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CHITOSAN NANOPARTICLES IN PULMONARY DRUG DELIVERY HELPFUL FOR COVID-19 TREATMENT: A REVIEW

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ABSTRACT: Objective- Chitosan is derived from chitin through deacetylation process. Production of Chitosan takes place in 4 steps. Chitosan is natural cationic polysaccharide which is rich in source. Chitosan has unique physiochemical properties, good biocompatibility and satisfactory biodegradability. Chitosan contain amino group. Chitosan has been popular biomaterial in pharmaceutics from decades and widely used in drug delivery. Chitin is extracted by removing protein and calcium carbonate from the raw shell.

Purpose- Chitosan is soluble in acidic solution but precipitate obtained i.e. solids has very high PH values. By treating Chitosan with various PH, changes in their physical forms can be seen. Basically Chitosan is non-toxic to humans, plants, animals and because of its lack in toxicity where lot of application can be observed in environmental, agricultural, food, pharmaceutical industry. The importance of Chitosan can be also seen in drug delivery in humans to solve various diseases.

Results- Due to its sub-micron size it is suitable for mucosal routes i.e. oral, nasal and ocular nanoparticle showed to be a good adjuvant for vaccine development. Chitosan is also used is polymeric nanoparticle through various route. Chitosan is added in aqueous acidic solution and then the aqueous solution of TPP is added under vigorous stirring. In this Anionic molecules diffuse in positively charged chitosan molecule and then crosslinking occurs leading to nanoparticle formation. Various production method for drug delivery take place. Using multiple method, application can also be seen in Covid-19 drug delivery.

Index Terms - chitosan, nanoparticle, pulmonary drug delivery, covid-19

1.INTRODUCTION

1.1 Chitosan From Chitin –

Seafood processing waste are very high rich source of useful products. The waste recycled has wide range of application because of its rich source of vitamins in it. Chitosan is very economically, as it does not required more amount. In general Chitosan is produced from the waste i.e. ‘ BEST OUT OF WASTE ’. Chitosan is bio-waste material after cellulose. The increasing consumption of Krill oil and Mushrooms has also been additional source for commercial Chitin. Basically Chitosan is obtained from Chitin. Chitin is polysaccharide containing hydroxyl (+OH) and amide(R-CO-NH2) groups. Chitosan is obtained when deacetylation reaction occurs, a byproduct come that is named as Chitosan in which amide group of chitin gets hydrolyzed to primary group (RNH2). Raw crab shell are deproteinized in incubation (in a solution) of 1M sodium hydroxide at 90°C for 24 hours followed by demineralization in 1M HCL for 24 hours. A complete demineralization of shrimp cells at room temperature is achieved in 15 min using 0.25M HCL liquor ratio 40:1.In deproteinization incubation is involves for 1M NaOH at 70°C for 24 hours. A lower concentration (0.3M) is used in deproteinized for chitinous materials (80-85°C), however using NaOH during deproteinized can cause blowing of chitinous materials.Catenoids which is present in prawn of shrimp shell may also cause unwanted reddish color, to avoid this bleaching process which is added before deacetylation of Chitin. Traditionally organic solvent like (Acetone, Ethanol, Chloroform, Ethyl acetate) and oxidizing agent (Sodium hypochlorite and hydrogen peroxide) where used for decolorizing in Chitin. Final process is deacetylation where thermo chemical reaction using 4% (wt/wt) NaOH or KOH solution at 100°C.

