

Chitosan Nanoparticle And Its Application In Non-Parenteral Drug Delivery

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Abstract

This study's main goals are to give an overview of chitosan-based nanoparticles used in a variety of non-parenteral applications and to call attention to new research on mucoadhesive and sustained release chitosan dosage forms. Chitosan is a biodegradable, biocompatible polymer that has been certified for use in wound dressings and is suitable for inclusion in human diets. For a variety of drug delivery methods, chitosan has been employed as a drug carrier in polymeric nanoparticles. Chitosan is a polymer with numerous possible uses since it has chemical functional groups that can be altered to serve particular purposes. The positive surface charges and mucoadhesive qualities of nanoparticles (np) made of chitosan and chitosan derivatives enable them to stick to mucous membranes and gradually release the therapeutic payload. This review will include examples of non-parenteral drug delivery techniques for treating eye infections, cancer, gastrointestinal disorders, pulmonary disorders, and cancer. Both in vitro and a few in vivo investigations show that chitosan has a low level of toxicity. This review looks at recent investigations on the characteristics, modifications, toxicity, pharmacokinetics, and preclinical trials of nanoparticles (np) made of chitosan for non-parenteral drug delivery.

Keywords: chitosan; mucoadhesive; polymeric nanoparticles; sustained release; oral drug delivery.

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1. INTRODUCTION

The mucosal method is becoming more popular since it can administer medications noninvasively via the nasal, vaginal, pulmonary, or oral routes (1). Additionally, nanoparticle technology has become a popular means of administering medication, providing opportunities for regulated release, targeted retention, and protection of active ingredients against enzymatic or environmental destruction. The production of nanoparticles may be scaled up and adapted to a variety of pharmaceuticals with ease. All polymeric nanoparticles have seen a substantial increase in importance as nanoparticle-based drug delivery systems. Applications for a wide range of chemical medication classes and dosages have been added as a result of their biocompatibility,

biodegradability, and the availability of more widely used formulation techniques. Forms (2). Because of their mucoadhesion, low toxicity, and flexible physical characteristics, chitosan-based np are particularly well-suited for the mucosal route. Examples of chitosan-based nanoparticles that have been utilized to treat eye infections, cancer, gastrointestinal issues, lung issues, and other conditions will be given. The basis for current research on chitosan-based np for non-parenteral drug administration is the field's expanding understanding of chitosan properties and methodologies for chemical or physical modification, which are employed to optimize nanoparticle drug loading and release aspects. We will also discuss the current understanding of in vivo and in vitro toxicity as well as the influence of chitosan nanoparticle composition on drug pharmacokinetics in preclinical research.

Chitosan:

Figure 1 shows how to remove the acetate moiety from chitin to produce the most important chitin derivative, chitosan.

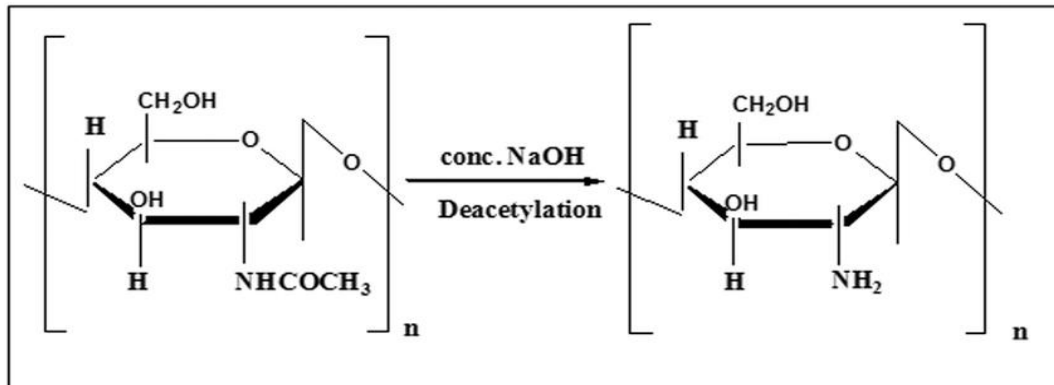


Figure 1. Deacetylation of chitin to chitosan

It originates from both the fungal cell walls and the crustacean shells of creatures like prawns and crabs. The USA FDA has approved it as a naturally occurring polysaccharide, mucoadhesive, biocompatible, cationic, highly basic polymer for tissue engineering and drug delivery.

