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POLYELECTROLYTE COMPLEXATION AND IONOTROPIC GELLATION: THE POTENTIAL NOVEL APPROACH TO DESIGN HYDROGEL PARTICULATE FOR SUSTAINED, MODULATED DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT: The interest in using natural and chemically modified polysaccharides as a part of drug development has increased in the past two decades. For potential carriers in controlled, modulated drug delivery, great interest has also been focused on biopolymer-based hydrogels. Due to their advantages like biocompatibility, biodegradability, and low cost, biopolymers have been widely used in the development of hydrogels. Indeed, by tuning the physicochemical properties of the hydrogels with varying the degree of crosslinking either by chemical or physical or physical-chemical means these networks can be made suitable as the modulated drug delivery devices. In this present review, a focus is made on various natural polymers and their mechanism to form cross-linked hydrogel beads with suitable cations and various methods of preparation of beads. Here, it was also tried to explain the significance of polyelectrolyte complexation and ionotropic gelation approaches, as these methods show great pledge as a tool for the development of the encapsulation process and also plays an important role in controlled and modulated drug delivery system.

INTRODUCTION: In the past few years, the advances in the ground of biomaterials has led to numerous studies on alternative biocompatible materials and the development of these materials focusing on properties, benefits, limitations, and the use of substitute resources (such as polysaccharides and proteins) for its preparations. Among the most studied biomaterials, hydrogels (HGs) have been standing out owing to their advantages, like biocompatibility, biodegradability, mechanical properties, and responsiveness.

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HGs are soft materials composed of three-dimensional networks of hydrophilic polymers, which can swell either in water or in biological fluids [1, 2, 3]. Because of this behavior, great attention was devoted to these systems for biomedical applications. Indeed, by tuning the physicochemical properties of the hydrogels with varying the degree of crosslinking either by chemical or physical or physical-chemical means these networks can be made suitable as the modulated drug delivery devices.

Several methods have been investigated for the formulation of controlled release dosage forms of different therapeutic agents, including proteins, peptides, and even cells [4]. The polymeric gel beads are formed by using various natural, chemically modified, and biodegradable polymers. The beads are distinct spherical microcapsules that serve as

the solid substrate on which the drug is coated or encapsulated in the core of the beads [5]. Microbeads are small, solid and free-flowing particulate carriers containing dispersed drug particles either crystalline or in solution form that allows a sustained release or multiple release profiles for treatment with various active agents without major side effects [6].

As compared to monolithic formulations microbeads provide better control of the release of the active ingredients. Through the oral route, for example, the passage time through the intestinal tract and the presence of food should not affect the release of active ingredient from microbeads. The release the active ingredient/s from microbeads occurs through a double mechanism: diffusion and biodegradation of the polymer. Microbeads can be administered orally, parenterally, or topically as an alternative to the usual injectable formulations, thereby convalescing patient compliance due to a decrease in the frequency of administration.

The cross-linked microbeads can be administered as long-lasting medications due to its biodegradability and biocompatibility. The use of coating material which can dissolve either in different areas of the gastrointestinal tract (depending on pH and the enzymes present) or after a preset time (depending on the thickness) allows coated microbeads to be used both in a space-and-time focused way [7]. Beads can be formed in millimeter; micrometer size ranges [8].

Beads can give sustained release properties and uniform distribution of drugs, including within the gastrointestinal tract. Hence, the bioavailability of drugs incorporated in beads can be enhanced [9]. Possible toxicity in chronic dosing due to the presence of even traces of organic solvents in the dosage forms, the flammability, the environmental pollution associated with stringent governmental regulations that restrict their use have put into question its long term viability [10]. Subsequently, much research efforts have been strenuous on the development of hydrogel beads using natural polymers as they are derived from natural sources; do not require organic solvents, easily available and competent for some chemical modification. Drug-loaded hydrogel beads provide an inert environment within the matrix, and encapsulation is usually achieved in a media free of organic solvent [11].

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

Polyelectrolytes: The polymers having a net negative or positive charge at near-neutral pH are called polyelectrolyte. Polyelectrolyte complexes are the result of interaction between the two oppositely charged polymer **Fig. 1**.

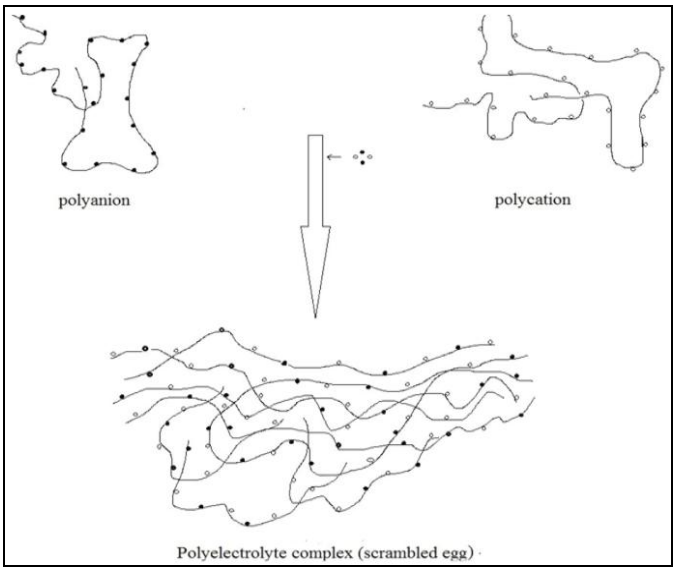

FIG. 1: SCHEMATIC REPRESENTATION OF PEC FORMATION

Polyelectrolyte complexes (PECs) are the association complexes formed between oppositely charged particles (*e.g*., polymer-polymer, polymer-drug, and polymer-drug-polymer). Electrostatic interaction between oppositely charged polyions is responsible for the formation of polyelectrolyte complexes [12]. The probable toxicity and other unwanted effects of the reagents can be minimized because this avoids the use of chemical cross-linking agents.

