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Stimuli-Responsive Alginate Nanogels in Cancer Treatment

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3D nanoscale networks that are created with polymers physically or chemically are called Nanogels (NGs). Their biocompatibility, high stability, drug loading capacity, and ability to bind ligands for active targeting make them ideal for drug delivery systems. Moreover, they can respond to both internal and external stimuli, such as temperature, light, pH, and more. This makes it easier to consistently deliver the drug to the target area. Alginate (ALG) biopolymers are used for the encapsulation of anticancer drugs because of their biocompatibility, hydrophilicity, and affordability. These ALGs nanogel-based systems are effective in treating cancer, with several studies supporting their development. The ALG and its underlying systems are reviewed in this article.

INTRODUCTION

Unluckily, the primary cause of mortality in developed countries is cancer. In the absence of regulation, due to a genetic predisposition and uncontrolled cell proliferation, cancer spreads through the blood or lymphatic system to other tissues [1, 2]. Nanogels (NGs) are tiny hydrogels or particles that can absorb large amounts of water. They range in size from 20 to 200 nanometers and are composed of polymer networks crosslinked in three dimensions [3]. The biomedical industry has started to take notice of these materials because of their attractive properties. NGs have a wide range of designs, are easy to formulate, have high drug-loading capacity, and are stable in terms of the drug being entrapped. They also have good physical stability, can swell in aqueous mediums, and possess other desirable characteristics. Furthermore, NGs can control the release of various bioactive compounds and have a responsive nature to stimuli. Drug delivery systems benefit from the small size and high permeability of these substances [4, 5]. Among the production methods of NGs, it is possible to mention crosslinking of hydrophilic monomers and copolymers with functional groups through cross-linkers and in-situ polymerization [6, 7]. Drugs, usually bioactive molecules, can enter NGs with functional groups in the polymer network through physical or chemical interaction [8]. The gel structure employs ligands to ensure drug delivery and accuracy to prevent medication build-up in unexpected locations [9]. There are two categories of NGs, which are determined by

the method of production and the types of links formed in the polymeric network by physically and chemically crosslinked NGs. In physically crosslinked NGs, the polymer chains forming the three-dimensional network interact through non-covalent bonds [8, 9]. Covalently crosslinked polymer networks lead to chemically crosslinked NGs. A chemical or enzymatic agent is used to cross link the polymer chains. Chemical NGs are more durable and long-lasting than physical ones because of their covalent nature. Occasionally, they exhibit crosslinking through enzymatic or photo-induced mechanisms and via disulfide or amine-based linkages [8]. NGs have the ability to be used for various biological purposes, such as bioimaging, tissue engineering, wound healing, and medication administration. NGs are particularly useful in drug delivery systems due to their unique physicochemical and biological properties, which enable site-specific drug distribution [10]. The administration of NGs can come in different ways, such as parenteral, intraocular, nasal, pulmonary or oral [9]. Alginate (ALG) is a biopolymer sourced from the sea and has unique biological properties. It can be used to create groundbreaking materials offering numerous benefits [11]. ALG, a widely available natural material, has the potential to be an ideal alternative to petroleum-based polymers in combination with other polysaccharides –such as cellulose and chitosan making it a promising material for the circular economy [12].

ALG has become more prevalent in various industries lately due to its unique features. These characteristics include being biocompatible, readily available, biodegradable, soluble in water, low in immunogenicity, adaptable, relatively inexpensive, capable of thickening, and capable of forming gels [13]. ALG is a fascinating material that can be utilized for environmental applications. It possesses surface carboxyl and hydroxyl functional groups on the ALG backbone, making it highly attractive. Additionally, ALG has a high-water adsorption capacity. ALG's versatility in combination with other organic and inorganic fillers, natural and synthetic polymers, and bioactive substances such as proteins has been a key factor in its success [14]. The unique properties of ALG make it a biomaterial with great potential. It can be formed into a variety of goods, including hydrogels, films, fibers, and beads. These unique properties make ALG a versatile material that can be used for many applications. The use of ALG as a scaffold material has been extensively studied in tissue engineering over the past decade [15, 16].

