Praise Worthy Prize

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Potential Drug Delivery Applications of Chitosan Based Nanomaterials

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Abstract – *Polymeric nanoparticles have long been sought after as carriers for systemic and targeted drug delivery. Chitosan is biopolymers having immense structural possibilities for chemical and mechanical modifications to generate novel properties, functions and applications especially in biomedical area. Chitosan is effective material for biomedical applications because of their biocompatibility, biodegradability and non-toxicity, apart from their antimicrobial activity and low immunogenicity, which clearly points to an immense potential for future development. These candidate biopolymers can be easily processed into gels, sponges, membranes, beads and scaffolds forms. This review emphasizes recent research on different aspects of chitosan based nanomaterials, including the preparation and applications of chitosan based nano material and macro particle. This review also includes the factors that affect the entrapment efficiency and release kinetics of drugs from chitosan microspheres.*

Keywords*: Biopolymer, Carrier, Chitosan, Drug Delivery, Nanoparticles*

I. Introduction

Nanotechnology, although not a new concept, has gained significant momentum in recent years. Primarily in the materials science standard, the term ‘‘nanotechnology’’ is now commonly used to refer to the fabrication of new materials with nanoscale dimensions between 1 and 100 nm [1].

Nanoparticles of different sizes have different biomedical purposes. The potential use of polymeric nanoparticles as drug carriers has led to the development of many different colloidal delivery vehicles. The main advantages of this kind of systems lie in their capacity to cross biological barriers, to protect macromolecules, such as peptides, proteins, oligonucleotides, and genes from degradation in biological media, and to deliver drugs or macromolecules to a target site with following controlled release.

In the last years, several synthetic as well as natural polymers have been examined for pharmaceutical applications. A basic requirement for these polymers to be used in humans or animals is that they have to degrade into molecules with no toxicity for biological environments. In recent years, biodegradable polymers have attracted attention of researchers to be used as carriers for drug delivery systems [2]-[13]. New drug delivery technologies are revolutionizing the drug discovery; development and creating R&D focussed pharmaceutical industries to increase the momentum of global advancements. In this regard, novel drug delivery systems (NDDS) have many benefits, which includes improved therapy by increasing the efficiency and duration of drug activity, increased patient compliance through decreased dosing frequency and convenient routes of administration and improved site specific delivery to reduce the unwanted adverse effects [14].

Carrier-mediated drug delivery has emerged as a powerful methodology for the treatment of various pathologies. Polymer composites were proposed as drug carriers over 30 years ago and have received growing attention since, mainly due to their stability, enhanced loading capabilities and control over physicochemical properties. Chitosan (CS) is a biodegradable, biocompatible cationic polymer with low toxicity, mucoadhesive properties, biodegradability and ability to enhance the penetration of large molecules across mucosal surfaces [15]-[17].

CS is a cationic linear polysaccharide composed essentially of (1→4) linked glucosamine units, with some proportion of N-acetylglucosamine units. CS is mainly obtained by extensive deacetylation of chitin present in the shells of crustaceans and molluscs, the cell walls of fungi and the cuticle of insects [18]. Chitosans are widely used as delivery matrix for controlled release of drugs in humans and animals, and non-steroidal agrochemicals in agriculture [19]-[21]. The antifungal activity of chitosan [22] and the reported ability to induce metabolic changes in plants allows it to increase the yield of crops, increasing the germination of seeds and resistance against plagues [23]. Its employment has motivated numerous studies about the influence of CS acetylation degree on its fungicide activity, chemical properties and applications [24]-[26].

Chitosan nanoparticles have gained more attention as drug delivery carriers because of their better stability,

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low toxicity, simple and mild preparation method, and providing versatile routes of administration. Their sub-micron size is not only suitable for parenteral application, but also applicable for mucosal routes of administration, i.e., oral, nasal, and ocular mucosa, which are non-invasive routes. The application for mucosal delivery was also facilitated by chitosan absorption enhancing effect.

These combination drug-loaded delivery systems offer some interesting features: (1) combination drug-loaded system can be formed in aqueous solution without the use of organic solvent, surfactant, and high shearing force; (2) the CS nanoparticles are positively charged, therefore can improve the site-specific targeting due to the strong affinity towards negatively charged biological membranes; (3) the components are made from water soluble CS and the hydrophilic drugs can be effectively encapsulated into the nanoparticles; and (4) two drugs were encapsulated into one drug delivery system, which provided a standard therapy for colon cancer treatment.

