Review Article
Volume 15:S1, 2021

Journal of Molecular and Genetic Medicine

ISSN: 1747-0862

Open Access

Applications of Chitosan in the Field of Medicine

Kianirad S[1], Haddadi M[2]*, Saghafi MJ[3] and Adibi M[4]

[1]*Department of Biochemistry, Faculty of Biological Science, Tarbiat Modares University, Tehran, Iran*
[2]*Department of Life Sciences Engineering, Faculty of New Sciences and Technologies, University of Tehran, Tehran, Iran*
[3]*Department of Chemical and Petroleum Engineering, Sharif University of Technology, Tehran, Iran*
[4]*Department of Chemical and Petroleum Engineering, Hakim Sabzevari University, Sabzevar, Iran*

Abstract

Chitosan has special physicochemical properties such as short-term biodegradability, biocompatibility with human tissues, antibacterial and antifungal activity and non-toxicity, so it has high potential in various industries. In addition, biological properties such as bioadhesion, anti-cancer, antimicrobial, anti-inflammatory and analgesic, antioxidant, blood coagulant and cholesterol-lowering distinguish it from other biological polymers. It has been used as a safe compound in drug formulations for more than a decade. Different samples of chitosan can be prepared with different molecular weights as well as different degrees of deacetylation. In this way, it took advantage of the multi-stage de-acetylation process. In this case, the reaction temperature, reaction time and number of reaction steps are considered as effective parameters. Molecular weight and percentage of deacetylation play a decisive role in the biological properties of chitin, chitosan and their derivatives. So far, various derivatives of chitin and chitosan have been obtained. By manipulating the extraction steps (removing mineral and protein compounds), higher purity derivatives can be prepared. In other words, changes in the structural properties of the material are very effective on the final characteristics of the product**.**

Keywords: Chitosan • Chitin • Biopolymer • Cosmetics • Biomedicine • Desalting • Industrial applications

Introduction

Chitosan is a biopolymer obtained from the deacetylation process of the chitin base in the presence of potassium hydroxide or sodium hydroxide. Chitin is a natural polysaccharide and is found prominently in the skin of crustaceans such as crabs and shrimp, insect cuticles, and fungal cell walls. In general, crustacean skin is composed of 30-30% protein, 30-30% calcium carbonate and calcium phosphate, and 20-30% chitin. The process of chitosan production from shrimp skin includes three key processes of mineral removal, protein degradation and chitin deacetylation. The first two processes are related to the extraction of pure chitin and the last process is related to the conversion of chitin to chitosan [1]. These three processes are summarized below:

Chemical separation (extraction) of chitin from shrimp skin lesions involves two basic steps:

- Removal of minerals (separation of calcium carbonate and calcium phosphate) and de-proteinization using alkalis (protein separation). It is noteworthy that the removal of minerals and proteins to increase the purity of the final product and thus make the product more practical, including use in medical applications.
- If proteins are present in clinical biomedical applications, the immune system responds to these proteins.
- The final product grade also depends on the purity of the chitosan.

Conversion of chitin to chitosan (acetylation)

Chitin is generally exposed to a concentrated solution of sodium hydroxide (40-50%) at 100°C or higher to remove some or all of the acetyl groups from the chitin to obtain chitosan. This stage is considered as the key process of chitosan production, because chitosan is produced in this stage.

***Address for Correspondence:** Dr. Mozhdeh Haddadi, Department of Biochemistry, Tarbiat Modares University, Tehran, Iran; E-mail: mozhdeh_haddadi_777@yahoo.com*

Received 25 February 2021; **Accepted** 09 March 2021; **Published** 16 March 2021

In the three steps mentioned above, several factors affect the quality of chitosan produced, including reaction temperature, reaction time, stirring during the reaction, washing and concentration of materials used. Each of the mentioned parameters must be optimized during research and development in order to reach an acceptable level in terms of quality (appropriate to the application for which it is intended) and to have economic justification. The relationship between these parameters and product features is summarized below:

Concentration of alkaline solution in the processes of protein removal and deacetylation

In the process of protein removal, alkaline substances are used to split the cell wall and release its contents, including protein, which in the next step can be removed by washing the remaining protein materials. Alkalis also deacetylate chitin, even partially at low concentrations. Therefore, at this stage, this concentration should be adjusted to prevent excessive de-acetylation of chitin within the cell wall and its conversion to chitosan. Therefore, with increasing alkaline concentration in the deacetylation stage, we will see more deacetylation and increase the degree of deacetylation. Of course, it should be noted that with increasing concentrations of alkalis, we will see the breaking of polymer chains and a decrease in molecular mass [2].

