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THIOLATED CHITOSAN FOR BIOMEDICAL APPLICATION

BY

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Abstract. The chitosan is synthesized from chitin by partially de-acetylation. The free amino groups are very important in chitosan modifications. The biodegradability, non-toxicity, bacteriostatic and biocompatibility proprieties represent the reasons why it is promising in different applications. The functionalization with thiol groups with different reagents improved its qualities. The Elman’s reagent method, the Fourier Transform Infrared (FTIR) spectra, the Nuclear Magnetic Resonance Spectroscopy (NMR), the X-ray diffraction (XRD) analysis and the thermogravimetric analysis (TGA)have shown improvements of the characteristics according to the reagents used. In vivo studies have indicated the high degree of viability of cells tested with thiolated chitosan or formulations based on thiolated chitosan. The modified chitosanis used for nanoparticles, liposomes coating due the strong mucoadhesive properties and in the compositions of hydrogels, matrix tablets, hydrogels and nanoparticles for drug release over different mucous membranes in various diseases, for antibacterial activity or for wastewater treatment like as bio-sorbent for methyl orange.

Keywords: thiolated derivates; biodegradability; mucoadhesive; biocompatibility; drug release.

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1. Introduction

Chitosan is an alternating linear copolymer composed of β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine. It is cationic polysaccharide obtained from the shells of crustaceans, in particular crabs and shrimps, by the alkaline partially de-acetylation of chitin (Fig. 1). The solubility of the polymer is influenced by the degree of deacetylation. The amino groups are very important for the immobilization of thiol groups (Britto and Campana-Filho, 2007; Sarti and Bernkop-Schnurch, 2011). Chitosancan be widely used for the preparation of biomaterials with adjustable properties through physical interaction and chemical modification because has two hydroxyl groups and one amino group on each structural unit (Peptu *et al*., 2019).

Chitosan is one of the most important candidates for biomedical applications because of the biological properties like a bacteriostatic, haemostatic, fungistatic, anticarcinogenic and anticholesteremic properties. Biodegradability, biocompatibility and non-toxicity proprieties are essential, chitosan being a natural polymer, approved by the Food and Drug Administration (Peptu *et al*., 2019; Diab *et al*., 2012).

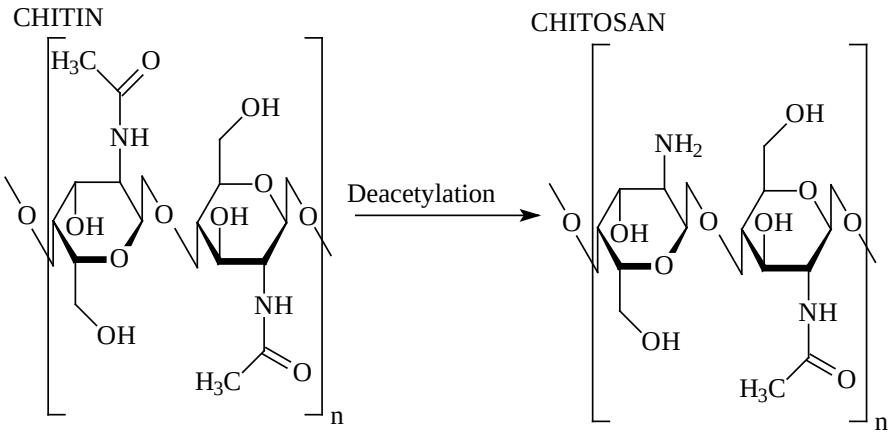

Fig. 1 – Chitin de-acetylation (Peptu *et al*., 2019).

The biological proprieties are essential in medical applications. The mucoadhesion proprieties have the explanation in hydration with water molecules. The electrostatic interactionof positively charged amine groups of chitosan and negatively charged functionalities of the mucus gel, with hydrogen bonds are the way for mucus to attract the water molecules (Peptu *et al*., 2019; Nanaki *et al*., 2017).

