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A Review on Chitosan based Nanoparticulate drug delivery system

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ABSTRACT

Chitosan has prompted the continuous movement for the development of safe and effective drug delivery systems because of its unique physicochemical and biological characteristics. The primary hydroxyl and amine groups located on the backbone of chitosan allow for chemical modification to control its physical properties. When the hydrophobic moiety is conjugated to a chitosan molecule, the resulting amphiphile may for self-assembled nanoparticles that can encapsulate a quantity of drugs and deliver them to a specific site of action. Chemical attachment of the drug to the chitosan throughout the functional linker may produce useful prodrugs, exhibiting the appropriate biological activity at the target site. Muco-adhesive and absorption enhancement properties of chitosan increase the in vivo residence time of the dosage form in the gastrointestinal tract and improve the bioavailability of various drugs. The main objective of this review is to provide an insight into various target-specific carriers, based on chitosan and its derivatives. The first part of the review is concerned with the organ-specific delivery system using chitosan and its derivatives. The subsequent section considers the recent developments of drug delivery carriers for cancer therapy with special focus on various targeting strategies.

Keywords: Amphiphile, effective drug delivery system s, target-specific.

Abbreviations: TPP - Tripolyphosphate anions, NPs – Nanoparticles, CS – chitosan, SEM - Scanning Electron Microsco pe, 5-FU - 5-fluorouracil, GCS - glycol chitosan, CPT – Camptothecin, HGC - Hydrophobically modified glycol chitosan.

1. INTRODUCTION

Chitosan is a natural cationic biopolymer consequent commencing the hydrolysis of chitin. One perceptible improvement of this substance is that it can be obtained from ecologically sound natural sources, namely crab and shrimp shell wastes. Together with chitin, Chitosan is well thought-out the second most profuse polysaccharide subsequent to cellulose (Suh and Matthew, 2000). Chitosan (Poly [-(1, 4)-2-amino- 2-deoxy-D-glucopiranose]) has a structure as shown in Fig .1. Chitin is isolated from shells of crustacean

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(for example shrimp, crab and lobster) by treating the shells with 2.5 N NaOH at 75°C and with 1.7 N HCl at room temperature for 6 hours. Deacetylation can be done by alkaline treatment or by enzymatic reaction. The alkaline deacetylation is carried out by treating chitin with NaOH at high temperature. The degree of deacetylation increases with increasing temperature or NaOH concentration. The polymer differs from chitin in that a majority of the N-acetyl groups in Chitosan is hydrolyzed. The degree of hydrolysis has a significant effect on the solubility and rheological properties of the polymer. The amino group on the polymer has a pKa in the range of 5.5 to 6.5, depending on the sourc e of the polymer (Koide, 1998). At low pH, the polymer is soluble, with the sol-gel transition occurring at approximate pH 7. The pH sensitivity coupled with the reactivity of the primary amino groups makes chitosan a unique polym er for and drug delivery applications. Chitosan is now available commercially in various molecular weights (50 kDa – 2,000 kDa) and different degree of deacetylation (40% to 90%).

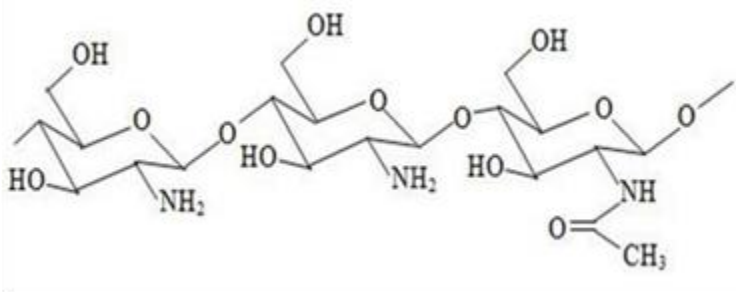

Figure 1
Chemical structure of Chitosan, The polymer is obtained by the partial deacetylation of naturally occurring polymer, chitin.

2. IN-VITRO EVALUATI ON OF FOLATE-TARGETED CHITOSAN NANOPARTICLES LOADED WITH HYDRO XYCAMPTOTHECIN

FA-targeted and 10-hydroxycamptothecin loaded chitosan nanoparticles (FA-HCPT-N Ps) with a combination of emulsion-solvent evaporation and chemical cross linking method. In vitro cytotoxicity test to the Human Cervix Carcinoma cells (HeLa) was evaluated by cell morphology and internalization observation. The specificity of the FA-HCPT-NPs targeting cancerous cells was demonstrated by comparative intracellular uptake of HCPT-NPs and commercial available HCP T injection. Laser confocal scanning imaging proved that FA-HCPT-NPs could greatly enhance up-take by HeLa cells. The morphological changes of HeLa cells showed the FA -HCPT-NPs could inhibit HeLa cells more effectively than HCPT-NPs and HCPT. The results indicated that the novel FA-HCPT-NPs could be a potential drug delivery system for tumor cell-selective targeting therapy (Grenha et al., 2005).