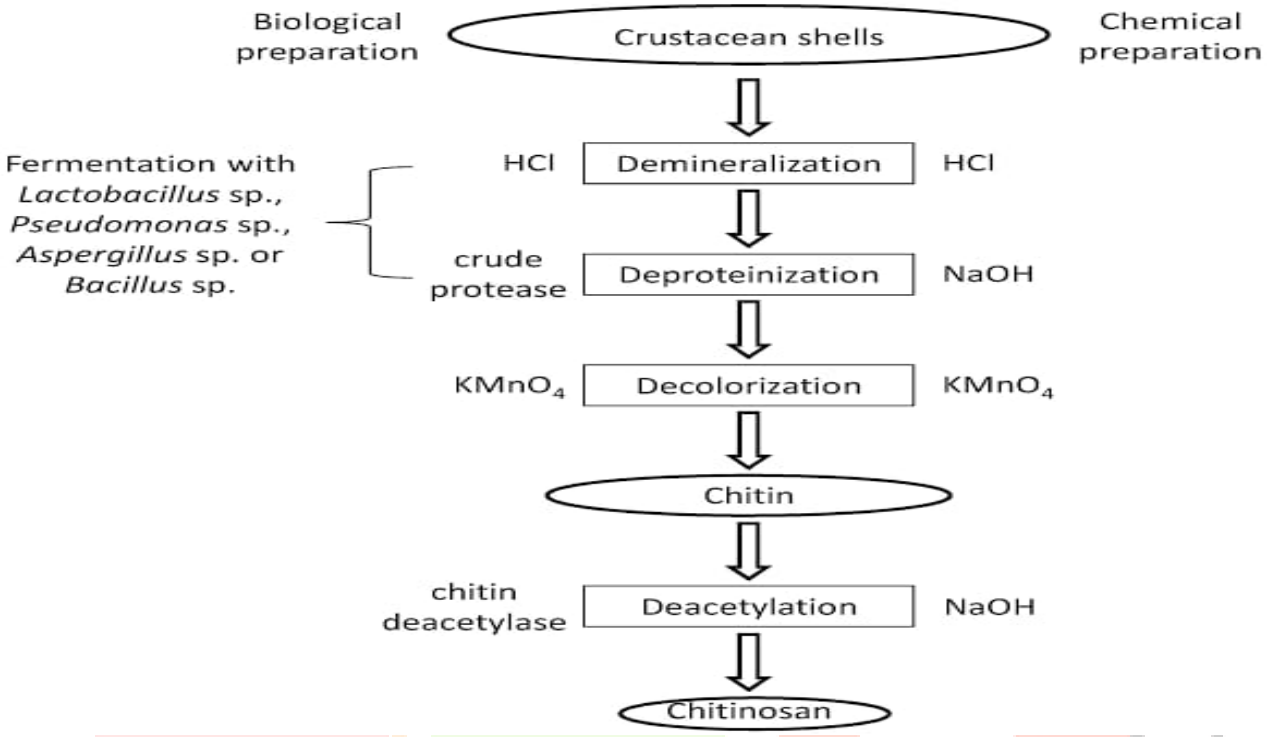

Fig. 1: Process of chitosan from chitin

1.2 Chitosan Nanoparticles -

Chitosan is a remarkable polymer that has been used extensively within the medical field. It's either partially or fully deacetylated chitin. As chitin occurs naturally (in fungal cell walls and crustacean shells, for example), chitosan could be a fully biodegradable and biocompatible and might be used as an adhesive and as an antibacterial and antimitotic.

Formation of Chitosan Nanoparticles –

Chitosan has been investigated extensively as a possible drug carrier, thanks to its biocompatible properties. Some studies have suggested using chitosan to coat nanoparticles product of other materials to scale back their impact on the body and increase their bioavailability. The degree of deacetylation and also the mass of chitosan may be modified to get different physical mechanical properties. The basic composition of the chitosan polymer is carbon (44.11%), hydrogen (6.84%) and nitrogen (7.97 %). The viscosity average relative molecular mass of chitosan is ~5.3 x 105 Daltons.