The stoichiometry of complex formation is the most important characteristic of polymeric complexes formed by charge-charge interaction. This aspect plays a very important role in the molecular design and the morphological structure of the ultimate polyelectrolyte complex [13].

Polyelectrolyte Classification: [14] The poly-electrolytes are classified into various types. By origin, they are classified as natural polyelectrolytes, synthetic polyelectrolytes, and chemically modified biopolymers, and by electrochemistry, they are classified as polyacids/ polyanions, polybases/polycations, and poly-ampholytes. Few important polyelectrolytes are exemplified in **Table 1**.

TABLE 1: TYPES OF POLYELECTROLYTE

Name	Category (based on the charge)
Natural	**Polyelectrolytes**
Nucleic acids	Polyanion
Poly (L-lysine)	Polyanion
Poly (L-glutamic acid)	Polyanion
Carrageenan	Polyanion
Alginates	Polyanion
Hyaluronic acid	Polyanion
Chemically modified biopolymers	
Pectin	Polyanion
Chitosan (deacetylation of chitin)	Polyanion
Cellulose-based	Polyanion
Starch-based	Polyanion or Polycation
Dextran-based	Polyanion or Polycation
Synthetic polyelectrolytes	
Poly (vinylbenzyl trialkyl ammonium)	Polycation
Poly (4-vinyl-N-alkyl-pyridimiun)	Polycation
Poly (acryloyl-oxyalkyl-trialkyl ammonium)	Polycation
Poly (acryamidoalkyl-trialkyl ammonium)	Polycation
Poly (styrene sulfonic acid)	Polyanion
Poly (acrylic or methacrylic acid)	Polyanion
Maleic acid/diallyl amine copolymer	Polyampholytes

Types of Polyelectrolyte Complex: The types of polyelectrolyte complex are given below-

Polyelectrolyte Complex Between Natural Polymers: Chitosan now days used for the preparation of various polyelectrolyte complex products with natural polyanions as carboxymethyl cellulose, carboxymethyl dextran, alginic acid, dextran sulfate, carrageenan, xanthan, and pectin. Macromolecular interactions between negatively and positively charged polymers have been reported to enhance functional properties, including foaming and aggregation phenomena or gelation. The interaction and amount of precipitation varied depending on the concentration of each polymer in the mixture, the ionic strength and pH of the solution[15].

Polyelectrolyte Complex between a Natural and Synthetic Polymer: Polymeric complexes of protein with synthetic polyelectrolyte formation is of concern to stimulate the intermolecular interactions during the formation of the biological system and represented by phase separation as complex coacervates. This is observed by the potassium poly (vinyl alcohol sulfate) and carboxyhemoglobin in the presence of poly (dimethyl diallyl ammonium chloride), lysozymes and poly (acrylic acid), lysozymes and poly (methacrylic acid), RNA polymerases and poly (ethyleneimine), poly (dimethyl diallyl ammonium chloride) and bovine serum albumin [15].

Polyelectrolyte Complex between Synthetic Polymers: Polyelectrolyte complex formation between synthetic polymers was done by using conductometric, potentiometric, or turbidimetric titration. The preparation of three types of PECs formed between poly (vinyl benzyl trimethyl-ammonium chloride) and poly (methacrylic acid) have been reported. The stoichiometry of the reactions between polyanions and polycations has been investigated. It was found that they reacted almost stoichiometrically to give a polyelectrolyte complex [15].

Protein - Polyelectrolyte Complexation: Proteins forms complex with both synthetic and natural polyelectrolyte. These interactions may give an amorphous precipitate, complex coacervates, gels, fibers, or the development of the soluble complex. The practical approach of polyelectrolyte complexation of the protein includes:

- Immobilization or stabilization of enzyme;
- Protein separation, protein recovery;
- Modification of protein-substrate affinity and
- Electrostatic interaction between protein and nucleic acids [15].

Polyelectrolyte complex between polymers and oppositely charged drugs: Mainly the complexes are formed by ionic drugs with a polyelectrolyte, and the bound drug is released or free in exchange of ions present in the dissolution medium. Various factors such as pH, the viscosity of the polymer solution, ionic nature of dispersing the drug, and ionic strength of the dissolution medium affect the drug-polymer interaction [16, 17].

Formation of PECs: [18] This process involves mainly 3 steps, as shown in **Fig. 2**.

