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IONOTROPIC GELATION AND POLYELECTROLYTE COMPLEXATION: THE NOVEL TECHNIQUES TO DESIGN HYDROGEL PARTICULATE SUSTAINED, MODULATED DRUG DELIVERY SYSTEM: A REVIEW

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The utilization of natural and chemically modified polysaccharides as a part of drug development has increased in the past two decades. Great attention has also been focused on biopolymer based hydrogels for use as potential carriers in controlled drug delivery. Hydrogels are three dimensional, hydrophilic networks capable of imbibing large amount of water or biological fluids, mimics biological tissues. Because of this nature, great attention was devoted to these systems for biomedical applications. Indeed, these networks can be made suitable as the modulated drug delivery devices by tuning the physicochemical properties of the hydrogels with varying the degree of crosslinking either by physical or chemical or physical-chemical means. Numerous approaches have been investigated for formulation of controlled release dosage forms of different therapeutic agents including proteins, peptides, and even cells. In this present review, an attempt was made to narrate the different natural polyanions and their mechanism to form cross-linked hydrogel beads. This review was also focused on various methods of preparation of beads. Here, it was also tried to explain the importance of ionotropic gelation and polyelectrolyte complexation approaches, as these methods show great promise as a tool for the development of encapsulation process. Each method has its own advantages as well as limitations. For further improvement in this area, it is important to understand the strength and drawbacks of each method. Hence, an attempt was also made to discuss the same.

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1. Introduction

The interest of using natural and chemically modified polysaccharides as a part of drug development has increased in the past two decades. Great attention has also been focused on biopolymer based hydrogels for use as potential carriers in controlled drug delivery [1, 2]. Hydrogels are three dimensional, hydrophilic networks capable of imbibing large amount of water or biological fluids, mimics biological tissues [3]. Because of this nature, great attention was devoted to these systems for biomedical applications. Indeed, these networks can be made suitable as the modulated drug delivery devices by tuning the physicochemical properties of the hydrogels with varying the degree of crosslinking either by physical or chemical or physical-chemical means. Numerous approaches have been investigated for formulation of controlled release dosage forms of different therapeutic agents including proteins, peptides, and even cells. Microencapsulation has become a common technique in the production of controlled release dosage forms [4]. The polymeric gel beads are prepared by using number of natural, biodegradable polymers. The beads are discrete spherical microcapsules that serve as the solid substrate on which the drug is coated or

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encapsuled in the core of the beads [5]. Beads can provide sustained release properties and a more uniform distribution of drugs, include within the gastrointestinal tract [6-8]. Further more bioavailability of drugs formulated in beads can be enhanced. The encapsulation techniques although have become popular, are based on organic solvents. Possible toxicity in chronic dosing due to presence of even traces of organic solvents in the dosage forms, the flammability, the environmental pollution associated with stringent governmental regulations that restricts their use have put into question its long term viability [9]. Consequently, much research efforts have been concentrated on the development of hydrogel beads using natural polymers as they are derived from natural sources, do not require organic solvents, easily available and qualified for a number of chemical modifications [10]. Drug-loaded hydrogel beads offer an inert environment within the matrix and encapsulation is usually achieved in a media free of organic solvents.

In this present review, an attempt was made to discuss the different natural polymers and their mechanism to form cross-linked hrdoygel beads with suitable cations and various methods of preparation of beads. Here, it was also tried to explain the importance of ionotropic gelation and polyelectrolyte complexation approaches, as these methods show great promise as a tool for the development of encapsulation process. Each method has its own advantages as well as limitations. For further improvement in microencapsulation techniques, it is important to understand the strength and drawbacks of each method. Hence, an attempt was also made to discuss the advantages and disadvantages of various techniques.

2. Ionotropic gelation technique

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogels. Since, the use of alginates, gellan gum, chitosan, and carboxymethyl cellulose for the encapsulation of drug and even cells, ionotropic gelation technique has been widely used for this purpose [11]. The natural polyelectrolytes inspite, having a property of coating on the drug core and acts as release rate retardants contains certain anions on their chemical structure. These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The cations diffuses into the drug-loaded polymeric drops, forming a three dimensional lattice of ionically crossed linked moiety. Biomolecules can also be loaded into these hydrogel beads under mild conditions to retain their three dimensional structure.

