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PREPARATION AND EVALUATION OF ALGINATE BEADS: A REVIEW

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ABSTRACT

The objective of this review is to elaborate the potential of alginate beads as a biopolymer within the formulation development and its applications. There is a growing trend in pharmaceutical in food industry to avoid the tough condition within the preparation for administration to the body or for the storage purpose because it induce the side effects, instability or loss of therapeutic effect of the medicament. The alginate beads could also be a flexible functional biomaterial for viscosity enhancement, stabilizer, matrixing agent, encapsulation polymer, bioadhesive and film former in transdermal and transmucosal drug delivery. This review includes the preparation, properties, compendial standards, methods utilized for preparation of drug delivery systems using sodium alginate and its applications.

KEYWORDS: Sodium alginates, microbeads, biopolymer, drug delivery.

INTRODUCTION

The design and interest in development of controlled release dosage forms has been found increasing steadily during the last 50 years. In most works the purpose is to make a formulation that keeps a prolonged therapeutic effect at a reduced dosing frequency. It is worthless to mention that the drugs are almost never administered in an unformulated state. Generally a dosage form consists of one or more active principles together with a varying number of other substances (excipients). These excipients enormously influence the physicochemical characteristics of the final products. It is now recognized that excipients can potentially influence the rate and/or extent of absorption of a drug (e.g. by complex formation). Therefore a well-established formulation depends on the careful selection of excipients. By reviewing the present and past scenario it is never worthless to mention, the use of polymers as a formulation aid in controlled drug delivery systems become an important area of research and development.[1]

The alginates were discovered by a British Pharmacist, E.C.C. Stanford; commercial production started in 1929. The annual production of alginates in the world is about 30,000 tones; 30% of this is utilized by the food industry, the rest being used in industrial, pharmaceutical, and dental applications.

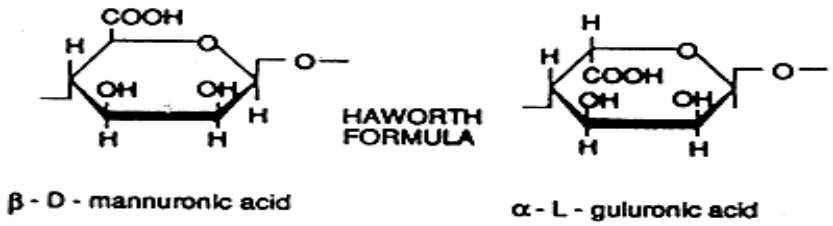
Source of Alginate

Alginates are produced by brown seaweeds (*Phaeophyceae*, mainly *Laminaria*). Commercial varieties of alginate are extracted from seaweed, including the giant Kelp *Macrocystis pyrifera*, *Ascophyllum nodosum*, and various types of *Laminaria* like *Laminaria hyperborean.*

Structure of Alginate

Alginate polymers are a family of linear unbranched polysaccharides which contain varying amounts 1, 4 – linked β – D – Mannuronic acid (M – residue) and 1, and 4- linked α – L – guluronic acid residues (G – residue). These monomers are connected in blocks of M homopolymers (M-M-M), G homopolymers (G-G-G) and MG heteropolymers, which can be alternated (M-G-M-G) or not.[2]

Structural units of alginate are seen in Figure 1.



Molecular Structure

Alginates are not random copolymers but, according to the source *algae*, consist of blocks of similar and strictly alternating residues (that is, MMMMMM, GGGGGG and GMGMGMGM), each of which have different conformational preferences and behavior. As examples, the **M**/**G** ratio of alginate from *Macrocystis pyrifera* is about 1.6 whereas that from *Laminaria hyperborea* is about 0.45. Alginates may be prepared with a wide range of average molecular weights (50 - 100000 residues) to suit the application. Molecular structure of alginate is seen in Figure 2.

