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A review: Properties and Applications of Chitosan in Biomedicine

Ola Al-Bhadly Intidhar Mohammed Mnati
Ola.L.h@ihcoedu.uobaghdad.edu.iq
Department of Biology, Collage of Education for Pure Science (Ibn Al- Haitham),
University of Baghdad, Baghdad, Iraq.

Abstract :

Chitosan has sparked widespread interest due to its characteristics and potential applications. Each year, the number of papers and patents on this polymer grows. Chitosan exhibits all of the major medical qualities, including biocompatibility, biodegradability, and hydrophilicity. Chitosan is currently gaining a lot of attention in a variety of fields and applications, such as a drug tablet binder, antioxidant, antimicrobial, antifungal, anti-inflammatory, wound healing, drug delivery and immune therapy. Moreover, chitosan exhibits anticancer effect by stimulating the immune system and strengthening it when combined with anticancer medications thus chitosan's exceptional biological features offer unique prospects for biomedical and pharmaceutical applications Three reactive or functional groups make up chitosan so, numerous chemical alterations are potential resulting in polymers with unique characteristics and behaviors. Chitosan's characteristics have been improved by nanoparticles synthesis. The purpose of using chitosan nanoparticles is to increase the therapeutic efficiency of some drugs that are affected by human body activities. The most interesting character of nanoparticles for its small size and quantum dots estimation influence may make chitosan nanoparticles display prevalent uses. In this review, we discuss some of the main biological properties of chitosan and the relationship with the physicochemical properties of the polymer and the purpose of this review is to give an overview of chitosan applications

Keywords: Chitosan, chitin, Polysaccharide, Deacetylation, Nanoparticles, Biomedicine.

مراجعة: خصائص وتطبيقات الشيتوزان في الطب الحيوي

علا لواء حسن البهادلي ، انتظار محمد مناتي
قسم علوم الحياة، كلية التربية للعلوم الصرفة (ابن الهيثم)، جامعة بغداد، بغداد، العراق.

مستخلص

اثار الشيتوزان اهتماما واسع النطاق بسبب خصائصه وتطبيقاته المحتملة وفي كل عام يتزايد عدد الأوراق البحثية وبراءات الاختراع المتعلقة بهذا البوليمر. يمتلك الشيتوزان معظم الصفات الطبية الرئيسية ومنها التوافق الحيوي، والقابلية للتحلل الحيوي، والمحبة للماء. يحظى الشيتوزان حاليا بالكثير من الاهتمام في الكثير من المجالات والتطبيقات الطبية المتنوعة وتتمثل مادة رابطة في أقراص الدواء ومضاد للأكسدة والميكروبات والفطريات والالتهابات ويعمل أيضا على التئام الجروح فضلا عن دوره في توصيل الأدوية والعلاج المناعي علاوة على ذلك، حيث يظهر الشيتوزان تأثيرا مضادا للسرطان عن طريق تحفيز جهاز المناعة وتقويته عند دمجه مع الأدوية المضادة للسرطان وبالتالي فإن الخصائص البيولوجية والاستثنائية للشيتوزان توفر آفاقا فريدة من نوعها في التطبيقات الطبية الحيوية والصيدلانية. هنالك ثلاث مجاميع تفاعلية أو وظيفية تعمل على تكوين تركيب الشيتوزان والتي من خلالها تجرى بعض التحويرات الممكنة في تركيبة الكيميائي لمواكبة التطبيق المستخدم اليه. تم تحسين خصائص الشيتوزان عن طريق تصنيعه بشكل جسيمات نانوية ويكمن الغرض من استخدام هذه الجسيمات هو زيادة الكفاءة العلاجية لبعض الأدوية التي تتأثر بأنشطة جسم الإنسان نظرا لصغر حجمها وتأثيرها في تقدير النقاط الكمومية. الهدف من هذه المراجعة هو مناقشة بعض الخصائص البيولوجية الرئيسية للشيتوزان والعلاقة مع الخواص الفيزيائية والكيميائية للبوليمر فضلا عن إعطاء لمحة عامة وتسليط الضوء عن تطبيقات الشيتوزان الممكن استعمالها في الوقت الحالي.