3. Polyelectrolyte complexation technique

The quality of hydrogel beads prepared by ionotropic gelation method can also be further improved by polyelectrolyte complexation technique. The mechanical strength and permeability barrier of hydrogels can be improved by the addition of oppositely charged another polyelectrolyte to the ionotropically gelated hydrogel beads. For instance, addition of polycations allows a membrane of polyelectrolyte complex to form on the surface of alginate beads [12, 13]. Large numbers of natural and chemically modified polyelectrolytes have been investigated and a schematic diagram of the preparation of hydrogel beads through ionotropic gelation and polyelectrolyte complexation is shown in below fig.1

Polyelectrolyte solution [alginate (-)/Gellun gum (-)/CMC (-) + Drug]
↓5% HPMC phthalate as a coating material
Added dropwise under magnetic stirring by 21 G needle
↓
Calcium chloride solution (+)
Chitosan solution (+)
↓
Hydrogel beads

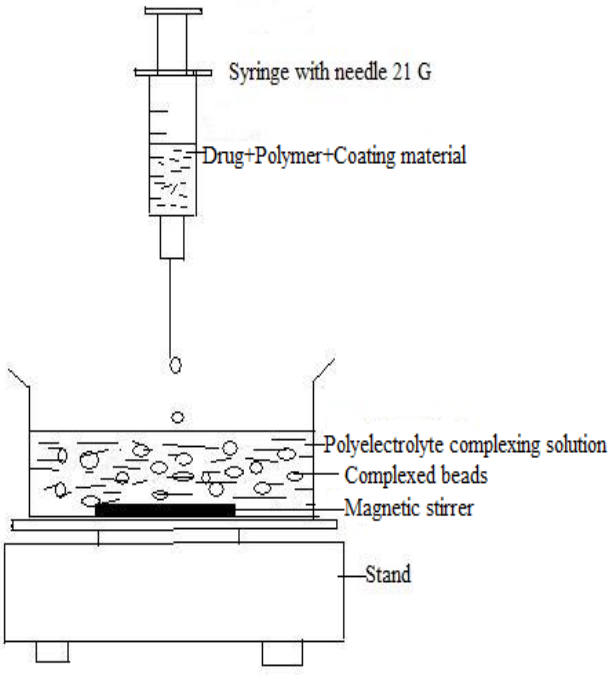

Fig. 1. Schematic diagram of the preparation of hydrogel beads by ionotropic gelation and polyelectrolyte complexation.

4. Polyelectrolyte biopolymers employed in hrdrogel preparation

Few important polyelectrolyte polymers are utilized in the preparation of hydrogel matrix beads. A few among these polyelectrolytes are discussed here.

4.1. Alginates

Alginate is a non-toxic, biodegradable, naturally occurring polysaccharide obtained from marine brown algae, certain species of bacteria. Sodium alginate is a sodium salt of alginic acid a natural polysaccharide and a linear polymer composed of 1,4-linked β-D-Mannuronic acid (M) and α-D-gluronic acid (G) residues in varying proportions and arrangements. The homopolymer regions composed of M-blocks and G-blocks are interspersed with M G heteropolymeric regions known as “egg box junction” [14].

Sodium alginate is soluble in water and form a reticulated structure which can be cross-linked with divalent or polyvalent cations to form insoluble meshwork. Calcium and zinc

cations have been reported for cross-linking of acid groups of alginate. Alginate appeared to be highly promising owing to its non-toxic, biodegradable and biocompatible nature and has been investigated in details. Its unique property of forming water insoluble calcium alginate gel through ionotropic gelation with calcium ions is a simple, mild and eco-friendly condition has made possible to encapsulate macromolecular bio-active agents like cell, enzyme, protein and vaccine [15-18]. Recently, much research efforts have been concentrated to develop calcium alginate beads loaded with various low molecular weight therapeutic agents. In various studies, alginate beads have been used as excellent vehicles. Rabbit articular chondrocytes immobilized in alginate beads maintained normal morphology and metabolic activity for more than two weeks using calcium, barium, and strontium as gel forming agents [19]. Another important property of alginate beads is their re-swelling ability. This property is sensitive to the environment pH. Hence, acid-sensitive drugs incorporated within the beads can be protected from the gastric juice.

