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Research progress in application of alginate gel as tumor drug delivery carrier, for tumor localization and 3D tumor cell model

Lili Huang [a], Yicong Lei [b], Yucheng Chen [b], Xin Hu [b], Chengyu Huang [c], Huaqing Lin [b,*]

[a] Shenzhen Traditional Chinese Medicine Hospital of Guangdong Province, Shenzhen, 518033, China
[b] Key Laboratory of Advanced Drug Delivery Systems of Guangdong Province, Guangdong Pharmaceutical University, Guangzhou, 510006, China
[c] Pharmacology Laboratory of the School of Pharmacy, Guangdong Pharmaceutical University, Guangzhou, 510006, China

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ABSTRACT

As one of the hot materials in biomedical research, alginate gel shows great potential in tumor therapy with its unique physical and chemical properties. In order to better meet the complex needs of cancer treatment, alginate brine gel composite system has come into being. This system not only inherits many advantages of single alginate brine gel, but also significantly improves the mechanical properties of the material through compounding, and effectively overcomes the limitations of application. These composites have been applied to drug delivery carriers, tumor targeting systems and three-dimensional tumor cell models in various forms, showing a wide range of application prospects. This paper aims to review the basic structure and properties of alginate gel and analyze the research progress of alginate gel composite systems in the field of cancer in recent years, to provide a valuable reference for the further expansion of the application of this material in tumor therapy.

1. Introduction

Cancer is recognized as the leading cause of death worldwide and poses a significant challenge to extending life expectancy across all countries.[1] According to the World Health Organization (WHO), in 2020, out of 185 countries/regions, there were 19.3 million new cancer cases and nearly 10 million cancer-related deaths. Cancer remains a prominent cause of illness and death globally, emerging as a significant public health concern worldwide.[2] Current treatment modalities for cancer include surgical intervention, chemotherapy, radiation therapy, or a combination of these approaches. While chemotherapy is the most commonly utilized treatment, it often leads to significant toxic side effects and contributes significantly to patient mortality. As a result, there is a growing demand for the development of new materials with controllable and targeted delivery functions to enhance the effectiveness of anticancer chemotherapy drugs while minimizing adverse effects.[3]

In recent years, researchers have made strides in developing multifunctional materials with high biocompatibility, such as polymer hydrogels,[4,5] inorganic carriers,[6] and biological macromolecule scaffolds,[7] all tailored to tumor biology. Among these versatile drug carriers, hydrogels are particularly favored. Hydrogels, three-dimensional cross-linked networks comprised of hydrophilic polymers with high water content, exhibit strong water-absorbing capacity and closely resemble the soft tissue microenvironment of the human body. The highly porous structure of hydrogels allows for precise control over the density, swelling, drug loading, and release kinetics of the gel matrix.[8,9] Furthermore, hydrogels demonstrate a high drug-loading capacity and various stimulus-responsive properties triggered by pH, temperature, redox reactions, or specific enzymatic activity.[10] These exceptional qualities render them suitable for accommodating a diverse range of drugs to combat complex diseases,[11] including cancer, neurological disorders, and osteoporosis.[12–14] Alginate, possessing benefits such as ease of preparation, biocompatibility, biodegradability, and non-toxicity, has found wide applications in the food and biopharmaceutical industries.[15] Alginate can form gels through ion exchange with multivalent cations, resulting in cross-linked hydrogels suitable for controlled release of bioactive molecules.[16] Additionally, alginate hydrogels exhibit excellent biocompatibility, water-absorbing capacity, and moisturizing properties. Combining hydrogels with alginate creates a composite system that leverages the strengths of both materials, enhancing drug efficacy while minimizing toxic side effects, particularly in the context of cancer drug delivery systems. Moreover, this composite system can be employed for tasks such as *in vitro* tumor cell modeling, scaffold filling, cell localization, and other applications.

This paper provides an overview of the structure, properties, and preparation methods of alginate and its polymers, followed by a

* Corresponding author.
E-mail address: prof_huaqing@126.com (H. Lin).

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discussion on the current research landscape regarding alginate composite hydrogel systems in cancer therapy. The aim is to offer insights for further research and treatment involving tumors utilizing alginate composite hydrogels.

2. Overview of alginate composite hydrogel

2.1. Alginate

Alginate is a block linear polymer composed of two monomers, β-D-mannuronic acid (M) and α-L-guluronic acid (G), linked by 1 → 4 linkages, and is often present in three regions in one alginate molecule, consisting of a continuous M residue, a continuous G residue, and alternating anionic polymers composed of M and G residues (as shown in Fig. 1).[16,17]

The commonly used alginates include sodium alginate (AGS) and calcium alginate (AGC). AGS solution is a typical polymer electrolyte solution that can undergo lateral crosslinking to form a gel in the presence of divalent cations.[18] The physical and chemical properties of alginates, such as viscosity, sol-gel transition, and water absorption, are largely dependent on the type and density of crosslinking, as well as the molecular weight and chemical composition (i.e., M/G ratio) of the polymer.[19–21] Furthermore, the pH of the solution plays a crucial role in determining the viscosity of alginate. A decrease in pH results in an increase in viscosity due to the protonation of the carboxylic acid groups in the alginate backbone, leading to the formation of hydrogen bonds. In commercial alginates, the molecular weight is represented as the average number of molecules in a given sample and can vary between 33,000 and 400,000 g/mol. Altering the molecular weight of alginate can have a significant impact on the physical properties of the synthesized gels, with high-molecular-weight alginate solutions exhibiting considerably higher viscosity. Unlike alginate, brown algae are insoluble in both water and organic solvents. Alginate with M or G structures undergoes precipitation at low pH, whereas those with alternative M and G segments remain soluble under the same conditions.[22] Alginate is commonly used as a stabilizer for suspensions and emulsions, as well as a thickener and viscosity enhancer in the food and pharmaceutical industries due to its unique ability to undergo sol-gel transitions, thereby forming semi-solid or solid structures.