Introduction

Historically Rouget in 1859 was the first to depicted chitosan and formally by Hoppe-Seyler in 1894 named 1)) Chitin is the most abundant natural amino polysaccharide and is following to cellulose in abundance on the world, chitin is the second largest natural biopolymer only after cellulose, and exists extensively in marine organisms, such as the shells of crab, shrimp, algal bacterial cell membranes and skeletons of mollusks and cell walls of higher plants. chitin is a renewable recyclable, and inexhaustible resource, generally distributed in coastal areas3) (2)). Chitosan is gained by deacetylation of chitin. Chitosan is being researched by academic and industrial scientists as an underutilized resource and as a new functional material of high potential in various fields(4) , both chitin and chitosan are present in the shells of crustaceans and aquatic microorganisms such as shrimps, crabs, the insect exoskeleton or wings or fungal cell walls (5, 6).Chitosan has gathered much interest because its properties and possible applications. Every year the number of patents and publications based on this polymer rise(7). The purpose of using chitosan nanoparticles is to increase the therapeutic efficiency of some drugs in the human body(٨).Commercial chitosan was mainly produced from chemical deacetylation of chitin from crustacean sources, fungi and production from insect cuticles is also gaining interest (9). Since 1970, the use of natural polymer chitosan has been accelerated in numerous countries. Also, the number of papers published this completely reflects that people are more interested in the application worth of chitosan with abundant resources(10). In this regard, scientific literature exhibited that chitosan properties could be the smart polymers for many biomedical purposes. Chitosan can be biodegraded in the human body, thus it is not accumulated. It is in general considered well biocompatibility and plays a very important role in human physiological activities. Also, chitosan has biological activity, biodegradability, biocompatibility, antibacterial, antiseptic, and wound healing and other different functions, but its application is limited due to its poor water solubility(11). Chitosan shows anticancer activity through activating the immune system and promotes it when applied to combine with anticancer drugs. So,

it has become a research hotspot in the biomedical field in recent years due to these bioactive activities(12) Chitosan can be chemically and enzymatically modified because of the presence of free amine group that resulting after the deacetylation step, these properties of chitosan permit its availability in several forms, such as beads flakes, powder, sponges, membranes, fibers and gels(13). The properties of chitosan have been advanced by making their nanoparticles. The unique character of nanoparticles for their tiny size and vast surface-to-volume proportion and they are mucoadhesive in nature because of which they give great security and increase its drug release time and stability in the body. In this way, they are appropriate to a general classification of medications(14).

1- Chemical structure and composition of chitin and chitosan

Chitin is a partially crystalline mono polymer and contains of more than 5000 β-(1,4)-linked *N*-acetyl-d-glucosamine. Chitosan is totally deacetylated product of chitin consists of β-(1→4)-2-amino-d-glucose and β-(1→4)-2-acetamido-d-glucose units where "n" specifies the degree of polymerization of glucosamine and *N*-acetylglucosamine units (Figure 1)(15) (16). Chitosan has a complex double helix structure, it possesses many active groups such as hydroxyl group and amino group, which has high reactivity and can be chemically modified to obtain unique chemical, physical, and physiological properties(17).

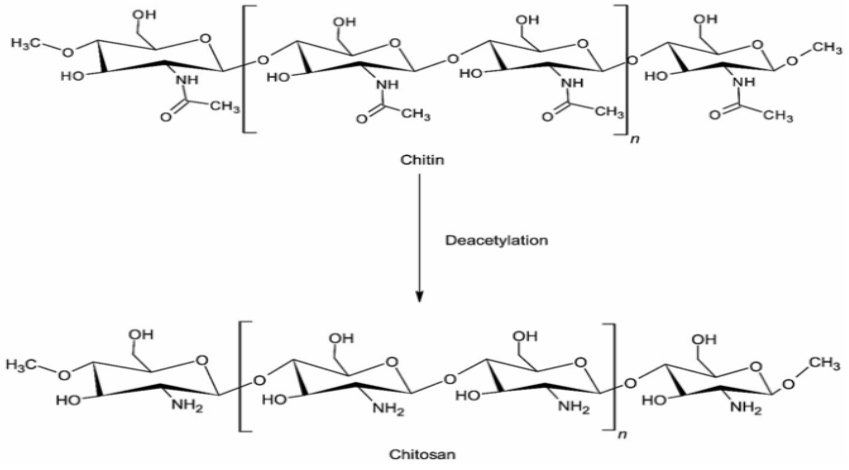

Figure (1): Chemical structure and composition of chitin and chitosan (18)