Chitosan presents useful proprieties like increased permeation for chitosan with high degree of de-acetylation and molecular weight, inhibition of

the pump efflux – thiolated chitosan derivatives presented improved oral delivery, transfection activity of big nucleic acid molecules through different physiological and anatomical barriers, active polymer for bypassing biological barriers for cellular level and tissue level, skin barrier – the electrostatic bonds improve the transdermal drug passage, interactions with anionic drugs (Peptu *et al*., 2019).

2. Thiolated Chitosan - Chemical Reactions, New Proprieties and Advantages

Thiolated polymers were studied for applications in some fields of biomedicine. In particular, the free thiol groups of thiolated chitosan along his backbone present some improved proprieties. For biocompatibility, non-toxicity and biodegradability features, it was considered very interesting for tissue engineering (Moreno *et al*., 2017). An additional advantage is to improve drug penetration. Permeation enhancement, strong antibacterial (Stefanov *et al*., 2018) and in situ gelling capacity represent others promising properties. This derivative polymer is able of forming covalent bonds with the mucus constituents (Sarti and Bernkop-Schnurch, 2011).

By now, many thiolated chitosan derivatives have been synthesized: chitosan-thioglycolic acid conjugate (Fig. 4), chitosan-L-cysteine conjugate (Fig. 3), chitosan-N-acetylcysteine conjugate, chitosan-2-thio-ethyl-amidine conjugate, chitosan-glutathione conjugate, chitosan-4-mercaptobenzoic acid, chitosan-6-mercaptonicotinic acid, chitosan-thiolactic acid conjugate (Fig. 2), chitosan-homocysteinethiolactone conjugate (Fig. 5) (Sarti and Bernkop-Schnurch, 2011).

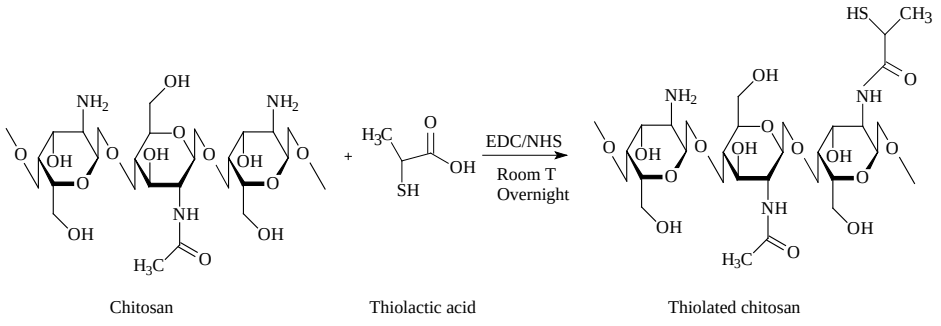

Fig. 2 – The synthesis of thiolated chitosan by reaction with thiolactic acid (Guaresti *et al*., 2019).

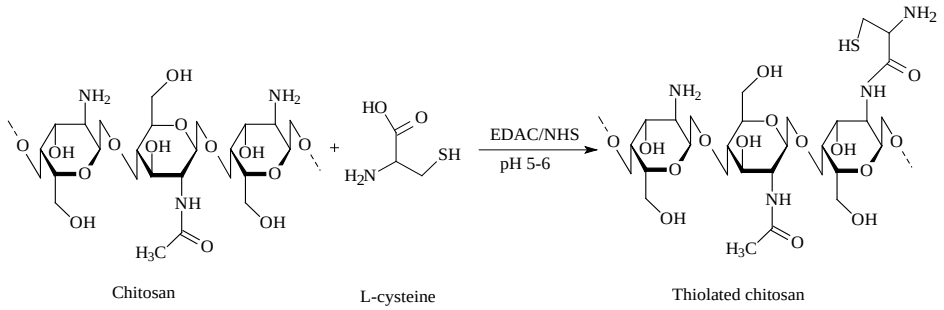

Fig. 3 – The synthesis of thiolated chitosan by reaction with L-cysteine (Li *et al*., 2017).