2.2. Hydrogel

Hydrogels are highly versatile materials that can be used for localized drug delivery and can respond to various internal or external triggers.[23] These three-dimensional networks are capable of holding a large amount of water, making them highly compatible with biological environments like the human body.[24] In earlier technology, hydrogels were formed through strong covalent bonds between the monomers that make up the polymer chains or permanent cross-linked polymer networks.[25] Due to the difficulty in handling the required fixated structures and the inability of hydrogels to be directly applied after formation without surgical intervention or the use of large-diameter needles, the biological engineering applications of hydrogels were generally limited to surface environments such as the surface of the eye, open wounds, or exposed surgical sites. Nevertheless, research on hydrogels has never ceased, with polysaccharides showing promising properties when used in conjunction with hydrogels. AGS is one of the most commonly used natural polysaccharides, with its molecule consisting of β-D-mannuronic acid (M) and α-L-guluronic acid (G) linked via (1 → 4) bonds. The gelation and cross-linking of alginate are achieved through the exchange of sodium ions with multivalent cations, resulting in cross-linked hydrogels that can be used for the controlled release of bioactive molecules,[26] as scaffolds for tissue engineering[16] and Localization within the organism.[27]

2.3. Alginate hydrogel

Hydrogels formed by the polymerization of alginate possess a three-dimensional network structure similar to that of the extracellular matrix in human physiology[28,29] and have potential as drug delivery scaffold materials. However, natural alginate hydrogels have inherent limitations such as slow biodegradation in the body, poor recognition and adhesion by cells, and instability in gel structure under traditional ion-crosslinking methods,[30] which limit their use in drug delivery. To enhance the physical properties of alginate, it is commonly mixed with other substances to form alginate composites, such as natural polymers like collagen, chitosan, and gelatin, synthetic polymers like polypropylene and polypyrrole, and inorganic compounds such as tetraethyl orthosilicate (TEOS) and hydroxyapatite (HA).[31,32] Alginate composite hydrogels can be tailored to adjust their biodegradability and crosslinking methods

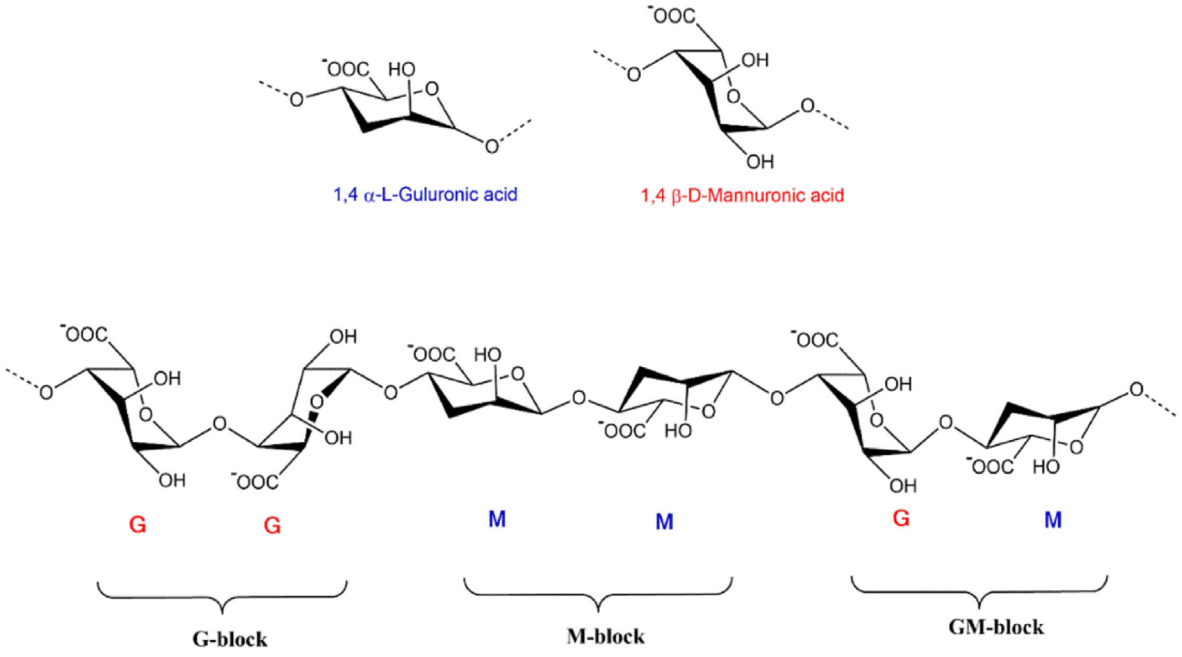

Fig. 1. The conformation of monomers and blocks distribution of alginate salt.[16]

to improve the limitations mentioned above, making them ideal candidates for delivering both small-molecule and large-molecule drugs (including protein and gene maintenance or targeting).[30,33] They are widely used in medical, food, and daily chemical products.

Alginate composite hydrogels, as a type of alginate polymer, can be prepared by ion crosslinking, covalent crosslinking, phase transition (thermal gelation), cell crosslinking, and free radical polymerization.[32,34] The most common method of ion crosslinking is to combine the solution with an ion crosslinking agent (such as a divalent cation (such as Ca^{2+})) (as shown in Fig. 2[16]), and the gel conditions are relatively mild.[32] Covalent crosslinking (as shown in Fig. 3[35]) can establish covalent bonds between polymer chains through amide reaction, isocyanate reaction with -OH/NH_2, Schiff base reaction, condensation reaction, addition reaction, and high-energy radiation, thereby forming a miscible hydrogel,[36] providing more precise degradation rates and controllable mechanical stiffness.[37] Free radical polymerization crosslinking introduces polymerizable groups into water-soluble polymers, and then chemically crosslinks hydrogels through free radical copolymerization under the action of crosslinking agents (as shown in Fig. 4[38]). Calcium, sodium, ammonium, and potassium salts of alginate have been recognized as GRAS (Generally Recognized as Safe) by the US Food and Drug Administration.[39] Gels formed by cross-linking show promise for a wide range of applications in drug delivery vehicles, tumour targeting systems and various forms of 3D tumour cell models (see Fig. 5).

