

TARGETED DRUG DELIVERY SYSTEM; NANOPARTICLE BASED COMBINATION OF CHITOSAN AND ALGINATE FOR CANCER THERAPY: A REVIEW

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ABSTRACT

This review aimed to determine the potential of the combination of chitosan and alginate as a targeted drug carrier in cancer therapy. This article is based on the results of previous research journals collected from Google Scholar, Scopus, PubMed and Science Direct sites using the keywords chitosan, alginate, targeted drug delivery for cancer, nanoparticle chitosan alginate. With the inclusion criteria, only English-language journals, journals published in the last 10 y, related to chitosan and alginate-based formulations. Meanwhile, the exclusion criteria were journals on pharmacological properties and bioactivity, food and cosmetics. The combination of cationic chitosan and anionic alginate forming strong cross-links showed good mucoadhesive properties, higher resistance to low pH and high-efficiency encapsulation without showing any obvious cytotoxicity. Ch/Alg can overcome the shortcomings of the active substance, such as its rapid release process and the required active ingredient is lower than that required to enter the cancer target cells so as to minimize side effects of the drug by providing drug-induced release. In response to various stimuli that are well suited to the intended purpose, such as pH stimuli, redox gradients, light, temperature, and magnetism. It is shown that the combination of chitosan and alginate base has great potential in targeting cancer therapy by increasing its therapeutic effectiveness and selectivity.

Keywords: Nanoparticles, Chitosan, Alginate, Cancer therapy, Targeted delivery, Polymer

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INTRODUCTION

Cancer cells arise from the transformation of normal cells so that anticancer drugs can usually damage normal cells so that a drug delivery system that is specifically targeted towards cancer cells is needed such as nanoparticles [1, 2]. Nanoparticles can be defined as nano-sized systems with diameters generally ranging from 10 to 1000 nm [3], which has been recognized to have great potential in changing the pharmacokinetic profile, reducing side effects, and being able to increase therapeutic efficiency [4, 5]. In the development of this delivery system, there are three main aspects, namely the targeting group, the therapeutic agent, and the carrier system. Drugs can be conjugated into carrier molecules through passive and active absorption, in this case, the selection of a suitable carrier molecule that must be biodegradable is very important. Biodegradable polymers have proven to be the most promising potential for building anticancer drug delivery systems and can be classified based on the source consisting of synthetic polymers and natural polymers [1, 2, 6].

One type of polymer being developed at this time is chitosan; chitosan is a polymer derived from the distillation process of chitin which is widely found in invertebrates, especially crustaceans, such as crabs, crabs, and shrimp, has mucoadhesive properties, biodegradable, biocompatible, low immunogenicity and Non-toxic makes this polymer

widely used in biomedicine and pharmaceuticals, besides that it is also a strong nucleophile and has a lone pair of electrons from the amine group making chitosan cationic. Alginate is a polymer whose main components come from brown algae, such as *sargassum*, *durvillaea*, *macrocystis*, and *ascophyllum*. There are two types of monomers in alginic acid, namely β -D-mannopyranosyl uronic and α -D-mannopyranosyl uronic acid-L-glucopyranosil uronate, which causes colloidal, hydrophilic and gel-forming properties, so it is widely used as a thickening agent, emulsifier, and stabilizer in pharmaceutical preparations [7-10]. Combination anionic chitosan and alginate will form cross-links that maximize targeting by regulating encapsulation and release rate as well as excellent and proven mucoadhesive properties. can be well received by the body, improve encapsulation efficiency [11-13] and is known to increase absorption and cellular uptake by widening the narrow film on the preparation [10, 14, 15].

The nanoparticle formulation based on the combination of chitosan alginate can produce a significant difference in the healing process of cancer therapy compared to the single base. But in this combination the selection of the appropriate method is very important to achieve the formula results with the desired targeting location. The purpose of this review article is to provide a comprehensive view of the potential of nanoparticle targeted delivery systems from a combination of chitosan and alginate-based for cancer therapy.