3. HYDROPHOBICA LLY MODIFIED GLYCOL

Chitosan nanoparticles-encapsulated camptothecin enhance the drug stability and tum or targeting in cancer therapy. To prepare a water-insoluble camptothecin (CPT) delivery carrier, hydrophobically modified glycol chitosan (HGC) nanoparticles were constructed by chemical conjugation of hydrophobic 5-cholanic acid moieties to the hydrophilic glycol chitosan backbone. Insoluble anticancer drug, CPT, was easily encapsulated into HGC nanoparticles by a dialysis method and the drug loading efficiency was above 80%. CPT-encapsulated HGC (CPT-HGC) nanoparticles formed nano-sized self-aggregate in aqueous media (280-330 nm in diameter) and showed sustained release of CPT for 1 week. Also, HGC nanoparticles effectively protected the active lactone ring of CPT from the hydrolysis under physiological condition, due to the encapsulation of CPT into the hydrophobic cores in the HGC nanoparticles. The CPT-HGC nanoparticles exhibited significant antitumor effects and high tumor targeting ability towards MDA-MB231 human breast cancer xenografts subcutaneously implanted in nude mice (Tozaki et al., 200 2). Tumor growth was significantly inhibited after i.v. injection of CPT-HGC nanoparticles at doses of 10 mg/kg and 30 mg/kg, compared to free CPT at dose of 30 mg/kg. The significant antitumor efficacy of CPT-HGC nanoparticles was attributed to the ability of the nanoparticles to show both prolonged blood circulation and high accumulation in tumors, as confirmed by near infrared (NIR) fluorescence imaging systems. Thus, the delivery of CPT to tumor tissues at a high concentration, with the assistance of HGC n anoparticles, exerted a potent therapeutic effect. These results reveal the promising potential of HGC nano particles -encapsulated CPT as a stable and effective drug delivery system in cancer therapy

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4. METHOTREXATE-LOADED CHITOSAN- AND GLYCOL-CHITOSAN- BASED NANOPARTICLES

A Promising Strategy for the administration of the Anticancer Drug to Brain Tumors. Brain tumor treatment employing methotrexate (MTX) is limited by the efflux mechanism of Pg-p on the blood–brain barrier. We aimed to investigate MTX-loaded chitosan or glycol chitosan (GCS) nanoparticles (NPs) in the presence and in the absence of a coating layer of Tween 80 for brain de livery of MTX. The effect of a low Tween 80 concentration was evaluated. MTX NPs were formulated following the ionic gelation technique and size and zeta potential measurements were acquired. Transport across MDCKII-MDR1 monolayer and cytotoxicity studies against C6 glioma cell line were also performed. Cell/particles interaction was visualized by confocal microscopy (Sinha and Kumria, 2001). The particles were shown to be cytotoxic against C6 cells line and able to overcome MDCKII-MDR1 cell barrier. GCS based NPs were the most cytotoxic NPs. Confocal observations highlighted the internalization of Tween80-coated fluorescent NPs more than Tween 80-uncoated NPs. The results suggest that even a low concentration of Tween 80 is sufficient for enhancing the transport of MTX from the NPs across MDCKII-MDR1 cells. The nanocarriers represent a promising strategy for the administration of MTX to brain tumors which merits further investigations under in vivo conditions.

