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CHITOSAN: A NOVEL EXCIPIENT IN PHARMACEUTICAL FORMULATION: A REVIEW

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ABSTRACT

Chitosan is a cationic natural polysaccharide which is derived from the chitin of crustaceans, with crabs and shrimp-shell wastes as its principal source. Its properties includes extent of deacetylation and the average molecular weight of polymer as well as low toxicity and good bioavailability make it a novel excipient in pharmaceutical formulation as a relatively new development. Together with chitin, chitosan is well thought-out the second most abundant polysaccharide subsequent to cellulose. But in contrast to cellulose, the application of Chitosan in pharmaceutical field is a pretty new development. Recently there are so many formulation were prepared and evaluated within different dosage forms such as ophthalmic, nasal sublingual, buccal, periodontal, gastrointestinal, colon specific, vaginal, transdermal as well as gene carrier which is based on the application of chitosan and its derivatives. Chitosan is biocompatible and show the activities such as antimicrobial and antifungal activities, which makes it a favourable option for biomedical applications. It has been proven to be useful in tissue growth, in tissue repair and accelerating wound-healing and bone regeneration. Microcrystalline chitosan (MCCh) is a highly crystalline grade of chitosan base may be particularly valuable as an excipient. Mucoadhesive tendency of chitosan might also depend on its crystallinity. Efficient gel formation by MCCh could result in substantial mucoadhesion, at least as far as "adhesion by hydration" is concerned. The objective of this review is to summarized the application and formulation based on the chitosan and its derivatives and also to elaborate the importance of chitosan in pharmaceutical field.

INTRODUCTION: Chitosan is a cationic polymer derived from the chitin of crustaceans. Its use in pharmaceutical field has received considerable attention, because it can be obtained from ecologically sound natural sources, namely crab- and shrimp-shell wastes. However Chitosan has been widely studied in the biomedical field, and has been found to be highly biocompatible [1]. Together with chitin, Chitosan is second most abundant polysaccharide subsequent to cellulose. However contrasting cellulose, the employ of Chitosan as an excipient in pharmaceutical formula is a pretty new development.

Now chitosan is available in different grades having difference in their physicochemical properties, and as a base or a salt of a base. This existence of different grades could also be valuable. The properties of chitosan-based dosage forms could be controlled by altering the grade of chitosan in formulations. Chitosan base seems likely to be more useful than chitosan salts in relation to development of slow-release

formulations because it is in general less soluble than Chitosan salts. The Chitosan is differs from chitin in that a majority of the N-acetyl groups in chitosan are hydrolyzed. The degree of hydrolysis (deacetylation) has a significant effect on the solubility and rheological properties of the polymer. The amine group on the polymer has a pKa in the range of 5.5 to 6.5, depending on the source of the polymer [2].

From a biopharmaceutical point of view, chitosan act as both the mucoadhesive as well as permeability enhancing property across the epithelia. It has been proved that chitosan could enhance insulin absorption across human intestinal epithelial cells without injuring them [3, 4, 5].

Microcrystalline chitosan (MCCh) is a highly crystalline grade of chitosan base[6], may be particularly valuable as an excipient, which can be prepared on a large scale using a method developed by the Finnish company Novasso [7]. MCCh has been studied in relation to various technical applications [8] and in cholesterol-lowering formulations [9]. Most drug formulation studies involving chitosans have used material produced commercially by conventional methods. Chitosan of this kind are fairly amorphous.

However, it was reported that increasing the crystallinity of chitosan could offer advantages in relation to manufacturing process of pharmaceutical formulations, e.g. by making the chitosan more suitable for direct compression into tablets [10]. Perhaps more significantly, the crystallinity of a chitosan could affect the behaviour of a formulation in which it was incorporated. Effects of the crystallinity of chitosan therefore required evaluation. One specific property of MCCh is its high capacity for retaining water [6].

Another advantage of Chitosan as pharmaceutical excipient is that it opens the tight junction of the mucosal barrier and facilitates the paracellular transport of hydrophilic macromolecules [11].

Due to mucoadhesive properties of chitosan drug strongly adheres to mucosa and MCC is decreased thus increasing the residence time of drug in nasal cavity which results in increase in absorption [12, 13]. It has been claimed that chitosan entraps lipids in the intestine, because of its cationic nature [14, 15]. Chitosan may also have technical applications, including, e.g., use as a seed coating and nitrogen source in agriculture, and as an adsorbent for water-purification[16].

Origin, Chemistry and Derivatives of Chitosan:

Origin: Henri Bracannot, Director of the Botanical Garden in Nancy, France, who firstly discovered Chitosan in 1811, pragmatic that a definite substance (chitin) set up in mushrooms did not dissolve in sulphuric acid. It was till 20 years regarding Chitosan after that, there was a man who identified that amazing substance was present in the structure of insects as well as the structure of plants, called as “chitin” which is derived from Greek, connotation “tunic” or “envelope”.

