REVIEW ARTICLE

Applications of Amphiphilic Chitosan Derivatives in Drug Delivery Systems: A Review Article

Zainab N. Aljashaami

Department of Pharmacy, Al Nisour University College, Baghdad, Iraq

Received: 10th October, 2022; Revised: 20th November, 2022; Accepted: 10th December, 2022; Available Online: 25th December, 2022

ABSTRACT

Chitosan has unique physicochemical characteristics to make it safe and effective as a carrier of some drugs. However, some drawbacks restricted its applications in drug delivery systems. Chemical modifications occurred on the backbone of chitosan to overcome the disadvantages properties of chitosan. Chitosan derivatives were synthesized by inserting the hydrophobic moieties into the chitosan molecule. The resulting amphiphilic derivatives with low toxicity may form self-assembled nanoparticles that can deliver a drug to different body sites. The preparation and applications of the hydrophobic chitosan derivatives will be reviewed in this article.

Keywords: Chitosan, Chitosan derivatives, Self-assembled nanoparticles and Drug delivery.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.4.69

How to cite this article: Aljashaami ZN. Applications of Amphiphilic Chitosan Derivatives in Drug Delivery Systems: A Review Article. International Journal of Drug Delivery Technology. 2022;12(4):1897-1900.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Chitosan could be a nontoxic copolymer of N-acetyl glucosamine and glucosamine units dispersed randomly (Figure 1). Alkaline deacetylation of chitin, the major ingredient of crustaceans' exoskeleton, is a popular method for producing this polycationic biopolymer.[1] pH sensitivity, biocompatibility, and low toxicity are only a few of the biopharmaceutical properties of chitosan.[2,3] Furthermore, chitosan is biodegradable and is digested *via* several human enzymes, notably lysozyme.[4] The utilization of chitosan and its derivatives as drug carriers has grown in recent years as a result of these beneficial qualities.[5,6] The popularity of chitosan originates mostly from the fact that it may be used to create biocompatible and biodegradable drug delivery systems. Chitosan must be soluble in aqueous fluids and positively charged to be useful. Because of these features, it may connect with negatively charged polymers and macromolecules in an aqueous environment. Chitosan has a unique capacity for adhesion to mucosal surfaces, making it a valuable polymer for mucosal medication administration.[7,8] The utilization of chitosan in creating microspheres and nanoparticles has been documented in several studies.

Chitosan has a limited solubility at a physiological pH of 7.4, which restricts its utility as an absorption improvement in nasal or oral administration systems, for example. Another drawback of chitosan for constructing maintained release systems is its fast water adsorption and increased swelling amount in aqueous settings, resulting in prompt drug release.

A variety of chemically adjusted chitosan derivatives have been produced and studied to address these concerns. Chitosan can be chemically altered to increase its solubility and expand its uses.[9,10]

The purpose of this revision is to mention the various production techniques and uses of chemically modified chitosan intended for drug association and delivery.

Production and Properties of Chitosan

Because chitosan is seldom found in nature, it cannot be harvested straightforwardly from natural resources. Chitosan is very certainly derived of natural chitin. Chitosan is usually made *via* deacetylation of the N-acetyl glucosamine units of chitin, which is done largely by hydrolysis at high temperatures under alkali conditions. Chitin deacetylation is seldom complete. Chitin is converted to chitosan when the degree of acetylation goes below 60 mol%.[11]

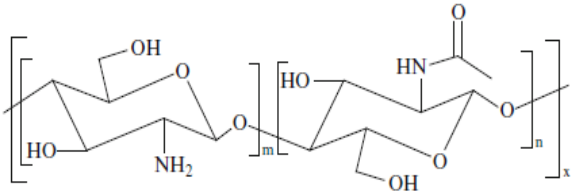

Figure 1: Chemical structure of chitosan

**Author for Correspondence: zainab8891@yahoo.com*

Chitosan has significant biological features, which have cleared the way for its applied in innovative drug delivery methods in the pharmaceutical and biomedical areas. Because of its positive charge, chitosan has excellent mucoadhesive qualities, which enhances adherence to the mucosa and hence the period of contact for medication permeation. Furthermore, chitosan's antibacterial properties reduce the risk of a variety of illnesses.[12]