This review proposes to consolidate and discuss the recent applications of chitosan based nanofibers, nanocomposite membranes and scaffolds as well as nanoparticles including the preparation and applications of medicinal. This review also includes the factors that affect the entrapment efficiency and release kinetics of drugs from chitosan based materials as well as the potential role in the medical application (Fig. 1).

We also discussed the recent development on synthesis of chitosan nanoparticles and their applications towards clinical approach.

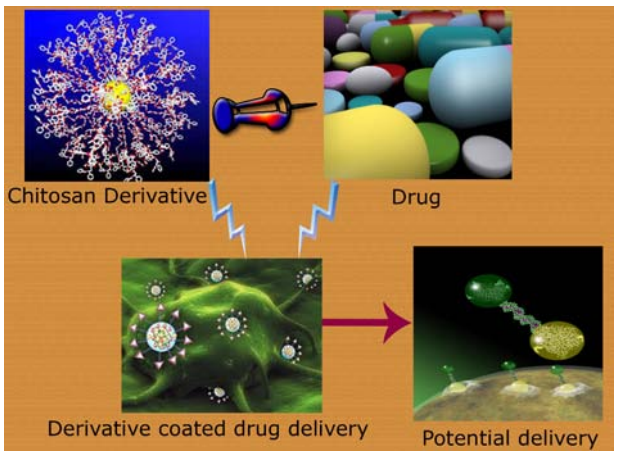

Fig. 1. Schematic representation chitosan based drug delivery

II. Applications of Chitosan

II.1. Carboxylated Chitosan

Chitosan (CS) nanoparticles using carboxymethylated molecule as an anionic polymer were developed to achieve complex coacervation for the incorporation and controlled release of drug [27], [28]. Carboxymethyl starch (CMS) is widely used in pharmaceuticals; however, it may need to be further modified for some special applications [29].

Among diverse approaches that are possible for modifying polysaccharides, grafting of synthetic polymer is a convenient method for adding new properties to a polysaccharide with minimum loss of its initial properties [30], [31]. Saboktakina et al., were synthesized chitosan-carboxymethyl starch (CMS) nanoparticles as drug delivery system to the colon and used as a 5-aminosalicylic acid (5-ASA) model drug molecule [32]. Its nanoparticles were formulated by a complex coacervation process under mild conditions. In vitro release of 5-ASAwas evaluated, and the integrity of 5-ASA in the release fraction was assessed using sodium dodecyl sulfate-polyacrylamide gel electrophoresis.

The CS–CMS nanoparticles developed based on the modulation of ratio show promise as a system for controlled delivery of drug to the colon. Carboxymethyl chitosan (CMCs) was further modified via grafting of sodium acrylate (AAs) onto its backbone in a mild aqueous medium using ammonium persulphate (APS) as initiator [33]. The main purpose of grafting was to increase the number of carboxylic groups in CMCs by developing Ca^{2+}-crosslinked hydrogel microspheres based on alginate with CMCs-g-AAs.

The in-vitro biodegradation study of the microspheres was carried out in SIF at 37 °C in presence of lysozyme and showed promising degradation rates. The more reduction in concentration of extracellular divalent ion can also help in opening of tight junctions and consequently improves the paracellular transport of protein drugs across the intestinal epithelium [34]. In addition, the mucoadhesive characteristics exhibited by these polymers increase the residence time of oral dosage forms at the epithelial surface and accordingly enhance the drug absorption [35].

Anitha et al, have evaluated the ability of O-CMC as a carrier for hydrophobic drugs in cancer drug delivery applications [36]. They used a simple method of solvent evaporation followed by ionic gelation to develop a nanoformulation based on O-CMC into which, the hydrophobic anticancer drug, curcumin was loaded. Fluorescence microscopic image showing green fluorescence confirmed the successful delivery of curcumin from the nanoparticle matrix and its anticancer effect was confirmed by MTT (3-(4,5-Dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium) assay.

In order to improve hydrophobic drug's bioavailability, novel composite nano particles of O-CMC/β-CD were synthesized by a simple ionic cross-linking method [37] Ibuprofen, a hydrophobic drug, was selected as the model compound. The loading capacity of the O-CMC/ β-CD was higher than O-CMC NPs, which indicated that β-CD had the strong effect on increasing the solubility of the hydrophobic drug and improving the loading capacity of NPs.

The more suitability of CMC-g-β-CD was further thiolated using a two step procedure. The first step involves the formation of amide bond between the primary amino groups of CMC and the carboxyl groups of CM β-CD.