2- Sources of chitosan

Chitosan can be extracted from insects, mushroom, yeast, fungi cell walls and marine shellfish such as krill, crab, lobster, shrimp and cuttlefish in shellfish. Chitin forms the outer protective wall as a covalently bound network with proteins and some metals and carotenoids. Crustacean shells consist of 20–30 % chitin, 30–40 % proteins, 30–50 % calcium carbonate and also contain pigments. These proportions differ with species and with seasons. Prawn, shrimp and crab wastes are the main source of commercial chitin and chitosan production. The increase in consumption of shellfish and the increase of aquaculture have led to a wonderful increase in the quantity of shrimp and prawn being processed and later in the amount of waste available for chitin and chitosan production (19-21). In general, dissolving a substance in a solvent or mixture of solvents is the most popular extraction technique for removing a substance from materials or a matrix. chemical-solution will subsequently be collected, and it will then be possible to extract the chemical from solution using partial techniques including concentration, precipitation, and crystallization. based on the variations between the chemical and physical characteristics of solvents and solutes. This technique has been used to extract the majority of biological polymers, including gelatin, agar, and alginate. Chitin extraction, on the other hand, happens in the reverse way. Chitin is insoluble, therefore all other ingredients in raw materials dissolve before chitin does, which prevents it from dissolving and gathering on its own. This is why there are a lot of challenges while making chitin. First, many need to remove unnecessary components. These explain why chitin production technology necessitates a variety of approaches, and there are still numerous challenges that must be addressed. Furthermore, chitin has a variety of qualities that are determined by its structure, raw material attributes, and extraction process. Therefore, in chitin and chitosan production technology, is functions must be examined in order to select the extraction method with the right parameters. Several methods can be used to extract chitin, depending on the basic ingredients. The three primary procedures used in these methods are typically decolorization, demineralization, and deproteinization. Before

going on to the primary process, raw materials will first be cleaned, dried, crushed, and processed into a powder (11, 22). An overview of the chitin synthesis process is shown in Figure (2).

Chitosan is produced from chitin through a process called chemical deacetylation, which involves replacing the acetyl group on C^2 glucosamine with a -NH2 group (23, 24). Alkalis or acids can carry out the deacetylation process. Alkali deacetylation is recommended because acid treatments break polymer chains by affecting glycosidic linkages. Alkali techniques create insoluble residual chitosan as the final product with DD up to 85-99% by treating acetyl groups with hot, concentrated alkalis (NaOH is more efficient than KOH) for a few hours (23) (Figure 2). Seven criteria were used to investigate the effects of deacetylation parameters: temperature, concentration of the alkali reagent, number of consecutive baths, performance time, addition of sodium borohydride (NaBH4), and reducing reagent. The outcomes demonstrated that alkali reagent and temperature are important variables. Using additional alkali baths, increasing the alkali's concentration, and lengthening the reaction time all considerably increased the deacetylation degree DD. Whereas reducing reagent (NaBH4) and atmospheric conditions only affected on Mw and reducing depolymerization (24).