3. Alginate composite hydrogel in cancer

The global burden of cancer incidence and mortality is rapidly increasing; according to the International Agency for Research on Cancer's estimate of the incidence and mortality rates of 36 major types of cancer worldwide, female breast cancer ranks first (11.7%), followed by lung cancer (11.4%), colorectal cancer (10.0%), prostate cancer (7.3%), and stomach cancer (5.6%) in 2020, and the cancer population is predicted to increase by 47% by 2040.[2] The continuous growth of cancer indicates the urgent need to strengthen prevention and treatment interventions. Therefore, finding appropriate materials to increase the bioavailability of drugs and reduce toxic side effects has become an urgent need. Alginate composite hydrogel materials can optimize some of the physical properties of alginate hydrogels, such as low adhesion and excessive hydrophilicity, making this system gradually become a hot spot in cancer applications. This article will review the application of alginate composite hydrogel systems in tumors.

3.1. Delivery of oncology drugs as a carrier

The selection of clinical cancer treatment methods is influenced by multiple factors, including cancer stage, tumor biology, risks and benefits of proposed therapy, anticipated clinical outcomes, patient preferences, and overall treatment costs. Presently, the primary treatment modalities for cancer include surgery, chemotherapy, and radiation therapy, with chemotherapy remaining a vital component. The rapid division of cancer cells renders them more vulnerable to the effects of chemotherapy drugs. However, chemotherapy has its limitations. Notably, anticancer drugs often struggle to penetrate malignant tumors efficiently and lack specificity, leading to inadequate drug concentration at the tumor site and suboptimal treatment outcomes. Furthermore, chemotherapy drugs elicit significant side effects due to their broad impact on all dividing cells, including normal tissues, particularly rapidly dividing cells like those in the oral cavity, pharynx, stomach, intestines, airways, and skin. Additionally, certain chemotherapy agents may affect the functionality of vital organs such as the heart, lungs, kidneys, central nervous system, or peripheral nerves.[40] Hence, the development of novel drug delivery systems to target cancer drugs effectively can help mitigate adverse effects on normal tissues.

According to tumor biology, we have developed multifunctional materials with enhanced bioavailability, including polymers, lipids, polymeric hydrogels, nano-microspheres, inorganic carriers, and biomolecular scaffolds. These materials typically exhibit excellent biocompatibility and biodegradability. The effectiveness of drug delivery is largely influenced by the design of carriers. By incorporating dynamic covalent bonds like disulfide, borate, and carbon-nitrogen bonds into the carrier construction process,[41] or by cross-linking with other materials such as folic acid,[42] nanogold,[43] and indocyanine green (ICG)-entrapped perfluorocarbon nanoemulsions,[44] drug penetration into tumor cells can be enhanced. Additionally, these modifications provide stimulus-responsive sites for the carriers, enabling targeted drug release triggered by stimuli like pH, light, and enzymes during the drug delivery process. Among these materials, alginate hydrogel stands out due to its exceptional characteristics such as high water content, non-toxicity, softness, cohesiveness, biocompatibility, and biodegradability, making it a suitable candidate for drug delivery applications. For instance, Bevacizumab (BVZ), a protein macromolecule known for its complex three-dimensional structure and sensitivity to the environment, has limitations in its use. Ferreira et al.[45] leveraged the unique properties of alginate to develop an anti-angiogenic delivery system by incorporating BVZ into an alginate-calcium hydrogel, the measured biological properties showed a 50% increase in anti-angiogenic activity compared to commercially available anti-VEGF drugs, which enhances the stability and efficacy of BVZ for local treatment. In another study, Matai et al.[46] designed an alginate-G5.0 polyamide (PAMAM) dendritic polymer hybrid nanogel, and thermal and swelling experiments and surface area estimation demonstrated that alginate-G5 nanogels have improved

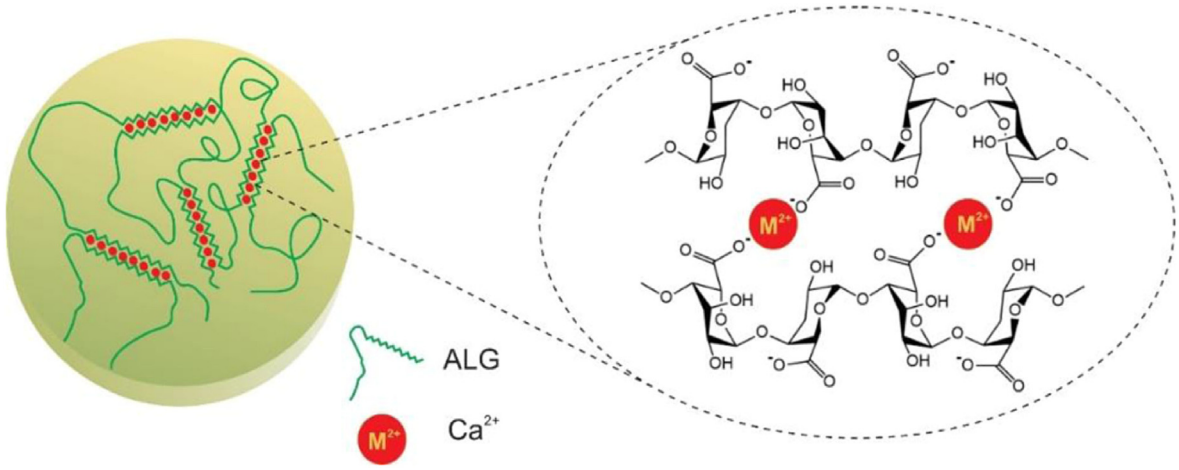

Fig. 2. Schematic diagram of ionic cross-linking of alginate with divalent cations.[16]