In the second step, carboxyl groups of the resultant CMC-g-β-CD were conjugated with the amino groups of CMEH. The feasibility of the tablets as mucoadhesive delivery carriers for the transfection of the hydrophobic model drug, keto profen, was investigated [38]. Due to the presence of β-CD, the resultant polymers will have an ability to release the encapsulated drug molecules in a controlled manner to the surrounding mucosal tissues. It was reported that the pH value during the thiolation reactions has a great impact on the amount of thiol groups bounded onto the polymer back bone [39], [40].

Yanqin Lianga et al., prepared and characterized carboxylated mPEG-grafted chitosan (N-CS-g-mPEG) nanoparticle hydrogel [41], and their aqueous dispersion can undergo reversible gel–sol transition as the temperature changes.

The interior morphologies of N-CS-g-mPEG NP hydrogels has exhibited a highly macroporous spongelike structure. To the drug-loaded hydrogel, the drug can be released through different mechanisms [42]. The drug release can be driven by not only diffusion of drug but also erosion of the gel. However, the degradation of N-CS-g-mPEG NP hydrogels is so slow that the impact of degradation on the release can be ignored. Therefore, for the same drug, the gel network structure is the main factor of drug diffusion rate.

II.2. Carbohydrate Derivatives of Chitosan

The chitosan Oligosaccharide (COS) was coated with nanostructured lipid carrier (NLC) for ocular drug delivery [43]. The NLC was loaded with flurbiprofen was prepared by melt-ultrasonic method and then coated with COS with a molecular weight of 3000–6000 kDa.

The enhanced transcorneal penetration was achieved by using the COS coating with a corresponding apparent permeability coefficients which had a 2.4-fold increase on comparing with the reference.

Hezhong Wang and Maren Roman has been investigated on the formation of Polyelectrolyte Macroion Complexe (PMC) from chitosan and cellulose nano crystals (CNCs) at different CNC concentrations and mixing sequences and to determine the properties of the resulting PMC particles with regard to their potential application as a multiparticulate oral drug delivery system [44].

The concentration of CNCs in the reaction medium has a strong effect on PMC formation, with higher CNC concentrations resulting in larger or more highly aggregated PMC particles. For the colon drug delivery, a polyelectrolyte complex (PEC) of carboxymethyl starch (CMS) and chitosan is prepared and tested in vitro as a carrier for oral drug delivery [45].

The PEC seems to be a more suitable drug carrier for colon targeting than CMS, since it can prolong acetaminophen release time from 8 h to 11 h and aspirin release time from 13 h to 30 h. In contrast, chitosan used as a coexcipient accelerated aspirin release from matrices based on a CMS: chitosan physical mixture.

The linoleic acid (LA)-grafted chitosan oligosaccharide (CSO) was synthesized to construct a micellar delivery system for intracellular delivery [46].

The doxorubicin base (DOX) as a model drug. The cytotoxicities of DOX encapsulated in CSO-LA micelles against drug resistance tumor cells were improved significantly, comparing to that of Doxorubicin·HCl solution. These results suggest that the CSO-LA micelles can be a promising carrier for intercellular antitumor drug delivery and reverse drug resistance of tumor cells.

The NPs conjugated with multiple galactose residues in an antennary fashion (the Gal-m-CS NPs) suspended in an aqueous environment were rather stable during storage [47].

It was demonstrated that the Gal-m-CS NPs had a high affinity to HepG2 cells. Therefore, the prepared Gal-m-CS NPs may be a novel galactosylated carrier for specific liver-targeting drug/gene delivery. And the linking of dicarboxylic diosgenin monoesters with chitosan is exceptional drug carrier to their controlled release [48].

II.3. Multi-Functionalised Chitosan

Multi-functional nanoparticles now become alternative systems for drug delivery. Nanoparticles offer opportunities for multi-functionalization to allow for the targeted delivery of drugs with imaging agents. Polymeric nanocarriers can provide versatile platforms for the delivery of multiple pharmacological agents, specifically to enhance therapeutic effect and overcome drug resistance to cancer [49]-[54]. Commonly defined nanoparticle carriers include: liposomes, micelles, dendrimers, solid lipid, metallic, semiconductor and polymeric nanoparticles [55].

Therefore, multifunctionalised chitosan is an ideal drug delivery carrier for durgs. Suphiya Parveen et al have devoleped a surface coating by hydrophilic polymers such as chitosan (CS) and polyethylene glycol (PEG) which were used to curb the phagocytic effects and to enhance the longevity of the nanoparticles [56]. Hydrophilic poly 82 ethylene glycol (PEG) was introduced as an additional polymer coating to form PEG coated (PLGA–CS–PEG) nanoparticles and to evaluate the effect of optimal chitosan and PEG modification for reducing the macrophage uptake in vitro and in vivo. In this type encapsulated 5-FU and LV in CS nanoparticles, it has high promising drug encapsulation efficiency and loading capacity.