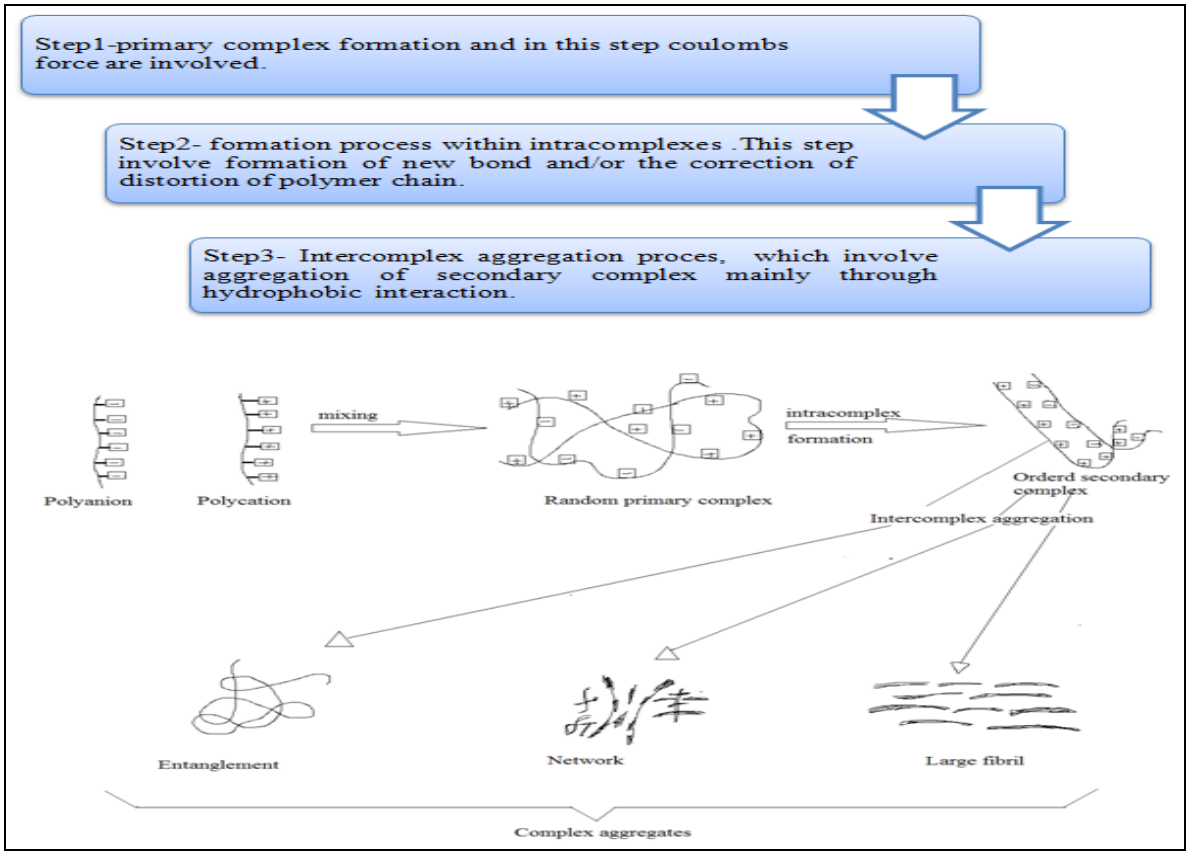

FIG. 2: SCHEMATIC REPRESENTATION OF FORMATION AND AGGREGATION OF PEC

Factors Influencing Formation of PECs: Various parameters are known which affect the formation of PECs. These are ion site, charge density, pH, ionic strength, polyelectrolyte concentration, solvents, and temperature. Several researchers evaluated the factors affecting the formation of polyelectrolyte complexes with different polymeric blends. Due to charge fluctuations and by short-range attractions between monomers precipitation may occur. Interesting in the context of the polyion stoichiometry are studies of layer formation from strongly asymmetric pairs of polyions. Employing polyions with a reduced charge density along the chain, *i.e.*, consisting of charged and uncharged co-monomers, it was observed that a minimum charge density is required for polyelectrolyte adsorption. By the addition of salt, the ionic strength will be the change which alters the electrostatic interactions in a polyelectrolyte solution.

The electrostatic interactions can be smashed by the addition of inorganic salts into the solutions. Thus, on increasing the ionic strength of the solution, the complexation between polyions depresses, because of the screening of opposite charges of the macromolecules by low molecular weight ions.

Changes in the pH environment during PEC formation control the degree of ionization of weak polyelectrolytes. As a result may affect multilayer properties such as layer thickness, the degree of interpenetration between layers, surface wettability, and several unbound functional groups. Therefore, by applying the appropriate pH conditions, a platform may be obtained with properties that are favorable for loading charged small molecules into the film *via* electrostatic interactions [19, 20, 21, 22].

Technologies Used for the Preparation of PEC Beads: Generally there are two ways for preparation of PEC beads preparation are as follows:

A) Syringe Dropping or Extruding Method: According to this method, beads can be prepared by dropping a polyanion solution into a solution of the cation **Fig. 3**. Although this is a simple, fast, and economical method for preparing particulate drug carriers, this method involves in a major limitation consisting of drug loss during beads preparation [23, 24, 25].

