CHITOSAN: AS HIGHLY POTENTIAL BIOPOLYMER OBTAINABLE IN SEVERAL ADVANCE DRUG DELIVERY SYSTEMS INCLUDING BIOMEDICAL APPLICATIONS

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Abstract:
Chitosan, a biomaterial, has shown potential in developing innovative drug delivery systems (NDDS) and has various biomedical uses. Chitosan is a polysaccharide originating from chitin and is both biocompatible and biodegradable. A biopolymer known as chitosan is extracted from chitin, which is a natural polymer present in the exoskeleton of crustaceans like lobster, shrimp, and crab, as well as in the cell walls of fungi. In the past few years, there has been significant research conducted on Chitosan due to its vast range of possible uses in fields such as agriculture, cosmetics, food, and medicine. The various innovative drug transportation techniques utilizing chitosan have been developed for a range of routes including topical, oral, ophthalmic, transdermal, and nasal administration methods. Chitosan has the capability to create hydrogels when exposed to alterations in pH or ionic strength. This review article provides the sourcing or origin of chitosan, including the biomedical activities of chitosan. Chitosan plays role in various applications in innovative drug delivery systems including advance drug delivery systems, TDDs and Nasal drug delivery as well as included bone regeneration and wound healing. Lastly, the crucial role of chitosan derived from chitin extensive operations in vaccination and cosmetics products.

Keywords: Chitin, Chitosan, Advance novel drug delivery system (NDDS), Wound healing, Cosmeceuticals.

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1. INTRODUCTION

Chitosan is a biopolymer, which means that it is a natural polymer that is produced by living organisms. It may be a direct polysaccharide composed of β-(1-4)-linked d-glucosamine and N-acetyl-d-glucosamine units. Chitosan may be a versatile biopolymer with a wide range of applications. It is biodegradable, biocompatible, and non-toxic, making it an attractive choice for many applications.

Chitosan is a biopolymer that has been used as an excipient in pharmaceutical formulations due to its unique physicochemical properties. Chitosan has been used in various pharmaceutical applications such as drug delivery, wound healing, and tissue engineering. Recent studies have used chitosan as an excipient in advanced drug delivery. Chitosan has been found to have excellent mucoadhesive properties, making it useful in nasal, ocular, and oral drug delivery [1]. It has also been shown to enhance drug permeability across biological barriers such as the blood-brain barrier. Different types of chitosan, which have varying molecular weights and degree of deacetylation, are frequently utilized to create new modes of transporting drugs. Chitosan has been used as a coating material for drug delivery systems such as nanoparticles, liposomes, and microspheres, enhancing their stability and preventing drug degradation. Chitosan has also been used as a matrix material for controlled drug release systems, allowing for SR over an extended period [2]. Chitosan has been used as a wound dressing material due to its hemostatic, antimicrobial, and tissue regeneration properties. It has been found to promote wound healing and reduce inflammation.

Chitosan is a promising excipient in the field of pharmaceuticals due to its unique properties and potential applications. However, further studies are needed to fully understand its potential and optimize its use in drug delivery systems. It has been extensively studied for its various applications in fields such as *food, agriculture, medicine,* and *environmental science* [3, 4].

There are some recent works has been done on chitosan as a recent advance excipient in the different novel delivery formulation such as includes:

- ***Chitosan-based nanocomposites*:** Researchers have been exploring the use of chitosan in combination with other materials to create nanocomposites with improved properties. For example, a recent study published in the journal Carbohydrate Polymers demonstrated the fabrication of chitosan-based nanocomposites reinforced with cellulose nanocrystals, which exhibited enhanced mechanical and thermal properties.

- ***Chitosan as a drug delivery system:*** Chitosan has been investigated as a potential carrier for drugs due to its biocompatibility, biodegradability, and low toxicity. A recent review published in the journal Carbohydrate Polymers discussed the various strategies for preparing chitosan-based drug delivery systems and highlighted their potential applications in cancer therapy [5].

- ***Chitosan in wound healing:*** Chitosan has moreover been considered for its wound healing properties. Chitosan accelerates the wound mending process by stimulating inflammatory cells, macrophages, and fibroblasts, thus boosting the inflammatory phase. In this way, the inflammatory phase is reduced, and the proliferative phase starts sooner in the wound healing process. (**Fig. 01**)

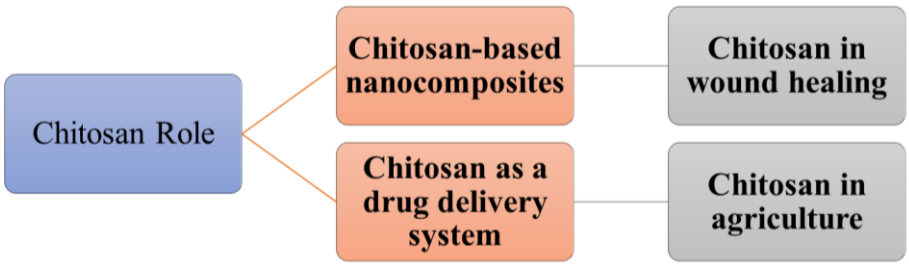

Figure: 01. The role of chitosan in various areas with highly potential purpose

- ***Chitosan in agriculture:*** Chitosan has been used in agriculture as a natural pesticide and fungicide due to its antimicrobial properties. Recent studies have demonstrated the efficacy of chitosan-based formulations in controlling plant diseases and pests while minimizing the use of synthetic chemicals [6,7].

1.1. PROPERTIES OF CHITOSAN: Chitosan is a versatile biopolymer with unique properties that make it suitable for various applications. Some of the most important properties of chitosan include its *biocompatibility, biodegradability, antimicrobial activity*, and ability to form films and gels [8]. Chitosan has unique properties that make it attractive for use in novel drug delivery systems. In those some of properties of chitosan explained as below section:

1.1.1. *Biocompatibility:* Chitosan is biocompatible, biodegradable, and non-toxic, making it safe for use in drug delivery systems.

1.1.2. *Mucoadhesiveness:* Chitosan has the ability to adhere to mucosal surfaces, such as those found in the gastrointestinal tract and respiratory system, which can enhance drug absorption and bioavailability.

1.1.3. *Controlled drug (CR) release:* Chitosan can be used to create drug delivery systems that release drugs in a controlled manner, which can improve therapeutic efficacy and reduce side effects.

1.1.4. *Targeted drug delivery (TDDS):* Chitosan can be modified to target specific tissues or cells, such as cancer cells, which can improve the effectiveness of the drug and reduce damage to healthy tissues.

1.1.5. *Stability:* Chitosan is stable under a wide range of pH and temperature conditions, which can improve the shelf-life of drug delivery systems [8, 9].

Chitosan is a versatile and promising material for use in novel drug delivery systems, with potential applications in areas such as *cancer therapy*, *wound healing*, and *gene therapy*. Chitosan is also a cationic polymer, which means that it can bind to negatively charged molecules such as DNA and proteins, making it useful in **drug delivery** and **gene therapy** [10]**.**

1.2. THE VARIOUS SOURCES OF CHITOSAN: There are the various different sources involving in the production of chitosan which are mainly of marine, natural, microbial as well as synthetic production of chitosan explained in the below section briefly. Chitosan is not naturally found in the environment. It is made by removing acetyl groups from chitin. Chitin has been taken out of different things found in nature, like the ocean, land, and tiny organisms. The makeup of chitin varies depending on factors like how old it is, the time of year, if it's male or female, and the surroundings it's in. The chitosan origin sources are more important such as including two Marine and microbial fermentation process:

1.2.1. *Marine Sources:* The biopolymer known as chitin is present in various marine microorganisms, including crustaceans, amongst others. Some possible ways to paraphrase this text smartly are; A group of aquatic organisms (such as crabs, lobsters, and barnacles). Various sea creatures (such as crustaceans, like lobsters, and shellfish, like barnacles) [11]. Marine lifeforms that include crustaceans (such as lobsters) and sessile filter feeders (such as barnacles).
The sources of marine origin depicted in (**Fig. 02**).

Figure. 02 The various marine sources of chitosan production

A collection of arthropods (such as crabs and lobsters) and marine invertebrates (such as barnacles). Diverse marine species, ranging from large clawed animals (like lobsters) to tiny encrusting creatures (like barnacles) and mollusks (such as cuttlefish and octopus), as well as green and brown algae, including diatoms [12]. The all-other marine sources with their families and uses briefly described in the **Table. 01** as below section:

Table 01: The list of the marine sources including their origin, species, class, and use

Origin	Species	Class	Use
Crustacean shells	Shrimp, crab, lobster	*Malacostraca*	Biomedical, food, nutraceutical, cosmetic, agricultural, and industrial applications
Mollusk shells	Oyster, clam, mussel	*Bivalvia*	Biomedical, food, nutraceutical, cosmetic, and agricultural applications
Fish scales	Salmon, cod, tuna	*Actinopterygii*	Biomedical, food, nutraceutical, and cosmetic applications
Seaweed	Kelp, agar, nori	*Phaeophyceae*	Food, nutraceutical, and cosmetic applications

The well-established industrial extraction techniques of crustacean shells make them a paramount source of chitosan and chitin. According to the FAO, around **11. 2 million** metric tons of shells from crustaceans were manufactured during the year 2022. Extracting chitosan from squid shells is another known practice [13].