These multi-functional nanoparticles can effectively be used for targeted drug delivery and imaging the path of drug carrier by the fluorescence of ZnS:Mn attached to the system. The drug delivery and cancer cell imaging of novel FA–CMC– ZnS:Mn nanoparticles was evaluated by Mathew et al [57]. This study becomes important in the field of anticancer drug delivery because it aims controlled drug delivery using CMC at the same time imaging the path of this drug carrier system with the help of fluorescence from ZnS:Mn quantum dot.

The in vitro drug release studies showed controlled release of 5-FU from FA–CMC–ZnS:Mn nanoparticles. In situ immobilization of MPA-capped CdTe quantum dots (QDs) into the chitin nanogels was loaded with BSA protein drug [58].

The distinction in the stability of hybrid nanogels is important for the designed multiple functions. The succinyl linkage of chitosan modified glycol chitosan (CHGC) conjugation was synthesized, investigated its self aggregation behavior by Jing-Mou Yu et al [59].

The IND loaded nanoparticles assembled from amphiphilic graft polyphosphazenes [60]. These results indicated that CHGC self-aggregated nanoparticles could be potential carriers for the drug delivery.

II.4. Hydrogelated Chitosan

Chitosan polymer is widely used as delivery matrix for controlled release of drugs in humans. CS-TPP nanoparticles and CS-TPP nanoparticles loaded with tea catechins were successfully prepared via the ionic gelation method [15].

It is concluded, that the formation of desirable CS-TPP nanoparticles and CS-TPP nanoparticles loaded with tea catechins are possible by controlling the critical fabricating parameters including CS molecular mass, CS concentration, and CS-TPP mass ratio. Cafaggi et al, prepared a matrix chitosan salts and poloxamer 407 and evaluated for its buccal drug delivery system [61]. Different chitosan salts were perpared by reaction of chitosan with acetic, citric, and lactic acid. Chitosan lactate gave good sustained release, controlled swelling, and higher mucoadhesion when combined with P407 present in the matrix at the above concentration. These results indicate that such a matrix chitosan salts could find useful application in buccal drug delivery systems.

Chitosan has been blended with different amounts of polycaprolactone (PCL) to use them for controlled delivery of ofloxacin [62]. Blending two polymers is an approach to develop new biomaterials exhibiting combinations of properties that could not be obtained by individual polymers [63]. Blends made of synthetic and natural polymers can imbibe the wide range of physicochemical properties and processing techniques of synthetic polymers as well as the biocompatibility and biological interactions of natural polymers.

The poor cell adhesion normally associated with poly (2 hydroxyethylmethacrylate) was mitigated by blending with gelatin [64]. A kind of slow release drug-loaded microsphere were prepared with gelatin, chitosan and montmorillonite by an emulsification/chemical cross-linking method using glutaraldehyde as crosslinking agent and acyclovir as model drug. The linking process was more efficient, when reaction was conducted in homogeneous conditions.

The preparation of CS–steroid conjugates will allow achieving the controlled delivery of these steroids combining the well documented effects of brassinosteroids on biological properties of chitosan plants and animals [65]. Sustained release profile was obtained for diosgenin monosuccinate linked to diosgenin. These results indicate that by introducing the appropriate changes in the steroid structure and linking to chitosan, it would be possible to design efficient pH dependent delivery systems for the sustained release of steroid based agrochemicals and anticancer drugs. Mohammad Reza Saboktakina et al found that the ratio of chitosan to the oppositely charged polymer influences the formulation and properties of hydrogel [66]. They have chosen 5- aminosalicylic acid (5-ASA) as a model drug [67]. The hydrogel shrank and a densely cross-linked gel structure was formed.

The superparamagnetic chitosan–dextran sulfate hydrogel offer a high degree of protection from premature drug release in simulated upper conditions. Thus, spherical superparamagnetic hydrogel is a potential system for colon delivery of 5-ASA. In this type of specific application, the effect of molecular weight (MW) and degree of quaternisation (DQ) of N-trimethyl chitosan (TMC), as well as hydrogel composition was investigated on the thermosensitivity and rheological behaviour of nasal formulations [68]. Co-formulation of poly (ethylene glycol) and glycerophosphate with TMC of medium average molecular weight and low degree of quaternisation yields an aqueous formulation that exhibits a sol–gel transition at 32.5°C and within 7 min.