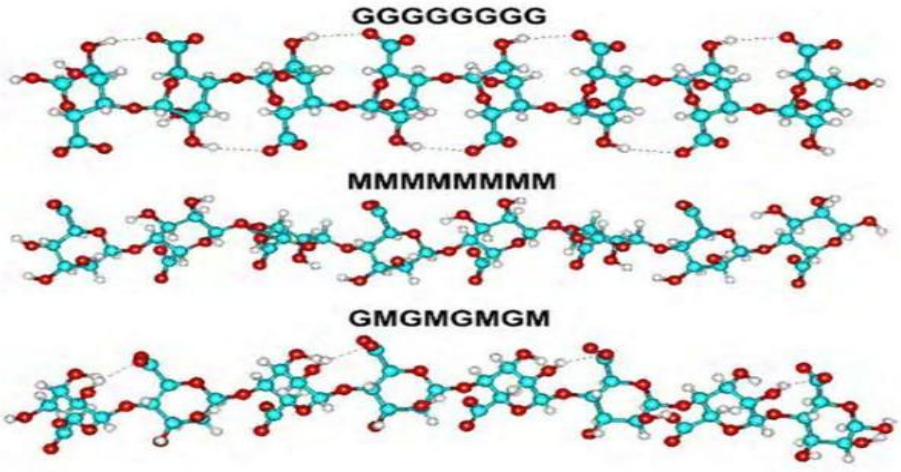


Figure 2: Molecular structure of alginate.

Properties of Alginates

Solubility

Sodium alginates are slowly soluble in cold water, forming viscous, colloidal solution. It is insoluble in alcohol and hydro alcoholic solutions in which alcohol content is greater than 30% by weight. It is also insoluble in other organic solvents e.g. Chloroform and ether, and in acids where the PH of the resulting solution falls below 3.0. A 1% solution in distilled water has a PH of approximately7.2. Calcium alginate, is however, practically insoluble in water and organic solvents but soluble in sodium citrate.[3]

Iscosity

Various grades of sodium alginates are available, yielding aqueous solutions of varying viscosity within a range of 20-400 centipoises (0.02-0.4 PaS) in 1% solution at 200C. Due to distribution of chain lengths, alginate solutions are not clearly Newtonian and behave as pseudo plastic fluid. When dissolved in pure water, their reduced viscosity is expected to increase very rapidly with dilution as observed by Focus and Straues. In the presence of supporting electrolyte rheological behavior of polyelectrolyte solution is known to depend on the ionic structure of the aqueous solvent, e.g. increasing the concentration of a strong electrolyte such as NaCl in the alginate solution up to 100mM was shown to reduce the solution viscosity due to the change in polymer conformation.[4]

Chemical stability and degradation

Degradation of a Ca_2^+ crosslinked alginate gel can occur by removal of the Ca_2^+ ions. This can be accomplished by the use of a chelating agent such as ethylene glycol-bis (b-amino ethyl ether)-*N, N, N', N'*- tetra acetic acid (EGTA), lactate, citrate and phosphate or by a high concentration of ions such as Na^+ or Mg_2^+. As Ca 2+ ions are removed, the cross-linking in the gel decreases and the gels are destabilized. This can lead to leakage of entrapped material and solubilization of the high molecular weight alginate polymers. Alginate gels will also degrade and precipitate in a 0.1 M phosphate buffer solution and will completely dissolve in 0.1 M sodium citrate at pH 7.8. If Ca_2^+ is used in the cross-linking solution and phosphate is used as the dissolution medium, the dissolution medium will turn turbid due to the Ca dissociating from the polymer network and forming calcium phosphate precipitate. This phenomenon is more evident when a high guluronic content alginate is used. Low a-L- guluronic acid content

alginate and lower molecular weight alginate are known to release encapsulated proteins at a much faster rate. Degradation of the gel can be prevented by storing the gel beads in a medium that contains free Ca_2^+ ions and to keep the Na^+:Ca_2^+ ratio less than 25:1 for high a-L-guluronic acid alginates and 3:1 for low a-L-guluronic acid alginates.[5]

Table 1: Pharmacopoeial standards of Sodium alginate.

Test	National Formulary/ & United States Pharmacopoeia	British Pharmacopoeia British Pharmaceutical Codex	Indian Pharmacopoeia
Microbial limits	Total bacterial count <200/g *Salmonella* species and *E. coli* absent	Total viable aerobic count <103/g complies with *E. coli* and *Salmonella*	1.0g free from *E. coli*, 10.g test free from *Salmonellae*
Loss on drying	≤15% by weight	≤15% by weight	≤15% by weight
Ash	18.0–24.0%	-	-
Lead	≤0.001%	≤10 ppm	-
Arsenic	≤1.5 ppm	≤3 ppm	-
Heavy metals	≤0.004%	≤20 ppm	≤40.0 ppm
Chloride	-	≤1.0 %	≤1.0 %

Methods of Preparation of Alginate beads[6,7]

1. Air atomization

Requires an extrusion device with a small orifice through which alginate solutions containing drug are forced. Beads of 5- to 200-µm particles can be produced. The size of beads can be controlled by either adjusting gas and liquid flow or operating pressure or distance between the orifice and the surface of the cross linking solution.

