International Journal of Innovation and Applied Studies
ISSN 2028-9324 Vol. 41 No. 4 Feb. 2024, pp. 1298-1304

http://www.ijias.issr-journals.org/

Synthesis and study of morphological structure of N-methyl, N-benzyl derivative of chitosan

F. Samira Safaraliyeva[1], B. Dilgam Taghıyev[2], A. Nizami Zeynalov[3]

[1]Ph.D student ARESM Institute of Catalysis and Inorganic Chemistry Named After Acad.M.Nagiyev, Azerbaijan

[2]Academician, Director ARESM of named after acad. M.Nagiyev Institute of Catalysis and Inorganic, Chemistry, Azerbaijan

[3]Prof., Head of Department of «Nanostructured Metal-Polymer Catalysist», ARESM Institute Catalysis and Inorganic Chemistry named after Acad. M. Nagiyev Baku AZ1143, Azerbaijan

ABSTRACT: The products obtained as a result of the simultaneous reaction of chitosan, a Schiff-based natural polyaminosaccharide, with formaldehyde and benzaldehyde were synthesized by the method indicated in the experimental part of the article. The two amine groups formed were then reduced with NaBH4 to give the corresponding tertiary amine derivative. The structure of the obtained product was characterized by scanning electron microscopy and elemental analysis was determined. The introduction of hydrophobic methyl and benzyl groups into the macromolecule of chitosan reduces the intermolecular interaction and hydrogen bonding. causes. This leads to an increase in the degree of polarization and better solubility of the functional groups of the product in the polar environment.

KEYWORDS: N-Benzyl N-Methyl Chitosan, Alkylation, Polymers, Drug delivery, levotiroxin-Na pentahydrate, Arylation.

1 INTRODUCTION

Polymers are widely used in drug delivery and formulation due to their many superior properties. Polymers used in colloidal drug delivery systems consisting of small particles have great advantages in drug delivery systems due to optimized drug loading and release properties [1]. Novel drug delivery systems include micelles, dendrimers, liposomes, polymeric nanoparticles, microcapsules, and lipoproteins. Recent advances in polymer-based encapsulation and controlled release of drugs help regulate drug administration by preventing under- or over-dosing [2]. These advanced systems play a promising role in improving biocompatibility, minimizing side effects, and preventing adverse effects in patients. Polymers have also become an integral part of drug delivery systems due to their improved pharmacokinetic properties. They have a better circulation time (circulation) than conventional small drug molecules, so they target tissues more precisely. Unlike the free drug, when it is used in a polymer-bound form, the polymer carrier leads to its longer-lasting effect, reduces its toxicity, and increases its safety and effectiveness by controlling the rate, time and place of drug release in the body. Also, drug delivery systems improve the pharmacodynamic and pharmacokinetic properties of the drug, e.g. increases plasma residence time, stability, improves solubility of small molecule drug and has a wide potential for targeted drug delivery [3]. Such polymers are mostly used in the field of polymer therapy and nanomedicine. [4,5]. In traditional drug delivery systems, preparations are used in the form of capsules, pills, coatings and encapsulation of biologically active drug molecules [1,2].

Polymers play a universal role in such compositions; they function as binding agents in capsules, film coating agents in tablets, and viscosity enhancers in emulsions and suspensions.

Polymeric drug delivery systems are used for controlled drug delivery that ensures patient compliance. The polymers used in these systems must be non-toxic, biodegradable and biocompatible. The most commonly used polymers in drug delivery include cellulose derivatives, poly-N-vinyl pyrrolidone, polyethylene glycol, etc. includes.

Most "smart" polymers are used for immobilization and transportation of biologically active compounds and drugs. Smart polymers have the ability to change their shape and properties depending on environmental conditions [6-10]. Various environmental irritants include temperature, pressure, pH, electric and magnetic fields, light, changes in density, ionic strength, reduction potential, etc. belongs to Dissolution, precipitation, swelling, change in conformation, as well as changes in hydrophobic and hydrophilic properties are the responses to such irritants.

Among the "smart" polymers, stimuli-responsive, pH-sensitive hydrogels are the most studied. These polymers have the ability to change their volume under the influence of various factors, especially external factors such as pH, temperature and ionic strength of the environment [11-15].

