IJPAR |Volume 2 | Issue 4 | Oct-Dec - 2013 **ISSN: 2320-2831**

INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

Available Online at: www.ijpar.com

[Review article]

Chitosan Versatile Biodegradable Polymer and its Importance – Review

[*1]Pitchai Pillai M, [2]Anbarasu D, [3]Varatharajan R, [4]Sriram N

[1]E.G.S.Pillay College of Pharmacy, Nagapattinam-611002 Tamilnadu, India.
[2]Thanthai Roever college of Pharmacy,Perambalur,Tamilnadu, India.621212
[3]Faculty of Pharmacy, AIMST University, Kedah Darul Aman, Malaysia
[4]Smt.Sarojini Rammulamma college of Pharmacy, Mahabubnagar, A.P. India.

ABSTRACT

Chitosan is a polysaccharide derived from renewable resources. Chitosan is a biodegradable, biocompatible, positively charged nontoxic mucoadhesive biopolymer. These unique features of chitosan have interested in development of delivery systems for a wide range of biological agents. The properties, biodegradability, and biological role of chitosan is frequently dependent on the relative proportions of N-acetyl-D-glucosamine and D-glucosamine residues. Sources of chitin are the shell wastes of crab, shrimp, lobster and crawfish etc. Chitosan is usually prepared by the deacetylation of chitin. It is having the biological activity like Haemostatic, Fungistatic, Spermicidal and accelerate the wound healing. It can be used in various drug delivery systems like mucoadhesive drug delivery, insulin oral drug delivery, colon drug delivery etc.It can be used in cosmetics preparation, and in agricultures used for growth and better yield.

Key Words: Chitosan, Polysaccharide, Biodegradable polymer, Drug delivery, Antimicrobial.

INTRODUCTION

Chitosan is a biodegradable polymer derived from renewable resources (1).It is the second most abundant natural polysaccharide and originates from shells of crustaceans. Chitosan is a biodegradable, biocompatible, positively charged nontoxic mucoadhesive biopolymer. Since chitosan contains primary amino groups in the main backbone that make the surfaces positively charged in biological fluids, biodegradable nano/microparticles can be readily prepared by treating chitosan with a variety of biocompatible poly anionic substances such as sulfate, citrate, and tripolyphosphate. These unique features of chitosan have interested in development of delivery systems for a wide range of biological agents .Its natural mucoadhesive properties allows design of bioadhesive drug carrier systems that can bind to the intestinal mucosa, and thus improve the residence time of many drugs in intestinal mucosa and improve the bioavailability (3).The structure of chitosan is very similar to that of cellulose, made up of b (1-4)-linked D-glucose units, in which there are hydroxyl groups at C-2 positions of glucose rings. The properties, biodegradability, and biological role of chitosan is frequently dependent on the relative proportions of N-acetyl-D-glucosamine and D-glucosamine residues (3).The term chitosan is used to describe a series of polymers of different Mw and DD, defined in terms of the percentage of primary amino groups in the polymer backbone. The DD of typical commercial

*** Corresponding author: Pitchai Pillai M.**
E-mail address: m.pitchaipillai@gmail.com

chitosan is usually between 70 and 95%, and the Mw between 10 and 1,000 kDa (3). Chitosan is a amino polysaccharide comprising of copolymer of glucosamine and N- acetyl glucosamine. It can be derived by partial deacetylation of chitin from crustacean shells. Chitosan salts are soluble in water, its solubility is depend on the degree of deacetylation, pH and influenced by the addition of salts .Its relative low degree of deacetylation 40% have been found to be soluble upto pH 9, whereas chitosan with degree of deacetylation maximum about 85% have been found to be soluble only upto pH6.5 (2). Viscosity is an important factor in the determination of molecular weight of chitosan and its commercial applications. Chitosan viscosity is found to decrease with increased time of the demineralization step in its preparation Bough et al found that in the treatment of chitin to make chitosan, Deproteinization with 3% NaOH and elimination of the demineralization step decrease the viscosity of the final chitosan product. No et al. demonstrated that chitosan viscosity is considerably affected by physical treatments (grinding, heating, autoclaving, ultrasonicating, but not freezing) and chemical treatments (e.g. ozone),wherein it decreases with an increase in treatment time and temperature. Kim et al noted a sharp decrease in chitosan viscosity in some organic acid solutions (40-60% in one day). However, the viscosity of chitosan solution stored at 4oC was found to be relatively stable. No et al. reported a decrease in the viscosity of chitosan (1% chitosan in 1% acetic and/or lactic acid solution) with increased storage time and temperature. The decrease in viscosity recorded over time was related to the partial degradation of chitosan by the organic acid solutions. However, reports that relate the viscosity of chitosan to the type of solubilising organic acid solution are barely found in the literature (6).

The remarkable properties of these natural polymers that favour their utilization in pharmaceutical and medical fields are their biodegradable and nontoxic nature. Further the solubility of chitosan in dilute acids forming viscous Polyelectrolyte solutions (cationic) film forming properties and complexation with anions make it most favourable ingredient in these fields (4).