5. CYTOTOXIC EFFECT S OF CHITOSAN AGAINST ORAL CANCER CELL LINES IS MOLECULAR-WEIGHT- DEPENDENT AND CELL-TYPE-SPECIFIC

The elucidations of the anticancer mechanisms of many anticancer agents from natural sources with minimal toxicity to normal cells are still being performed. Chitosan is a poly cation polysaccharide, which is an N-deacetylated derivative of chitin. It is naturally and abundantly present in crab and shrimp shells, and has been widely used as a multipurpose biomaterial. Antitumor activity is one of many attractive biological properties of chitosan. Report of its antitumor activities on oral squamous cell carcinoma (SCC) cells is scarce despite many in-vitro and in-vivo reports on other cancer types. Physical characteristics of chitosan have been reported to influence its antitumor activity, the effects of which vary depending on ce ll types. Therefore, this study examined whether cytotoxic effects and doses of chitosan are affected by its molecular weight (MW) in oral SCC and non-cancer cell line. Cytotoxic effects of two types of chitosan with different MWs (average 50 - 190 kDa and 310->375 kDa) were tested on three oral SCC (HSC-3, HSC-4 and Ca9-22) cell lines and a keratinocyte cell line (HaCaT) using MTT assay. However, chitosan had opposite effects on HaCaT cells at certain concentrations. Both types of chitosan induced proliferation of HaCaT cells at concentrations that showed cytotoxic effects on HSC-3 and Ca9-22 cells (200 – 300 mg/ml).

6. GALACTOSYLATED N ANOCRYSTALLITES OF INSOLUBLE ANTICANC ER DRUG FOR LIVER-TARGETING THERAPY: AN IN VITRO EVALUATION

Low solubility in water has become an intrinsic property of many anticancer drugs, which poses a hurdle in the translation from the bench to the clinic. In this study, we developed a facile method to prepare 10-hydroxycamptothecin (HCPT) nanocrystallites and testified their feasibility for liver-targeting therapy. HCPT nanocrystallites were prepared under the soft template effect of galactosylated chitosan. The internalization profile, intracellular trafficking, drug activity and cell viability were evaluated by exposing these nanocrystallites to human hepatocellular carcinoma HepG2 cells. Galactosylated chitosan located on the HCPT nanocrystallites not only stabilized the formulation i n aqueous medium, but also enhanced the cellular internalization through a glycoprotein receptor mediated pathway.

7. 5-FLUOROURACIL ENCAPSULATED CHITOSAN NANOPARTICLES FOR PH-STIMULATED DRUG DELIVERY: EVALUATION OF CONTROLLED RELEASE KINETICS

Nanoparticles consisting of human therapeutic drugs are suggested as a promising strategy for targeted and localized drug delivery to tumor cells. In 5-fluorouracil (5-FU) encapsulated chitosan nanoparticles were prepared in order to investigate potentials of localized drug delivery for tumor environment due to pH sensitivity of chitosan nanoparticles. Optimization of chitosan and 5-FU encapsulated nanoparticles production reveal nm particle size diameters with narrow size distributions, which are confirmed by scanning electron microscope (SEM) images. The challenge was to investigate drug delivery of 5-FU encapsulated chitosan nanoparticles due to varied pH changes. In vitro release studies indicated a controlled and sustained release of 5-FU from chitosan nanoparticles with the release amounts of 29.1–60.8% due to varied pH environments after 408 h of the incubation period. pH sensitivity is confirmed by mathematical modeling of release kinetics since chitosan nanoparticles showed stimuli-induced release.

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Results suggested that 5- FU encapsulated chitosan nanoparticles can be launched as p H-responsive smart drug delivery agents for possible applications of cancer treatments.

8. FORMULATION AND EVALUATION OF CHITOSAN-BASED AMPICILLIN TRIHYDRATE NANOPARTICLES

Development of ampicillin trihydrate-loaded chitosan nanoparticles by modified ionic gelation method and evaluates their antimicro bial activity. Ampicillin trihydrate-loaded chitosan nanoparticles were prepared by ionic gelation method with the aid of sonication. Parameters such as the zeta potential, polydispersity, particle size, entrapment efficiency and in vitro drug release of the nanoparticles were assessed for optimization. The antibacterial properties of the nanoparticle formulation were evaluated and compared with that of a commercial formulation. Scanning electron microscopy revealed that the nanoparticles were in the nanosize range but irregular in shape. Concentrations of 0.35 %w/v of chitosan and 0.40 %w/v sodium tripolyphosphate (TPP) and a sonication time of 20 min constituted the optimum conditions for the preparation of the nanoparticles. In vitro release data showed an initial burst followed by slow sustained drug release.