Among polymers, natural polymers are considered to be the most widely used materials that enhance the therapeutic effects of pharmaceutical preparations. Natural polymers are biodegradable, biocompatible and safe compared to synthetic polymers. Carbohydrate polymers are widely studied in biomedicine and pharmaceuticals. Polysaccharides include starch, pectin, guar gum, etc. It is used in the preparation of various types of medicinal forms. Preparations for the controlled separation of isoniazid and diltiazem were prepared by using quartz crystal. The importance of natural polymers is that they are not only used in traditional medicine, but also play a major role in the development of new delivery systems [16].

One of the natural polymers used in drug delivery is chitosan. Chitosan is used in various industries, including pharmaceuticals, lipid blocker and cholesterol-lowering additives [17], cosmetics, [18,19], medical tissue regeneration and wound healing preparations [18,19,20]. Among the various biopolymers available in nature, chitosan has attracted attention due to its unique antimicrobial properties [21]. In addition, chitosan is a non-toxic, biodegradable polymer with high biocompatibility, mucoadhesive properties, high absorption [22,23]. Due to such useful properties, chitosan is widely used in drug delivery systems [24,25]. Despite these attractive properties, chitosan also has its drawbacks, which include its poor mechanical properties and high degree of degradation. To overcome this problem, they are usually either sutured with occlusive agents or impregnated with other natural or synthetic polymers. The effect of various properties of chitosan is particularly important in terms of their utility in the development of innovative, multipurpose drug delivery systems [26]. Chitosan nanoparticles have anticancer properties, which have been confirmed by many researchers [27-39]. Evidence shows that they exhibit satisfactory biocompatibility with normal developing cells or tissues against oral [35], breast [36–39], prostate [40,41], glioblastoma [42], liver [43,44] and colon cancers. has been done. Apart from the release kinetics, the main evaluation of the anticancer effect of the emerging nanoparticles was to obtain the pH dependence of the release, which is very useful in targeted therapy [46]. Sensitivity to environmental pH helps overcome the problem of premature release of chemotherapeutic drugs during delivery. It eliminates the problems related to the difficulty of drugs entering cancer cells and side effects in normal organs. All these reports are extremely important; however, most of them require verification in the form of in vivo studies.

2 MATERIALS

Chitosan Mn=35 kDa (degree of deacetylation 85-87%), acetic aldehyde (≥99.0%), NaBH4 (purum p.a., ≥96%), acetic acid (Glacial), ethanol (95%), acetone (residue analysis, ≥ 99.9%), diethyl ether (containing 1 ppm BHT as inhibitor, anhydrous, ≥99.7%), NaCl (BioXtra, ≥99.5%), acetonitrile from Sigma-Aldrich (anhydrous, 99, 8%). Methyl iodide (99%) stabilized with copper is from Acros Organics.

3 PREPARATION OF HYDROGEL BASED ON N-METHYL, N-BENZYL CHITOSAN

The synthesis of N-methyl N-benzyl based hydrogel of chitosan was carried out in two stages - first, both alkylation and arylation were carried out at the same time, and then the reduction process was carried out [47]. The synthesis process was carried out according to the known methodology based on the Schiff reaction. 1.5 g is suspended in 60 ml of 2% CH3COOH solution (which retains 7.29 mmol of -NH2 groups). A mixture of 0.81 ml of formaldehyde and 0.74 ml of benzaldehyde is added drop by drop and intensively mixed. 30 min. then the color of the solution changes from light brown to a white milky suspension. Stirring is continued for 4 hours under inert nitrogen atmosphere. In the end, a viscous-fluid gel is formed. After coming to a boil, the mass is allowed to rest for 12 hours, 8 ml of solution dissolved in 0.36 g of NaBH4 is added dropwise and stirring is continued for 2-3 hours. At this time, the pH of the environment is 4.0-4.5. After 4 hours, the acidity of the solution is raised to pH=10 by adding 1M NaOH (50ml). As a result, the gel collapses. First, the gel is washed with distilled water until the filtrate is neutral. Then it is washed successively with alcohol and collapsed in acetone. Finally, after extraction with diethyl ether for 4 days in Soxhlet, it is freed from diethyl ether until a constant weight is obtained at 40-50 ºC.

4 CHARACTERIZATION OF N-METHYL, N-BENZYL CHLORIDE CHITOSAN BY SCANNING ELECTRON MICROSCOPY

Morphological surface images of chitosan, intermediate and final product were obtained by scanning electron microscope (SEM, JSM-6390, Japan).

