or crosslinkers, as well as degradation byproducts[16]. Furthermore, hydrogels are capable of responding to external stimuli, including variations in pH, temperature, or certain ions or molecules, which alter their swelling and drug release properties. Due to their ability to control drug release and precisely target specific tissues or

affected areas, stimuli-responsive hydrogels are of great interest for drug delivery applications [17].

A. Types of Hydrogels Used in Drug Delivery:

A wide variety of hydrogels have been investigated for drug delivery applications, each with distinct properties and advantages[18]. Natural, synthetic and hybrid hydrogels are among the most commonly used hydrogel types for drug delivery, each with different benefits depending on its application. In general, natural hydrogels are made from polysaccharides (such as alginate, chitosan, hyaluronic acid) or proteins (such as gelatin, collagen) [19]. These hydrogels are biocompatible and often exhibit excellent biodegradability, making them suitable for applications where minimal foreign body response is desired[20]. Hydrogels are highly adaptable to biological systems and are useful for tissue engineering and regenerative medicine applications. Add motifs to natural hydrogels or bioactive molecules to improve interactions with biological systems [21]. In contrast, synthetic hydrogels are synthesized from artificial polymers such as polyethylene glycol (PEG), poly(N-isopropylacrylamide) (PNIPAAm), or poly(vinyl alcohol) (PVA). These synthetic hydrogels provide precise control over their chemical and mechanical properties, allowing researchers to tailor their behavior for specific drug delivery applications [22]. These hydrogels are often more robust and long-lasting compared to natural counterparts, rendering them suitable for prolonged drug delivery or implantable devices. Hybrid hydrogels integrate both natural and synthetic components to leverage the benefits of both materials [23]. By blending natural polymers with synthetic polymers or incorporating inorganic nanoparticles, hybrid hydrogels can exhibit enhanced mechanical strength, biocompatibility, and drug loading capacity compared to their individual components[24]. Hybrid hydrogels can also be engineered to respond to multiple stimuli or exhibit multifunctional properties, making them highly versatile for drug delivery applications[3]. In addition to these broad categories, hydrogels can also be classified based on their physical structure (e.g., physically crosslinked, chemically crosslinked) or their responsiveness to specific stimuli (e.g., pH-responsive, temperature-responsive). Each type of hydrogel offers unique advantages and limitations, and the choice of hydrogel for a particular drug delivery application depends on factors such as the desired release profile, target tissue, and route of administration[25].

C. Biocompatibility and Biodegradability:

Biocompatibility and biodegradability are critical considerations in the design of hydrogel-based drug delivery systems, as they determine the compatibility of the hydrogel with biological systems and the fate of the hydrogel following administration. Biocompatible hydrogels are those that do not elicit adverse reactions when in contact with living tissues and cells, ensuring minimal inflammatory response and tissue damage[26]. Biodegradable hydrogels, on the other hand, are capable of undergoing degradation and clearance from the body over time, either through enzymatic degradation, hydrolysis, or cellular uptake and metabolism. Natural hydrogels are often inherently biocompatible and biodegradable, as they are derived from natural polymers that are recognized and metabolized by the body. For example, alginate hydrogels are composed of polysaccharides extracted from seaweed and are enzymatically degraded by enzymes present in the body, such as alginate lyase. Similarly, hyaluronic acid hydrogels are biocompatible and biodegradable due to their structural similarity to native extracellular matrix components and their susceptibility to enzymatic degradation by hyaluronidases[27]. Synthetic hydrogels can also be engineered to exhibit biocompatible and biodegradable properties by selecting polymers that are metabolizable or incorporating degradable linkages into the polymer backbone. For example, polyesters such as poly(lactic acid) (PLA) and poly(glycolic acid) (PGA) are commonly used in the synthesis of synthetic hydrogels due to their biodegradability and biocompatibility. By adjusting the molecular weight and composition of the polymer, researchers can control the degradation rate of synthetic hydrogels to match the desired release profile of the encapsulated drug. Hybrid hydrogels offer the flexibility to tailor their biocompatibility and biodegradability by adjusting the ratio of natural to synthetic components or incorporating degradable linkages into the hybrid structure[28]. For example, hybrid hydrogels composed of alginate and PEG exhibit enhanced biocompatibility and tunable degradation kinetics compared to pure alginate hydrogels, making them suitable for various biomedical applications.

DRUG DELIVERY STRATEGIES FOR CANCER IMMUNOTHERAPY

Cancer immunotherapy revolutionizes treatment landscape for various cancers by harnessing the immune system to detect and eradicate cancer cells. However, despite its remarkable success in some cases, cancer immunotherapy still faces several challenges that limit its efficacy and applicability [29].

A. Challenges in Cancer Immunotherapy:

The immune system is enhanced by cancer immunotherapy to identify and eradicate malignant cells. Several mechanisms, including immune checkpoint inhibition, adoptive cell therapy, and cancer vaccines, can accomplish this. Although these methodologies have exhibited notable clinical advantages in specific populations, they are confronted with a number of obstacles that impede their extensive implementation [30]. A significant obstacle in the field of cancer immunotherapy is tumour heterogeneity, a characteristic characterised by the existence of varied cell populations within a tumour. These cell populations may display distinct degrees of immunogenicity and vulnerability to immune-mediated eradication[22]. Tumor heterogeneity can limit the effectiveness of immunotherapy by enabling the emergence of resistant clones or suppressing the immune response within certain tumor microenvironments. As well as immunosuppressive tumor microenvironments that dampen the immune response to cancer, regulatory T cells, suppressor cells derived from myeloid cells, and inhibitory cytokines also pose a challenge. In order for immunotherapy to be effective, strategies need to be developed to overcome immunosuppression and increase the infiltration of effector immune cells into tumor sites. [31]. Additionally, systemic toxicity and off-target effects pose significant challenges in cancer immunotherapy, particularly with systemic administration of immunomodulatory agents such as immune checkpoint inhibitors. These agents can elicit immune-related adverse events (irAEs) that affect various organs and tissues throughout the body, necessitating careful monitoring and management[21]. Moreover, the short half-life and rapid clearance of therapeutic agents from the bloodstream can limit their exposure to the tumor site, reducing their efficacy. Strategies to improve drug stability, prolong circulation time, and enhance tumor accumulation are therefore essential for optimizing the delivery of immunotherapeutic agents[32].

