IJPSR (2016), Vol. 7, Issue 5 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 December, 2015; received in revised form, 05 February, 2016; accepted, 06 April, 2016; published 01 May, 2016

NANO-THERAPEUTICS ARSENALS FOR INTERVENTION OF COLON CANCER

Ruchika* and Himanshi

RPIIT Technical and Medical Campus, Karnal, Haryana, India

Key words:

Nanoparticles, Drug delivery system, Formulation, Application

Correspondence to Author:
Ruchika
Assistant Professor
RPIIT Technical and Medical Campus, Karnal, Haryana, India.

E-mail: ruchisachdeva2002@gmail.com

ABSTRACT: Nanoparticles have attracted the interest of many research groups and had been utilized in an increasing number of fields during the last decades. Various methods can be used to produce nanoparticles such as ionic gelation, solvent evaporation, microemulsion, emulsion cross linking and precipitation. This review covers the general description, preparation and the detailed description of crucial parameters involved in techniques designed to obtain the desired properties of nanoparticles.

INTRODUCTION: Colon-specific drug delivery systems have not only gained increasing attention for the treatment of diseases such as Crohn's disease, ulcerative colitis, and irritable bowel syndrome [1, 2] but also for potential of it holds for the systemic delivery of proteins and therapeutics peptides. The large intestine, through difficult to reach by peroral delivery, is still deemed to be the ideal site for the delivery of agents to cure the local disease of the colon.[3] The conventional treatment of inflammatory bowel disease requires daily intake of anti-inflammatory drugs at high doses. Chemical compounds requiring frequent intake at high doses by oral route after lead to absorption in small intestine, thereby causing the possible adverse side effects. Therefore, several strategies have been followed for an oral drug delivery, which includes the development of prodrugs delivering conventional drugs specifically in the large bowel after cleavage of active part from the carrier [4, 5]

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.7(5).1857-65

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (5).1857-65

and solid-dosage forms that release the drug in the colon when activated by specific enzymes only present in the colon. The administration of drugs by rectal route is also currently used. However, it is not effective when inflamed tissues are located in the upper parts of the colon. Although prodrugs lead to reduced adverse effects, a more comfortable dosage frequency cannot be achieved. Sustained drug release carrier for example pellets capsules or tablets, delivering the drugs specifically in the colon for a longer time period have been developed.

However, their effectiveness seems to be decreased in many cases due to the diarrhea, a symptom of inflammatory bowel disease that enhances the elimination and reduces the possible drug release time.[6] Thus, a carrier system that delivers the drug specifically and exclusively to the inflamed region after oral administration for a prolonged period of time would be desirable. Such a system could reduce side effects significantly in the case of conventional chemical anti-inflammatory compounds.[7]

As reported from the previous work, drug carrier systems with a size larger than 200µm are subjected to diarrhea resulting in the decreased

gastrointestinal transit time and therefore to a distinct decrease in the efficacy. Since all the microscopic drug delivery systems are at risk for this type of therapy failure, alternative strategies are needed. So, size reduction of drug carriers is one of the options to circumvent this problem.[8]

So, nanoparticle drug delivery systems have been successfully developed for experimental treatment of inflammatory bowel disease by specific accumulation [9, 2] in the region with inflamed tissue increasing the selectivity of local drug delivery. This observation was based on two phenomenon uptake into immune related cells infilterating inflamed tissue and adhesion to the mucus, which is highly excreted in the areas of inflamed tissue.[8] Subsequently, increase in the residence time, which would be postulated for the small particles compared with existing drug delivery system, allows for a dose reduction. One parameter of major importance drug carrier system in the case is the particle size.[6]

Use of nanoscaled drug carriers in drug delivery system is expected to increase specificity of drugs and thus reduces side effects. Moreover, encapsulation of biologically active molecules into nanocarriers may increase their bioavailability and may induce sustained release. The most prominent advantage of nanoscaled drug carriers over conventional drug delivery system is the option to improve selective delivery of drugs to the site of the action, so called drug targeting which can be classified into the active and passive targeting approaches.[10]

Several reviews have been published reporting the research that has gone into development of per-orally delivered single unit colon targeted drug delivery system.[11, 12, 1, 5] In general four approaches have been proposed for colon targeted drug delivery namely prodrug, pH dependent system, time dependent systems and colonic microflora activated systems.[5]