1.2.2. *Microbial Fermentation Sources:* Microbial fermentation is a process that uses microorganisms to produce a desired product. In the case of chitosan, microbial fermentation is a promising alternative to traditional methods of chitosan production, such as acid or alkaline extraction. There are a number of microorganisms that can be used to produce chitosan through microbial fermentation [14].

Chitosan can be produced by fermenting chitin with certain microorganisms, such as fungi or bacteria, which produce chitinase enzymes that convert chitin into chitosan. This method is cost-effective and produces chitosan with a high degree of deacetylation. The utilization of fungus is mostly focused on extracting chitin from a microbial origin. The cell wall of fungi contains chitin, beta-glucan, and chitosan. Fungi's structural elements consist of chitin, which makes up approximately 22-44% of its composition [15].

Cultivating and extracting fungi for chitin and chitosan is an easy and eco-friendly process that promotes their use as the main source of these materials. Chitin can be found in a variety of organisms, such as *chrysophyte algae, molds, yeast, fungi, prosthecate bacteria, ciliates*, as well as specific bacterial strains like *Streptomyces sps.* which are capable of producing spores [16].

The various types of microbial sources for the origin source of chitosan with their various application in the given **Table. 02** as below:

Table: 02 List of the microbial fermentation sources of chitosan, with their class and uses

Microbial source	Class	Uses
Lactobacillus	*Bacilli*	Biomedical, food, nutraceutical, and cosmetic applications
Saccharomyces cerevisiae	*Ascomycetes*	Biomedical, food, nutraceutical, and cosmetic applications
Aspergillus niger	*Eurotiomycetes*	Biomedical, food, nutraceutical, and cosmetic applications
Trichoderma reesei	*Hypocreales*	Biomedical, food, nutraceutical, and cosmetic applications
Mucor	*Mucoromycota*	Biomedical, food, nutraceutical, and cosmetic applications

These are some microbial fermentation sources of chitosan with their various applications. Microbial fermentation is a promising alternative to traditional methods of chitosan production. It is a more environmentally friendly, versatile, and efficient process.

1.2.3. *Synthetically (Chemical Deacetylation) Sources:* Chitin can undergo a chemical reaction with a powerful base such as sodium hydroxide to eliminate the acetyl functional groups, resulting in the development of Chitosan [17].

Table 03: List of the synthetically sources of chitosan, with their uses

Source	Uses
N-acetylglucosamine	Biomedical, food, nutraceutical, and cosmetic applications
Chitosan oligosaccharides	Biomedical, food, nutraceutical, and cosmetic applications
Chitosan derivatives	Biomedical, food, nutraceutical, and cosmetic applications

This method produces chitosan with varying degrees of deacetylation, which affects its properties.

1.3. PRODUCTION OF CHITOSAN:

The production of chitosan excipients typically involves several steps, including the extraction of chitin from crustacean shells, deacetylation of chitin to produce chitosan, purification of chitosan, and formulation of chitosan into various

pharmaceutical dosage forms. The degree of deacetylation (DD) of chitosan is an important parameter that determines its properties and various applications. Chitosan with a high DD is more soluble in acidic solutions and has a higher *antimicrobial activity* than chitosan with a low DD [18-19]. The production of chitosan can be achieved by different methods, including chemical and enzymatic methods, and has been extensively studied in recent years. The complete production of chitosan shown in the given (**Fig. 03**) as following:

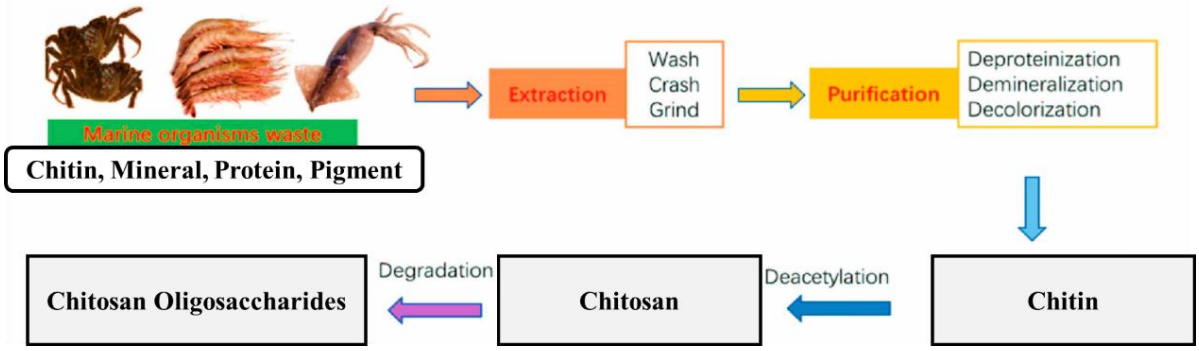

Figure. 03 The steps involving in the production of chitosan from the marine sources

Here are the basic various steps or process involved in the production of advance chitosan excipients used in the different advance novel drug formulations:

1.3.1. ***Extraction of chitin from crustacean shells:*** The first step in chitosan production is the extraction of chitin from crustacean shells. This is typically done by treating the shells with acid or alkali to remove proteins and minerals, followed by washing and drying to obtain pure chitin [20].

1.3.2. ***Deacetylation of chitin:*** Chitin is typically deacetylated to produce chitosan, which involves the removal of the acetyl groups from the chitin molecule. This can be achieved by treating chitin with an alkaline solution such as sodium hydroxide or potassium hydroxide. The degree of deacetylation (DD) of chitosan can be controlled by adjusting the concentration and duration of the deacetylation process.

1.3.3. ***Purification of chitosan:*** Once chitosan has been produced, it is typically purified to remove any impurities or residual chitin. This can be done by washing and filtering the chitosan solution, or by precipitation with a non-solvent such as ethanol or acetone.

1.3.4. ***Formulation of chitosan into dosage forms:*** Chitosan can be formulated into various pharmaceutical dosage forms such as tablets, capsules, films, and gels. The formulation process typically involves mixing chitosan with other excipients such as fillers, binders, and lubricants, and then compressing or molding the mixture into the desired shape [21- 22]**.**

The production of chitosan excipients requires careful attention to quality control and regulatory compliance, particularly with regard to the source and purity of the raw materials, the degree of deacetylation, and the formulation process.

1.4. CHITIN AND CHITOSAN EXTRACTION TECHNIQUES:

Biological and chemical techniques are utilized to withdraw chitin and chitosan from fungi, crustaceans, and insects. The methodology and process of extraction vary, contingent upon the origin of the raw material, encompassing fungi, crustaceans, and insects. Chitin is present in large quantities in the outer skeletons of crustaceans and insects. There are a number of techniques that can be used to extract chitin and chitosan from crustacean shells [23]. The most common techniques are:

1.4.1. ***Acid-alkali extraction:*** This is the most common method for extracting chitin and chitosan. The crustacean shells are first demineralized with an acid, such as hydrochloric acid, and then deproteinized with an alkali, such as sodium hydroxide. The chitin is then extracted from the deproteinized shells by dissolving it in an alkaline solution.

1.4.2. ***Enzymatic extraction:*** This method uses enzymes to deproteinize the crustacean shells. The enzymes break down the proteins in the shells, leaving the chitin behind. This method is often used for extracting chitin from shrimp shells.

1.4.3. ***Solvent extraction:*** **This** method uses solvents to dissolve the chitin from the crustacean

shells. The solvents used are typically organic solvents, such as acetone or ethanol. This method is often used for extracting chitin from crab shells [24].

The choice of extraction technique will depend on the source of the chitin and chitosan, the desired degree of deacetylation, and the desired purity of the product.

Chitin, along with some chitosan content, also exists in the cell walls of fungi [25]. Furthermore, the skeletal structure of crustaceans is composed of various mineral substances such as inorganic carbonates, chitin-protein compounds, carotenoids (namely astaxanthin), and lipids.

Fungi possess a cell wall that consists of various components such as chitin-glucan complex, glycoprotein, and a small percentage of lipids, pigments, and inorganic salts. (**Fig. 04**)

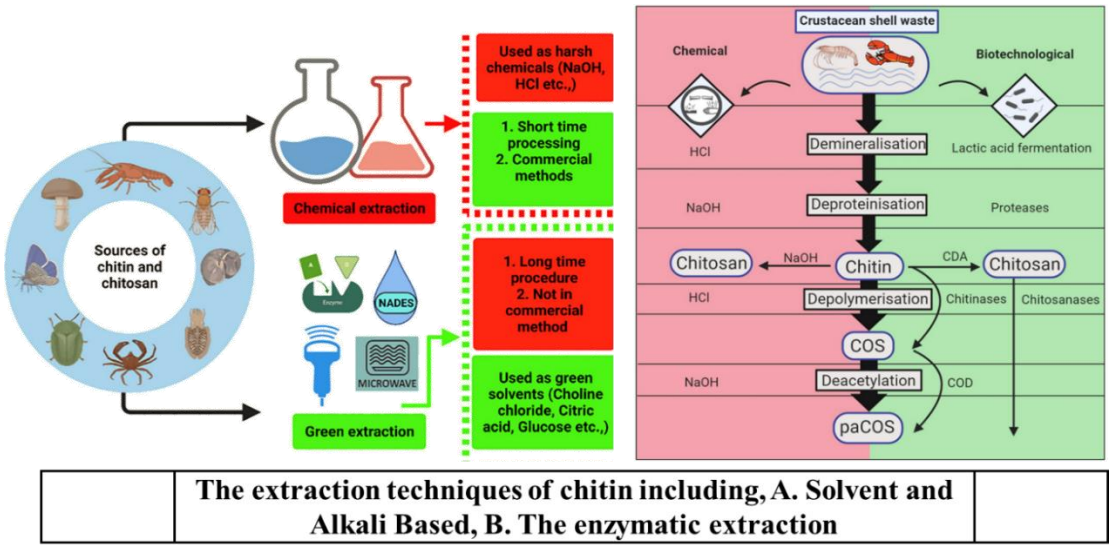

Figure 04: The representation of various extraction techniques of the chitin through A. solvent and acid alkali, B. The enzymatic extraction techniques

Typically, crustaceans have a chitin content of 20-30%, while insects contain around 5-25% chitin. Fungi consist of a chitin content ranging from 2% to 44%, which is chemically linked to glucans composing 80% to 90%. This proportion varies according to the species' growing environment [24-26]. Several processes such as *demineralization, deproteinization, bleaching* and *deacetylation* are involved in the extraction of chitosan.