Chitin from natural sources needs to be separated from its connections to proteins and minerals using acidification and alkalization processes before chitosan can be produced. Then, pure chitin is n-deacetylated to create chitosan. This technique can be changed to adapt the final product properties, such as molecular weight and pka, by changing the reaction parameters (concentration, ratios of chitin to alkali, temperature), chitin supply, and reaction extent (6-7.5). (3,4). By adjusting the reaction's parameters (concentration, temperature, chitin to alkali ratios), the chitin's supply, and the reaction's range, it is possible to manage the degree of deacetylation. Chitosan

improves penetration by reducing the tight connections within the epithelium. Figure 2 illustrates how chitosan facilitates the transcellular and paracellular transport of drugs. Chitosan interacts with hydrophobic molecules, ionic bonds, and hydrogen bonds to generate a compound with negatively charged mucus. The primary amine of chitosan has a pka of roughly 6.5, depending on the degree of n-deacetylation. This group contributes to the solubility of chitosan in acidic environments, and reports of chitosan aggregation at neutral to high pH values may be explained by the partial neutralization of this primary amine (5). It is well known that chitosan can dissolve even at physiological pH levels when its acetylation level is between 40 and 60%, despite the fact that this may be the tendency for chitosan with a proportion of acetylated units of 0.4 and medium to high molecular weight (4). The nanoparticle formulator must therefore carefully match the chitosan processing procedure to the chitosan's necessary chemical and physical qualities as well as the anticipated biological environment.

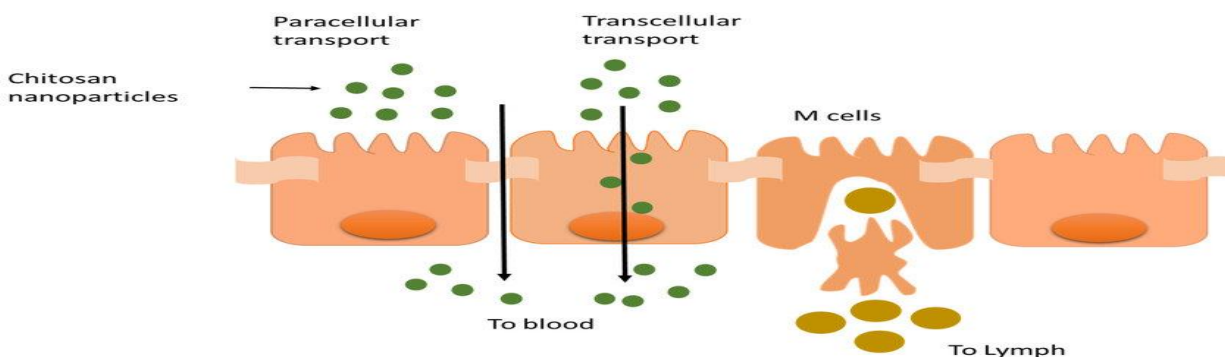


Figure 2. Schematic-illustration-of-the-presumed-mechanism-of-transcellular-and-paracellular transport of chitosan np across the epithelium.

2. Preparation of chitosan nanoparticle:

Micro-emulsion, ionotropic gelation, and emulsification the most notable techniques for creating chitosan-based nanoparticles are dissolvable dispersal and emulsion-based dissolvable disappearance. One of the main benefits most of these techniques give is the use of less common dissolvable and less power. Sub-nuclear weight and the degree of chitosan acetylation are discovered to be the main factors that influence the particle size and surface charge of chitosan nanoparticles structured by these processes. Hydrophobic correspondences, hydrogen holding, and electrostatic correspondences all play a role in how medications are held inside the polymeric matrix. Drug release and stacking are not, by any means, the main characteristics. The intended use of the nanoparticles and the physiological environment at the site of association should be taken into consideration, including factors like pH security in addition to ionic strength, salt content, and the presence of mixes, proteins, and salts (ponder the milieu of the eye versus the GI package). We currently have a variety of enumerating methods to look at, which is fortunate.