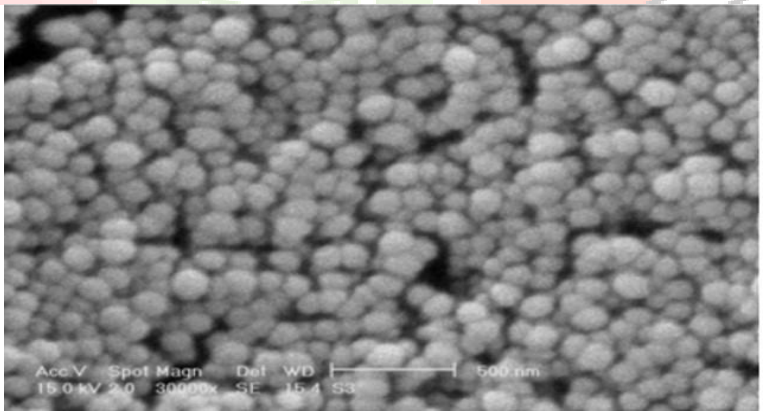

Fig. 2: Microscopic structure of chitosan

1.3 Chitosan Nanoparticles in Pulmonary Drug Delivery –

Several research groups have studied the properties of chitosan nanoparticles with a view to using them as a drug delivery agent. The biocompatibility and non-toxicity of the fabric makes it attractive as a neutral agent for delivery of active agents. Research in 2005 confirmed that ionic gelation may be accustomed produce chitosan-TPP nanoparticles of sufficient quality to be used in clinical applications. The researchers also determined the effect of certain manufacturing parameters on the particle properties, to confirm repeatable results from the assembly process.

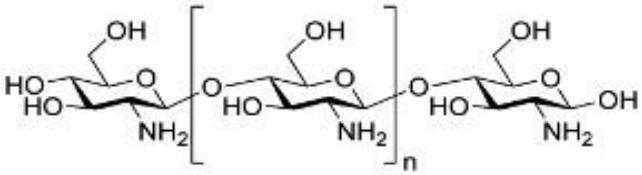

Fig. 3: Chemical Structure of Chitosan

Research disbursed in 2006 then focused on the in vitro and in vivo interaction of chitosan nanoparticles (CSNPs), as a replacement particulate drug carrier, having epithelial cells on the ocular surface. Inotropic gelation was accustomed produce the CSNPs labeled with fluorescein isothiocyanate-bovine albumin. Three different CSNP concentrations were taken and human conjunctival epithelial cells (IOBA-NHC) were exposed to them for 15, 30, 60 and 120 minutes. Viability and cell survival were measured after a 24-hour recovery period within the substance and immediately after treatment.

Confocal microscopy was accustomed measure the link between CSNPs and IOBA-NHC cells. Fluorometry was to study the impact of temperature and metabolic inhibition. The acute tolerance and therefore the in vivo uptake of the ocular surface to CNSPs were studied in rabbits. It was observed that the uptake of CSNPs was continuous during the time of the experiment and was addicted to temperature. There was no impact on CNSP uptake because of metabolic inhibition by sodium azide.There were no signs of alteration or inflammation after CSNP exposure on the rabbit's ocular surface. Microscopy of lid sections and rabbit eyeball confirmed in vivo uptake by corneal and conjunctival epithelia. These nanoparticles were well accepted by the ocular surface tissues. For drug delivery via non-injection to mucosal sites, one in every of the key challenges is that the absorption of the drugs at these sites. The drug delivery system should have mucoadhesive particles and release the drug over time. Due to the electric charge of chitosan, it can bind with the charged mucus. Thus, chitosan can act as a wonderful carrier for mucoadhesive drugs. Chitosan-based nanoparticles are accustomed deliver drugs to the lungs, with chitosan helping to connect to the lung mucosa. Dry powder inhalation of rifampicin, an anti-tubercular drug, formulated with chitosan because the polymer carrier showed sustained drug release for twenty-four hours. Similarly, the pulmonary deposition of itraconazole, an anti-fungal drug, increased when formulated as spray-dried micro particles of itraconazole loaded with chitosan nanoparticles.

