Polysaccharide-Based Hydrogels Drug Delivery in Cancer Therapy

Subjects: Polymer Science | Materials Science, Biomaterials

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Hydrogels are three-dimensional crosslinked structures with physicochemical properties similar to the extracellular matrix (ECM). By changing the hydrogel's material type, crosslinking, molecular weight, chemical surface, and functionalization, it is possible to mimic the mechanical properties of native tissues. Hydrogels are currently used in the biomedical and pharmaceutical fields for drug delivery systems, wound dressings, tissue engineering, and contact lenses. Polysaccharide-based hydrogels can be used as drug delivery systems for the efficient release of various types of cancer therapeutics, enhancing the therapeutic efficacy and minimizing potential side effects.

Keywords: polysaccharide ; hydrogels ; cancer treatment ; drug delivery ; chitosan ; alginic acid ; cellulose ; hyaluronic acid ; carrageenan

1. Drug Delivery in Cancer Therapy

Cancer is the leading cause of death and an important barrier to increased life expectancy in every country in the world [1]. Current strategies, such as chemotherapy, surgery, and radiotherapy, are widely adopted for cancer treatment. In particular, chemotherapy represents the standard cancer therapy and is known to be effective in the treatment of several types of tumors, while it does not have curative effects on other types of cancer. Drawbacks related to chemotherapy lie in the numerous side effects, which can be mild, moderate, or severe according to the intensity of the treatment [2]. The main problem at present is represented by the lack of specificity of many antitumor drugs, which are not able to cause the selective death of tumor cells. The use of delivery systems to control the release of chemotherapeutics allows us to avoid some disadvantages of conventional therapies. Polysaccharide-based hydrogels' application has drawn increasing attention in cancer treatment research because of their easy and low-cost production, biocompatibility, degradability, and non-toxicity [3]. The presence of multi-functional groups in their backbone, such as hydroxyls, amines, and carboxyls, permits easy chemical modifications to obtain polysaccharide derivatives with unique properties for specific applications. Moreover, several polysaccharides have the unique, innate ability to recognize specific receptors overexpressed on the surfaces of diseased cells, enabling the design of targeted DDS that can selectively deliver therapeutic agents through receptor-mediated endocytosis [4]. Below, the researchers present recent advances in drug delivery system applications for different types of tumors (**Table 1**).

Table 1. Polysaccharide-based hydrogels and their latest applications as drug delivery systems in different types of cancer.

Cancer Type	Hydrogel Origin	Loaded Drug	In Vitro/In Vivo Outcomes	
Breast cancer	**Hyaluronic acid**	**Doxorubicin**	**HA scaffold had great antitumor activity when combined with near-infrared light, showing synergistic antitumor and photothermal effect.**	**[5]**
Breast cancer	**CMC**	**Doxorubicin**	**The system showed tumor inhibition effect with a strong apoptotic signal and no significant changes in bodyweight.**	**[6]**
Glioblastoma	**Cellulose/chitosan**	**TRAIL**	**Hydrogel scaffolds maintained cell viability and released TRAIL at concentrations that exhibited in vitro efficient tumor cell killing.**	**[7]**
Colorectal cancer	**CMC/alginate**	**Methotrexate/aspirin**	**The system showed concentration-dependent cytotoxicity with a colon cancer cell viability decrease of up to 10%.**	**[8]**

Cancer Type	Hydrogel Origin	Loaded Drug	In Vitro/In Vivo Outcomes	
Colorectal cancer	Chitosan/chondroitin sulfate	Curcumin	Hydrogel scaffold did not present significant level of cytotoxicity and allowed efficient drug release and absorption preferentially by cancer cells.	[9]
Lung cancer	Acylhydrazide-functionalized CMC	Limonin	Limonin-loaded hydrogels exhibited enhanced tumor suppression efficiency through a sustained release process with no difference in tissue morphology.	[10]
Melanoma	Chitosan	Ytterbium (Yb^{3+})	Chitosan hydrogel induced in vitro melanoma cells' anoikis and inhibited tumor growth in animal experiment.	[11]
Melanoma	HPMC/Cyclodextrins	3-O-Methylquercetin (3OMQ)	The formulation achieved complete 3OMQ release using a Franz cell model, reaching the whole skin layer.	[12]
Prostate cancer	Alginate/ cyclodextrins	Paclitaxel	The combined ALG–CD complex prevented Paclitaxel crystallization and allowed its diffusion out of the network, decreasing the metabolic activity of prostate cancer cells in a dose-dependent manner.	[13]
Hepatocellular carcinoma	N-carboxyethyl chitosan	Doxorubicin	The pH-responsive system showed good degradability properties in tumor acidic microenvironment with enhanced drug efficiency to kill tumor cells and less side effects for normal tissue.	[14]
Renal cell carcinoma	K-carrageenan/ chitosan	Sunitinib	In vitro release studies showed pH-dependent release of the drug, with an increase at acidic pH similar to damaged cancerous tissues.	[15]