2.1. Reverse micellar method:

A natural dissolvable is used to break up the surfactant, and then chitosan, a crosslinking agent and medicine, is expanded under constant short-term vortex blending. The natural dissolvable is removed to leave a pure dry mass. Next, the final choice is dispersed in water, and then a reasonable amount of salt is added to help the surfactant (6,7). We see a very small nanoparticle and use natural solvents to dissolve it (8). By using a turn-around micellar approach, doxorubicin-dextran form stacked chitosan nanoparticles were created. This method's surfactant, sodium bis (ethylhexyl) sulfosuccinate was dispersed in n-hexane. The np are constructed by including fluid alkali, 0.01% glutaraldehyde, 0.1% chitosan in an acidic corrosive, and doxorubicin-dextran forms after constant mixing at room temperature (9,10).

2.2. Micro-emulsion method:

In this process, a surfactant is combined with glutaraldehyde in a typical dissolvable, such as hexane, and chitosan in an acidic destructive strategy. The nanoparticles are allowed to temporarily approach while the cross-interfacing process is carried out while this mixture is kept on constant mixing at room temperature. The regular dissolvable is then removed by low-pressure evaporation. Surfactant overflow in the thing at hand can be removed by centrifuging after running calcium chloride through it. The final suspension of nanoparticles is then dialyzed and lyophilized (10). With this technology, a very little size scattering is seen, and the

size can be influenced by the accumulation of glutaraldehyde during the synthesis of the nanoparticles. This process achieves the action of poorly characterized nanoparticles (11). This method's flaws include the usage of common dissolvable, a lengthy cycle, and a perplexing washing step (2).

2.3. Emulsification solvent diffusion method:

To set up an oil-in-water emulsion, a liquid plan of chitosan and a stabilizer is mixed in with a whiz dissolvable by mechanical shaking joined by extended pressure homogenization (12). Precipitation is achieved predominantly of water into the emulsion, and the nanoparticles are molded with a size running between 300 nm and 500 nm. This framework is a fair choice to stack hydrophobic particles, with a high ensnarement capability (ee%); regardless, a key stipulation is the prerequisite for an extended shear force (13).

2.4. Emulsion based solvent evaporation method:

This system, which differs only slightly from the method described above, avoids excessive shear powers. With this technique, it is possible to produce particles smaller than 300 nm. By adding normal dissolvable to a mixture of chitosan and surfactant, followed by ultrasonification, an emulsion is created. The described emulsion is then added to a surfactant solution, blended, and allowed to dissolve until the usual dissolvable is gone, resulting in the formation of nanoparticles. The nanoparticles are then lyophilized to produce freeze-dried nanoparticles after being rinsed and centrifuged on many occasions to remove excess surfactant (9,14).

2.5. Ionotropic gelation:

Here, the chitosan strategy (strongly charged) is compromised by acidic damaging or any polynomic strategy (unfavorably charged), regardless of a balancing trained expert, like poloxamer. A parcel of chitosan is produced in round particles of various sizes and surface charges by mechanically mixing positive and negative charged species, leading to the rapid formation of nanoparticles. The exposed atom size ranges from 20 to 200 and 550 to 900 nm all around. Chitosan-tppl-ascorbic corrosive nanoparticles were created by ionotropic gelation between the two substances' strongly charged amino social events over the course of just one hour of continuous blending at room temperature (15,16). Ionotropic gelation has two or three benefits, including low harmfulness and the utilization of a liquid environment, as well as a little probability of altering the study of the medicine being used as an example. The main drawbacks of this method are the difficulty in capturing medicines with high nuclear weights and its terrible resilience in acidic circumstances (2,17).

2.6. Complex coacervation method:

By combining fluids with electrostatically defined properties, the process of coacervation isolates spherical particles. DNA-chitosan nanoparticles are created through the coacervation of DNA phosphate clusters with chitosan's strongly charged amine groups (18,19). The sub-atomic loads of the two polymers signify entanglement proficiency and drug discharge (20,21). The cycle can be completely operated in a watery arrangement at low temperature, which is a benefit of sophisticated coacervation. This offers a better chance of guarding against the mobility of the epitomized chemicals. The main downsides of this approach include the unfavorable soundness of the nanoparticles, low drug stacking, and the need to crosslink the complex with a chemical reagent, such as toxic glutaraldehyde (2, 16,22). In the polyelectrolyte complex (pec) method, a cationic polymer (such as chitosan arrangement broken down in acidic corrosive, gelatin, and polyethyleneimine) is added to an anionic solution (for example, dextran sulphate DNA arrangement), under mechanical mixing at room temperature, followed by charge balance. Benefits include the simplicity of the procedure, the absence of harsh environmental factors, and the instantaneous formation of nanoparticles (2, 16). The pec method was used to produce low sub-atomic weight water-solvent chitosan (lmwsc) nanocarriers for insulin, resulting in insulin-stacked chitosan nanoparticles with a precise mean measurement of 200 nm and supported discharge profile in vitro (16).