9. LOW MOLECULAR WEIGHT BIODEGRADABLE POLYMER BASED NANOPARTICLES A S POTENTIAL DELIVERY SYSTEMS FOR THERAPEUTICS

Chitosan is the most promising biodegradable polymer for LMWBP based nanoparticle preparation for therapeutic applications. According to the literature, Low molecular weight chitosan-poly-γ-glutamic acid (LMW-CPGA) nanoparticles were prepared by a simple ionic-gelation method for oral insulin delivery. The average molecular weights (MW) of chitosan and γ-glutamic acid were used 80 kDa and 60 kDa, respectively. The diameters of the prepared nanoparticles were in range of 110-150 nm depending upon acid us ed. Zeta potential of Chitosan -poly (γ-glutamic acid) nanoparticles were recorded ranging from 5.1 to 36.8 nm. Finally, insulin loaded these nanoparticles were applied on rat (Cacoo -2 cell monolayers). In-vivo results clearly indicated that thee insulin loaded Chitosan-poly (γ-glutamic acid) nanoparticles could effectively reduce the blood glucose level in a diabetic rat model. In an another study, low molecular weight chitosan/hyaluronic acid (LMWCHA) nanoparticles were made by using commercially available chitosan (MW of 5kDa) and hyaluronic acid (MW of 64 kDa) with a ratio of 4:1 (w/w). Average diameter and zeta potential were obtained 146 ±1 nm with a polydispersity index of 0.073 and +32 mV, respectively.

10. PREPARATION OF CHITOSAN NANOPARTICLES LOADED BY DEXAMETHASONE SODIUM PHOSPHATE

Biodegradable nanoparticulate carriers, have important potential applications for administration of therapeutic molecules. Chitosan based nanoparticles have attracted a lot of attention upon their biological properties such as biodegradability, biocompatibility and bioadhesivity. The aim of the present investigation was to describe the synthesis and characterization of novel biodegradable nanoparticles based on chitosan for encapsulation of dexamethasone sodium phosphate. To achieve this objective, ionic gelation method were used. Drug containing nanoparticles were prepared with different amounts of drug.

11. EX-VIVO EVALUATION OF INSULIN NANOPARTICLES USING CHITOSAN AND ARABIC GUM

Polymeric delivery systems based on nanoparticles have emerged as a promising approach for per oral insulin delivery. The aim of the present study was to investigate the release of insulin nanoparticulate systems and ex-vivo studies. The nanoparticles we're prepared by the ion gelation method. Particle size distribution, zeta potential, and polydispersity index of the nanoparticles were determined. It was found that the nanoparticles carried positive charges and showed a size distribution in the range of 170–200 nm. The electrostatic interactions between the positively charged group of chitosan and negatively charged groups of Arabic gum play an important role in the association efficiency of insulin in nanoparticles (Ahn et al., 2001). In vitro insulin release studies showed an initial burst followed by a slow release of insulin.

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12. ENCAPSULATION OF CURCUMIN IN ALGINATE-CHITOSAN- PLURONIC COMPOSITE NANOPARTICLES FOR DELIVERY TO CANCER CELLS

We report a nano formulation of curcumin with a tripolymeric composite for delivery to cancer cells. The composite nanoparticles (NPs) were prepared by using three biocompatible polymers—algiinate (ALG), chitosan (CS), and pluronic—by ionotropic pre-g elation followed by polycationic cross-linking. Pluronic F127 was used to enhance the solubility of curcumin in the ALG-CS NPs. Atomic force and scanning electron microscopic analysis showed that the particles were nearly spherical in shape with an average size of 100 ± 20 nm. Fourier transform– infrared analysis revealed potential interactions among the constituents in the composite NPs. Encapsulation efficiency (%) of curcumin in composite NPs showed considerable increase over ALG-CS NPs without pluronic. The in vitro drug release profile along with release kinetics and mechanism from the compo site NPs were studied under simulated physiological conditions for different incubation periods. A cytotoxicity assay showed that composite NPs at a concentration of 500 μg/mL were nontoxic to HeLa cells.