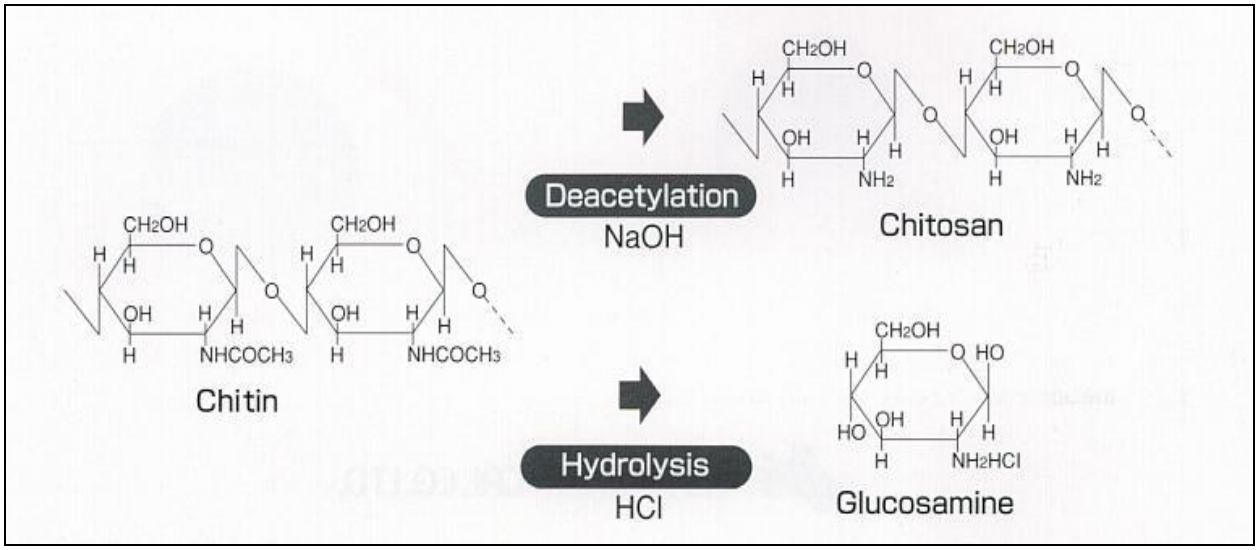
TABLE 1: A BRIEF SUMMARY OF SOME OF THESE APPROACHES HAVE BEEN MENTIONED IN

Method	Advantages	Disadvantages	Common used polymers	References
Time dependent systems	Small intestine transit time fairly consistent	Substantial variation in gastric retention times Transit through the Colon more rapid than normal in patient with Colon disease	soluble ethylcellulose and swellable polymer Hydroxy Propyl Cellulose polymer	Yang et al 2002 Ashford and Fell 1993b Watts and Illum 1997
pH Dependent system	Formulation well protected in the stomach	pH levels in the small intestine and colon vary between in the individuals pH levels in the end of the small intestine and caecum are similar	Eudragit®L100, Eudragit®S100, Eudragit®L30D, Eudragit®L100-55, Polyvinyl acetate phthalate, Eudragit®FS30D, HPMC phthalate, HPMC phthalate 50, HPMC phthalate 55, CAP	Friend et al 1991 Ashford and Fell 1993 Kinget et al. 1998 Yang et al. 2002 Ashford et al. 1993
Micro-flora activated system	Good site specificity with prodrugs and polysaccharides	Diet and disease can affect colonic micro-flora[i] Enzymatic degradation may be slow Few have been accepted for use in relation to medicines	Amylase, Arabinogalactan, Dextran, Guar gum, Xanthan Gaum, Chondroitin sulphate, chitosan, Cyclodextrin, dextran, Pectin, Xylan	Yang et al 2002

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 form 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. Mucoadhesive 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.[13] Chitosan is a linear amino polysaccharide composed of randomly distributed (1→4) linked D-glucosamine and N-acetyl-D-glucosamine units, is obtained by the deacetylation of chitin, a widespread natural polysaccharide found in the exoskeleton of crustaceans such as crab and shrimp.[14]