PREPARATION OF CHITOSAN

Sources of Chitosan

Chitin is found in the exoskeleton of some anthropods, insects, and some fungi. Commercial sources of chitin are the shell wastes of crab, shrimp, lobster and crawfish etc. Chitosan is usually prepared by the deacetylation of chitin (3).

Figure1: Crawfish/Crabs (24).

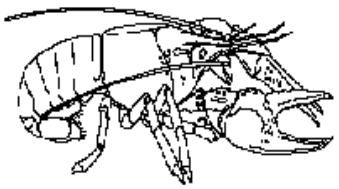
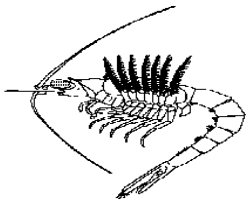


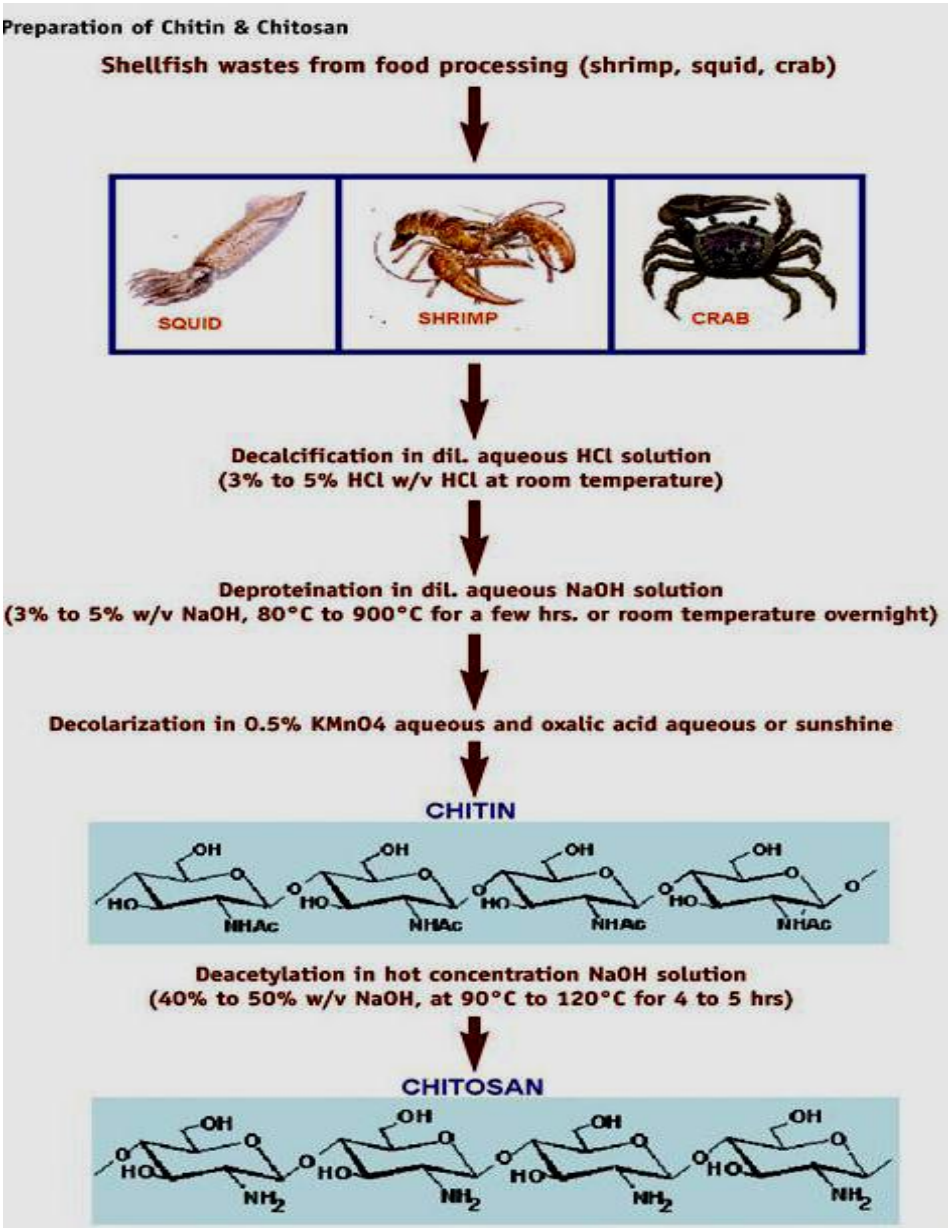
Figure 2: Shrimp (24).