B. Importance of Targeted Drug Delivery:

To minimize systemic toxicity and off-target effects, selective delivery of therapeutic compounds to tumors is promising [12]. This approach holds potential to overcome common challenges encountered in cancer immunotherapy. By leveraging the unique characteristics of malignant cells and their surrounding microenvironment, targeted delivery systems have the capacity to improve the precision and efficacy of immunotherapy [33]. Precision drug

delivery provides a notable benefit by boosting the concentration of medicinal substances within tumor tissue via active and passive delivery methods. Passive targeting capitalizes on the enhanced permeability and retention (EPR) effect, concentrating on tumor tissues with impaired lymphatic drainage and permeable blood vessels. In contrast, active targeting entails affixing targeting ligands (such as antibodies or peptides) to drug carriers, facilitating selective binding to antigens or receptors found on tumor cells to enhance absorption [34]. Furthermore, targeted drug delivery can overcome multidrug resistance mechanisms that often limit the effectiveness of conventional chemotherapy and immunotherapy. By encapsulating therapeutic agents within nanoparticle carriers or hydrogels, researchers can shield them from efflux transporters and other drug resistance mechanisms, thereby improving their intracellular accumulation and cytotoxicity. Moreover, targeted drug delivery can facilitate the co-delivery of multiple therapeutic agents with synergistic or complementary mechanisms of action, allowing for combination therapies that target different aspects of tumor growth and immune evasion simultaneously. This approach can enhance therapeutic efficacy while minimizing the development of drug resistance and off-target effects[35].

C. Role of Hydrogels in Overcoming Delivery Challenges:

The administration of drugs via hydrogel in cancer immunotherapy has developed as a multifunctional platform. Traditional drug delivery systems pose some challenges that can be effectively overcome through these systems. Since hydrogels are capable of containing a wide range of therapeutic agents, they are very suitable for the targeted delivery of immunomodulators to tumor sites [36]. As a result of their sustained delivery ability, hydrogels have a number of important advantages. The utilisation of hydrogel matrices to encapsulate immunomodulatory agents enables scientists to attain regulated release kinetics, thereby preserving therapeutic concentrations within the tumour microenvironment while reducing the risk of systemic exposure and toxicity [37]. To improve the efficacy of immunotherapy, sustained release profiles offered by hydrogels can extend the exposure of immune cells to therapeutic agents, overcoming the short half-life of many immunomodulators. In addition, hydrogels can be engineered to deliver targeted drugs on-demand, depending on the environment within the tumor. In tumor microenvironments characterized by high levels of proteolytic enzymes or acidic pH, stimuli-responsive hydrogels can selectively deliver therapeutic agents based on changes in enzyme activity or

pH [38]. The therapeutic agent is released only when specific tumor stimuli are present, ensuring that the off-target effects are minimized and the therapeutic efficacy increases. Furthermore, hydrogels can be functionalized with targeting ligands or antibodies to actively target therapeutic compounds to specific cell types or receptors within the tumor microenvironment. By conjugating targeting moieties to the surface of hydrogel nanoparticles or incorporating them into the hydrogel matrix, researchers can enhance the specificity and selectivity of drug delivery, leading to improved therapeutic outcomes and reduced systemic toxicity [39].

Table 1: Combinatorial Immunotherapies Delivered with Hydrogels

Payloads	Hydrogel	Features	Stage of Study	Results	Mode of Administration	Reference
Checkpoint inhibitors, Cytokines, Chemotherapeutic agents	Alginate-based hydrogel	Tunable degradation rate, Injectable, Biocompatible	Preclinical studies	Enhanced therapeutic efficacy, Reduced systemic toxicity	Local injection	[5]
Immunomodulatory agents	Polyethylene glycol-based hydrogel	Controlled release, Biodegradable, Injectable	Clinical trials	Improved tumor regression, Enhanced immune response	Intratumoral injection	[8]
Immune checkpoint inhibitors, Small molecule inhibitors	Gelatin methacryloyl-based hydrogel	Injectable, Biocompatible, Tailorable mechanical properties	Preclinical studies	Prolonged release of therapeutics, Increased infiltration	Local injection	[53]

				of immune cells		
Cytotoxic T-lymphocyte response enhancers	Injectable polypeptide hydrogel	Dual-delivery capability, Injectable, Biocompatible	Preclinical studies	Enhanced dendritic cell activation, Increased tumor regression	Subcutaneous injection	[6]
CAR-T cells, Anti-PDL1-conjugated platelets	Injectable hydrogel depot	Post-surgery tumor recurrence inhibition, Biocompatible	Preclinical studies	Reduced tumor recurrence, Prolonged survival	Intratumoral injection	[12]

DESIGN CONSIDERATIONS OF HYDROGEL-BASED DRUG DELIVERY SYSTEMS

Hydrogel-based drug delivery systems offer a means of administering therapeutic agents with regulated release in a range of biomedical contexts, encompassing treatments for cancer and beyond [40].

A. Selection of Hydrogel Material:

As well as their physical, chemical, and biological properties, hydrogel materials are also biocompatible and functional for drug delivery systems [41]. Hydrogels can be crafted from diverse natural and synthetic polymers, each offering unique merits and drawbacks. Their biocompatibility, biodegradability, and resemblance to components of the extracellular matrix render these polymers well-suited for hydrogel-based drug delivery systems [42]. These natural polymers can be modified with cell-targeting ligands or bioactive molecules, enabling their utilization for precise drug delivery to specific cells. It is also common for natural polymers to react to external stimuli, enabling them to release drugs in response to changes in pH, temperature, or enzyme activity within the tumor microenvironment. PEG, PNIPAAm,

and PVA are synthetic polymers that enable hydrogels to be developed with precise mechanical and chemical properties suited for tailored drug delivery applications [43]. Manipulating the swelling behavior, degradation kinetics, and release profiles of synthetic hydrogels enables the creation of drug delivery systems that meet specific therapeutic needs. Furthermore, synthetic polymers can be modified with functional groups or nanoparticles to enhance their targeting capabilities and optimize drug loading efficacy [12]. The hybrid hydrogel can achieve specific characteristics, such as increased mechanical strength, enhanced biocompatibility, and prolonged drug release, by combining inorganic nanoparticles with natural and synthetic polymers. Hybrid hydrogels can be tailored to combine the advantages of both materials [44]. By carefully selecting the appropriate blend of nanoparticles and polymers, researchers can fabricate hybrid hydrogels with enhanced drug delivery properties, catering to specific applications such as cancer immunotherapy. In drug delivery system design, the performance and efficacy of the resulting formulation are significantly influenced by the selection of hydrogel material. Through thorough examination of the attributes and properties of various polymers, researchers can develop drug delivery systems based on hydrogels that precisely meet the requirements of their intended function, whether it be sustained release, targeted drug administration, or responsiveness to stimuli [45].