2. Breast Cancer

The clinical and molecular heterogeneity of breast cancer is well known. Worldwide, it is emerging as the leading cancer type, threatening human health, and has a mortality-to-incidence ratio of 15%. There is an urgent need to identify and improve systemic treatments that specifically target tumor cells [16]. In this regard, Ma et al. used microfluidic electrospraying for the synthesis of CMC-based hydrogel microparticles for the efficient and specific local delivery of DOX. CMC's highly active hydroxyl and carboxyl groups allowed its effective crosslinking by multivalent metal cations, $FeCl_3$, to generate hydrogels [17]. Drug-loaded microparticles were then formed by soaking CMC hydrogels in a DOX solution and subsequent freeze-drying. Hydrogels' biocompatibility was evaluated on murine breast cancer 4T1 and human breast cancer MDA-MB-231 cells, showing no cytotoxic effect and confirming the cytocompatible and non-toxic nature of CMC. Free DOX and CMC–DOX microparticles' activity was then compared in a 4T1 tumor-bearing mouse model. The first treatment caused some systemic toxicity, which was negligible in the second group, due to sustained DOX release. Interestingly, the CMC-based delivery system showed biocompatibility properties and lower systemic toxicity, thus representing a potential therapeutic approach for cancer treatment [6].

3. Melanoma

Skin cancer is a global public health challenge and its mortality rate continues to increase in several regions of the world. Melanoma only represents 2.3% of all skin cancers, but it is the most aggressive form, responsible for over 75% of skin cancer-related deaths [18]. Recently, an yttrium (Yb)-loaded CHI hydrogel was developed to selectively induce cell death in B-16 mouse melanoma cells (Yb). As a matter of fact, lanthanides have been widely used for cancer treatment in several types of tumors [19]. CHI and Yb^{3+} were mixed to form a composite hydrogel. The in vitro and in vivo release studies showed the inhibition of melanoma growth, induced by Yb^{3+} ions, without causing any harmful effects on skin union and peripheral normal tissue damage [11].

4. Colorectal Cancer

Colorectal cancer comprises colon and/or rectum cancer and is the second most deadly type of cancer. Its global incidence is becoming constantly higher, and it is estimated to reach more than double by 2035, especially in less developed nations, where early diagnosis and treatment are rarely available [20]. The design of novel therapeutic approaches for targeting the colorectal region is a high priority. A noteworthy example has been reported by Sheng et al.

In this study, an ALG/CMC hydrogel crosslinked with $CaCl_2$ was developed as a dual drug delivery system for Methotrexate and aspirin, providing both chemotherapy and pain relief to cancer patients [8]. $CaCO_3$, a naturally non-toxic inorganic biomineral successfully used as a carrier for the delivery of drugs, genes, and proteins [21], was added during hydrogel preparation to improve the mechanical performance of the matrix. The addition of CMC considerably increased aspirin's entrapment efficiency compared to ALG alone, and the combination of the two polysaccharides avoided MTX's absorption in the stomach and small intestine simulated fluid, showing the ability of the DDS to release both drugs at appropriate organs with a specific pH [8].

5. Renal Cell Carcinoma

Renal cell carcinoma (RCC) consists of a group of cancers originating from renal tubular epithelial cells, such as clear cell RCC, papillary RCC, and chromophobe RCC, and accounts for >85% of cancers of the kidney [22]. Risk factors for RCC include obesity, hypertension, and cigarette smoking, as well as medical conditions and genetic factors [23]. Sunitinib, a multi-targeted tyrosine kinase inhibitor (TKI), has been investigated in metastatic renal cell carcinoma. Several Sunitinib-loaded hydrogels have been synthesized, from both synthetic [24] and natural polymers. Recently, Jafari et al. developed a promising Sunitinib-carrying hydrogel using a mixture of *κ*-CRG and CHI, in the presence of magnetic montmorillonite. Clay was added to the CHI solution to improve the mechanical strength, and *κ*-CRG was used for its anionic sulfate groups, able to crosslink to amines on CHI. This system enabled the release of the drug, with an increase at an acidic pH, typical of damaged cancerous tissues [15].

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