Chitin is the primary structure component of the outer skeleton of the crustaceans, molluscs, insects and fungi. While experimenting with chitin, Rouget first discovered Chitosan in which He observed that by the manipulation in the compound of chitin through chemical and temperature treatments it become soluble. Several other researchers continue to build on the original finding of Bracannot, discovering new uses for chitin as they find different forms of it in nature. In 1878, Ledderhose described chitin that it is made of glucosamine and acetic acid [17, 18]. Chitin accounts for approximately 70% of the organic components in such shells. It is a reinforcing material, which occurs in three polymorphic forms, a-, b- and g-chitin.

When chitin is heated in a strong solution of sodium hydrochloride (>40%) at high temperature (90-120^{o}), mostly of N-acetyl-D-glucosamine-units (left) of chitin, are deacetylated to D-glucosamine –units (right).

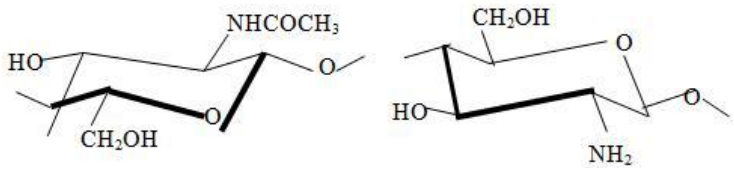

FIG. 1: STRUCTURAL UNITS OF CHITOSAN AND ITS PARENT SUBSTANCE CHITIN

Chitin consists mostly of N-acetyl-D-glucosamine-units (left). During the preparations of Chitosan, most units are deacetylated to D-glucosamine –units (right)

Chemistry: Chitosan (Poly[-(1, 4)-2-amino-2-deoxy-D-glucopiranose]) has a structure as shown in figure –2.Chitin is isolated from shells of crustacean(for example shrimp, crab and lobster) by treating the

shells with 2.5 N NaOH at 75°C and with 1.7 N HCl at room temperature for 6 hours [19]. Deacetylation can be done by alkaline treatment or by enzymatic reaction. The alkaline deacetylation is carried out by treating chitin with NaOH at high temperature. The degree of deacetylation increases with increasing temperature or NaOH concentration. Determined the optimum deacetylation is done by mixing 23 ml of 60% NaOH per gram of chitin 170°C [20].

Chitin deacetylation by enzymatic reaction is described. Chitin deacetylase isolated from Mucor rouxii has been used successfully to deacetylate chitin almost completely (98%) [21].

The polymer differs from chitin in that a majority of the N-acetyl groups in Chitosan is hydrolyzed. The degree of hydrolysis has a significant effect on the solubility and rheological properties of the polymer. The amino group on the polymer has a pKa in the range of 5.5 to 6.5, depending on the source of the polymer. At low pH, the polymer is soluble, with the sol-gel transition occurring at approximate pH 7. The pH sensitivity coupled with the reactivity of the primary amino groups makes chitosan a unique polymer for and drug delivery applications. Chitosan is now available commercially in various molecular weights (50 kDa – 2,000 kDa) and different degree of deacetylation (40% to 90%) [22].

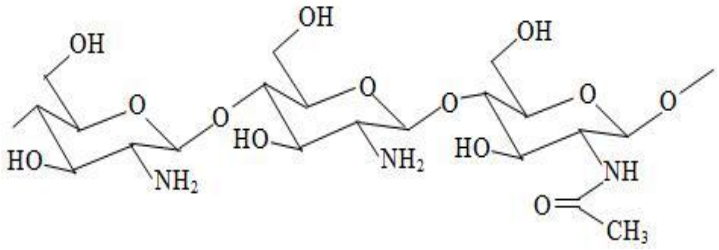

FIG. 2: CHEMICAL STRUCTURE OF CHITOSAN

The polymer is obtained by the partial deacetylation of naturally occurring polymer, chitin

Derivatives of chitosan: Chitosan provides a number of excellent properties, further derivatization of the amine functionalities can be carried out to obtain polymers with a range of properties. A number of approaches, both chemical and enzymatic, have been tried to exploit the reactivity of the amine functional groups [2].

