Journal of Pharmaceutical Research International

33(49A): 179-186, 2021; Article no.JPRI.76468
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

A Mini-Review on Chitosan Microsphere Drug Delivery

Cinnayyagari Mahesh Reddy[1], S. Parimala Krishnan[1*] and Challa Balashekar Reddy[1]

[1]Department of Pharmacy, Annamalai University Annamalai Nagar, Chidambaram, Tamil Nadu, India.

Authors' contributions

This review was done in collaboration between all authors. All authors contributed equally. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i49A33318
Editor(s):
(1) Rafik Karaman, Al-Quds University, Palestine.
Reviewers:
(1) Seema Venkatrao Pattewar, Savitribai Phule Pune University, India.
(2) Ghada Abd Alrhman Taqa, University of Mosul, Iraq.
Complete Peer review History: https://www.sdiarticle4.com/review-history/76468

Mini-Review Article

Received 01 September 2021
Accepted 04 November 2021
Published 11 November 2021

ABSTRACT

The study aims to determine the drug therapy of any disease to attain the desired therapeutic concentration of the drug in plasma or at the site of action and maintain it for the entire duration of treatment. A drug on being used in conventional dosage forms leads to unavoidable fluctuations in the drug concentration leading to under medication or overmedication and increased frequency of dose administration as well as poor patient compliance. To minimize drug degradation and loss, to prevent harmful side effects and to increase drug bioavailability various drug delivery and targeting systems are currently under development. Handling the treatment of severe disease conditions has necessitated the development of innovative ideas to modify drug delivery techniques. Drug carrier systems include polymers, micelles, microcapsules, Liposomes and lipoproteins etc. Different polymer carriers exert different effects on drug delivery. Synthetic polymers are usually no biocompatible, non-biodegradable and expensive. Natural polymers such as chitin and chitosan are devoid of such problems. Chitosan is a biocompatible, biodegradable, and nontoxic natural polymer with excellent film-forming ability. Being of cationic character, chitosan is able to react with polyamines giving rise to polyelectrolyte complexes. Hence chitosan has become a promising natural polymer for the preparation of microspheres or nanospheres and microcapsules. This

**Corresponding author: E-mail: kalki.vijay@yahoo.co.in;*

review focuses on the preparation, characterization of chitosan microspheres and their role in novel drug delivery systems. This review also aims to include the process variables factors that affect the release of drugs from the microspheres.

Keywords: Chitosan; microspheres; process variables; ionotropic gelation; complex coacervation.

1. INTRODUCTION

Drug delivery emphasizes on maximizing bioavailability at specific places in the body and over a period of time. Nano medical approaches to drug delivery concentrate on the development of nanostructure devices like the microcapsules or nanospheres to improve the bioavailability of the drug and target it to the specific site of interest [1]. In this present era, science and technology are giving their maximum stress on the development of sustained-release pharmaceuticals. This matter continued to be the focus of a great deal of attention in both industrial and academic laboratories. There currently exist numerous products in the market formulated for both oral and injectable routes of administration that claim sustained or controlled drug delivery. The strength of drug delivery system is its ability to alter the pharmacokinetics and bio-distribution of the drugs [2]. Nanotechnology appears to possess the potential to improve drug delivery and drug targeting leading to increased efficacy and reduced toxicity , which would result not only in a great benefit to patients but also to pharmaceutical and drug delivery companies by creating new market opportunities [3]. Drug delivery sometimes is aimed at crossing specific barriers such as the blood brain barrier, in order to increase the drug concentration at the site of action to improve effectiveness; or to find alternative and acceptable route of delivery for protein drugs that cannot be delivered through gastro-intestinal tract due to degradation [4]. A novel drug delivery system (NDDS) is a system that offers multiple drug delivery solutions such as: Oral Drug Delivery Systems and Materials, Parenteral and Implant Drug Delivery Systems, Pulmonary and Nasal Drug Delivery, Transmucosal Drug Delivery, Transdermal and Topical Drug Delivery, Delivery of Proteins and Peptides, Drug Delivery Pipelines, Drug Delivery Deals. Use of lipid or polymer based nanoparticles have shown improved pharmacological and therapeutic actions and have overall benefits in the novel drug delivery systems. In the design of controlled release dosage formulations choice of polymer is of vital importance since it acts as drug carrier. Chitosan is a polysaccharide comprising copolymers of glucosamine and N-acetyl glucosamine. Being biodegradable and biocompatible, chitosan has been used in the formulation of particulate drug delivery systems to achieve controlled drug delivery. Chitosan has been widely investigated as a drug carrier for many possible routes of administration as chitosan has favorable biological properties, such as nontoxicity, biocompatibility, biodegradability, and antibacterial characteristics. The physical and chemical properties of Chitosan, such as inter- and intra-molecular hydrogen bonding and the cationic charge in acidic medium, makes this polymer more attractive for the development of conventional and novel pharmaceutical product. Chitosan can serve a number of purposes including as a coating agent, gel former, controlled release matrix, with desirable properties, such as mucoadhesion and permeation enhancement to improve oral bioavailability of drug. Chitosan is a good candidate for site specific drug delivery [5].