Sol-to-Gel With Specific Crosslinking Divalent Cations

Chemical structure and properties of alginate

ALG is a type of polyelectrolyte that comprises both 1,4-linked -D-mannuronic acid (M) and -L-glucuronic acid (G) units, which are irregularly spaced and carry a negative charge [17]. The blocks are composed of alternate M and G segments (GM), consecutive G segments (GG), and consecutive M segments (MM) (Figure 1) [18]. The M segments display a straight and adaptable form, while the G segments take on a rigid and creased structure, providing support for the molecular chains' inflexibility [17]. ALGs from various sources and block structures can be different [19]. ALG is a naturally occurring mixture of cations, mainly sodium, magnesium, and calcium ions, that may be found in saltwater [20].

Mineral acid is commonly utilized to dissolve

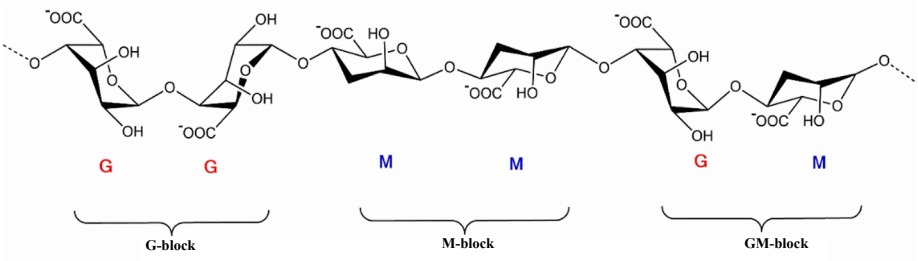

Figure 1: Chemical Structures of Consecutive M, G Segments, and Alternating M and G [21](License: This is an open access article published under a BMC AuthorChoice License, which permits copying and redistribution of the article or any adaptations for non-commercial purposes)

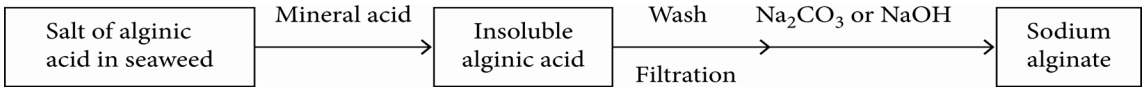

Figure 2: Procedure for Alginate Extraction From Seaweed [24](License: This is an open access article published under a Hindawi AuthorChoice License, which permits copying and redistribution of the article or any adaptations for non-commercial purposes)

counterions and create insoluble alginic acid. Afterward, alginic acid is neutralized using sodium hydroxide or sodium carbonate to create sodium ALG, which is obtained by extracting algae [22] (Figure 2). ALG can be produced by bacteria from the Pseudomonas and Azotobacter species. However, because they are not commercially viable, their use is primarily limited to small-scale research projects [23].

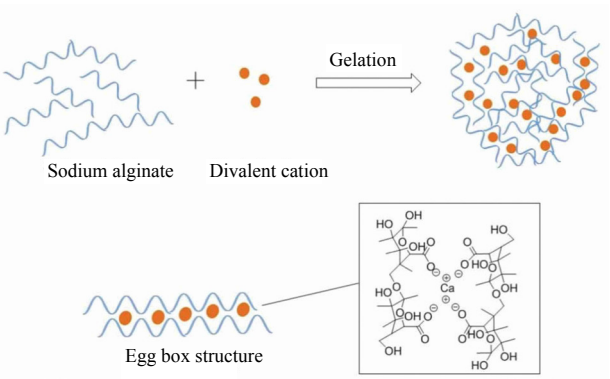

Figure 3: Formation of Alginate Gel by Divalent Cations and Egg Box Structure [24](License: This is an open access article published under a Hindawi AuthorChoice License, which permits copying and redistribution of the article or any adaptations for non-commercial purposes)