N-Trimethylene Chloride Chitosan (TMC): A number of studies demonstrated that the charge on chitosan has a role in providing intestinal permeability. Hence, a quaternary derivatized chitosan (N-trimethylene chloride chitosan) was shown to demonstrate higher intestinal permeability than chitosan alone. The TMC derivative was used as a permeation enhancer for large molecules, such as octreotide, a cyclic peptide. It was showed that the degree of quaternization of TMC influences its drug absorption-enhancing properties. Polymers with higher degrees of quaternization (> 22%) were able to reduce the transepithelial electrical resistance and thereby epithelial transport *(in-vitro)* in a neutral environment (pH 7.4). The maximum reduction in transepithelial resistance was reached with TMC with a degree of quaternization of 48%. This degree of quaternization was also seen to be optimum for in vitro transport of model drugs across a Caco-2 monolayer [23].

Chitosan Esters: Chitosan esters, such as chitosan succinate and chitosan phthalate have been used successfully as potential matrices for the colon-specific oral delivery of sodium diclofenac [24]. By converting the polymer from an amine to a succinate form, the solubility profile is changed significantly. The modified polymers were insoluble under acidic conditions and provided sustained release of the encapsulated agent under basic conditions. The same researchers also synthesized an iron cross-linked derivative of hydroxamated chitosan succinate, as a matrix for oral theophylline beads [25]. A similar colon-targeting application was suggested for this polymer as well.

Chitosan Conjugates: Reactivity of the amine functionality can be exploited to covalently conjugate functional excipients to the polymer backbone. For example, Guggi and Bernkop attached an enzyme inhibitor to chitosan. The resulting polymer retained the mucoadhesivity of chitosan and further prevented drug degradation by inhibiting enzymes, such as trypsin and chymotrypsin [26]. This conjugated chitosan demonstrated promise for delivery of sensitive peptide drugs, such as calcitonin.

Water-soluble derivative of chitosan at neutral pH: Chitosan and its derivatives soluble in pH values of lower than 6.0 may not be desirable for usage in medicine, cosmetics and food [27].

To improve its solubility at neutral pH, it is first derivatized with substituent's containing quaternary amino group [28], caboxymethylation and then sulfatation by adding strongly hydrophilic substituent [29].

N- Sulfonated derivatives of Chitosan: These are amphoteric in nature. They can be prepared under heterogeneous reaction condition using 2-sulfobenzoic acid anhydride [30], N-sulfonato-N, O-carboxymethyl-chitosan: a novel polymeric absorption enhancer for the oral delivery of macromolecules [31].

Quaternarized Derivatives: The simplest derivative is the trimethyl ammonium salt of chitosan. A repeated treatment of chitosan in N-methyl-2 pyrrolidone containing sodium iodide and methyl iodide with chloride ion in presence of sodium hydroxide results into the trimethyl ammonium salt of chitosan with high degree of substitution [32]. Anionic changes of iodide with chloride ion are necessary for stabilization. The resulting product is water soluble at neutral pH [33].

Carboxyalkylation: The process of carboxyalkylation introduces acidic group on the polymer backbone. This derivative exhibits amphotericity due to the presence of native amino group. Water solubility is attained at pH values above or below the isoelectric point. Formation of N- carboxyalkylation uses carboxyaldehyde in a reductive amination sequence [34]. The reaction is carried out under homogeneous condition provided that the aldehyde used is water, allowing for greater degree of substitution distribution along the polymer back-bone. However, sequential substitution gives rise to the formation of bis-carboxymethyl derivatives have been observed using glyoxalic acid [35].

Microcrystalline Chitosan: MCCh differs from conventional chitosan in respect of greater crystallinity, energy of hydrogen bonds, and water retention. Both high energy of hydrogen bonds and high water retention are properties reflecting the increase in crystallinity and the substantial surface area of MCCh. The ability of MCCh to retain high amounts of water is a property which could be of particular value in relation to slow-release formulations. MCCh can retain three to four times much water as the parent chitosan [6]. This might result in MCCh having a greater capacity than conventional chitosan to form gels in formulations, and result in marked retardant effects on drug release.

Mucoadhesive tendency of chitosan might also depend on its crystallinity. Efficient gel formation by MCCh could result in substantial mucoadhesion, at least as far as "adhesion by hydration" is concerned. Results of studies relating to technical applications of chitosan have indicated that the reactivity of MCCh is greater than that of conventional chitosan, because of the greater ability of MCCh to form hydrogen bonds [8]. Because adhesion of chitosan to mucosa takes primarily through hydrogen bonding and electrostatic interactions, differences in ability to form hydrogen bonds might be reflected in differences in capacity to adhere to mucosa.

Stability and storage condition: Chitosan powder is a stable material at room temperature, although it is hygroscopic after drying. It should be stored in cool, dry place; preferably at a temperature of 2-8°C. Chitosan is incompatible with strong oxidizing agent [36].