2. PREPARATION OF CHITOSAN MICROSPHERES

Various methods have been used for the preparation of Chitosan microspheres. Reacting chitosan with controlled amount of multivalent anion results in cross linking between chitosan molecules. The cross linking may be achieved in acidic, neutral or basic environments depending on the method applied. This cross linking has been extensively used for the preparation of chitosan microspheres.

2.1 Spray Drying

In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, Acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100 µm. Micro particles are separated from the hot air by means of the cyclone separator while

the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions. This process is rapid and this leads to the formation of porous micro particles [6].

2.2 Solvent Evaporation

In a liquid manufacturing vehicle, this procedure is carried out. The microcapsule coating is dispersed in a volatile solvent that is immisible with the liquid manufacturing vehicle phase of the process. In the coating polymer solution, a core material to be microencapsulated is dissolved or dispersed. To obtain the appropriate size microcapsule, the core material combination is dispersed in the liquid manufacturing vehicle phase by agitation. When the solvent for the polymer of the core material is dispersed in the polymer solution and the polymer shrinks around the core, the mixture is heated if necessary to evaporate the solvent. Matrix-type microcapsules are formed when the core material is dissolved in the coated polymer solution. The solvent evaporation approach for producing microcapsules can be used with a wide range of core materials. Water soluble or water in soluble materials can be used as the core components. The formation of an emulsion between a polymer solution and an immiscible continuous phase, whether aqueous (o/w) or non-aqueous, occurs during solvent evaporation [7].

2.3 Precipitation – Chemical Cross Linking

The Process involves the precipitation of the polymer followed by chemical cross linking. Precipitation can be done by sodium sulphate followed by chemical crosslinking using glutaraldehyde. Aqueous solution of CS (3% (w/v) in 4% (v/v) glacial acetic acid) was added into agitating medium and stirring continued to obtain wet microspheres, which were then filtered, washed and finally dried at room temperature [8]. The result show that solvent emulsification technique can also be used to prepare microspheres using heat as cross linking agent and avoiding the use of chemical as cross linking agent .

2.4 Multiple Emulsion Method

Multiple emulsion method involves formation of (o/w) Primary emulsion (non-aqueous drug solution in CS solution) and then addition of primary emulsion to external oily phase to form o/w/o emulsion followed by either addition of glutaraldehyde (crosslinking agent and evaporation of organic solvent [9]. CS microspheres prepared by multiple emulsion method loaded with hydrophobic drug (ketoprofen) were found to have good morphological character and satisfactory production yield when prepared using this method.