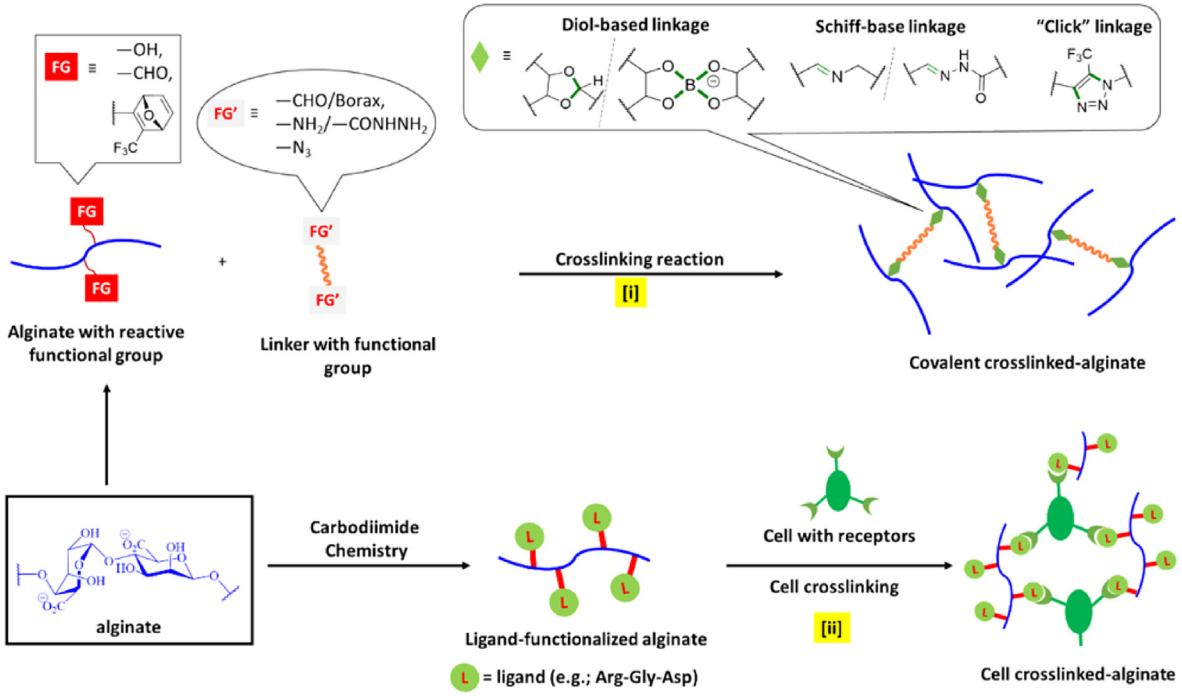

Fig. 3. Schematic diagram of alginate gel formation by covalent cross-linking.[35]

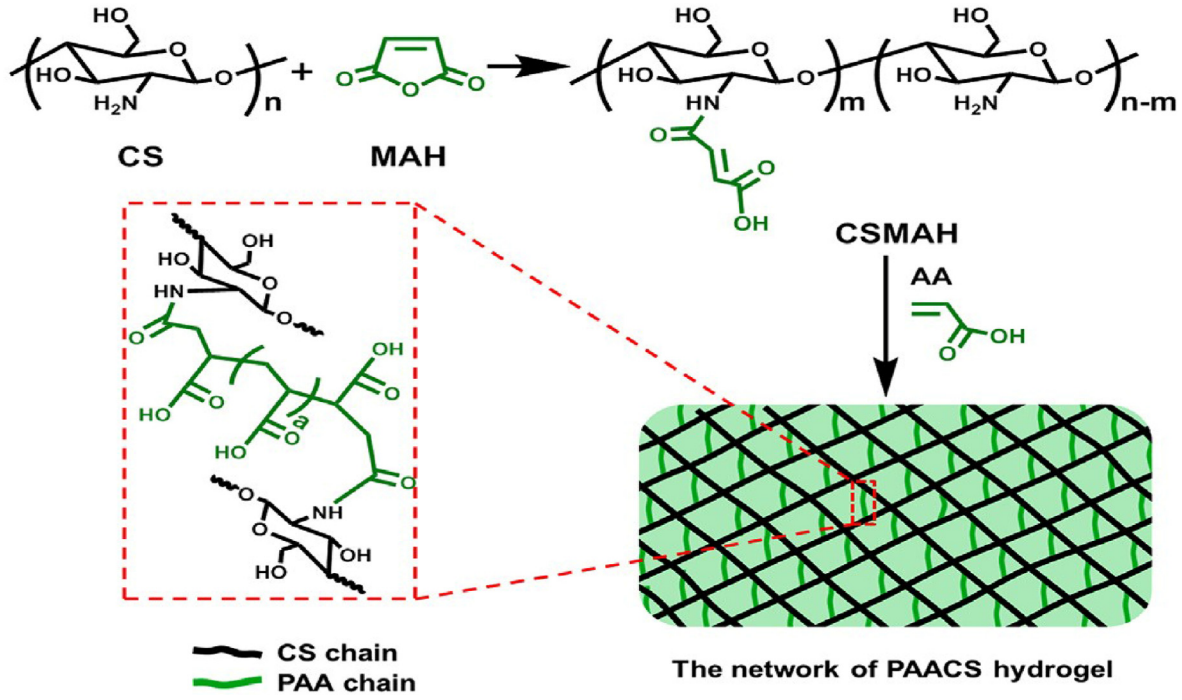

Fig. 4. Schematic representation of free radical polymerization crosslinking of poly(acrylic acid)/chitosan (PAACS) hydrogels.[38]

stability and porosity for effective and sustained delivery of chemotherapeutic drugs with potential to induce apoptosis. In addition, alginate can increase the solubility and compatibility of the drug. Curcumin is commonly used as an anticancer drug, and it has good efficacy in lung cancer,[47] liver cancer[48] and breast cancer.[49] However, its pharmacodynamic effect of curcumin is poor, mainly due to its low water solubility and fast metabolism, which limits its therapeutic effect. However, it has been found that the combination of Cur with alginate can significantly improve its solubility and cytocompatibility.[50] In summary, alginate can be combined with different composite materials to form composite hydrogels, and also exhibit different mechanical properties to enhance the application range of anticancer drugs. Examples of alginate hydrogels used as carriers to deliver other drugs are shown in Table 1 and Appendix 1.