Thire specific apparent viscosity (350 mPa s) and viscoelasticity (200 Pa) values significantly reduce the mucociliary transport rate [69]. A novel approach involving supercritical carbon dioxide ($scCO_2$) induced phase inversion technique was developed to produce chitosan devices using moderate temperatures and very environmentally acceptable solvents [70]. The stable and sterile chitosan porous devices with controlled morphology were devoleped using the more sustainable supercritical carbon dioxide induced phase inversion process.

II.5. Metal Incorparated Chitosan

Metal nanoparticles are new generation materials being widely investigated for biomedical and therapeutic applications. To this end, interest in this field has increased by utilizing non-toxic and biocompatible naturally occurring polysaccharides such as chitosan [71] and gellan gum [72] for rapid synthesis of metal nanoparticles and subsequent use for drug delivery applications. The chitosan–alginate beads were mainly focused on single calcium crosslinking, such as chitosan-coating alginate calcium beads [73]-[76], which were endowed with bioadhesion. On the other hand, alginate calcium beads contained chitosan powder were also widely researched [77]-[79], but the controlled properties of pH sensitivity stability and site specific release under the gastrointestinal condition have not been sufficiently investigated. The stable ALG–CS beads was prepared by easy methods, which are endowed with controlled release properties in oral such as stomach, small intestine or

colon site-specific delivery [80]. Yongmei Xu et al prepared a stable alginate–chitosan blend gel beads based on calcium chloride and sodium sulfate dual ionic crosslinking and studied their release behaviors of protein model drug BSA in oral site specific delivery system, which was different from traditional single crosslinked beads [81].

They have also investigated the influence of mass proportion of alginate and chitosan and compared with single crosslinked gel beads on delivery property.

The beads were incubated in gastricintestinal tract conditions, which indicated dual crosslinked ALG–CS blend gel beads are potential drug carriers for small intestinal or colon specific drug delivery system. The dual cross linked polymeric carrier for oral delivery alginate/N-γ-glutaric acid chitosan (GAC) was prepared [82]. The homogeneous alginate/GAC solution was dropped into calcium chloride solution and crosslinked by Ca^{2+} ions. Sequentially, the crosslinked beads were suspended in sodium sulfate solution for forming dual crosslinked beads.

The dual cross linked alginate/GAC gel could be an excellent candidate of polymeric carrier for oral delivery of bioactive protein drugs. In order to improve copper complex modifies the chitosan due to its interaction with Cu^{2+} ion, different studies in aqueous media between CS and Casiopeina III-ia (Cas III-ia) were carried out. Cas III-ia is stable and maintains its effectiveness under acid conditions in the presence of CS. Since, it can be used through a pH change to get Cas III-ia-loaded chitosan submicron particles guaranteeing drug stability during each step of the method [83].

Marianne Hiorth et al., developed a pellets with calcium and chitosan in the core and then immersion coat the cores with pectin or alginate in combination with calcium or chitosan [84]. The encapsulation efficiency was tested for one of the coating combination: 2% pectin in combination with 5% $CaCl_2$. The encapsulation efficiency was close to 70% for both types of pellets. The uniform microsphere and nanospheres of calcium carbonate/carboxymethyl chitosan ($CaCO_3$/CMC) hybrid were prepared by the precipitation of calcium carbonate in an aqueous solution containing CMC [85]. The drug loading and release properties of hybrid microspheres and nanospheres were studied and the results showed that the water soluble doxorubicin hydrochloride could be effectively loaded in the hybrid microparticles and nanospheres with high encapsulation efficiency, and the drug release could be effectively sustained, indicating the hybrid microspheres and nanospheres were suitable for delivery of water-soluble drug.

II.6. Quantum dots

The synthesis of stable quantum dots has been a challenge in recent years. Weitai Wu et al, reported a new class of chitosan-based hybrid nanogels by in-situ immobilization of Cd-Se quantum dots (QDs) in the chitosan poly (methacrylic acid) (chitosan-PMAA) networks (Fig. 2) [86]. The multifunctional chitosan PMAAeCd-Se hybrid nanogels can be prepared in an aqueous solution via in-situ immobilization of Cd-Se QDs into the chitosan-PMAA nano- gels. The covalently crosslinked hybrid nanogels with chitosan chains semi-interpenetrating in the crosslinked PMAA networks exhibit excellent colloidal and structural stability as well as reversible physical property change in response to a pH variation across the physiological condition.