4.2. Gellan Gum

Gellan gum is a bacterial exopolysaccharide prepared commercially by aerobic submerged fermentation of Sphingomones Eloda, in a manner similar to xanthan gum [20]. Deacetylated gellan gum is an anionic microbial polysaccharide, secreted from S. Eloda, consisting of repeating tetrasachharide units of glucose, glucuronic acid, and rhamnose residues in a 2:1:1 ratio: [→3)-β-D-glucose-(1→4)-β-D-glucoronic acid-(1→4)-β-D-glucose-(1→4)-α-L-rhamnose-(1→]. In the native polymer, 2-acyl substituents, L-glyceryl at 0(2) and acetyl at 0(6), are present in the 3'linked glucose. On average, there is one glyceryl per repeating unit and one acetyl for every two repeating units. Deacetylated gellan gum is obtained by alkali treatment of the native polysaccharide [21]. Both native and deacetylated gellun gum are capable of physical gelation [22]. A concentrated water solution of gellan gum is made warm up preliminary to induce the gellan gelation. When the temperature is decreased, the chains undergo a conformational transition from random coils to double helicles (coil-helix transition). Then rearrangement of a double helicles occurs leading to the formation of ordered junction zones (sol-gel transition) [23]. Thus, giving a thermo-reversible hydrogel [24]. Much stronger physical thermo-reversible hydrogels are also obtained by the addition of mono and divalent cations to gel solutions [25, 26].

The physical gelation ability of this polysaccharide makes it suitable as structuring and gelling agent in foods and toothpastes, binder, as a sustained release matrix [27, 28]. The gellan gum is also utilized in the fields of modified release of bioactive molecules. Aqueous solutions of gellan are used as in-situ gelling systems, mainly for ophthalmic preparations [29], and for oral drug delivery [30]. Physical gellan hydrogels, prepared with mono or divalent cations, are used also for the preparation of tablets, beads [31] or microspheres. Interpenetrating polymer networks or co-cross linked polymer networks based on gellan and other polysaccharide systems have also been developed as drug delivery matrices [32-39].

4.3. Chitosan

Chitosan is a biopolymer which could be used for the preparation of various polyelectrolyte complex products with natural polyanions such as xanthan, alginate, and carrangeenan [40-44]. Chitosan-polyanions complexes have been widely investigated for the applications like drug and protein delivery, cell transplantation, enzyme immobilization [45-47]. Among these, complexes, chitosan-alginate complex may be the most important drug delivery hydrogel system [48, 49]

The strong electrostatic interaction of amine groups of chitosan with the carboxyl groups of alginate lead to the formation of Chitosan-alginate complex. The chitosan-alginate gel beads with a chitosan core and a chitosan-alginate skin are prepared by dropping a solution of alginate into chitosan solution. Due to the protonation of amino group on chitosan and the ionization of carboxylic acid group on alginate, the stability of chitosan influenced by the environmental parameters such as pH and ionic strength. It was found that the macromolecular chitosan rapidly

bind onto the surface of alginate droplet, but ere limited to diffuse into the inner core [50]. In order to increase the stability of chitosan-alginate complex, chitosan solution, consisting of calcium chloride was used for the gelation of alginate [51]. The presence of calcium ions in the chitosan solution during the incubation had a great effect on the ability of a gel bead to bind chitosan. As the concentration of calcium chloride increases, the rate and extent of chitosan binding process also proportionally increases.