Specifications & characteristics of Pharmaceutical-Grade Chitosan (table 1):

TABLE 1: THE PHARMACEUTICAL REQUIREMENTS FOR CHITOSAN INCLUDE [37]

Specification	Control specification	Result	Remark
Purity	-	>99.75%	-
Appearance	white or yellow	Off white powder or flake	External shape estimation
Residue on ignition	N/A	N/A	-
Protein content	Less than 0.5 %	0.14 %	Kjheldal method
Degree of deacetylation	More than 85 %	90 % ±5	(FTIR test)
Molecular weight	100,000-1,000,000	>500,000	HPLC
Heavy metals	-	10 ppm max	-
Ash content	-	2% max (with calcium supplement)	-
Viscosity (1% solution/1% acid)	-	50 cps	Intrinsic viscosity (capillary test)
Odor	No taste and smell	Odourless	-
Moisture content	Less than 10 %	<8.0 %	ASTM D5142, Dry 3hr at 105°C
Total plate count	-	Less than 10.00/g	-
Coliform/*E. coli* bacteria	-	Absent	-
Salmonella	-	Absent	-

Formulations based on Chitosan: Chitosan evaluated as conventional excipient applications, e.g. as a directly compressible diluent in tablets [48], as well as it was evaluated as binder in wet granulation[38], also it was described as a novel applications, e.g. as a carrier for mucosal delivery of antigens in connection with oral vaccination [39, 40]. Chitosan has also recently been approved by the authorities, and a monograph relating to chitosan hydrochloride was included in the fourth edition of the European Pharmacopoeia (2002).

It was confirmed that several properties of chitosan like good biocompatibility and low toxicity of chitosan and the fact that sources of chitosan are abundant, make it potentially valuable as a pharmaceutical excipient [1, 41, 42, 43].

Chitosan evaluated in-vitro as a drug carrier in hydrocolloids and gels. One property that makes chitosan particularly interesting for study as an excipient is its ability to become hydrated and form gels in acidic aqueous environments. Because of its gel-forming ability, a major area of interest since studies began has been use of chitosan to prepare slow release drug delivery systems [44, 45]. They prepared a hydrophilic matrix which retarding the drug release in tablets [46, 47].

It was described that the hydrophilic nature of chitosan has also aroused interest in its use in immediate-release formulations, e.g. as a disintegrant in small amounts in tablets, where it has been found to have effects similar to or better than those of microcrystalline cellulose [48, 49]. Chitosan is evaluated as an excipient which increases the rate of dissolution of poorly soluble drug substances [50, 51, 52].

Chitosan evaluated as a mucoadhesive material in-vitro. Many commercially available chitosans exhibit fairly good mucoadhesive properties and interest in use of chitosan to prepare mucoadhesive systems has therefore been aroused [53].

It has been suggested that times of residence of formulations at sites of drug action or absorption could be prolonged through use of chitosan. It has also been suggested that chitosan might be valuable for delivery of drugs to specific regions of the gastrointestinal tract, e.g. the stomach [54, 55], small intestine [53, 56, 57], and buccal mucosa [58, 59]. Delivery to other mucosal surfaces, e.g. delivery of peptide drugs on to the nasal epithelia has also been studied [60, 61, 62].

The potential value of chitosan as a novel excipient which could find extensive application in pharmaceutical products has been highlighted in several reports, and in numerous review articles relating to the field [16, 63, 64, 65, 66, 67].

Despite the substantial research relating to chitosan that has been carried out in recent decades, many questions remain unanswered. More information is needed about the effect of chitosan grade on the properties of pharmaceutical formulations. The fact that commercially available chitosan is not always well characterized has limited use of chitosan [65]. Comparison of results obtained by different research groups has been difficult because the properties of the chitosans studied, e.g. degree of deacetylation and/or molecular weight, have not been specified.

However, in recent years attention has been paid producing chitosans with particular physicochemical properties, and desired combinations of *DD* and *Mw*. The progress made has allowed studies in which the effect of altering chitosan grade on the properties of pharmaceutical formulations could be determined. Another important issue is the in vivo behaviour of chitosan-based formulations. A major deficiency of studies in this field is that many have determined the properties of the chitosan-based formulations solely by means of in vitro methods.

Information on the in vivo behaviour of the formulations, especially in human beings, has been lacking. Results of in vivo studies would reveal the value or otherwise of chitosan as a pharmaceutical excipient, and allow products containing chitosan to be marketed.

Chitosan-based dosage forms of this kind could be useful in relation, e.g., to the administration of antibiotics used for eradication of *Helicobacter pylori* from the stomach [55, 68].

Chitosan prepared as capsules for colon-specific delivery to treat ulcerative colitis. It was observed that Chitosan capsules disintegrated specifically in the large

intestines as compared to the control formulation (in absence of Chitosan), which demonstrated absorption of the drug in small intestines. This data is a representative example of utility of Chitosan for colon-specific delivery [69, 70].