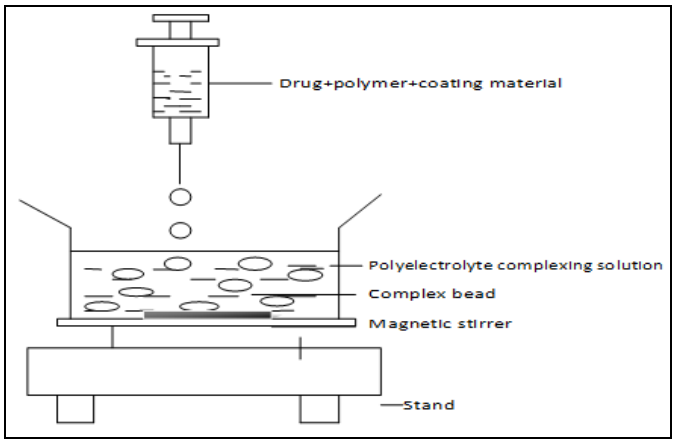

FIG. 3: PREPARATION OF BEADS BY SYRINGE DROPPING OR EXTRUDING METHOD

B) Air Atomization Technique: The beads can also be prepared by the vibration system or air atomization method. Relatively smaller droplets can be prepared by using a vibration system or air atomization method to extrude the polyanions solution. The later involves a Turbotak air-atomizer. In this method pressurized air is fed to merge with the polyanions solution, forcing small liquid droplets out through the orifice of the nozzle. The cations cross-link the polyanions droplet on contact to form a bead, which was further cross-linked by polyelectrolytes such as poly-L-lysine to form a membrane on the bead. The beads obtained using this method were within the size range 5-15 µm [26]. This method may have some drawback which includes special extrusion device or atomization device, which may be of higher cost and possible clogging [27].

Applications of Polyelectrolyte Complex: People have extensively studied the PECs and their applications for the last forty years. Nowadays, PECs are mainly utilized for such large-scale industrial applications as flocculants, coatings, and binders and special purposes in biotechnology and medicine [28]. Potential fields include PEC-microencapsulation of drugs, enzymes, cells and microorganisms, immobilization of proteins by the complex formation and polycation complexes with polynucleotides or oligonucleotides as vectors in gene therapy and for designing of microcapsules for drug delivery [29, 30, 31, 32].

Also, they are mixed with many foods and to concrete mixtures (superplasticizer). Polyelectrolytes that appear on food labels are pectin, carrageenan, alginates, and carboxymethyl cellulose. Eventually, they are used in a variety of materials, including cement. Because few of them are water-soluble, they are also used for biochemical and medical applications.

Ionotropic Gelation Method: The ability of polyelectrolytes to cross-link in the presence of counter ions to form hydrogel beads lead to the ionotropic gelation. Beads are mainly spherical crosslinked hydrophilic polymeric units accomplished of widespread gelation and swelling in simulated biological fluids, and the drug release from the beads is guarded by polymer relaxation. The preparation of hydrogel beads is done by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. Three-dimensional network of the ionically crosslinked moiety is formed by the diffusion of cation into the drug-loaded polymeric drops. Biomolecules can also be incorporated into these beads under mild conditions to maintain their three-dimensional configuration [33, 34].

The natural polymer having biocompatibility and biodegradability are used as drug carriers in ionotropic gelation technique. The natural or semisynthetic polymers, *i.e.*, alginates, chitosan, pectin, gellan gum, and carboxymethyl cellulose, are extensively used for the encapsulation of drug by this technique. The chemical structures of these natural polyelectrolytes contain some anions/ cations and these anions/cations forms meshwork configuration by combining with the counterions and provoke gelation by cross-linking. The natural polymers are having a property of coating on the drug core that's why these also act as release rate retardant [35].

TABLE 2: POLYELECTROLYTES USED IN IONOTROPIC GELATION

Natural Polymer	Synthetic Polymer	Crosslinking Cation
Chitosan	Hydroxyethyl methacrylate	Calcium (Ca^{++})
Alginate	Vinyl acetate	Potassium (K^{+})
Fibrin	Methacrylic acid	Ferric (Fe^{++})
Collagen	N-isopropylacrylamide	Sodium (Na^{+})
Gelatin	N-vinyl- 2-pyrrolidine	Barium (Ba^{++})
Hyaluronic acid	Acroylic acid	Aluminum (Al^{+++})
Dextran	Polyethylene glycol acrylate	Zinc (Zn^{++})

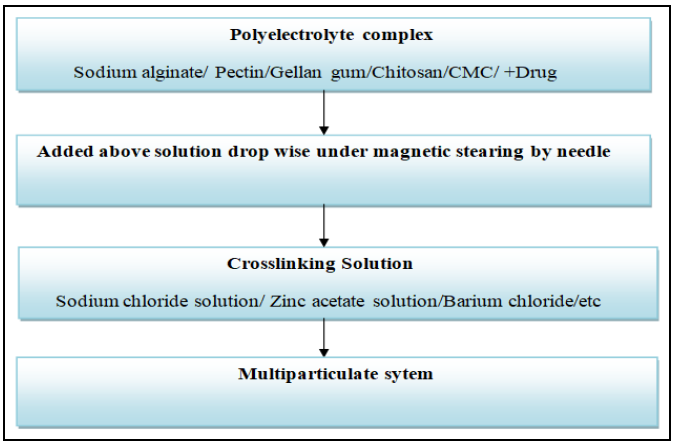

FIG. 4: BASIC TECHNIQUE FOR PREPARATION OF MULTIPARTICULATE SYSTEM [33]