Reaction temperature in the process of protein removal and deacetylation

As the reaction temperature in the mineral removal process increases, we will see acceleration in the reaction. Reaction temperature directly affects reaction time, molecular mass and degree of deacetylation. In the deacetylation process, with increasing temperature at the time of reaction and constant alkali concentration, we see an increase in the degree of deacetylation and a decrease in molecular mass [3].

Stirring during the process of protein removal and deacetylation: With the stirrer in the process of protein removal, we will see the acceleration of the reaction. In the deacetylation process, by stirring at temperature, concentration of raw materials and constant reaction time, we will see the production of chitosan with a higher degree of deacetylation and lower molecular mass [4].

Reaction time of protein removal and deacetylation

As the reaction time increases, more proteins are usually extracted, but this time at this stage should be optimal so that the deacetylation is not too much and less energy is consumed. Also increasing the reaction time while keeping other parameters constant will increase the degree of deacetylation and reduce the molecular mass. However, in order to increase the quality of the product and use it for biomedical, pharmaceutical, medical, and cosmetic applications, we may need to perform some side processes on the product to make it usable in that particular application. These processes include the removal of pigments, increasing the degree of deacetylation, and regulating or reducing molecular mass. Although the pigment removal process is included in the by-product of chitosan production, it determines the value of the final product, and the chitosan industry prefers this stage to exist. Therefore, due to the use of chitosan, a suitable method should be used for the synthesis and preparation of chitosan so that the ether bonds in the polymer are broken in such a way that they are suitable for use and in many cases the final product needs to be hydrogel [5-7]. The Table 1 shows the advantages and disadvantages of the methods used in chitosan extraction.

Applications of Chitosan

Chitosan is obtained by the deacetylation reaction of chitin. In the process of purification of chitin from salts, proteins and pigments, and deacetylation reaction, process conditions such as temperature, time and concentration of materials used are effective; Thus, the mentioned conditions directly affect the main properties of chitosan, including the degree of deacetylation and molecular mass. The degree of deacetylation and molecular mass of chitosan determine its application. Chitosan with 95% deacetylation percentage in biomedical and pharmaceutical industries, special chemical industries and Chitosan with 75% in industries such as food supplements, cosmetics, water purification and also Chitosan-grade 85 with lower degree of deacetylation in agro-industries textiles, fibers and paper production technology are used. The most important applications of this valuable biological substance can be specifically introduced [6] (Table 2).

Clinical applications of chitosan: Chitosan in scar differentiation, chitosan hydrogels are useful in chemical chemistry and experimental surgery, inhibition of matrix proteinases by chitosan, chitosan dressing is useful in homeostasis and angiogenesis, chitosan activates microphages for tumour-killing activity and interleukin-1 production and chitosan, which is used to prepare scaffolding and hydrogels.

Biomedical applications of chitosan: In wound healing, in different drug delivery systems, in gene delivery and tissue engineering.

Drug release systems

Controlled drug release technology emerged as a common commercial practice during the 1980s. This method increases the type of controlled release dose, safety, efficiency and reliability of drug treatment. The release of adsorbed or encapsulated drugs by polymers allows the planned release of the drug. Chitosan is non-toxic, easily bioabsorbable, and capable of forming gels at low pH. The formulation of the chitosan matrix in the acidic environment appears floating and gradually swells. All these properties of chitosan make this natural polymer an ideal choice for the controlled release formulation of the drug. Also, chitosan has anti-acid and anti-ulcer activity that reduces the discomfort and heartburn caused by the drug or Kelly prevents it [7].