2.5 Thermal Cross-linking

CS solutions of varying concentration were prepared maintaining a constant molar ratio between CS and citric acid. The citric acid crosslinker solution was added then cooled at 0°C and added to corn oil followed by thermal crosslinking at 120°C [10].

2.6 Complex Coacervation

Chitosan microparticles can also prepared by complex co acervation. Sodium alginate, sodium CMC, Carregnan and sodium polyacrylic acid can be used for complex coacervation with chitosan to form microspheres. These microparticles are formed by interionic interaction between oppositely charged polymers solutions and KCl& $CaCl_2$solutions. The obtained capsules were hardened in the counter ion solution before washing and drying [11].

2.7 Ionotropic Gelation

The counter ions used for ionotropic gelation can be divided into 3 categories. Low molecular counter ions like pyrophosphate and tripolyposphate. Hydrophobic counter ions(e.g.: alginate carragenan), and High molecular weight ion(e.g.: octylsulphate , lauryl sulphate. The chitosan solution in acetic acid was extruded drop wise through a needle into different concentrations on aqueous solutions of magnetically stirred tripolyposphate or some other an ion. The beads were removed from the counter ion solution by filtration washed with distilled water and dried [12].

2.8 Wet Inversion

In this method of preparation chitosan solution in acetic acid was dropped in to an aqueous solution of counter ion sodium tripolyposphate through a nozzle. Microspheres formed were allowed to stand for one hour washed and cross

linked with 5%ethylene glycol diglysidyl ether. Finally the microspheres were washed and freeze dried [13]. Changing the pH of the coagulation medium could modify the pore structure of chitosan microspheres.

3. PROCESS VARIABLES WHICH HAVE AN EFFECT ON THE ENTRAPMENT EFFICIENCY OF THE DRUGS IN CHITOSAN MICROSPHERES

Many factors affect the entrapment efficiency of the drugs in the chitosan microspheres e.g. nature of the drug, chitosan concentration, drug polymer ratio, stirring speed etc., Generally low concentration of chitosan shows low encapsulation efficiency. However, at higher concentrations, chitosan forms highly viscous solutions, which are difficult to process. A number of reports have shown that entrapment efficiency increases with an increase in chitosan concentration. This may be explained on the basis that an increase in viscosity of the chitosan solution with increase in concentration prevents drug crystals from leaving the droplet. Microspheres made with a mixture of high molecular weight/low molecular weight chitosan (1:2w/w) showed good drug content and encapsulation efficiency and these were independent of polymer/ drug ratio [14].

The acetic acid concentration in the polymeric solution influenced the ketoprofen content of the microspheres. Maximum drug concentration efficiency was obtained for the lowest theoretical drug chitosan ratio. It also reported, when nifedipine was dispersed in the chitosan solution with stirring during preparation of microspheres, the entrapment efficiency increased. Nifedipine was found to be in crystalline in the microspheres. The decrease in entrapment efficiency was attributed to the removal of crystals present on the surface before washing [15].

4. FACTORS AFFECTING THE DRUG RELEASE FROM CHITOSAN MICROSPHERES

There are many factors that determine the drug release behaviour from Chitosan microspheres. these include molecular weight and concentration of the Chitosan, the cross linking agent used and it's concentration, process variables like stirring speed, type of oil, additives, cross linking process used, drug Chitosan ratio, etc. Various kinetic models have been proposed for the release of drugs from Chitosan microspheres. It was observed that the best fit for release of diclofenac sodium from Chitosan microspheres was obtained by Higuchi equation [16]. It was reported that when the release data of piroxicam from Chitosan microspheres was subjected to simple power law equation, the mode of release was found to be non-fickian and super case II type.