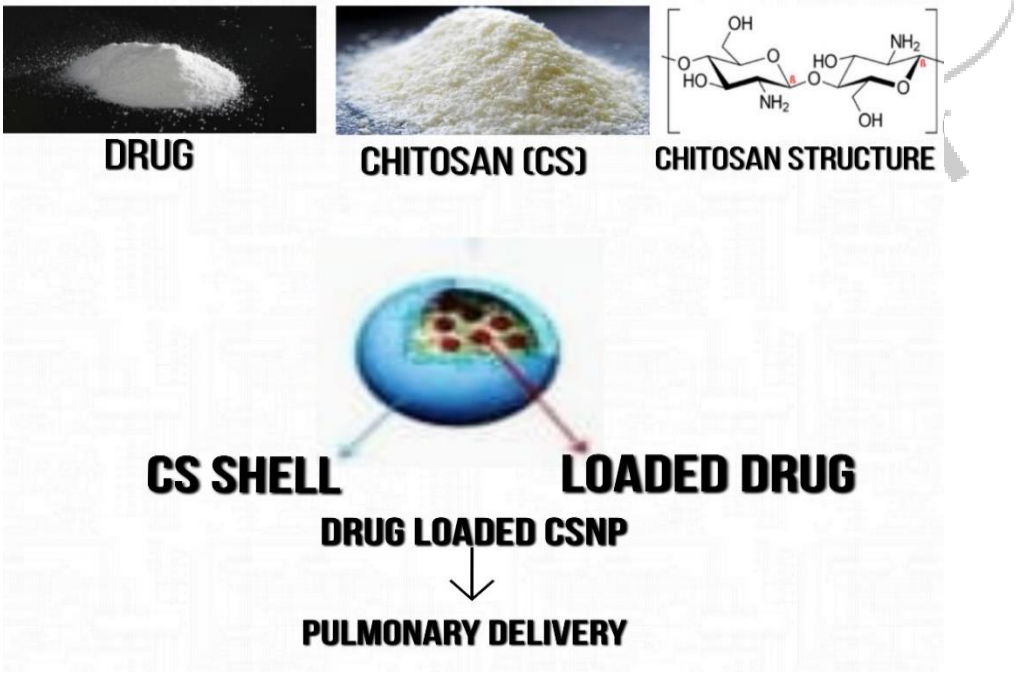

Fig. 4 : Chitosan Nanoparticles in Pulmonary drug

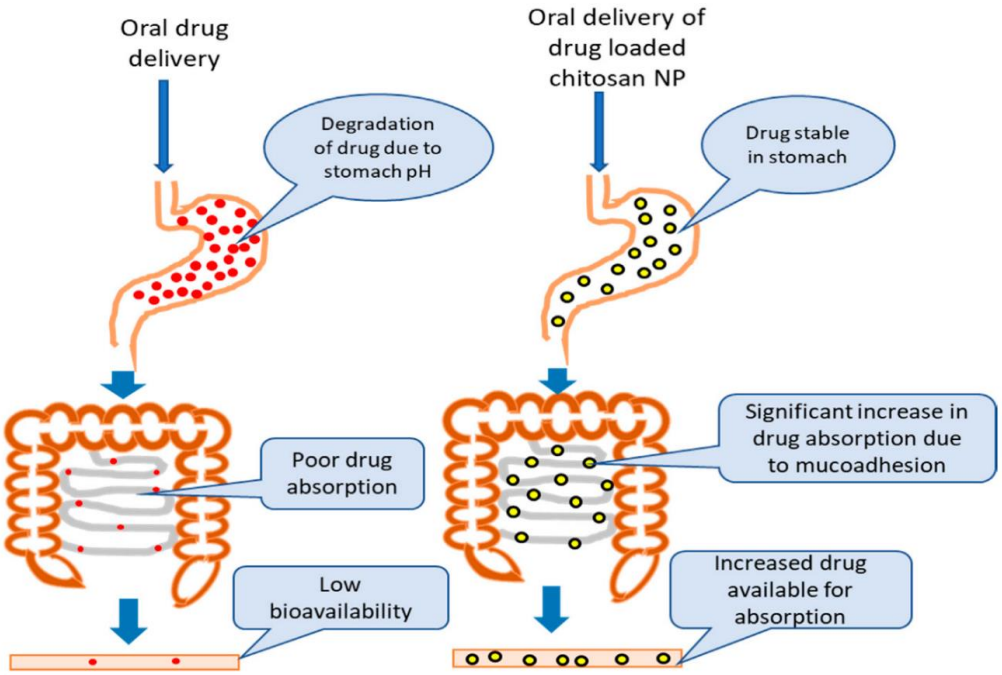

Fig. 5: Drug Delivery System

1.3.1 Drug -

[Itraconazole]

Itraconazole may be a synthetic triazole antifungal drug wont to treat various fungal infections. It belongs to a category of medicine referred to as the azoles. Itraconazole is also administered orally as a capsule or as an answer formulation. It's going to lean intravenously (directly into a vein) further. Bioavailability varies supported the kind of formulation given. Absorption of itraconazole is erratic and requires gastric acid, so it's recommended that it's not an enamored meal. Drugs that decrease gastric acid shouldn't be administered concurrently.

