Review Article

Drug delivery using alginate and chitosan beads: An Overview

Abstract

Alginate and chitosan are commonly used polymers in modifying the drug release. These two polymers can be used together or separately to form drug loaded modified release beads. The ionotropic gelation method and a slight modification in various ways are used to prepare these beads of different characteristics. The bead characteristics like morphology, buoyancy, swelling nature, drug entrapment efficiency, adsorption, and release behavior are of importance. Also the therapeutic uses of the different modifications of the beads can be immense for the drugs which have low water solubility, short biological half life, require organ specific targeting, and are proteineous in nature.

Key words:
Alginate, chitosan, ionotropic gelation, beads

Introduction

Alginate, a naturally occurring biopolymer, finds increasing applications in various fields. It has been successfully used for many years in the food and beverage industry as a thickening agent, gelling agent, and a colloidal stabilizer. It also has several unique properties that have opened the field of its use as a matrix for the entrapment and/or delivery of a variety of proteins, drugs, and cells. These properties include: (i) a relatively inert aqueous environment within the matrix; (ii) a mild room temperature encapsulation process free of organic solvents; (iii) a high gel porosity which allows for high diffusion rates of macromolecules; (iv) the ability to control this porosity with simple coating procedures; and (v) dissolution and biodegradation of the system under normal physiological conditions.[1]

Alginate is a water-soluble linear, polyanionic; polysaccharide extracted from brown seaweed and is composed of alternating blocks of 1–4 linked α-L-guluronic and β-D-mannuronic acid residues.[2] The gel beads are prepared through the sol-gel transformation of alginate which is brought about by cross-linking the alginate with divalent cations like Ca^{2+}, Zn^{2+}. Guluronic acid is responsible for the formation of gel by the alginate with the cations in the solution. The alginate matrix consisting of an open lattice structure forms porous beads. The beads have low retention capacity for encapsulating low molecular weight and water soluble drugs.[3]

Chitosan is a biocompatible, biodegradable, nontoxic, 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) units and has the structural similarity to cellulose (made up of β (1–4)-linked D-glucose units). Chitosan is the *N*-deacetylated derivative of chitin, although this *N*-deacetylation is never complete, which has a number of amino groups exposed making it polycationic polysaccharide. Depending on the amount/extent of deacetylation, different grades of chitosan are found. Due to its gel-forming property, it has been used in the designing of drug delivery system.[3]

The more effective beads for the drug delivery can be formed by using the combination of both alginate and the chitosan. The interaction between alginate and chitosan has been systematically investigated. Their polyelectrolyte complex has been widely used to obtain devices for the controlled release of drugs.[4] The interaction between the alginate and the chitosan forms the polyelectrolyte complex via the ionic

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interaction between the carboxyl residue of alginate and the amino residue of chitosan. The complexation of alginate with chitosan decreases the leakage of the encapsulated drug from the beads. Due to this reason, the previously used alginate beads and the chitosan-tripolyphosphate beads which had low mechanical strengths are replaced by the alginate chitosan beads which can be prepared by various methods.

Method of Preparation of Beads

The beads can be prepared by ionotropic gelation method.[5] The method has been modified as per the need as mentioned below.

i. *Syringe or dropper method*
ii. *Extrusion method*
iii. Laminar jet break-up or *prilling method*

Ionotropic gelation method

This includes the formation of the hydrogel beads by treating the alginate solution with the solution containing polyvalent (mostly divalent) ions. The polyvalent ions help in the formation of the gel by forming a bond with the alginate. This is the commonest method employed and it can be modified in many different ways to bring about the desired shape, size, and therapeutic effects.[6-9]

(a) The solution of the sodium alginate is prepared (different concentration). To that solution, the drug (if required in suitable vehicle) in different concentrations is added. The mixture is stirred and allowed to stand for required time. The mixture is then dropped into the solution containing divalent ion (different concentration) and if required at different pH conditions. The beads thus formed are washed (different solutions) and dried (different conditions). The wet beads thus formed can then be coated with the polymers like chitosan and then dried to modify the release
(b) The solution of sodium alginate is mixed with the drug solution and the polymer like chitosan is added to it. Then the mixture is gelled with divalent ion solution as above
(c) Further modification can be the addition of the alginate solution into the mixture of divalent ion salt and the polymer (chitosan). Then the beads formed are passed through the same processes.