One of the main ALG features is its ability to undergo the sol/gel transition in the presence of divalent cations [23]. External and internal gelation are the two typical processes involved in gelation. Cooling, inverse, interfacial, and multistep interrupted gelation are further potential gelation techniques [25]. The egg-box shape in Figure 3 resulting from the stacking of G blocks with divalent cations leads to the formation of gel networks between different ALG chains [26]. The use of external crosslinked films, where cations and ALG polymer crosslink from the outside of the droplet, provides some advantages over internally crosslinked films. These advantages include thinner films with smoother surfaces, better matrix strength, stiffness, and permeability. Internal gelation, unlike outward gelation, begins in the droplet's center [27]. It is sometimes referred to as in situ gelation since it develops from the ALG droplets inside. For coating and drug encapsulation, external gelation appears to be the preferred way of creating crosslinked ALG [27].

Gel formation

ALG gelation is carried out with non-toxic reactants under friendly circumstances. To produce gels, two methods can be used. Initially, the use of lactones such as Glucono delta-lactone is employed to decrease the pH level of ALG monomers to levels below their pKa. Alternatively, by substituting the sodium ions from the guluronic acids with divalent cations like Ca+2, the ions interconnect the polymer chains with the help of the "egg-box" concept [28-31]. The research indicates that various crucial features such as porosity, swelling conduct, stability, degradability, gel potency, immunological traits, and compatibility with the human body are considerably affected by multiple factors that involve the composition, molecular weight, gel-forming speed, and the cation [32]. Controlling the gelation rate is a crucial aspect of the process. The mechanical stability of the gel formations is maintained by a slow process of gelation [33]. Carboxylate and phosphate groups compete with calcium ions, which is what causes the rapid and unpredictable gelation of ALG. It causes the ALG's gelation process to take longer [34]. ALG gelation is a quick and uncontrollable process caused by calcium chloride, which is the primary source of calcium cations. However, the solubility of calcium sulfate and calcium carbonate is restricted, which prolongs the formation of the gel [35]. Reduced temperatures result in reduced Ca2+ reactivity due to lower gelation rates [36]. The M to G block ratio of brown algae is not the same as that of other plant parts and species. The physicochemical properties of ALG are greatly affected by this ratio. In contrast to G-blocks,

which are twisted or deformed, M-blocks are long and flat.

The intermolecular crosslinking between G-blocks and divalent cations like Ca2+ creates hydrogels, resulting in a diamond-shaped hole with appropriate dimensions. This process only occurs with ALG G-blocks when two regains are lined side by side [37]. Figure 4 illustrates how crosslinking is accomplished by substituting sodium ions in G-blocks with divalent cations, such as Ca2+, and curving the guluronic groups to create an egg carton shape [38]. ALG gels containing numerous poly G-block units are recognized for their brittle, rigid, and robust mechanical stability. Moreover, they possess exceptional porosity, minimal shrinkage during gelation, and do not show swelling upon drying. In contrast, the addition of M blocks to ALG gradually results in the formation of softer, more flexible gels with reduced porosity and shrinkage. - [31]. The MG blocks were used to measure the ALG gel's flexibility and shrinkage [39]. ALG with a predominate M-block content swaps ions more readily due to increased water absorption, similar to ALG with more G-block residues [30, 31, 40]. Notably, the source of the polymer affected the chemical structures of ALG. Azotobacter-derived bacterial ALG has a high G-block concentration and gels with a comparatively high rigidity [41].

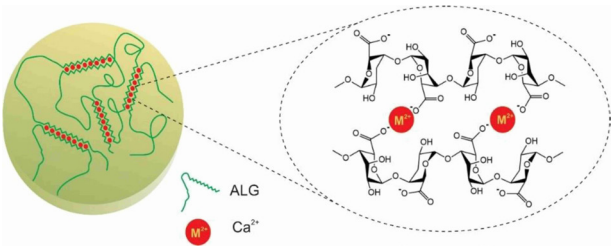

Figure 4: Egg-Box Structure for Alginate Gelation as A Result of Ionic Interaction Between Alginate and A Divalent Cation [21](License: This is an open access article published under a BMC AuthorChoice License, which permits copying and redistribution of the article or any adaptations for non-commercial purposes).

