



REVIEW ARTICLE

CHITOSAN MICROSPHERES AS POTENTIAL CARRIERS FOR COLON TARGETING

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Chitosan microspheres have been in the focus of increasing interest as polymeric drug carriers due to their appealing properties such as biocompatibility, biodegradability, low toxicity, mucoadhesion and relatively low cost of production. Gel formation can be obtained by interactions of chitosan with low molecular weight counter-ions such as polyphosphates. However, one drawback of using this natural polysaccharide for oral controlled release dosage forms is its fast dissolution rate in the stomach. Since chitosan is positively charged at low pH values (below its pKa value), it spontaneously associates with polyanions to form polyelectrolyte complexes (PEC). These PEC exhibit favorable physicochemical properties with preservation of chitosan's biocompatible characteristics. These complexes are therefore good candidates for the design of colon-targeted dosage forms. Various techniques are used for preparing chitosan microspheres which have been reviewed. This review also includes factors that affect the release characteristics of drugs from chitosan microspheres.

INTRODUCTION

Colon-specific drug delivery systems have gained increased interest in the last decades due to the well-recognized importance of this region of the GIT both for local and systemic administration of medicinal agents. Much interest has been given in directing drugs and dosage forms to affect primary drug release in the colon¹. Systems which can deliver drugs specifically to the colon without losing them in the upper parts of the GIT are referred to as colon-specific drug delivery systems².

Rationales for colon targeting

The rationales for development of orally administered colonic drug delivery systems include: (a) The opportunity to reduce adverse effects in the treatment of local colonic disorders; (b) Elucidation of the mode of action of some non-steroidal anti-inflammatory drugs (NSAIDs) such as sulindac³; (c) The recognition that the colon is capable of absorbing drugs efficiently; (d) Accumulated evidence that drug absorption enhancement works better in the colon than in the small

intestine⁴; (e) The anticipation that protein drugs can be absorbed better from the large bowel owing to the reduced proteolytic activity in this organ⁵ and (f) The unique metabolic activity of the colon that makes it an attractive organ for the design of drug delivery systems⁶.

Approaches utilized to achieve colonic targeting

Various approaches have been utilized for the development of colon specific drug delivery systems. They can be categorized as: (a) Prodrug approach⁷; (b) Pressure-based systems^{8&9}; (c) The temporal control of delivery¹⁰; (d) pH-based systems¹¹⁻¹³ and (e) Enzyme-based systems¹⁴. Among these approaches, the one in which the drug release is triggered by the colonic microflora seems to be the most specific due to its unique selectivity^{15&16}.

The universal polysaccharide systems which suffer hydrolysis of their glycosidic bonds in the colon, appear to be the most promising because of their practicality and exploitation of the most distinctive property of

the colon, its abundant microflora¹⁷. Colonic bacterial enzymes are capable of degrading these natural polymers in the colon, despite being not affected either in the stomach or in the small intestine¹⁸.

Microspheres as multiple-unit dosage forms

Polymeric microspheres have emerged as a safe and efficient oral drug delivery systems by virtue of their interesting properties, such as their smaller size and larger surface area that improve drug absorption as compared to larger carriers¹⁹. In addition, these matrix-type microspheres, in which the drug is dispersed or dissolved, showed a potential to enhance the drug stability and improve the oral bioavailability of water-insoluble or hydrophobic drugs such as nifedipine, curcumin,.... etc.^{20&21}.

These multiparticulate systems were shown to quickly spread out on their arrival to the colon with a sharp increase in the surface area exposed to bacterial breakdown which produces a rapid drug release and thereby improve drug absorption²². Polysaccharide-based microspheres have an additional unique advantage which is their ability to adhere to mucus layers of the colon.

Chitosan (CS)

Chitosan is a cationic polysaccharide obtained by the alkaline N-deacetylation of chitin, the main component of the protective shells of crustaceans²³. It is the second most abundant natural polymer on Earth next to cellulose²⁴. It is a linear co-polymer polysaccharide consisting of β (1-4)-linked 2-amino-2-deoxy-D-glucose (D-glucosamine) and 2-acetamido-2-deoxy-D-glucose (N-acetyl-D-glucosamine units²⁵ as depicted in figure 1.