1.5. PREPARATION OF CHITIN:

The preparation of chitin mainly included as to the chemical and biological extraction process; certain preparatory techniques are employed to ready the biomass for chitin extraction. This may incorporate delicate tissue expulsion by scratching, bubbling, and squeezing. After the biomass has been bubbled, it must be mechanically dried and smashed. Mechanical crushers change over the biomass into little particles. This fine-particle crude fabric is utilized in ensuing preparing [27].

1.5.1. CHEMICAL METHOD: The chemical method includes four subsequent processes, such as *demineralization, deproteinization, decoloration, and deacetylation*. Certain writers have employed alternative processing sequences for the demineralization and deprotonation procedures involved in extracting substances from shrimp and crab shells. Specifically, when extracting from shrimp shells, they initiate the process with deproteinization, whereas when extracting from crab shells, they commence with demineralization. Some researchers conclude that this interchangeable process had no effect on yield or quality [26-28].

a) *Demineralization Process:* Opting for demineralization is advisable in instances where the biomatter comprises a substantial amount of minerals, like the 50% of CaCO3 that forms part of the exoskeleton of crustaceans [28]. During chemical demineralization, minerals like calcium phosphate and calcium carbonate are removed from the shell by an acidic solvent. The most widely used acids are HCl, HNO_3, H_2SO_4, CH_3COOH, and HCOOH. HCl is most commonly used acid for the removal of the minerals [29]. To remove minerals, the shell is exposed to acid. Once this is done, the shell is demineralized and filtered through a vacuum. The resulting demineralized shell is thoroughly rinsed with distilled water until it reaches a neutral pH. The demineralized shell is

then dried in an oven at approximately 55-61°C for 24 hours [30].

b) *Deproteinization of chitin:* The protein matrix contains a demineralized chitin chain. To minimize the risk of allergic reactions, it is advisable to steer clear of this particular protein whenever feasible. Therefore, it is recommended to take out all of the protein when using chitin in medicine or the food industry. Removing the protein requires careful processing because the amino group, which is not connected to chitin, is attached to the protein by a strong bond and multiple hydrogen bonds.
Demineralization is the process of removing minerals from chitin. This is a necessary step in the production of chitosan, as the minerals can interfere with the deacetylation process. In the deproteination process, biomass is treated with the alkaline reagent. NaOH, Na_2CO_3, $NaHSO_3$, $CaHSO_3$, Na_2SO_3, K_2CO3 and Na_2S are commonly used reagents. The protein is removed in this process when alkali reacts with the biomass with constant stirring for 2 hours at approximately 90°C [31].
Deproteinization is the process of removing proteins from chitin. This is necessary in order to obtain pure chitin, which is used in a variety of applications. There are a number of different methods that can be used for deproteinization, including:

- ***Alkaline treatment:*** This is the most common method for deproteinization. It involves treating chitin with an alkaline solution, such as *sodium hydroxide or potassium hydroxide.* The alkaline solution disrupts the bonds between the proteins and chitin, causing the proteins to precipitate out.

- ***Acidic treatment:*** This method is less common than alkaline treatment, but it can be effective in some cases. It involves treating chitin with an acidic solution, such as *hydrochloric acid or nitric acid.* The acidic solution disrupts the bonds between the proteins and chitin, causing the proteins to precipitate out.

- ***Enzymatic treatment:*** This method involves using enzymes to break down the proteins. Enzymes such as *chitinase and pectinase* can be used to deproteinize chitin.

- ***Ultrasonic treatment:*** This method uses ultrasonic waves to disrupt the bonds between the proteins and chitin. Ultrasonic treatment is a relatively new method for deproteinization, but it is becoming increasingly popular [31-32].

The choice of deproteinization method will depend on the source of the chitin, the desired purity of the chitin, and the cost of the method.

c) *Decolorization/bleaching and post treatment:* The decolorization stage marks the last phase in the chitin extraction process. It is advantageous to carry out this process to eliminate pigments, specifically the rosy hue found in crustaceans. CH3CH2OH and CHCl3, which are organic solvents, were utilized for decolorizing chitin. Additionally, hydrogen peroxide (H2O2) and potassium permanganate (KMnO4) were utilized for the purpose of bleaching the chitin [32]. For instances, Crustacean decolorization has been performed by bleaching agents such as NaCl or $KMnO_4$, H_2O_2, or $(COOH)_2$, decolorizing insect chitin has been successfully achieved by combining chloroform, methanol, and alcohol.

1.5.2. BIOLOGICAL EXTRACTION: The procedure of chemical extraction involves subjecting the biomass to high temperatures for an extended time period with the use of severe chemicals, leading to alterations in the physical and functional properties of chitosan. This substance poses a severe threat to the surroundings. The process of purifying chemically obtained chitin is laborious, requiring significant amounts of energy and time, and it poses environmental risks because of the caustic soda and mineral content in chitin [33]. Biological extraction enables the achievement of higher reproducibility in the production of chitin. The biological extraction process can be carried out using two distinct techniques, namely *enzyme-based* and *fermentation-based methods*.

1.5.1. *Enzymatic Method Involving:* Using a powerful acid treatment is an effective means of removing minerals such as calcium carbonate while carrying out the chemical demineralization process. The enzymatic method for the biological extraction of chitosan involves the use of enzymes to deproteinize and deacetylate chitin. The deproteinization step is necessary to remove the proteins that are naturally present in chitin. The deacetylation step is necessary to convert chitin into chitosan. The various steps of the extraction of chitosan through the enzymatic extraction of biological extraction in the given (**Fig. 05**)

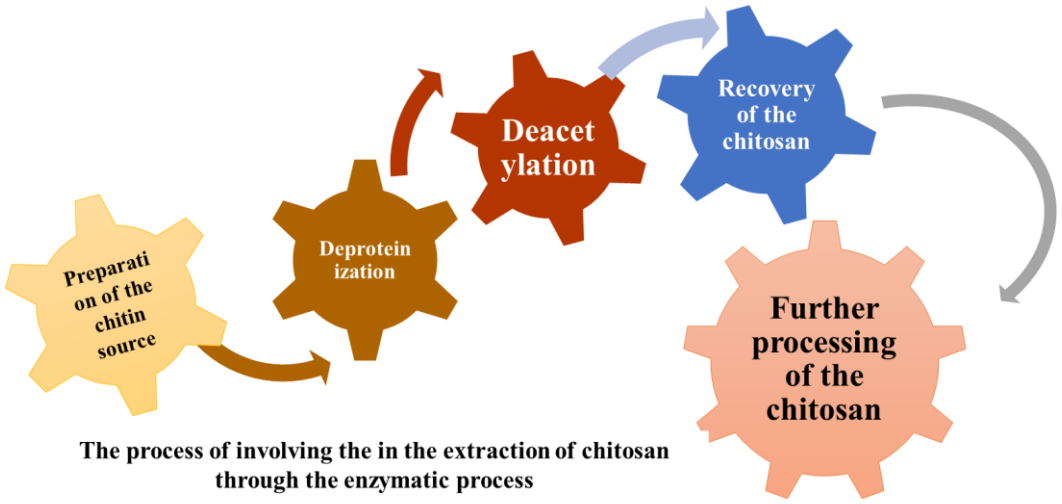

Figure 05: The process steps for the extraction of chitosan by enzymatic method

The enzymes that are commonly used for the enzymatic extraction of chitosan include:

- ***Proteases:*** Proteases are enzymes that break down proteins. They are used to deproteinize chitin by hydrolyzing the peptide bonds that hold the proteins together.
- ***Chitinases:*** Chitinases are enzymes that break down chitin. They are used to deacetylate chitin by hydrolyzing the acetyl groups that are attached to the chitin backbone.

The enzymatic method for the biological extraction of chitosan is a relatively simple and straightforward process. The lots of number of factors that can affect the yield and quality of the chitosan produced. These factors include the type of chitin source, the type of enzymes used, the reaction conditions, and the further processing method used [33-34].

The widespread use of the alclase enzyme is attributed to its ability to manage hydrolysis and generate nonbitter hydrolysate, which is crucial for chitin, protein hydrolysate, and astaxanthin production. *Bacillus licheniformis* is used for the extraction of alclase [34]. Enzymatic deproteination is a gentler process than chemical deproteination and as a result, the chitin chain retains a protein residue and undergoes a smaller degree of deacetylation [41]. By utilizing a chemical reaction, the inefficiency of the enzymatic reaction was addressed, resulting in enzymatic extraction becoming an amalgamation of both enzymatic and chemical reactions [34-36].

