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Review Article

A REVIEW ON CHITOSAN-BASED HYDROGLES FOR THE DRUG DELIVERY SYSTEM

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ABSTRACT
Chitosan is a natural polymer obtained by deacetylation of chitin. It is biologically safe, non-toxic, biocompatible and biodegradable polysaccharide. Chitosan is a good candidate for site-specific drug delivery. Hydro gels are potential candidates in controlled release applications. It is due to their soft tissue biocompatibility, the ease with which the drugs are dispersed in the matrix and high degree of control achieved by selecting physical and chemical properties of polymer network. The aim of this review is to provide insight into the applications of chitosan based hydro gels for the drug delivery through different routes. These chitosan-based hydro gels are very essential in the sustained release of antibiotics to reach the target site. This article reviews focused on entire features of chitosan-based hydrogles in both as a drug delivery matrix system and a system for tissue engineering as well as its potential therapeutic applications. Finally it can be concluded that chitosan-based hydro gels offers a novel way for the sustained release of drugs to treat localized infections.

KEY WORDS: Chitosan, Hydro gel, Drug delivery, Sustained release, ph-sensitive, 5-Amino salicylic acid

INTRODUCTION

Chitosan is a deacetylated derivative of chitosan. It shows favorable properties like biodegradability and biocompatability.It is non-toxic and exhibits mucoadhesive properties[1,2]. This polymer plays a very important role in controlled drug delivery systems. Chitosan nano and micro particles are suitable for controlled drug release.

Chitosan exhibits wide range of biological applications like hypercholesterolemia, anti-microbial and wound healing properties. Chitosan is a linear polysaccharide consisting of (1-4) linked 2-amino-2-deoxy-b-D-glucopyranose.[3, 4] Hydro gels are the cross linked three-dimensional network polymers, which swell but do not dissolve in water. They become soft and rubbery in the swollen state which resembles living tissues. Hydro gels exhibit good biocompatibility and they are highly responsive to temperature, pH, electrical pulses etc.

The disadvantage of using this hydro gels is their poor mechanical properties as due to extensive swelling. To overcome this problem and to use this for the controlled delivery applications , attempts are made to modify their structures by physical blending with other polymers , grafting, developing interpenetrating polymer networks(IPN'S) or by cross-linking. Hydro gels are of special interest in controlled release applications because of their soft-tissue biocompatibility, the ease with which the drugs are dispersed in the matrix and high degree of control achieved by selecting physical and chemical properties of polymer network.

APPLICATIONS OF CHITOSAN-BASED HYDROGELS

Colon Delivery

Targeting of drugs to colon is advantageous in the treatment of diseases such as amoebiasis, crohn's disease, ulcerative colitis and colorectal cancer. Chitosan has drawn attention for its potential to achieve

site-specific to colon. Chitosan Nano particles are prepared by ionic gelation, complex coacervation, emulsion cross linking and spray-drying methods.

Dextran sulfate was used to formulate chitosan-based hydro gels to achieve complex coacervation for incorporation and controlled release of anti-angiogenesis hexapeptide.5-Amino salicylic acid (5-ASA) was taken as drug model .These chitosan-dextran sulfate hydro gels deliver most of the drug load in the colon, an environment rich in bacterial enzymes that degrade chitosan-dextran sulfate and allow drug release to occur at desired site. Spherical super paramagnetic hydro gel is potential system for colon delivery of 5-ASA. Hence chitosan-dextran hydrogel is very potential in the controlled delivery of drug.[5]

Oral Delivery

Beads loaded with antibiotics are very useful for oral delivery to treat gastric diseases such as peptic ulcer and for ulcerative colitis, carcinomas and infections in the intestine.[4] Chitosan is useful excepient for sustained release of water-soluble drugs and for enhancing bioavailability of poorly water soluble compounds. Chitosan gel beads and micro spheres are chemically cross-linked with glutaraldehyde and ethylene glycol diglycidyl ether to achieve stability.[5]Chitosan-alginate multi layer beads are cross-linked with poly phosphate to develop stable , nontoxic, inter polymer complex of ionic-cross linked chitosan-alginate-tri polyphosphate beads to improve drug release properties.