Commercial Sources of Chitin/Chitosan in Asia (24)

Company	Location	Products
Industrial Research Ltd (IRL)	5 Sheffield Crescent Bishopdale P.O. Box 20-028 Christchurch, NZ	b-chitin from squid pen
Meron Biopolymers	Santo Gopalan Road, Chullickal, Cochin - 682005 Kerala, India	Chitin/Chitosan (Enzymatic processing)
Yuhuan Ocean Biochemical Co., Ltd	89 Zhongxing Middle Road Li'ao, Yuhuan County Post Code: 317602, China	Glucosamine Chitin/Chitosan "Jinke" Chitosan
Korean Chitosan Co. Ltd.	San 2 Wonjig-Ri Kangku-Myun, Youngdeok-Kim Kyoungbuk-Do, South Korea	Chitin/Chitosan

Preparation of Chitin/Chitosan(33)



Processing of Chitosan(5)

Four steps are involved in the processing of chitosan derived from the crustacean shells. These are

- Deproteinization.
- Demineralization.
- Decolouration.
- Deacetylation.

Processing steps

Crustacean shells → Size reduction → Protein separation → NaOH → Washing
Demineralization (Hcl) → Washing and Dewatering → Decolouration → Chitin →
Deacetylation (NaOH) → Washing and Dewatering → Chitosan (5).

Chemical Structure of Chitosan (13)

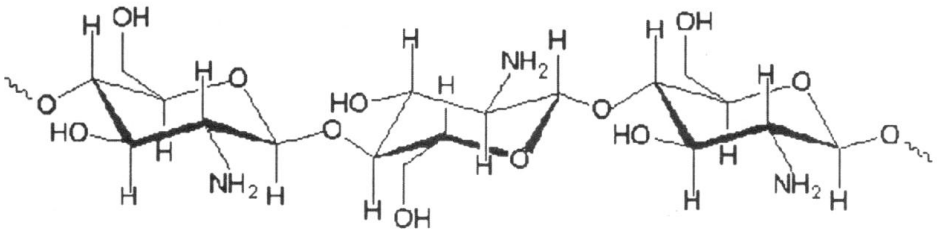


Figure 3 Chitosan molecular structure.

Key Specifications for Chitosans (24)

S.No	Property	Chitosan
1	Molecular weight in Dalton	
	Processed	10^5-10^6
	Deacetylation%	60 - 90
2	Viscosity of 1% solution in 1% Acetic Acid, cps	200 - 2000
3	Moisture Content	< 10%
4	Dissociation Constant, Ka	6.0-7.0
5	Soluble in	Dilute acids

Chemical properties of Chitosan (5)

- Reactive amino groups.
- Reactive hydroxyl groups.
- Linear polyamine (5).
- Amenable to Chemical Modification (24).
- Adheres to negatively charged surfaces forms gels with polyanions chelates transition metals (24).

Biological Properties of Chitosan (5)

- Accelerate bone formation.
- Haemostatic.
- Fungistatic.
- Spermicidal (5).
- Antibacterial and Antiviral activity towards plant pathogens (7).
- Ant diabetic and Ant obesity activity (8).
- Develops enhanced performances in regenerating hyaline cartilage and reconstitution of the subchondral bone (9).
- It is a good carrier for growth factors; it inactivates metalloproteinase thus preventing collagen degradation (9).
- Bone and soft tissue healing (10).
- The regeneration of bone, nerve and meniscus tissues, leg ulcer treatment (10).
- Accelerate the wound healing (10).
- Chitosan based nanofibers, nanoparticles and nanocomposite scaffolds for tissue engineering, wound dressing, drug delivery and cancer diagnosis (11).
- Immunity-enhancing, antitumor, and anticancer effects (12).
- Anti-inflammatory effects and repair of arthritic tissue (12).
- Acceleration of calcium and iron absorption in vivo (12).
- Antioxidant activity (12).
- Angiotensin-I-converting enzyme (ACE) inhibition (12).
- Wound healing and reduce scar formation (14).
- Inhibited the proliferation of keloid fibroblast (14).

BIOMEDICAL&CLINICAL APPLICATIONS OF CHITOSAN

Applications in Dentistry

P.L. Sapelli et al have remarked that many advantages are attainable with use of chitosan in parodontology such as decrease subjective symptomatology, good homeostatic action, delayed release of antibiotics, wound healing acceleration and better conditions for asepsis. For the first time they have reported clinical applications of chitosan in dentistry. Chitosan has been used in 24 patients

all of which recovered completely. No allergic reactions or infections took place. Chitosan could be used as transparent membrane or preferably as a thin powder soaked in antibiotic solution, it accelerated wound healing, promoted regular fibrin formation and favored the epithelialization (4).