1.5.2. *Fermentation Method:* The utilization of fermentation as an alternative approach to the enzyme-based method, which involves the use of acid-producing microbes and proteolytic enzymes, effectively addresses the associated challenges. Fermentation is a biological extraction technique that can be used to produce chitin and chitosan from a variety of sources, including crustacean shells, insect exoskeletons, and fungi. The fermentation process involves the use of microorganisms, such as lactic acid bacteria or fungi, to produce organic acids that help to demineralize the chitin. The demineralized chitin can then be further processed to produce chitosan [37]. Fermentation process mainly involving in the various steps as following:

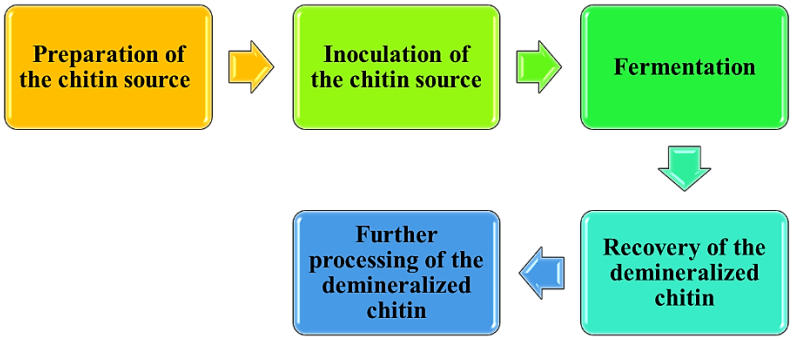

Figure 06: The various steps of fermentation process of the chitosan extraction

Fermentation has several advantages over traditional chemical extraction methods for producing chitin and chitosan. First, it is a more environmentally friendly process. Second, it can be used to produce chitin and chitosan from a wider variety of sources. Third, it can produce chitin and chitosan with a higher degree of purity.

The main drawback of fermentation is that it is a slower process than chemical extraction. However, the advantages of fermentation outweigh the disadvantages in many cases [38]. The various microorganisms that are commonly used in fermentation for chitin and chitosan production:

- ***Lactic acid bacteria:*** These bacteria produce lactic acid, which is an effective demineralizing agent. Some common lactic acid bacteria used for chitin and chitosan production include *Lactobacillus plantarum, Lactobacillus paracasei, and Lactobacillus helveticus.*

- ***Fungi:*** Some fungi, such as *Aspergillus niger* and *Mucor circinelloides*, can also produce organic acids that can be used to demineralize chitin.

The demineralized chitin can then be further processed to produce chitosan. This process typically involves treating the chitin with an alkaline solution, such as sodium hydroxide. Fermentation is a promising biological extraction technique for producing chitin and chitosan. It is a more environmentally friendly and versatile process than traditional chemical extraction methods. However, it is a slower process, so it may not be suitable for all applications [38-39].

2. THE BIOACTIVITIES OF CHITOSAN AS BIO-POLYMER:

The range of biological functions exhibited by chitosan and its derivatives is broad and varied. Chitosan displays efficacy against a diverse range of microorganisms including *bacteria, filamenteous fungi* and *yeasts* [40]. In the following passage, a succinct overview is provided outlining the various bioactivities exhibited by chitosan. The bioactive nature of chitosan biopolymer is demonstrated in the figure provided below. According to their effectiveness in performing certain tasks, such as (**Fig. 07**):

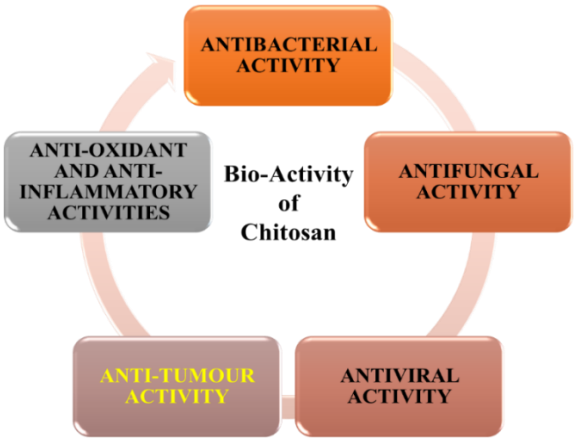

Figure. 07 The various bioactivity of chitosan as biopolymer

2.1. ***Antibacterial Activity:*** Chitosan exhibits a wide range of effectiveness against various bacterial pathogens, with a significant ability to eliminate both gram-positive and gram-negative strains [41- 42]. Scientific investigations have revealed that chitosan has varying effects on various bacterial species.

The precise mechanism by which chitosan and its derivatives exhibit its antibacterial action is not fully understood, however several investigations have been undertaken to speculate on the underlying antimicrobial processes [42]. The mechanism of antibacterial action of chitosan has been the subject of several hypotheses. The antibacterial exercises had by chitosan and one of its subsidiaries named chitosan oligosaccharide lactate (COL), were explored against to three pathogens specifically, Edwardsiella ictaluri, Aeromonas hydrophila, and Flavobacterium columnare.

2.2. Antifungal Activity: Chitosan is a natural polymer that has been shown to have antifungal activity against a wide range of fungi, including *Candida albicans, Aspergillus niger, and Trichophyton rubrum*. The antifungal activity of chitosan is thought to be due to a number of factors, including its ability to:

- ***Destabilize the cell membrane of fungi:*** Chitosan can bind to the cell membrane of fungi, causing it to become leaky and unable to maintain its osmotic balance. This leads to cell death.
- ***Inhibit the growth of hyphae:*** Chitosan can inhibit the growth of hyphae, which are the long, thread-like structures that fungi use to grow and spread.
- ***Induce the production of reactive oxygen species:*** Chitosan can induce the production of reactive oxygen species, which are highly reactive molecules that can damage the DNA and proteins of fungi [43-44].

The antifungal activity of chitosan has been demonstrated in a number of studies, both in vitro and in vivo. In one study, chitosan was shown to be effective in inhibiting the growth of Candida albicans in both cell culture and in a mouse model of candidiasis [43]. In another study, chitosan was shown to be effective in treating onychomycosis, a fungal infection of the nails.

2.3. ***Antiviral Activity:*** Chitosan, as well as its derivatives, have been found to exhibit antiviral properties and other noteworthy bioactivities. Chitosan is a natural polymer that has been shown to have antiviral activity against a wide range of viruses, including HIV, influenza, and herpes simplex virus. The antiviral activity of chitosan has been demonstrated in a number of studies, both in vitro and in vivo. In one study, chitosan was shown to be effective in inhibiting the replication of HIV in cell culture. In another study, chitosan was shown to be effective in preventing the transmission of influenza virus from animals to humans [44]. The antiviral activity of chitosan makes it a potential candidate for use in a number of applications, including:

- ***Preventing the spread of viruses:*** Chitosan can be used to prevent the spread of viruses by inhibiting the attachment, penetration, and replication of viruses.
- ***Treating viral infections:*** Chitosan can be used to treat viral infections by inhibiting the replication of viruses and inducing the production of interferon.
- ***Developing new antiviral drugs:*** Chitosan can be used to develop new antiviral drugs by targeting the mechanisms of action of chitosan.

The antiviral activity of chitosan is a promising property that has the potential to be used in a number of different applications. Chitosan with a atomic weight underneath 10 kDa has detailed to show antiviral impacts against several influenza infection subtypes, suggesting that molecular weight plays a part within the antiviral activity [44-45].

2.4. ***Anti-tumour Activity:*** The use of chitosan, which has a positive charge that assists in non-covalent bonding with biological tissues, has been investigated as a possible solution for addressing the drawbacks of existing chemotherapy methods. Therapeutic agents conjugated with chitin or chitosan derivatives have demonstrated remarkable anticancer activity with fewer side effects than the original drugs [46].

The anti-tumor activity of chitosan is thought to be due to a number of factors, including its ability to:

- ***Induce apoptosis:*** Chitosan can induce apoptosis, which is a programmed cell death. This is thought to be one of the main mechanisms by which chitosan kills cancer cells.
- ***Inhibit angiogenesis:*** Angiogenesis is the growth of new blood vessels. Cancer cells need a supply of blood to grow and spread. Chitosan can inhibit angiogenesis, which can starve cancer cells and lead to their death.
- ***Activate the immune system:*** Chitosan can activate the immune system, which can help to fight cancer cells.

The anti-tumor activity of chitosan has been demonstrated in a number of studies, both in vitro and in vivo. In one study, chitosan was shown to be effective in inhibiting the growth of human breast cancer cells in cell culture. In another study, chitosan was shown to be effective in shrinking tumors in a mouse model of breast cancer [45-46]. Chitosan is a natural polymer that has been shown to have anti-tumor activity.

2.5. ***Anti-oxidant and anti-inflammatory activities:*** Chitosan and its derivatives have the ability to act as antioxidants by effectively neutralizing harmful oxygen radicals such as hydroxyl, superoxide, alkyl and stable DPPH radicals. Chitosan and its derivatives are recognized for their ability to obstruct the oxidative chain reaction through their role as donors of hydrogen [47].