This cationic polysaccharides has drawn increasing attention within pharmaceutical and biomedical applications, owing to its abundant availability, unique mucoadhesivity, inherent pharmacological properties, and other beneficial biological properties such as biocompatibility, biodegradability, non toxicity and low-immunogenicity.[14] The physicochemical and biological properties of chitosan are greatly influenced by its molecular weight and degree of deacetylation. The presence of reactive functional groups in chitosan offers great opportunity for chemical modification, which affords a wide range of derivatives such as quaternized chitosan (N,N,N-trimethyl chitosan; TMC), carboxyalkyl chitosan, thiolated chitosan, sugar-bearing chitosan, bile acid-modified chitosan and cyclodextrin-linked chitosan. [15, 16, 17]

These chitosan derivatives have been designed to improve specific properties of native chitosan. For example, thiolation of chitosan remarkably improves its mucoadhesive properties because of the formation of disulfide bonds with cysteine-rich subdomains of mucus glycoproteins. The chemical modification of chitosan imparts amphiphilicity, which is an important characteristic for the formation of self-assembled nanoparticles, potentially suited for drug delivery applications. The hydrophobic cores of the nanoparticles could act as reservoirs or microcontainers for various bioactive substances. Because of their small size, nanoparticles can be administrated via the intravenous injection for targeted drug delivery. Conjugation of the targeting moieties to the surface of drug-loaded nanoparticles may improve therapeutic efficiency of the drug.[18] Chitosan has been widely utilized as drug delivery systems for low molecular drugs, peptides and genes.[19]

This review is aimed at collating and understanding novelty and feasibility of nanoparticle formulations design, targeting approaches in development of successful colon targeted drug delivery system. The nanoparticle formulations has all the advantages of single unit formulation yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation, change in gastrointestinal pH and enzyme population. A generally accepted view is that multiparticulate systems perform better in-vivo absorption than single unit systems, as they spread out throughout the length of the intestine causing less irritation, enjoy a slower transit through the colon and give a more reproducible drug release.

Nanoparticle formulation methods:

Nanoparticles are defined as small colloidal particles which are made up of non-biodegradable and biodegradable polymers. There diameter vary from 10-1000 nm. Term nanoparticle is coined by Speise and his co-worker.[20] Nanoparticle including nanocapsules and nanospheres can be prepared according to numerous methods that have been developed over the last 30 years. At first, Nanoparticles were made by emulsion polymerization of acrylamide and dispersion polymerization of methylmethacrylate**.** These techniques can roughly be divided into 2 groups: those involving high energy dispersion of the lipid phase (melt and cold homogenization, preparation from solvent in water emulsions) and those based on precipitation from homogenous systems (warm microemulsions) solution in water miscible organic solvents.

The choice of appropriate technique depends on various parameters such as physicochemical properties and stability of drugs to be incorporated desired particle size, concentration and stability of colloidal formulation and available equipment.

TABLE 2: COMPARISON OF DIFFERENT PREPARATION METHODS

Method	Advantages	Disadvantages	Particularly suitable for processing of
Hot homogenization	Suitable dispersions, good reproducibility, no organic solvents required, established technology,	Use of heat and shear forces, special manufacturing equipment needed	Highly lipophillic thermally stable drugs
Cold homogenization	Thermal stress limited, no organic solvent required,	Use of shear forces, high energy input is required, special manufacturing equipments needed.	Heat sensitive lipophillic and hydrophilic drugs.
Precipitation from solvent-in-water emulsion	Can generate very small particles, no heat required.	Use of organic solvents and shear forces, low lipid concentration	Heat sensitive lipophillic and drugs.
Precipitation from warm microemulsions	No shear forces involved, simple process, conventional equipment	Often very low initial lipid concentration	Shear sensitive, lipophillic drugs
Precipitation from organic solution	Simple process, conventional equipment, no shear or heat forces involved	Use of organic solvents, very low lipid concentration	Heat and Shear sensitive lipophillic drugs

(A)Polymers used to formulate Nanoparticles:

Nature of polymers constituting the formulation significantly influences nanoparticles size and their release profiles. The main criteria dictating polymer eligibility for drug delivery have been bioavailability, biocompatibility straightforward production and degradation rate, which provide a sustained release of drugs encapsulated in nanoparticles. Polymeric natural used for the formulation of nanoparticles include natural polymers (albumin, gelatin, alginate, collagen or chitosan) or synthetic (poly-DL-(lactic acids) [PLA], Poly (lactic-co-glycolic acids) [PLGA], poly (ε-caprolactone) (PCL), poly (methyl methacrylates) and poly (alkyl cyanoacrylates), polyesters, alone or in combinations with other polymers). PLGA and PLA are highly compatible and biodegradable polymers. Chitosan has been reported to be very suitable for preparation of nanoparticles for controlled drug release. Chitosan, particularly, chitosan nanoparticles offer many advantages due to their better stability, low toxicity, simple and mild preparation methods, providing versatile routes of administration and has gained more attention as a drug delivery carrier. They have ability to control the release of active agents. They avoid the use of hazardous organic solvents while fabricating particles since they are soluble in aqueous acidic solution. Moreover, chitosan is a linear polyamine containing a number of free amine groups that are readily available for cross linking whereas its cationic nature allows for ionic cross linking with multivalent anions.[20]

Formulation Methods for preparation of chitosan nanoparticles:-

Formulations Factors influencing:-

The selection of materials is dependent upon many factors including

a) Size of nanoparticle required.

b) Inherent properties of drug such as aqueous solubility and stability.

c) Surface characteristics such as charge and permeability.

d) Degree of biodegradability, biocompatibility and toxicity.

e) Drug release profile desired.

f) Antigenicity of the final drug product.

1. Ionotropic Gelation Method:

The method is based on electrostatic interaction between amine group of chitosan and negatively charged group of polyanion such as tripolyphosphate. The size and surface charge of nanoparticles can be changed by changing the ratio of chitosan and stabilizer. For a high yield of nanoparticles, the critical processing parameter chitosan : tripolyphosphate (TPP) weight ratio should be controlled and was found to be within the range of 3:1-6:1. The mean particle size of nanoparticle decrease with increasing solution temperature in ultrasonic radiation samples. With the change in physicochemical conditions, like pH of the medium, a volume phase transition takes place. Structural changes can also be introduced by ionic strength variations like presence of KCl at low and moderate concentrations emphasize swelling and weakness of chitosan-TPP ionic interactions, in turn particle disintegration. In the ionic gelation method, Chitosan is dissolved in aqueous acidic solution to obtain the cation of chitosan.

This solution is then added dropwise under constant stirring to polyanionic TPP solution. Due to the complexation between oppositely charged species, chitosan undergoes ionic gelation and precipitates to form spherical particles. After Bodmeier et al. in 1989 reported the preparation of TPP-CS complex by dropping CS droplets into a TPP solution, many researchers have explored its potential pharmaceutical usage. Insulin-loaded chitosan nanoparticles have been prepared by mixing insulin with TPP solution and then adding this to chitosan solution under constant stirring.[21]

2. Polyelectrolyte Complex (PEC) Method:

The mechanism of formulation of chitosan nanoparticles by polyelectrolyte complex method is the electrostatic interactions between the negative group of anion like carboxylic groups of Alginate or sulfate groups of dextran sulfate and the positive group of cation like amine groups of chitosan and thus charge neutralization between cationic polymers and anionic group, which in turn lead to a fall in hydrophilicity due to the self assembly of the polyelectrolyte components. The size of the complexes can be varied from 50 to 700 nm. Chitosan and Alginate are polycation and polyanion polyelectrolyte respectively that can be used to form a polyelectrolyte complex for the delivery of proteins, peptide drugs and DNA. Recently, chitosan has been investigated as the carrier of a hydrophilic 5-FU by forming PEC nanoparticles with polyaspartic acid sodium salt. The drug-loaded nanoparticles showed sustained release of 5-FU both at the in vitro and in vivo conditions, compared to the pure 5-FU solution.[22]

2. Emulsification-Cross Linking Method:

This method involves the preparation of novel surfactant-polymer nanoparticles for efficient encapsulation and sustained release of water-soluble drugs. In this method, a water-in-oil (w/o) emulsion is prepared by emulsifying the chitosan aqueous solution in the oil phase. Aqueous droplets are stabilized using a suitable surfactant. The stable emulsion is cross-linked by using an appropriate cross-linking agent such as glutaraldehyde to harden the droplets. Microspheres are filtered and washed repeatedly with n-hexane followed by alcohol and then dried.[23] By this method, size of the particles can be controlled by controlling the size of aqueous droplets. However, the particle size of final product depends upon the extent of cross-linking agent used while hardening in addition to speed of stirring during the formation of emulsion. The emulsion cross-linking method has few drawbacks since it involves tedious procedures as well as use of harsh cross-linking agents, which might possibly induce chemical reactions with the active agent. However, complete removal of the un-reacted crosslinking agent may be difficult in this process.