B. Incorporation of Therapeutic Agents:

The successful incorporation of therapeutic agents into hydrogel matrices is essential for achieving controlled drug release and maintaining therapeutic efficacy[11]. Various methods can be employed to load therapeutic agents into hydrogels, including physical encapsulation, chemical conjugation, and electrostatic interactions, each with its advantages and limitations. Physical encapsulation is the most common method for incorporating therapeutic agents into hydrogel matrices, whereby the drugs are physically entrapped within the hydrogel network during gelation[46]. This method provides a straightforward and flexible means of encapsulating various hydrophilic and hydrophobic drugs without requiring chemical alterations. However, the release behavior of physically encapsulated drugs may be influenced by factors such as interactions between the drug and polymer, diffusion through the hydrogel structure, and degradation of the polymer network, potentially impacting the effectiveness of the drug delivery system. Chemical conjugation entails the covalent bonding of therapeutic agents to the polymer backbone or crosslinking sites within the hydrogel

matrix [47]. This approach offers precise control over drug loading and release kinetics, as well as enhanced stability and bioavailability of the conjugated drugs. However, chemical conjugation may require complex synthesis procedures and may alter the pharmacokinetics and pharmacodynamics of the therapeutic agents, necessitating careful optimization and characterization of the resulting drug delivery system. Electrostatic interactions involve the incorporation of charged therapeutic agents into hydrogel matrices through electrostatic interactions with oppositely charged polymers or nanoparticles[48]. This approach is particularly useful for loading small molecule drugs, peptides, or nucleic acids into hydrogels, as it allows for high loading capacities and controlled release profiles. However, the stability and release kinetics of electrostatically loaded drugs may be influenced by factors such as ionic strength, pH, and the presence of competing ions, requiring optimization of the formulation conditions to achieve desired drug release characteristics[49]. The incorporation of therapeutic agents into hydrogel matrices is a critical step in the design of drug delivery systems, as it determines the loading capacity, release kinetics, and stability of the resulting formulation. In order to maximize the effectiveness of therapy, researchers can optimize drug delivery systems based on hydrogels using appropriate loading methods and optimization strategies [50].

C. Tuning Release Kinetics:

In hydrogel-based drug delivery systems, controlling the release of therapeutic agents is imperative for optimizing therapeutic outcomes and minimizing systemic toxicity. Tuning the release kinetics of these systems requires adjusting hydrogel composition, crosslinking density, and drug loading concentration [51]. Modifying the composition and structure of the hydrogel matrix allows for the manipulation of drug release kinetics. For instance, increasing the crosslinking density of hydrogels can prolong drug release rates and reduce drug diffusion through the polymer network [52]. Similarly, adjustments to the hydrogel matrix's porosity or particle size can influence drug diffusion within the matrix and subsequently alter release kinetics. Additionally, the chemical or physical properties of the therapeutic agents can be modified to control the release kinetics of hydrogel-based drug delivery systems. For example, hydrophobic drugs may exhibit reduced release rates from hydrogel matrices due to their limited solubility and diffusion compared to hydrophilic drugs [53]. Additionally, drug-loaded nanoparticles or microparticles have a variety of physical properties that can influence their interactions with hydrogel matrixes and affect their release rates. Additionally, stimuli-

responsive components may be integrated into hydrogel matrixes to adjust the release kinetics of drug delivery systems. When exposed to external stimuli, reversible changes in swelling behavior can occur in stimuli-responsive hydrogels, such as those reactive to pH and temperature changes. This enables controlled release of encapsulated drugs [54]. By selecting suitable stimuli-responsive polymers or incorporating crosslinkers that respond to specific stimuli into the hydrogel matrix, researchers can create drug delivery systems capable of responding to cues within the tumor microenvironment, facilitating targeted and on-demand drug release. Overall, fine-tuning the release kinetics of hydrogel-based drug delivery systems is crucial for their design, as it dictates the timing and distribution of therapeutic agents within the body. Through careful optimization of formulation parameters and integration of stimuli-responsive elements, researchers can develop hydrogel-based drug delivery systems with precise control over drug release kinetics, thereby improving therapeutic effectiveness and minimizing adverse effects [55].

D. Strategies for Targeted Delivery:

By delivering therapeutic agents directly to the tumor site, targeted drug delivery enhances the effectiveness and safety of cancer treatment while minimizing systemic toxicity and unintended effects [56]. Through the creation of hydrogels sensitive to stimuli, integration of nanoparticles responsive to stimuli, and adoption of fabrication methods based on microfluidics, scientists are surmounting obstacles to drug delivery within tumors. These efforts aim to refine the effectiveness of hydrogel-based drug delivery systems in treating cancer. As a result of their prolonged circulation times, nanoparticles or microparticles encapsulating therapeutic agents in hydrogels can facilitate their preferential accumulation in tumor tissues by utilizing the EPR effect [57]. Through refining the dimensions, surface characteristics, and makeup of drug-containing nanoparticles, scientists can bolster their ability to target tumors and enhance treatment efficacy. Active targeting involves attaching targeting agents to the surface of drug-loaded nanoparticles or hydrogel matrices; these agents may include small molecules, peptides, antibodies, or ligands. By selectively binding to receptors or antigens that are overexpressed on the surface of cancer cells, these targeting ligands enable the drug delivery system to be specifically internalised and absorbed by tumour cells. Drug delivery systems with active targeting may improve therapeutic outcomes by increasing tumor cell uptake and reducing systemic exposure to healthy tissues [58]. Moreover, stimuli-responsive targeting involves integrating stimuli-responsive components

into the hydrogel matrix or drug-loaded nanoparticles, allowing for triggered release of therapeutic agents in response to specific signals within the tumor microenvironment. In response to pH, temperature, or enzyme activity in tumor microenvironments, stimulus-responsive hydrogels can undergo structural changes or degradation, controlling the release of drugs. Such hydrogels are sensitive to pH, temperature, or enzyme activity. Researchers can target tumor tissues with precision by incorporating stimuli-responsive elements into hydrogel matrixes or drug carriers, thereby minimizing unintended side effects and facilitating targeted drug release [59].