It was prepared a novel mucoadhesive polymer by template polymerization of acrylic acid in the presence of Chitosan for transmucosal drug delivery system, where polymer complex was formed between poly (acrylic acid) (PAA) and Chitosan through hydrogen bonding [71].

Microcrystalline Chitosan (MCCh) may be particularly valuable as an excipient. As a highly crystalline grade of Chitosan base, one specific property of MCCh is its high capacity for retaining water. This property could be advantageous in relation to the development of slow-release formulations because it might facilitate the formation of gels that would control drug release. The pronounced ability of MCCh to form hydrogen bonds could theoretically result in efficient mucoadhesion by MCCh. The properties of MCCh mentioned made it particularly interesting for study as a hydrophilic excipient-controlling rate of drug release from formulations that were also intended to be mucoadhesive in the stomach [72].

It was studied that the mucoadhesive polymers carbomer 934P and Chitosan hydrochloride are able to enhance the intestinal absorption of buserelin in vivo in rats, and may therefore be promising excipients in peroral delivery systems for peptide drugs [73].

It was investigated that glycol Chitosan (degree of polymerization 800 approx) for its ability to form polymeric vesicular drug carriers. Chitosan is used because the membrane penetration enhancement of Chitosan polymers offers the possibility of fabricating a drug delivery system suitable for the oral and intranasal administration of gut-labile molecules and also the efficiently to entrap the water-soluble drugs. Glycol Chitosan modified by attachment of a strategic number of fatty acid pendant groups (11-16 moles %) assembles into unilamellar polymeric vesicles in the presence of cholesterol. These polymeric vesicles are found to be biocompatible and haemo compatible and capable of entrapping water-soluble drugs like bleomycin where the drug polymer ratio was found to be 0.5 units mg [74].

There was prepared N-palmitolyl Chitosan (PLCS), a new Chitosan-based polymer which can form micelles in water. Swollen Chitosan coupling with palmitic anhydride in dimethyl sulfoxide (DMSO) carried out the preparation of PLCs. The degree of substitution (DS) of PLCs was in the range of 1.2 – 14.2% and the critical aggregation concentration (CAC) of PLCs micelles was in the range of 2.0×10^{-3} to 37.2×10^{-3} mg/ml. The properties of PLCs micelles such as encapsulation capacity and controlled release ability of hydrophobic model drug ibuprofen (IBU) has evaluated[75].

Chitosan film was fabricated in order to deliver paclitaxel at the tumour site in therapeutically relevant concentration. Paclitaxel could be loaded at 31% wt/wt in films, which were translucent and flexible. Chitosan films containing paclitaxels were obtained by casting method with high loading efficiencies and the chemical integrity of molecule was unaltered during preparation according to study [76].

It was concluded that a quaternary derivative chitosan (N-trimethylene chloride Chitosan) was shown to demonstrate higher intestinal permeability than chitosan alone. The TMC derivative was used as a permeation enhancer for large molecules, such as octreotide, a cyclic peptide. They also concluded that the degree of quaternization of TMC influences its drug absorption-enhancing properties [77].

Chitosan esters, such as Chitosan succinate and Chitosan phthalate were used as potential matrices for the colon-specific oral delivery of sodium diclofenac[78].

Nanosystem was prepared with chitosan for the transmucosal delivery of hydrophobic compounds. They prepared nanoparticles including hydroxylpropylcyclodextrins by the ionic cross linking of chitosan with sodium tripolyphosphate in the presence of cyclodextrins. Two hydrophobic drugs, triclosan and furosemide, were selected as models for complexation with the cyclodextrin and further entrapment in the chitosan nanocarrier. The resulting nanosystems were thoroughly characterized for their size and zeta potential and also for their ability to associate and deliver the complexed drugs [79].

Mucoadhesivity of Chitosan was evaluated after attachment of an enzyme inhibitor to Chitosan. The resulting polymer retained the mucoadhesivity of Chitosan and further prevented drug degradation by inhibiting enzymes, such as trypsin and chymotrypsin. This conjugated Chitosan demonstrated promise for delivery of sensitive peptide drugs, such as calcitonin[80].

The effect of absorption enhancers was evaluated for nasal administration by using chitosan and randomly methylated b-cyclodextrin (RAMEB). They concluded that chitosan and randomly methylated b-cyclodextrin could combine to enhance the absorption and elevate the bioavailability of estradiol after nasal administration [81].

Microspheres of Glipizide were prepared with chitosan by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. Microspheres were discrete, spherical, and free flowing. The microspheres exhibited good mucoadhesive property in the in vitro wash-off test and showed high percentage drug entrapment efficiency [82].