Biological Properties

ALG has been extensively studied for its biocompatibility and immunogenicity in the laboratory and living organisms. However, the effect of ALG composition is still a topic of discussion. It is worth noting that natural sources of ALG may contain various impurities, such as proteins, heavy metals, endotoxins, and polyphenolic chemicals. This confusion is most likely caused by various degrees of purity in the ALG examined in various papers. ALG is refined using multiple-step extraction techniques; however, it seldom causes serious responses to foreign bodies [42]. Various studies have found that when ALG is administered intravenously, it is eliminated from the body through the kidneys only if it has molecular weights below the renal clearance threshold. On the other hand, longer macromolecules are not accumulated in the tissue but remain in the bloodstream [43]. Mammals lack the ALG enzyme, which prevents ALG from being broken down. However, partly oxidizing the polymer backbone is one possible strategy to get around this restriction [44, 45]. ALG has also been claimed to have strong antioxidant, anti-inflammatory, and possibly prebiotic properties [46-48]. Some studies have also examined the antibacterial and anti-bacteriostatic properties of materials made from ALG. These studies explain how the polymer backbone's negative charges or chelation properties contribute to this process [18, 49, 50]. ALG possesses admirable mucoadhesive properties primarily due to its carboxyl and hydroxyl groups, which actively participate in mucosal delivery systems. This feature assists in enhancing the potency and bioavailability of drugs [51, 52].

Cancer Treatment

AG-G5 hybrid NGs were created by Ishita Matai and her team using carbodiimide chemistry, which involved the reaction of ALG with G5.0 poly (amidoamine) (PAMAM) dendrimer. These NGs have potential as anticancer drug carriers and show improved therapeutic effects when combined with Epirubicin. They can greatly reduce the size of their NGs by including a G5 PAMAM dendrimer in the AG network, which improves stability and strength as well as capacity in response to changes in pH. In a laboratory, the EPI drug was successfully released through testing with AG-G5 NGs. Through cell-based experiments, it was demonstrated that EPI-AG-G5 NGs are effective

and self-protective. The absorption of the ELI-NA gel in MCF-7 cells was dependent on both doses and duration, which could result in cell death. In the future, researchers hope to use markers on the surface of AG-G5 NGs to target cancer cells [53]. Figure 5 shows the synthesis steps for EPI⊂AG-G5 NGs.

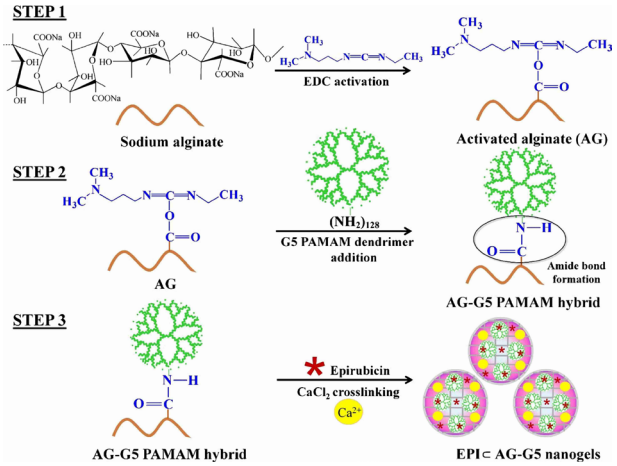

Figure 5: Step-Wise Representation of Synthesis Scheme for EPI⊂AG-G5 Nanogels [53]. (License: Reprinted (adapted) with permission from Matai I, Gopinath P. Chemically Cross-Linked Hybrid Nanogels of Alginate and PAMAM Dendrimers as Efficient Anticancer Drug Delivery Vehicles. ACS Biomater Sci Eng. 2016 Feb 8;2(2):213-223. DOI: 10.1021/acsbiomaterials.5b00392. PMID: 33418634. Copyright 2016 American Chemical Society.)