Hypocholesterolemic effects

Growing evidence indicates that chitosan can lower plasma and liver triacylglycerol (TG) as well as total cholesterol (TC) levels exhibiting hypocholesterolemic and hypolipidemic effects. It has been reported that chitosan can reduce the risk of cardiovascular diseases and had potent fat-binding capacity in vitro. In addition, it was shown to increase fecal neutral- steroid and bile-acid excretion in rats and lower the postprandial plasma TG level in broiler chickens .Maezaki et al. (1996) reported the hypocholesterolemic effect of chitosan in humans for the first time and found that chitosan effectively decreased plasma lipid levels without side effects. However, the mechanisms of the hypocholesterolemic and hypolipidemic effects of different chitosans remained unclear. Recently, our group systematically studied the mechanism of the hypocholesterolemic and hypolipidemic effects of different chitosans in vitro and in vivo (12).

The hypocholesterolemic activity of LMW chitosan was higher when its DA was lower (90% deacetylated) at equal Mw and particle size; this might be due to the electrostatic attraction between LMW chitosan and anionic substances such as fatty acids and bile acids (36).

Angiotensin-I-converting enzyme (ACE) inhibition

Chitosan has also been reported to prevent increases in blood pressure. A high-salt diet can raise blood pressure because Cl_ activates angiotensin-converting enzyme (ACE), while chitosan can bind Cl_ and remove it, preventing the blood pressure from rising (Xia, 2003). Moreover, other researchers found that chitosan oligomers also had ACE-inhibitory activity. They reported that the ACE inhibitory activity of hetero-COS was dependent on the degree of deacetylation and that COS with the relatively lowest DD exhibited the highest ACE-inhibitory activity (Park, Je, & Kim, 2003); substitution of the hydrogen atom at the C-6 position of the pyranose residue with the aminoethyl group promoted the ACE-inhibitory effects of COS (800e3000 Da and 90%DD) (Ngo, Qian, Je, Kim, & Kim, 2008) (12).

Antimicrobial Activity

The antimicrobial activity of chitosan against a wide range of Gram-positive and Gram-negative bacteria, filamentous fungi, and yeasts is well documented in the literature. The antibacterial activity of chitosan is attributed to its polycationic structure, which exerts a strong electrostatic interaction with the negatively charged bacterial cell surface, disturbing the cell membrane and inducing leakage. Chitosan is soluble in dilute acid and antimicrobial activity is pH dependent, with the molecule becoming polycationic at a pH below the pKa . Chitosan derivatives that dissolve under neutral conditions have been found to lose some of their bactericidal activity. The antimicrobial activity of chitosan against a wide range of Gram-positive and Gram-negative bacteria, filamentous fungi, and yeasts is well documented in the literature (15).

Chitosans antimicrobial activity has been well documented. It displays a broad spectrum of antibacterial activity against both gram-positive and gram-negative bacteria, with minimum inhibitory concentrations (MICs) reported to range from 100 to 10 000 mg L-1 against gram negative bacteria , and from 100 to 1250 mg L-1 against gram-positive bacteria. Chitosan's antimicrobial activities are thought to be affected by chemical, physical and biological factors that include chitosan concentration, molecular weight, degree of deacetylation, pH, temperature, salinity, divalent cations, chitosan solvent, suspending medium, and bacterial growth phase (16).The presence of a large number of non-protonated amino groups as well as the poor solubility of chitosan at pH 7 mean that chitosan's bactericidal activity is minimal. Helander *et al.*reported that chitosan displayed antibacterial activity not only in an acid environment, although showed a stronger inhibitory effect at lower pHs with the inhibitory activity weakening with increasing pH. Kong *et al.* and Yang *et al.* observed that the antibacterial activity of the *N*-alkylated chitosan derivatives against *E. coli* increased as the pH rises from 5.0 reaching a maximum around pH 7.0–7.5 (27).

Gene Delivery

Chitosan shows particularly high biocompatibility and fairly low cytotoxicity. However, chitosan is insoluble at physiological pH. Moreover, it lacks charge, so shows poor transfection. In order to develop a new type of gene vector with high

transfection efficiency and low cytotoxicity, amphiphilic chitosan was synthesized and linked with low-molecular weight polyethylenimine (PEI) (17).Gene therapy aims at the treatment of many genetic diseases as it is a technique for correcting defective genes that are responsible for these genetic diseases. Specifically, the delivery of the appropriate, therapeutic gene (DNA) into the cells that will replace, repair or regulate the defective gene that causes the disease is a vital step for gene therapy. DNA, however, is a negatively charged, hydrophilic molecule; thus its delivery into the nucleus of the cell which requires it to pass through the also negatively charged and hydrophobic cell membrane is not feasible. Consequently, gene delivery carriers (also called vectors or vehicles) have been developed . Nature's way to carry genes is viruses and these were the first carriers used for gene delivery . However viruses have many disadvantages, the most severe of which is the immune response that they can cause and this is why non-viral carriers have been developed . Many of these are polymer-based because polymers are cheaper and safer than viruses and also easier to tailor compared to other gene delivery carriers like liposome's (18).