5. CHARACTERIZATION OF CHITOSAN MICROSPHERES [17]

The chitosan microspheres prepared by the different techniques discussed above will be characterized for their morphology like size, size distribution and shape analysis using optical microscopy, SEM and particle size analysis. Swelling kinetics can be studied in different physiological conditions. Once the technique is well standardized, drug is to be incorporated into chitosan as a function of concentration at different pH. Drug loading in micro/nanoparticulate systems can be done by two methods, i.e., during the preparation of particles (incorporation) or after the formation of particles (incubation). In these systems, drug is physically embedded into the matrix or adsorbed onto the surface. Various methods of loading have been developed to improve the efficiency of loading, which largely depends upon the method of preparation as well as physicochemical properties of the drug. Maximum drug loading can be achieved by incorporating the drug during the formation of particles, but it may get affected by process parameters such as method of preparation, presence of additives, etc. Both water-soluble and water-insoluble drugs can be loaded into chitosanbased particulate systems. Water-soluble drugs are mixed with chitosan solution to form a homogeneous mixture, and then, particles can be produced by any of the methods discussed before. Water-insoluble drugs and drugs that can precipitate in acidic pH solutions can be loaded after the formation of particles by soaking the preformed particles with the saturated solution of drug. Water-insoluble drugs can also be loaded using the multiple emulsion technique. In this method, drug is dissolved in a suitable solvent and then emulsified in chitosan solution to form an oil-in-water (o/w) type emulsion. Sometimes, drug can be dispersed into chitosan solution by using a surfactant to get the suspension. Thus, prepared o/w emulsion or suspension can be further

emulsified into liquid paraffin to get the oil-water-oil (o/w/o) multiple emulsions. The resulting droplets can be hardened by using a suitable cross-linking agent.

5.1 Morphological Study of Microspheres

Photomicrographs of the unloaded chitosan microspheres can be obtained using a digital optical microscope. Microspheres were characterized in terms of sphericity and clumping of microspheres, as observed from the photomicrograph.

5.2 Determination of Mean Particle Size and Particle Size Distribution

Particle size analysis of unloaded and drug-loaded chitosan microspheres can be performed by optical microscopy using a compound microscope. A small amount of dry microspheres was suspended in purified water (10 ml). The suspension was ultrasonicated for 5 seconds. A small drop of suspension thus obtained was placed on a clean glass slide. The slide containing chitosan microspheres was mounted on the stage of the microscope and Ferret's diameter of at least 300 particles was measured using a calibrated ocular micrometer.

5.3 Determination of Percentage Drug Entrapment

Efficiency of drug entrapment for each batch can be calculated in terms of percentage drug entrapment (PDE) as per the following formula:

$$PDE = \frac{Practical\ drug\ loading}{Theoritical\ drug\ loading} \times 100$$

Theoretical drug loading was determined by calculation assuming that the entire drug present in the chitosan solution used gets entrapped in microspheres and no loss occurs at any stage of preparation of microspheres. Determination of Practical drug loading can be done by taking a weighed quantity of chitosan microspheres (approximately 25 mg) in a 25-ml volumetric flask. Sufficient quantity of methanol is to be added to make the volume 25 ml. After shaking the suspension vigorously it was left for 24 h at room temperature with intermittent shaking. Supernatant was collected by centrifugation and drug content in supernatant was determined by UV spectrophotometer at suitable wavelength.

5.4 Scanning Electron Microscopy

A monolayer of dry microspheres was mounted on an aluminium slab using double-sided carbon tape. The sample was coated with a 10 nm thick gold film using a sputter coater. Coated samples were examined using an electron acceleration voltage of 20 KeV. Size distribution and average particle diameter can be determined analyzing 5 to 10 images.

6. APPLICATION OF CHITOSAN MICROSPHERES IN DRUG DELIVERY

Chitosan microspheres have several applications in novel drug delivery systems. Some of which are mentioned below.

6.1 GI-Delivery-systems

Floating systems have a density lower than the density of the gastric juice. Thus, the gastric residence time and hence the bioavailability of drugs that are absorbed in the upper part of the GI- tract will be improved. Both chitosan granules and chitosan laminated preparations could be helpful in developing drug delivery systems that will reduce the effect of gastrointestinal transit time. Floating hollow microcapsules of melatonin produced have an interesting gastro retentive controlled-release delivery system for drugs.