2. Coaxial bead generator

Coaxial air stream pulls droplets from a needle tip into gelling bath can produce spherical beads ranging in size down to around 400 µm.

3. Dropping method

It is a Simple method Involves use of syringe with a needle or pipette. It is a most extensively utilized method for preparing the >500 µm particles. The size of beads formed is dependent on the size of needle used and viscosity of the alginate solution.

4. Electrostatic bead generator

Electrostatic force pulls droplets from needle tip into gelling bath. By this method150- to 1000-µm particles can be produced. Bead size depends on the voltage and distance between the needle tip and the gelling bath, solution viscosity, flow rate of the solution as well as on needle diameter.

5. Emulsification

Used only for stable drugs because it involves use of harsh chemical reagents to remove oil at the end of the process. Particles of size range 1- to 150-µm can be produced by this method. Size of micro beads produced depends on stirring speed and the rate of the addition of the cross-linking solution.

6. Laminar jet

A device based on laminar jet breaks up induced by applying a sinusoidal frequency break up technique with defined amplitude to the nozzle. Normally 300-to 600 mm particles can be produced.

7. Mechanical cutting

Bead formation is achieved by means of a rotating cutting tool which cuts jet into uniform cylindrical segments, which form spherical beads due to surface tension while falling down into a gelling bath. 150-µm to 3-mm particles can be produced.

8. Spinning disk atomization

Bead formation is achieved by specially designed spinning disk atomizer. It is suitable for 300- to 600-µm size particles.

9. Vibrating nozzle technique

The encapsulation technique is based on a harmonically vibrating nozzle. By this method >200-µm particles can be produced.

10. Complex coacervation

Under specific conditions of polyion concentration, pH and ionic strength, the polyelectrolyte mixture can separate into two distinct phases; a dense coacervate phase which contains the microbeads and a dilute equilibrium phase. Oppositely charged complex poly-electrolytes have been commonly used. Optimum condition for maximum coacervate yield is pH of 3.9, an ionic strength of 1 mM and a 0.15% w/v total polyion concentration.

Useful properties of alginate as matrix for controlled drug delivery

Alginates have been widely used as tablet disintegrant, binding agent, viscosity modifying agent, as a stabilizer in disperse system in the production of suspension and emulsion and also as thickening agent in pharmaceutical industries. The most important advantage of using alginate as a matrix for Controlled release (CR) formulations is its biodegradability, because it is degraded and is absorbed by the body during and/or after

drug release without any toxic effects. This allows bypass of surgical removal of the device. Hence, it can be a suitable matrix for sustained release of various drugs.[8]

The following properties of alginates have enabled it to be used as a most acceptable matrix for controlled drug delivery.

A. It is readily available and is relatively inexpensive.
B. It contains ingredients that are accepted food additives.
C. It is non-toxic when taken orally and also has a protective effect on mucous membranes of upper gastrointestinal tract.
D. It is haemo-compatible and does not accumulate in any organ of the human body.
E. It is biodegradable so there is no need for surgical removal after the drug is exhausted.
F. It can form hydro gels under mild conditions.
G. It is water soluble so it eliminates use of noxious solvents during processing and hence stability, toxicological, and environmental problems associated with solvents can be minimized.
H. It forms gel at room temperature and hence reduces chances of destroying activity of sensitive drugs at elevated temperatures.
I. Soluble sodium alginate cross-linked with a variety of cross-linking agents, forms insoluble gel, which is used to delay release of some drugs.
J. Flow properties of drugs with needlelike crystals (e.g., Sulfadiazine) can be improved by incorporating in alginate beads. This method of agglomeration also avoids polymorphic transformations as agglomerates are formed from drug dispersions.
K. Beads formed are mechanically strong so they could be coated with enteric polymers to prepare enteric drug delivery systems.
L. Adopted by European Pharmacopoeia.