The structural stability of hybrid nanogels produces very different outcomes for their biomedical applications. In this way Yuan et al, synthesized monodispersed ZnO QDs by a chemical hydrolysis method and the drug response of doxorubicin-loaded ZnO-QD-chitosan-folate carrier was characterized [87]. The fabrication of water dispersed ZnO-QD–chitosan–folate carrier was loaded with anti-cancer drug (DOX). The experimentally observed drug-loading efficiency was 75%. Chitosan enhances the stability of the QDs because of its hydrophilicity and cationic charge characteristics.

The drug release response of DOX-loaded ZnO-QD–chitosan–folate carrier was characterized by an initial rapid drug release followed by a controlled release.

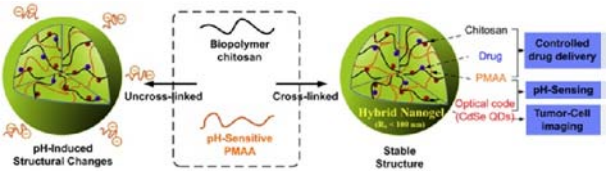

Fig. 2. The Schematic representation of multifunctional chitosan PMAAe CdSe hybrid nanogel

II.7. Enzymes Based Chitosan

Various approaches used for targeting the drugs to the colon include time, pressure, pH, and enzyme based systems [88]. Microbial activated delivery systems are considered to be preferable and promising, since the abrupt increase of the bacteria population and associated enzymatic activities in ascending colon represents a non-continuous event independent of GI transit time and pH [89]-[91].

Recently, a study by McConnell et al. [92] showed that microbially triggered drug delivery to the colon was more site-specific than pH-responsive drug delivery. The hydrophobic polymer has been selected to combine with chitosan as a film-coating material for colonic drug delivery.

The chitosan easily dissolved in acidic conditions, and most of the water-insoluble film-coating materials are not dissolved or stable in an acidic medium.

Other film-coating materials, such as Eudragit, will form interpolyelectrolyte complexes with chitosan in an aqueous medium [93]-[95], which are not suitable to be utilized as film-coating materials for pellets, tablets or other dosage forms. The purpose of this study was to prepare and characterize the properties of the chitosan/kollocoatSR30D mixed films for colonic drug delivery [96].

Priscileila et al. prepared relative simple systems constituted by coevaporates containing metronidazole (MT), CS and gastric resistant polymers and assessed their ability to release the drug in the colonic region [97].

The use of CS in combination with enteric polymers showed great potential as a system for colonic drug delivery, since the MT release in the colon could be controlled by varying the materials composition. In order to protect the delivery system in the acidic gastric conditions, enteric polymers were added and the drug release was triggered from coevaporates into the colonic fluids due to dissolution and degradation of CS by pectinase.

II.8. Colon Delivery Chitosan

The development of a more specific colon drug delivery system combining time, enzyme, and pH controlled systems using chitosan acetate (CSA) prepared from low molecular weight chitosan as a new compression coating material in combination with hydroxypropyl methylcellulose (HPMC) for 5-ASA tablets [98].

The specific delivery of colon was developed in the acidic gastric conditions; an outer enteric layer was prepared. The outer enteric layer is a triple-layer coated multi-unit dosage form, consisting of inner hydrophobic layer and middle, chitosan/succinic acid containing release triggering layer [99]. The drug release in the colon could be controlled by manipulation of the coating level of the middle combination layer. The resultant coated beads reached the large intestine of male, Sprague–Dawley rats in 2–4 h after oral administration; the drug release was triggered from the beads in the colonic fluids due to dissolution and degradation of chitosan by the colonic enzymes. The drug release rate was successfully enhanced in colonic conditions by the inclusion of organic acid in the middle polymeric layer of the triple-layer coated delivery system.

Formulation parameters showed significant influence on drug release pattern. Zinc–pectin–chitosan composite microparticles were designed and developed as colon-specific carrier [100]. The formulation was prepared at pH 1.5, 1% chitosan, 120 min cross-linking time, and pectin:drug at 3:1 ratio demonstrated colon-specific drug release. Resveratrol was used as model drug due to its potential activity on colon diseases. In vivo pharmacokinetics of the zinc-pectinate particles was compared with the zinc–pectin–chitosan composite particles in rats. Pharmacokinetic study indicated in vivo colon-specific drug release from the zinc–pectin–chitosan composite particles only. Cross-linking solution pH, cross-linking time, and chitosan concentration in the cross-linking solution exhibited major influence on drug release pattern.

The formulation lectin-conjugated 5-fluorouracil was loaded with chitosan–calcium–ALG micro particles by combining different principles of targeting and controlled release with muco/bioadhesivity of the system evaluate the ability of functionalized micro particles to improve oral delivery of 5-FU to colon region [101].