The antioxidant and anti-inflammatory activities of chitosan make it a potential candidate for use in a number of applications, including:

- ***Preventing and treating oxidative stress:*** Oxidative stress is a condition in which there is

an imbalance between free radicals and antioxidants. This can lead to damage to cells and DNA. Chitosan can help to prevent and treat oxidative stress by scavenging free radicals.

- ***Treating inflammation:*** Chitosan can help to treat inflammation by inhibiting the production of pro-inflammatory cytokines and inducing the production of anti-inflammatory cytokines.
- ***Developing new drugs:*** Chitosan can be used to develop new drugs by targeting the mechanisms of action of chitosan.

The antioxidant and anti-inflammatory activities of chitosan are promising properties that have the potential to be used in a number of different applications. More research is needed to fully understand the mechanism of action of chitosan and to optimize its use for antioxidant and anti-inflammatory applications [47-48].

3. THE VARIOUS APPLICATIONS OF CHITOSAN IN NOVEL DRUG DELIVERY SYSTEM:

Chitosan has a wide range of potential applications in various fields, including *medicine, agriculture, food,* and *cosmetics*. In medicine, chitosan has been used as a wound dressing, drug delivery system, and in gene therapy. Chitosan has also been used in agriculture as a natural pesticide, soil conditioner, and seed coating agent [49]. The applications shown in the given (**Fig. 08**) as following:

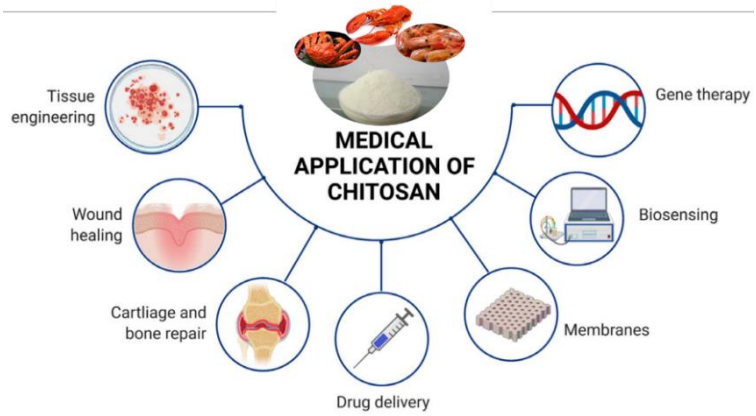

Figure 08: The various medical applications of chitosan as biopolymer

In the food industry, chitosan has been used as a preservative, food packaging material, and fat replacer [48]. In cosmetics, chitosan has been used in anti-aging creams, hair care products, and sunscreen formulations. Chitosan mainly involved in the various advance drug delivery system as advance approach such as (**Table. 04**):

Table 04. The delivery system and chitosan-based approach

Drug delivery system	Application
Chitosan nanoparticles	Sustained release of drugs, targeted delivery of drugs, gene delivery
Chitosan microparticles	Controlled release of drugs, targeting of drugs to specific tissues
Chitosan films	Controlled release of drugs, wound dressings
Chitosan hydrogels	Controlled release of drugs, tissue engineering
Chitosan-coated tablets	Controlled release of drugs, improved bioavailability of drugs
Chitosan-coated implants	Controlled release of drugs, sustained release of drugs

The all applications explained in the below section with briefly:

3.1. *ADVANCED DRUG DELIVERY APPLICATIONS:*

Modern medicine relies heavily on efficient drug delivery systems to ensure the effectiveness and safety of therapeutic substances. To achieve precise drug delivery inside the body, multiple obstacles must be overcome, including liver/kidney drug clearance, quick degradation in the blood, and restricted ability to pass through biological membranes. It is imperative to have an appropriate means of transportation or conveyance to safeguard the medication from deterioration, prolong its duration in the body, and improve its concentration at the intended destination. A drug carrier that is considered ideal should have certain fundamental qualities, including the ability to be compatible with the biological system, break down naturally, and have controlled release properties [50].

Chitosan has been found to be safe for systemic consumption through various acute toxicity

studies, with an LD50 that exceeds 16 g/kg when administered orally to mice [50-51]. The vital amino group within the glycosidic residue found in chitosan is responsible for chemical bonding, resulting in a positive charge for the molecule. A few broadly utilized chitosan-based conveyance frameworks have been examined within the taking after areas (**Table. 05**).

Table 05. Chitosan systems utilized in the fields of medicine and biotechnology

Type of system	Overview	Method of preparation
Microspheres	These are curved entities from 10 μm to 1000 μm in diameter. Various microspheres (e.g., hollow, core-shell, and fibrous) control release pattern.	• Emulsion or thermal cross-linking • Ionotropic gelation/Spray drying [51]
Tablets	In tablet production, it is employed as a base material to manage the discharge of medication, extend the longevity, and augment the physical attributes of the tablets.	• Direct compression • Wet granulation [52]
Nanoparticles	They're tiny systems used for size control (1-100 nm) and surface modification to deliver drugs, proteins, and genes.	• Emulsion-Solvent Evaporation • Modified ionic gelation/ • Emulsification & cross-linking [53]
Hydrogels	They're cross-linked polymers that create a 3D network for water retention. Gelation can be controlled for creating hydrogels for biomedical use.	•Physical/Chemical/Enzymatic crosslinking • Photo-crosslinking [54]
Powder/ microgranules	Subcategories of solid dosage forms with micron-sized drug aggregates and chitosan.	• Spray drying and Gelation •Salt-/Organic solvent-induced precipitation [55]

The (**Table. 01**) presented above. Elucidate the various formulations utilizing chitosan, along with the preparation techniques involved in the production of chitosan, along with a comprehensive explanation. The chitosan used in the different type of formulation such *nanomedicines, powder, microspheres* and many more formulation **[50-55]**.

3.2. *TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS):*

The vast surface area of the skin makes it an ideal pathway for delivering a variety of medications. When compared to the delivery methods of IV and oral, transdermal administration has several advantages such as bypassing first-pass metabolism, sustained levels of blood concentration, and the ability to deliver localized and systemic treatment. It is effective in addressing chronic pain, imbalances in hormonal levels, as well as illnesses related to cardiovascular health [56].

The stratum corneum often hinders the efficacy of transdermal delivery. The structure contains keratin threads that are surrounded by a tough layer and coated with a double layer of lipids. This double layer serves as a barrier that prevents drugs from entering. Despite the fact that there are commercially available transdermal treatments such as patches, ointments, and sprays, concerns remain regarding their effectiveness due to issues such as limited drug absorption, side effects like skin irritation, and the difficulty of having patients comply with treatment [55-56].

Chitosan and its subsidiaries are detailed to upgrade the skin penetrability by means of an assortment of atomic components. The use of low molecular weight chitosan is common in transdermal drug delivery systems as a means of improving permeability.

Several types of transdermal drug delivery systems that utilize chitosan have been developed, including composite films, vesicular systems, dendrimers, microspheres, microneedles, and a variety of nanocarriers such as nanoparticles, nanogels, nano-emulsions, and nano-lipid carriers [57]. The complete composition of transdermal patch shown in the given (**Fig. 09**) as following with the using of chitosan as biopolymer:

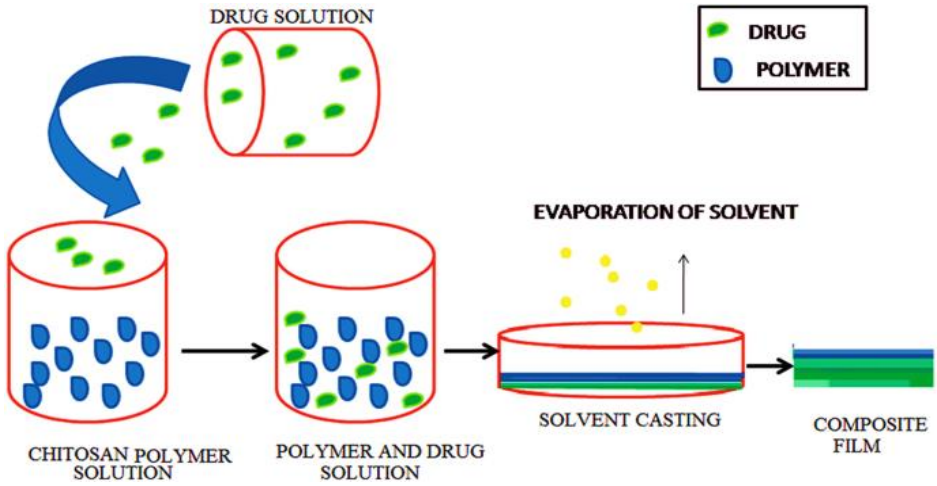

Figure 09: Representation of composite film of transdermal patch using chitosan solution

To tackle the aforementioned problems, scientists are exploring the utilization of artificial polymers with high molecular weight, like PEG and PLA, due to their remarkable stability and bonding properties. Nevertheless, their lack of degradation, potential toxicity, and consequent immune response pose restrictions to their usefulness. Chitosan and its derivatives have the potential to enhance drug penetration in situations like this [57-58].