3.2. *For tumor localization*

With the development of technology, the diagnosis and treatment of

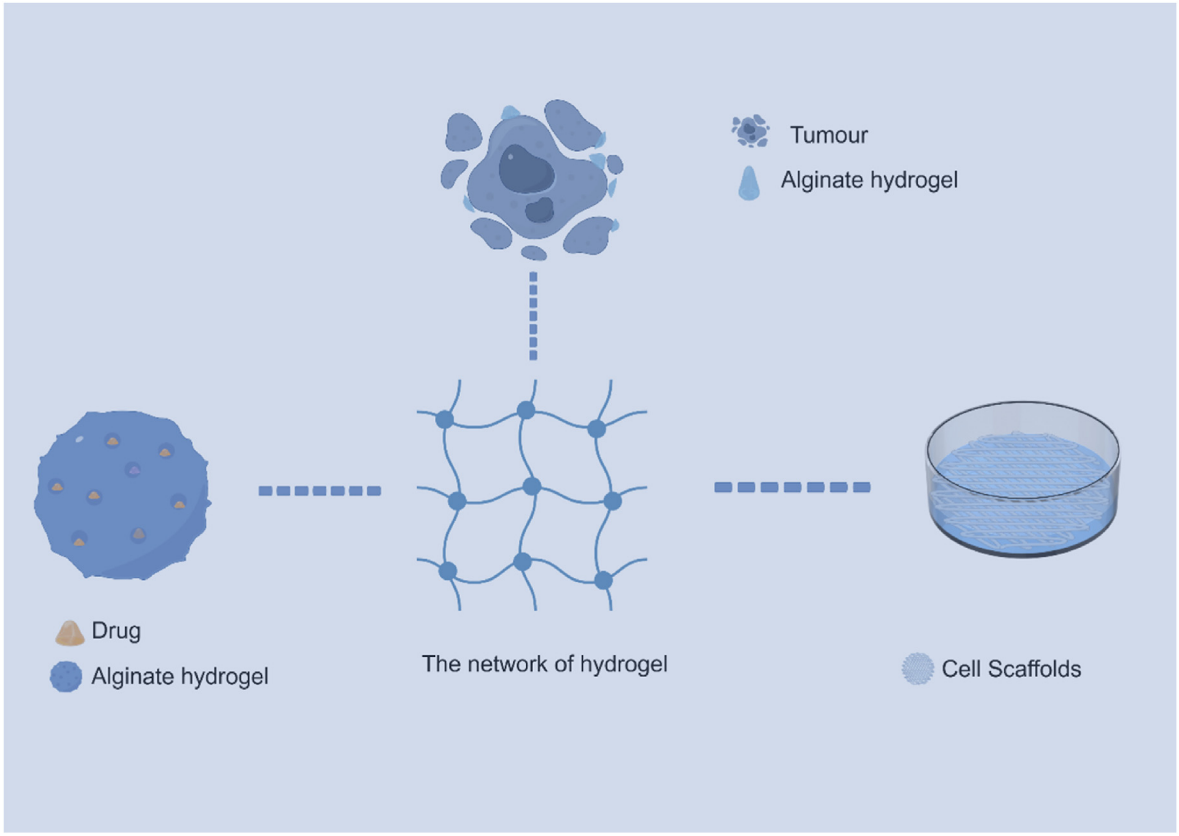

Fig. 5. Schematic representation of various applications of alginate hydrogel.

Table 1
Alginate hydrogel as a vehicle for delivery of other cancer drugs.

Description of the carrier	Advantages	Loaded drug	Results	References
pH-sensitive AGS hydrogel/micellar composites based on novel cross-linked monomolecular micelles of chitosan	It can be used as a slow-release or site-specific delivery system for unstable or hydrophobic drugs.	Rhodopsin (EMO)	Hydrogel/micelles (1:1) showed slow release characteristics, while hydrogel/micelles (3:1) showed colon specific characteristics.	51
Alginate hydrogels for polydopamine nanoparticle nanovaccines (TCLN)	EH/TCLN treatment effectively creates an immune microenvironment conducive to the induction of anti-tumour immunity and improves the anti-tumour immune response.	Endostar (EH)	EH/TCLN treatment resulted in a significant decrease in the expression of tumour angiogenesis and tumour microenvironment-associated cytokines (TMCs), an increase in the proportion of $CD8^+$ T cells in the spleen, lymph nodes and tumors, an elevation in the activity of cytotoxic T lymphocytes (CTLs) and apoptosis of tumour cells.	52
Nanoemulsion-filled sodium alginate (AGS) hydrogel beads	Increases the solubility of curcumin (Cur) in aqueous solution.	Cur	Cur release behaviour is consistent with the Hixcon-Crowell model, and this study provides a practical technique for combining emulsions and ionogels to increase the application of hydrophobic drugs in delivery systems.	53
Nanocomposite hydrogels composed of poly(N-isopropylacrylamide) (PNIPAM)-alginate interpenetrating polymer- GO-Fe_3O_4 nanomaterials	GO-Fe_3O_4 nanomaterials dissolve PNIPAM hydrogels and accelerate adriamycin release under NIR light and an alternating magnetic field; composite hydrogel (NCH) with rapid gelation, enhanced mechanical properties, and pH-responsive performance characteristics.	Adriamycin	*In vitro* cytotoxicity tests have confirmed that the NCH platform can achieve NIR light, magnetic and pH-responsive drug release to effectively kill cancer cells.	54
Superparamagnetic iron oxide nanoparticles (SPION)-disulfide modified alginate derivatives for magnetic and dual-response hybrid algae nanogels	The resulting gel has magnetic targeting properties, high drug loading capacity, co-triggered release behaviour, high toxicity to tumour cells, low side effects on normal cells, and magnetic resonance imaging (MRI) capabilities.	Doxorubicin (DOX)	The acidic and reducing microenvironment of the gel allowed DOX to be released into tumour cells and showed potent cytotoxicity, but with low side effects on normal cells.	55

tumors have undergone significant changes, among which minimally invasive surgery has become one of the preferred methods of treatment. Compared with traditional surgery (usually with a hole of 24–36 cm), minimally invasive surgery can be performed through small holes (usually 0.5–1.5 cm),[56] with the advantages of less bleeding, less pain, faster recovery, and shorter hospital stay.[57] However, unlike traditional surgery, minim invasive surgery cannot diagnose suspicious areas directly through contact, cannot judge the treatment site directly, and

can hardly detect small soft lesion resection sites. Therefore, the size of the incision may vary depending on the operator's skill. To reduce such errors and improve the accuracy of surgery, preoperative marking of the surgical site is essential. To improve the accuracy of tumor localization, various marking methods have been developed including fluorescent imaging,[58] barium imaging,[59] metal clip labeling,[60] and the use of methylene blue.[61] However, each of these methods has limitations. For example, barium imaging requires the use of radiation, which may cause secondary harm to the patient. Metal clips are expensive and may move before or during surgery due to their small size, resulting in inaccurate results or even toxicity.[62] Therefore, new surgical labeling and imaging methods are needed.