Ampicillin is taken as model drug. Single and multi layer beads are prepared by ionotropic gelation.Single layer beads released 70% of drug within 4hr where as multi-layer beads released 20-30% in the same period. The release of drug was controlled by changing chitosan concentration and degree of cross-linking using polyphosphate. Multi-layer beads especially those cross-linked with tripolyphosphate (TPP) are suitable for oral sustained release of low molecular and highly hydrophilic compounds.[6]

Cationic hydro gels with pH-sensitive swelling properties serve as candidates for stomach-targeted drug delivery system. Such matrices can be used to provide adequate release in gastric (low pH) environment. pH sensitive chitosan-polyvinyl pyrrolidone semi interpenetrating polymer network-based controlled release antibiotic delivery system is well suited for use in gastric environment. Porous freeze-dried hydro gels exhibit superior pH-dependent swelling properties over non-porous air-dried hydro gels. Amoxicillin was taken as model drug. Increased swelling of hydro gels under acidic condition was observed which was due to protonation of primary amino group on chitosan.Freeze-dried membranes released around 73% of amoxicillin (33% by air dried) in 3hrs at pH 1.0.Freeze-dried membranes serve as potent candidates for antibiotic delivery in an acidic environment.[7]

Thermo reversible hydro gels are extensively studied for drug delivery. These systems are injectiable fluids that can transform gels insitu at body temperature. The application of commercially available thermo gelling polymers is limited because they are not biodegradable. So chitosan, due to its intensive properties can be used as ideal candidate for delivery of macromolecular compounds such as drugs, proteins and genes. Hydro gels using chitosan copolymers in combination with poly (N-isopropyl acryl amide) and proloxamer are good candidates for insitu, reversible hydrogel formation.Poly (ethylene glycol)-grafted chitosan was used as injectiable thermo sensitive hydrogel for the sustained release of drug and tissue engineering. The aqueous dispersion of carboxylated methoxy PEG-grafted chitosan (N-cs-g-m-PEG) nanoparticle freeze-dried powder (NP-FDP) can undergo reversible gel-sol transition as temperature changes.Dexamethasone (DXM), Bovine serum albumin (BSA), 5-Fluoro uracil was taken as drug models. Invitro drug release behavior indicate that N-cs-g-m-PEG hydrogel provide sustained release for BSA and DXM.These hydro gels are potent for the drug controlled delivery systems of hydrophobic and bio-macro molecular drugs.[8]

Chitosan hydro gels are used in controlled release, implants, tissue engineering but their use is limited because of their poor water solubility under neutral physiological conditions, poor solubility in organic solvents and lack of amphipathicity.Novel chitosan derivative (carboxy-methyl-hexanoyl chitosan, CHC) was developed which exhibits excellent water solubility under neutral conditions. The presence of both carboxymethyl (hydrophilic) and hexanoyl (hydrophobic) groups affords amphiphilic nature, which makes CHC suitable for use as drug- loaded implant material for poorly water soluble agents.CHC hydro gels also exhibits pH sensitive behaviour.The pH sensitivity was more pronounced in CHC than in N,O-

Carboxy methyl chitosan. When used with Ibuprofen, the bursting release of the drug was less prominent in CHC samples having high degree of car boxy methyl substitution.[9]

Poly (lactic acid) / chitosan nanoparticles are very potential for the controlled delivery of anti-HIV drug Lamivudine.These nanoparticles are prepared and characterized by emulsion solvent evaporation method. Controlled release preparation using poly (lactic acid)/chitosan nanoparticles achieved maximum therapeutic effect with minimization of adverse effects. Drug loaded PLA/CS nanoparticles were purified without contaminants and then lyophilized by using dichloromethane as solvent and PEO as stabilizer. The invitro drug release studies showed that drug release rate was lower in acidic pH when compared to alkaline pH. Degradation rate increases rapidly when pH increase in the range of 8-13.Therefore these nanoparticles can entrap and protect the drug at stomach environment (acidic pH) and then provide sustained release at neutral pH.[10]

Semi-interpenetrating polymer network hydro gels were prepared by UV irradiation of water soluble N-carboxyethyl chitosan (CECS) and 2-Hydroxyethyl methacrylate (HEMA) aqueous solutions in the presence of D-2959 as photo initiator. These hydro gels could be used as drug-delivery matrix or wound dressing materials.[11]