1.3.2 Mechanism –

Itraconazole acts by inhibiting the fungal cytochrome P-450 dependent enzyme lanosterol 14-α-demethylase. When this enzyme is inhibited it blocks the conversion of lanosterol to ergosterol, which disrupts fungal cell wall synthesis. Itraconazole exhibits fungi static (slows the growth) activity against yeast-like fungi and fungicidal (kills the fungus) activity against Aspergillums spp.

1.3.3 Uses –

With its broad spectrum antifungal activity itraconazole is employed to treat a range of fungal infections including:

1.Blastomycosis
2.Histoplasmosis
3.Aspergillosis
4.Sporotrichosis
5.Candidiasis
6.Onychomycosis

Furthermore, itraconazole is that the drug of choice for Sporotrichosis, Histoplasmosis and Blastomycosis. Onychomycosis is treated with a novel plan, called pulse dosing. Under this plan, itraconazole is run at the next dose for one week monthly, rather than daily. Interestingly, itraconazole is typically wont to treat or prevent additional fungal infections in patients with Human Immunodeficiency Virus (HIV) and bought Immunodeficiency Syndrome (AIDS).

1.3.4 Side Effects and Special Considerations –

Itraconazole can cause minor side effects and infrequently serious side effect. Side effects like constipation, indigestion, headache, sore or bleeding gums, depression, nervousness, sweating and muscle pain are noted. More serious side effects like nausea, yellowing of skin or eyes, pale stools, fever, dark urine, rash, hives, and difficulty swallowing must be addressed immediately. These side effects could also be caused by an allergy to the medication, hypokalemia or rarely hepatotoxicity. Due to the mechanism of action, inhibiting cytochrome 3A4, itraconazole may cause drug interactions. Drugs like 5-hydroxy-3-methylglutaryl-coenzyme. A reeducates inhibitors, benzodiazepines, quinidine and warfarin may have dose adjustment or discontinuation for the duration of itraconazole administration.

The Food and Drug Administration has labeled itraconazole as a pregnancy category C, meaning animal studies have shown adverse effects on fetus development but there's inadequate data on human fetus development. Taking itraconazole while pregnant or breastfeeding should be discussed together with your doctor.

1.4 COVID-19 –

Since December 2019, the planet was littered with an outbreak originated by a unique coronavirus (SARS-CoV-2) chargeable for a severe respiratory syndrome called COVID-19. The severity of COVID-19 disease, allied with its high contagiousness (e.g., direct human contact or contact with contaminated surfaces/waste, airborne/respiratory droplets and oral-faecal transmission and also the absence of a secure and effective vaccine, has raised attention and fear from governments, medical staff, the scientific community, and also the general public towards prevention and control of its transmission. Alongside, the creation of provisory treatment facilities for COVID-19 patients with moderate to severe symptoms, the limited access to hospitals and healthcare facilities by family/visitors, the mandatory quarantine (self-isolation) of COVID-19 patients with minor symptoms, and also the mandatory use of non-public protective equipment (PPE) by frontline workers (which use dramatically increased within the communicable disease units), are implemented to safeguard the Hospitals and other Healthcare system of breaking down.

Fig. 6: Covid-19

1.4.1 Chitosan Nanoparticles Pulmonary Drug Delivery For COVID-19 Pandemic -

Chitosan Nanoparticles, materials with a size but 100 nm, are used widely in many applications. Their small size makes their surface to volume ratio large, which has been used advantageously. Chitosan Nanoparticles are made of a good sort of materials, including inorganic, metals, and organic materials. The use of Chitosan nanoparticles in pharmaceutical applications has many benefits. These materials can improve drug solubility, controlled drug release, and targeting of specific cells. In addition, they show efficient adsorption of the many varieties of biomolecules and other chemicals and may be used both for therapy and diagnostics.

Chitosan Nanoparticles are often manufactured from a size the same as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). They'll interact with the virus proteins and will disrupt virus replication. Chitosan Nanoparticles also can be wont to deliver therapies in several forms. Drugs may be encapsulated in liposomes, allowing them to be eaten. Liposomes may protect sensitive materials like mRNA, Nanoparticle systems may also be designed to be inhaled, which can be particularly useful for treating COVID-19.