Chitosan is a polycation with a charge density that varies depending on acetylation and pH sensitivity. As a result, chitosan chains can interact with negatively charged molecules *via* electrostatic interactions. Regardless, chitosan has a low water dissolvability, which might be a major disadvantage in medication formulations. Acidic solution is only the media for solubilize chitosan with a pH below 6.5, which is necessary for the main amine to be protonated. Positive charges on the chitosan molecule increase the repulsion between the multiple polymer chains in such instances, allowing for their solubilization. Chitosan is slightly soluble within organic solvents such as dimethyl sulfoxide (DMSO) and p-toluene \ sulfonic acid.[12]

The destiny of chitosan within the body after absorption or injection is an important property for its use in drug delivery systems. The normal elimination of chitosan *via* renal clearance; however, enzyme breakdown is necessary if the molecular weight is too high. Three chitinases were discovered to be involved in the production of smaller chains within the human body. The pace of degradation, however, is determined by the starting substance's molecular weight and degree of acetylation.[13]

Modification of Chitosan

Amphiphilic Chitosan Derivatives for Drug Delivery

Hydrophobic particles were inserted into chitosan derivatives to make amphiphilic chitosan derivatives. To begin, the easiest technique to add amphiphilic characteristics to chitosan is introducing hydrophobic alkyl chains onto it. Consequently, alkyl ketones or alkyl aldehydes were preferentially inserted onto chitosan's major amino groups, resulting in the Schiff base. With the production of the corresponding N-alkyl chitosan derivatives, the imine group was transformed into the further stable amine *via* a reduction process driven by sodium cyanoborohydride (NaBH3CN) or sodium/potassium borohydride (NaBH4/KBH4) (Figure 2).[13]

Several research groups proposed incorporating fatty acids into chitosan-based amphiphilic copolymers in order to make them using solely natural and renewable ingredients. In most cases, the insertion was accomplished by forming an amide linkage between the main amine group of chitosan and the terminal carboxylic acid of the fatty acid in a water/alcohol combination under rapid mixing, mediated by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (Figure 3). In two situations, this approach efficiently inserts saturated stearic acid and unsaturated lineoic acid onto chitosan. In some studies, the carboxylic acid of oleic acid has been converted

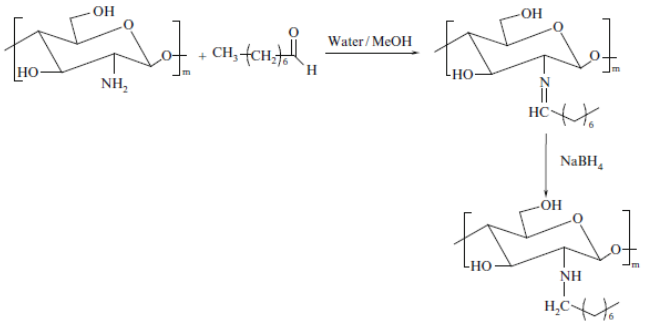

Figure 2: Inserting of alkyl chain by reductive amination

into acid chloride before reacting with chitosan in chloroform within the presence of pyridine. The same method was used to apply octanoic, palmitic, and stearic anhydride to chitosan.[13]

Steroid derivatives were used in the same way as conventional chemicals capable of producing chitosan's amphiphilic characteristics. In the literature, there are a few examples of cholesterol being inserted into O-glycol-chitosan (Figure. 4). The approach depends on N-hydrosuccinimide activation of the carboxylic acid to improve insertion efficacy on the main amine group of glycol chitosan, which EDC mediates.[14]

Pharmaceutical Application of Chitosan Derivatives

Chitosan derivatives to Delivery of Slightly Water-soluble Drug

Chemical conjugation of doxorubicin (an antitumor medicine) to glycol chitosan resulted in hydrophobically modified glycol chitosans capable of generating nanosized self-aggregates.[15]