By conducting reversible chemical reactions with sodium ALG, poly (allylamine hydrochloride), and formyl phenylboronic acid in an inverse mini-emulsion, Xu et al., produced pH-and-oxidation responsive nanoparticles. The nanostructures remained stable at pH 7.4, even without GSH, but released DOX rapidly at either pH 5.0 or 10 mM GPH. Recent lab tests have shown that CDNGs have enhanced the targeting of 4T1 tumor cells. When stimulated by the tumor microenvironment, CDNGs produced enough DOX, which prevented tumor formation. These findings suggest that CDNGs could serve as an excellent drug carrier for targeted release during tumor treatment [54]. Jia et al., utilized PEGylated composite NGs, comprising -sodium ALG and carbon dot, to deliver doxorubicin for breast cancer treatment. Their study revealed that incorporating carbon dots into PEGylated -nanogel facilitated better doxorubicin release and increased body penetration [55]. ALG aldehyde-gelatin (Alg Ald-Gel) NGs were created by Sarika and coworkers. The nanogel is created using the inverse mini-emulsion process. Acetone-containing dissolved CUR was added to a nano gel emulsion to achieve encapsulation. The precipitation process results in CUR being enclosed within the crosslinked polymer network. Spherical NGs measured between 320 and 390 nm. The in vitro release study revealed that CUR was released through a controlled 48-hour period, with approximately 72% of the NGs' surface area encapsulated. In comparison to neutral pH, the release of CUR is more pronounced in acidic pH. The presence of NGs loaded with CUR leads to anticancer activity in MC-7 cells [56].

As a carrier for curcumin, Alg Ald-Gel NG made using the inverse mini-emulsion process can be used. The bioavailability and water solubility of curcumin were improved by NGs. The shape is spherical and they possess negative zeta potential. At a low pH level, NGs release higher amounts of curcumin and can effectively kill MCF-7 cells. The in vitro absorption of curcumin-containing NGs was demonstrated using confocal laser scanning microscopy. This study indicates that a curcumin-loaded Alg Ald-Gel NG drug delivery system may be highly effective against breast cancer [56]. To detect and treat cancer, Pei et al., developed an ALG-based pH and reduction dual-responsive NG [57]. The oxidized ALG was altered by the addition of rhodamine B- and folate-terminated poly (ethylene glycol). Then, to create NG, they employed Cystamine to crosslink it. They connected DOX to NG using a special bond called Schiff base, which can be affected by acid. When applied to the tumor site, the DOX-NG combination was found to be more effective in accelerating the release of DOX. In tests on HepG2 cells, this combination killed them more efficiently than DOX alone. Peng et al., created a type of nanogel that exhibits both magnetic and pH/reduction responses and can be used for the targeted treatment of tumors [58]. A hybrid material, the NG, was created by combining a core of superparamagnetic iron oxide nanoparticles with an ALG derivative shell. The NGs' susceptibility was minimized using disulfide bonds. The superparamagnetic iron oxide nanoparticles were able to trap DOX, an anticancer

drug that contains an amine, thanks to their ability to interact with uncrossed carboxyl groups through electrostatic interactions.