Chitosan is a weak base which is insoluble in water and organic solvents, however, it is soluble in dilute aqueous acidic solution (pH < 6.5), which can convert the glucosamine units into a soluble form $R-NH_3^+$ ²³. It represent a series of polymers of different degrees of deacetylation (DD), expressed as the percentage of primary amino groups present in the polymer backbone and the average molecular weights (Mw). The DD for commercial-grade chitosan ranges between 70% and 95%, and the Mw between 10 and 1000 kDa.. It has a pKa around 6.3. The physico-chemical properties and biodegradability of chitosan are both highly dependent on the relative proportions of N-acetyl-D-glucosamine and D-glucosamine residues²⁵.

Chitosan has been extensively investigated as an adjuvant in many pharmaceutical applications such as (a) vehicle for directly compressed tablets²⁶, (b) disintegrant²⁷, (c) binder²⁸, (d) granulating agent in tablet manufacture²⁹, (e) co-grinding diluent for improving the dissolution characteristics and bioavailability of poorly water-soluble drugs³⁰ as well as (f) drug carrier for sustained release preparations³¹⁻³³.

Additionally, chitosan combine many interesting features, such as safety, inertness, non-toxicity, biocompatibility, biodegradability as well as mucoadhesion. Chemically, chitosan has one primary amino and two free hydroxyl groups in each building block and due to the availability of this amino group, chitosan carries positive charges, at pH values ≤ 6.5 , that enable it to react with a variety of negatively charged polymers and surfaces³⁴.

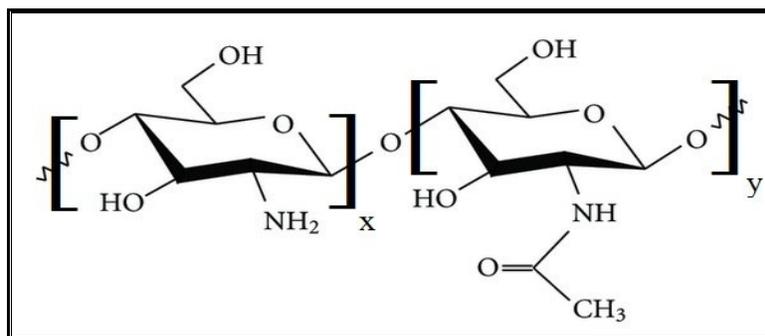


Fig. 1: Chemical structure of chitosan. The indices x and y represent the mole fractions of D-glucosamine and N-acetyl-D-glucosamine moieties, respectively

Chitosan microspheres

Chitosan microspheres have been widely studied as a matrix for the controlled release of drugs³⁵⁻³⁹. However, these microspheres have shown limited strength along with very fast drug release in the stomach due to the high solubility of chitosan in acidic media⁴⁰⁻⁴². Despite this fact, the use of chitosan for colonic targeting offers a great advantage by virtue of its insolubility at pH values above 6.5 that prevail in the jejunum and ileum parts of the small intestine while it gets soluble again at pH of the colon⁴³. Thus chitosan has to be combined with another polymer, usually polyanion, to prevent premature drug release in the stomach and ideally release it in the colon⁴³.

Chitosan polyelectrolyte complexes

Polyelectrolyte complexes (PECs) are biocompatible hydrogel networks formed by interaction between macromolecules, bearing a relatively large number of oppositely charged functional groups, in an aqueous medium⁴⁴. Mixing of these polyelectrolytes in solution results in their spontaneous self assembly due to the promotion of strong, but reversible, electrostatic linkages between them⁴⁵.

PEC are, generally, characterized by having hydrophilic micro-structure with a high water content and electrical charge density⁴⁶. In addition, these PEC exhibit a pH-dependent swelling behavior which represent an interesting property allowing the controlled-release of different entrapped substance such as, medicinal agents, enzymes or bacteria until it reaches the colon^{47&48}. This pH-sensitive swelling behavior could be explained in light of their higher degree of swelling at pH between the pKa values of the functional groups involved in the PEC formation, where both become ionized⁴⁹.

Over the last years, PEC between chitosan and many polyanions have been prepared and investigated as drug carriers such as, chitosan-alginate PEC^{50&51}, chitosan-pectin PEC⁵²⁻⁵⁴, chitosan-NaCMC PEC^{55&56}, chitosan-carrageenan PEC^{57&58}, chitosan-xanthan gum PEC^{59&60}, chitosan-hyaluronic acid PEC^{61&62}, chitosan-kondagogu gum PEC⁶³ and chitosan-gelatin PEC^{64&65}.