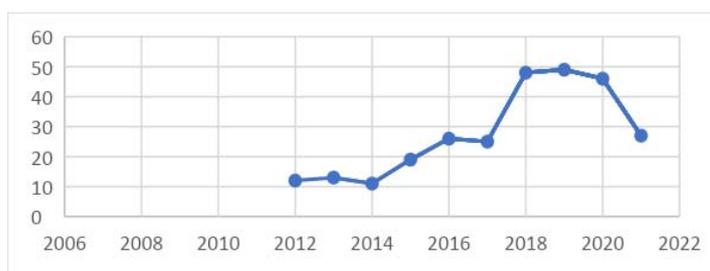


Fig. 1: Distribution of nanoparticle chitosan alginate articles based on the year of publication (self-made)

METHODS

This article is based on the results of previous research journals collected from the Google Scholar, Scopus, PubMed and ScienceDirect sites using the keywords chitosan, alginate, targeted drug delivery for cancer, nanoparticle chitosan alginate. With the

inclusion criteria, only English-language journals, journals published in the last 10 y, relevant to based chitosan and alginate formulations. Meanwhile, the exclusion criteria were journals on pharmacological properties and bioactivity, food and cosmetics, the distribution of articles based on the year of publication can be seen in fig. 1, and for the flowchart of the methodology can be seen in fig. 2.

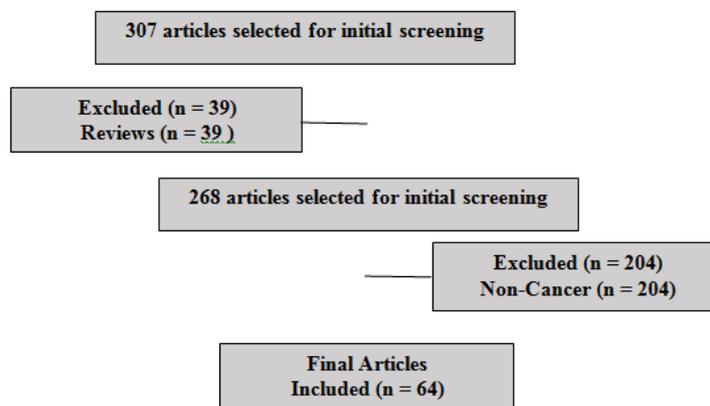


Fig. 2: Flowchart of the literature search (self-made)

Chemical structure and properties of chitosan and alginate

Chitosan

Chitosan is a biological polysaccharide with cationic properties, a compound having the chemical formula poly(1,4)-2-amino-2-deoxy-D-glucose which can be produced from the hydrolysis of chitin using a strong base (deacetylation process) [16] found in *crustacean shells, exoskeletons* of arthropods, insects, and fungal cell walls. The elements that make up chitosan are almost the same as the elements C, H, N, O and other elements, which are used as very promising nanomaterials with wide medical applications [11, 12, 16] and is an abundant biopolymer because it is obtained from its structure, chitosan is a representative polysaccharide, positively charged amine group consisting of N-acetyl-D-glucosamine (GlcNAc) and D-glucosamine (GlcN) which gives cationic character at physiological pH [17-19]. This nanomaterial has unique properties, namely resistance to mechanical stress, nontoxic, mucoadhesion, biocompatibility, biodegradability, and bioactivity [16, 20, 21]. Because of its nature that can be degraded by internal enzymes such as lysozyme and chitosanase so as to obtain oligosaccharides and monosaccharides which can then be easily absorbed by the body [22].

However, chitosan has low solubility and poor mechanical properties [19, 25] but can form salts with inorganic acids and organic acids such as hydrochloric acid, glutamic acid, acetic acid and lactic acid. When chitosan dissolves, the amine group is protonated and the charge becomes positive [24]. To cover these deficiencies, modifications have been developed [27, 28], such as the use of amino and hydroxyl groups to produce derivatives that have a high degree of solubility [29, 30]. So now it has been widely used in biomedical and pharmaceutical applications such as tissue engineering, wound healing, drug delivery systems, and cosmetic products [29-33]. The active ingredients combined in the matrix

must have good solubility in chitosan, because it greatly affects the speed of drug release. These polymers can be used alone or in combination with other polymers to obtain better drug release [34].