2.7. Co-precipitation method:

When chitosan is converted from a low pH acidic destructive strategy to a high pH 8.5–9.0 game plan, such as ammonium hydroxide, co-precipitation occurs and a considerably monodisperse nanoparticle population is improved. Nanoparticles with a great capacity for exemplification and incredibly low estimates (2, 16). This method reveals a wide range of particle sizes, which can be a drawback. Lactic destructive linked together chitosan (la-g-chitosan) nanoparticles were created using a co-precipitation approach, and coacervate drops were created using ammonium hydroxide. Round and consistently adapted nanoparticles were produced by this technique.

3. Biological ligands for nanoparticle drug delivery systems

3.1. Passive targeting

Through epr impacts, nanoparticles (np) can increase total at the developing cells (23). EPR adds to calm accumulation in angiogenic tissues, for instance,

development, in a striking way. With the help of slow lymphatic leakage, nanoparticles that use detached targeting engrave deeper into the vascular networks at the illness location. The physicochemical characteristics of nanoparticles, such as size, shape (morphology), surface charge, and surface science, are not completely resolved. By altering the part molecules or the production cycle, it is possible to affect their physicochemical qualities in a beneficial way. (24)

Nanocarriers can enter disease cells by endocytosis and boost the quantity of medications that return to the cells if they lack a specific receptor target. To avoid extending drug focus and further generating prescription stream in the body, nanomedicine must have an estimation of d 100 nm with a hydrophilic surface. Their size has an impact on the overall energy of the nanomaterials accumulating at the development cells. The size of the vehicle has a significant impact on extravasation to the development, and the nanocarrier should be less intrusive than the neovasculature's cutoff point (24). The developing cells, which include a lengthy drug progression, are an idle framework. Disengaged focusing is definitely not a precise and skilled prescribed movement technique (25).

3.2. Active targeting

We identified and examined a number of ordinarily enormous ligands to assist in the compelling centering of nanoparticles. Additionally, these regular ligands bind to specific receptors on the goal cell layer. Participation of ligand-receptors will increase the uptake of nanoparticle-containing prescriptions and also promote supportive practicality (24). Dynamic zeroing in on is employed to increase development accuracy and transport capacity, and it also requires proclivity-based evidentiary support and maintenance that is combined with the consumption of the objective cells (26). The target cells will assemble pharmacologically distinct particles (such as antibodies or monoclonal medications) augmented with ligands on the nanocarrier (25).

As a result, many different types of ligands have been employed, such as proteins, polysaccharides, nucleic acids, and tiny particles [36], as well as monoclonal antibodies, aptamers, and these other substances. Nanoparticles with this ligand capacity function in two different ways. They may bind to np sections that had already advanced, such as polymers, or they could be precisely adsorbed to np after np's outlining (24). The cause of manufactured love for dynamic zeroing in on is several express nuclear interactions, such as receptor-ligand-based associations, charge-based affiliations, and worked with point of view based correspondences with substrate particles. Figure 3 illustrates how various biomolecules, including as antibodies, proteins, nucleic acids, peptides, carbohydrates, and minimum normal

particles, might contact with ligands. The target substrate may be surface molecules imparted in dead cells, proteins, carbohydrates, or lipids found in organs, particles found

in the weak cell's microenvironment, as well as the physicochemical environment containing them (26).