Extrusion method

Extrusion is a process of creating an object of a fixed dimension by pushing or drawing the material through a die of the desired cross-section.[3] The solution of sodium alginate is mixed with the drug solution and is introduced drop wise into the solution of divalent metal salt by means of extrusion through a silicone tubing using a peristaltic pump. This method can be used for all the aforementioned preparations of the drug, alginate solution, chitosan solution, and the gelling polyvalent electrolyte solution. The beads obtained are filtered and dried at the optimum temperature.

Prilling method

It is the method of preparation of small droplets by the upward flowing air when it comes in contact with the falling thermostated sodium alginate solution.[10] The droplets of the solution is used for making beads by using a vibrating nozzle device pumping through the nozzle at different rates into the solution of divalent metal salts. The beads thus formed are filtered and dried at the optimum temperature. This method has been extensively used to obtain microparticles of a narrow dimensional range and high encapsulation efficiency especially in biotechnology for cell immobilization.

Preparation of chitosan beads

General method

Acetate buffered chitosan solution (pH 4.5) is mixed with the drug and is left to stand for 24 hours at room temperature for complete hydration of polymer. The solution is then covalently cross-linked with glutaraldehyde followed by precipitation in an aqueous medium by a changing pH i.e., making basic by adding of sodium hydroxide solution. The beads are separated and dried if required.[11-16]

Modifications

Cross-linking chitosan succinate with iron ($FeCl_3$) leads to further cross-linking and allows pH independent drug release.[13]

Chitosan gel beads can also be prepared by complexing chitosan with divalent metal ions such as Cu^{2+} which improve the stability and absorption of peptide and protein drugs (water soluble e.g. insulin) which cannot be obtained by employing cross-linking with glutaraldehyde.[14]

Tripolyphosphate cross-linked chitosan beads show a more homogenous structure as a result of more homogenous cross-linking process; hence, beads are strengthened greatly and have increased drug loading efficiency.[15-16]

Characterization of beads

Buoyancy

The buoyancy of the stomach specific preparation is measured using standard pycnometer or electronic densimeter. Gas pycnometer compares the change in pressure caused by a measured change in a closed volume containing a reference (usually a steel sphere of known volume) with the change in pressure caused by the sample under the same conditions. The difference in change of pressure represents the volume of the sample as compared to the reference sphere.[17] Lower the density of the beads more is the buoyancy. The bead containing drug and the vegetable oil in it float to provide the stomach specific delivery.[18]

Morphological studies/particle size using scanning electron microscope

Dried beads with low concentration of alginate lose

the spherical shape when dried, but beads with high concentration retain the shape. The beads from method (i) b show increasing size, but lose the spherical structure on drying. The beads from (i) a calcium alginate beads coated with the chitosan (polymer) show the spherical structure in both the dry and wet conditions.[6] But at times the coating with higher concentration of polymer leads to cracks and holes on the surface,[19] and even ethanol drying decreases the surface roughness.[20] Some authors have observed the spherical shape of beads when eudragit, a acrylic polymer, is used for the preparation of calcium alginate beads and when the beads are coated with chitosan.[21]

Swelling studies

Swelling behavior of the beads is studied by measuring the diameter of the beads by digital camera. The magnitude of swelling is presented by the ratio of the mean diameter of the swollen beads to the mean diameter of the dried beads before the test and the increase in diameter is determined. Chitosan coated beads swell less than the uncoated ones due to the formation of skin layer with chitosan.[6,21] The swelling behavior is pH dependent. The beads swell slightly in stomach, but swelling gradually increases in the intestinal pH and maximum in the colon for the colon specific delivery.[20]

Entrapping efficiency

The entrapping efficiency of the water soluble drug is less as the medium used is mostly aqueous and the drug will be lost more in the medium. Longer the curing time, lesser the extent of entrapment.[19] The water insoluble drugs have good entrapping efficiency.[15] The more the concentration of the drug, more will be the entrapment. The increase in the coating polymer concentration also increases the entrapping efficiency.[8]

Uptake of bile acids

The alginate chitosan beads show increasing adsorption of bile acids with the increase in the concentration of the bile acids in the medium, when the acidic drugs like ascorbic acid or nicotinic acids are used. Latter acids form the strong links with the amino groups of chitosan so can easily be incorporated in the beads.[8,9]

Release behavior

Drug release is determined by introducing the beads into buffered simulated dissolution media at 37±0.5°C[21], 37±0.1°C,[16] 37°C [11,14] and stirred at 50 rpm. The XXIII USP basket apparatus,[22] Japanese Pharmacopoeia 13th edition (JPXIII) paddle type dissolution test apparatus[11] are used. The samples are withdrawn at specific time interval and assayed spectrophotometrically at the wavelength of maximum absorbance.[22] The percentage of the drug release is calculated with respect to the drug content of the beads. The drug content is expressed as the percentage of drug encapsulated in a unit weight of beads. The experiments are carried out in triplicate and the results averaged.[23]