Evaluation of Placebo Microbeads

Percentage Practical Yield

The yield of microbeads was determined by comparing the whole weight of microbeads formed against the combined weight of the copolymer and drug.

$$\% \text{ Practical yield} = \frac{\text{Mass of microbeads obtained}}{\text{Total weight of drug and polymer used}} \times 100$$

Particle Size Analysis

The sample of prepared microbeads was randomly selected and their size was determined using an optical microscope with the help of eye piece and stage micro meter. In all measurements at least 50 beads in five different fields were examined. Each experiment was carried out in triplicate.

Swelling Index Study

The extent of swelling was measured in terms of % weight gain by the beads. The swelling behaviors of all the Formulations were studied. In this test 20 mg of beads from each formulation was kept in Petridis containing distilled water. At the end of 1 hour, the beads were withdrawn, soaked with tissue paper, and weighed. Then for Every 1 hour, weights of beads were noted and the process was continued till the end of 8 hours. The % weight

Gain by the beads was calculated by the following formula:

Swelling Index (SI) = [{Wt – W0}/ W0)] x 100

Where, Wt= Mass of swollen beads at time t
W0= Mass of dry beads at t=0

Percentage Drug Entrapment Efficacy (%DEE)

Accurately weighed microbeads equivalent to 100mg were suspended in 100ml of simulated intestinal fluid of pH 7.4±0.1 and kept for 24hrs. Next day it was stirred for 5min and filtered. After suitable dissolution, the drug content in the filtrate was analyzed spectrophotometrically at 241 nm using Shimadzu UV spectrophotometer.

Finally, drug encapsulation efficiency is calculated by-

$$\text{Percentage Drug Entrapment Efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Loose Surface Crystal Study (LSC)

This study was conducted to estimate the amount of drug present on the surface of the microbeads which showed immediate release in dissolution media. 100mg of microbeads were suspended in 100ml of phosphate buffer (pH 7.4), simulating the dissolution media. The samples were shaken vigorously for 15min in a mechanical shaker. The amount of drug leached out from the surface was analyzed spectrophotometrically at 241 nm. Percentage of drug released with respect to entrapped drug in the sample was recorded.[9]

Fourier Transform Infrared Spectroscopy

FTIR spectral measurement was performed using Shimadzu FTIR spectrophotometer to confirm the presence of any interaction between the polymer and drug. The polymer and the drug were finely ground with KBr to prepare the pellets under a hydraulic pressure of

600psi and spectra were scanned between 400 and 4000cm-1.

Scanning Electron Microscopy

The surface morphology of drug-loaded beads obtained from various percentages of polymer, CaCl2 and drug were studied by using a scanning electron microscope (model JEOL JSM-6360, Japan). The beads were mounted on an appropriate stub and then coated with carbon and gold (100 and 50 Å thickness respectively) sputter module in a vacuum evaporator in an argon atmosphere. The coated samples were then observed under a scanning electron microscope operated at 15 KV.

In- vitro Dissolution Study

Dissolution studies of microbeads was performed according to USP XXII type I dissolution apparatus in pH 1.2 for first 2 h and rest of the release study was performed in phosphate buffer of pH 7.4. The temperature was maintained at 37±0.5°C and the rotation speed was 100 rpm. The 5 ml of sample was withdrawn at various time intervals and replenished with an equal volume of fresh dissolution media. The drug content in the sample was analyzed spectrophotometrically at 241nm.

Mucoadhesive Test

The mucoadhesive property of microbeads was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised pieces of chicken intestinal mucosa were mounted on to glass slides with cotton thread. About 20 microbeads were spread on to each prepared glass slide and immediately thereafter the slides were hung to USP II tablet disintegration test. When the test apparatus was operated, the sample is subjected to slow up and down movement in the test fluid at 37 0C contained in a 1-litre vessel of the apparatus. At an interval of 30min up to 8 hours the machine is stopped and number of beads still adhering to mucosal surface was counted. The test was performed at intestinal (phosphate buffer pH 7.4) condition.

CONCLUSION

In conclusion, the sodium alginate as biopolymer has wide range of applications in the food and pharmaceutical industry. It has versatile pharmaceutical utility starting from thickening agent to polymeric backbone in sustained release dosage forms. Being biopolymer of high biological tolerability, it has a special role to play in the formulations of proteins or peptides and other biological products. Its capability of fabrication in all aqueous systems, cross-linking with variety of agents, miscibility with other polymers of biological or synthetic origin offers the most widely applicable polymeric systems avoiding harsh conditions.

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