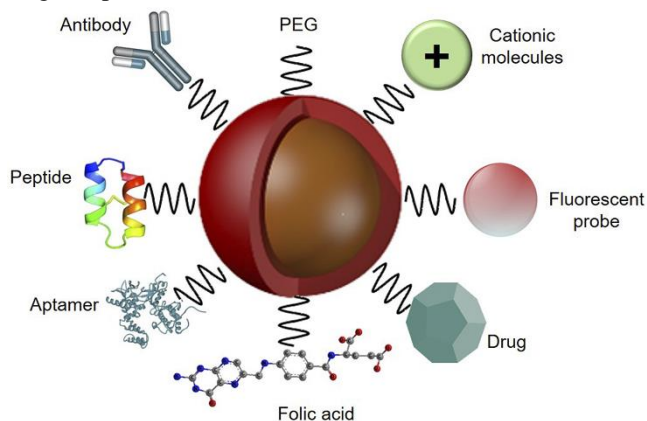


Figure 3. Active targeting ligand

An ideal active target moiety should have the following qualities:

- Development cells have more target moieties than normal tissues (27).
- It should also be evaluated in areas that nanocarriers can definitely get to, like superficial receptors rather than intracellular targets.
- For gifted individuals to focus, the fixation must be strong enough.
- In order to focus on these sabotage developments on actually serious reasons, it should ideally correlate its levels with dangerous actions, whether drug block or dynamic centers.
- Zeroing in on can chip away at strategies that work with the transport of drugs (25).

4. Chitosan in Nasal Drug Delivery:

Nasal delivery is a safe way to deliver medication to the respiratory system, the brain, and other potentially essential pathways. The mucociliary freedom of drugs poses a significant challenge to their delivery through the nasal route. Due to their poor penetration into the nasal epithelium, hydrophilic drugs, proteins, peptides, nucleic acids, and polysaccharides also pose difficulties. Nasal intake is essential for the drugs to work. Atomic weight, lipophilicity, and charge are true characteristics of drugs that facilitate nasal assimilation. Mucociliary leeway is used for drugs that don't reach the nose layer. By

encouraging a mucoadhesive framework, this constraint can be overcome. Chitosan has low poisonousness, is biodegradable, biocompatible, clings to biological fluid, and opens the nasal layer's constrictions. These characteristics suggest that chitosan has uses in nasal delivery (28). Nasal assimilation can occur in three different ways: through the trigeminal nerves, the paracellular pathway, and the transcellular pathway (29).

It is essential that carbamazepine crosses the blood brain barrier while treating epilepsy (BBB). The bioavailability and brain targeting of carbamazepine nanoparticles (NPs) of carboxymethyl chitosan have been identified. When carbamazepine was administered intravenously as chitosan nanoparticles, the ratio of brain to plasma exposure was (30). The hormone 17-estradiol, which is linked to sex and a risk factor for Alzheimer's disease (AD), was found in relatively low amounts in women with the disease, according to studies. The powerful sex hormone estradiol has been used to treat and prevent AD. Estradiol must build up in the brain's tissue at a sufficient tissue concentration for it to have an effect.

After oral treatment, there is hardly much estradiol in the cerebral fluid. It was shown that the levels of estradiol in the cerebrospinal fluid were higher than those in the plasma when it was administered intranasal as chitosan NPs. These results suggest that estradiol is directly delivered to the brain when given as chitosan NPs via the nasal route. Another example is the finding that leuprolide, a medication used to treat diseases caused by hormones such as prostate cancer, has a better bioavailability when it is created as thiolated-chitosan nanoparticles (29). Both chitosan NPs and chitosan NPs with leuprolide thiolation were produced. Leuprolide was more effectively transported through the pig nasal mucosa when it was incorporated into chitosan nanoparticles or

thiolated-chitosan nanoparticles as contrasted to leuprolide solution. The area under the plasma concentration vs. time curve AUC shows that the drug exposure rose 6.9-fold with thiolated-chitosan NP (31).

5. Chitosan in pulmonary drug delivery:

Both the general public and the local community may be affected by drug delivery to the lungs. A few benefits of administering medication via the lungs over other routes are quick and supportive drug administration, high survivability, and no hepatic first-pass effect. Drug transport into the lungs is facilitated by the lungs' enormous surface area, high tissue vascularity, and thin ingestion barrier (32). Drug transport into the lungs is hampered by the bronchial body fluid layer, alveolar coating liquid, epithelial cells, macrophage leeway, and proteolytic debasement (33). According to a recent assessment by Islam and Ferro (34), chitosan-based nanoparticles can be used to deliver medication to the lungs. The positive charge on the outer layer of chitosan delivers mucoadhesive qualities, which the creators assured would be beneficial for the delivery of pneumonic medicine. It has recently been demonstrated that the positive charge on chitosan opens the intercellular tight junctions of the lung epithelium, increasing take-up. This adhesion to the lung mucosa increases the potential for drug absorption. Chitosan has an odd antibacterial effect that only affects phosphoryl groups and lipopolysaccharides on bacterial cell walls, which is an added benefit in the fight against aspiratory bacterial infections.