3.Coacervation/ precipitation Method:

This method utilizes the physicochemical property of chitosan since it is insoluble in alkaline pH medium, but precipitates/coacervates when it comes in contact with alkaline solution. Particles are produced by blowing chitosan solution into an alkali solution like sodium hydroxide, NaOH-methanol or ethanediamine using a compressed air nozzle to form coacervate droplets. Separation and purification of particles was done by filtration/centrifugation followed by successive washing with hot and cold water.[24]

4.Spray-drying:

Spray-drying is a well-known technique to produce powders, granules or agglomerates from the mixture of drug and excipient solutions as well as suspensions. The method is based on drying of atomized droplets in a stream of hot air. In this method, chitosan is first dissolved in aqueous acetic acid solution, drug is then dissolved or dispersed in the solution and then, a suitable cross-linking agent is added. This solution or dispersion is then atomized in a stream of hot air. Atomization leads to the formation of small droplets, from which solvent evaporates instantaneously leading to the formation of free flowing particles.[24] He et al. prepared both un-cross-linked and cross-linked CS microparticles by spray-drying method for the delivery of cimetidine, famotidine and nizatidine.

5. Solvent Evaporation Method/Emulsion-droplet coalescence method:

The novel emulsion-droplet coalescence method utilizes the principles of both emulsion cross-linking and precipitation. However, in this method, instead of cross-linking the stable droplets, precipitation is induced by allowing coalescence of chitosan droplets with NaOH droplets. First, a stable emulsion containing aqueous solution of chitosan along with drug is produced in liquid paraffin oil and then, another stable emulsion containing chitosan aqueous solution of NaOH is produced in the same manner. When both emulsions are mixed under high-speed stirring, droplets of each emulsion would collide at random and coalesce, thereby precipitating chitosan droplets to give small size particles.[25]

6. Reverse Miscellar method:

Reverse micelles are thermodynamically stable liquid mixtures of water, oil and surfactant. In this method, the surfactant is dissolved in an organic solvent to prepare reverse micelles. To this, aqueous solutions of CS and drug are added with constant vortexing to avoid any turbidity. The aqueous phase is regulated in such a way as to keep the entire mixture in an optically transparent microemulsion phase. Additional amount of water may be added to obtain nanoparticles of larger size. To this transparent solution, a cross-linking agent is added with constant stirring, and cross-linking is achieved by stirring overnight. The maximum amount of drug that can be dissolved in reverse micelles varies from drug to drug and has to be determined by gradually increasing the amount of drug until the clear microemulsion is transformed into a translucent solution. The organic solvent is then evaporated to obtain the transparent dry mass. The material is dispersed in water and then adding a suitable salt precipitates the surfactant out. The mixture is then subjected to centrifugation. The supernatant solution is decanted, which contains the drug-loaded nanoparticles. The aqueous dispersion is immediately dialyzed through dialysis membrane for about 1 h and the liquid is lyophilized to dry powder.

Pharmaceutical applications of chitosan particulate systems:

Chitosan-based particulate systems are attracting pharmaceutical and biomedical applications as potential drug delivery devices. Some important applications are discussed below.

1.Colon targeted drug delivery:

Chitosan is a promising polymer for colon drug delivery since it can be biodegraded by the colonic bacterial flora [26] and it has mucoadhesive character. Sodium diclofenac was efficiently entrapped within these chitosan microcores and then microencapsulated into Eudragit L-100 and Eudragit S-100 to form a multireservoir system. In vitro release study revealed no release of the drug in gastric pH for 3 h and after the lag-time, a continuous release for 8–12 h was observed in the basic pH. Colon targeted drug delivery is useful in improving the absorption of peptide drugs via the GI tract. Site specific drug delivery to the colon is

of special interest for drugs instable in the upper part of the GI tract, because of the peptidase activity in the small intestine. The colon is thought to have lower enzymatic activity than other regions of the GI, hence a greater absorption efficiency in this region would be expected, as long as the proteins/peptides are released locally62.