II.9. Ocular Drug Delivery

Low molecular weight chitosan coated liposome (LCHL) was prepared and evaluated for ocular drug delivery [102]. Diclofenac sodium (DS) was encapsulated in the liposome as model molecule. LCH with an appropriate molecular weight was coated on negatively charged liposome. LCH coating of liposome has brought a significant modification on its ocular drug delivery behaviors. LCHL also demonstrated an improved transcorneal drug penetration rate, which was attributed to the penetration enhancing effect of LCH. Hanjie Wang et al., were studied the performance of folated polymeric liposomes by incorporated calcium with polymeric liposome [103]. A new type of amphiphilic octadecyl-quaternized lysine modified chitosan (OQLCS), FA-OQLCS and PEG-OQLCS were synthesized successfully. In aqueous solutions, these polymers could form Folate- PEG coated polymeric liposomes (FPLs) that showed multi-lamellar structure similar to that of traditional liposomes prepared from phosphatidylcholine/cholesterol (PC/Chol). The in vitro release profiles indicate that FPLs could be a very promising vehicle for the administration of controlled release of drugs. The FPLs were prepared by a facile potentially scalable process with predictable and controllable outcomes and thus it may be suitable as a potential drug delivery system.

The potential of pectin as a carrier for colonic drug delivery has been demonstrated previously [104]. The use of high-methoxy pectin or cross-linking with calcium has been investigated as methods for reducing the inherent solubility. Azza et al., studied ionic gelation technique for the encapsulation of Econazole nitrate (ECO) as a model drug into CS nanoparticles and to evaluate their potential as drug nanocarrier [105]. Chitosan/pectin based nasal insert were improved to the bioavailability of antipsychotic drugs in the treatment of psychotic symptoms [106]. Chitosan/pectin polyelectrolyte complexes can be employed for the formulation of mucoadhesive nasal inserts with different drug release properties. The results showed the higher amount of pectin in the complexes, with respect to higher amount of chitosan, produced a more evident porous structure of the nasal inserts, improving water uptake ability and mucoadhesion capacity.

Jyh-Ping Chena et al, examined the preparation of chitosan-coated magnetic nanoparticle (MNP) (chitosan-MNP) and the feasibility of using tissue plasminogen activator (tPA) covalently bound to chitosan-MNP surface (chitosan-MNP–tPA) for magnetic targeted delivery of the thrombolytic drug [107]. Under magnetic guidance, chitosan-MNP–tPA can reduce the blood clotlysis time by 58% compared with runs without magnetic targeting or by 53% compared with free tPA using the same drug dosage.

Biocompatible chitosan-MNP–tPA developed in this study can be useful as a magnetic targeted drug to improve clinical thrombolytic therapy. A water-soluble chitosan derivative, methylated N-(4-N,N-dimethylaminocinnamyl) chitosan chloride (MDMCMChC) was investigated as novel mucoadhesive polymeric nanocomplex plat formfor sustained-release drug delivery in comparison with widely used chitosan derivative, N,N,N-trimethylammonium chitosan chloride [108].

Diclofenac sodium (DS) was used as model negatively charged drug in this study. Self-assembled nanocomplexes between water-soluble chitosan derivatives, MDMCMCSC, and negatively charged DS were successfully formed. It indicates that the introduction of a relatively more hydrophobic group of N-(4-N,N,N-trimethylammoniumylcinnamyl) moiety to chitosan backbone would provide better incorporation of DS into the nanocomplexes by hydrophobic interaction, while the presence of a quaternary ammonium group would initiate electrostatic interactions with carboxylate group of DS. The high potential of methylated N-(4-N,N-dimethylaminocinnamyl) chitosan chloride as novel mucoadhesive polymeric nanocomplex platform for sustained-release drug delivery.

The chitosan nanoparticles surface was modified with glycyrrhizin (CS-NPs-GL) as potential new hepatocyte-targeted delivery vehicles [109]. Adriamycin (ADR) was used as a model drug. The nanoparticles were also labeled with rhodamine B isothiocyanate and their interaction with rat hepatocytes was examined by flow cytometry (FCM) and confocal lasermicroscopy (CLSM). The results of drug loading and release experiments indicate that this system seems to be a very promising vehicle for encapsulation of ionizable drugs under acidic or neutral conditions. CS-NPs-GL has been developed a drug delivery system targeted the liver by the specific interaction between GL and hepatocytes. Nasti et al., prepared chitosan/triphosphate (TPP) nanoparticles and their coating with hyaluronic acid (HA) and it optimized various parameters [110]. Three optimised nanoparticles have been developed (two uncoated and one HA-coated) and their toxicity on fibroblasts and macrophages has been evaluated. Three different kinds of nanoparticles deposited on mica surfaces from dispersions in deionised water. Yun Sik Nam et al, studied the relationship between the physical stability of the microspheres based on alginate-chitosan system and their drug release profiles [111]. Bovine serum albumin (BSA) was encapsulated in selected microspheres to monitor the relationship between the carrier stability and protein release profile. Chitosan coating on top of alginate core beads provide much better stability.