Orthopedics

Chitosan functional groups allow it to interact with many materials, which allow it to be used in conjunction with materials such as hydroxyapatite, or other calcium based minerals to form composites that have multiple applications within the orthopedic and periodontal industries. These calcium-chitosan composites can be used as a coating in conjunction with joint prostheses. As the chitosan is degraded, new bone can be deposited adjacent to the prosthesis to stabilize the implant within bone. An additional use for chitosan in orthopedics includes a direct replacement of bone or hard tissue. It is also a natural bioadhesive used to improve bone cement which is used to secure implants as well as to fill bone cavities (19).

Surgical adhesion

Biological adhesives are used for tissue adhesion, hemostasis, and sealing of the leakage of air and body fluids during surgical procedures. An adhesion is the formation of fibrous tissue that causes internal organs to be bound together in an unnatural fashion. These adhesions often occur during pelvic, abdominal or gynecological surgeries such as hysterectomies, cesarean sections, colectomies, and hernia repairs. After these procedures are completed and the body is attempting to heal its self through normal wound healing responses, swelling occur causing organs to be in closer proximity to one another than under normal internal conditions. Another component of natural wound healing is for the body to deposit fibrin to help repair damaged or injured tissues. This type of tissue formation can lead to infertility when adhesions twist ovaries and or tubes resulting in the blocking of the egg to the uterus. A photocross linkable chitosan to which both azide and lactose moieties were introduced (Az-CH-LA) was prepared as a biological adhesive for soft tissues and its effectiveness was compared with that of fibrin glue. A cytocompatible chitosan solution that is space-filling, gels within minutes, and adheres to cartilage and bone in situ was developed (19).

Wound healing

Since its discovery approximately 200 years ago, chitosan, as a cationic natural polymer, has been widely used as a topical dressing in wound management owing to its haemostatic, stimulation of healing, antimicrobial, nontoxic, biocompatible and biodegradable properties. This article covers the antimicrobial and wound-healing effects of chitosan, as well as its derivatives and complexes, and its use as a vehicle to deliver biopharmaceuticals, antimicrobials and growth factors into tissue. Studies covering applications of chitosan in wounds and burns can be classified into invitro, animal and clinical studies. Chitosan preparations are classified into native chitosan, chitosan formulations, complexes and derivatives with other substances. Chitosan can be used to prevent or treat wound and burn infections not only because of its intrinsic antimicrobial properties, but also by virtue of its ability to deliver extrinsic antimicrobial agents to wounds and burns. It can also be used as a slow-release drug-delivery vehicle for growth factors to improve wound healing. The large number of publications in this area suggests that chitosan will continue to be an important agent in the management of wounds and burns (20).To improve the wound-healing ability of chitosan, heparin, known to be effective in wound healing, was complexed with water-soluble chitosan (38).

APPLICATIONS OF CHITOSAN IN DRUG DELIVERY SYSTEM

Permeation Enhancer

Chitosan enhances the permeability of intestinal, nasal, buccal and corneal epithelia by opening the tight junctions between cells, thereby favoring paracellular drug transport.On carboxymethylation, some of the chitosan monomer residues retained the protonated structure, which is a requisite for enhancing paracellular drug absorption across the epithelial tight junctions. On this basis, verification of similar uses of CMC was persuaded. Thanou et al. tested mono-N-carboxymethyl chitosan (mono-NCMC) on Caco-2 cells for their efficiency to decrease the transepithelial electrical resistance (TEER) and to increase the paracellular permeability of the anionic macromolecular anticoagulant - low molecular weight heparin (LMWH) . For in vivo studies, LMWH was administered intraduodenally with or without mono- NCMC to rats. Results showed that mono-NCMC (of two different viscosity grades) managed to significantly decrease the TEER of Caco-2 cell monolayers at pH 7.4 when they were applied apically at concentrations of 3-5% w/v and to increase LMWH permeation substantially as compared to controls. A recent study by DiColo et al. showed that polyanionic NCMC failed to enhance intraocular (pH 2) drug penetration but increased precorneal ofloxacin retention due to its viscosity increasing effect and mucoadhesive binding to ofloxacin.(21).Quaternized chitosan has potential as an absorption enhancer across the intestinal epithelium due to its mucoadhesive and permeability enhancing properties (32).

Nanoparticles Drug Delivery

Chitosan and its derivatives have strong potential for application as drug carriers.Chitosan nanoparticles are a drug carrier with wide development potential and have the advantage of slow/controlled drug release, which improves drug solubility and stability, enhances efficacy, and reduces toxicity. Because of their small size, they are capable of passing through biological barriers in vivo (such as the blood–brain barrier) and delivering drugs to the lesion site to enhance efficacy. Drugs carried by chitosan nanoparticles can be released through degradation and corrosion of chitosan, leading to a clear sustained-release effect. A pH-sensitive nanocarrier is a drug delivery system that increases drug release by changing carrier properties under a certain acid-base environment in vivo, and targets the lesion tissue (25).