ADVANCES IN HYDROGEL-BASED DRUG DELIVERY FOR CANCER IMMUNOTHERAPY

There has been a surge of interest in using hydrogel-based drug delivery systems to improve cancer immunotherapy [22]. Hydrogel formulations, controlled drug release strategies, and tumour microenvironment targeting have all made substantial contributions in recent times to the advancement of therapeutic interventions that are more precise and efficacious [60].

A. Recent Developments in Hydrogel Formulations:

Novel hydrogel formulations with enhanced properties have been developed in recent years for cancer immunotherapy drug delivery applications [3]. These advancements encompass various aspects of hydrogel design, including composition, structure, and functionalization, to optimize drug loading, release kinetics, and targeting capabilities[61]. In the field of drug delivery systems using hydrogels, nanotechnology is a significant advancement. Nanocomposite hydrogels have been developed based on this integration that have improved drug loading capacities and controlled release properties. Compared to hydrogels, nanocomposite hydrogels have improved properties including biocompatibility, high water content, and the ability to adjust surface chemistry [8]. Using nanoparticles in hydrogels, researchers can improve drug loading efficiency, enable stimuli-responsive drug release, and deliver targeted drugs to tumor tissues. This can be done by incorporating mesoporous silica nanoparticles, gold nanoparticles, or magnetic nanoparticles [62]. Moreover, advances in biomaterials science have enabled the development of bioresponsive hydrogels that can dynamically interact with biological cues within the tumor microenvironment. Bioresponsive

hydrogels are designed to undergo specific changes in swelling behavior, degradation kinetics, or drug release properties in response to biochemical signals, such as enzymatic activity or changes in pH, oxygen levels, or redox potential. These hydrogels offer precise control over drug release kinetics and targeting specificity, making them promising platforms for personalized cancer therapy. Furthermore, the emergence of 3D bioprinting technologies has revolutionized the fabrication of hydrogel-based drug delivery systems, enabling the precise deposition of cells, growth factors, and therapeutic agents within customizable scaffolds[63]. 3D bioprinted hydrogels offer the potential to mimic the complex architecture and microenvironment of tumors, facilitating the study of tumor biology and drug response in vitro and enabling the development of personalized treatment strategies. By incorporating patient-derived tumor cells or immune cells into 3D bioprinted hydrogel scaffolds, researchers can create realistic tumor models for drug screening and immunotherapy optimization[54]. Overall, recent developments in hydrogel formulations have led to the creation of innovative drug delivery systems with enhanced capabilities for cancer immunotherapy. Researchers are developing more effective, personalized approaches to cancer treatment by integrating nanotechnology, biomaterials science, and 3D bioprinting technologies [64].

B. Novel Strategies for Controlled Drug Release:

When using hydrogel-based drug delivery systems in cancer immunotherapy, precise control of drug release kinetics is crucial to maximizing efficacy and safety. There have been significant developments in modulating drug release profiles, improving targeted drug delivery, and overcoming intratumoral drug delivery challenges in recent years [65]. One promising avenue of research involves the advancement of stimuli-responsive hydrogels, capable of altering their swelling characteristics, degradation rates, or drug release properties in response to specific stimuli found in the tumor microenvironment. Stimulus-responsive hydrogels, such as those sensitive to temperature, pH, or enzymatic activity, enable precise manipulation of drug release in a spatial and temporal manner, leading to improved specificity in targeted drug delivery and reduced off-target effects. Researchers can enhance the selective delivery of therapeutic agents in response to tumor-specific cues by incorporating stimuli-responsive components into hydrogel matrices, such as thermo-sensitive copolymers, pH-sensitive polymers, or enzyme-sensitive linkers [66]. Additionally, advancements in nanotechnology have led to the development of drug carriers responsive to

external stimuli. These drug-loaded nanoparticles or liposomes can be encapsulated within hydrogel matrices to facilitate controlled drug release [12]. Stimuli-responsive nanoparticles, such as polymer-drug conjugates, lipid-based nanoparticles, or inorganic nanocarriers, can be designed to respond to specific stimuli, such as changes in pH, temperature, or redox potential, leading to triggered release of encapsulated drugs within the tumor microenvironment. By incorporating stimuli-responsive nanoparticles into hydrogel-based drug delivery systems, researchers can achieve precise control over drug release kinetics and enhance therapeutic efficacy while minimizing systemic toxicity. Furthermore, advances in microfluidic technologies have enabled the development of microscale hydrogel particles with tunable size, shape, and porosity for controlled drug delivery applications[67]. Microfluidic-based synthesis techniques, such as droplet microfluidics, allow for the precise control over the size and composition of hydrogel particles, enabling the fabrication of monodisperse drug-loaded microspheres or microcapsules with uniform drug release kinetics. By varying the flow rates, mixing ratios, and polymer concentrations during microfluidic fabrication, researchers can tailor the properties of hydrogel-based microcarriers to achieve desired drug release profiles and targeting specificity[68]. Overall, novel strategies for controlled drug release are advancing the field of hydrogel-based drug delivery and enhancing the efficacy of cancer immunotherapy[5]. Due to advancements in nanotechnology, numerous nanoparticle-driven drug delivery platforms, including dendrimers, polymeric nanoparticles, and liposomes, have emerged to selectively target particular cell types or receptors within the tumor microenvironment [69].