AGS is easy to prepare, biocompatible, biodegradable and non-toxic, and alginate composite hydrogels have better tissue adhesion and cell compatibility than ordinary hydrogels. Considering the convenience and safety of alginate hydrogels for drug delivery, injectable sodium alginate (AGS) hydrogels can be chosen to deliver tumor markers. For example, Lee et al.[63] applied the physical complex of ICG and human serum albumin (HSA) with AGS to form an injectable hydrogel system. In this gel system, the fluorescence detection time was effectively extended to 96 h after injection, while effectively preventing the diffusion of ICG from the injection site, indicating that this alginate hydrogel system can be used as an effective surgical marker. In addition, Ji et al.[64] developed a catechol-coupled alginate (C-ALG) hydrogel for precise localization of lung nodules in clinical practice. They added sufficient oxidant and catalase to make the C-ALG hydrogel rapidly gel (less than 5 min), and showed mechanical properties similar to lung tissue, slight swelling and good cell compatibility, and can adhere to the tissue for easy localization around lung tissue, thus it can be used for preoperative precise localization of lung nodules. Similarly, the use of AGS-Fe_3O_4 magnetic gel for X-ray guided localization of small lung nodules showed that the gel boundaries were well defined, there was no diffusion of magnetic fluid, all tissues maintained good histological morphology, and no magnetic fluid was observed, thus suggesting that this novel gel for tumour localization has a certain degree of safety and feasibility.[65] Alginate composite hydrogels can be adjusted to their composition ratio to have better performance, providing more precise localization, and have accuracy and safety in clinical applications.

Micro/nanotechnology combined with alginate composites is currently a hot topic of research. Micro/nanocarrier systems can protect therapeutic agents from degradation and enhance their delivery to immune cells. Alginate hydrogels have good biocompatibility and can reduce unnecessary cell toxicity. For example, Zhang et al.[66] loaded cancer embryonic antigen (CEA) probes, consisting of quantum dots (QD) and gold nanoparticles (AuNP), into AGS gel to detect CEA for monitoring and locating tumors. They took advantage of the fact that anti-PD-L1 antibodies21 (PDL1 inhibitors) bind specifically to PDL1, which is highly expressed in cancer cells, and carcinoembryonic antigen CEA 22 which is a typical tumour marker, and *in vivo* tumour assays have shown that the fluorescence intensity of this gel when injected subcutaneously increases with the concentration of CEA. It can be used to monitor and localise cancer; In addition, they modified AGS nanogels loaded with ICG with anti-PD-L1 antibody (ICG@AGS-anti-PD-L1 nanogels) to monitor and inhibit tumor metastasis.

3.3. As an in vitro tumor cell model with scaffold

Many cancers only exhibit symptoms in the advanced stages, such as lung,[67] liver,[68] stomach,[69] rectal[70] and prostate cancers.[71] Therefore, using new model systems to understand the development of these cancers or tumors is more conducive to designing new cancer treatment plans. Currently, traditional two-dimensional (2D) cell experiments still dominate *in vitro* cancer model research. However, 2D culture cannot simulate the complex 3D microenvironment of tumors *in vivo*,[72,73] such as cell-cell and cell-matrix interactions and tissue fluid that affect cell differentiation and function.[74] To improve 2D culture models, a sandwich culture has been developed to produce a 3D effect that better simulates the tumor microenvironment. *In vitro* 3D tumor models with human cancer cells have attracted scientists to accurately mimic the characteristics of human cancer tissue,[75] improving the situation where cells in 2D cell cultures cannot form contact with other cells.[76] In 3D model systems, simulating the structural and functional systems of the extracellular matrix (ECM) requires appropriate mechanical properties and chemical composition to promote cell growth and maintenance, promote nutrients, gases, and metabolic waste, as well as signal transduction conditions.[77,78]

The tumor microenvironment (TME) is a highly dynamic system, where cancer cells often aggregate and assemble into multicellular tumor spheroids. Considering the complexity of the TME, materials used must have the ability to control cell-cell interactions and allow cells to grow and communicate within the internal space. Alginate is a biologically inert polysaccharide, whose structure is stable for a long time, making it necessary for pharmacological testing *in vitro* models. Additionally, alginate salts can easily arrange into 3D gel-like structures and mechanical properties of the obtained gels can be precisely adjusted by divalent cation crosslinking.[79,80] The *in vivo* tumour model had a tumour formation rate of 88%, with 76% of the tumors having a near spherical shape. Moreover, drug tolerance within the 3D tumour model was higher compared to traditional 2D cultured cells, suggesting better predictability of anticancer drug efficacy for *in vitro* 3D cancer models based on HA-alginate matrices.[81] This reduces the inaccurate assessment of cancer biology caused by 2D models[82] and highlights the importance of alginate hydrogels as a class of important biomaterials that can mimic the extracellular matrix, with high biocompatibility and efficient transport of oxygen and nutrients. In addition, Dios-Figueroa[83] exploited the swelling properties of gelatin and alginate after cross-linking with good bioavailability to develop an *in vitro* model of live HER2 and cells embedded in 3D gelatin alginate hydrogels as an immunotherapy for cancer, and the encapsulated BT-474/GFP cells maintained HER2 expression and could be detected by fluorescent antibodies to trastuzumab, developing a novel method for the evaluation of HER2-targeted therapies. Alginate hydrogel has been used as a tumor model[84] or scaffold for other applications, as summarized in Table 2.