II.10. Proteinated Chitosan

Microspheres containing chitosan nanoparticles were efficiently encapsulated in the microspheres, being homogeneously distributed within the whole particle and the dispersed in mannitol were structurally characterized using various innovative techniques [112]. It was confirmed that this drug delivery system is a promising carrier of protein-loaded nanoparticles and, hence, of therapeutic proteins to the lung. The gene targeting with MDR1on the A2780/TS cells to paclitaxel was investigated by synthesised chitosan/RNA plasmid nanoparticles [113]. Chitosan can effectively encapsulate the pshRNA plasmid targeting MDR1, form spheroidal chitosan/pshRNA plasmid nanoparticle with a size of 80–120 nm. Chitosan is a promising candidate for pshRNA plasmid delivery and can facilitate reversal of MDR in cancer cells.

The combined chitosan/siRNA nanoparticles with microstructured implants are promising canditate for local delivery of siRNA for guided neuroregeneration [114]. This is the first combinatorial approach of siRNA nanotherapeutics and biomaterial implants for the regeneration of the nervous system. Such a combination provides a means to address two major issues in spinal cord repair, bridging the cystic lesion site and desensitizing axons for regrowth into neighboring neuronal tissue. The brain delivery of the neurotransmitter Dopamine (DA) is evaluated with chitosan nanoparticles [115].

These CS nanoparticles represent an interesting technological platform for DA brain delivery and, hence, may be useful for Parkinson's disease treatment. The protein loaded chitosan nanoparticles is prepared through ionotropic gelation technique and its co-spray dried with mannitol resulting in a dry powder with adequate aerodynamic properties. The intratracheal administration to rats, both quantitative analyses of hypoglycemic effect and lung distribution studies have demonstrated that this system is able to deliver CS NPs into the deep lungs and, thus, transport the released INS in its bioactive form to systemic circulation to induce a hypoglycemic effect.

Sang-Yoon Kim et al produced the microsized chitosan capsules containing insulin by a combined process of ionic gelation with electrohydrodynamic atomization (EHDA) [116].

Produced airborne chitosan-insulin droplets were reacted with phytic acid to induce the binding between chitosan and phytic acid, resulting in chitosan capsules containing insulin. Jong-Ho Kim et al was studied a therapeutic approach to the enhancement of the antiangiogenic and antitumor effects of RGD peptide in a solid tumor model [117]. Due to the sustained RGD peptide delivery, RGD-HGC nanoparticles via intratumoral administration significantly decreased tumor growth and microvessel density compared to native RGD peptide injected either intravenously or intratumorally.

The advantages of chitosans based nanoparticulate systems were combined with the beneficial effects of pH-sensitive formulation for enhancing the oral delivery of peptide drugs [118]. The in vivo data clearly evidenced the ability of CS/HPMCP NPs to enhance the peroral delivery of insulin.

The system also affords the potential to control the release rate of the drug and facilitate its transport across the intestinal barrier. The fabricated two new mesoporous silicon devices prepared by electrochemistry and intended for protein delivery, namely mesoporous silicon microparticles and chitosan-coated mesoporous silicon microparticles [119].

Both carriers were investigated for their capacity to load insulin and bovine serum albumin by adsorption.

The characteristics of these drug delivery devices indicate its potential interest for formulating labile biopharmaceuticals, and particularly as transmucosal delivery devices.

III. Conclusion

This review summarizes the biomedical applications of multifunctional chitosan based nanomaterials in tissue engineering, wound dressing, drug delivery and cancer diagnosis. In addition, this review also opens up the novel applications for which these natural biopolymers can be put to use in a variety of nanostructural forms and sizes.

Multifunctional use of chitosan based nanomaterials has been proved to aid simultaneous cancer targeting and drug delivery. This review emphasizes recent research on different aspects of chitosan based nanomaterials, including the preparation and applications of chitosan based nano material and macro particle. This review also includes the factors that affect the entrapment efficiency and release kinetics of drugs from chitosan microspheres.

We expect that this review will provide insights on the use of these important of chitosan nanomaterials for researchers working in nanobiotechnology.

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