The challenges of anticancer treatment by chemotherapeutic agents include nonselective delivery of cytotoxic drugs to tumor sites that lead to severe side effects due to their effects on normal nontargeted organs and tissues Nanoscale drug delivery systems have achieved advantages by overcoming the challenges of common cancer treatments Recent anticancer research has focused on polymeric nanoparticles based on chitosan. Chitosan is a natural linear polycationic polysaccharide obtained by partial *N*-deacetylation of chitin. Chitosan has many advantages as a carrier in nanoparticulate drug delivery systems. It is nontoxic, biocompatible, and biodegradable and has been proven to control the release of drugs, proteins, and peptides. It is soluble in aqueous media, avoids the use of organic solvents, and doesn't require further purification of nanoparticles. With the presence of free amine groups in its linear structure, Chitosan has a cationic nature and can interact with various cross linkers to form nanoparticles. The positive charge of Chitosan caused by the primary amino groups in its structure is responsible for its mucoadhesive properties and therefore prolonging the residual time at the absorption site. Chitosan nanoparticles are expected to be appropriate carriers for oral absorption of drugs (22).

Insulin Oral Delivery

Insulin is a polypeptide hormone and usually administered for treatment of diabetic patients Subcutaneously, administering proteinous drugs orally is a formidable challenge due to their very short life in the gastric and intestinal fluids (26).The possibility of formulating an oral insulin delivery system using nanoparticulate complexes made from the interaction between biodegradable, natural polymer called chitosan and anionic surfactant called sodium lauryl sulfate (SLS). The nanoparticles were prepared by simple gelation method under aqueous-based conditions. The nanoparticles were stable in simulated gastric fluids and could protect the encapsulated insulin from the GIT enzymes. Additionally, the in vivo results clearly indicated that the insulin-loaded nanoparticles could effectively reduce the blood glucose level in a diabetic rat model. However, additional formulation modifications are required to improve insulin oral bioavailability (23).

Chitosan in Colon Targeted Drug Delivery

Chitosan is used for the colon targeted drug delivery because it has a tendency to dissolve in acidic pH of stomach but get swollen in the intestinal pH(29).Chitosan is a well accepted and a promising polymer for drug delivery in colonic part, since it can be biodegraded by the microflora present in the human colon proposed by Vipin Bansal,et *a*l. M.L. Lorenzo-Lamosa et a*l.* proposed the design of microencapsulated chitosan microspheres for colonic drug delivery (28).

Chitosan capsules were used for colonic delivery of an antiulcerative colitis drug. 5-Aminosalicylic acid (5-ASA) was used as model drug. A marked increase in the release of drug from chitosan capsule was observed in the presence of the rat ceacal content. From the results of this study it was concluded that chitosan capsules could be an effective carrier for the colon targeted delivery of anti-inflammatory drugs. Chitosan dispersed system was newly developed for colon-specific drug delivery which was composed of drug reservoir and the outer drug release-regulating layer dispersing chitosan powder in hydrophobic polymer. It was observed that the thickness of the outer layer controls the drug release rate. Since the dispersed chitosan dissolves easily under acidic conditions, an additional outer enteric coating was also provided to prevent the release of drug from chitosan dispersed system in the stomach. Different salts of chitosan were prepared by dissolving chitosan in various acidic solutions and then spray drying these solutions. From the results of the study it was concluded that drug release was reduced in acidic and alkaline pH when drug was mixed with chitosan salts (29).

Aceclofenac NSAID was successfully en capsulated into chitosan microspheres. Various formulations were prepared by varying the ratio of chitosan proposed by S.K.Umadevi et al(30).

Chitosan-based delivery systems have been widely studied for colonic drug targeting since this system can protect therapeutic agents from the hostile conditions of the upper gastrointestinal tract and release the entrapped agents specially at the colon through degradation of the glycosidic linkages of chitosan by colonic micro.ora. Yamamoto et al. investigated the use of chitosan capsules for colon-specific delivery of 5- amino salicylic acid (5-ASA). Chitosan capsule-based formulations showed better therapeutic effect than a carboxymethylcellulose suspension in vivo (31).

Muco adhesive delivery

Chitosan and its half-acetylated derivative have been compared as excipients in mucoadhesive tablets containing ibuprofen proposed by Williams,A.and Khutoryanskiy, V(34).Interactions of chitosan and half-acetylated chitosan with porcine stomach mucin were studied in aqueous solutions at different pHs and in the presence of various low molecular weight additives (urea,NaCl,ethanol). This study allowed establishing the nature of excellent mucoadhesive performance of chitosan (35).

Ala'a F.Eftaiha et al prepared the formulation contains chitosan-xanthan gum mixture as a hydrophilic polymer matrix resulted in a superior pharmacokinetic parameters translated by better rate and extent of absorption of metronidazole increase in bioavailability might be explained by the bioadhesion of the preparation at the upper part of the small intestine that could result in an increase in the overall intestinal transit time (37).