C. Advances in Targeting Tumor Microenvironment:

A therapeutic intervention in the tumor microenvironment may be effective at preventing cancer progression and immune evasion [9]. Recent advancements in targeting the tumor microenvironment have focused on developing strategies to modulate immunosuppressive signals, enhance immune cell infiltration, and promote anti-tumor immune responses within the tumor microenvironment[70]. Immunomodulatory hydrogels are one innovative approach to modulating the immune response against tumors by delivering immunomodulatory agents directly to the tumor site, such as cytokines, chemokines and immune checkpoint inhibitors[24]. An immunomodulatory hydrogel increases immune cell activation, inhibits immunosuppressive signals, and induces anti-tumor immune responses by releasing therapeutic agents within the tumor microenvironment in a controlled manner. Researchers

are able to minimize systemic toxicity and off-target effects by encapsulating immunomodulatory agents within hydrogel matrices or conjugating them to hydrogel surfaces[71]. In addition, recent advances in biomaterials science have resulted in the development of hydrogels that mimic tumor extracellular matrix (ECM), which is intended to stimulate immune cells to migrate to tumor microenvironments and activate. By replicating both mechanical and biochemical properties of native ECMs, these hydrogels are known as ECM-mimetic hydrogels [4], which create conditions conducive to immune cell migration, recruitment, and adhesion within tumor tissues. Enhancing the presence and activity of immune cells within the tumor microenvironment can be achieved by integrating bioactive compounds like growth factors and cell adhesion peptides into hydrogel matrices. These compounds, which include dendritic cells, natural killer (NK) cells, and T cells, contribute to improved immune responses against tumors when embedded within hydrogel matrices [33]. Due to advancements in nanotechnology, numerous nanoparticle-driven drug delivery platforms, including dendrimers, polymeric nanoparticles, and liposomes, have emerged to selectively target particular cell types or receptors within the tumor microenvironment. It is possible to functionalize nanoparticles with targeting ligands (e.g., aptamers, peptides, antibodies) to ensure that tumor-associated antigens or receptors are specifically bound [72]. By conjugating targeting ligands onto the surface of hydrogel matrices or drug-loaded nanoparticles, researchers can selectively deliver therapeutic agents to stromal cells or immune cells that have infiltrated the tumor microenvironment, thereby enhancing therapeutic efficacy and reducing off-target effects. Overall, advances in targeting the tumor microenvironment are enhancing the efficacy of cancer immunotherapy and improving patient outcomes[32]. By developing immunomodulatory hydrogels, ECM-mimetic hydrogels, and nanoparticle-based drug delivery systems, researchers are harnessing the unique properties of hydrogels and nanomaterials to modulate immune responses within the tumor microenvironment and overcome immune evasion mechanisms, ultimately leading to more effective and durable anti-tumor immune responses[73].

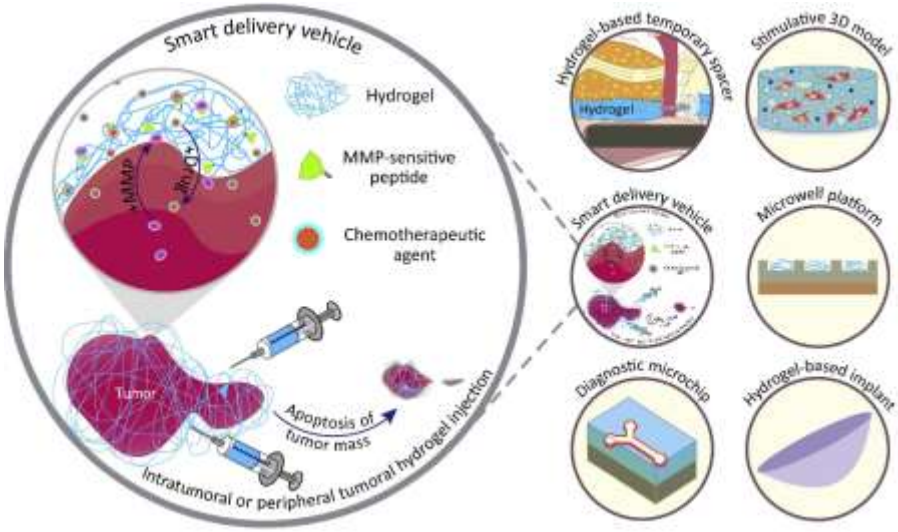

Figure 1: Hydrogels in Cancer Therapy and Diagnosis

APPLICATIONS OF HYDROGEL-BASED DRUG DELIVERY IN CANCER IMMUNOTHERAPY

Hydrogel-based drug delivery systems have emerged as promising platforms for advancing cancer immunotherapy, offering precise control over the delivery of immunomodulatory agents, facilitating combination therapies with immune checkpoint inhibitors, and enabling targeted delivery to specific cancer types[13,74].

A. Delivery of Immunomodulatory Agents:

Immunomodulatory substances are pivotal in cancer immunotherapy as they adjust the immune response to identify and eradicate cancerous cells [40]. However, systemic administration of immunomodulatory agents can lead to dose-limiting toxicities and off-target effects. Hydrogel-based drug delivery systems offer an attractive solution by providing sustained release of immunomodulatory agents directly to the tumor site, thereby maximizing therapeutic efficacy while minimizing systemic toxicity[75]. A way to utilize hydrogel-based drug delivery in cancer immunotherapy involves administering cytokines like interleukin-2 (IL-2) or interferon-alpha (IFN-α) to boost the activation and multiplication of immune cells [21]. Through encapsulation of cytokines within hydrogel matrices, scientists can regulate the rate of release, ensuring that therapeutic levels are sustained within the tumor microenvironment. This sustained release fosters heightened activation of cytotoxic T cells

and natural killer (NK) cells, consequently enhancing the body's immune response against tumors [19]. Moreover, hydrogel-based delivery of cytokines can overcome the short half-life and rapid clearance of these agents in vivo, leading to sustained immune activation and durable anti-tumor effects[76]. Another application is the delivery of immunomodulatory antibodies, such as anti-CTLA-4 or anti-PD-1/PD-L1 antibodies, which block immune checkpoint pathways and unleash anti-tumor immune responses[19]. Hydrogel-based methods for delivering drugs can support the gradual release of immune checkpoint inhibitors in the tumor's surroundings. This extended exposure helps to continuously block inhibitory signals, promoting increased activation of effector T cells. By enclosing immune checkpoint inhibitors within hydrogel matrices, scientists can ensure targeted transportation to the tumor site, decrease overall exposure to the body, and mitigate the possibility of immune-related side effects, all while optimizing treatment effectiveness [77].