3.4. Other aspects

The application of alginate hydrogels in oncology is mainly focused on drug carriers and tumor cell models, with few studies reported in other areas. Cancer cell metastasis is the main cause of death in cancer patients, accounting for 90% of cancer deaths.[91] Currently, chemotherapy is mainly relied upon to treat cancer cell metastasis. However, with time, cancer cells may develop resistance to chemotherapy, leading to high recurrence rates and ultimately uncontrollable cancer cell metastasis, resulting in death. In order to halt the malignant progression of cancer cells, it is critical to address metastasis. This requires a more thorough understanding of how to attenuate aggressive tumour phenotypes, which can be achieved by establishing models that limit malignant transformation or by studying models that enhance transplantation. Bridget et al.[92] used alginate microbeads to encapsulate embryonic stem cells to investigate cancer cell metastasis, and the results showed that co-culturing with alginate microbeads significantly limited the metastatic potential of highly invasive cancer cells. The study confirmed that stem cell-derived microenvironments can limit the growth and survival of cancer cells,[93] promoting research on tumor metastasis. It has led to an initial exploration of the study of tumour metastasis.

Due to its good biocompatibility and biodegradability, alginate hydrogel is often used in tumor photothermal therapy (PTT). PTT is a non-invasive treatment method that converts near-infrared light energy into heat energy, with advantages such as high selectivity, strong tumor ablation ability, and minimal damage to normal tissue. Simplifying the synthesis and administration processes of photothermal agents, increasing their accumulation in tumors, and ensuring good biocompatibility and biodegradability are in promoting the clinical application

Table 2
Alginate hydrogel for *in vitro* tumour cell models with scaffold filling.

Description	Type	Specify	References
Cross-linked alginate-gelatine (ADA-GEL) matrixes	3D cell culture models	colon cancer (HCT116 cells)	[85]
Alginate and polycaprolactone (PCL) were coelectrospun as composite scaffolds	3D enriched cell scaffold	Cancer stem cells (CSCs)	[86]
50% Alginate and 50% Matrigel composite gels	3D cell culture models	Breast cancer cell	[82]
Engineered composite hydrogels consisting of gelatin and alginate components	Physiological mimicking 3D models	Breast cancer cells (MDAMB-231)	[87]
Calcium ion cross-linked HA and alginate mixed aqueous solution	3D cell culture models	Prostate cancer cell	[81]
Utilizing the synergy of alginate, gelatin, and microfluidically embedded voids	Hydrogel scaffold	Breast cancer cells (MDA MB 231)	[28]
Alginate - dopamine - coupled hybrid ink	3D cell scaffold	Breast cancer	[88]
An *in vitro* 3D cocultured tumor-vascular barrier model by the combination of alginate hydrogels beads and Transwell system	3D cell culture models	Prostate cancer cells (PC-3) and fibroblasts (NIH/3T3)	[89]
Porous 3D printed alginate scaffolds were seeded with fibroblasts, which proliferated and produced extracellular matrix. The pore is injected with oxidized peptide modified alginate saline gel containing MCF10A cells to form a parenchymal compartment	3D cell culture models	Breast cancer	[90]

of PTT. Haiyan et al.[94] proposed the in-situ formation of calcium/magnesium ion-responsive ICG-alginate hydrogel based on the principle stable fluid circulation ions, for local tumor PTT. The prepared hydrogel has a strong ICG fixation capacity, and the loading capacity of ICG in the hydrogel can be as high as 10 mg/mL, and the formation of a uniform hydrogel can achieve the encapsulation of ICG and effectively overcome the sudden release of ICG, which greatly facilitates the accumulation of high photothermal agents, minimizing potential side effects caused by ICG diffusion into surrounding tissues. In addition, some studies have improved the therapeutic efficiency of PTT by reduction and separation from the surrounding environment, such as dispersing iodine-starch complexes into calcium ions of alginate, thus successfully preparing iodine-starch-alginate hydrogels with good photothermal heating ability based on iodine-starch chromophores.[95] However, current photothermal formulations are difficult to meet the requirements of clinical drugs from synthesis to delivery, and perhaps combining with nanomaterials and computers is a way to improve the efficacy of PTT. Furthermore, Juyoung et al.[96] synthesized an injectable hydrogel based on alginate collagen, a thermo-responsive gel, with tumour temperatures as high as about 63° after injection (there was no significant change in the control group). Through the combination of PTT and immunotherapy, experiments have shown that the modified hydrogel is an effective material that not only treats primary tumors, but also protects CT-26 tumour-injected mice from lung metastasis and recurrence. This shows the advantages shown by alginate hydrogel drug delivery systems in cancer PTT, where they can deliver drugs to specific tumour sites, facilitate drug clearance from the circulatory and immune systems, improve the physicochemical properties of the drug and reduce the dose of the drug and control the release of the drug. By combining them with other therapeutic tools such as immunotherapy, which has been studied from models to mouse experiments, alginate composites are opening up new possibilities for research into the prevention of cancer metastasis.

4. Summary

In summary, alginate hydrogels are optimistic for research and development due to their unique “customization”. Alginate hydrogels have the advantages of good biocompatibility, good swelling, adhesion and sol-gel conversion, high water absorption, mechanical stability and viscoelasticity, and can be used in many biomedical applications, including drug delivery vehicles, tumour localization and tumour models in the field of oncology. In conclusion, alginate has proven to have great utility and potential as a biomaterial.

However, the current research on cancer therapeutic applications based on alginate hydrogels and their composite systems mainly focuses on small- and medium-sized animal experiments, and there is a lack of newer and sufficient results from large-scale animal experiments; moreover, further clinical trials deserve more in-depth studies, such as the release rate of the formulations *in vivo*, their *in vivo* distribution, their biodegradation properties, and the effects of the degradation products on the human body. Secondly, the research on quality process control has not yet been in-depth, and it is also difficult to produce and test the products by traditional and simple methods, and it is recommended to develop relevant indicators to judge the products. Therefore, in the future, it is necessary to search for more potential composite systems, to gain an in-depth understanding of the interaction mechanism between alginate hydrogels and each composite material, to optimize the preparation parameters and to obtain a gel system with good performance. Exploring the specific application of alginate composite hydrogels in oncology, in order to have high-quality products from laboratory service to clinical application in the future, it is believed that alginate composite systems will have broader application prospects in the future.

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Data availability statements

All data included in this study are available upon request by contact with the corresponding author.