Alginate

Alginate is an anionic copolymer obtained from the extraction of brown algae alginophyt, from Phaeophyceae that produce alginates, including macrocystis, Ecklonia, Fucus, lessonia and sargassum, which contain calcium, potassium, sodium ions [36,37] consists of 1,4-linked units of D-mannuronic acid (M) and L-glucuronic acid (G) arranged in a clockwise direction [37]. To extract alginate from algae, mineral acid is used to remove contaminants and produce insoluble alginic acid, to dissolve it is neutralized with alkalis such as sodium hydroxide or sodium carbonate to form sodium alginate [38]. In the formation of sodium alginate gel, there is a replacement reaction of more than 35% Na⁺ cations with Ca²⁺ which stops the molecular shift. The active ingredients combined in the matrix must have good solubility in chitosan, because it greatly affects the speed of drug release. These polymers can be used alone or in combination with other polymers to obtain better drug release [34].

Methods for constructing nanoparticle-based chitosan/alginate targeted drug delivery

The cationic nature of chitosan, which is able to increase adhesion through electrostatic interactions of the mucosal surface, which has a negative charge is one of the most prominent characteristics and has been proven to be an efficient drug carrier to target cells. However, the most significant drawback is that it is only able to dissolve in acidic media, so it is important to make modifications to cover this deficiency. Several modification methods can be carried out for the manufacture of nanoparticles based on a combination of chitosan and alginate. Methods for constructing nanoparticle Based chitosan and alginate can be seen in fig. 3.

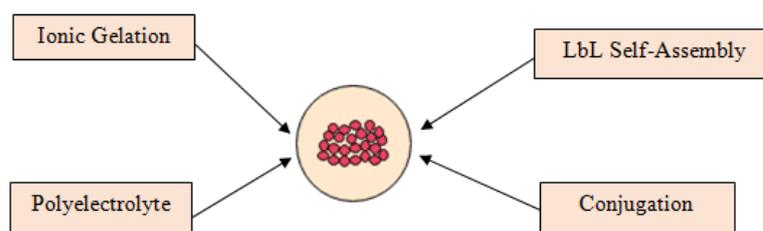


Fig. 3: Methods for constructing nanoparticle based chitosan and alginate (self-made)

Ionic gelation

There are two types of ionic crosslinking: first, the manufacturing process is simple, does not use organic solvents or high temperatures, and does not involve chemical interactions. These benefits make this procedure effective for thermolabile drugs. Ionic crosslinking is carried out due to the interaction between positively charged chitosan and negatively charged macromolecules or anionic crosslinking agents. An acid solution of chitosan was prepared, together with stirring and sonication, and the ionic crosslinker was applied dropwise. Second, through chemical interactions between crosslinking agents, primary amine groups, chitosan nanoparticles are formed. Glutaraldehyde, formaldehyde, vanillin, and genipine are common crosslinkers [39].

Ionic gelation method in the process of making nanoparticles is widely used because the process is simple, does not need to use organic solvents and can be controlled easily [40]. Behind these advantages, this method also has disadvantages, namely poor stability under acidic conditions and difficult to trap drugs with high molecular weights [41].

LbL self-assembly

Layer by Layer (LbL) with electrostatic assembly is often used in surface modification of some materials [41, 42]. This technique has seen the application of two-dimensional and three-dimensional self-constructed structures that are nanostructured and easily adaptable [44]. Due to its compatibility with highly organized construction materials and its high versatility, the LbL deposition method is used to construct new biomaterials and has seen promising applications in the biological field [31, 43–45].

The use of LbL assembly with different standard tools and procedures and different processing requirements related to substrates such as porous membranes, particles and biological materials used in its development, including dipping, dewetting, roll-to-roll, centrifugation, creaming, calculated saturation, immobilization, rotating, high gravity, spraying, atomization, electrodeposition, magnetic assembly, electrical connection, filtration, fluidics, and fluidized bed fluid. Currently there is a growing realization that the assembly method not only determines the process properties (such as time, scalability, and manual intervention) but also directly affects the physicochemical properties of the film such as thickness, intralayer homogeneity. The advantages of this method are that the process is cheaper than other methods and the percentage of success is high. But behind these advantages, this method has a big challenge because the process occurs without human intervention, so it is important to know how to regulate and maintain the formation of directed supramolecules as desired [47-62].