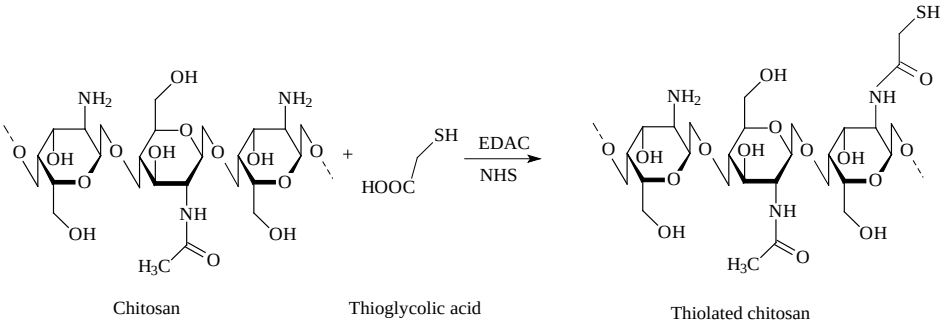

Fig. 4 – The synthesis of thiolated chitosan by reaction with Thioglycolic acid (Zhao *et al*., 2016).

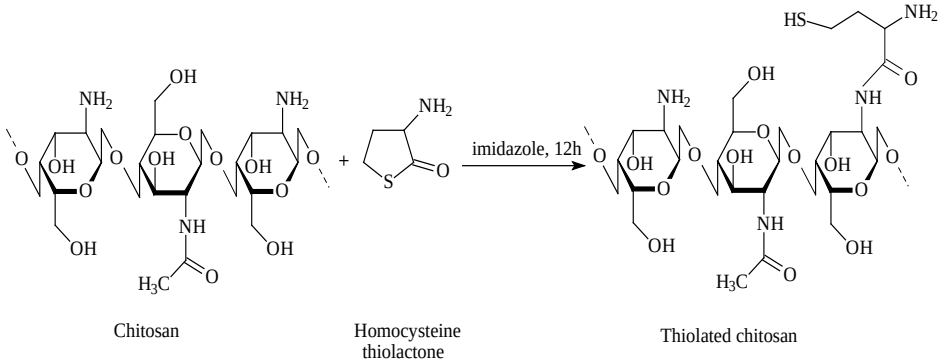

Fig. 5 – The synthesis of thiolated chitosan by reaction with homocysteinethiolactone (Juntapram *et al*., 2012).

The mucoadhesive properties with the ability to extent the sitting time of drugs on different types of mucosa represent an advantage in drug delivery which permit an enhancement in the absorption level of the drug. The formation of inter-

and/or intra-molecular disulfide bonds under physiological pH, inside the polymeric matrix proves a better in situ gelling properties for thiolated chitosan. For different routes: nasal drug delivery or intestinal drug delivery, thiolated chitosan has been shown an increase of the paracellular permeability of drugs determined by the opening of tight junctions. This aspect along with the mucoadhesive properties demonstrates a great permeation-enhancing effect. Moreover, thiolated chitosan has a low systemic side effects due lack of toxicity. The inhibition of efflux pumps depends on the interaction of the reagent subunit of the transmembrane region of P-glicoprotein - proteins which are efflux pumps from different tissues like liver, kidney, intestine and brain, with the thiol moieties expressed on the polymeric backbone. For stable and unitary drug formulation, controlled release is essential in quickly metabolized and eliminated from the body after their administration. Thiolated chitosan has these controlled drug release properties. (Sarti and Bernkop-Schnurch, 2011; Meng *et al*., 2016).