6. Chitosan in mucoadhesion:

One of the main disadvantages of delivering proteins, peptides, or macromolecules via a non-infusion course is the restricted retention at mucosal destinations. On the other hand, nasal/buccal depression or to the vaginal, urethral, or pneumonic destinations, or mucoadhesive mucoadminister the medication for local delivery in the GI tract. By sticking to the bodily fluid layer and dispensing the medication over an extended length of time, mucoadhesive Nano and microparticles have the potential to decrease dosage recurrence. Drugs can enter the fundamental flow when certain polymers, like chitosan, temporarily and reversibly relax the tight connections between epithelial cells (35). Alginate, guar gum, gelatin, carrageenan k sort ii, poly (vinyl pyrrolidone), poly (vinyl amine), poly (ethylene glycol), poly (ethylene oxide), and their copolymers, as well as poly (acrylic corrosive) and poly (methacrylic corrosive) subordinates, make up a portion of the other

mucoadhesive polymers that have been separated from chitosan (36).

The chitosan's substantial positive charge, which helps it form a bond with negatively charged mucus, is what gives it its mucoadhesive qualities, as was already mentioned. Mucus is produced by both the respiratory tract and the GIT organs. DNA and protein/peptide medications are difficult to provide orally due to the GIT's unstable pH and enzyme environment. Chitosan is an excellent carrier for these drugs because it is mucoadhesive, enhances penetration, and forms a barrier to shield the medicines (37). Particle size has an impact on chitosan nanoparticles as well since smaller particles may have a better chance of penetrating the mucous layer.

7. Chitosan in Parenteral route of administration:

Parenteral administration, in reality, refers to the placement, injection, or infusion of substance(s) into blood vessels, tissue spaces, or bodily compartments. The medication is subsequently transported from the administration location to the crime scene. The parenteral route of administration is viewed as an invasive way of medication delivery because it involves a body incision or puncture. Intramuscular (IM), intravenous, subcutaneous (SC), and intradermal Intravenous (IV) and intra-arterial techniques are the most common forms of parenteral administration. Figure 6 displays these paths. The produced particles' size, surface charges, and hydrophilic or hydrophobic makeup determine their biodistribution and intravenous parenteral administration. (38) The smallest bodily microvessels have a diameter of between 5 and 10 m, making intravenous administration of nanoparticles the simplest method. The reticuloendothelial system (RES) in the spleen, lung, liver, and bone marrow entraps larger particles than 100 nm after intravenous administration of nanoparticles, but those of smaller size are characterized by prolonged circulation duration. (2) Despite several efforts, no conclusive explanation has been provided for how surface charges on nanoparticles affect pharmacokinetics and tissue distribution. Hydrophilic particles have a tougher time navigating the tissues than hydrophobic ones do. On the other hand, hydrophilic nanoparticles coated with PEG or nonionic surfactants and smaller than 100 nm will evade macrophage phagocytosis. It has been demonstrated that PEGylating the produced particles lengthens circulation time and prevents RES entrapment. However, PEGylation is still the most feasible and well-liked technique. Other polymers such poloxamers, polyvinyl alcohol, and polysaccharides have been studied in various attempts. (39) The mushroom conformation at low PEGylation and the brush conformation at high PEGylation are the two forms of conformation for coating the nanoparticle surface with PEG. The latter is the strategy that stops serum absorption of nanoparticles the

best. The process of opsonization, in which a specific serum protein binds to a substance to facilitate uptake of this serum protein substance-binding complex by RES, is decreased by PEGylation. Due to the RES cells' inability to recognize the nanoparticles, they are able to remain in the blood pool. (40) In addition to the IV method, which is still a parenteral approach, nanoparticles may be administered via the subcutaneous and intramuscular routes. Many drugs in the form of chitosan particles when administered parenterally showed better pharmacological effects and reduced systemic toxicity. Animal experiments showed that doxorubicin-chitosan nanoparticle IV therapy significantly reduced tumour growth and improved survival.