Moreover, hydrogel-mediated drug delivery platforms can be designed to simultaneously transport a variety of immunomodulatory substances, including cytokines, antibodies, and small molecule agonists or antagonists. This multifaceted approach aims to collaboratively regulate the immune response and counteract resistance mechanisms present within the tumor microenvironment [14]. By entrapping various immunomodulatory substances within a shared hydrogel framework or integrating them into distinct sections within versatile hydrogel nanoparticles, scientists can attain meticulous management over the timing of drug release and exploit the synergistic effects of therapy. This strategy can result in amplified immune responses against tumors and better patient outcomes in clinical settings [78].

B. Combination Therapies with Immune Checkpoint Inhibitors:

Antibodies targeting immune checkpoints like CTLA-4 and PD-1/PD-L1 have transformed cancer therapy by stimulating immune reactions against tumors and eliciting lasting benefits in certain individuals [56]. However, many patients fail to respond to immune checkpoint blockade alone, highlighting the need for combination therapies that enhance the efficacy of these agents and overcome resistance mechanisms within the tumor microenvironment[79]. Hydrogel-based drug delivery systems offer a versatile platform for delivering combination therapies with immune checkpoint inhibitors, enabling synergistic effects and improved therapeutic outcomes.

One strategy is the co-delivery of immune checkpoint inhibitors with other immunomodulatory agents, such as cytokines, costimulatory agonists, or immune adjuvants,

to enhance immune cell activation and overcome immune evasion mechanisms within the tumor microenvironment[29]. Through encapsulating immune checkpoint inhibitors and complementary immunomodulators within a singular hydrogel matrix or delivering them together in distinct compartments within multifaceted hydrogel nanoparticles, scientists can exert meticulous regulation over the release patterns of drugs and exploit therapeutic synergy. This approach fosters heightened anti-tumor immune reactions and advances clinical results [80]. Moreover, hydrogel-based drug delivery systems can be engineered to deliver combination therapies with conventional chemotherapy, radiotherapy, or targeted therapies, to enhance tumor cell killing and promote immunogenic cell death within the tumor microenvironment[34]. By co-encapsulating immune checkpoint inhibitors with chemotherapeutic agents, such as doxorubicin or paclitaxel, within hydrogel matrices, researchers can achieve synergistic effects that enhance tumor cell apoptosis, antigen presentation, and immune cell infiltration, leading to improved therapeutic efficacy and durable responses in cancer patients[81]. Furthermore, hydrogel-based drug delivery systems can facilitate combination therapies with novel immunotherapeutic modalities, such as chimeric antigen receptor (CAR) T cell therapy or tumor-infiltrating lymphocyte (TIL) therapy, by providing a supportive microenvironment for immune cell expansion, activation, and persistence within the tumor site. By encapsulating CAR T cells or TILs within hydrogel matrices or incorporating them into hydrogel-based scaffolds, researchers can enhance the survival, function, and anti-tumor activity of adoptively transferred immune cells, leading to improved clinical responses and long-term remission in cancer patients[82].

C. Targeted Delivery to Specific Cancer Types:

A significant obstacle in cancer treatment lies in effectively delivering therapeutic substances to particular cancer variants while limiting adverse effects on healthy tissues [18]. Hydrogel-based drug delivery systems offer a promising solution by providing precise control over drug release kinetics and targeting specificity, thereby enhancing therapeutic efficacy and minimizing systemic toxicity. application of targeted delivery in cancer immunotherapy is the development of tumor-targeting hydrogels that can selectively deliver therapeutic agents to tumor cells while sparing healthy tissues[83]. By modifying hydrogel nanoparticles or microparticles with tumor-specific ligands, such as antibodies, peptides, or aptamers, scientists can facilitate precise attachment to antigens or receptors associated with tumors. This targeted binding promotes increased absorption and uptake of the drug delivery system

by cancerous cells. Moreover, by incorporating stimuli-responsive elements into the hydrogel matrix, researchers can achieve triggered release of therapeutic agents in response to specific cues within the tumor microenvironment, further enhancing targeting specificity and therapeutic efficacy[34]. Another application is the development of organ-specific hydrogels that can deliver therapeutic agents to metastatic sites or sanctuary sites within the body[84]. By engineering hydrogel-based drug delivery systems with tissue-specific homing peptides or chemokines, researchers can achieve selective targeting of metastatic tumors or tumor microenvironments within specific organs, such as the liver, lung, or brain. Moreover, by encapsulating therapeutic agents within hydrogel matrices that are designed to degrade or release drugs in response to specific biochemical signals or mechanical cues within the target tissue, researchers can achieve precise control over drug release kinetics and localization, leading to enhanced therapeutic efficacy and reduced off-target effects[85]. Furthermore, hydrogel-based drug delivery systems can be tailored to exploit the unique physiological properties of different cancer types, such as the acidic pH, elevated levels of proteolytic enzymes, or increased vascular permeability within the tumor microenvironment. Through the integration of pH-responsive polymers, enzyme-sensitive connectors, or vascular-targeting peptides into hydrogel matrices, scientists can accomplish targeted transportation of medicinal substances to particular cancer varieties or tumor microenvironments. This approach enhances the effectiveness of therapy while minimizing unintended impacts [86].

APPLICATION OF HYDROGELS IN VACCINE DEVELOPMENT

The utilization of hydrogels in vaccine development presents a promising approach to enhance vaccine effectiveness, stability, and delivery. Hydrogels, which are three-dimensional networks of hydrophilic polymer chains capable of absorbing large amounts of water, offer distinct advantages for vaccine delivery, including sustained release, protection of antigens from degradation, and targeted delivery to specific tissues or cells. This article explores the application of hydrogels in vaccine development and underscores their potential to enhance vaccination strategies [87]. Hydrogels have emerged as promising candidates for vaccine delivery vehicles owing to their capacity to encapsulate antigens and adjuvants, safeguarding them from degradation and facilitating controlled release. Antigens, the pivotal components of vaccines that trigger the immune system to generate protective immunity, can be encapsulated within hydrogel matrices to improve their stability and immunogenicity [5,9]. By entrapping antigens within hydrogel networks, researchers can protect them from

enzymatic degradation and preserve their structural integrity during storage and administration, thereby improving vaccine stability and shelf life[88].

Moreover, hydrogels can serve as reservoirs for adjuvants, immunostimulatory molecules that enhance the immune response to vaccines. Adjuvants may be integrated into hydrogel matrices to stimulate antigen absorption, facilitate antigen presentation, and activate immune cells, thereby improving vaccine effectiveness. By delivering antigens and adjuvants together in a single hydrogel formulation, researchers can achieve synergistic effects that enhance immune responses and improve vaccine potency[89].