Most Commonly Used Natural Polymers in Ionotropic Gelation Method:

Alginates: Alginate is a non-toxic, highly swellable, biodegradable, naturally occurring polysaccharide extracted from marine brown algae and some species of bacteria. Sodium alginate is a sodium salt of alginic acid a natural polysaccharide and a linear polymer consist of 1,4-linked β-D-Mannuronic acid (M) and α-D-guluronic acid (G) residues in altering proportions and arrangements. Due to the solubility of sodium alginate in water, it can form a reticulated structure which can be cross-linked with divalent (Ca^{++}, Cu^{++}, Zn^{++}) or polyvalent cations (Al^{3+}, Pb^{3+}) to form insoluble meshwork. Calcium, zinc and other cations have been reported for cross-linking of acid groups (COO^{-}) of alginate [36, 37].

Nowadays, many research is going on to prepare calcium alginate beads incorporated with a variety of low molecular weight therapeutic agents. In various studies, alginate beads have been used as an excellent drug carrier. By using calcium, barium, and strontium as gel-forming agents, the rabbit articular chondrocytes immobilized in alginate beads maintained normal morphology and metabolic activity for more than two weeks. Another significant feature of alginate beads is their re-swelling capacity. This feature is susceptible to environmental pH. Hence, acid-labile drugs loaded within the beads can be protected from the gastric environment [38].

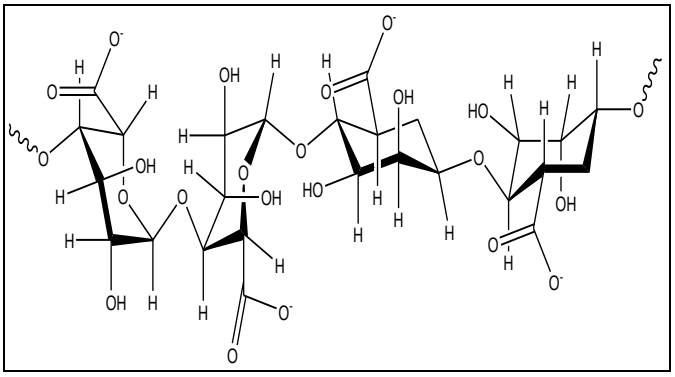

FIG. 5: CHEMICAL STRUCTURE OF ALGINATE

Gellan Gum: Gellan gum is a bacterial exopolysaccharide obtained commercially by aerobic submerged fermentation of *Sphingomones eloda*. *S. eloda*, secreted deacetylated gellan gum which is an anionic microbial polysaccharide, consist of repeating tetrasaccharide units of glucose, glucuronic acid, and rhamnose residues in a 2:1:1 ratio: [→3) –β -D-glucose -(1→4) –β -D-glucuronic acid -(1→4)- β -D -glucose -(1→4)-α-L-rhamnose-(1→]. To induce the gellan gelation, a concentrated water solution of gellan gum is made warm-up preliminary.

The chains undergo a conformational transition from random coils to double helices (coil-helix transition) when the temperature of the solution is decreased. Then the double helices are rearranged resulting in the formation of ordered junction zones (sol-gel transition), thus providing a thermo-reversible hydrogel [39, 40].

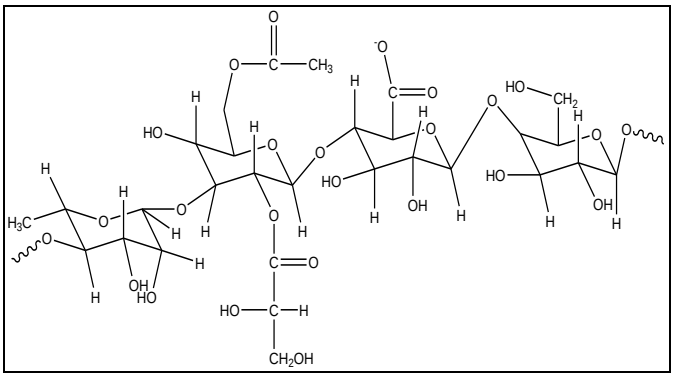

FIG. 6: CHEMICAL STRUCTURE OF GELLAN GUM

Chitosan: Chitosan is natural poly-(amino saccharide), obtained from deacetylation of chitin is a non-toxic, biocompatible, and a biodegradable natural polymer having structural characteristics similar to glycosaminoglycans, is non-hazardous and easily bioabsorbable. Chitosan prevents or weakens drug irritation in the gastric environment due to its antacid and antiulcer characteristics. Chitosan is a natural polymer which could be used for the formation of various polyelectrolyte complex products with natural or synthetic polyanions such as xanthan, alginate, carrageenan and polyacrylic acid to provide the required physicochemical properties for the design of specific drug delivery systems. Chitosan-polyanions complexes have been largely investigated for applications like drug and cell transplantation, protein delivery, enzyme immobilization. Among these complexes, the chitosan-alginate complex may be the most significant drug delivery hydrogel system [41]. Chitosan polyanion complexes have been used in an ample range of pharmaceutical applications such as those formed with DNA to serve as non-viral vectors for gene delivery, and the research is going on for the use of chitosan polyanion complexes used as biosensors, scaffolds in tissue engineering, for waste-water treatment and drug delivery in various forms [42].