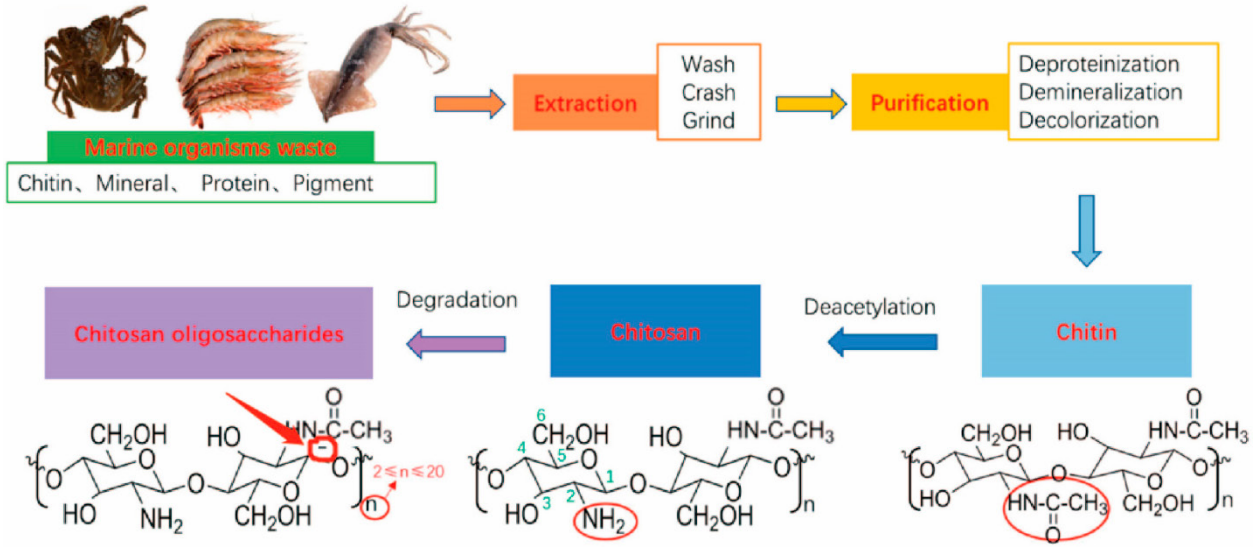

Figure (2): Production of chitosan (25)

3- Chitosan Properties

Physicochemical Properties

Three reactive or functional groups make up chitosan: two hydroxyl groups at C3-OH and C6-OH, and an amino group (-NH2) at C2-NH2. Compared to the hydroxyl group at C3-OH, the one at C6-OH has greater chemical activity. Another way the glycosidic bond as a functional group is one that permits chemical alterations to create a polymer with unique characteristics (26). Numerous alterations are possible with these functional groups, resulting in polymers with unique characteristics and behaviors. Derivatives of chitosan have been created with the intention of enhancing its solubility and biodegradability as well as adding new features. For example, among other techniques, quaternization, depolymerization, and deacetylation have been used to increase solubility in water-aqueous systems (27). The relationship between the chemical structure of chitosan compounds and their prospective applications in many scientific and industrial fields is determined by their physicochemical properties (22). average molar mass (molecular weight) and deacetylation degree (DD) are the most often evaluated qualities, independent of the purpose for which a particular product is meant to be used. Other characteristics including solubility, crystallinity, viscosity, water, nitrogen, and ash content, as well as water retention value all that are important variables that affect how it is used as a biomaterial (28). One of the most fundamental parameters characterizing a macromolecule is its molecular weight. Knowledge of the molecular weight of polysaccharides is of fundamental importance for the understanding of their applications and their role in living systems. The molecular weight of chitosan depends largely on the conditions of deacetylation and can be determined by methods such as chromatography (29), light scattering (30), and viscometry (31). Chitosan is available commercially with molecular weight ranging from 10,000 to 1,000,000 Da (4). Extensive investigation has shown that chitosan activity increases with decreasing molar mass and DD (7). The ratio of glucosamine groups to the total number of N-acetylglucosamine (GlcNAc) and glucosamine (GlcN) groups is known as the deacetylation degree (DD). The polymer's classification as chitosan or chitin is based on the level of DD value. If the polymer's

DD is greater than 60%, it is referred to as chitosan (32).

Chitosan's solubility qualities are determined by the degree of deacetylation. A high degree of deacetylation indicates better solubility, while a low degree of deacetylation indicates poor solubility. (33).Solubility Chitosan is created by deacetylating chitin, which converts certain N-acetylglucosamine moieties into glucosamine units.The presence of a significant number of protonated NH2 groups on the chitosan structure explains for its solubility in acidic aqueous conditions, as its pKa value is around 6.5 (34) When approximately half of all amino groups are protonated, chitosan becomes soluble (35). Chitosan solubility is determined by a variety of parameters, including polymer molecular weight, degree of acetylation, pH, temperature, and crystallinity. At low pH, the amines protonate and become positively charged, making chitosan a water-soluble cationic polyelectrolyte. However, as the pH rises above 6, chitosan amines become deprotonated, causing the polymer to lose its charge and become insoluble. At higher pH levels, precipitation or gelation occurs, and the chitosan solution forms a poly-ion complex with the anionic hydrocolloid, culminating in gel formation (36). The soluble-insoluble transition occurs at pKa values between 6 and 6.5 pH. Chitosan readily forms quaternary nitrogen salts at low pH levels. Thus, organic acids like acetic, formic, and lactic acids can dissolve chitosan. The most often used solvent for chitosan is 1% acetic acid at roughly pH 4.0 (35).

Chitosan viscosity is determined by the polymer's molecular weight and the degree of deacetylation, and it lowers as the molecular weight of chitosan is reduced. In fact, viscosity can be used to estimate the durability of a polymer in solution, as it decreases during polymer storage due to degradation (37).