6.2 Colon and Intestinal Drug Delivery

Since, chitosan is degraded by the microflora that are available in the colon it was found to be promising for colon-specific drug delivery. Chitosan esters, such as chitosan succinate and chitosan phthalate have been used successfully as potential matrices for the colonspecific oral delivery of diclofenac sodium. Systems for colon delivery containing paracetamol, mesalazine, and insulin have been studied and give satisfactory results. Sustained intestinal delivery of drugs, such as 5-fluorouracil (choice for colon carcinomas) and insulin (for diabetes mellitus) seems to be a feasible alternative to injection therapy. A formulation was developed that could bypass the acidity of the stomach and release the loaded drug for long periods into the intestine by using the bioadhesiveness of polyacrylic acid, alginate, and chitosan tract [18,19,20].

6.3 Ophthalmic Drug Delivery

Chitosan is found to be a unique material for designing ocular drug delivery vehicles. Due to

its elasticity ophthalmic chitosan gels have shown excellent adhesion to mucin, which coats the conjunctiva and the corneal surface of the eye. Chitosan based colloidal systems were found to work as transmucosal drug carriers, facilitating the transport of drugs to the inner eye (chitosan-coated colloidal system containing indomethacin) or their accumulation into the corneal/conjunctival epithelia (chitosan nanoparticulate containing cyclosporin). The microparticulate drug carrier (microspheres) seems a promising means of topical administration of acyclovir to the eye [21].

6.4 Oral, Buccal and Sublingual Drug Delivery

Being a muco/bioadhesive polymer, chitosan is considered a good candidate for oral cavity drug delivery [22]. Chitosan is a biologically safe polymer and prolongs the adhesion time of oral gels and drug release from them. Chitosan also inhibits the adhesion of Candida albicans to human buccal cells and has antifungal activity. Chitosan containing quick hardening paste was developed as a bone substitute for dental purpose. The use of this paste will minimize the inflammation in gums. Chitosan gel and chitosan film containing chlorhexidine gluconate for local delivery were developed. A monolayer and multilayered film of chitosan PLGA containing ipriflavone were showed to prolong drug release for 20 days in vitro [23].

6.5 Nasal and Transdermal Drug Delivery

Various chitosan salts (chitosan lactate, chitosan aspartate, chitosan glutamate, and chitosan hydrochloride) showed nasal sustained release of vincomycin hydrochloride. Bioadhesive chitosan microspheres of pentazocine for intranasal systemic delivery showed improved bioavailability with sustained and controlled blood level profiles in comparison to intravenous or oral administration. Diphtheriatoxoid (DT) associated to chitosan microparticles results in systemic protection and local immune response against DT, and enhances significant IgG production after nasal administration. Different types of nasal vaccine systems include cholera toxin, microspheres, nanoparticles, liposomes, attenuated virus and cells, and outer membrane proteins (proteosomes). Nasal formulations induced significant serum IgG responses similar to that induced by a parenteral administration of the vaccine microspheres, nanoparticles, liposomes, attenuated virus and cells, and outer membrane proteins (proteosomes). Nasal formulations induced significant serum IgG responses similar to that induced by a parenteral administration of the vaccine [24]. Chitosan-alginate poly electrolyte complex (PEC) has been prepared as in situ in beads and microspheres for potential applications in transdermal controlled release systems, and wound dressings [25]. Chitosan gel was used as the drug-reservoir. The drug-release profiles showed that drug delivery is completely controlled by the devices. The rate of drug release was found to be dependent on the type of membrane used. A combination of chitosan membrane and chitosan hydrogel containing lidocaine HCl, a local anesthetic, is a good transdermal system for controlled drug delivery. Chitosan gel beads containing the anti-inflammatory drug prednisolone showed sustained release of drug with reduced inflammation and resulted in improved therapeutic efficacy.