Encapsulation of anti-hormonal drugs (glycyrrhizin) in chitosan nanoparticles: Glycyrrhizinic acid indirectly inhibits progesterone metabolism by inhibiting the production of triphosphoperidine nucleotides or directly by inhibiting the production of progesterone. Glyceric acid has therapeutic effects such as anti-inflammatory, anti-tumour and anti-hepatotoxic activity. Glycyrrhizic acid plays an important role in the biological activity of glycerin oral administration because after oral administration of glycerin, only glycyrrhizic acid is detected in the bloodstream. Chitosan nanoparticles have a unique capacity to accompany ammonium glycyrrhizinate. Surface modification with triphosphate and 3PEG glycerol anions is only possible with fabrication. The release of ammonium glycyrrhizinate from the particles has a pronounced explosive effect, followed by a slow-release phase. Nanoparticles may improve oral absorption of ammonium glycyrrhizinate [8].

Insulin encapsulation in chitosan nanoparticles: Insulin is directly internalized by enterocytes by contact with the small and large intestines, and storage of the drug in absorbed areas with mucosal adhesive carriers is a factor of cooperation. The effect of hypoglycemia and insulin level is greater than that of insulin obtained from insulin solution and the physical mixture of oral insulin and empty nanoparticles. The mechanism of insulin uptake appears to be a combination of insulin internalization through the vesicular structure in enterocytes and the uptake of nanoparticle-loaded insulin by culture medium cells [9].

Table 1. Advantages and disadvantages of the methods used in chitosan extraction [2].

Methods	Terms	Advantages	Disadvantages
Physical	Low product production Requires special equipment	Ease of scale increase	use of gamma radiation, X-ray, microwave Electrochemical reduction
Chemical	The difficulty of controlling the process, the high cost of the steps involved in the process of producing environmental pollution	cheap	Uses of strong acids or Oxidizers (HCl, HNO_2, HF, H_2O_2, $K_2S_2O_4$)
Enzymatic	High cost of production	Mass production of the product Convenient and safe process control	Use of enzymes (cellulose, chitosanase, etc.) at room temperature

Table 2. Applications of chitosan [6].

Industrial Applications	
Water engineering and wastewater treatment	Chelating agent to precipitate heavy metal ions / coagulating agent / paint removal / water purification
Paper making and packaging	Production of moisture-resistant and recyclable papers / creating a smooth, flexible and tear-resistant surface / food packaging due to its antimicrobial properties
Textile Industry	Antibacterial fibers suitable for fabrics with anti-allergy and anti-odor properties
Cosmetics	Absorption of ultraviolet rays and reduction of its adverse effects on the skin / used in hair care and beauty supplements such as: shampoo, mask, emulsion, varnish, cream, toothpaste, mouthwash, contact lens
Food industry	Increase the quality of the product as a food additive and component in packaging materials
Agriculture	Product maintenance / Reducing pathogens by preserving plant tissue / Increasing crop yields as a controlled release agent for compounds such as pesticides and ...
Chromatography	Absorbent in stationary phase for separation of phenols and chlorophenols in high performance liquid chromatography
Biomedical Applications	
Tissue Engineering	Temporary scaffolds to repair and stimulate new tissue growth / repair and regenerate cartilage, nerve cells and liver tissue
Heal wounds and burns	Accelerating effect on wound healing / burn healing due to its high oxygen permeability
Drug release	Transfer and release of proteins and peptides, growth factors, analgesics and anti-inflammatory drugs, anti-cancer drugs and antibiotics / Treatment of gene defects / Prevention of reducing the effect of drugs in the stomach by antacid activity

Table 3. Medicinal and cosmetic applications of chitosan [15].