3. Thiolated Chitosan's Characterization. Results

Thiol functionalization of chitosan was obtained through conjugation of chitosan with thiol reagent like thiolactic acid (Guaresti *et al*., 2019), L-cysteine (Li *et al*., 2017; Moreno *et al*., 2017; Netsomboon *et al*., 2017; Medeiros Borsagli *et al*., 2018; Zahir-Jouzdani *et al*., 2018), N-acetyl-L-cyteine (Fernandes *et al*., 2013; Liu *et al*., 2020; Teng *et al*., 2010), thioglycolic acid (Zhao *et al*., 2016; Kazemi *et al*., 2019; Singh *et al*., 2015; Iqbal *et al*., 2012; Nanaki *et al*., 2017; Mahmood *et al*., 2017), homocysteinethiolactone (Juntapram *et al*., 2012), 2-iminothiolane (Liu *et al*., 2016), 6-mercaptonicotinic acid (Moreno *et al*., 2017), 11-mercaptoundecanoic acid (Medeiros Borsagli *et al*., 2019). The thiolated chitosan obtained was dialyzed and then lyophilized in all these cases, for to be used in different applications.

The amount of thiol groups immobilized on chitosan was generally determined spectrophotometrically at UV-Vis using Ellman's reagent: 5, 5'-dithiobis(2-nitrobenzoic acid). The methods are slightly different due to the reagent used in chitosan thiolation. A calibration curve for thiol groups reagent is established according to the same protocol and at a specific absorbance of this reagent. Then, the calibration curve for the thiolated chitosan will be performed and used to determine the amount of thiol groups including those of disulphide bonds. (Zhao *et al*., 2016), (Netsomboon *et al*., 2017). It is noticeable the very high content of thiol groups of thiolated chitosan with thiolactic acid – 2162 [$\mu mol \cdot g^{-1}$] (Guaresti *et al*., 2019) and of thiolated chitosan with L-cysteine (N-acetylated, previously, with 11-mercaptoundecanoic acid) - (2218 ± 100) [$\mu mol \cdot g^{-1}$]. (Medeiros Borsagli *et al*., 2018). The N-acetylation of chitosan using 11-mercaptoundecanoic acid and next, the thiolation with N-hydroxysulfosuccinimide (sulfo-NHS) and N-(3-dimethylaminopropyl)-N'-

ethylcarbodiimide hydrochloride was presented a high content of thiol groups too - (1637 ± 37) [μmol·g^{-1}] (Medeiros Borsagli *et al*., 2019).

The Fourier Transform Infrared (FTIR) spectra of samples: chitosan and thiolated chitosan qualitatively confirmed the thiolation of chitosan. The presence of new characteristic absorption bands as a signals of sulphur-based groups at 796 - 730 cm^{-1} (-S-C), of thiol groups at 2680-2500 cm^{-1} (-S-H) and of carbonyl groups at 1742 - 1630 cm^{-1} (-C=O) proved the success of the modification (Medeiros Borsagli*et al*., 2018), (Zhao *et al*., 2016; Guaresti *et al*., 2019; Prabaharan and Gong, 2008; Mahmood *et al*., 2017; Liu *et al*., 2016; Liu *et al*., 2020; Juntapram *et al*., 2012; Nanaki *et al*., 2017; Kazemi *et al*., 2019).

Chitosan and its thiolated derivatives have been analysed also by Nuclear Magnetic Resonance Spectroscopy (NMR), especially using ^{1}H NMR spectroscopy. For the most part was used deuterium water as solvent, thiolated chitosan being soluble in water. The new peak of methylene protons at 2.65 - 2.92 ppm in the spectrum of modified chitosan and others peaks detected at 2.25 - 2.43 ppm for thiol groups indicated the successful of functionalization. (Medeiros Borsagli *et al*., 2018; Li *et al*., 2017; Liu *et al*., 2016; Juntapram *et al*., 2012; Zhao *et al*., 2016; Liu *et al*., 2020; Prabaharan and Gong, 2008).

The crystalline structure was study with the help of X-ray diffraction (XRD) analysis. In almost every cases, chitosan present two crystal form: one have the peak at 2θ = 10.3° - 10.6° and two at 2θ = 19.78°- 20.08°, which is the strongest peak. After thiolation, the most intense peak disappeared and the other was weaker. This process decreased the degree of crystallinity, perhaps due to smaller amount of the free amino groups, thus the loss of the hydrogen bonding. Thiolated chitosan had an amorphous form which can be an advantages in its applications (Juntapram *et al*., 2012; Guaresti *et al*., 2019; Nanaki *et al*., 2017).