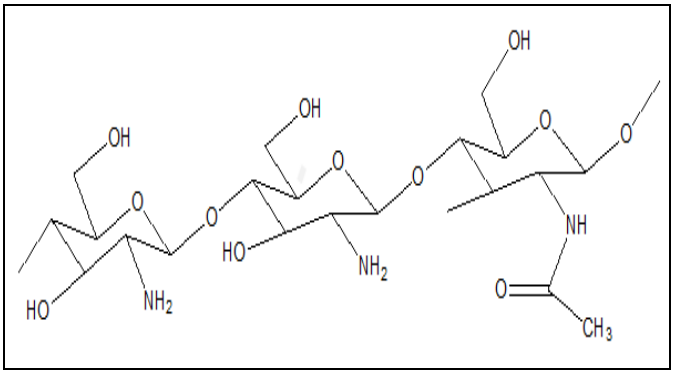

FIG. 7: CHEMICAL STRUCTURE OF CHITOSAN

Pectin: The polysaccharide pectin is an economical, nontoxic product obtained from citrus peels or apple pomaces and has been used as a food additive, a thickening agent, and a gelling agent. Also, the interfacial tension between an oil phase and a water phase can be diminished by pectin and hence it is effectively used for the preparation of the emulsion. Pectin is a linear polysaccharide composed of α-D galacturonic acid with 1→4 linkages. This chain is regularly interrupted by some rhamnogalacturonan segments that combine galacturonic acid residues and α-L-rhamnopyranose by a 1→2 linkage. The research is going on for using pectinate calcium hydrogels as a carrier material for various controlled release systems because of its stability in low pH solutions. Nowadays, gel beads of calcium pectinate have been prepared as an exclusive carrier for drug delivery. The prepared gel beads have been utilized in various ways in the gastrointestinal tract, for example, for sustained release of drugs or for targeting drugs to the colon [43].

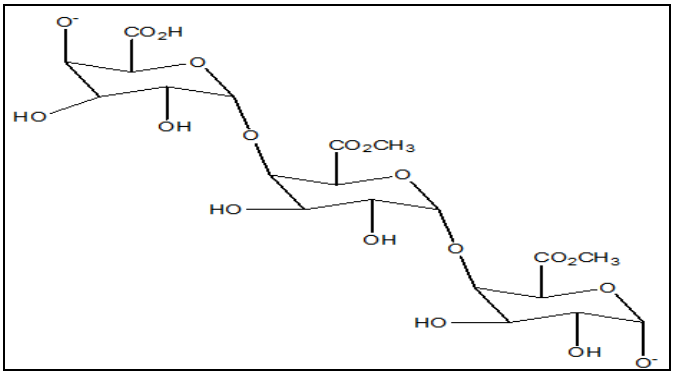

FIG. 8: CHEMICAL STRUCTURE OF PECTIN

Carboxymethyl Cellulose: The cellulose is a plant product which on carboxymethylation process, can be customized as carboxymethylcellulose (CMC). The ionotropic gels form due to the interactions between the carboxylic groups (COO^-) of the CMC, and the electrostatic interactions can primarily stabilize multivalent metal ions. Also, the stability and the water insolubility of these polyelectrolyte complex may be due to the interactions between the –OH groups of the polymer and the metal ions. For the preparation of biodegradable hydrogel beads, the CMC mainly cross-linked with aluminum/ferric salt [44, 45].

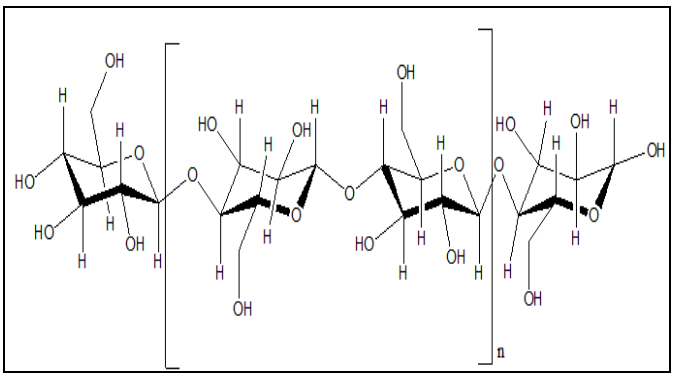

FIG. 9: CHEMICAL STRUCTURE OF CMC

Factors Influencing Ionotropic Gelation Method: [46]

The concentration of Polymer and Crosslinking Electrolyte: Polymer and electrolyte ratio shows a major effect on the formulation of beads by ionotropic gelation method. The concentration of polymer and electrolyte should in the ratio calculated from several crosslinking units. Percent entrapment efficiency depends upon the nature of electrolytes and also the concentration of electrolytes.

Temperature: Temperature affects the size of beads formed by ionotropic gelation technique and also on the curing time, *i.e.*, the time required for crosslinking.

Crosslinking Solution pH: Crosslinking solution pH also a substantial factor during the formation of beads because it can affect the reaction rate, size, and shape of beads.

Drug Concentration: Drug to be incorporated in the beads should be in the appropriate ratio with the polymer, as the drug concentration affects the entrapment efficiency, if drug: polymer ratio higher in the range then bursting effect may occur, beads density increases and the size and shape of beads may also increase.