5 CONCLUSION

In the course of the studies, the derivative of the protons in the amine groups in the chitosan macromolecule, in which both methyl and benzyl groups were included, was also used for the immobilization of levotrioxin-Na pentahydrate. The inclusion of both alkyl and aromatic radicals in the structure is of great interest in terms of properties of the newly obtained carrier, in terms of drug capacity, sorption, isotherms, thermodynamic parameters and release in certain environments for levotrioxin-Na pentahydrate. The synthesis of N-methyl N-benzyl chitosan in the presence of methanal and benzaldehyde in an acidic environment and UV, IR and X-ray studies of the structure of the obtained product were carried out in [47].

The synthesis of the main matrix was carried out according to the method indicated in the work, the formation process of N-methyl N-benzyl chitosan was studied depending on the molar ratio of its components, the density and nature of aldehydes, the average molecular mass of chitosan, and the reaction time. It was determined that, as shown in the work, the hydrogen atoms in the amino groups in the chitosan structure are not completely replaced, and the structural composition of the final product obtained corresponds to the following chemical structure:

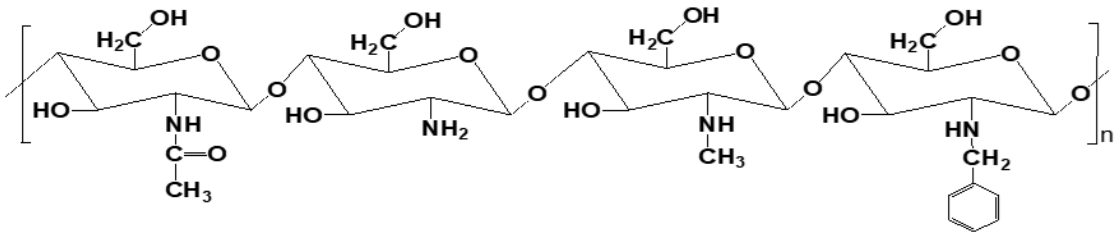

Fig. 1. Proposed chemical structural composition of N-benzyl N-methyl chitosan

Unlike the structural and spectroscopic analyzes conducted in the previous study [47], SEM morphological measurements of the product were performed and comparative analyzes were performed. SEM micrographs of the initial chitosan and the final product were recorded at the Institute of Biomaterials and Composites, Italy. First, the SEM surface morphologies of chitosan before alkylation, and then of the final product obtained after reaction with methanal and benzaldehyde were studied (Figure 2).

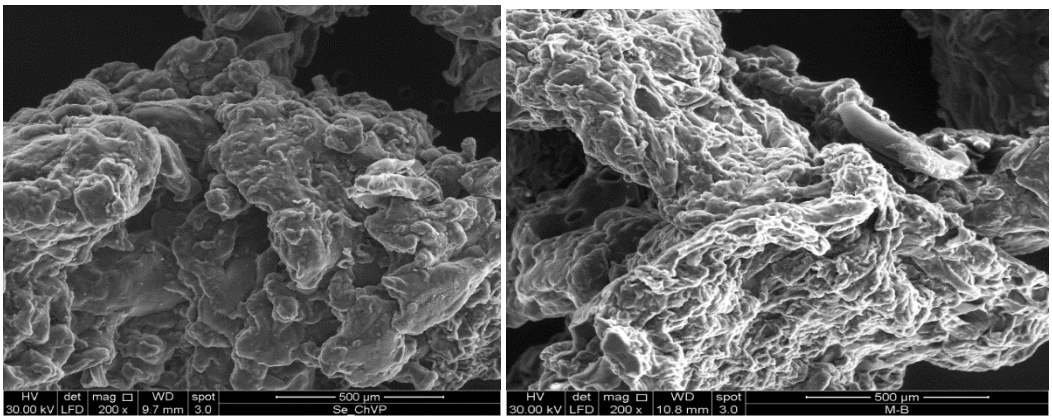

Fig. 2. SEM micrographs of chitosan (left) and N-methyl N-benzyl chitosan

As can be seen from the picture, the surface microstructures of the samples at the same 500 µm size and 200x magnification differ from each other. While the surface of chitosan appears smooth and microparticles, after alkylation, more wrinkles and unevenness are observed. Visible surface folds and densifications prove that the chitosan has undergone chemical

transformation. During the SEM analysis, the surface structure of the main product was viewed with 800 and 1500 magnification and clearer images were obtained (Figure 3.)