By using the thermogravimetric analysis (TGA) the thermal stability of pure chitosan and thiolated chitosan were investigated. While chitosan showed one stage weight loss at 26 - 60°C for water loss and the second stage at 208-288°C for degradation of backbone, thiolated chitosan had three stages. In the first and the third stages was observed a progressive water loss and in the second stage between 192 and 262°C, a degradation of thiol groups occurred. The thiolated chitosan degradation started earlier compared to pure chitosan, which indicated a lower thermal stability because the ordered structure was disrupt (Juntapram *et al*., 2012; Guaresti *et al*., 2019; Nanaki *et al*., 2017).

4. Formulations of the Thiolated Chitosan for Biomedical Applications

Thiolated chitosan with mucoadhesive properties with different precursors for drug delivery system (Juntapram *et al*., 2012) has been tested for treatment of ocular calcium deposits (Netsomboon *et al*., 2017) or for corneal

injuries as anti-angiogenic and anti-fibrotic and therapeutics with promising results (Zahir-Jouzdani *et al*., 2017). Also, for gene and drug delivery applications, the thiol modified chitosan doesn't prove any cytotoxicity on normal gingiva human cells (Kazemi *et al*., 2019).

Zhao *et al.* have demonstrated that chitosan modified with thioglycolic acid was a very good application potential vascular stent surface coating because the cytotoxicity assay showed stronger cell adhesion and repair (Zhao *et al*., 2016).

Another application for chitosan functionalized with thiol groups was highlighted for antibacterial activity due the interactions with the negatively charged phospholipid heads and next, the phospholipid tails (Fernandes *et al*., 2013).

4.1. Nanoparticles

Thiolated chitosan nanoparticles enhance with selegiline hydrochloride were studied for the nose-to-brain delivery in antidepressant activity. The results proved that these nanoparticles attenuated oxidative stress and the activity of the mitochondrial complex was recovered (Singh *et al*., 2014).

In a study, through the electrostatic interaction between negative charge of poly(β-amino ester)sand positive charge of thiolated chitosan, it was prepared polyelectrolyte complexes nanoparticles. Their properties of mucus permeability and mucoadhesion were evaluated at different amounts of the thiol groups (Oh and Borrós, 2016). Rahbarian et al. have observed that the thiolated N-triethyl chitosan had a great potential to achieve insulin nanoparticles for buccal delivery because it had a good permeability and viability (Rahbarian *et al*., 2018).

In another study, these thiol derivatives of chitosan showed an important contribution in oral drug delivery. For eradication of Helicobacter pylori nanoparticles with amoxicillin have been testes and they present a pH-sensitive profile and excellent mucoadhesive properties (Arif *et al*., 2018).

4.2. Thiolated Chitosan as Coating Agent

Li *et al.* was studied the coating of curcumin liposomes with thiolated chitosan that improved their stability for potential drug delivery system. After 24 h, the treatment of cells with curcumin liposomes coated with thiolated chitosan performed a higher viability than the others treated only with curcumin. And these formulations proved a cytotoxicity which depends of concentrations and time (Li *et al*., 2017).

An attempt was made to cover some microspheres with thiolated chitosan for intranasal delivery of paliperi done. The coating layer of these microspheres embedded with mesocellular silica foam, on the drug release rate had no influence (Nanaki *et al*., 2017).

Also, a micelle surface was decorated with thiol groups for improving the mucoadhesive properties for drug release over intestinal and vaginal mucosa. The drug from simple micelles was released faster than the drug from micelles coated with thiolated chitosan (Mahmood *et al*., 2017).

4.3. Hydrogels

Thiolated chitosan was used, also, for a wide range of hydrogels with various applications. For example, Yang et al. was evaluated an in situ hydrogel with excellent biodegradation properties and a marked sustained release in treatment of solid tumors (Yang *et al*., 2019).