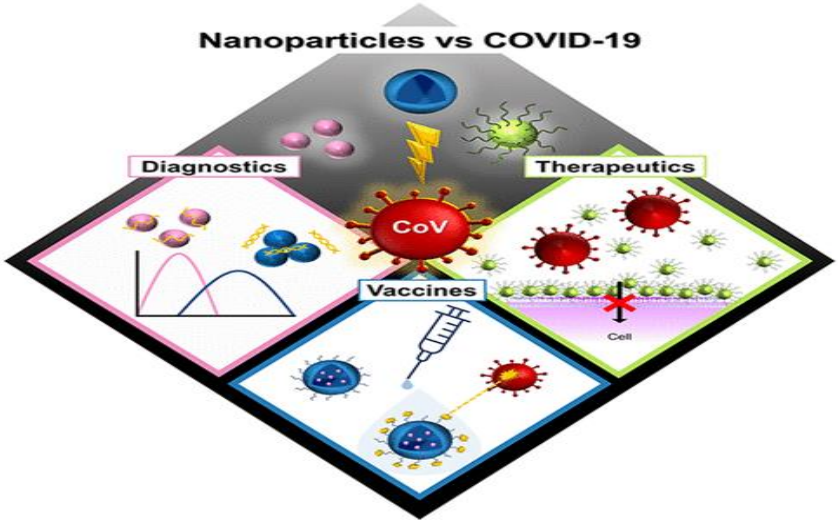

Fig. 7: Nanoparticles VS Covid-19

1.4.2 Chitosan Nanoparticles Based Drug For Covid -19 –

Chitosan nanoparticles, which are used before against the viral hepatitis virus, could potentially be used for COVID-19. Chitosan nanoparticles can deliver drugs to their specific target site and release them over an extended period. In current corona crisis, chitosan nanoparticles may well be a technique to release potential COVID-19 drugs specifically within the lungs of affected patients. A possible drug delivery system for the treatment of SARS-CoV-2 infected persons is NovochizolTM , consisting of chitosan-based nanoparticles. The corporate Bioavanta-Bosti developed the assembly of NovochizolTM . A two-step activation of chitosan and also the addition of a possible Covid-19 active ingredient could produce nanoparticles that are ideal for intra-pulmonary drug release. Therefore the active substances can be released locally, thus inhibiting the inflammatory reaction and preventing damage to lung tissue. In current studies of NovochizolTM aerosols with other drugs (e.g. Losartan), the manufacturers have already been ready to determine the successful drug release from therapeutic doses over 25 minutes to 3 hours. Bioavanta-Bosti has developed of a 48-hour manufacturing process, using its NovochizolTM chitosan polysaccharide nanotechnology to encapsulate APIs –small molecules or biologics for localized delivery and sustained release, to get intra-pulmonary drug delivery formulations suitable for treating COVID-19 patients. Vladislav Fomenko, the inventor of NovochizolTM technology explains that the chitosan nanoparticles are fully biocompatible, strongly adhere to lung epithelial tissues and ensure sustained release, without systemic distribution. Extensive preclinical testing, conducted by Bioavanta-Bosti academic partners, indicates that NovochizolTM may be a safe and effective drug delivery technology.

Fig. 8: NovochizolTM drug

1.5 Applications of Chitosan Nanoparticles in Various Field –

Chitosan nanoparticle has various applications in human as well as in plants. Some industry in which its applications are tissue engineering, food industry, fertilizer delivery, cancer diagnosis, gene therapy etc. Chitosan nanoparticle is approved by US Food and drug Administration and has application in food additives. It can be use for antimicrobial coating for fruits and vegetables. Wide range of unique application can also include preservative of food from microbial deterioration, shelf line extension, formation of biodegradable firms and food packaging. Chitosan nanoparticle exhibits efux pump inhibit properties. Chitosan and its derivative can also be used in solution gels, tablets, capsule etc. Consequently they may be used in oral, ocular, nasal, vaginal implants for drug delivery.