The biodistribution of the self-aggregates *in-vivo* was examined after systemic delivery through the tail vein of tumor-bearing mice. According to the findings, the number of scattered self-aggregates within the tumor area steadily rose as blood circulation time expanded. The doxorubicin-loaded self-aggregates significantly reduced tumor development *in-vivo*, suggesting that the glycol chitosan nanoparticulate framework has intriguing potential as a hydrophobic drug carrier.[15]

A novel sequence of amphiphilically altered chitosan particles with long alkyl chains as hydrophobic moieties and glycol groups as hydrophilic moieties (N-octyl-O-glycol chitosan, OGC) was created to use as a drug carrier.[16]

Paclitaxel, a water-insoluble anticancer medication, has been effectively loaded onto OGC self-aggregates by applying a common dialysis approach.[16]

A technique was discovered to generate micelles depending on amphiphilic chitosan derivatives that were

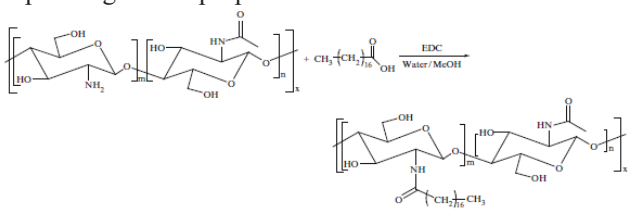

Figure 3: Inserting of stearic acid onto chitosan

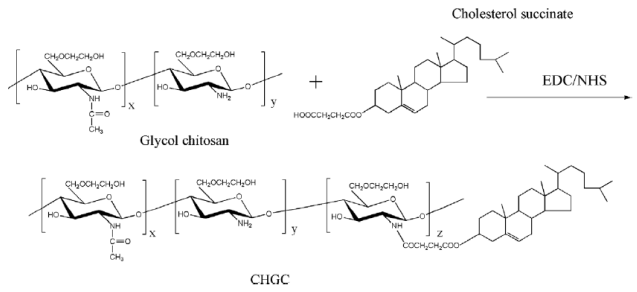

Figure 4: Inserting of cholesterol succinate onto glycol chitosan

made *via* adding hydrophobic octanoyl, palmitoyl and stearoyl aliphatic chains onto a molecule of chitosan with varying degrees of substitution. The N-fatty acylations occurred *via* conjugating chitosan with carboxylic anhydride in dimethyl sulfoxide solvent.[17]

Cholesterol-modified glycol chitosan (CHGC) has been evaluated using nuclear magnetic resonance (NMR) and fourier transform infrared spectroscopy (FTIR).

The physicochemical characterizations of CHGC-generated self-aggregated nanoparticles have been investigated by fluorescence spectroscopy, transmission electron microscopy (TEM) and dynamic light scattering (DLS),.[18]

Indomethacin, a hydrophobic non-steroidal anti-inflammatory medication, was efficiently confined in CHGC nanoparticles. A 12-hour gradual release followed a two-hour fast release. The findings suggested that CHGC nanoparticles might be used as a medication delivery vehicle.[18]

Spray drying was utilized to create solid dispersions of dexamethasone, a water-insoluble corticosteroid, and synthetic chitosan derivatives (chitosan phthalate, CP and chitosan succinate, CS). The drug loading, as well as the drug release profile of the resulting microspheres, were calculated. Using CP and CS as polymers, high drug-loading levels were achieved. The rate of drug release was significantly increased after the solid dispersions were formed, also when the percentage of chitosan derivatives within the microspheres increased, the rate of drug release was increased.[19]

The prodrug of Lamivudine LA, Lamivudine stearate LAS was established by establishing an ester link between LA and stearic acid. The researchers developed stearic acid-g-chitosan oligosaccharide polymeric micelles that would self-assemble in an aqueous solution and could efficiently and effectively load the slightly water-soluble LAS prodrug. The CSO-SA/LAS self-aggregates delivery method displayed low cytotoxicity, high absorption, and in vitro anti-HBV (hepatitis B virus) efficacy.[20]