Heavy metals are dangerous polluting agents in water. This danger is due to their bioaccumulation and non-biodegradability. The free amino group of chitosan gives it a better ability to chelate ions of transition metals and other natural compounds such as cellulose derivatives. This chelating property helps us to recover metals.Chitosan hydrogel beads were studied for adsorption of lead ions and humic acid from aqueous solutions to examine adsorption behaviors and mechanisms. To increase uptake capacity of mercury ions, several chemical modifications of chitosan beads cross-linked with glutaraldehyde was performed. Among them, aminated chitosan bead performed through chemical reaction with ethylene diamine had a high uptake capacity.Inorder to form new hydro gels for the uptake of metal ions and waste water treatment modification of chitosan was made to the basic matrix using heterocyclic compounds such as N.N'-biisomaleimide, N,N'-biisophthalimide and N,N'-phthalimidomaleimide.Swelling in different solvents decreases in the following order- N,N'-biisomaleimide > N,N'-phthalimidomaleimide > N,N'-biisophthalimide.The hydro gels obtained from modified chitosan are able to recover heavy metals such as copper and co bolt from aqueous solutions.Chitosan- N,N'-biisophthalimide hydrogel can recover copper ions with efficiencies reaching 42.5% and co bolt ions with efficiencies up to 51.5%.Thermal stability of reaction products of heterocyclic compounds with chitosan can be arranged as –N,N'-biisophthalimide > N,N'-phthalimidomaleimide > N,N'- biisomaleimide.[12]

The hydro gels are gaining importance due to its low toxicity and biocompatability.Blending of chitosan with polyvinyl alcohol produce biodegradable polymer blend system that can be used in controlled release of drug. Temperature and pH responsive hydrogel based on chitosan grafted with polyacrylic acid (PAAC). Polyhydroxy propyl methacrylate (PHPMA), poly (vinyl alcohol) (PVA) and gelatin was prepared for oral drug delivery. Prepared hydro gels represented different swelling and gelatin degree depending on composition of chitosan, monomers and radiation dose.Oxttetracyclin was taken as model drug. The hydrogel of lower content of PAAC and PVA and in the absence of PHPMA showed high degree of swelling and release rate of oxttetracyclin.Most preferable hydrogel for drug release is that of (PAAC/PVA) g- chitosan prepared at lower radiation doses when compared to gelatin based hydrogels.The invitro release profiles of drug showed that release of drug increased as the time, temperature and pH increased and reached to maximum after 48 hr at pH 9. Therefore these hydro gels can be used for localized drug delivery to treat infections on the respiratory tracts, skin and gonorrhea.[13]

Injectiable thermo-activated hydro gels have great potential in biomedical applications including use in therapeutic delivery vehicles. The feasibility of these delivery systems is their ability to gel at physiological conditions and to release entrapped molecules in a sustained manner.Mono basic and tri basic phosphate salts were not effective in inducing gelation of chitosan solution. In the presence of dibasic phosphate salt such as dipotassium hydrogen orthophosphate (DHO), the acidic chitosan solution was neutralized and gelling temperature and time were regulated by varying chitosan and salt concentration. Potential of chi/DHO as potential drug delivery vehicle was demonstrated using FITC-

dextran, beta-galactoglobulin and BSA.The neutral hydrophilic macromolecule FITC-dextran showed fast release from the gel than protiens.Therefore chi/DHO hydrogel are used as potential delivery systems for different therapeutic agents with controlled release kinetics.[14]

Carboxy methyl chitosan, a water soluble chitosan derivative has been widely used for biomedical applications. Photo Induced grafting showed controlled generation of radical sites on polymer backbones in addition to attaining higher grafting efficiencies. The high hydrophilicity and biocompatibility, grafting of poly ethylene glycol onto CMC'S could be convenient route to synthesis drug carriers.Carboxymethylation of chitosan followed by its photo-induced graft copolymerization with poly(ethylene glycol) acryl ate(PEGA) in a mild aqueous medium with the aid of DMPA as photo initiator was carried out. The crystallographic patterns and thermal stability of copolymers was studied. The synthesized copolymers were used to develop pH-responsive hydro gels through photo-induced cross linking using methylene bis acryl amide (MBA).5-fluoro uracil was taken as model drug. Swelling behavior and invitro release profiles of 5-fluoro uracil from hydro gels were studied and thus these hydro gels matrices act as good candidates in drug delivery systems.[15]