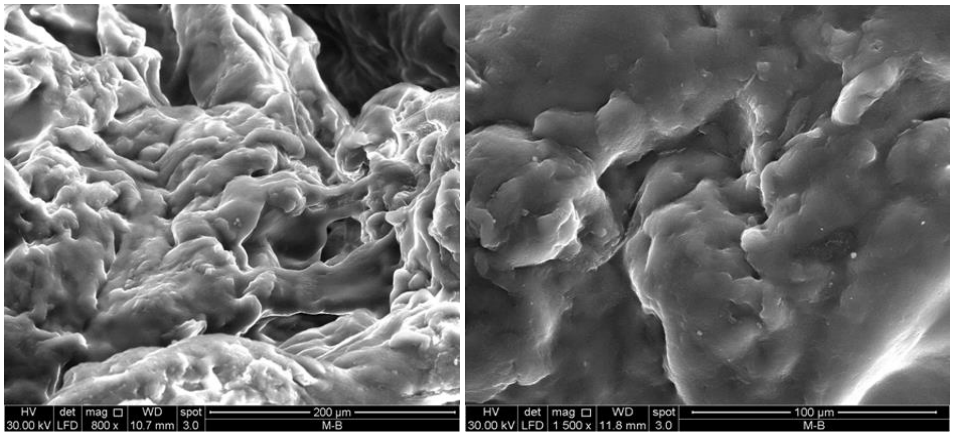

Fig. 3. SEM micrographs of N-methyl N-benzyl chitosan at different zoom states

As can be seen from the picture, the same similar microstructure was formed on all surface areas of the main product. This proves that alkylation occurred equally in all fragments of the polysaccharide macromolecule. Alkylation of N-methyl N-benzyl chitosan with aldehydes covered the entire chain and did not cause the formation of small particles resulting from the degradation and breakage of the polymer chain.

During the experiments, after the alkylation process, quaternization of N-methyl-N-benzyl chitosan and conversion from iodized derivative to chlorinated derivative was carried out, so SEM studies of that intermediate and final salt form were also conducted. Thus, the surfaces of N-methyl N-benzyl chitosan quaternized with methyl iodide and N-methyl N-benzyl chloride chitosan obtained from its ion replacement with NaCl have been proven to have different structures (Figure 4).

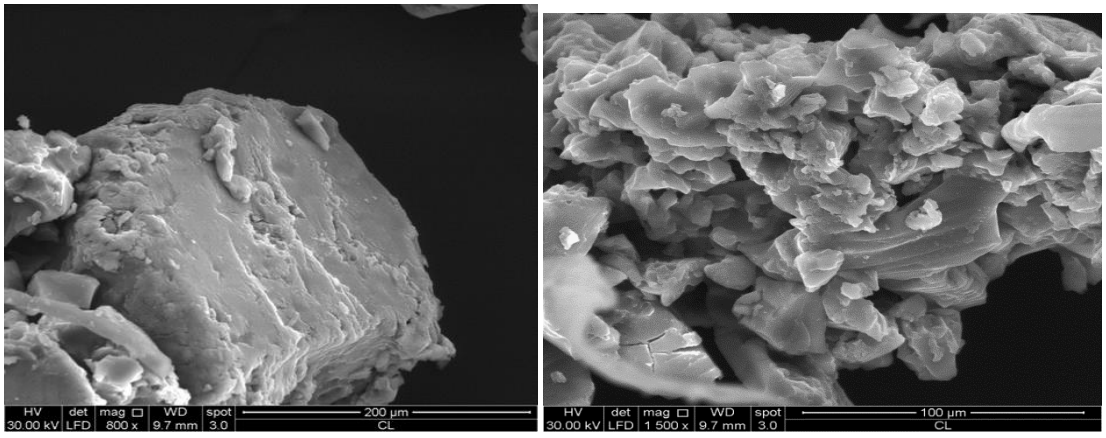

Fig. 4. SEM micrographs of N-methyl N-benzyl chitosan iodide (left) and N-methyl N-benzyl chitosan chloride

From the analysis, it was determined that when the main product was transformed into both iodized and chlorinated salt form, the crystallinity of the surface increased, and the sample showed itself in the characteristic form of crystalline substances with ionic bonds. This also proves that the main product quaternized with iodine and chlorine is in the form of an organic salt, and the ionic bond formed in the composition affects the surface morphology of the substance.

The obtained results were also manifested in the energy-dispersive spectra showing the elemental analysis of the samples. The following figure shows the energy-dispersive spectrum of N-methyl N-benzyl chitosan iodine by elements.