In their study of the pharmacokinetics and tissue distribution of doxorubicin chitosan nanoparticles following IV injection, (24) discovered that the drug was more efficiently delivered to the RES and had fewer systemic and cardio toxic effects. Paclitaxel was successfully loaded onto a modified chitosan carrier that was administered by IV and compared to commercial medication formulation. This chitosan carrier system was noted for having a greater tolerated dose and being less harmful. (41)

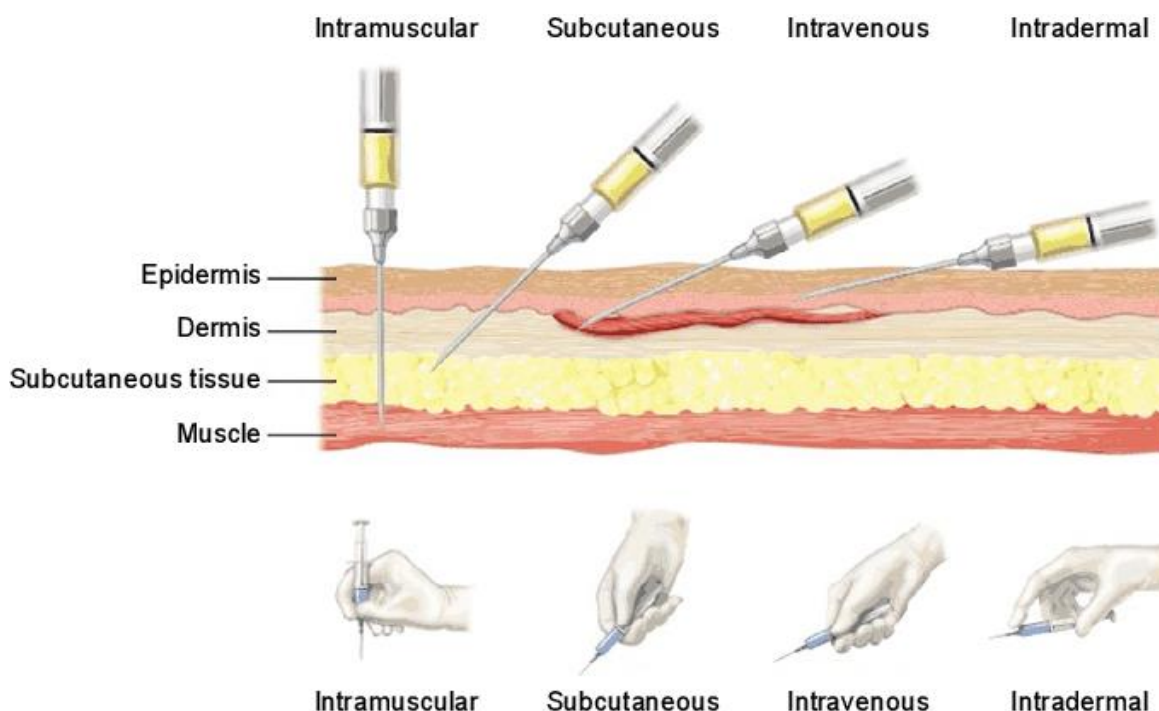


Figure 4. Structure of the skin, subcutaneous layers, and typical methods for administering parenteral drugs.

8. Conclusions and future work:

Chitosan has a wide range of potential applications in the delivery of medications via the GIT, nasal, and pulmonary routes, as this review illustrates. By keeping the drug localized for a long time to allow for absorption, Chitosan np can efficiently provide medication to specific regions. Medication can now be delivered directly from the nose to the brain because to chitosan's improved mucoadhesion and absorption. Locally targeting problems like colon and lung infections is possible with chitosan np. Phase 2 clinical trials for Rylominetm, a chitosan-based nasal morphine formulation, are currently taking place in the UK, the EU, and the US. When it hits the market, we

think it will pave the way for related products and make it easier to spot any unanticipated effects in people (42). Even though they are not specifically covered here, we foresee additional advancements in the utilization of chitosan nanoparticles in targeted cancer therapies, dermatological applications, and tailored parenteral drug delivery systems (43, 44). As new strategies for getting around chitosan's limitations have emerged for a wider range of medicines and even macromolecules, we anticipate seeing more chitosan research in the near future, particularly in nasal and pulmonary drug administration. Future studies on chitosan nanoparticles derived from chitosan or its derivatives are expected to focus on human toxicity evaluations.

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