Microencapsulate protein-loaded chitosan nanoparticles were prepared and evaluated using typical aerosol excipients, such as mannitol and lactose, producing microspheres as carriers of protein-loaded nanoparticles to the lung. The results showed that the obtained microspheres are mostly spherical and possess appropriate aerodynamic properties for pulmonary delivery (aerodynamic diameters between 2 and 3 micron, apparent density lower than 0.45 g/cm^3).

Moreover, microspheres morphology was strongly affected by the content of chitosan nanoparticles. These nanoparticles show a good protein loading capacity (65-80%), providing the release of 75-80% insulin within 15 min, and can be easily recovered from microspheres after contact with an aqueous medium with no significant changes in their size and zeta potential values [83]. It was found in study that the positively charged polysaccharide chitosan is able to increase precorneal residence time of ophthalmic formulations containing active compounds when compared with simple aqueous solutions. The purpose of the study was to evaluate tear concentration of tobramycin and ofloxacin after topical application of chitosan-based formulations containing 0.3% wt/vol of antibiotic and to compare them with 2 commercial solutions: Tobrex® and Floxal®, respectively [84].

Cross linked chitosan sponges were used as drug carrier system where Tramadol hydrochloride was used as a model drug. The sponges were prepared by freeze drying 1.25% and 2.5% (w/w) high and low molecular weight chitosan solution, respectively, using glutaraldehyde as a cross linking agent. The formulation made by those sponges has shown the release data followed the Higuchi model over 12 hours [85].

Insulin-chitosan nanoparticles were prepared by the ionotropic gelation as well by simple complexation. The nasal absorption of insulin after administration in chitosan nanoparticle formulations and in chitosan solution and powder formulations was evaluated in anaesthetised rats and/or in conscious sheep. Insulin-chitosan nanoparticle formulations produced a pharmacological response in the two animal models, although in both cases the response in terms of lowering the blood glucose levels was less (to 52.9 or 59.7% of basal level in the rat, 72.6% in the sheep) than that of the nasal insulin chitosan solution formulation (40.1% in the rat, 53.0% in the sheep).

The insulin-chitosan solution formulation was found to be significantly more effective than the complex and nanoparticle formulations. The hypoglycaemic response of the rat to the administration of post-loaded insulin-chitosan nanoparticles and insulin-loaded chitosan nanoparticles was comparable. As shown in the sheep model, the most effective chitosan formulation for nasal insulin absorption was a chitosan powder delivery system with a bioavailability of 17.0% as compared to 1.3% and 3.6% for the chitosan nanoparticles and chitosan solution formulations, respectively [86].

Mucoadhesive vaginal tablets of Metronidazole were formulated by direct compression method. They used natural cationic polymer Chitosan (loosely cross-linked with glutaraldehyde), together with sodium alginate with or without microcrystalline cellulose (MCC), and Sodium carboxymethylcellulose (CMC) was added to some of the formulations. The drug content in tablets

was 20%. Drug dissolution rate studies from tablets were carried out in buffer pH 4.8 and distilled water. The formula containing 6% chitosan, 24% sodium alginate, 30% sodium CMC, and 20% MCC showed adequate release properties in both media and gave lower values of swelling index compared with the other examined formulations. This also proved to have good adhesion properties with minimum applied weights [87].

The effect of different stirring speed and chitosan concentration as well as their interaction during the preparation of chitosan microspheres was evaluated by the chemical cross-linking method by using a chitosan solution of less than 1% w/v concentration. He found that microspheres thus obtained are significantly affected by stirring speed and chitosan concentration as well as their interaction. Effect of change in drug concentration on the pharmaceutical characteristics of drug-loaded chitosan microspheres is more prominent for water-soluble drug [88].

It was found that spray-dried chitosan particles, having irregular surface morphology and diameter of less than two µm, readily adsorbed to lactose-LPD particles following mixing. In contrast with the smooth spherical surface of lactose-LPD particles, spray-dried trimethyl chitosan-lactose-LPD particles demonstrated increased surface roughness and a unimodal particle size distribution (mean diameter 3.4 µm), compared with the multimodal distribution for unmodified lactose-LPD powders (mean diameter 23.7 µm). The emitted dose and in vitro deposition of chitosan-modified powders was significantly greater than that of unmodified powders [89].

It was investigated that the solubilising and absorption enhancer properties towards naproxen of chitosan and polyvinylpyrrolidone (PVP). They found that improved drug dissolution and their performance depended on the drug polymer ratio and the system preparation method. Chitosan was more effective than PVP, despite the greater amorphizing power of PVP as revealed by solid-state analyses. After different studies it found to be that the direct compression properties and antiulcerogenic activity, combined with the demonstrated solubilising power and analgesic effect enhancer ability towards the drugs, make chitosan particularly suitable for developing a reduced-dose fast-release solid oral dosage form of naproxen [90].