Chitosan derivatives for enhancement of poorly drug bioavailability

Carbamazepine is an antiepileptic medication (AEDs). The presence of multi-drug resistance transporters and p-glycoprotein in the blood-brain barrier might prevent AEDs from entering the brain, resulting in drug-resistant epilepsy. To address this problem, a carboxymethyl chitosan nanoparticle of carbamazepine (CBZ-NPs) has been created and delivered by the intranasal route to improve the drug's transport to the brain. When CBZ-NPs was delivered intranasally, it appeared that CBZ was preferentially entering the brain. *In-vivo*, the results suggest both the nasal route and the nanoparticle encapsulation of CBZ improved medication bioavailability and brain-targeting properties. According to the findings, it could create a nasal formulation of CBZ that caused fast and prominent absorption, within therapeutic use in acute situations.[21]

Chitosan derivatives for control release

Because chemically changed chitosan microspheres show pH- behavior, a number of researchers have demonstrated that they might be used as carriers of drug for control release. Because amphiphilic chitosan derivatives form polymeric micelles within the aqueous media, they could be employed as a competent delivery carrier to trap and control the release of hydrophobic medicines.[22]

MMC (mitomycin C) is a widely used anticancer agent. In this study, Song *et al.*[22] attempted to make water insoluble MMC conjugates with succinyl-chitosan. The drug release has been kept constant at a physiological pH level.[23]

A hydrophobic mucoadhesive thiolated chitosan was explored and made by conjugating p-coumaric acid (pCA) to enhance hydrophobic compatibility with medication through pi-pi reaction and after that, covalently attaching homocysteine thiolactone (HT) to the pCA-chitosan to boost mucoadhesive characteristics. Using electrospray ionization, piperine (PIP), a model hydrophobic medication, has been encapsulated within pCA-HT-chitosan with an encapsulation efficiency of around 80%. In vitro release experiments demonstrated a continuous release of PIP of >75 percent over 12 hours between pH 1.2 and 6.4.[24]

CONCLUSION

The purpose of this paper is to review some applications of chitosan derivatives for drug delivery. Based on research on chitosan and its derivatives, inserting hydrophobic moieties onto chitosan molecules will produce amphiphilic derivatives. Numerous drugs were loaded on these derivatives to improve their low solubility; other drugs have enhanced their bioavailability in addition to the use of these derivatives for control release of some drugs. Future explanations into the behavior of hydrophobic chitosan derivatives could be useful in finding further pharmaceutical applications.

REFERENCES

1. Toan NV, Ng CH, Aye KN, Trang TS, Stevens WF. Production of high-quality chitin and chitosan from preconditioned shrimp shells. Journal of Chemical Technology & Biotechnology: International Research in Process, Environmental & Clean Technology. 2006 Jul;81(7):1113-8.
2. Prabaharan M, Mano JF. Chitosan derivatives bearing cyclodextrin cavitiesas novel adsorbent matrices. Carbohydrate Polymers. 2006 Feb 3;63(2):153-66.
3. Prabaharan M, Borges JP, Godinho MH, Mano JF. Liquid crystalline behaviour of chitosan in formic, acetic, monochloroacetic acid solutions. InMaterials Science Forum