Due to negligible activity of brush-border membrane and much less activity of peptidases and pancreatic enzymes, the colon has been considered suitable for the delivery of peptides and proteins. Bayat *et al.*61 developed a nanoparticulate system using two new quarternized derivatives of chitosan, triethylchitosan (TEC) and dimethylethylchitosan (DMEC) nanoparticles, for insulin colon delivery. The three kinds of nanoparticles showed a positive charge that could facilitate insulin uptake, allowing a low bursting effect and a steady release of insulin *in vitro*. DMEC nanoparticles and TEC nanoparticles had smaller particle size, higher insulin loading capacity and improved transport and absorption of insulin, as compared with chitosan nanoparticles. The blood glucose lowering effect of TEC nanoparticles and DMEC nanoparticles, after injection into ascending colon, was superior to that obtained with free insulin or chitosan nanoparticles. This study indicated that administration of proteins and peptides via colon absorption.

2 Mucosal delivery:

Nowadays, mucosal surfaces such as nasal, peroral and pulmonary are receiving a great deal of attention as alternative routes of systemic administration. Chitosan has mucoadhesive properties and therefore, it seems particularly useful to formulate the bioadhesive dosage forms for mucosal administration (ocular, nasal, buccal, gastro-enteric and vaginal-uterine therapy).[27] Chitosan has been found to enhance the drug absorption through mucosae without damaging the biological system. Here, the mechanism of action of chitosan was suggested to be a combination of bioadhesion and a transient widening of the tight junctions between epithelial cells. Genta et al. studied the influence of glutaraldehyde on drug release and mucoadhesive properties of chitosan microspheres. Chitosan nanoparticles enhanced the nasal absorption of insulin to a greater extent than the aqueous solution of chitosan.

3 Cancer therapy:

Tokumitsu et al. demonstrated the potential usefulness of Gd-NCT using gadolinium-loaded nanoparticles. The potential of gadolinium neutron-capture therapy (Gd-NCT) for cancer was evaluated using chitosan nanoparticles as a novel gadolinium device. Jameela et al. have prepared glutaraldehyde cross-linked chitosan microspheres containing mitoxantrone. Mitra et al. have encapsulated doxorubicin–dextran conjugate into long circulating chitosan nanoparticles. In an attempt to minimize cardiotoxicity of doxorubicin, a conjugate with dextran was prepared and encapsulated in CS nanoparticles.

4 Gene delivery:

Gene therapy is a challenging task in the treatment of genetic disorders. In case of gene delivery, the plasmid DNA has to be introduced into the target cells, which should get transcribed and the genetic information should ultimately be translated into the corresponding protein. To achieve this goal, number of hurdles are to be overcome by the gene delivery system. Transfection is affected by: (a) targeting the delivery system to target cell, (b) transport through the cell membrane, (c) uptake and degradation in the endolysosomes and (d) intracellular trafficking of plasmid DNA to the nucleus. Chitosan could interact ionically with the negatively charged DNA and forms polyelectrolyte complexes. In these complexes, DNA becomes better protected against nuclease degradation leading to better transfection efficiency. DNA-chitosan nanoparticles have been prepared[28] to examine the influence of several parameters on their preparation. Self-aggregates were prepared by hydrophobic modification of CS with deoxycholic acid in aqueous media. Self-aggregates can form charge complexes when mixed with plasmid DNA. The usefulness of self-aggregates/DNA complex for transfer of genes into mammalian cells in vitro has been suggested.

5 Topical delivery:

Due to good bioadhesive property and ability to sustain the release of the active constituents, chitosan has been used in topical delivery systems.

Bioadhesive chitosan microspheres for topical sustained release of cetyl pyridinium chloride have been evaluated. Improved microbiological activity was shown by these microparticulate systems. Conti et al. prepared microparticles composed of chitosan and designed as powders for topical wound-healing properties. Blank and ampicillin-loaded microspheres were prepared by spray-drying technique. In vivo evaluation in albino rats showed that both drug-loaded and blank microspheres have shown good wound healing properties.