In addition to their role in antigen and adjuvant delivery, hydrogels offer advantages for vaccine administration and delivery routes. Hydrogel-based vaccines can be formulated as injectable gels, patches, or implants, allowing for convenient and painless administration via subcutaneous, intramuscular, or mucosal routes. Injectable hydrogels can be administered using standard needles and syringes, eliminating the need for specialized delivery devices and cold chain storage requirements, which is particularly advantageous for mass vaccination campaigns and resource-limited settings[90].

Moreover, vaccine formulations utilizing hydrogels can be designed to accomplish regulated discharge of antigens and adjuvants over prolonged durations, resulting in continuous immune activation and extended safeguarding against infectious illnesses [12,1]. By modulating the composition, crosslinking density, and degradation kinetics of hydrogel matrices, researchers can tailor the release kinetics of vaccine components to match desired immune response kinetics, optimizing vaccine efficacy and durability[91]

Hydrogels present possibilities for precise delivery of vaccines to particular tissues or cells, thus amplifying immune responses and reducing unintended impacts. By modifying hydrogel surfaces with targeting molecules like antibodies, peptides, or aptamers, they can selectively attach to cell receptors or antigens on target cells, facilitating precise vaccine delivery. Moreover, hydrogels can be designed to respond to specific stimuli, such as changes in pH, temperature, or enzyme activity in the microenvironment, enabling triggered release of vaccine components at desired sites or times[44].

Despite these benefits, there are still various obstacles that need to be overcome to facilitate the extensive utilization of hydrogels in vaccine development [28]. These challenges include the optimization of hydrogel formulations for specific vaccine antigens and adjuvants, the development of scalable manufacturing processes, and the evaluation of safety and immunogenicity in preclinical and clinical studies. Moreover, regulatory approval and market acceptance of hydrogel-based vaccines require rigorous testing and validation to ensure their

safety, efficacy, and quality in accordance with regulatory guidelines and standards[33].

PRECLINICAL AND CLINICAL STUDIES

Preclinical research serves a crucial function in evaluating the practicality, effectiveness, and safety of hydrogel-based drug delivery systems using animal models of cancer [7].

A. Overview of Preclinical Studies:

Preclinical research serves a crucial function in evaluating the practicality, effectiveness, and safety of hydrogel-based drug delivery systems using animal models of cancer [92]. These studies offer valuable insights into the pharmacokinetics, biodistribution, and therapeutic outcomes of drugs formulated with hydrogels, thus informing the design and refinement of subsequent clinical trials involving human subjects[7]. In preclinical assessments, hydrogel-based drug delivery systems are usually examined to determine their ability to transport therapeutic substances to the tumor location, extend the retention of drugs within the tumor microenvironment, and provoke immune responses against the tumor [93]. Animal models of cancer, including mouse xenograft models or genetically engineered mouse models, are commonly employed to assess the pharmacological properties and therapeutic potential of drugs formulated with hydrogels in vivo. One key focus of preclinical studies is to investigate the pharmacokinetics and biodistribution of hydrogel-formulated drugs following local or systemic administration[55]. By labeling therapeutic agents with fluorescent dyes or radioisotopes, researchers can track their distribution and accumulation within the body over time, elucidating the kinetics of drug release, clearance, and tumor targeting[9]. Furthermore, in preclinical investigations, imaging techniques such as positron emission tomography (PET) or magnetic resonance imaging (MRI) are frequently utilized to observe and measure the dispersion of drugs within the tumor microenvironment. These methods offer valuable insights into the temporal and spatial aspects of drug delivery [22]. Furthermore, preclinical studies assess the therapeutic efficacy of hydrogel-formulated drugs in inhibiting tumor growth, inducing tumor regression, and prolonging survival in animal models of cancer[19]. By comparing the anti-tumor effects of hydrogel-formulated drugs with conventional formulations or vehicle controls, researchers can evaluate the impact of hydrogel-based drug delivery on therapeutic outcomes and identify optimal formulation parameters for further

clinical development[89]. Overall, preclinical studies provide essential preclinical data on the pharmacokinetics, biodistribution, and therapeutic efficacy of hydrogel-based drug delivery systems, laying the groundwork for clinical translation and informing the design of clinical trials in cancer patients[18].

B. Clinical Trials Utilizing Hydrogel-Based Drug Delivery:

Clinical trials are pivotal in propelling hydrogel-based drug delivery systems from laboratory experimentation to real-world use, as they assess these systems' safety, efficacy, and practicality in human subjects. Multiple clinical trials have been undertaken to gauge the effectiveness and tolerability of hydrogel-based formulations in individuals with cancer [99], consistently demonstrating their potential as viable therapeutic options. For instance, a clinical trial utilizing chemotherapy formulations delivered via hydrogels has shown promising results in treating solid tumors [54]. By facilitating sustained delivery of cytotoxic agents directly to the tumor site, hydrogel-based drug delivery systems can enhance chemotherapy's therapeutic index, reducing systemic toxicity and boosting antitumor activity. Clinical trials have demonstrated the safety and feasibility of hydrogel-formulated chemotherapy in treating various cancer types, including brain tumors, pancreatic cancer, and breast cancer, leading to significant improvements in patient outcomes and quality of life. Furthermore, clinical trials investigating the use of hydrogel-based drug delivery systems in cancer immunotherapy have explored targeted administration of immunomodulatory compounds [94]. By encapsulating cytokines, immune checkpoint inhibitors, or tumor-targeting antibodies within hydrogel matrices, precise delivery to the tumor site can be achieved, enhancing immune cell activation and overcoming immune evasion mechanisms in the tumor microenvironment [19]. Immunotherapies incorporated into hydrogel formulations have demonstrated both safety and efficacy in enhancing the body's immune responses against tumors, thereby enhancing patient outcomes in cancer treatment. This success signals a promising pathway for continued advancement and refinement of these pioneering treatment modalities. Furthermore, clinical investigations have been undertaken to assess the efficacy of hydrogel-based drug delivery systems in administering precision oncology treatments, including monoclonal antibodies and small molecule inhibitors [10]. By encapsulating targeted agents within hydrogel matrices or conjugating them to hydrogel carriers, researchers can achieve selective delivery to tumor cells expressing specific molecular targets, thereby maximizing therapeutic efficacy and minimizing off-target effects.