In particular, PECs formed between pectin and chitosan are considered as promising

candidates for colon-targeted delivery of therapeutically-active moieties because of its physiological inertness and relatively higher resistance to enzymatic degradation^{66&67}. Microspheres based on this complex were proven to have better protective effect against immature drug release in the stomach as the interaction between pectin or and chitosan is more favored at low pH values⁶⁸.

Preparation of chitosan PECs

The preparation of such PECs is a mild and reversible process requiring only the reacting species. It requires no auxiliary molecules as initiators or catalysts, no additional purification steps, and is almost done in aqueous medium⁴⁴. Therefore, this electrostatic interaction was found to be superior to the chemical (covalent) crosslinking reaction, with respect to the safety and avoidance of organic solvents and chemical cross-linkers thereby, reducing toxicity and undesirable side-effects⁶⁹.

Two methods were reported for the formation of chitosan PEC. The single step method is a simple and efficient one in which, an aqueous solution of the polyanion is added dropwise into the crosslinking medium containing chitosan⁵¹. Alternatively, a two-stage method is available which involves coating of the preformed Ca-pectinate or Ca-alginate beads with an external membrane of chitosan⁷⁰.

Drugs formulated as chitosan microspheres for colonic targeting

Various categories of drugs could be targeted to the colon, including drugs which are unabsorbed in the upper GIT or those required for treatment of local colonic pathologies. Moreover, the colonic delivery is also beneficial for systemic absorption of some drugs. Chitosan-based microspheres were extensively investigated for various classes of drugs, such as anticancer drugs including Fluorouracil⁷¹, Cisplatin⁷², Mitoxantrone⁷³, Methotrexate⁷⁴ and Taxol⁷⁵; anti-inflammatory drugs including Indomethacin⁷⁶, Diclofenac sodium⁷⁷, Prednisolone⁷⁸, Ketoprofen⁷⁹, Piroxicam⁸⁰ and Sulfasalazine⁸¹; cardiovascular drugs including Diltiazem⁸², Nifedipine⁸³, Propranolol⁸⁴ and Isosorbide mononitrate⁸⁵; antibiotics including Amoxicillin⁸⁶,

Ampicillin⁸⁷, tetracycline¹⁶ and sulfathiazole⁸⁸ in addition to protein hormones including Insulin⁸⁹ and Growth hormone⁹⁰,... etc.

Factors affecting drug release behavior from chitosan microspheres

Many parameters can influence the drug release behavior from chitosan microspheres. These include concentration and molecular weight of the chitosan, the type and concentration of crosslinking agent, variables like stirring speed, type of oil, additives, nature of the crosslinking process used, drug: chitosan ratio,... etc. The most important factors can be summarized as following:

1. Effect of cross-linking degree

The crosslinking density appears to be the most crucial parameter affecting the release of drugs from chitosan microspheres. Jameela *et al.*⁹¹ have revealed that highly cross-linked microspheres released only 35% of the progesterone in 40 days as compared to 70% release from microspheres cross-linked lightly. Also, Ko *et al.*⁹² prepared felodipine-loaded chitosan microparticles with tripolyphosphate (TPP) by ionic crosslinking. The release of drug from TPP–chitosan microparticles was markedly reduced upon increasing the crosslinking time as well as TPP concentration. Mitoxantrone release from chitosan microspheres was also controlled by the extent of crosslinking. The crosslinking was carried out using glutaraldehyde-saturated toluene⁷³. Only about 25% of the drug was released over 36 days from highly crosslinked microspheres. Moreover, Kumar *et al.*⁹³ encapsulated curcumin in bovine serum albumin and chitosan microspheres to form a depot forming drug delivery system. *In-vitro* release studies indicated a biphasic drug release pattern, characterized by burst-effect followed by a slow release which was highly dependent on the cross-linking density.

2. Effect of chitosan concentration

Several authors have reported that the rate of drug release from chitosan microspheres was reduced upon increasing chitosan concentration. Nishioka *et al.*⁹⁴ have found that the release rates of cisplatin from such microspheres decreased significantly upon increasing chitosan concentration. Similar

finding was reported later by Ko *et al.*⁹² for chitosan microspheres loaded with felodipine. These results were consistent with those obtained by Aiedehe *et al.*⁹⁵ who prepared chitosan-based biodegradable system for oral delivery of insulin. The release rate of insulin could be increased considerably by decreasing chitosan content in the preparative solution.