Chitosan microspheres were evaluated for sustained-release of recombinant human interleukin-2 (rIL-2). It found that rIL-2 was released from chitosan microspheres in a sustained manner. The efficacy of rIL-2 loaded chitosan microspheres was studied using two model cells, HeLa and L-strain cell lines. Chitosan microspheres were added to the cells at different concentrations, and the amount of rIL-2 was assayed using the ELISA kit. Cell culture studies indicated that microspheres were up taken by cells, and rIL-2 was released from the microspheres. Cellular uptake of rIL-2-loaded microspheres was dose dependent. It can be said that chitosan microsphere is a suitable carrier for rIL-2 delivery [91].

Topical formulations containing 5-FU loaded liposome embedded into a structured vehicle of chitosan was prepared and evaluated. The release rate of 5-FU from topical liposome gels was affected by the formulation variables. Comparing the liposome gels with hydrogel formulations, the release rate of liposome-entrapped drug was prolonged, while a steady-state release rate, established after 1.5 hours, suggests that chitosan liposome function as a reservoir system for continuous delivery of the encapsulated drug substance [92].

Antimicrobial activity of chitosan was investigated in lipid emulsions as well as in aqueous solution. It was originate that lipid emulsions containing 0.5% chitosan conformed to the requirements of the preservation efficacy test for topical formulations according to the European Pharmacopoeia while the emulsion without chitosan and a lactic acid solution with and without the biopolymer did not conform. In haemolysis studies on human erythrocytes, the haemolytic activity of the lipid emulsions with chitosan was assessed. These emulsions showed a negligible haemolytic behaviour. The results point toward a use of chitosan as antimicrobial preservative in emulsion formulations for mucosal as well intended for parenteral applications [93].

Mucoadhesive vaginal tablets were developed for the local controlled release of acriflavine, an antimicrobial drug. The tablets were prepared using drug-loaded Chitosan microspheres and additional excipients (methyl cellulose, sodium alginate, sodium

carboxymethylcellulose or carbopol 974) by using spray-drying method. The formulation has done with carbopol 974 was studied with in-vitro mucoadhesion tests showing good mucoadhesive properties [71].

The effect of chitosan oligomers was examined on pulmonary absorption of interferon-alpha (IFN) by means of an in-vivo pulmonary absorption experiment. Chitosan oligomers used in this study were chitosan dimer, tetramer, hexamer, and water-soluble (WS) chitosan. A significant increase in serum IFN concentrations was observed after intratracheal administration of IFN with these oligomers. In these chitosan oligomers the concentration of 0.5% w/v chitosan hexamer appeared to be more effective in enhancing the pulmonary absorption of IFN than other oligomers at the same concentration, and the AUC value of IFN with chitosan hexamer increased 2.6 –fold as compared with the control. Therefore these findings indicated that the use of chitosan oligomers would be a promising approach for improving of the pulmonary absorption of biologically active peptides including IFN [94].

General application of Chitosan & its derivatives (table 2):

TABLE 2: CHITOSAN POLYMER PLAY A VERY IMPORTANT ROLE IN CURRENT DRUG DELIVERY SYSTEMS DESCRIBED AS;

Applications	References
Drug carrier in micro-particle systems	Thanoo *et al*., 1992; Chandy and Sharma, 1993; Okhamafe *et al*., 1996
Slow release of drugs from tablets and granules	Kawashima *et al*., 1985; Hou *et al*., 1985; Acartürk, 1989
Bioadhesive polymer	Lehr *et al*., 1992; Miyazaki *et al*., 1995; Bernkop-Schnürch *et al*., 1998
Disintegrant and biodegradable polymer (implants, micro particles)	Sawayanagi *et al*., 1982a,b; Ritthidej *et al*., 1994; Song *et al*., 1996; Jameela *et al.*, 1998
Binder in wet granulation	Upadrashta *et al*., 1992; Tapia *et al*., 1993; Henriksen et al., 1993
Diluents in direct compression of tablets	Sawayanagi *et al*., 1982a,b; Knapczyk, 1993a
Films controlling drug release	Remuñan-López and Bodmeier, 1997; Senel *et al*., 2000
Carrier in relation to vaccine delivery or gene therapy	Lee *et al*., 1998; Aral *et al*., 2000; Van der Lubben *et al*., 2001a,b
Site-specific drug delivery (e.g. to the stomach or colon)	Tozaki *et al*., 1997; 1999; 2002; Shah *et al*., 1999; Remuñan-López *et al.*, 2000
Absorption enhancer (e.g. for nasal or oral drug delivery)	Illum *et al*., 1994; Schipper *et al*., 1996; 1997; 1999; Kotzé *et al*., 1997
To increase pre-corneal residence time of ophthalmic formulations	Karteek *et al*.,2010
As antimicrobial activity of Chitosan	Karteek *et al*.,2010
As controlled released drug matrices and sponges	Nagwa *et al*., 2004
Microcrystalline Chitosan as gel forming and controlled release components for mucosa	Struszczyk and Kivekäs, 1992