The degradation of electrostatic connections in acidic environments results in the rapid release of drugs. Different doses of DOX have been found to reduce viability in vitro in HepG2 cells, as demonstrated by in vivo toxicity tests. Moreover, HepG2 cells have displayed increased cytotoxicity when exposed to DOX-loaded NGs in the presence of an external magnetic field. Research on intracellular distribution has revealed that a significant portion of DOX-loaded NGs has been assimilated into the cells and accumulated in the nucleus. A protein/polysaccharide complex microcarrier NG was developed by design engineers with feather keratin serving as a bifunctional crosslinking. The covalent crosslinking in the NGs was pH- and reduction-sensitive. Due to its dual crosslinked structure, the NG was able to remain stable in a natural environment and promptly deliver medication to tumor cells. NGs with a diameter of 430 nm exhibited an increase in negatively charged surface characteristics that were responsive to pH changes within the range of 4 to 8, indicating greater resilience and easier accumulation in tumors. The NG can load drugs up to 65 percent and release them to the simulated tumor intracellular environment at a rate of 57 percent. Nevertheless, after 133 hours in the simulated normal physiological media, it only shows a small premature drug leakage of 14%. The data on cellular uptake and in vitro cytotoxicity indicates that the NG can effectively target HepG2 cancer cells [59]. Sun et al., have created a type of cancer treatment using a combination of human hair keratin and ALG. This treatment can respond to two types of stimuli. The gels have been found to have - high efficiency for loading hydrophilic drugs and high stability. The drug is gradually released under normal physiological conditions thanks to macromolecular hydrogen bonding and interfacial disulfide crosslinking [60]. Gierszewska-Druyska et al., presented proof indicating that ionic crosslinks were created between the sodium ALG and tripolyphosphate (TPP) ions and the NH3+ groups in chitosan (CS) [61]. To enhance the characteristics of CS-based NG and add functionality, researchers developed multi-component CS-based NGs, such as CS/TPP-based NGs and CS/TPP/ ALG [62].

Su et al., produced doxorubicin-loaded manganese-ALG NGs (DOX@Mn-Alg) for synergistic chemo-dynamic treatment (CDT) and cancer immunotherapy via a microfluidic device that self-supplies hydrogen peroxide [63]. A microfluidic method was used to create ALG NGs that were effective at encapsulating polypeptides and proteins and releasing them over time [64]. A new approach to treating colorectal cancer involves the use of FA-conjugated HA-coated ALG NGs with DOX. Through CD44 receptor-mediated endocytosis, the HT29 cell line has been inhibited by up-regulation of BAX and down-regulating Bcl-2, which both promote anti-apoptotic growth [65]. The fabrication of DOX-loaded dual pH/ oxidation-responsive NGs significantly enhanced their ability to target 4T1 breast cancer cells by forming an inverse mini-emulsion with poly (allylamine hydrochloride), formyl phenyl boronic acid, sodium ALG, and DOX and coating it with membranes from 4T1 breast cancer cells. Future translational applications of this cutting-edge nano platform for tumor-targeted chemotherapy look promising [54]. The reduction-triggered property of a superparamagnetic NG has been established through the connection of the chemical bond. Under ideal circumstances, the suitable size of NG with a high surface negative charge was produced. Because of its abundant carboxylic groups, ALG was chosen.

Due to its magnetic targeting, good biocompatibility, hyperthermia, improvement in MRI, etc., SPION was used. The release behaviors are shown by the NG in a reduction-triggered way, with a preference for the release of DOX in a malignant environment. It was discovered that chemical conjugation effectively restrained DOX release in a typical environment, such as one with a pH of 7.4, without the use of GSH. Studies conducted in vivo show high therapeutic efficacy, high-targeted release, and little systemic toxicity. All tests showed that the current NG offers a potential tumor therapeutic platform with excellently targeted effectiveness and few systemic side effects [66]. By enclosing superparamagnetic iron oxide nanoparticles (SPIONs) inside an ALG shield that has been modified with disulfide, Peng et al., created a

new class of hybrid NGs. These NGs are effective imaging agents for diagnostic use and can be released specifically in acidic or reductive tumor environments. The researchers also found that the SPIONs and biocompatible ALG derivatives were highly effective in delivering drugs and imaging tumor cells [58]. Phase inversion temperature emulsification was used to encapsulate glycyrrhizin (GL) and doxorubicin (DOX) into ALG NG particles. The resulting drug-loaded ALG NGs demonstrated GL's ability to target hepatocellular carcinoma and the combined antitumor effects of GL and DOX [67].