CRediT authorship contribution statement

Lili Huang: Writing – original draft. **Yicong Lei:** Formal analysis. **Yucheng Chen:** Investigation. **Xin Hu:** Writing – review & editing. **Chengyu Huang:** Writing – review & editing. **Huaqing Lin:** Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix 1

Description of the carrier	Advantages	Loaded drugs	Results	References
Hydrogen Bonding with Polyethylene Glycol (PEG) Crosslinking to Form 3D Network Structures of Novel Glutathione (GSH) and pH Bi-Responsive Hydrogels	Release is triggered by click-response intelligent stimulation and has a high drug loading capacity.	Doxorubicin (DOX)	The DOX-loaded Glu-Cys-SA hydrogels showed significantly more than 76% release in response to GSH and exhibited antitumor activity against HepG-2 cells comparable to that of the positive control.	97
ACA nanocomplexes loaded with cisplatin and gold nanoparticle (AuNP) alginate hydrogel networks	Effective targeted delivery of anticancer drugs and radiosensitizers to tumors, reducing the clinical dose of anticancer drugs and X-rays administered.	Cisplatin and gold nanoparticles	ACA nanocomplexes improved the efficiency of standard chemotherapy treatment and produced significant growth inhibition of colon adenocarcinoma tumors.	98,99
Self-repairing chitosan/alginate hydrogels encapsulated with magnetic gelatin microspheres (MGM)	Expanding injectable hydrogel stent capabilities	5-Fluorouracil (5-Fu)	The hydrogel has higher compression modulus and stability, and compression and rheological tests indicate good self-healing properties.	100
Polydopamine (PDA)-concentrated alginate temperature-sensitive hydrogels	Drugs can be released from the prepared core-shell fibers in a controlled manner in the near infrared.	Doxorubicin hydrochloride (DOX-HCl)	The photothermal effect and the released therapeutic drugs effectively kill breast cancer cells and inhibit tumor growth.	101
Alginate -G5.0 polyamide (PAMAM) dendritic polymer hybrid nanogels	This nanogel system enhanced intracellular EPI accumulation in breast cancer (MCF-7) cells.	Epirubicin (EPI)	Achieve effective and sustained delivery of chemotherapeutic agents with potential to induce apoptosis.	102
Pept-alginate nanocomposite hydrogel (AlgNP/IRN)	Nanocomposite hydrogels can address the differential release of CDDP and irinotecan (IRN) to maximize the synergistic effect of both drugs.	CDDP and IRN	Better synergistic efficacy of the drugs in inhibiting the growth of cancer cell A549 and better anticancer effects than single drug formulations or two-drug solution mixtures in a mouse model of cancer cell A549 xenografts.	103
pH-sensitive alginate-polydopamine polymer carriers	pH-dependent release of drug molecules	Bortezomib (BTZ)	The composite vector targets BTZ to cancer cells in a pH-dependent manner. In vitro cell culture assays showed that Alg and AlgPD are highly biocompatible and AlgPD-BTZ enhanced cytotoxicity against colon and squamous cancer cells.	104
Ca^{2+} - Sodium alginate (AGS) multifunctional in situ hydrogel	Enhances therapeutic efficacy by increasing the accumulation of Ink and AIPH and avoids potential side effects caused by spreading to surrounding normal tissues.	2,2′-Azobis2-(2-imidazolin-2-yl)propane azo initiator dihydrochloride (AIPH)	Significant inhibition of tumor growth was observed in subcutaneous colorectal cancer with few side effects.	105
Polydopamine-modified injectable hydrogel with oxidized AGS chitosan	By immobilizing DDP through the abundant functional groups on polydopamine (PDA), hydrogels exhibit sustained release properties of DDP.	Cisplatin (DDP)	The hydrogel effectively ablates tumor cells (4T1 cells) and inhibits tumor growth *in vitro*, promotes the adhesion and proliferation of bone marrow mesenchymal stem cells *in vitro*, and further induces bone regeneration *in vivo*.	106
Iron-based magnetic nano-alginate-based biopolymer hydrogel beads (nano-Fe-CNB) pH-responsive drug carriers	Good drug-carrying capacity and pH-responsive controlled release behavior.	Doxorubicin (DOX)	In release study experiments, low release (8.3%) at physiological pH (7.4) and relatively high release (38.7%) at cancer cell pH (5.4) indicate that controlled release and therapeutic drug concentrations can be achieved at tumor cells.	107
Hydrogels of alginate and sodium carboxymethyl cellulose (CMC) cross-linked with Ca^{2+}	Dual pH response can be achieved by a dual drug delivery system (DDDS).	Methotrexate (MTX)	The hydrogel protects MTX from gastric and small intestinal absorption, is well degradable, and displays concentration-dependent cytotoxicity against SW480 colon cancer cells while maintaining good biocompatibility with normal cells.	108
Oxidized alginate-gelatin hydrogel/ unilamellar vesicles	Loading relatively higher concentrations of the drug, and it increases the likelihood that the drug will be taken up by cancer cells rather than non-malignant cells	Curcumin	The combined system represents a highly reliable and robust method for embedding and delivering complex insoluble chemotherapeutical molecules, and it is less invasive than other alternative methods in the literature.	109
An interpenetrating network comprising alginate blended with aloe was examined as a cervical cancer treatment	The antioxidant properties of aloe vera gel reduce cancer cell viability, while alginate hydrogel improves mucosal adhesion	DOX	Alginate improved mucin interactions and isolated hydrogel retention. *Aloe vera* shows high antioxidant properties and is highly potent against cervical cancer cells	110
Sodium-alginate capped silver nanocomposite microgel beads via bio-reduction	Synthesis of AGS gel beads with multifunctional antibacterial and apoptosis characteristics by bioreduction	Perilla frutescens	Cancer cells showed significant cytotoxicity with minimal side effects. The cytotoxic effects induced by nanocomposites in related to ROS expression, caspase-3 expression, apoptosis, etc.	111
3D-printed gelatin–alginate scaffold	The stent exhibits biodegradability and sustained drug release properties.	Niosomes	The expression of BCL2, CCND1, MMP2 and CDK4 genes was significantly reduced, and the expression of BAX and P53 genes, as well as the activity of Caspase 3/7, were significantly increased.	112

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