For tissue engineering was investigated in situ cross-linked hydrogels using Michael addition reaction with good biodegradability, rheological and swelling properties (Guaresti *et al*., 2019) and with the viability cells for hydrogel without poly(ethylene glycol) higher than with poly(ethylene glycol) (Teng *et al*., 2010).

Cartilage repair represent another important application for thiolated chitosan, which with silk fibroin realized dual network hydrogels. These hydrogels supported well the growth of chondrocytes (Liu *et al*., 2020).

Also, Liu et al. prepared a thermo-sensitive hydrogel with water soluble thiolated chitosan for bone tissue engineering as a injectable scaffold. The simple hydrogel had lower numbers of osteocalcin – positive osteoblasts than the hydrogel loaded with peptide 24 (Liu *et al*., 2016).

Other researchers have studied the versatility of thiolated chitosan hydrogels for delivering proteins and the stability of realized in treatment of ocular diseases. More precisely, the delivering proteins and the stability of realized were highlighted and they found that higher protein retention proved a higher crosslinking density (Moreno *et al*., 2017).

A gel formulation based on chitosan-thioglycolic acid conjugate was realized for improving the intestinal uptake of peptides because it presented an increased permeation and mucoadhesive properties (Iqbal *et al*., 2012).

Madeiros Bordagli et al. have developed 3D bio – scaffolds based on thiolated chitosan with applications in cartilage repair because it presented over 90% of the cell viability responses (Medeiros Borsagli *et al*., 2018) and for antibacterial activity and wastewater treatment like as bio-sorbent for methyl orange, which showed in neutral conditions, the highest methyl orange uptake (Medeiros Borsagli *et al*., 2019).

4.4. Matrix Tablets

Other formulations for chitosan conjugate with thiol groups are matrix tablets for controlled drug delivery carriers. Thus, the presence of thiolated

carboxymethyl chitosan–g-β-cyclodextrin improved the swelling and muchoadhesive properties (Prabaharan and Gong, 2008).

5. Conclusions

Chitosan is an important polysaccharide due to the biocompatibility, non-toxicity, mucoadhesive and biodegradability features. The chitosan functionalization with thiol groups from different precursors improved these properties. With an amorphous form, thiolated chitosan presented an amount higher or lower of thiol groups according with the reagents involved. It can be used in various biomedical applications, depends on the type of the formulations and their properties. The efficacy and huge biomedical potential of thiolated chitosan in most of cases have been demonstrated by the in vivo studies.

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CHITOSAN TIOLAT PENTRU APLICAȚII BIOMEDICALE

(Rezumat)

Chitosanul se obține din chitină prin deacetilare parțială. Grupările aminice libere sunt foarte importante pentru modificările chimice ale chitosanului. Proprietățile de biodegradabilitate, netoxicitate, bacteriostatice și biocompatibilitate reprezintă motivele pentru care este promițător în diferite aplicații. Funcționalizarea cu grupări tiolice, utilizând reactivi diferiți i-a îmbunătățit calitățile. Metoda reactivului Elman, spectroscopia în infraroșu al transformatei Fourier (FTIR), spectroscopia de rezonanță magnetică nucleară (RMN), analiza difracției cu raze X (XRD) și analiza termogravimetrică (TGA) au arătat îmbunătățiri ale caracteristicilor în funcție de reactivii utilizați. Studiile *in vivo* au indicat gradul ridicat de viabilitate a celulelor testate cu chitosan tiolat sau formulări pe bază de chitosan tiolat. Chitosanul modificat este utilizat

pentru obținerea de nanoparticule, pentru acoperirea lipozomilor datorită proprietăților mucoadezive puternice și în compozițiile de hidrogeluri, tablete, hidrogeluri pentru eliberarea medicamentelor pe diferite membrane mucoase în diferite afecțiuni, pentru activitatea antibacteriană sau pentru tratarea apelor uzate, precum bio - sorbent pentru metilorange.