6.6 Vaginal Drug Delivery

Chitosan vaginal tablet containing metronidazole, acriflavine, and other drugs gave adequate release, therapeutic action, and good adhesion properties. By introducing thio groups, the mucoadhesive properties of the polymer were strongly improved, and this resulted in an increased residence time of the drug in the vaginal mucosa tissue ensuring good controlled drug release in the treatment of mycotic infections [24].

6.7 Vaccine Delivery System

Various chitosan-antigen nasal vaccine have been developed whose responses were found to be same or superior when compared with the parenteral administration of the vaccine. Bovine serum albumin and diptheria toxoid loaded chitosan microspheres showed prolonged drug release action in vivo [24].

6.8 Gene Delivery System

Many hereditary disorders, multi genetic diseases can be treated by genetic delivery. Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems. Chitosan has been used as a carrier of DNA for gene delivery applications [26,27]. Also, chitosan could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract.

7. CONCLUSION

Chitosan is a versatile biopolymer exhibiting a wide variety of applications range from weight supplement in the market to a drug carrier in formulation research. Being characterized by biocompatibility, non-toxicity, lack of allergenicity, biodegradability chitosan is really an attractive biopolymer for delivering a wide variety of drugs in a controlled/sustained manner and can be successfully targeted for site specific drug delivery. The entrapment efficiency of drugs in the Chitosan microspheres is dependent upon the Chitosan concentration i.e. efficiency increases with increase in Chitosan concentration. The Release of drug from Chitosan microspheres is dependent upon the molecular weight of Chitosan, drug content and density of cross- linking. Problems associated with dose dumping, burst out effect, unavoidable fluctuations in drug concentrations (mostly associated with conventional dosage form) can be eliminated. The usage of biopolymers like these has resulted in increased efficacy and fewer drug-related side effects.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

The authors are thankful to staff department of pharmacy of Annamalai University for their support. Those authors declare that no funding has received for the research or in the preparation of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Charman WN, Chan HK, Finnin BC, Charman SA. Drug delivery: A key factor in realising the full therapeutic potential of drugs. Drug Development Research. 1999;46:316-27.
2. Kopecek J. Smart and genetically engineered biomaterials and Drug delivery systems. Eur J Pharm Sci. 2003;20:1-16.
3. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM. Recent advances on Chitosan-based micro and nanoparticles in drug delivery. J Control Release. 2004;100:5-28.
4. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices.J Control Release. 2001;70:1-20.
5. Kas. Chitosan: Properties, preparations and application to microparticulate systems. J Microencapsulation. 1997;14:689-711.
6. Gohel, Sheth, Patel, Jani, Patel.Design of chitosan microspheres containing diclofenac sodium. Indian J Pharm Sci. 1994;56:210-214.
7. Lim, Martin, Berry, Brown. Preparation and evaluation of the in vitro drug release properties and mucoadhesion of novel microspheres of hyaluronic acid and chitosan. J Control Release. 2000;66:281-292.
8. Aggarwal Kaur, Tiwary Gupta. Chitosan microspheres prepared by an aqueous process: Release of indomethacin. J Microencapsulation. 2001:18:819-23.
9. Pavanetto, Conti, Modena, Genta. Evaluation of process parameters involved in chitosan microsphere preparation by the o/w/o multiple emulsion method. J Microencapsulation. 1996;13:679-88.
10. Orienti, Aiedeh, Gianasi, Bertasi, Zecchi. Indomethacin loaded chitosan microspheres. Correlation between the erosion process and release kinetics. J Microencapsulation. 1996;13:463-72.
11. Ohya, Takei, Kobayashi, Ouchi. Release behaviour of 5-fluorouracil from chitosan-gel microspheres immobilizing 5-fluorouracil derivative coated with polysaccharides and their cell specific recognition. J Microencapsulation. 1993;10:1-9.
12. Aydin, Akbuga. Chitosan beads for the delivery of salmon calcitonin: Preparation and release characteristics. International Journal of Pharmaceutics. 1996;131:101-3.
13. Mi, Shyu, Kuan, Lee, Lu, Jang. Chitosan–Polyelectrolyte complexation for the preparation of gel beads and controlled release of anticancer drug. Effect of phosphorous polyelectrolyte complex and enzymatic hydrolysis of polymer. Journal of Applied Polymer Science. 1999;74:1868-79.
14. Nishioka, Kyotani, Okamura, Miyazaki, Okazaki, Ohnishi, Yamamoto, Ito. Release Characteristics of Cisplatin Chitosan Microspheres and Effect of Containing Chitin. Chem Pharm Bull (Tokyo). 1990;38(10):2871-3.