Applications	Benefits
Pill production	Bonding, Prevent disintegration , coating, lubricating, diluting
Gels	Uniform release of the drug, increased absorption
Films and membranes emulsions	Drug release stabilizer
Microspheres and microcapsules	Mucosal adhesion, uniform delivery of drugs, increased penetration
Skin transfer delivery system	Increased penetration of epithelial cells, control of drug release
Drug delivery in the large intestine	Drug delivery through decomposition by colon bacteria
Delivery of peptide drugs	Improving the delivery of oral peptide and protein drugs
Gene and nucleic acid delivery	Safe and without virus system
Deodorant formulation	Skin compatibility, irritant, increase adhesion, perfume and deodorant
Skin and hair protection products	Preservative, hair thickener, moisturizer, soothing effect on the skin

Capsulation of ophthalmic drugs (cyclosporine a) on chitosan nanoparticles: Cyclosporine A has the ability to inhibit the activity of T-shaped cells in the treatment of diseases such as nephrotic syndrome, severe disease, biliary cystosis, aplastic anemia, rheumatoid arthritis, myasthenia gravis (muscle weakness) and dermatomyocitis. Further considerations in the last decade underscore the mentality that topical immunosuppression with cyclosporine is effective in treating ocular diseases. Despite the evidence that the target areas of the delivery systems are for the treatment of eye, corneal and conjunctival diseases, studies have so far been unsuccessful. Due to the positive charge, chitosan nanoparticles charged with this substance can come into close contact with the negatively charged corneal and conjunctival surfaces and thus deliver to the outer tissues of the eye without damaging the internal structures of the eye and systemic drug exposure increase. This contributes to the high level of drug effectiveness in the target tissues [10].

Burn healing and wound healing

Hundreds of thousands of people around the world need to be hospitalized every year for burn injuries. Accelerating healing and preventing infection is one of the goals of topical treatment of burn wounds. Inhibiting the transmission of microorganisms and removing wound secretions are among the ideal dressing properties. Fibers made of chitin and chitosan are very effective in preparing absorbable sutures as well as preparing fabrics for wound healing. Modified chitosan gel with silver nanoparticles can also be used as a good candidate for the treatment of secondary burns [11].

Tissue engineering

Another application of chitosan is in tissue engineering and for the production of scaffolds to replace damaged tissues with artificial skin. Accordingly, chitosan can be used in the regeneration of nerves, bones and cartilage. Chitosan acts as a biodegradable scaffold for new skin synthesis. Chitosan, due to its structural properties similar to glycosaminoglycans, may be suitable for the development of this layer for skin replacement [12].

Cosmetics

For cosmetic applications, where organic acids are usually good solvents, chitin and chitosan have fungicidal and antifungal properties. Chitosan is the only natural cationic gum that becomes viscous and concentrated when neutralized with acid. This substance is used in creams, lotions and permanent thickening hair lotions and also some of its derivatives are used as nail polish.

1. Chitosan-based creams
2. Innovative supplements based on chitosan
3. Chitosan face mask
4. Anti-wrinkle skin serum

Also, its bio and cationic adhesion properties have led to its use in hair protection products. It is also made on the basis of chitosan body shampoo. The Japanese company Chitocure has produced special hair and skin care products for pets using chitosan and its by-products [13].

Chitosan is effective in the health and healing of facial skin. The antifungal properties of chitin and chitosan have led to its use in a variety of creams and lotions. Because chitosan derivatives make the skin soft and supple, it is used in moisturizing creams as well as shampoo ingredients. Chitosan soap, without damaging the outer layers of the skin, in addition to removing cosmetics, oil and dirt, from the surface of the skin (especially glycerine soaps) causes health and freshness of the skin and does not have the negative effect of synthetic and chemical substances.

1. Skin lightener
2. Anti-acne and antibacterial
3. Antifungal and blackheads
4. Cleanses the skin without damaging the skin layers

Two important properties of chitin, chitosan and their derivatives have made them a good candidate for skin protection. A) They are positively charged electrically B) Their molecular weight is generally high and they cannot penetrate the skin. Therefore, they are used as moisturizers. They are also used in nail polish, creams, eye shadows, etc. provides examples of applications (Table 3) [14,15].

Discussion and Conclusion

The main obstacles and problems for the economic production of chitin and chitosan in the world are limitation of available natural resources and raw materials, low percentage of chitin in these sources and high costs of collecting and storing natural raw materials. The global demand for chitin is estimated at 4 tons per year, while the current production is 4 tons per year. The impossibility of further production is due to the limited resources available and the seasonality of crustacean fishing. Due to the importance and many applications of these materials, achieving a high percentage of quality product is considered by many countries. However, the compounds and derivatives of these biopolymers are used in the pharmaceutical industry, food, biotechnology and cosmetics as imports.