Biological properties of chitosan

Chitosan's exceptional biological features provide unique prospects for the creation of many various applications, including biocompatibility, biodegradability, antibacterial activity, mucoadhesion, and affinity for anionic components(38). Chitosan has been employed in various industries, including food (39), pharmaceutical (40) , textile (6), water treatment (41). Both the DD and the preparation technique affect biocompatibility and toxicity (biocompatibility increases with

increase in DD). A range of cell types have been used in numerous in vitro investigations to assess the biocompatibility of Chitosan, including neural cells (42), fibroblasts (43), osteoblasts (42) , chondrocytes (44), keratinocytes (6), and hepatocytes (45). According to the results, Chitosan is nontoxic and can help these kinds of cells adhere and multiply, indicating that chitosan is compatible with these kinds of cells (46). Chitosan is degraded specifically by enzymes known as chitosanases (EC 3.2.1.132) and chitinases (EC 3.2.1.14). Chitosanases are glycosyl hydrolases that break down β-1,4-glycosidic linkages in partly acetylated chitosan to produce chitosan oligosaccharides (COS) with little monomer release (47). Chitosanase breaks down chitosan by cleaving glycosidic linkages in the -DD·DA or -DD·DD patterns. Chitinases, found in the GH18 and GH19 families, are glycosyl hydrolases capable of degrading both A-A and A-D links but not D-D bonds. Chitinases are categorized into two types based on their method of action (endochitinases and exochitinases) (48).

Properties of Chitosan Nanoparticles

For the past decade, chitosan has been researched as a material for shaping nanoparticles. Chitosan's characteristics have been improved by forming nanoparticles. The innovative character of nanoparticles for their small size and quantum estimation influence may make chitosan nanoparticles display prevalent practices. They are simple and inexpensive to manufacture and scale up, with an interesting size and large surface-to-volume ratios. They are mucoadhesive and hydrophilic in nature, which provides considerable security to the characterized sedate, increases its freedom time, and ensures its stability in the body. In this sense, they are ideal for a broad category of medications: small particles, proteins, and polynucleotides. The benefits of characterizing dynamic specialists in a polymer framework include their protection from the surrounding medium or handling conditions and their controlled discharge (14).

4- Applications of chitosan

Chitosan has applications in a variety of fields, from agricultural sector to more advanced, biotechnology and nanotechnology disciplines .

Chitosan as a binder in drug tablets

Chitosan has recently been accepted by the researchers and a studies relating to chitosan hydrochloride was comprised in the 4th edition of the European Pharmacopoeia (2002). Despite the many uses of chitin and chitosan as new functional materials of high potential in different fields, so they are still behind several directly compressible DC excipients (DC excipient is any material added to the drug except the active substance) already dominating pharmaceutical applications. There are still new tries to exploit chitin and chitosan in co processing techniques that provide a product with potential to act as a direct compression excipient (49).

Chitosan has received extensive attention as a possible pharmaceutical excipient in recent decades. It has been evaluated in all conventional excipient applications, such as a as a binder in wet granulation during the preparation drug tablets (50), directly compressible diluent in tablets and also in novel applications, such as a carrier for mucosal delivery of antigens in linking with oral vaccination (51-53). (50) one of studies that used chitosan as a binder for chlorpheniramine maleate tablets (Allermine) in comparison with other cellulose binders such as hydroxyl propyl methyl cellulose, sodium carboxy methyl cellulose, and methylcellulose. The effects of binder concentration on the mechanical properties of tablets in addition to on dissolution time and disintegration were studied. Results showed that chitosan tablets exhibited best dissolution profiles and tablets prepared with methylcellulose had lowest percentage of fines and friability. Numerous properties of chitosan make it actually valuable as a pharmaceutical excipient. Good biocompatibility and low toxicity of chitosan (54) (11, 55) and the fact that sources of chitosan are very abundant, are properties that any new excipient substance should have. One of them properties that makes chitosan mostly interesting for studies as an excipient is its capability to become hydrated and form gels in acidic aqueous environments. Due to its gel forming ability, a main area of interest since studies started has been use of chitosan to make slow release drug delivery systems (56).

Antioxidant activity

Antioxidant activities against hydroxyl, superoxide free radicals and 2,2-Diphenyl picrylhydrazyl (DPPH).

Studies have shown that the chitosan has strong antioxidant properties. According to the results, chitosan might be used as a natural antioxidant, in addition to a dietary supplement or component in medicines and nutraceuticals (57-59). The antioxidant activity of water soluble phosphorylated chitosan, including hydroxyl radicals, DPPH, and superoxide, also its ferrous ion chelating capacity (57).