6 Ocular delivery:

De Campos et al. investigated the potential of chitosan nanoparticles as a new vehicle to improve the delivery of drugs to ocular mucosa. Cyclosporin A (CyA) was chosen as a model drug. A modified ionic gelation technique was used to produce CyA-loaded CS nanoparticles.

7 Chitosan as a coating material:

Chitosan has good film forming properties and hence, it is used as a coating material in drug delivery applications. Chitosan-coated nanoparticles have many advantages such as improvement of drug payloads, bioadhesive property and prolonged drug release properties over the uncoated particles.

CONCLUSION: Chitosan has the desired properties for safe use as a pharmaceutical excipient. This has prompted accelerated research activities worldwide on chitosan micro and nanoparticles as drug delivery vehicles. These systems have great utility in controlled release and targeting studies of almost all class of bioactive molecules as discussed in this review. Recently, chitosan is also extensively explored in gene delivery. However, studies toward optimization of process parameters and scale up from the laboratory to pilot plant and then, to production level are yet to be undertaken. Majority of studies carried out so far are only in in vitro conditions. More in vivo studies need to be carried out. Chemical modifications of chitosan are important to get the desired physicochemical properties such as solubility, hydrophilicity, etc. The published literature indicates that in the near future, chitosan-based particulate systems will have more commercial status in the market than in the past.

FUTURE PROSPECTS: Recent reports indicate interest in colon as a site where poorly absorbed drug molecules may have improved bioavailability. The distal colon is considered to have less hostile environment as well as enzyme activity compared to stomach and small intestine. The development of a dosage form that improves the oral absorption of peptide and protein drugs whose bioavailability is very low because of instability in the GI tract (due to pH or enzymatic degradation) is one of the greatest challenges for oral peptide delivery in the pharmaceutical field. Colon targeted multiparticulate systems like microspheres and nanoparticles can provide a platform for spatial delivery of candidates like peptides, proteins, oligonucleotides and vaccines.

REFERENCES:

1. Chourasia MK, Jain SK. Polysaccharides for colon targeted drug delivery. Drug Deliv. 11 2004; 129–148.
2. Jain A, Jain SK. In vitro and cell uptake studies for targeting of ligand anchored nanoparticles for colon tumors. Eur J Pharm Sci. 2008; 35 (5), 404-416.
3. Ali Asghar LF, Chandran S. Multiparticulate Formulation Approach to Colon Specific Drug Delivery: Current Perspectives. J Pharm Pharm Sci. 2006; 9 (3): 327-338.
4. Nagpal D, Singh R, Gairola N, Bodhankar SL, Dhaneshwar SS. Mutual azo prodrug of 5-ASA for colon targeted drug delivery system: Synthesis, Kinetics Studies and Pharmacological Evaluation. Ind. J. Pharm. Sci. 2006; 171-177.
5. Chourasia MK, Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Pharm Sci. 2003; 6: 33-66.
6. Lamprecht A, Schafer U, Lehr CM. Size-dependent bioadhesion of micro- and nanoparticulate carriers to the inflamed colonic mucosa. Pharm Res. 2001a; 18: 788–793.
7. Lamprecht A, Ubrich N, Yamamoto H, Schäfer U, Takeuchi H, Maincent P, Kawashima Y, Lehr CM. Biodegradable nanoparticles for the targeted drug delivery in the treatment of inflammatory bowel disease. J. Pharmacol. Exp.Ther. 2001b; 299: 775–781.
8. Meissner Y, Pellequer Y, Lamprecht A. Nanoparticles in inflammatory bowel disease: particle targeting versus pH-sensitive delivery. Int J Pharm. 2006; 316: 138-143.
9. Sartor R.B. Microbial Influences in Inflammatory Bowel Diseases. Gastroenterology. 2008; 134 (2): 577-594.
10. Ulbrich W, Lamprecht A. Targeted drug-delivery approaches by nanoparticulate carriers in the therapy of inflammatory diseases. J R Soc Interface. 2010; 7: S55–S66.
11. Minko T. Drug targeting to the colon with lectins and neoglycoconjugates. Adv Drug Deliv Rev. 2010; 56: 491-509.