The undried beads show decreased drug release with increased chitosan concentration, but increased alginate show decreased release at low concentration of chitosan and increased release with high concentration of chitosan.[6] The beads containing oils in it release the drugs gradually.[17]

For the dried beads, due to the destruction of the alginate chitosan film, the drug release was more. The increased concentration of coated chitosan showed the decreased drug release.[6,18,24] Also the increased drug concentration increases the drug release.[16]

Therapeutic applications

The alginate, chitosan or alginate-chitosan beads can have various therapeutic uses depending upon the drug loaded into them.

1. NSAIDs like diclofenac sodium may be made into beads which show reduced release in the acidic environment of the stomach. This minimizes the adverse effects of oral administration and avoids direct contact between the drug and the gastric mucosa.[25] The other NSAID, ibuprofen, may also be the candidate for the prolonged and the controlled release formulation because of its short half life and gastric irritation activity both of which can easily be overcome by using the alginate beads[26]
2. The beads loaded with the antibiotics (like ampicillin) may be useful for the oral delivery for the treatment of gastric and intestinal diseases. The sustained and the controlled release of ampicillin may be useful to overcome its short biological half-life of 0.75-1.5 hours[27]
3. Antihypertensive drugs, like verapamil HCl, with low bioavailability due to first pass metabolism may be formulated in the alginate chitosan beads so that their controlled release may be obtained for the prolonged therapeutic effect.[24] Another antihypertensive calcium channel blocker, nicardipine, may be a candidate for the controlled release beads as it has a very short half life of 1 hour[20]
4. The sustained release dosage form which delivers melatonin over the period of 8 hours may be useful for those who have disordered circardian rhythm and that could be maintained through the use of polymer reinforced and coated alginate beads.[19] Melatonin has short half life so is not very effective as immediate release dosage form
5. Sustained release of prednisolone from chitosan gel beads allows minimum effective dose to be delivered locally (subcutaneous) and prolongs the duration of drug activity. So, it improves the therapeutic efficacy and decreases side effects by minimizing the transportation of the drug to the systemic circulation against inflammation[11]
6. Theophylline, a poorly water soluble bronchodilator and the targeted drug for sustained delivery, showed

the retarded drug release under physiologically simulated pH conditions (acidic and neutral).[13] So, it could be a good candidate for the modified dosage forms

7. Cefadroxil, an antibiotic used in the treatment of bacterial infections, has a biological half-life of 1.2-2.0 hours. Its short half-life may be enhanced by the use of the sodium alginate interpenetrating network beads[28]
8. Insulin, an antidiabetic polypeptide drug, and albumin are degraded in the acidic medium when given orally. Formulating them in the modified alginate beads may deliver them in the intestinal region without significant degradation in the stomach[29]
9. Brilliant blue (poorly water soluble dye) showed the extended release and dextran (water soluble polysaccharide) showed a faster release indicating that the water insoluble drugs may be used for the controlled delivery[15]
10. Alginate-chitosan beads containing nicotinic acid and ascorbic acid (a water soluble vitamin), drugs for hyperlipidemia, show controlled release of these drugs. Bile acids are responsible for the breakdown and the absorption of the fatty substances. The beads may also be useful in absorbing the bile acids and may prove to be very valuable in treatment of hyperlipidemic patients[8,9]
11. Unpredictable and incomplete absorption limits the oral delivery of 5-fluorouracil, an anticancer drug. So their local use in the treatment of breast cancer may be justified in polymeric bead forms[30]
12. Metronidazole, an antiulcer drug, in bead form to be retained in stomach for sufficient time to exert anti *Helicobactor pylori* effect.[17,31] The gastro-retention of the drugs, especially antiulcer and antacid, by formulating them in the floating beads, could open new doors for the treatment of gastric ulcer and acidity.

Conclusion

The drug loaded beads of alginate, chitosan, and alginate coated or mixed with chitosan may be of immense importance in the drug delivery through the oral route as well as the other routes as sustained and controlled release dosage forms. The desired effects in the drug release and the therapeutic value may be obtained by modifying various materials and/or their concentration. As these beads are nontoxic, biodegradable, biocompatible, they have to be studied in detail so that they may be used in practice for the delivery of the drugs in controlled and sustained release manners.

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