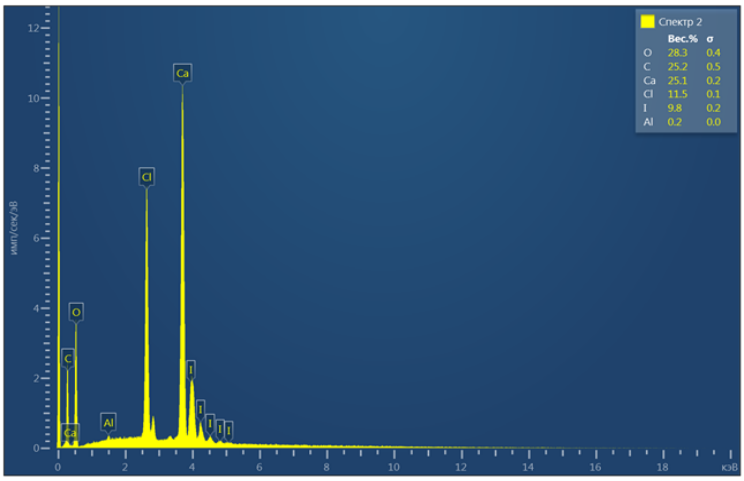

Fig. 5. Energy-dispersive spectrum of N-methyl N-benzyl chitosan iodine

As can be seen from the spectrum, since the sample was initially quaternized with iodine, the share of iodine in the composition is 9.8%. The percentage of carbon, oxygen and chlorine is 25.2, 28.3 and 11.5%, respectively. After ion substitution with NaCl, the change in the share of elements in the composition proves that the process is effective (Figure 6).

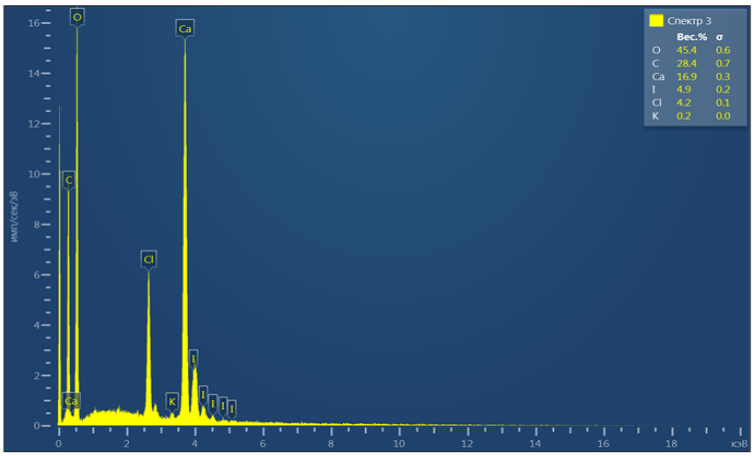

Fig. 6. Energy-dispersive spectrum of N-methyl N-benzyl chitosan chloride

REFERENCES

[1] Apurva Srivastava, Tejaswita Yadav, Soumya Sharma, Anjali Nayak, Akanksha Akanksha Kumari, Nidhi Mishra. Polymers in Drug Delivery. Journal of Biosciences and Medicines. Vol.4 No.1, January 2016.

[2] Liechty, W.B., et al. (2010) Polymers for Drug Delivery Systems. Annual Review of Chemical and Biomolecular Engineering, 1, 149-173.

[3] Duncan R; The dawning era of polymer therapeutics. Nature Reviews Drug Discovery, 2003; 2: 347–360.

[4] Schmaljohann, D. (2006) Thermo and pH Responsive Polymers in Drug Delivery. Advanced Drug Delivery Reviews, 58, 1655-1670.

[5] V. Sri Vajra Priya, Hare Krishna Roy, N jyothi, N Lakshmi Prasanthi. Polymers in Drug Delivery Technology, Types of Polymers and Applications. Scholars Academic Journal of Pharmacy (SAJP) Sch. Acad. J. Pharm., 2016; 5 (7): 305-308.

[6] Yang, W. and Pierstorff, E. (2012) Reservoir Based Polymer Drug Delivery Systems. Journal of Laboratory Automation, 17, 50-58.

[7] Sh.Z.Tapdiqov, N.A.Zeynalov, S.F.Humbatova, S.M.Mammedova. Spectroscopic Investigated Interaction between Silver Nanocomposites Based of poly-N-vinylpyrrolidone and Doxorubicine for Drug Delivering//Jornal of Chemistry and Chemical Engineering, 2014, vol.8. p.800-804.