The Concentration of Gas Forming Agent: To develop porous beads gas-forming agents such as sodium bicarbonate, calcium carbonate added into the formulation, which extremely affects the size and shape of the beads. As gas-forming agent forms porous beads, breaks the lining of beads and results into the rough surface.

Recent Development in Ionotropic Gelation:

Polyelectrolyte Complexation Technique / Ionotropic Pre-Gelation: With the help of polyelectrolyte complexation technique, the quality of hydrogel beads formed by ionotropic gelation method can be improved. The mechanical strength and permeability barrier of hydrogels can be enhanced by the addition of oppositely charged another polyelectrolyte to the ionotropically gelated beads. For example, a membrane of polyelectrolyte complex is formed on the surface of alginate beads on the addition of polycations Authors Anil K. Anal, Willem F. Stevens reported a method for polyelectrolyte beads of ampicillin prepared by ionotropic gelation method. Authors chose alginate and chitosan for complexation and reported enhancement in encapsulation efficiency and improved properties of controlled release of formed multilayer ampicillin [45, 46].

Emulsion-Internal Ionotropic Gelation: It is the newly developed method in ionotropic gelation with the inclusion of oily phase and emulsifier. As reported by Singla and colleagues the dispersed phase consisting of 40 ml of 2% v/v aqueous acetic acid containing 2.5% w/v chitosan was added to the continuous phase consisting of hexane (250 ml) and spanned 85 (0.5% w/v) to form a w/o emulsion. After 20 min of motorized stirring, 15 ml of 1N NaOH solution was added at the rate of 5 ml per min at 15 min intervals. The stirring speed of 2000 to 2200 rpm was continued for 2.5 h. The microspheres were separated by filtration and subsequently washed with petroleum ether, followed by distilled water and then air-dried.

Author Deepak Singh and his colleagues developed dry powder inhalation system of terbutaline sulfate for treatment of asthma and the microspheres of Terbutaline sulfate formed by emulsification-ionotropic gelation and heat crosslinking agent. According to this method, aqueous solutions of chitosan and terbutaline sulfate (in 0.5% acetic acid) were emulsified in the oil phase (100-200 ml) consisting of dichloromethane and light liquid paraffin using homogenizer for 15 min. Span 80 was used as an emulsifier and lecithin as a co-emulsifier and deaggregating agent. Cross-linking solution (citric acid, tripolyphosphate 1%; 5-15 ml) was added to this emulsion and homogenization was continued for another 30 min.

This emulsion was then added slowly to light liquid paraffin (50 ml) which was formerly heated and maintained at 120° ± 10°C with continuous stirring for another one hour. The hot oily dispersion of microspheres was then allowed to cool to room temperature with continuous stirring at the same speed and finally centrifuged on a high-speed centrifuge at 10000 rpm for 10 min, to separate the microspheres. The sediment was dispersed in diethyl ether to eliminate the oil, and this dispersion was again centrifuged for 3 min at the same speed. Also, Anita G. Sullad, Lata S. Manjeshwar and Tejraj M. Aminabhav prepared

microspheres of abacavir sulfate by w/o emulsion method using carboxymethyl guar gum, an anionic synthetic derivative [47, 48].

Ionotropic Gelation Followed by Coacervation: Jaejoon Han, Anne-Sophie Guenier and colleagues successfully developed a new encapsulation method involving two polymers (alginate and chitosan) and using methods of acylation and ionotropic gelation followed coacervation to enhance the stability and physicochemical properties of the beads. Beads were prepared by ionotropic gelation *via* calcium cross-linking and by alginate-chitosan complex coacervation. The main distinction among native and functionalized beads consisted of the presence of fatty acid chains in the core (palmitoylated alginate) and an external layer (palmitoylated chitosan) of beads. Hence, insolubility of beads improved by ionotropic gelation and alginate-chitosan coacervation, which lead to polyionic links between the core bead and the external layer. Hydrophobic interactions into a polymeric matrix can be increased by functionalization and by involving structural changes, the polymers barrier property may also improve by reducing water uptake and water vapor pressure. The mechanical properties and stability of micronutrients encapsulated in native and functionalized beads cannot be improved by functionalized polymers.

Authors also confirmed that encapsulation had a great capacity to guard bioactive molecules against temperature, humidity, and acidic conditions and allowed a controllable release of these compounds during gastrointestinal transit. C.L. Gerez, G. Font de Valdez and colleagues also developed novel microencapsulation of Lactobacillus rhamnosus by ionotropic gelation using pectin (PE) and pectin-whey protein (PE-WP). Both types of beads were covered with a layer of whey protein by complex coacervation to enhance the survival rate of L. *rhamnosus* in Gastric environment [49, 51].

Multi-Polyelectrolyte Particulate System: Viness Pillay, Michael P. Danckwerts statistically developed and evaluated calcium-alginate-pectinate-cellulose acetophthalate beads. Authors mainly focus on the complex dynamics associated with the three key textural parameters, namely matrix resilience, fracture energy, and matrix hardness, which were affected by the degree of crosslinking achieved under different conditions of the reaction. In this technique crosslinking polymer solution prepared as 1.5 g of disodium hydrogen orthophosphate was dissolved in 80 ml of deionized water to which cellulose acetophthalate (1.5% w/v) was added. The solution was magnetically stirred at 658 °C for dissolution of cellulose acetophthalate, taking safety measures not to introduce air bubbles. After that, sodium alginate and pectin (1.5% w/v each) were added to this solution. This multi-component solution was then made up to volume 100 ml with deionized water. By dissolving 150 ml of glacial acetic acid in 1000 ml of deionized water, the crosslinking solution was prepared. To this acidified solution, 2% w/v calcium chloride was integrated. By the titration of the polymer suspension at 2 mL/min with the crosslinking solution using flat-tip 19-gauge opening, the beads were formed. The beads formed were allowed to cure for a period of 24 h at 218 °C, then the crosslinking solution decanted and beads washed and dried for 48 h at 218 °C [52].