The positively charged polysaccharide chitosan is able to increase precorneal residence time of ophthalmic formulations containing active compounds when compared with simple aqueous solutions [95].

The antimicrobial activity of chitosan in lipid emulsions as well as in aqueous solution was investigated. It was originate that lipid emulsions containing 0.5% chitosan conformed to the requirements of the preservation efficacy test for topical formulations according to the European Pharmacopoeia [81]. In controlled released drug matrices cross linked chitosan sponges has been used as drug carrier system. Here, Tramadol hydrochloride, a centrally acting analgesic, was used as a model drug. The sponges were prepared by freeze drying 1.25% and 2.5% (w/w) high and low molecular weight chitosan solution respectively, using glutaraldehyde as a cross linking agent [85].

Other important utilizations of chitosan polymer:

Cholesterol-lowering effects: Chitosan and cellulose were used as examples of fibres with high, intermediate and low bile acid-binding capacities, respectively. The serum cholesterol levels in a control group of mice fed a high fat/high cholesterol diet for 3 weeks increased about 2-fold to 4·3mM and inclusion of any of these fibres at 7·5% of the diet prevented this increase from occurring. In addition, the amount of cholesterol accumulated in hepatic stores due to the HFHC diet was reduced by treatment with these fibres. The three kinds of fibres showed similar hypocholesterolaemic activity; however, cholesterol depletion of liver tissue was greatest with cholestyramine. The mechanisms underlying the cholesterol-lowering effect of cholestyramine were,

- Decreased cholesterol (food) intake,
- Decreased cholesterol absorption efficiency, and
- Increased faecal bile acid and cholesterol excretion.

The latter effects can be attributed to the high bile acid-binding capacity of cholestyramine. In contrast, incorporation of chitosan or cellulose in the diet reduced cholesterol (food) intake, but did not affect either intestinal cholesterol absorption or faecal sterol output. The present study provides strong evidence that above all satiation and satiety effects underlie the cholesterol lowering [95].

Increase stability of drug: Chitosan polymer is used to increase the stability of the drug in which the drug is complexed with chitosan and make slurry and kneading for 45 minutes until dough mass. This dough mass is pass through sieve no. 16 and make a granules is completely stable at different condition.

Orthopaedic patients: Chitosan is a biopolymer that exhibits osteo-conductive, enhanced wound healing and antimicrobial properties which make it attractive for use as a bioactive coating to improve Osseo integration of orthopaedic and craniofacial implant devices. It has been proven to be useful in promoting tissue growth in tissue repair and accelerating wound-healing and bone regeneration [85].

Cosmetics industry: Cosmetic compositions are disclosed for the treatment of hair or skin, characterized by a content of new quaternary chitosan derivatives of the formula. The chitosan derivatives have a good substantial, particularly to hair keratin, and prove to have hair strengthening and hair conditioning characteristics. e.g.; Hair setting lotion, Oxidation Hair-colouring Composition, Hair toning Composition, Skin Cream, Hair-treatment Composition, Gel-form.

CONCLUSION: Biologically degradable polymers can be loosely distinct as a class of polymers, which degrade to smaller fragments due to chemical present inside the body. Natural polymers are always biodegradable because they undergo enzymatically promoted degradation. Chitosan is one of them, which exhibits biodegradability, scrawny antigenecity and better-quality biocompatibility compared with supplementary natural polymer. Chitosan is biocompatible and show the activities such as antimicrobial and antifungal activities, which makes it a favourable option for biomedical applications. It has been proven to be useful in tissue growth, in tissue repair and accelerating wound-healing and bone regeneration.

It can be engineered into poles apart shapes and geometrics such as nanoparticles, micro spheres, membrane, sponge and rods. On drug delivery special preparation techniques are used to put in order chitosan drug carriers by culturing such parameters as cross linker concentration, Chitosan molecular weight, drug / polymer ratio and processing conditions all of which impinge on the morphology of Chitosan drug carriers and release rate of the loaded drugs.

Chitosan has strong positive charge and this charge helps it to bind fats and cholesterol and initiates clotting of red blood cells. Chitosan have fibre like properties which can be used to replace calories in foods.

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