[8] S.Z.Tapdigov. Immobilization of trypsin in polymer gels. Ph.D. Dissertation. Baku, 2011, p. 180.

[9] Sh.Z.Tapdigov, N.A.Zeynalov, D.B.Taghiyev, S.M.Mammedova.Investigation Chemical Interaction type of Polyacrylic acid based Hydrogel with Doxorubicin Hydrochloride, American Chemical Science J, 2016, v.12, p.1-9.
[10] Tapdigov Sh.Z. Polymer carriers based on poly-N-vinylpyrrolidone and arabinogalactan for trypsin immobilization/ Zeynalov, N.A., Ahmadov I.D. [etc.]//Azerbaijan Chemistry Journal, - 2009, 2, - p.39-44.
[11] O.E. Filippova. «Smart» polymer hydrogels. «Nature», No. 8, 2005 No. 8.
[12] Humbatova, S.F.Chitosan Polymer Composite material Containing of Silver Nanoparticle / Shamo Tapdiqov, Nizami Zeynalov [et. al]//Digest Journal of Nanomaterials and Biostructures, - 2016, 11 (1) - p. 39-44.
[13] Tapdiqov, Sh.Z. Optimal Conditions for Graft Radical Copolymerization of N-Vinylpirrolidon and 4-Vinylpiridine into Chitosan / Zeynalov, N.A., Tagiyev, D.B. [et al.]//Chemical Problems, - 2018, Vol.16, No4, - p.505-513.
[14] Mammadova S.M., Tapdigov Sh.Z., Humbatova S.F., Zeynalov N.A., Guliyeva A.R., Gasimov E.M., Research into Sorbtion Properties and Structures of Polymer Hydrogel Immobilized by Doxorubicin//Chemical Problems, 2018, 16 (3), p. 316-322.
[15] Sh.Z.Tapdiqov, N.A.Zeynalov, S.F.Humbatova, J.A.Nagiev, A.Isazadeh, M.Hasanova, S.Safaraliyeva. Content of arabinogalactan from cherry gum (Prunus avium) and as a polymer carrier for immobilization of trypsin//Asian Journal of Chemistry, İndia, 2016, vol.28, No 1, p.189-193.
[16] Manjit & Brahmeshwar Mishra. Natural Polymers for Drugs Delivery. Natural Polymeric Materials based Drug Delivery Systems in Lung Diseases pp 25–59.
[17] Moraru, C.; Mincea, M.M.; Frandes, M.; Timar, B.; Ostafe, V. A Meta-Analysis on Randomised Controlled Clinical Trials Evaluating the Effect of the Dietary Supplement Chitosan on Weight Loss, Lipid Parameters and Blood Pressure. Medicina 2018, 54, 109.
[18] Jiménez-Gómez, C.P.; Cecilia, J.A. Chitosan: A Natural Biopolymer with a Wide and Varied Range of Applications. Molecules 2020, 25, 3981.
[19] Guzmán, E.; Ortega, F.; Rubio, R.G. Chitosan: A Promising Multifunctional Cosmetic Ingredient for Skin and Hair Care. Cosmetics 2022, 9, 99.
[20] Song, E.-H.; Shang, J.; Ratner, D.M. Polysaccharides. In Polymer Science: A Comprehensive Reference; Elsevier: Amsterdam, The Netherlands, 2012; pp. 137–155.
[21] Pramanik, S.; Sali, V. Connecting the Dots in Drug Delivery: A Tour d'horizon of Chitosan-Based Nanocarriers System. Int. J. Biol. Macromol. 2021, 169, 103–121.
[22] Ładniak, A.; Jurak, M.; Palusińska-Szysz, M.; Wiącek, A.E. The Influence of Polysaccharides/TiO2 on the Model Membranes of Dipalmitoylphosphatidylglycerol and Bacterial Lipids. Molecules 2022, 27, 343.
[23] Ways, T.M.M.; Lau, W.M.; Khutoryanskiy, V.V. Chitosan and Its Derivatives for Application in Mucoadhesive Drug Delivery Systems. Polymers 2018, 10, 267.
[24] Hasnain, M.S.; Nayak, A.K. Chitosan as Mucoadhesive Polymer in Drug Delivery. In Chitosan in Drug Delivery; Academic Press: Cambridge, MA, USA, 2022; pp. 225–246.
[25] Elkomy, M.H.; Ali, A.A.; Eid, H.M. Chitosan on the Surface of Nanoparticles for Enhanced Drug Delivery: A Comprehensive Review. J. Control. Release 2022, 351, 923–940.
[26] Cao, S.; Deng, Y.; Zhang, L.; Aleahmad, M. Chitosan Nanoparticles, as Biological Macromolecule-Based Drug Delivery Systems to Improve the Healing Potential of Artificial Neural Guidance Channels: A Review. Int. J. Biol. Macromol. 2022, 201, 569–579.
[27] Karolina Jafernik, Agata Ładniak, Eliza Blicharska, Katarzyna Czarnek, Halina Ekiert, Agnieszka E. Wiącek, Agnieszka Szopa. Chitosan-Based Nanoparticles as Effective Drug Delivery Systems. Molecules 2023, 28 (4), 1963. https://doi.org/10.3390/molecules28041963.
[28] Tousian, B.; Ghasemi, M.H.; Khosravi, A.R. Targeted Chitosan Nanoparticles Embedded into Graphene Oxide Functionalized with Caffeic Acid as a Potential Drug Delivery System: New Insight into Cancer Therapy. Int. J. Biol. Macromol. 2022, 222, 295–304. [Google Scholar], [CrossRef].
[29] Mi, Y.; Chen, Y.; Gu, G.; Miao, Q.; Tan, W.; Li, Q.; Guo, Z. New Synthetic Adriamycin-Incorporated Chitosan Nanoparticles with Enhanced Antioxidant, Antitumor Activities and pH-Sensitive Drug Release. Carbohydr. Polym. 2021, 273, 118623. [Google Scholar], [CrossRef].
[30] Wang, F.; Li, J.; Tang, X.; Huang, K.; Chen, L. Polyelectrolyte Three Layer Nanoparticles of Chitosan/Dextran Sulfate/Chitosan for Dual Drug Delivery. Colloids Surf. B Biointerfaces 2020, 190, 110925. [Google Scholar], [CrossRef], [PubMed].
[31] Rajalakshmi, R.; Sivaselvam, S.; Ponpandian, N. Chitosan Grafted Fe-Doped WO3 Decorated with Gold Nanoparticles for Stimuli-Responsive Drug Delivery Systems. Mater. Lett. 2021, 304, 130664. [Google Scholar], [CrossRef].
[32] Sohail, R.; Abbas, S.R. Evaluation of Amygdalin-Loaded Alginate-Chitosan Nanoparticles as Biocompatible Drug Delivery Carriers for Anticancerous Efficacy. Int. J. Biol. Macromol. 2020, 153, 36–45. [Google Scholar], [CrossRef].