A novel multifunctional nano system was created to deliver chemotherapy and photothermal therapy using ALG NGs co-loaded with cisplatin and gold NPs. The produced nano system's anticancer effectiveness was assessed using the CT26 colorectal tumor model. As a result, a rise in chemotherapeutic effectiveness over free cisplatin was noted, leading to impressive tumor suppression results. The in vivo thermometry results revealed that the gold nanoparticles' optical absorption properties caused the tumors treated with this nano system to heat up more quickly and receive significantly higher thermal doses. Researchers were able to dramatically reduce tumor development and boost animal survival rates by using this nano system for combination therapy. Tumor growth was reduced by up to 95% compared to the control [68]. Zhou et al., created new oxidized ALG-doxorubicin (mPEG-OAL-DOX/Cys) prodrug nanohydrogels with dual pH/reduction responsiveness. The findings demonstrated that the supramolecular crosslinking of the adjacent pseudo polyrotaxanes, regardless of the cyclodextrin species, improved the pH/reduction dual-responsive controlled the release performance of the mPEG (CD)-OAL-DOX/Cys prodrug nanohydrogels. The cleaved DOX complexation with β-CD would delay the DOX release, so the cyclodextrin inclusion complex with β-CD was shown to be a promising method to customize the structure and subsequently control the release performance of the finished prodrug nanohydrogels.

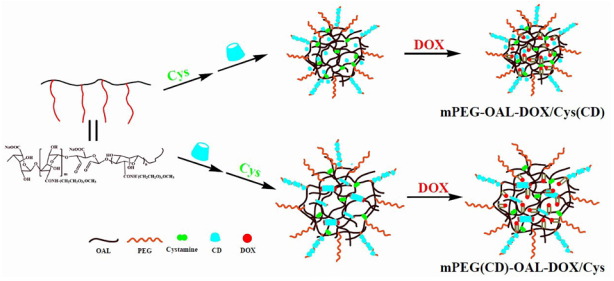

Figure 6: Schematic of The Synthesis of Cyclodextrin Inclusion Complex Prodrug Nanohydrogels [69]. (License: Reprinted (adapted) with permission from Zhou T, Li J, Jia X, Zhao X, Liu P. pH/Reduction Dual-Responsive Oxidized Alginate-Doxorubicin (mPEG-OAL-DOX/Cys) Prodrug Nanohydrogels: Effect of Complexation with Cyclodextrins. Langmuir. 2018 Jan 9;34(1):416-424. DOI: 10.1021/acs.langmuir.7b03990. PMID: 29237263. Copyright 2018 American Chemical Society.)

Table 1: Alginate Systems for Cancer Therapy

Drug Delivery System	Characterization Techniques	Cancer Cell Line	Size, nm	References
pH-responsive Alginate Nanogel (pH-Alg)	Zeta, DLS, TEM	HeLa	210	[70]
Alginate based Magnetic Nanogel (SPIONAlg and SPIONAlgSS)	13C NMR, FTIR, XPS, PDI, Zeta, TGA, CLSM, TEM	HepG2 (Adenocarcinoma cell line)	135.2	[58]
Cystamine Crosslinked PEGylated-Oxidized Alginate Nanogel (mPEG-OAL-DOX/Cys)	FT-IR, TEM, DLS, UV–vis	HepG2	194	[69]
Glycyrrhizin- Alginate Nanogel Particle (GL-ALG NGP)	FTIR, DSC, XRD, Zeta, DLS, TEM	HepG2	63	[67]
Collagenase immobilized Alginate Nanogels (Co@Alg Nanogel)	DLS, TEM, SEM	HepG2 and H22 (Hepatoma cell line); HepG2 Multicellular Tumor Spheroids	100	[71]
Alginate/ Cystamine Nanogel (Alg@Cys)	UV–vis Spectroscopy, FTIR, Zeta, DLS, SEM	CAL-72 (Osteosarcoma cell line)	100- 250	[72]
Alginate-poly(N-isopropylacrylamide) Nanogel (ALG-g-PNIPAM)	1H NMR, Zeta, TEM, UV–vis	CAL-72	147 ± 48	[73]
Dual-cross linked Dendrimer/ Alginate Nanogels (Alg/G5)	Zeta, DLS, SEM	CAL-72	433 ± 17	[74]
Keratin- Sodium Alginate Nanogels (KSA-Nanogels)	Zeta, PDI, CD Spectra, XPS, DLS, TEM, UV–vis	4T1 and B16 (Murine Melanoma cell line)	80	[60]