2006 (Vol. 514, pp. 1010-1014). Trans Tech Publications Ltd.
4. Prabaharan M, Rodriguez-Perez MA, De Saja JA, Mano JF. Preparation and characterization of poly (L-lactic acid)-chitosan hybrid scaffolds with drug release capability. Journal of Biomedical Materials Research Part B: Applied Biomaterials: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials. 2007 May;81(2):427-34.
5. Säkkinen M, Tuononen T, Jürjenson H, Veski P, Marvola M. Evaluation of microcrystalline chitosans for gastro-retentive drug delivery. European journal of pharmaceutical sciences. 2003 Aug 1;19(5):345-53.
6. Prabaharan M, Mano JF. Chitosan-based particles as controlled drug delivery systems. Drug delivery. 2004 Jan 1;12(1):41-57.
7. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers. International journal of Pharmaceutics. 1992 Jan 1;78(1-3):43-8.
8. Lueben, HL, Leeuw, BJD, Langemeyer, BW, Boer, AGD, Verhoef, JC and Junginger, HE. (1996). Mucoadhesive Polymers in Peroral Peptide Drug Delivery. VI. Carbomer and Chitosan Improve the Intestinal Absorption of the Peptide Buserelin *In-vivo*, Pharm. Res., 13(11): 1668–1672.
9. Jayakumar R, Prabaharan M, Reis RL, Mano J. Graft copolymerized chitosan—present status and applications. Carbohydrate Polymers. 2005 Nov 10;62(2):142-58.
10. Prabaharan M, Mano JF. Synthesis and Characterization of Chitosan-graft-Poly (3-(trimethoxysilyl) propyl methacrylate) Initiated by Ceric (IV) Ion. Journal of Macromolecular Science, Part A. 2007 Mar 1;44(5):489-94.
11. Sonia TA, Sharma CP. Chitosan and its derivatives for drug delivery perspective. Chitosan for biomaterials I. 2011:23-53.
12. Bonferoni MC, Sandri G, Rossi S, Ferrari F, Caramella C. Chitosan and its salts for mucosal and transmucosal delivery. Expert opinion on drug delivery. 2009 Sep 1;6(9):923-39.
13. Raphae¨l Riva, He´loı¨se Ragelle, Anne des Rieux, Nicolas Duhem, Christine Je´roˆme, and Ve´ronique Pre´at. (2011). Chitosan and Chitosan Derivatives in Drug Delivery and Tissue Engineering. Adv Polym Sci., 244: 19–44.
14. Yu JM, Li YJ, Qiu LY, Jin Y. Self-aggregated nanoparticles of cholesterol-modified glycol chitosan conjugate: Preparation, characterization, and preliminary assessment as a new drug delivery carrier. European Polymer Journal. 2008 Mar 1;44(3):555-65.
15. Park JH, Kwon S, Lee M, Chung H, Kim JH, Kim YS, Park RW, Kim IS, Seo SB, Kwon IC, Jeong SY. Self-assembled nanoparticles based on glycol chitosan bearing hydrophobic moieties as carriers for doxorubicin: in vivo biodistribution and anti-tumor activity. Biomaterials. 2006 Jan 1;27(1):119-26.
16. Huo M, Zhang Y, Zhou J, Zou A, Yu D, Wu Y, Li J, Li H. Synthesis and characterization of low-toxic amphiphilic chitosan derivatives and their application as micelle carrier for antitumor drug. International journal of pharmaceutics. 2010 Jul 15;394(1-2):162-73.
17. Yao Z, Zhang C, Ping Q, Yu LL. A series of novel chitosan derivatives: synthesis, characterization and micellar solubilization of paclitaxel. Carbohydrate Polymers. 2007 Apr 23;68(4):781-92.
18. Yu JM, Li YJ, Qiu LY, Jin Y. Self-aggregated nanoparticles of cholesterol-modified glycol chitosan conjugate: Preparation, characterization, and preliminary assessment as a new drug delivery carrier. European Polymer Journal. 2008 Mar 1;44(3):555-65.
19. Aiedeh KM, Al Khatib H, Taha MO, Al-Zoubi N. Application of novel chitosan derivatives in dissolution enhancement of a poorly water soluble drug. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2006 Apr 1;61(4):306-11.
20. Li Q, Du YZ, Yuan H, Zhang XG, Miao J, Cui FD, Hu FQ. Synthesis of lamivudine stearate and antiviral activity of stearic acid-g-chitosan oligosaccharide polymeric micelles delivery system. European journal of pharmaceutical sciences. 2010 Nov 20;41(3-4):498-507.
21. Liu S, Yang S, Ho PC. Intranasal administration of carbamazepine-loaded carboxymethyl chitosan nanoparticles for drug delivery to the brain. asian journal of pharmaceutical sciences. 2018 Jan 1;13(1):72-81.
22. Prabaharan M. Chitosan derivatives as promising materials for controlled drug delivery. Journal of biomaterials applications. 2008 Jul;23(1):5-36.
23. Song Y, Onishi H, Nagai T. Conjugate of mitomycin C with N-succinyl-chitosan: in vitro drug release properties, toxicity and antitumor activity. International journal of pharmaceutics. 1993 Aug 31;98(1-3):121-30.
24. Huang G, Liu Y, Chen L. Chitosan and its derivatives as vehicles for drug delivery. Drug Delivery. 2017 Nov 1;24(2):108-13.