[33] Chen, X.; Bremner, D.H.; Ye, Y.; Lou, J.; Niu, S.; Zhu, L.M. A Dual-Prodrug Nanoparticle Based on Chitosan Oligosaccharide for Enhanced Tumor-Targeted Drug Delivery. Colloids Surf. A Physicochem. Eng. Asp. 2021, 619, 126512. [Google Scholar], [CrossRef].

[34] Cardoso, V.M.d.O.; Brito, N.A.P.d.; Ferreira, N.N.; Boni, F.I.; Ferreira, L.M.B.; Carvalho, S.G.; Gremião, M.P.D. Design of Mucoadhesive Gellan Gum and Chitosan Nanoparticles Intended for Colon-Specific Delivery of Peptide Drugs. Colloids Surf. A Physicochem. Eng. Asp. 2021, 628, 127321. [Google Scholar], [CrossRef].

[35] Matos, B.N.; Pereira, M.N.; Bravo, M.d.O.; Cunha-Filho, M.; Saldanha-Araújo, F.; Gratieri, T.; Gelfuso, G.M. Chitosan Nanoparticles Loading Oxaliplatin as a Mucoadhesive Topical Treatment of Oral Tumors: Iontophoresis Further Enhances Drug Delivery Ex Vivo. Int. J. Biol. Macromol. 2020, 154, 1265–1275. [Google Scholar], [CrossRef], [PubMed].

[36] Hassanpour, M.; Jafari, H.; Sharifi, S.; Rezaie, J.; Lighvan, Z.M.; Mahdavinia, G.R.; Gohari, G.; Akbari, A.; Hassanpour, M.; Jafari, H.; et al. Salicylic Acid-Loaded Chitosan Nanoparticles (SA/CTS NPs) for Breast Cancer Targeting: Synthesis, Characterization and Controlled Release Kinetics. J. Mol. Struct. 2021, 1245, 131040. [Google Scholar], [CrossRef].