The Liposome are widely used in the treatment of Transdermal drug delivery system (TDDS), Liposomes consist of bilayer phospholipid molecules that form spherical vesicles ranging in diameter from 10 to 5000 nm. Liposomes are an effective carrier for delivering drugs through the skin due to their various benefits, including but not limited to: high drug capacity, lowered skin irritation from medication, small size, extensive surface area contact with the outermost layer of skin, skin coating ability, encapsulation properties, diminished water loss, enhanced drug transdermal penetration, and prolonged release duration.
Chitosan The application of its derivatives as a transdermal liposome coating can enhance the durability of the liposomes. N-succinyl chitosan, among certain other chitosan derivatives, has the potential to serve as a controlled release coating given its ability to react to changes in pH levels and release its contents in response to skin pH [59].
As research in this area continues, we can expect to see even more drugs being delivered through the skin using this promising technology. A (**Table. 05**) that summarizes the properties of chitosan that make it well-suited for transdermal drug delivery:

Table: 06 The list of property of chitosan with their complete description

Property	**Description on the basis of application of chitosan**
Biocompatibility	Chitosan is non-toxic and biodegradable, making it safe for use on the skin.
Permeability enhancer	Chitosan can increase the permeability of the skin to drugs, which can help to improve the delivery of poorly soluble or permeable drugs.
Mucoadhesive	Chitosan can adhere to the skin, which can help to keep the drug in place and prevent it from being washed away.
Film-forming ability	Chitosan can form films that can be used to encapsulate drugs. This can help to protect the drug from degradation and improve its stability.

Chitosan is a natural polysaccharide that has been widely studied for its potential use in transdermal drug delivery systems (TDDS). TDDS are designed to deliver drugs through the skin, bypassing the first-pass metabolism of the liver and providing a more direct route of administration. Chitosan is a promising material for TDDS, and it is currently being investigated for a variety of clinical applications **[59]**. It included various examples of TDDS that use chitosan highly based on their delivery vehicles:

01) ***Chitosan microneedles:*** Microneedles are small, needle-like structures that can be used to deliver drugs through the skin. Chitosan microneedles have been shown to be effective in delivering a variety of drugs, including insulin, fentanyl, and nicotine.

02) ***Chitosan patches:*** Chitosan patches are a type of TDDS that is applied to the skin. The patch contains a reservoir of drug that is slowly released over time. Chitosan patches have been shown to be

effective in delivering a variety of drugs, including fentanyl, nicotine, and estradiol.

03) ***Chitosan gels:*** Chitosan gels are a type of TDDS that is applied to the skin. The gel contains a drug that is dissolved in a water-based solution. Chitosan gels have been shown to be effective in delivering a variety of drugs, including lidocaine, diclofenac, and estradiol **[55-60]**.

The some of the other examples of advance vehicle which containing the chitosan highly operational biopolymer in the given **Table. 07.**

Table 07: List of advance vehicles of TDDS as chitosan characteristics uses with disease

Vehicle	Characteristics	Uses	Disease
Chitosan microneedles	Small, needle-like structures that can be used to deliver drugs through the skin.	Effective in delivering a variety of drugs, including insulin, fentanyl, and nicotine.	Diabetes, pain, smoking cessation
Chitosan patches	A type of TDDS that is applied to the skin. The patch contains a reservoir of drug that is slowly released over time.	Effective in delivering a variety of drugs, including fentanyl, nicotine, and estradiol.	Pain, smoking cessation, hormone replacement therapy
Chitosan gels	A type of TDDS that is applied to the skin. The gel contains a drug that is dissolved in a water-based solution.	Effective in delivering a variety of drugs, including lidocaine, diclofenac, and estradiol.	Pain, inflammation, hormone replacement therapy [61-62]
Chitosan nanoparticles	Small particles that can be used to deliver drugs through the skin.	Effective in delivering a variety of drugs, including antibiotics, antifungals, and anti-cancer drugs.	Infection, fungus, cancer

Chitosan is a promising material for TDDS, and it is currently being investigated for a variety of clinical applications. The development of TDDS that use chitosan is an active area of research. As our understanding of the properties of chitosan and its interactions with the skin improves, we can expect to see even more effective TDDS being developed in the future.

3.3. NASAL DELIVERY SYSTEM:

Medications can be administered through the nasal cavity using the technique of nasal drug delivery (**Fig. 06**). This technique utilizes the abundant bloodstream found in the membranes lining the nasal cavity to expedite the quick dissemination and intake of medications throughout the organism.

In the past, the intranasal method has been employed to apply medicinal substances for the treatment of local ailments in the upper respiratory system, such as nasal congestion, infections, and allergies. In recent times, there has been a growing trend in utilizing the nasal pathway for administering low-molecular-weight medications to effectively treat persistent illnesses including obesity and diabetes [63]. Scientists are currently investigating the nasal pathway as a possible avenue for the treatment of long-term CNS ailments, such as **Alzheimer's and Parkinson's diseases.** Additionally, it may prove beneficial in promptly addressing conditions like migraines and seizures [64]. (**Fig. 10**)

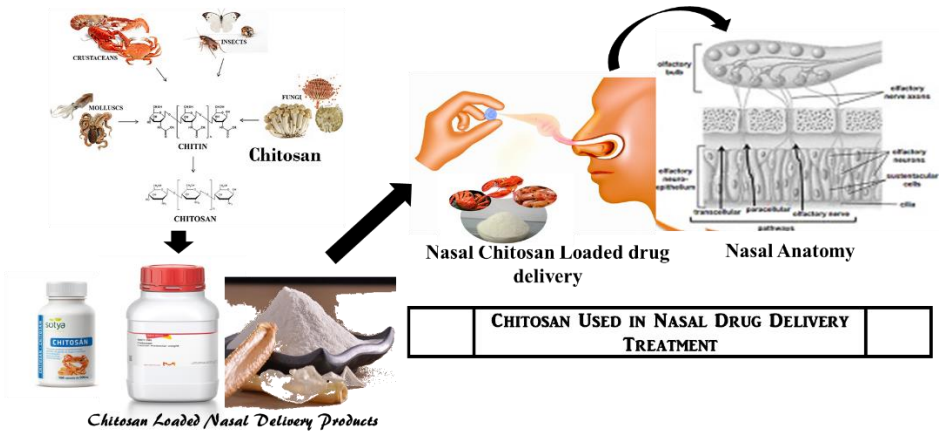

Figure 10: Representation of nasal drug delivery using chitosan as bio polymer

The advantage of taking medicine through the nose is the absence of initial metabolism, the absence of the nervousness related to needles in the parenteral route, and potentially being able to self-administer the treatment, resulting in increased ease for the patient. Nevertheless, the nasal pathway poses certain difficulties [62-64]. Nasal discharge can limit drug retention and medication administration is limited by solution amount. An effective method being explored entails the utilization of chitosan, which carries amino groups with a positive charge, enabling interaction with mucous layers containing negatively charged anionic elements, particularly sialic acid. Furthermore, due to its property of adhering to mucus and regulating the movement of cilia that clear the airways, chitosan has been utilized in the creation of various intriguing methods for delivering medication through the nasal route **[65]**.

The delivery of ibuprofen to the brain through the nose is made possible by a thermosensitive hydrogel that contains chitosan and β-glycerophosphate as a gelling agent [79]. IBU, a frequently prescribed non-steroidal anti-inflammatory medication, has been demonstrated to delay the start of Alzheimer's disease. The blood-brain barrier and low solubility restrict the quantity of IBU that enters the brain through oral or intravenous administration. To address these constraints, the scientists devised a nasal mist that can be simply administered and transforms from a liquid to a semi-solid substance with adhesive qualities to mucous membranes when exposed to bodily temperatures [64-66].

4. THE BIO-MEDICAL APPLICATIONS OF CHITOSAN:

4.1. *BONE REGENERATION:*

The utilization of bone regenerative therapy has the potential to effectively treat an array of skeletal issues such as breaks, osteoporosis, and congenital deformities that can result in ongoing discomfort, immobilization, and impaired quality of life. The traditional methods used to treat these ailments, such as medication and surgery, may not be fully effective and can come with certain restrictions. Chitosan-based solutions have the potential to promote bone regeneration by administering growth factors/drugs directly to the injury site or by constructing a biomimetic framework to facilitate the formation of new bone tissue. Chitosan plays a crucial role in stimulating the generation of extracellular matrix (ECM) elements, including collagen, that are vital for the growth and healing of bones. Furthermore, its ability to fight against microbes lowers the probability of contracting infections, and its capability to decompose naturally makes it a desirable alternative for extended usage [67]. Although chitosan shows potential for a range of medical uses, it is crucial to recognize its inadequacies in the context of bone tissue engineering [68].