OTHER APPLICATIONS

Cosmetics

In cosmetic industry, value of chitosan was perceived as moisturising agent, emollient, and film former (39).Chitosan can be tailored to produce different forms for use in different cosmetic fields such as skin- care, hair-care and deodorants. It is an essential component in skin-care creams, shampoos and hairsprays due to its antibacterial properties. It forms a protective, moisturizing, elastic film on the surface of the skin that has the ability to bind other ingredients that act on the skin. In this way, it can be used in formulating moisturizing agents such as sunscreens, organic acids, etc (28).

Agriculture

Chitosan has been used in agriculture as a coating material for fruits, seeds and vegetables .For controlled agrochemical release of fertilizers (Sukwattanasinitt et al. 2001), to stimulate plant immune systems, plant growth and plant production and also to protect plants against attack by microorganisms.Chitosan is an exogenous elicitor of response mechanisms and has been demonstrated to induce plant defences in tomato (Benhamou and Thériault 1992; Benhamou *et al*. The use of biotic or abiotic elicitors is one way to increase the yields of secondary metabolites in *in vitro* cultures (Eilert 1987; Bohlmann and Eilert

1994). It has been reported that chitosan increased the growth rates of roots and shoots of daikon radish (*Raphanus sativus* L.) (Tsugita *et al*. 1993).Chitosan was found to reduce plant transpiration in pepper plants resulting in a 26-43% reduction in water use while maintaining biomass production and yield. These results suggested that chitosan might be an effective antitranspirant to conserve water use in agriculture (Bittelli *et al*. 2001) (40).Chitosan increase the plant growth and yield in okra plant(ladies finger) with increase in concentration of chitosan from 100 ppm -125ppm to get maximum yield in early growth stage proposed by M.M.A. Mondal et al (41).

ACHKNOWLEDGEMENT

The author are gratefull to Management and Principal of E.G.S.Pillay college of pharmacy,Nagapattinam,Tamilnadu, India-611002, for their support and encouragement and for providing necessary facilities.

REFERENCES

[1] Rani et al. (2010) "Chitosan drug delivery system" Bioresources 5 (4) 2765- 2807.
[2] Ilium, Lisbeth, Chitosan and its use as a Pharmaceutical excipient, Pharmaceutical Research,15(9), 1998, 1326-1331.
[3] T.A. Sonia and Chandra P. Sharma "Chitosan and Its Derivatives for Drug Delivery Perspective" Adv Polym Sci (2011) 243: 23–54
[4] Yadav A.V* and Bhise S. B " Chitin and Chitosan: Versatile Polysaccharides of Clinical Importance" Indian J.Pharm. Educ. 39(1) Jan. - Mar. 2005.
[5] Pradip Kumar Dutta et al "Chitin and Chitosan: Chemistry, Properties and Applications" Journal of Scientific & Industrial Research Vol.63, January 2004,page 20-31.
[6] Esam A. El-hefian*, Abdul H. Yahaya and Misni Misran " Characterisation of chitosan solubilised in aqueous formic and acetic acids" Maejo Int. J. Sci. Technol. 2009, 3(03), 415-425.
[7] M. Wiśniewska-Wrona et al "Biological Properties Of Chitosan Degradation Products" Polish Chitin Society, Monograph XII, 2007.page 149-156.
[8] Marine biomaterials: Characterization, Isolation and Applications edited by Se-Kwon Kim,
[9] Riccardo A.A. Muzzarelli et al "Chitosan, hyaluronan and chondroitin sulfate in tissue engineering for cartilage regeneration: A review .Carbohydrate Polymers 2012 , 89,3 ,723-739.
[10] Riccardo A. A. Muzzarelli, et al "Biochemistry, histology and clinical uses of chitins and chitosans in wound healing" Chitin and Chitinases EXS Volume 87, 1999, pp 251-264.
[11] R. Jayakumar et al "Biomedical applications of chitin and chitosan based nanomaterials" Carbohydrate Polymers ,Elsevier ,Volume 82, Issue 2, 5 September 2010, Pages 227–232.
[12] Xia, W., et al., Biological activities of chitosan and chitooligosaccharides, Food Hydrocolloids (2010), doi:10.1016/j.foodhyd.2010.03.003
[13] R.Porta et al "Transglutaminase Cross Linked Pectin and Chitosan Based Edible Film: A Review"Critical Reviews in Food & Nutritions, 51:223-238(2011).
[14] X.-G. Chen et al "The effect of carboxymethyl-chitosan on proliferation and collagen secretion of normal and keloid skin fibroblasts" Biomaterials 23 (2002) 4609–4614.
[15] Aziz et al. **"**Antimicrobial Properties of a Chitosan Dextran-Based Hydrogel for Surgical Use" AAC Journal . asm.org,january 2012 Volume 56 Number 1.
[16] Tang et al. "Antibacterial action of a novel functionalized chitosan-arginine against gram-negative bacteria" *Acta Biomater*. 2010 July ; 6(7): 2562–2571. doi:10.1016/j.actbio.2010.01.002.
[17] Chengchu Liu et al "Degradable copolymer based on amphiphilic N-octyl-N-quatenary chitosan and low-molecular weight polyethylenimine for gene delivery" Int J Nanomedicine. 2012; 7: 5339–5350.
[18] Mark A. Ward * and Theoni K. Georgiou "Thermoresponsive Polymers for Biomedical Applications *:*Review*"*Polymers 2011, *3*, 1215-1242; doi:10.3390/polym3031215.
[19] Lee et al. "Advances in Chitosan Material and its Hybrid Derivatives: A Review" *The Open Biomaterials Journal, 2009,vol 1*,10-20.
[20] Dai et al. "Chitosan preparations for wounds and burns: antimicrobial and wound-healing effects" Expert Rev Anti Infect Theraphy. 2011 July ; 9(7): 857–879.