Stimuli-sensitive biodegradable and biocompatible films and hydro gels are widely used in controlled release drug delivery applications .By using radiation technique, the hydrophilicity as well as porosity can be controlled at low temperature, and it is very convenient for preparing drug delivery system.pH-sensitive hydro gels increased attention for oral delivery of protein drugs. These hydrogles were used as pH-sensitive based controlled system for protein drug delivery. The adsorption of bovine serum albumin in chitosan (cs)-poly vinyl pyrrolidone (PVP)(cs-PVP) hydro gels and their release behavior was studied. These hydro gels shown change in drug release rate in response to change in the environmental pH of buffer solution, ionic strength and composition of hydrogel system. BSA was taken as protein model. The release studies showed that the basic parameter affecting drug release behavior of cs-PVP hydro gels is pH of the solution.Poly electrolyte cs-PVP hydro gels with different compositions were prepared by irradiating cs/PVP/water mixtures with gamma rays at ambient temperature. Adsorption of BSA within cs-PVP hydro gels increased with increase in cs content in the hydrogels.When irradiation dose of hydro gels increased, the adsorption of BSA decreased. Albumin release was higher in pH 7.4 media compared with acidic media's-PVP hydro gels are novel and exhibit controlled release of protein, making it potential candidate for the controlled release of drugs in alkaline environment of the gastro-intestinal tract.[16]

Ophthalmic delivery

Various studies showed the potential of chitosan-based system for improving the retention and biodistribution of drugs applied topically onto the eye. In addition to its low toxicity and good ocular tolerance. Various formulations have been prepared like chitosan gels, chitosan-coated colloidal systems, and chitosan nanoparticals.it is evidence of the potential of chitosan gels for enhancing and prolonging the retention of drugs on the eye surface. The micro particulate drug-carrier (micro sphere) seem a promising means of topical administration of acyclovir to the eye.[17]

Nasal Delivery

The nasal mucosa presents an ideal site for bioadhesive drug delivery system[18] such as micro spheres, liposomes, and gels have been demonstrated to have good bioadhesive characteristics and swells easily when in contact with nasal mucosa. Bioavailability and residence time of the drugs that are administrated via the nasal route can be increased by bioadhesive drug delivery system. Various chitosan salts (chitosan lactate, chitosan aspartate, chitosan glutamate, and chitosan hydrochloride) showed nasal sustained release of vancomycin hydrochloride. [19]

Bioadhesive chitosan micro spheres of pentazocine for intranasal systemic delivery significantly improved bioavailability with sustained and controlled blood level profiles compared to intravenous, oral administration.[20]

Buccal delivery

An ideal buccal delivery system should stay in the oral cavity for few hours and release the drug in unidirectional way towards the mucosa in a controlled or sustained release fashion. Mucoadhesive

polymers will prolong the residence time of the device in the oral cavity. Bilayered device will ensure the release of the drug occurs in a unidirectional way.[21, 22] Chitosan is a excellent polymer to be used for buccal delivery because it has muco/ bioadhesive properties and can act as an absorption enhancer. The buccal bilayered device (bilaminated film, bilayered tablets) using a mixture of drug(nifedipine and propranolol hydrochloride) and chitosan, with these device show promising potential for using controlled delivery of the drug to the oral cavity.[23]

Vaginal Delivery

Chitosan, modified by the introduction of thioglycolic acid to the primary amino groups of polymer embeds clotrimazole, an imidazole derivative widely used for the treatment of mycotic infections of the genitourinary tract. by introducing thiol groups, the mucoadhesive properties of the polymer were strongly improved, and this resulted in an increased residence time of the vaginal mucosa tissue (26 times longer than the corresponding unmodified polymer), guaranteeing a controller drug release in the treatment of mycotic infections.[24]

CONCLUSION

Chitosan is a biopolymer which is non-toxic and is obtained from from deacetylation of chitin. The physical and chemical properties of chitosan such as inter and intra molecular hydrogen bonding and the cationic charge in the acidic medium , makes this polymer attractive for the development of conventional and novel pharmaceutical products .Chitosan-based hydro gels has numerous advantages as a biomaterial and is widely used as carrier system for the delivery of drug, protein and gene. These chitosan –based hydro gels are essentially employed for the slow release of the drug at a particular target site to improve the therapeutic activity.

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