[37] Liu, Q.; Tan, Z.; Zheng, D.; Qiu, X. PH-Responsive Magnetic Fe3O4/Carboxymethyl Chitosan/Aminated Lignosulfonate Nanoparticles with Uniform Size for Targeted Drug Loading. Int. J. Biol. Macromol. 2023, 225, 1182–1192. [Google Scholar], [CrossRef].

[38] Lohiya, G.; Katti, D.S. Carboxylated Chitosan-Mediated Improved Efficacy of Mesoporous Silica Nanoparticle-Based Targeted Drug Delivery System for Breast Cancer Therapy. Carbohydr. Polym. 2022, 277, 118822. [Google Scholar], [CrossRef].

[39] Chen, Q.; Jia, C.; Xu, Y.; Jiang, Z.; Hu, T.; Li, C.; Cheng, X. Dual-PH Responsive Chitosan Nanoparticles for Improving In Vivo Drugs Delivery and Chemoresistance in Breast Cancer. Carbohydr. Polym. 2022, 290, 119518. [Google Scholar], [CrossRef].

[40] Huang, S.J.; Wang, T.H.; Chou, Y.H.; Wang, H.M.D.; Hsu, T.C.; Yow, J.l.; Tzang, B.S.; Chiang, W.H. Hybrid PEGylated Chitosan/PLGA Nanoparticles Designed as pH-Responsive Vehicles to Promote Intracellular Drug Delivery and Cancer Chemotherapy. Int. J. Biol. Macromol. 2022, 210, 565–578. [Google Scholar], [CrossRef], [PubMed].

[41] Dhavale, R.P.; Dhavale, R.P.; Sahoo, S.C.; Kollu, P.; Jadhav, S.U.; Patil, P.S.; Dongale, T.D.; Chougale, A.D.; Patil, P.B.; Dhavale, R.P.; et al. Chitosan Coated Magnetic Nanoparticles as Carriers of Anticancer Drug Telmisartan: pH-Responsive Controlled Drug Release and Cytotoxicity Studies. J. Phys. Chem. Solids 2021, 148, 109749. [Google Scholar], [CrossRef].

[42] Kesavan, S.; Meena, K.S.; Sharmili, S.A.; Govindarajan, M.; Alharbi, N.S.; Kadaikunnan, S.; Khaled, J.M.; Alobaidi, A.S.; Alanzi, K.F.; Vaseeharan, B. Ulvan Loaded Graphene Oxide Nanoparticle Fabricated with Chitosan and D-Mannose for Targeted Anticancer Drug Delivery. J. Drug Deliv. Sci. Technol. 2021, 65, 102760. [Google Scholar], [CrossRef].

[43] El-Shafai, N.M.; Masoud, M.S.; Ibrahim, M.M.; Ramadan, M.S.; Mersal, G.A.M.; El-Mehasseb, I.M. Drug Delivery of Sofosbuvir Drug Capsulated with the β-Cyclodextrin Basket Loaded on Chitosan Nanoparticle Surface for Anti-Hepatitis C Virus (HCV). Int. J. Biol. Macromol. 2022, 207, 402–413. [Google Scholar], [CrossRef].

[44] Kandile, N.G.; Mohamed, H.M.; Nasr, A.S. Novel Hydrazinocurcumin Derivative Loaded Chitosan, ZnO, and Au Nanoparticles Formulations for Drug Release and Cell Cytotoxicity. Int. J. Biol. Macromol. 2020, 158, 1216–1226. [Google Scholar], [CrossRef].

[45] Idoudi, S.; Hijji, Y.; Bedhiafi, T.; Korashy, H.M.; Uddin, S.; Merhi, M.; Dermime, S.; Billa, N. A Novel Approach of Encapsulating Curcumin and Succinylated Derivative in Mannosylated-Chitosan Nanoparticles. Carbohydr. Polym. 2022, 297, 120034. [Google Scholar], [CrossRef], [PubMed].

[46] Rostami, E. Progresses in Targeted Drug Delivery Systems Using Chitosan Nanoparticles in Cancer Therapy: A Mini-Review. J. Drug Deliv. Sci. Technol. 2020, 58, 101813.

[47] Tapdigov. Sh.Z. Synthesis of N-Benzyl N-Methyl Chitosan by Simultaneous Alkylation of Formaldehyde and Benzaldehyde: Investigation of Chemical Structure and Composition//Oriental J. of Chemistry, 2020, 36 (2), p.254-261.