Anticancer activity

The majority of anticancer medicines work by unique mechanisms to kill cancer cells. The identification of molecules triggered by chitosan may help researchers better understanding the processes behind chitosan's cytotoxic effects on cancer cells(60), so chitosan has been showed to promote apoptosis and activate caspase-3 (61, 62), besides stimulating the extrinsic apoptosis pathway through caspase-8 activation (43, 63, 64). When cancer cells are exposed to chitosan nanoparticles, necrosis is thought to be the mechanism responsible for cell death (65).

Drug delivery

The process of safe transportation of the therapeutic effect of the pharmaceutical compounds in the body based on the nanotechnology is called drug delivery (66). Chitosan nanoparticles have several important potential applications for drug delivery in the body as oral, ocular, nasal, pulmonary, vaginal, and buccal in addition to applications in cancer therapy and tissue engineering (67-69). The process mostly facilitates site targeting inside the body and systemic pharmacokinetics by using nanoparticles or several methods. Later the unique features of chitosan have been discovered that are favorable for the medicinal fields, researchers have started thinking about its use in the advancement drug delivery process. The cationic character of chitosan makes unique, due to the presence of an amino group (positively charged) it can adhere to biological surfaces mucosal glycoproteins (negatively charged) as a bioadhesive material (Figure 3) (66, 70). The demonstrated potential use of chitosan nanoparticles as drug delivery systems has provided chances for the growth of a largely expanded range of chitosan nanoparticles based delivery vehicles (71, 72). Due to its biocompatibility character for chitosan is classified by the United States Food and Drug Administration as generally recognized as safe (73). like noted above,

the presence of the amino, hydroxyl functional groups, as well as the glycosidic bond, allows the loading of chitosan nanoparticles with drug molecules and DNA. Due to chitosan nanoparticles are soluble in acidic aqueous solutions, sustainable chemistry may be used in their synthesis without the use of harmful organic solvents (74). In addition, advantage of utilizing chitosan nanoparticles is mucoadhesion, they enable the organized release of drugs in *vivo* (75).

Drug release from chitosan nanoparticles occurs via a variety of mechanisms, including polymer swelling (76), diffusion of the adsorbed drug through the polymeric matrix and polymer erosion or degradation, and a combination of the two (77). The major burst nanoparticles released from chitosan are caused by either swelling of the polymer, which generates holes, or drug diffusion from the polymer's surface (78). Because of chitosan's solubility, nanoparticles demonstrate pH-dependent drug release (79).

Secondary to diffusion release, the drug penetrates the polymeric matrix's interior to reach the exterior media. Furthermore, polymer chains form the diffusion barrier, making it harder for the medication to pass through, and this barrier also serves as the rate-limiting membrane for drug release. Diffusion may also be associated with polymer degradation or swelling (80) (81).

Third degradation of polymers are interrelated features. Sometimes, degradation of the polymer may cause subsequent physical erosion as bonds break. Erosion of polymers is a complex phenomenon as it involves swelling, diffusion and dissolution. Erosion occurs in two ways: homogenous and heterogeneous. Homogenous erosion is erosion of the polymer at the same rate throughout the matrix whereas heterogeneous erosion is erosion of the polymer from the surface towards the inner core. Polymer degradation may be due to the surrounding media or the presence of enzymes. The degradation of the polymer also depends on the pH of the surrounding media, the copolymer composition and water uptake by the polymer. Drug release depends on the type of polymer and internal bonding as well as the shape and size of the nanoparticles as this reflects surface area and free energy (82, 83).

Mucoadhesion activity

One of the major problems of delivering proteins, peptides or macromol-

ecules through a non-injection route is the restricted absorption at mucosal sites. For local delivery in the gastro intestinal tract or to the vaginal, urethral or pulmonary sites or nasal buccal cavity the drug delivery system must be mucoadhesive and release the drug. Particle size of chitosan nanoparticles also plays a role in the case, smaller particles may be abler to penetrate the mucousal layer. Mucoadhesive nanoparticles or microparticles can adhere to the mucus membrane and release the drug over time with the potential to reduce dosing frequency. Uptake of drugs into the systemic circulation can be accomplished by passing and reversible opening of tight junctions between epithelial cells by certain polymers and chitosan is one such polymer (52). As noted earlier, the mucoadhesive property of the chitosan due to strong positive charge which helps in forming a strong bond with negatively charged mucus membrane. The gastro intestinal tract is characterized of varying pH and an enzyme environment which makes it difficult for oral drug delivery of protein and peptide drugs but chitosan is the best excellent carrier for such drugs as it is mucoadhesive and permeation enhancer also forms a protective barrier for the drug (84).