12. Liu L, Fishman ML, Kost J, Hicks KB. Pectin based systems for colon specific drug delivery via oral route. Biomaterials. 2003; 24: 3333-3343.
13. Patel P Manish, Patel R Ravi, Patel K Jayvadan Chitosan mediated targeted drug delivery reviews. J Pharm Pharm Sci. 2010; 13(3): 536-557.
14. Kumar MN, Muzzarelli RA, Muzzarelli C, Sashiwa H, Domb AJ. Chitosan chemistry and pharmaceutical perspectives. Chem. Rev. 2004; 104: 6017–6084.
15. Amidi M, Romejn SG, Borchard G, Junginger HE, Hennink WE, Jiskoot W. Preparation and characterization of protein-loaded N-trimethyl chitosan nanoparticles as nasal delivery system. J. Control Release. 2006;111: 107–116.
16. Wang Y, Jiang Q, Li R, Liu L, Zhang Q, Wang Y, Zhao J. Self-assembled nanoparticles of cholesterol-modified O carboxymethyl chitosan as a novel carrier for paclitaxel. Nanotechnology. 2008; 19: 145101.
17. Kim K, Kwon S, Park JH, Chung H, Jeong SY, Kwon IC, Kim IS. Physicochemical characterizations of self-assembled nanoparticles of glycol chitosan-deoxycholic acid conjugates. Biomacromolecules. 2005; 6: 1154-1158.
18. Dufes C, Muller JM, Couet W, Olivier JC, Uchegbu IF, Schatzlein AG. Anticancer drug delivery with transferrin targeted polymeric chitosan vesicles. Pharm Res. 2004; 21: 101–107.
19. Kim JH, Kim YS, Park K, Lee S, Nam HY, Min KH, Jo HG, Park JH, Choi K, Jeong SY, Park RW, Kim IS, Kim K, Kwon IC. Antitumor efficacy of cisplatin-loaded glycol chitosan nanoparticles in tumor-bearing mice. J Control Release. 2008; 127: 41–49.
20. Nagpal K, Singh SK, Mishra DN Chitosan Nanoparticles: A Promising System in Novel Drug Delivery. Chem Pharm Bull. 2010; 58(11): 1423-1430.
21. Sailaja AK, Amareshwar P, Chakravarty P. Different techniques used for the preparation of nanoparticles using natural polymers and their application. Int J Pharm Pharm Sci. 2011; 3(2): 45-50.
22. Zheng Y, Yang W, Wang C, Hu J, Fu S, Dong L, Wu L, Shen X. Nanoparticles based on the complex of chitosan and polyaspartic acid sodium salt: preparation, characterization and the use for 5- fluorouracil delivery. Eur J Pharm Biopharm. 2007; 67: 621-631.
23. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM. Recent advances on chitosan-based micro- and nanoparticles in drug delivery. J Contr Release.2004; 100: 5-28.
24. Dash M, Chiellini F, Ottenbrite RM, Chiellini E. Chitosan: A versatile semisynthetic polymer in biomedical applications. Prog Polym Sci. 2011; 36: 981-1014.
25. Patel JK and Jivani NP. Chitosan based nanoparticles in drug delivery. Int J Pharm Sci Nanotech. 2009; 2(2): 517-522.
26. Zhang H, Alsarra IA, Neau SH. An in vitro evaluation of a chitosan-containing multiparticulate system for macromolecule delivery to the colon. Int J Pharm. 2002; 239: 197-205.
27. Genta M, Costantini A, Asti B, Conti L. Montanari Influence of glutaraldehyde on drug release and mucoadhesive properties of chitosan microspheres. Carbohydr Polym. 1998; 36: 81-88.
28. Mao HQ, Roy K, Troung-Le VL, Janes KA, Lim KY, Wang Y, August JT, Leong K.W. Chitosan DNA nanoparticles as gene delivery carriers: synthesis, characterization and transfection efficiency. J Contr Release. 2001; 70: 399-421.

How to cite this article:
Ruchika and Himanshi: Nano-Therapeutics Arsenals for Intervention of Colon Cancer. Int J Pharm Sci Res 2016; 7(5): 1857-65.doi: 10.13040/IJPSR.0975-8232.7(5).1857-65.