Clinical trials have shown promising results with hydrogel-formulated targeted therapies in various cancer types, including melanoma, lung cancer, and colorectal cancer, highlighting their potential as personalized treatment options for patients with molecularly defined tumors[45,21]. Overall, clinical trials utilizing hydrogel-based drug delivery systems have demonstrated their safety, efficacy, and feasibility in cancer patients, providing evidence of their potential as effective therapeutic interventions in oncology. By harnessing the unique properties of hydrogels, researchers can overcome the limitations of conventional drug delivery approaches and develop innovative treatment modalities that improve patient outcomes and quality of life[95].

C. Challenges and Future Prospects:

Although substantial advancements have been made in both preclinical and clinical investigations of hydrogel-based drug delivery systems for cancer immunotherapy, numerous obstacles persist that need to be overcome to fully harness their capabilities in real-world clinical settings [13]. These challenges encompass technological, biological, and regulatory aspects, which require collaborative efforts from researchers, clinicians, and regulatory agencies to overcome. One challenge is the development of hydrogel formulations with optimal biocompatibility, biodegradability, and stability for clinical use[18]. Hydrogel-based drug delivery systems must be carefully engineered to minimize immune reactions, inflammation, and foreign body responses in vivo, ensuring their safety and tolerability in patients[14]. Moreover, the scalability and reproducibility of hydrogel manufacturing processes need to be addressed to facilitate clinical translation and commercialization of hydrogel-based therapies. Another challenge is the optimization of drug release kinetics, targeting specificity, and therapeutic efficacy of hydrogel-based formulations in clinical settings[34,43]. Drug delivery systems utilizing hydrogels need to be customized to match the distinct features of specific tumors, patient groups, and treatment protocols. This customization aims to optimize treatment effectiveness while reducing the occurrence of unintended side effects. Moreover, the integration of advanced imaging and biomarker technologies into clinical trials can provide valuable insights into the pharmacokinetics, biodistribution, and pharmacodynamics of hydrogel-formulated drugs, enabling personalized treatment strategies and patient monitoring[15]. Moreover, overcoming the hurdles of regulatory approval and garnering market acceptance for drug delivery systems based on hydrogels presents considerable obstacles in their journey towards clinical translation and

commercialization. Hydrogel-based therapies must undergo rigorous preclinical and clinical testing to demonstrate their safety, efficacy, and quality in accordance with regulatory guidelines and standards. Moreover, reimbursement policies, market dynamics, and healthcare economics need to be considered to ensure widespread adoption and accessibility of hydrogel-based therapies in clinical practice[96].

BIODISTRIBUTION AND CLEARANCE OF HYDROGELS

One of the significant challenges associated with the use of hydrogel-based drug delivery systems is their biodistribution and clearance from the body[87]. Hydrogels, owing to their unique properties, can exhibit varied biodistribution patterns and clearance rates, which can impact their efficacy and safety in vivo. Biodistribution refers to the distribution of hydrogel-based formulations throughout the body following administration[97]. The biodistribution of hydrogels can be influenced by factors such as their size, shape, surface properties, and composition[23]. Small hydrogel particles may be cleared rapidly from the bloodstream by the reticuloendothelial system, leading to limited accumulation at the target site. On the other hand, larger hydrogel constructs may exhibit prolonged circulation times but may also face challenges in extravasation and penetration into tumor tissues or other target sites[65]. Furthermore, the surface properties of hydrogels can affect their interactions with biological components, such as proteins and cells, which can influence their biodistribution. Hydrogels with charged or hydrophobic surfaces may interact differently with proteins in the blood, leading to altered clearance rates and tissue distribution profiles[98]. Additionally, hydrogels may undergo degradation or erosion in vivo, releasing encapsulated drugs or degradation by-products that can further influence their biodistribution and pharmacokinetics. Clearance mechanisms, including renal clearance, hepatic clearance, and lymphatic drainage, play a crucial role in the elimination of hydrogel-based formulations from the body[54]. Small hydrogel particles and degradation products may be cleared through renal filtration and excreted in the urine, while larger constructs may be taken up by macrophages in the liver or spleen and subsequently degraded or eliminated through the biliary or fecal route. Moreover, lymphatic drainage can contribute to the clearance of hydrogel-based formulations from peripheral tissues, particularly in lymphoid-rich areas[99]. However, the clearance of hydrogels from the body can be complex and dependent on various factors, including their size, charge, degradation kinetics, and the presence of targeting ligands or surface

modifications[6]. Clearance mechanisms may also be influenced by physiological factors such as renal function, hepatic function, and lymphatic drainage rates, which can vary among individuals and disease states. Addressing the challenges associated with the biodistribution and clearance of hydrogel-based drug delivery systems requires a comprehensive understanding of their pharmacokinetics and pharmacodynamics in vivo[100]. Strategies to optimize the size, surface properties, and degradation kinetics of hydrogels can enhance their biodistribution and clearance profiles, thereby improving their therapeutic efficacy and safety[32,1]. Moreover, the development of targeted delivery approaches and stimuli-responsive hydrogels may enable more selective tissue targeting and controlled release, minimizing off-target effects and enhancing therapeutic outcomes. Overall, addressing the challenges of biodistribution and clearance represents a critical area of research in the development of hydrogel-based drug delivery systems for clinical applications[101].

CONCLUSION

The application of hydrogels in vaccine development represents a significant advancement with the potential to revolutionize vaccination strategies. Hydrogels offer unique advantages such as enhanced stability, controlled release, and targeted delivery of vaccine components, which can improve vaccine efficacy, durability, and administration. By encapsulating antigens and adjuvants within hydrogel matrices, researchers can protect them from degradation, promote sustained immune stimulation, and achieve synergistic effects that enhance vaccine potency. Furthermore, hydrogel-based vaccines can be formulated for convenient administration via various routes, allowing for widespread vaccination campaigns and improved accessibility in resource-limited settings. Despite challenges such as formulation optimization, manufacturing scalability, and regulatory approval, the continued research and development of hydrogel-based vaccines hold promise for addressing global health challenges and improving public health outcomes. Overall, hydrogels offer a versatile platform for vaccine delivery and hold great potential for shaping the future of preventive medicine.

CONFLICT OF INTEREST

None

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