References

1. Yeul, Vijay S and Sadhana SR "Unprecedented Chitin and Chitosan: A Chemical Overview." *J Polym Environ* 21(2013): 606-614.
2. Jia, Zhishen and Dongfeng Shen. "Effect of Reaction Temperature and Reaction Time on the Preparation of Low-Molecular-Weight Chitosan using Phosphoric Acid." *Carbohydr Polym* 49(2002): 393-396.
3. De Queiroz, Antonino, Rayane Santa Cruz Martins, Bianca Rosa Paschoal Lia Fook and Vítor Alexandre de Oliveira Lima, et al. "Preparation and Characterization of Chitosan Obtained from Shells of Shrimp (*Litopenaeus vannamei boone*)." *Mar Drugs* 15(2017): 141.
4. El Knidri, H, Raja Belaabed and Abdellah Addaou. "Extraction, Chemical Modification and Characterization of Chitin and Chitosan." *Int J Biol Macromol* 120(2018): 1181-1189.
5. Younes, Islem and Marguerite Rinaudo. "Chitin and Chitosan Preparation from Marine Sources. Structure, Properties and Applications." *Mar Drugs* 13(2015): 1133-1174.

6. Synowiecki, Józef and Nadia Ali Al-Khateeb. "Production, Properties, and Some New Applications of Chitin and Its Derivatives." *Crit Rev Food Sci Nutr* 43(2004): 145-171.
7. Tian, Bingren, Shiyao Hua, Yu Tian and Jiayue Liu, et al. "Chemical and Physical Chitosan Hydrogels as Prospective Carriers for Drug Delivery: A Review." *J Mater Chem B* 8(2020): 10050-10064.
8. Bernela, Manju, Munish Ahuja and Rajesh Thakur. "Enhancement of Anti-Inflammatory Activity of Glycyrrhizic Acid by Encapsulation in Chitosan-Katira Gum Nanoparticles." *Eur J Pharm Biopharm* 105(2016): 141-147.
9. Wong, TW. "Chitosan and its Use in Design of Insulin Delivery System." *Recent Pat Drug Deliv Formul* 3(2009): 8-25.
10. Başaran, Ebru, Evrim Yenilmez, Murat Sami Berkman and Gülay Büyükköroğlu, et al. "Chitosan Nanoparticles for Ocular Delivery of Cyclosporine A." *J Microencapsul* 31(2014): 49-57.
11. Madhumathi, K, Sudheesh Kumar PT, Abhilash S and Sreeja V, et al. "Development of Novel Chitin/Nanosilver Composite Scaffolds for Wound Dressing Applications." *J Mater Sci Mater Med 21*(2010): 807-813.
12. Rodríguez-Vázquez, M, Vega-Ruiz B, Ramos-Zúñiga R and Saldaña-Koppel DA, et al. "Chitosan and its Potential Use as a Scaffold for Tissue Engineering in Regenerative Medicine." *Biomed Res Int* 10(2015): 1-15.
13. Yilmanz, F, Gizem Celep and T Gamze. "Nanofibers in cosmetics." In: Nanofiber Research-Reaching New Heights, 1st (edn), InTech Open, London, United Kingdom.
14. Savary G, Grisel M and Céline Picard. "Cosmetics and Personal Care Products." In *Nat Poly* 10(2016): 219-261.
15. Morin-Crini, Nadia, Eric Lichtfouse, Giangiacomo Torri and Grégorio Crini et al. "Applications of Chitosan in Food, Pharmaceuticals, Medicine, Cosmetics, Agriculture, Textiles, Pulp and Paper, Biotechnology, and Environmental Chemistry." *Environ Chem Letters* 17(2019): 1667-1692.

How to cite this article: Kianirad, Soheil, Mozhdeh Haddadi, Mohammad Javad Saghafi and Mostafa Adibi. “Applications of Chitosan in the Field of Medicine.” J Mol Genet Med 15(2021): 484.