Antibacterial activity

Due to the positively charged molecules of the chitosan so interact with the negatively charged microbial cell membrane and tend to breaks the cell membrane. Thus, chitosan uses in antimicrobial effect(85). The antibacterial activity of chitosan was tested by using the well diffusion method against clinically isolated human pathogens as (Gram-positive: *Streptococcus pneumoniae*, *Streptococcus* sp, and *Staphylococcus aureus*) (Gram-negative: *Vibrio cholerae*, *Escherichia coli*, V. *alginolyticus*). The results demonstrate that chitosan and phosphorylated chitosan have antibacterial activity dependent on concentration with variation against a variety of human pathogenic bacterial strains proposing that they might be used as antibacterial agents(86) (87, 88).

Permeation enhancer chitosan

Permeation enhancer chitosan can increase the permeation of nasal, intestinal and buccal epithelial cells, for this reason, chitosan can be used in the drug delivery system as a permeation enhancer (89). Figure (4) shows the chitosan performances a penetration enhancer through opening the tight

junctions of the epithelium, and the mechanism of this action involves the interaction of chitosan positive charge with the tight junction proteins as occludin and minor destabilization of plasma membrane (90).

Chitosan facilitates both paracellular and transcellular transport of medicines as shows in (Figure 3), by chitosan interacts with mucus membrane that negatively charged to form a complex via ionic or hydrogen bonding, in addition to though hydrophobic interactions. Also the pKa of the primary amine of chitosan is (~6.5) depending on the degree of N-deacetylation, this group also contributes to the solubility of chitosan in acidic pH environments, and the partial neutralization of this primary amine may be also explain why chitosan has been aggregate at neutral to high pH (91).

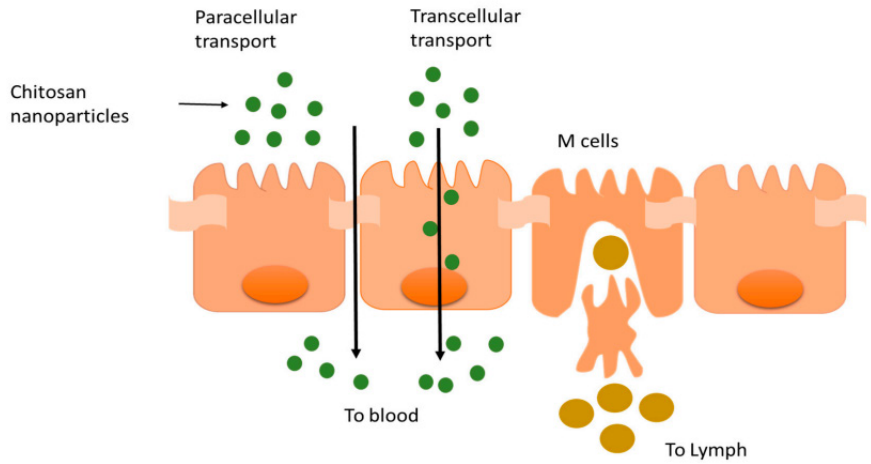

Figure (3): shows the mechanism of paracellular and transcellular transport chitosan nanoparticles (69)

Immune therapy

Chitosan has the ability to stimulate humoral immunity, complement system and CD4+ cells. Antibody titers and strong delayed-type hypersensitivity responses showed that chitosan induced both cell-mediated immune responses and humoral. Chitosan stimulates humoral immunity as the serum and interstitial fluid (92, 93). Chitosan also stimulates complement system as the activation of anaphylatoxins like C5a and C3a excepting for C4 by an alternative pathway. Amid them, C3a activates the mast cell to secrete histamine, and C5a to activation phagocytic

cell (94). Because of chitosan has high viscosity than water, so chitosan can be used effectively as an antigen depot, thus for this reason, it can be used with vaccination to create adaptive immune response over a long time, which demonstrated that chitosan can rise the immune system as an adjuvant (91, 92). Furthermore, due to unique characteristics of chitosan can be used in numerous vaccine constructions and delivery, like as influenza vaccine delivery, polio vaccine, and preparation of hepatitis B vaccine, etc.(95).