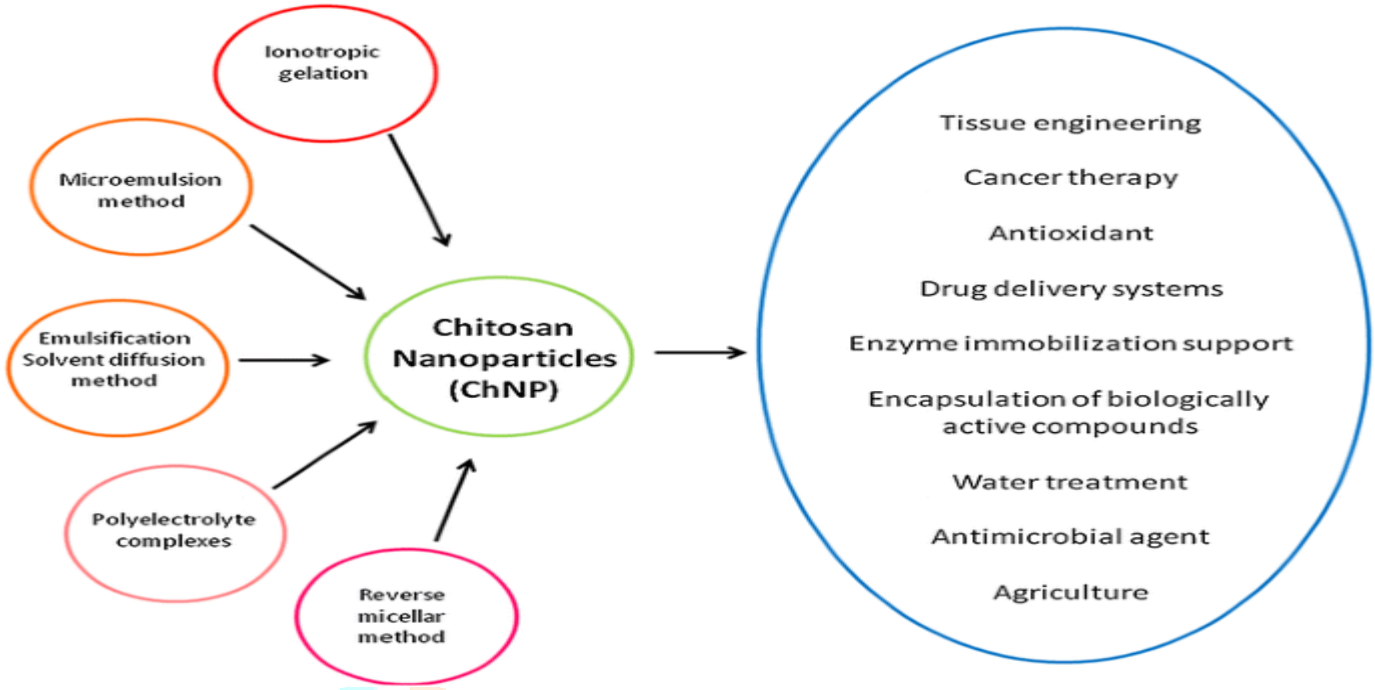

Fig. 9: Application of Chitosan Nanoparticles

1.5.1 Applications of Chitosan Nanoparticles in Pulmonary Drug Delivery –

Drug delivery has various advantages in rapid as well as in sustained drug delivery, metabolism and systemic effects can also be seen. The important part is large surface area, thin absorption barrier and high vascularity. Chitosan nanoparticle contain antibacterial properties which provide additional benefit of fighting the pulmonary bacterial infection. Chitosan used as polymer for dry powder inhalation for formulating. Jafarinejad et al developed chitosan nanoparticle in pulmonary drug delivery of intraconazole as a dry powder formulation due to its low solubility when taken orally. They formulate the drug causing lactose, manitol which improved its aerosolization process. This increase in deposition of intraconazole in pulmonary. Chitosan nanoparticle can deliver drugs to a specific target and help for long period of time. In current crisis, chitosan nanoparticle can be one of the way to release drug specially in lungs for covid-19 treatment.

CONCLUSION:

Despite all this, chitosan nanoparticle in pulmonary drug delivery has already made a remarkable success in past decade. It is also believed that in future, rapid development in material science, biotechnology, medical treatment and other scientific fields people will have more extensive and in depth unique properties with its derivatives. While great progress has been achieved in application of chitosan nanoparticle as drug carriers. Chitosan nanoparticle plays an important role in application of local and systemic disease treatment. In conclusion, chitosan and its derivative as drug carrier have potential for a wide application in market, but some problem remain unsolved like chitosan has poor solubility and unmodified chitosan nanoparticle can encapsulate only some hydrophilic drugs.

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