13. PREPARATION & IN VITRO RELEASE STUDY OF RHEGF/CHITOSAN NANOPARTICLE-LOADED FIBRIN-BINDING AMNIOTIC MEMBRANE

To synthesize a drug-loaded amniotic membrane, i.e. rhEGF/chitosan nanoparticle-loaded fibrin-binding amniotic membrane, and investigate its drug release kinetics in vitro method. The method included four steps: 1) rhEGF-loaded chitosan nanoparticles were prepared and their particle size, zeta potential, polydispersity index and encapsulation efficiency was examined. 2) The stability of the encapsulated rhEGF in the rabbit conjunctival homogenate was evaluated and compared with that of the free rhEGF. 3) The rhEGF-loaded chitosan nanoparticles with the maximal encapsulation efficiency were added into the thrombin solution. Then the thrombin solution was mixed and reacted with the fibrinogen solution which was placed on the surface of a piece of amniotic membrane to get a rhEGF/chitosan nanoparticle-loaded fibrin-binding amniotic membrane (rhEGF/CS-FBAM). The in vitro kinetic of rhEGF release from the rhEGF/CS-FBAM were investigated and compared with that of rhEGF/CS nanoparticles and rhEGF-FBAM, respectively. 4) The rhEGF released from the rhEGF/CS-FBAM was added to cell culture medium and its bioactivity was assessed in vitro by determining its ability to stimulate the proliferation of BALB /c 3T3 cells. As positive control, soluble rhEGF was addded daily to the cell medium in amounts equivalent to those released from the fibrin clots. Cell culture in the basal medium without rhEGF served as a negative control. The average particle size of the prepared nanoparticles ranged from 264.0±4.2 to 288.6±2.8 nm. The zeta potential ranged from 31.3±0.5～43.7±0.8 mV. The polydispersity index ranged from 0.19±0.02～0.26±0.02. The encapsulation efficiency (%) ranged from 54.87±2.94～67.03±1.22.2. The recovery of encapsulated rhEGF was higher than that of free rhEGF after incubation in the rabbit conjunctival homogenate with in 1, 2, 3, 4, 5, 6 h ($P< 0.05$).3. The release of rhEGF from the rhEGF/CS nanoparticles sustained for approximately 60 h with a burst release at the initial phase (Gang-Biao Jiang et al., 2006). The release of rhEGF fro m the rhEGF-FBAM sustained for approximately 96 hrs. Compared with the two systems above, the rhEGF/CS-FBAM released rhEGF more gradually and more steadily and had a release period of approximate 14 days. Moreover, as the concentration of fibrinogen or thrombin was increased in the rhEGF/CS-FBAM, the release of rhEGF from the rhEGF/CS-FBAM would be slowed. Significant increases in optical density were seen in the experimental group and positive control compared with the negative control ($P < 0.05$). There were no differences between experimental group and positive control ($P> 0.05$).In this study; we successfully developed a novel kind of composite biomaterial by combining rhEGF/CS nanoparticles, fibrin ge l and amniotic membrane. It possesses the properties below: (1) chitosan nanoparticles could protect rhEGF and improve its stability; (2) as a drug depot, fibrin gel could re lease rhEGF for a long time in a sustained and controllable way; (3) amniotic membrane could act as a basal membrane when used in wound healing. As a kind of biomaterial, rhEGF/CS-FBAM could efficiently release therapeutic growth factor at the same time when used in wound site, thus promote wound healing.

14. PREPARATION & EVALUATION OF CHITOSAN NANOPARTICLES CONTAINING ZIDOVUDINE

The zidovudine loaded nanoparticles were prepared by ionic gelation of chitosan with tripolyphosphate anions (TPP). Nanoparticles of different core: coat ratio were formulated and evaluated for process yield, loading efficiency, particle size, zeta potential, in-vitro drug release, kinetic studies and stability studies (Francesca Maestrelli et al., 2006). The chitosan nanoparticles have a particle diameter ranging approximately 342–468 nm and a zeta potential 20.4 to 37.08 mV. There was a steady increase in the entrapment efficiency on increasing the polymer concentration in the formulations. The in-vitro release behavior from all the drug loaded batches were found to follow first order and provided sustained release over a period of 24 hrs. No appreciable

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difference was observed in the drug content of product during 60 days in which nanoparticles were stored at 4◎C and room temperature. According to the data obtained, this chitosan- based delivery system opens new and interesting perspectives as drug carriers.

15. CONCLUSION

Due to the side effects associated with many pharmaceutical agents typically prescribed to treat nanoparticle preparation. Chitosan is the biodegradable polymer for LMWBP based nanoparticle preparation for effective therapeutic actions. Chemical attachment of the drug to the chitosan throughout the functional linker may produce useful prodrugs, exhibiting the appropriate biological activity at the target site and reduce the side effects of the Drug.

SUMMARY OF RESEARCH

This paper has provided an overview of research of Chitosan is more benefit for Drug loaded in nanoparticle. Chitosan is the treatment for targeted drug delivery system, and it's suitable for to load many drug in nanoparticles.

FUTURE ISSUES

In this review article, chitosan is the polymer based on nanoparticle preparation for LMWBP for the treatment cancer cells, HIV cells etc,. In future it is more effectively by improving the targeted drug delivery system and also less undesirable effect for the treatment.

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