The cellular toxicity results showed the excellent biocompatibility of the mPEG(α-CD)-OAL/Cys nanohydrogels and the similar inhibition against cancer cell growth compared to the free DOX. They demonstrate promising controlled release performance with dual responsiveness to pH and reduction, making them -viable DDS for DOX delivery [69]. Figure 6 shows the synthesis of cyclodextrin inclusion complex prodrug nanohydrogels. Table 1 compares some of these systems.

Challenges AND Future Perspectives

Polymeric materials, synthetic or natural, are highly preferred for synthesizing drug delivery systems for various biomedical applications due to their unique characteristics. ALG is one of the most promising polymeric materials due to its natural origin. It features biodegradability, biocompatibility, and non-toxicity. ALG-based drug delivery systems have found wide applications for chemotherapeutic drugs like doxorubicin for cancer therapy. ALG -based DDS in various forms (like hydrogels, nanoparticles, magnetic systems, etc.) has been explored for targeted and site-specific delivery of doxorubicin. Moreover, with advancements in chemical engineering, newer materials with improved properties have been developed. Many of these materials can be used simultaneously with ALG to perform additional functions and drug delivery. Extensive research is being done for developing such "multifunctional" delivery systems, which can find wide applications in the biomedical field. However, comprehensive in vivo studies are still required for clinical trials of ALG -based DDS on humans. Also, the delivery systems are being thoroughly studied for other anticancer drugs like paclitaxel, cisplatin, methotrexate, etc., to understand their benefit.

CONCLUSION

NGs are a ground-breaking platform that is necessary for developing cutting-edge treatments. NGs' physical and chemical features are affected by their manufacturing processes and polymer networks. Both hydrophilic and hydrophobic molecules can be modified non-structurally in these systems. Due to their capacity to co-encapsulate molecules with a wide variety of physicochemical properties, they present an excellent opportunity to develop an original, advantageous controlled release system. NGs' release of constituents has a crucial impact on the therapeutic index, toxicity, and bioavailability of encapsulated drugs. The nanogel structures' release kinetic is determined by how quickly they disintegrate and degrade, which can be modified using different precursors or crosslinks in manufacturing methods. It is therefore anticipated that the development of novel features in NGs will be beneficial. Flexible release times and locations allow for the distribution of encapsulated medications with a controlled release through these devices. NG-based systems are among the applications of the technology, which has recently been demonstrated in biology and medicine. The physicochemical properties of NGs have been shown to significantly affect the regulation of these nano-bio interactions. Platforms made of NGs should be considered if they have a variety of mechanical characteristics, such as rigidity, stiffness, hardness, elasticity, strength, etc. Their mechanical characteristics ought to be consistently tracked to obtain accurate data. These results might explain why soft materials like albumin and liposomes are used to make the most commercially available chemotherapeutic platforms. Thus, the use of soft materials for developing NG platforms suitable for clinical settings should be considered. Large-scale NG production should be economical, and all synthesis and crosslinking procedures should be carried out consistently to provide a uniform, pure product with the desired properties. The following step is to recognize technological difficulties and thoughtfully deal with them. Another concern for the substance's clinical application is its safety regarding biodistribution and biological fate. It should be emphasized that a safe, non-toxic crosslinking chemistry and biodegradable and biocompatible polymers should be used to create a therapeutically suitable NG. To improve clinical outcomes of medications while addressing concerns, NGs can be translated into the next generation of drug delivery platforms.

ACKNOWLEDGMENTS

None declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL

None declared.

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