Polyelectrolyte

Polysaccharides are an interesting type of polymer found in nature. They often allow a high degree of hydration, are biocompatible, and are often biodegradable [48]. Complex Polyelectrolytes (PEC) are formed from solutions that carry two polyelectrolytes. The formation of PEC is caused by intense coulomb interactions between polyelectrolytes of opposite strength to each other. The formation of this complex results in the charge neutralization of the polymer. Generally, the complex obtained will precipitate or leave the solution to produce a rich and complex liquid process (coacervate). An important driving force for the formation of PEC is the increase in entropy caused by the release of these low molecular weight counterions into the medium. While PEC formation is responsible for electrostatic interactions between the complementary ionic groups of polyelectrolytes, hydrogen bonding and hydrophobic interactions also contribute to the complexity [62, 63].

This method is used to overcome the weakness of chitosan properties; materials that have a carboxyl group are used so that they can form polyanions, for example, pectin and alginate. However, obstacles. The amino group in N-glucosamine chitosan,

which is positively charged in an acidic environment forms a basic polysaccharide or polycation. Ionic interactions that occur between polyanions (alginate) and polycations (chitosan) form the PEC complex. In addition, other interactions are formed between amino and carboxyl groups, such as hydrogen and covalent bonds formed using conjugation chemistry. The combination of chitosan and alginate is able to overcome the lack of polysaccharides and expand their benefits [65].

Conjugation

In the chitosan molecule there are C6-OH and C2-NH₂ groups which can be used to add other groups with different molecular designs. This modification is able to improve physical and chemical properties and expand its benefits and applications in various fields [66]. The functional groups C3-OH, C2-NH₂, C6-OH, amines and glycosides exist in chitosan. Acetyl-amino bonds and glycosidic bonds are not easily broken, making them stable [63]. Examples of other molecular groups that can be added to chitosan are alginate, alginate having an OH-group (anion) capable of being conjugated with chitosan which has a cationic group to form a complex bond [65].

Functionalization strategies of nanoparticle based chitosan and alginate for cancer targeting

Cancer targeting therapy is able to increase therapeutic efficacy with low side effects, because active compounds can accumulate at the tumor site and are able to recognize differences between normal cells and cancer cells [65–69]. This strategy can be divided into two mechanisms: passive targeting and active targeting.

Passive targeting

Passive targeting or so-called Enhanced Permeability and Retention (EPR) has the effect of increasing permeability and retention allowing nano-sized carriers to be explicitly distributed penetrate cancer cells through endocytosis and increase the number of drugs acting on cells [67] which is certainly one way to make therapy more efficient [68]. diameter of <100 nm with a hydrophilic surface to avoid increased drug targeting and improve drug circulation in the body, this measure affects the amount and kinetics of accumulation of nanomaterials in tumor cells which is expected to be smaller than the cutoff proportion in neovascularization [67]. In addition, under the microenvironment the pH of tumor tissue is lower than normal tissue, so it is possible to combine chitosan with alginate which is responsive to low pH, a hydrophobic substrate at a physiological pH of 7.4 becomes hydrophilic at a pH below 6.3 due to protonation during the drug release process triggered by pH [69].

Active targeting

Active targeting used for tumor accuracy and delivery efficiency, requiring affinity-based identification, retention, and facilitated uptake of target cells [70]. This targeting is also known as ligand-receptor conjugation, antigen-antibody, and other forms of molecular recognition to DDS to obtain targeted delivery to specific cells, tissues, or organs [71]. The interaction between the ligand and the receptor will increase the absorption of the drug-containing nanoparticles and increase the therapeutic efficacy [67]. Wicaksono *et al.* reported that the combination of chitosan and alginate together Ribosome-inactivating protein (RIP) It has been used successfully in the treatment of breast cancer by oral administration. And it has also been proven that the Ch/Alg folic acid conjugate is able to perform a better antitumor therapeutic effect than the free drug because of the selective affinity of Ch/Alg to intestinal cells [77, 78]. Gascon *et al.* developed modified CXCL12-conjugated Ch/Alg nanoparticles for the treatment of brain and spinal cancer because the IL-13RA2 receptor (also known as cluster of differentiation 213A2, is a membrane-bound protein is highly expressed in glioblastoma cancer tissue and is not present in normal brain tissue [74]. CXCL12 conjugated into nanoparticles was able to significantly increase drug accumulation at the cancer site, thereby enhancing the therapeutic effect.