3. Effect of molecular weight of chitosan

Generally, drug release studies from chitosan microspheres have shown that the drug release rates decreases with an increase in molecular weight (MW) of chitosan. Shiraishi *et al.*⁹⁶ and Al-Helw *et al.*⁹⁷ have reported that the release of indomethacin and phenobarbitone from crosslinked chitosan microspheres was slower from microspheres prepared with high MW chitosan as compared to medium and low MW chitosan microspheres, respectively. In another study, Polk *et al.*⁶⁹ reported that chitosan MW is a key variable in the release of albumin from chitosan microspheres. Decreasing the MW increased the release of albumin (from 37% after 4 h with high MW chitosan to 77% release with low MW chitosan). Capsules produced with a combination of high and low MW chitosan gave the best results for reducing leaching of albumin in the first 4 h and increasing elution in the subsequent hours. However, Genta *et al.*⁷⁹ reported that the fastest ketoprofen release profile from chitosan microspheres was obtained with medium MW chitosan. This was attributed to the swelling behavior of chitosan microspheres. An increase in MW of chitosan leads to increase in viscosity of the gel layer, which influences the diffusion of the drug as well as erosion of the microspheres.

4. Effect of drug content in the microspheres

The effect of drug content on the drug release properties from chitosan microspheres was controversial and seems to be related to the nature of loaded drugs. Bayomi *et al.*⁸² have shown that the release of the drug from microspheres increased with increasing drug content in the microspheres. Furthermore, Akbuga and Durmaz⁹⁸ reported that the release of furosemide from chitosan microspheres followed the Higuchi-matrix kinetic model i.e., increased drug release upon increasing the

amount of furosamide incorporated. However, contradictory results have been reported by Bodmeier *et al.*⁹⁹ who reported that the release of sulfadiazine decreased with increasing the drug content in microspheres. This was explained by virtue of the water-insoluble nature of the encapsulated drug (sulfadiazine).

Conclusion

Ionic crosslinking with counter-ions or polyanions is an extremely simple and mild method for preparing chitosan microspheres. Moreover, ionically cross-linked chitosan hydrogels are often biocompatible and well-tolerated with numerous potential medical and pharmaceutical applications. These hydrogels offer better safety profiles and opportunities as drug delivery systems when compared to covalently cross-linked hydrogels. They can be used for controlled release of medicinal agents, not only in acidic but also in basic media and as thermo-gelling systems. However, the main disadvantages accompanying the use of these polymeric systems as drug carriers are the possible lack of mechanical stability and the risk of rapid dissolution of the system, especially at low pH values, due to a highly pH-sensitive swelling behavior.

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كريات الكيتوزان الدقيقة كناقلات محتمله لاستهداف القولون

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لقد كانت كريات الكيتوزان الدقيقة محط اهتمام متزايد كناقلات بوليمرية للعقاقير وذلك بسبب خصائصها الجذابة كالتوافق الحيوي والتحلل البيولوجي والسمية المنخفضة والالتصاق بالأغشية المخاطية بالإضافة إلى تكلفة الإنتاج المنخفضة نسبياً. هذا ويمكن تكوين هلام بواسطة تفاعل الكيتوزان مع أيونات منخفضة الوزن الجزيئي مثل الفوسفات. ومع ذلك فإن استخدام هذا البوليمر الطبيعي لتكوين أشكال صيدلانية منضبطة الانطلاق عن طريق الفم له عيب وهو معدل الانحلال السريع في المعدة. وحيث أن جزيئات الكيتوزان تحمل شحنة موجبة في الوسط الحمضي، فإنها ترتبط تلقائياً مع الجزيئات سالبة الشحنة لتشكل معقدات عديدة الإلكتروليتات. وتظهر هذه المعقدات خصائص فيزيائية جيدة مع الاحتفاظ بخصائص الكيتوزان كتوافقه الحيوي ولذا يعتبر هذا المعقد مرشحاً جيداً لتصميم أشكال دوائية لاستهداف القولون. هذا ويمكن استخدام تقنيات مختلفة لإعداد كريات الكيتوزان الدقيقة التي ستناقش لاحقاً ويشمل هذا المقال أيضاً العوامل التي تؤثر على خصائص انطلاق العقاقير من هذه الكريات.