4.4. Carboxymethyl Cellulose

The chemical modification of polysaccharides is the most important route to modify the properties of the naturally occurring biopolymers and to use this renewable resource in the context of sustainable development. The cellulose, a plant product on carboxymethylation process, can be modified as carboxymethylcellulose (CMC). CMC is a chemically modified biopolymer was first prepared in 1918 and was produced commercially [52] in the early 1920's. Today CMC of different quality is applied in many areas of industry and human life.

The interactions of the carboxylic groups of the CMC with multivalent metal ions can be used to form so called ionotropic gels, which are predominantly stabilized by the electrostatic interactions. In addition, interactions between the –OH groups of the polymer and the metal ions contribute to the stability and the water insolubility of these polymeric aggregates. The CMC can be cross-linked with ferric/aluminum salt to get biodegradable hydrogel beads. Controlled release pattern can also be improved by coating these hydrogels with chitosan/gelation and by cross-linking.

5. Basic techniques of hydrogel praparation

Generally, the hydrogel beads are prepared in two ways depends on the intended particle size as follows.

5.1. Syringe dropping /extruding method

The hydrogel beads can be produced widely by dropping a aqueous solution of polyanion solution into a solution of cation usually calcium chloride. Although this is a simple and fast way of obtaining particulate drug carriers, the method presents a major limitation consisting of drug loss during bead preparation [53-55].

In addition, the matrix formed in usually very permeable and little or no drug release can actually be controlled in the core of soluble drugs [56, 57]. Hence, a preferential use for these hydrogel beads in the delivery of low solubility or micromolecular drugs has been suggested [58-60]. This problem can also be solved by mixing with other polyelectrolytes such as alginate-pectin, alginate-chitosan, alginate-ethyl cellulose, and alginate-Eudragit [61, 62]. However, the technique utilized in this study either may cause a high degree of particle aggregation or involve the use of methanol as a solvent [63-66]. Since, most of the droplets have been made with syringe needles; the particle sizes have been relatively large.

5.2. Air atomization method

Alternatively the beads can also be prepared by vibration system or air atomization method. Relatively smaller droplets can be formed using a vibration system or air atomization method to extrude the polyanion solution. The later involves a Turbotak air-atomizer. Pressurized air is fed to mix with the polyanion solution, forcing tiny liquid droplets out through the orifice of the nozzle. The cations cross-link the droplets of polyanions on contact to form microgel droplets,

which were further cross-linked by polyelectrolytes such as poly-L-lysine to form a membrane on the droplets. Microparticles obtained using this method were within the size range 5-15 μm [67]. This method requires special extrusion device or atomization device that can have the disadvantage of the high cost and possible clogging [68].

6. Conclusions

The use of naturally occurring polysaccharides functioning as biopolymers has been increased in the area of novel sustained release hydrogel formulations. These biopolymers are having a unique nature of forming hydrogel beads when they are cross linked with suitable polyvalent cationic cross linking agents. As these polyanions are capable to encapsulate large number of micro and macro therapeutic molecules in their hydrogel meshwork structure gained more importance in the development of biocompatible novel sustained and targeted drug delivery products. The techniques of ionotropic gelation and polyelectrolyte complexation are the exiting tools for a pharmaceutical scientist involved in the development of novel drug delivery system. By rightful utilization of these techniques the drug release rate can also be modulated by varying the exposure time and concentration of cross linking agents. Due to the new achievements of polymer chemistry and the development of intelligent, strategic encapsulation techniques the successful utilization of these biopolymers is increasing day by day. The explosive growth of biotechnology and genetic engineering has made easy to face the challenge of delivering most sensitive macromolecules such as proteins and peptides. These macromolecules can be successfully encapsulated into hydrogel meshwork, ensuring the constant release rate of these drugs over desired period by retaining their structural integrity. The utilization of expensive and toxic organic solvents in the microencapsulation process has been drastically reduced due to evolution of ionotropic gelation and polyelectrolyte complexation techniques. This also provided an eco friendly pharmaceutical product development process in the preparation of hydrogel beads. Expecting more number of protein drugs emerging from the genome projects, new hydrogel bead encapsulation methods that minimize utilization of toxic organic solvents and denaturing of such macromolecules will be invaluable tools in the future.

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