Table 1: Strategy targeting nanoparticle based chitosan and alginate cancer active

Active	Ligand type	Ligand	Receptor/Targeting site	Ref.
Passive	Protein	Ribosome-inactivating protein	rRNA N-glycosidase	[64]
		CXCL12	IL-13RA2	[74]
Passive	Vitamin	Folic acid	Folic Acid Receptors	[68-71]
	Conditions	Function	Molecule	Ref.
	pH Responsive	The drug delivery system remains stable in the circulation and releases the drug in response to pH at certain tissue locations	5-Aminolevulinic acid	[9]
	temperature	Release the drug to its temperature responsive	Boric Acid	[66]
	Magneto	Targeted delivery to a specific site via an external	TiO ₂ and Fe ₃ O ₄	[72,73]
	Responsive	magnetic field.	Fe ₃ O ₄	[77]

Humans have a body built with interconnected signals between organs and cells so great effort is needed in studying the deep mysteries associated with the signals of the human body [81, 82]. It has previously been determined that various receptors in the body can be developed in an effort to target drugs [83, 84]. There are various kinds of compounds used in the delivery of targeted drugs, including glucose, peptides and other types of biological molecules [83].

Cancer targeting therapy is able to increase therapeutic efficacy with low side effects, because the active compounds can accumulate at the tumor site and are able to recognize differences between normal cells and cancer cells [84-88]. Some other examples of nanoparticle combinations based of Chitosan and Alginate (Ch/Alg) nanoparticles designed in dosage formulations for targeted cancer therapy are presented in table 1.

Table 2: Targeted drug delivery of nanoparticle based Ch/Alg for cancer therapy

Agents of drug	Size (nm)	Method	Strategies of cancer-targeting	Effect	Cell line	Cancer type	Ref.
M. Jalapa L	130.7	Active	Conjugated with anti Ep-CAM antibody	Enhance Cytotoxicities, less selectivity	T47D	Breast Cancer	[64]
Iron saturated bovine lactoferrin	322	Passive	Polyelectrolyte	Improved antitumor by internalizing and regulating micro-RNA expression	MDA-MB-231	Breast Cancer	[89]
Curcumin	212-	Passive	Enhanced cellular uptake	The superior inhibitory effects on the viability of cancer cells and higher cytotoxicity	MDA-MB-23, HepG2 and Caco-2	Breast Cancer	[90]
diglutamic acid	552						
Doxorubicin	~80	Passive	Enhanced cellular uptake	Have high concentration to induce a therapeutic effect breast cancer cell line	4T1 murine	Breast Cancer	[91]
Curcumin	~200	Passive	Magneto-responsive	Enhanced the biocompatibility and can be controlled to specified targeting	MCF-7	Breast Cancer	[77]
5-Aminolevulinic acid	115	Passive	Depending on the pH of the environment	Improved the efficacy of the 5-ALA for photosensitizer.	HeLa Cell	Cervical Cancer	[9]
Methyl oxide	21	Passive	Enhanced cellular uptake	Exhibit better protein absorption capability suitable for cell attachment and growth	UC6 (Bladder tumor cell line), MG-63	Bladder Cancer	[78]
Temozolomide	70-	Active	Folic acid receptor-based endocytosis	Decrease tumor cell line, increase its absorption and selectivity	HeLa and NIH/3T3 Cell	Cervical Cancer	[75]
anddoxorubicin	120	Active	Folic acid	Improved antiproliferative activity of cancer cells	HCT116	Colon Cancer	[76]
5-Fluorouracil	130						
CXCL12	133-297	Active	Conjugated ligand	Control GBM cell invasion without enhancing their proliferation	GBM cells	Brain Cancer	[74]
α -mangostin	192	Active	Folic acid receptor-based endocytosis	Improved antiproliferative activity of cancer cells	HCT116	Colon Cancer	[73]
α -mangostin	100	Active	Folic acid	Improved antiproliferative activity of cancer cells	HCT116	Colon Cancer	[72]
Boric acid	136	Passive	Depending on the pH of the environment	Significantly reduce the cytotoxicity by 12-fold and increase the killing efficacy of tumor cells	SAS Cell	Oral Cancer	[66]