Biodegradability activity

Chitosan determined by its chemical structure, it is a kind of natural medical polymer material with unique biodegradability property(96). So it degrades under the action of a lysozyme in the body fluid or in *vitro* (97). Degradation products are oligosaccharide and methyl sugar and which are nontoxic for the body and after that can be decomposed, absorbed and metabolized. One of the degradation products is N-acetylglucosamine, which is important for scar repair of tissues and is nontoxic to some malignant tumors, so it can be used as cancer chemotherapy medicines. It's all degradation products are mostly nontoxic in the human body, no immunogenicity, no accumulation in the body, thus it can be used to surgical suture, manufacture artificial skin, contact glasses, bone repair materials, anticoagulant materials, and it has a very broad application view in the medical field (98).

5- Pharmacokinetics of chitosan

The best important property of chitosan must be exploited is its mucoadhesion. Many of the studies explore the pharmacokinetic features of chitosan based nanoparticles. A pharmacokinetic study was done in (beagle dogs) to measure the bioavailability of cyclosporin-A encapsulated into nanoparticles involved of chitosan, gelatin-A or sodium glycocholate, a control group received the standard oral micro-emulsion formulation (Neoral®). The Cmax was significantly increased in the case of both the gelatin and chitosan nanoparticles formulations while the Cmax decreased with sodium glycocholate nanoparticles compared to Neoral, there was a 2.6 double increase in the area under the curve (AUC) of cyclosporin-A from chitosan nanoparticles compared to sodium glycocholate nanoparticles and 1.8 double increase in AUC from gelatin nanoparticles compared to sodium

glycocholate nanoparticles, the comparative bioavailability of cyclosporin-A from sodium glycocholate nanoparticles was decreased about 36% when compared to marketed formulation. Because of the negative charge of the sodium glycocholate nanoparticles which could have prevented the nanoparticles from adhering to the lining intestinal mucus and consequently may have reduced the drug absorption through the intestinal epithelium. The idea is a positive charge of chitosan nanoparticles can advantage in mucoadhesion and rise in relative bioavailability, enhanced by 73% in this case (99). Chitosan based nanoparticles were developed with the primary goal of prolonging circulation time of the drug in blood. The improved intestinal absorption can be credited to either increased interaction between the (positive charge) of chitosan with the (negative charge) of cell membranes or the mucoadhesive characters of chitosan nanoparticles, allowing them to release drug over time in the intestine (100). Another study results, enoxaparin has little to no oral bioavailability, to improve oral bioavailability, enoxaparin loaded alginate coated chitosan nanoparticles were formulated, causing in a 3 double increase in AUC for oral enoxaparin (50 mg/kg in rats) and representative 20% of the AUC reached with (intravenous dosing 1 mg/kg). The improved intestinal permeation of enoxaparin could be because of improved paracellular transport of the drug across intestinal epithelium due to the mucoadhesive property of chitosan. So chitosan nanoparticles have many applications in increasing the oral bioavailability(101).

Conclusion and Recommendations

Chitosan is one of the most widely used biopolymers in biomedical science, ranking second only to cellulose, a naturally occurring amino polysaccharide. Chitosan biopolymer is made from de-acetylated chitin and its aminopolysaccharide, which occur naturally. Because it is biocompatible and biodegradable, it has sparked a lot of interest in biological applications. According to several studies, chitosan has been employed in a number of pharmaceutical applications, including antibacterial, antioxidant, anti-inflammatory, anticancer, and drug delivery systems, throughout the last few decades. Based on numerous recent publications, this review concluded that chitosan and its

nanocomposite have a promising future due to improved distinctive qualities such as especial biocompatibility, biodegradability, mechanical and thermal stabilities, barrier, and nontoxicity, indicating their uniqueness in biomedical applications. Chitosan nanoparticles have high potential as carriers for medication encapsulation and integration. Thus, due to their mucoadhesive qualities, chitosan nanoparticles have a high potential for effective drug administration, regulated drug release, and increased therapeutic efficacy. Chitosan nanoparticles are positively charged and exhibit advantageous in situ gel formation and mucoadhesive properties, making them useful for various organ medication delivery. Similarly, their capacity to open tight junctions of the mucosal membrane and improve drug absorption qualities makes them promising drug delivery carriers, whilst their ability to increase drug permeability makes them appropriate for a variety of drug delivery applications. Our goal is to create more chitosan nanoparticle-based applications for cancer treatment, therapy, imaging, and drug administration.

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