In order to conquer these constraints, scientists have developed bio-composites through the process of merging chitosan with various other biopolymers, including chitin, silk, and polycaprolactone, in addition to bioactive nanoceramics such as hydroxyapatite and zirconia [65-68]. These composite materials derived from biological sources possess enhanced resilience and structural integrity, rendering them better suited for use in the creation of bone tissue engineering products. Increasing osteo-conductivity can be achieved either through the administration of cytokines or by incorporating bioactive trace elements such as (Sn^{+2}, Zn^{+2}, Cu^{+2}, and Si^{+4}) [67]. A few cutting-edge chitosan-based stages for bone tissue recovery are talked about underneath (**Fig. 11**) as taking after:

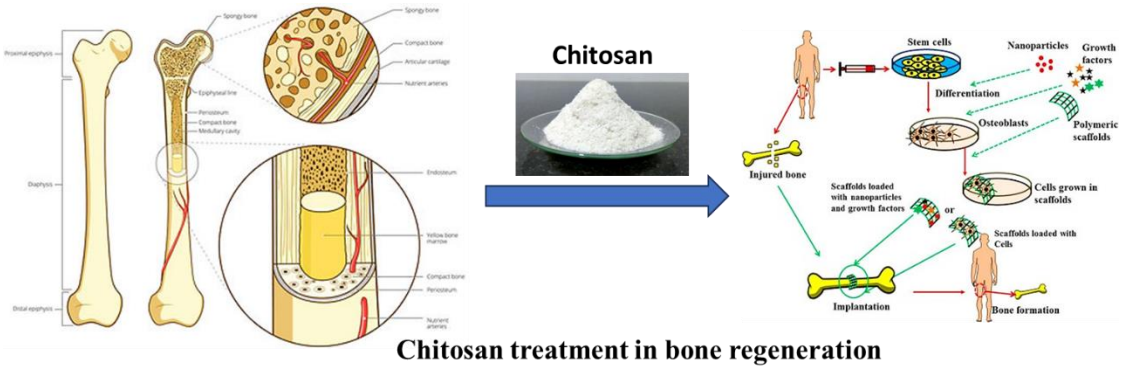

Figure 11: Representation of bone regeneration using chitosan as biopolymer

The primary factors for the lack of success in repairing bone defects are the delayed onset of an inflammatory response and inadequate formation of bone tissue. In order to tackle this issue, Wan and

colleagues. An intelligent composite hydrogel-microsphere was created by combining polydopamine-coated microspheres, which were sensitive to near-infrared (NIR) radiation, with a hydroxy butyl chitosan hydrogel that was responsive to temperature changes [67-69].

4.2. WOUND HEALING:

Disturbances within the skin's keenness can happen due to outside physical or warm harm, as well as inner neurotic conditions, coming about in wounds. There are two classifications for them: acute and chronic. Wounds that are considered acute typically heal within a time frame of 8 to 12 weeks with limited scarring. On the other hand, chronic wounds can have a tendency to recur and may take longer than 12 weeks to heal [68]. It is important to appropriately handle these injuries as they may be impeded by existing physiological conditions, which in turn could impede the recovery process. Chronic wounds encompass a range of conditions such as venous leg ulcers, pressure sores, diabetic foot ulcers, and surgical wounds that fail to heal properly. These wounds are evaluated based on the extent of skin layers impacted and the areas affected. (**Table. 08**)

Table 08: The various application of chitosan vehicle in wound dressings, wound fillers, and wound gels

Application	Description
Wound dressings	Chitosan can be used to make wound dressings that help to protect the wound, promote healing, and prevent infection. Chitosan dressings are typically made from a combination of chitosan and other materials, such as alginate, gelatin, or collagen. They can be used to treat a variety of wounds, including cuts, scrapes, burns, and ulcers.
Wound fillers	Chitosan can be used to make wound fillers that help to fill in the wound and promote healing. Chitosan fillers are typically made from a combination of chitosan and other materials, such as hyaluronic acid or gelatin. They can be used to treat a variety of wounds, including deep wounds, wounds with large defects, and wounds that have not responded to other treatments.
Wound gels	Chitosan can be used to make wound gels that help to keep the wound moist and promote healing. Chitosan gels are typically made from a combination of chitosan and water. They can be used to treat a variety of wounds, including cuts, scrapes, burns, and ulcers.

Chitosan is a promising material for use in wound dressings, wound fillers, and wound gels. It has a number of properties that make it well-suited for this application, including biocompatibility, antibacterial activity, wound-healing properties, and moisture retention [66-69].

The use of biopolymer as chitosan using promote the wound healing property shown in the given (**Fig. 12**) as following:

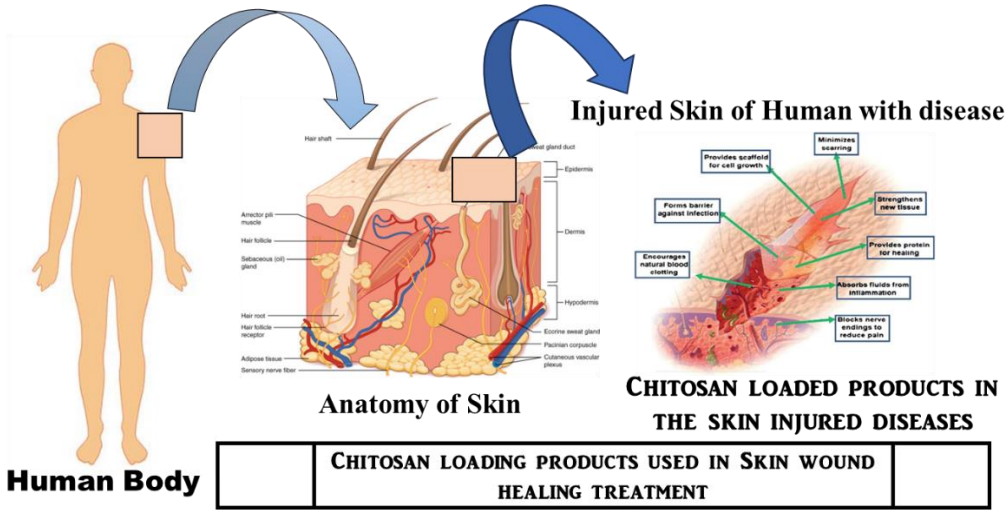

Figure 12: The chitosan promoting the wound healing property

The process of wound healing is intricate and involves various factors, necessitating an environment that fosters it to expedite the process. The body responds to damage with stages that restore skin integrity: hemostasis, inflammation, proliferation, and remodeling. Several different cellular components including enzymes, cytokines, proteins, and hormones act together in a coordinated manner during this procedure [70].

Chitosan has been used in a variety of wound healing applications, including:

- **Wound dressings:** Chitosan can be used to make wound dressings that help to protect the wound, promote healing, and prevent infection.
- **Wound fillers:** Chitosan can be used to make wound fillers that help to fill in the wound and promote healing.
- **Wound gels:** Chitosan can be used to make wound gels that help to keep the wound moist and promote healing.

The various applications of chitosan loaded advance vehicles in the treatment of wound healing given it the
Table. 09 as following:

Table 09: The list of advanced vehicles of chitosan loaded to treat wound vehicle

Chitosan advance Vehicle	Description
Chitosan nanoparticles	Chitosan nanoparticles are small particles that can be loaded with drugs or other therapeutic agents. They can be used to deliver drugs to wounds to promote healing. Chitosan nanoparticles have been shown to be effective in treating a variety of wounds, including diabetic foot ulcers, burns, and skin grafts.
Chitosan hydrogels	Chitosan hydrogels are gels that are made from chitosan and water. They can be used to keep wounds moist and promote healing. Chitosan hydrogels have been shown to be effective in treating a variety of wounds, including diabetic foot ulcers, burns, and skin grafts.
Chitosan films	Chitosan films are thin sheets that are made from chitosan. They can be used to protect wounds and promote healing. Chitosan films have been shown to be effective in treating a variety of wounds, including cuts, scrapes, and burns.
Chitosan scaffolds	Chitosan scaffolds are three-dimensional structures that are made from chitosan. They can be used to create artificial skin that can help to heal wounds. Chitosan scaffolds have been shown to be effective in treating a variety of wounds, including diabetic foot ulcers and burns [65-71].

These are just a few of the advanced vehicles of chitosan that are being used to treat wounds. The properties of chitosan and its interactions with the wound healing process improves, more advanced vehicles of chitosan being developed in the future.

5. THE VARIOUS OTHER APPLICATIONS OF CHITOSAN AS BIO-POLYMER:

Due to its exceptional biological and physicochemical characteristics, chitosan finds widespread application across a plethora of industries, including but not limited to medical, food, chemical, cosmetics, water treatment, metal extraction and recovery, biochemical, and biomedical engineering [70-71]. There are different lots of application with the use of chitosan as a biopolymer in the given formulation, which are mainly shown with their proper function in the given (**Table. 10**), such as:

Table 10: The list of areas in which chitosan having various functionality

Sr. No.	The Various Areas	Functionality
01	**Waste water treatment**	The elimination of metallic particles, coagulating and precipitating agents, protein structures, pigments, and organic compounds comprising amino acids.
02	**Food industry**	Removal of dye, suspended solids, preservatives, food stabilizer, thickener and gelling agent etc.
03	**Cosmetics**	Various products like moisturizer, creams for face, hands and body, as well as lotions for bath, among others.
04	**Biotechnology**	Enzyme immobilization and protein separation through chromatography for cell recovery.
05	**Agriculture**	Seed coating, fertilizers, controlled agrochemical release.
06	**Medicines**	Healing wounds, bones and skin, contact lenses, dental plaque inhibition, clotting agent [71-72].

There are lots of other areas where the chitosan used in broader range with their lots of biopolymer as similar other functional properties. In which below some of them discussed below description as following:

5.1. ***VACCINATION:*** It is commonly believed that trimethyl chitosan, a type of chitosan derivative, has the potential to act as a vaccine adjuvant. It can activate the innate immune response of the body by activating the Toll-like and other pattern-recognition receptors. This results in the release of certain substances known as cytokines and chemokines, which draw in immune cells towards the location of the antigen. One research indicated the utilization of emulsion stabilized with chitosan hydrochloride salt as an adjuvant for vaccines [71-73].