[21] V.K Mourya et al. "Carboxymethyl chitosan and its applications:Review Article". Adv. Mat. Lett. 2010, 1(1), 11-33.
[22] Hosseinzadeh et al "Chitosan–Pluronic nanoparticles as oral delivery of anticancer gemcitabine:preparation and in vitro study" International Journal of Nanomedicine 2012:7,1851–1863.
[23] Elsayed et al. "Chitosan–Sodium Lauryl Sulfate Nanoparticles as a Carrier System for the In Vivo Delivery of Oral Insulin" AAPS PharmSciTech, Vol. 12, No. 3, September 2011.
[24] Chitin and Chitosan, Under-utilized Resources In services of Newfoundland Marine Biotechnology By. www.npaf.ca
[25] Wang et al "Recent advances of chitosan nanoparticles as drug carriers" International Journal of Nanomedicine 2011:6 765–774.
[26] Jelvehgari et al. "Development of pH-sensitive Insulin Nanoparticles using Eudragit L100-55 and Chitosan with Different Molecular Weights" AAPS PharmSciTech, Vol. 11, No. 3, September 2010.1237- 1242.
[27] Jolanta Kumirska et al. "Biomedical Activity of Chitin/Chitosan Based Materials— Influence of Physicochemical Properties Apart from Molecular Weight and Degree of *N*-Acetylation" *Polymers* 2011, *3*, 1875-1901.
[28] Vipin Bansal, et al. "Applications of Chitosan and Chitosan Derivatives in Drug Delivery" Advances in Biological Research 5 (1): 28-37, 2011.
[29] H. Rajpurohit et al."Polymers for Colon Targeted Drug Delivery" Indian J Pharm Sci. 2010 Nov-Dec; 72(6): 689–696.
[30] S. K. Umadevi et al. "Formulation and evaluation of chitosan microspheres of aceclofenac for colon-targeted drug delivery" Biopharmaceutics & Drug Disposition Volume 31, Issue 7, Article first published online: 15 SEP 2010.
[31] Ravi R. Patelet al. "Chitosan Mediated Targeted Drug Delivery System: A Review" J Pharm Pharmaceut Sci (www.cspsCanada.org) 13(3) 536 - 557, 2010.
[32] Hitoshi Sashiwa et al. "Chemically modified chitin and chitosan as biomaterials" Prog. Polym. Sci. 29 (2004) 887–908.
[33] A Krishna Sailaja et al. "Chitosan nanoparticles as a drug delivery system" Research Journal of Pharmaceutical, Biological and Chemical Sciences July – September 2010 Volume 1 Issue 3 Page No. 476.
[34] Williams, A. and Khutoryanskiy, V."*Chitosan-based mucoadhesive tablets for oral delivery of ibuprofen".*International Journal of Pharmaceutics, 436 (1-2). pp. 602-610.
[35] Vitaliy Khutoryanskiy "Chitosan and its derivatives:from physicochemical properties to biomedicalApplications" University of Reading, Reading, United Kingdom.
[36] Jiali Zhang et al " Chitosan Modification and Pharmaceutical/Biomedical Applications" *Mar. Drugs* 2010, *8*, 1962-1987.
[37] Ala'a F. Eftaiha et al. "Bioadhesive Controlled Metronidazole Release Matrix Based on Chitosan and Xanthan Gum" Mar. Drugs 2010, *8*, 1716-1730.
[38] Dong-Keon Kweon et al "Preparation and Characteristics of a Water-Soluble Chitosan–Heparin Complex" Journal of Applied Polymer Science, Vol. 87, 1784–1789 (2003).
[39] Rapeepun Chalongsuk* and Namfon Sribundit "Usage of Chitosan in Thai Pharmaceutical and Cosmetic Industries" Silpakorn U Science & Tech J ,7 (1) : 49-53, 2013
[40] Uthairatanakij *et al*. "Chitosan for improving orchid production and quality" *Orchid Science and Biotechnology* 1(1), 1-5©*2007 Global Science Books*.
[41] M.M.A. Mondal, M.A. Malek et al. "Effect of foliar application of chitosan on growth and yield in okra" Australian Journal of Crop Science 6(5):918-921 (2012).

****