15. Singla, Sharma, Dhawan. Nifedipine loaded chitosan microspheres: characterization of internal structure. Biotech Histochem. 2001;76:165-171.
16. Acikgoz, Kas, Orman, Hincal. Chitosan microspheres of diclofenac sodium: Application of factorial design and evaluation of release kinetics. J Microencapsulation. 1996;13141-59.
17. Mitra A, Dey B. Chitosan Microspheres in Novel Drug Delivery Systems. Indian Journal of Pharmaceutical Sciences. 2011;73(4):355-66
18. Park HS, Lee JY, Cho SH, Baek HJ, Lee SJ. Colon delivery of prednisolone based on chitosan-coated polysaccharide tablets. Arch Pharm Res. 2002;25:964-8.
19. Tozaki H, Odoriba T, Okada N, Fujita T, Terabe A, Suzuki T, et al. Chitosan capsules for colon-specific drug delivery: Enhanced localization of 5-aminosalicylic acid in the large intestine accelerates healing of TNBS-induced colitis in rats. J Control Release. 2002;82:51-61.
20. Thanou M, Verhoef JC, Marbach P, Junginger HE. Intestinal absorption of octreotide: N-trimethyl chitosan chloride (TMC) ameliorates the permeability and absorption properties of the somatostatin analogue in vitro and in vivo. J Pharm Sci. 2000;89:951-7.
21. Genta I, Conti B, Perugini P, Pavanetto F, Spadaro A, Puglisi G. Bio-adhesive microspheres for opthalmic administration of acyclovir. J Pharm Pharmacol. 1997;49:737-42.
22. Ganza-Gonzalez A, Anguiano-Igea S, Otero-Espinar FJ, Mendez JB. Chitosan and chondroitin microspheres for oral-administration controlled release of metoclopramide. Eur J Pharm Biopharm. 1999;48:149-55.
23. Aiedeh K, Taha MO. Synthesis of chitosan succinate and chitosan phthalate and their evaluation as suggested matrices in orally administered, colon-specific drug delivery systems. Arch Pharm (Weinheim).1999;332:103-7.
24. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM. Recent advances on chitosan-based micro- and nanoparticles in drug delivery. J Control Release. 2004;100:5-28.
25. Conti B, Modena T, Genta I, Perugini P, Decarro C, Pavanetto F. Microencapsulation of cetylpyridinium chloride with a bioadhesive polymer. Proc Int Symp Control Release Bioact Mater. 1998;25:822-3.
26. Lee KY, Kwon IC, Kim YH, Jo WH, Jeong SY. Chitosan conjugated DNA nanoparticles in gene therapy. J Control Release.1998;51:213-20.
27. MacLughlin FC, Mumper RJ, Wang J, Tagliaferri JM, Gill I, Hinchcliffe M. Chitosan-DNA nanoparticles as non-viral vectors in gene therapy: Strategies to improve transfection efficacy. J Control Release.1998;56:259-72.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/76468