Chitosan is a natural polysaccharide that has been shown to have potential as an adjuvant in vaccines. Adjuvants are substances that are added to vaccines to enhance the immune response to the vaccine. Chitosan can do this by several mechanisms, including:

- ***Increasing the uptake of vaccine antigens by dendritic cells:*** Dendritic cells are the cells that present vaccine antigens to the immune system. Chitosan can increase the uptake of vaccine antigens by dendritic cells, which can lead to a stronger immune response.

- ***Promoting the maturation of dendritic cells:*** Once dendritic cells have taken up vaccine antigens, they need to mature in order to present the antigens to the immune system. Chitosan can promote the maturation of dendritic cells, which can also lead to a stronger immune response.

- ***Inducing the production of cytokines:*** Cytokines are proteins that help to regulate the immune response. Chitosan can induce the production of cytokines, which can lead to a more robust immune response to the vaccine.

A vaccine that uses chitosan as an adjuvant is the cholera vaccine. The cholera vaccine is a live attenuated vaccine, which means that it contains a weakened form of the cholera bacteria.

Chitosan is added to the cholera vaccine to enhance the immune response to the vaccine. Studies have shown that the cholera vaccine with chitosan is more effective than the cholera vaccine without chitosan.

Chitosan is a promising adjuvant for vaccines. It is safe, biodegradable, and has a number of mechanisms by which it can enhance the immune response to vaccines. Studies are ongoing to evaluate the efficacy of chitosan in a variety of other vaccines [72-73]. The examples of vaccines that have been developed using chitosan as an adjuvant:

- Hepatitis B vaccine
- Influenza vaccine
- Diphtheria, tetanus, and pertussis (DTP) vaccine
- Rotavirus vaccine
- Zika virus vaccine

The various vaccine vehicles composite of the chitosan as biopolymer mainly in the lots of vaccined with their application in **Table. 11** as below:

Table 11: The list of vaccines of chitosan loading vehicle with their applications

Vaccine	Adjuvant	Application
Cholera vaccine	Chitosan	Prevention of cholera infection
Hepatitis B vaccine	Chitosan	Prevention of hepatitis B infection
Influenza vaccine	Chitosan	Prevention of influenza infection
DTP vaccine	Chitosan	Prevention of diphtheria, tetanus, and pertussis infections
Rotavirus vaccine	Chitosan	Prevention of rotavirus infection
Zika virus vaccine	Chitosan	Prevention of Zika virus infection

The development of chitosan-based vaccines is an active area of research. As our understanding of the properties of chitosan and its interactions with the immune system improves, we can expect to see even more effective chitosan-based vaccines being developed in the future [73]. The provided diagram illustrates the utilization of chitosan, a biopolymer, in vaccine and drug delivery applications (**Fig. 13**), listed below:

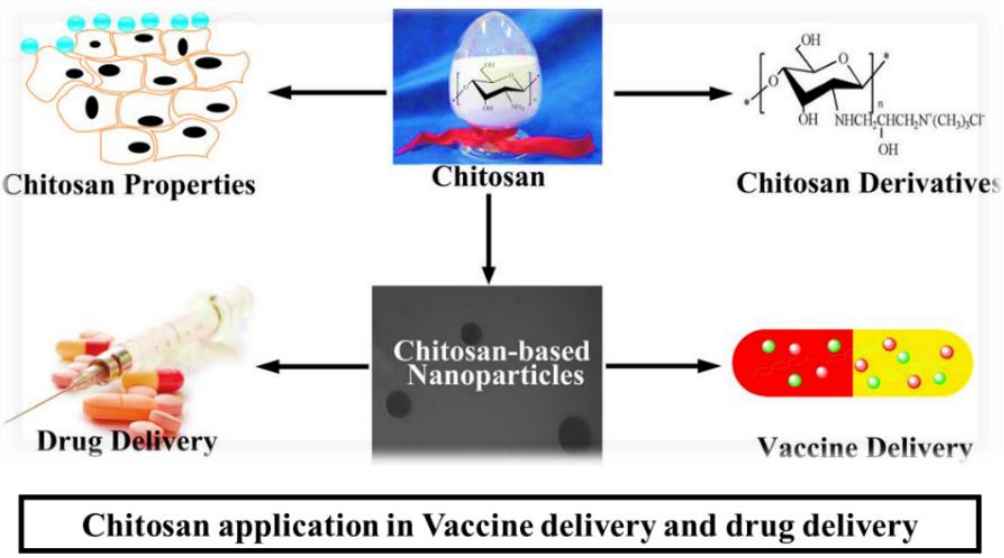

Figure 13: The chitosan applications in vaccination

The PLGA vaccines containing a triple fusion protein consisting of three antigens from Mtb were created and administered via subcutaneous injection or nasal route. The vaccines caused a change in the balance of Th1/Th2 towards a response that is dominant in Th1, and all of the PLGA vaccines that were created were capable of generating the production of mucosal IgA, IgG1, and IgG2a. Additionally, these vaccines led to the secretion of various cytokines such as IL-4, IFN-γ, IL-17, and TGF-β [71-73].

5.2. COSMECEUTICALS: Cosmetics encompass diverse products and compounds used to augment, sustain or modify one's physical features when applied to various body parts. Although synthetic substances are commonly used as the primary component in cosmetics, long-term use of these substances may lead to skin itchiness, irritation, sensitivity to light, and an allergic reaction caused by exposure to light [73]. The cosmetic industry has been actively researching and developing "*green cosmetics*" as a response to heightened global regulations and a growing demand for environmentally-friendly products. The different applications which widely utilized in cosmeceuticals as in the given (**Fig. 14)** as following:

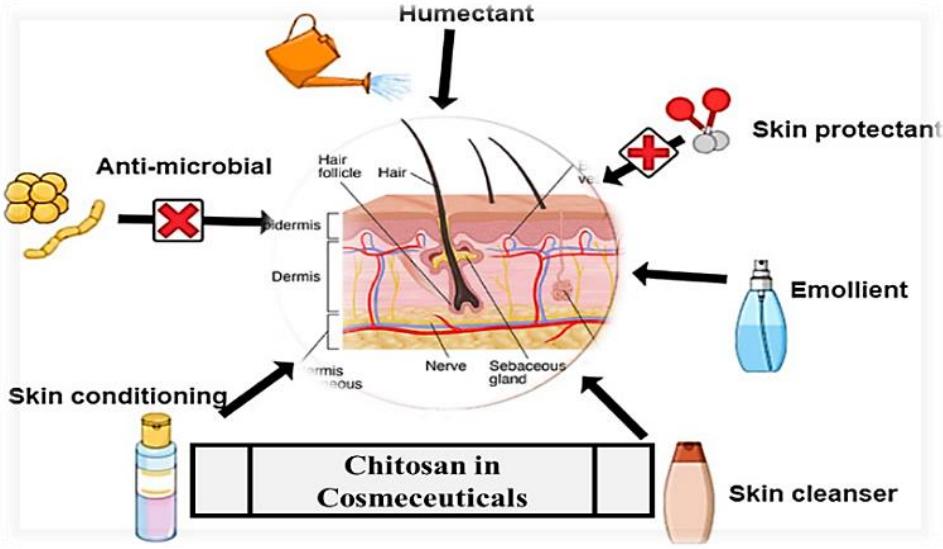

Figure 14: The various applications of chitosan in cosmeceuticals

Chitosan is a frequently employed substance in the beauty and skincare industry due to its ability to preserve skin hydration, enhance skin elasticity, alleviate acne, reinforce extracellular matrix, and stimulate the natural protective function of the skin [72]. (**Table. 12**)

Table 12. The list of various cosmetic product which contains chitosan polymer

Product Class	Application in cosmetics
Cosmetic masks	Moisturizing, exfoliating, and tightening the skin.
Hair care products	Improving hair hydration, helping to rebuild damaged hair, and providing a healthy shine.
Oral care products	Preventing plaque buildup and gum disease.
Sunscreens	Protecting the skin from UV damage.
Anti-aging creams	Reducing the appearance of wrinkles and fine lines.
Exfoliating scrubs	Removing dead skin cells and revealing fresh, new skin.
Moisturizers	Locking in moisture and keeping the skin hydrated.
Makeup removers	Removing makeup without stripping the skin's natural oils.

Chitosan, with its origin in nature and compatibility with living organisms, has become a prominent topic of interest in the beauty industry for its exceptional attributes including acting as a natural moisturizer and humectant, altering the consistency of substances, and increasing the endurance of products during manufacturing [71-73].

CONCLUSION AND FUTURE RELATED ASECTS:

Chitosan displays exceptional qualities that qualify it as a highly promising biopolymer with diverse applications in agriculture, medicine, cosmetics, and food production. Chitosan shows great potential in the fields of drug delivery and medical research due to its distinct characteristics and various uses. Numerous methods can be used to extract chitosan from chitin, and once obtained, it can be altered to improve its characteristics and biological functions. Customization of chitosan enables the creation of innovative materials with specific characteristics. Innovative drug delivery systems using Chitosan have been devised to aid in targeted and extended drug release through numerous routes of administration such as oral, ophthalmic, transdermal, nasal, and vaginal.

Due to its biocompatible nature and capability to promote cell growth and differentiation, Chitosan has been utilized in tissue engineering as a scaffold material. The review outlines several ways in which chitosan can be used in the field of biomedical research, such as promoting bone, cartilage, and cardiac tissue regeneration, as well as enhancing wound healing. The potential of chitosan is being increasingly recognized in gene delivery, bioimaging, and cosmeceuticals, revealing its adaptability and proving its worth.

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