Based on the data shown in table 2. Nanoparticles can enter cells through direct diffusion mechanisms or adhesive interactions, phagocytosis, and micropinocytosis. Chemical properties, such as shape, particle size, surface charge, and composition. In previous studies, smaller nanoparticles were easier to enter into cells through endocytosis or diffusion mechanisms, while larger nanoparticles were more likely to penetrate into cells through phagocytosis mechanisms [92]. Cells incubated in the presence of Ch/Alg complex and Ch/Alg filled with 5-ALA showed higher emissions compared to positive controls. As reported in previous studies, the higher emission of Ch/Alg is predicted to come from the surface properties of the nanoparticles which can increase the interaction with cell membranes accompanied by higher absorption and accumulation of

5-ALA [9, 92]. This value could be attributed to the decreased capacity of cells to degrade Chi/Alg carriers resulting in lower conversion rates and poor accumulation of Protoporphyrin IX in cells [9, 93].

Ch/Alg in the form of nanoparticles is very effective as a carrier for cancer drugs can be seen in table 2. However, there are several things that need to be considered in therapy, namely the increase in cytotoxicity, cell uptake, circulation time, and the level of selectivity to normal cells. This is associated with an increase in cytotoxicity in the form of effectiveness and efficiency of nanoparticles which can be done by optimizing their targeting strategies both actively and passively. Nanoparticles can bind to the physiological pH of the body

as short peptides that are both hydrophilic and hydrophobic, this increase in cellular uptake causes large membrane damage, which can penetrate cell membranes at low micromolar concentrations by increasing drug concentrations in cells. Drug concentration in cancer cells will increase cytotoxicity. The value of this effective diffusion coefficient is associated with the electrostatic interaction between positively charged protein/peptide, and negatively charged alginate core that composes Ch/Alg nanoparticles.

Ch/Alg nanoparticle technology has various modifications in drug development efforts to increase drug accumulation in cancer cells [72, 94-98], mobile uptake [99, 100], cytotoxicity [101] and selectivity to normal cells [102-104]. Taking into account the EPR effect and the active targeting portion, Ch/Alg-based nanoparticles will achieve all of these goals. Ch/Alg nanoparticles can work by delivering anticancer drugs to all cancer cells, which are widely used representing all types of cancer. Our objective research shows that chitosan-based nanoparticle technology synergizes the overall impact of the effects of EPR and active targeting components in delivering anticancer drugs to cancer cells. Decrease in nanoparticle size increases drug solubility and stability [105-108] and surface charge of nanoparticles, enhances drug protection in blood circulation [33, 109] and increases drug absorption in cancer cells [33, 66, 100] (table 2). This modification of the Ch/Alg combination will maximize other cancer cell-specific characteristics such as the pH gradient [110-112], temperature and the redox [30]. Therefore, the formulation of a nanoparticle based combination of chitosan and alginate is an option in overcoming the disadvantages of poor solubility in water and low selectivity for drug delivery to target cells.

CONCLUSION

Therapy using nanoparticles based combination of chitosan and alginate (Ch/Alg) can be applied to anticancer drugs to any cancer cells, such as for breast cancer, cervical cancer, bladder cancer, colon cancer, brain cancer, and oral cancer, working by increasing cytotoxicity and increasing drug accumulation, selectivity, and efficacy. The combination of cationic chitosan and anionic alginate forming strong cross-links showed good mucoadhesive properties, higher resistance to low pH and high-efficiency encapsulation without showing any obvious cytotoxicity. Ch/Alg can overcome the shortcomings of the active substance such as its rapid release process and the required active ingredient is lower than that required to enter the cancer target cells so as to minimize side effects of the drug, by providing drug-induced release. In response to various stimuli that are well suited to the intended purpose such as pH stimuli, redox gradients, light, temperature, and magnetism. Cancer therapy with nanocarrier combinations of chitosan and alginate offer great opportunities in the treatment of various types of cancer.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that we have no conflicts of interest in this work.

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