Ionotropic Gelation beneath a High Voltage Electrostatic Field: Lihua Ma and Changsheng Liu developed a modified ionotropic gelation method by joining it with a high voltage electrostatic field to prepare protein-loaded chitosan microspheres. This is a new method for sustain delivery of bovine serum albumin (BSA) by encapsulating in chitosan microsphere and also reported that when the mixture of sodium tripolyphosphate (TPP) and ethanol was applied as coagulation solution, the microspheres exhibited good sphericity and dispersibility. The results from the literature survey suggest that the ionotropic gelation method combined with a high voltage electrostatic field is a successful method for sustained delivery of protein by microspheres [53].

Ionotropic Gelation Followed by Compression: Yahya E. Choonara and colleagues developed a new method for alginate-hydroxyethylcellulose beads for controlled intrastriatal nicotine release in Parkinson's disease. Hydroxyethylcellulose was integrated as a reinforcing protective colloidal polymer to provoke interactions between the free carboxyl groups of alginate with hydroxyethylcellulose monomers. Further to prolong the release of nicotine, beads were

compressed within an external poly (lactic-co-glycolic acid) (PLGA) matrix [54, 55].

CONCLUSION: An ample range of research is going on the polyelectrolyte complex. Poly-electrolyte complex has exclusive properties to encapsulate the drug without losing their stability and biocompatibility. Polyelectrolyte complex has great potential and numerous application in future in the field of pharmaceutical technology, biotechnology, medicine, and in the design of novel drug delivery system. Ionotropic gelation is capable tool in the development of biocompatible novel sustained and targeted controlled drug delivery systems as naturally occurring polysaccharides functioning as biopolymers can encapsulate a large number of micro and macro therapeutic molecules in their hydrogel meshwork structure.

The technique of ionotropic gelation and polyelectrolyte complexation is the successful tools for a pharmaceutical scientist concerned with the development of a novel drug delivery system. By altering the exposure time and concentration of crosslinking agents' drug release rate can also be modulated by rightful utilization of these techniques. Due to the new achievements of polymer chemistry and the development of intelligent, strategic encapsulation techniques, the successful use of these biopolymers is increasing day by day.

Due to development of ionotropic gelation and polyelectrolyte complexation techniques the use of expensive and toxic organic solvents in the microencapsulation process has been reduced. This also provided an eco-friendly pharmaceutical product development process in the form of hydrogel beads. New hydrogel bead encapsulation methods that diminish the utilization of toxic organic solvents and denaturing of such macromolecules will be precious tools in the future.

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REFERENCES:

1. Kakkar P and Madhan B: Fabrication of keratin-silica hydrogel for biomedical applications. Materials Science and Engineering 2016; 66: 178-84.
2. Lima-Tenório MK, Tenório-Neto ET, Guilherme MR, Garcia FP, Nakamura CV, Pineda EA, and Rubira AF: Water transport properties through starch-based hydrogel nanocomposites are responding to both pH and a remote magnetic field. Chemical Engineering Journal 2015; 259: 620-9.
3. Ullah F, Othman MB, Javed F, Ahmad Z and Akil HM: Classification, processing and application of hydrogels: A review. Materials Science and Engineering: C 2015; 57: 414-33.
4. Pellá MG, Lima-Tenório MK, Tenório-Neto ET, Guilherme MR, Muniz EC and Rubira AF: Chitosan-based hydrogels: From preparation to biomedical applications. Carbohydrate Polymers 2018; 196: 233-45.
5. Asnani GP and Kokare CR: *In-vitro* and *in-vivo* evaluation of colon cancer-targeted epichlorohydrin crosslinked Portulaca-alginate beads. Biomolecular Concepts 2018; 9(1): 190-9.
6. Girhepunje KM, Krishna Pillai PR, Gevariya HB and Thirumoorthy N: Celecoxib loaded microbeads: A targeted drug delivery for colorectal cancer. Int J Chem Pharm Res 2010; 2: 46-55.
7. Forni F, Cameroni R, Furiosi G and Pifferi G: Bio-degradable microbeads for the pharmaceutical and cosmetic uses. Patent Number: 0563876, 1993.
8. Somo SI, Langert K, Yang CY, Vaicik MK, Ibarra V, Appel AA, Akar B, Cheng MH and Brey EM: Synthesis and evaluation of dual crosslinked alginate microbeads. Acta Biomaterialia 2018; 65: 53-65.
9. Cheewatanakornkool K, Niratisai S, Manchun S, Dass CR and Sriamornsak P: Characterization and *in-vitro* release studies of oral microbeads containing thiolated pectin-doxorubicin conjugates for colorectal cancer treatment. Asian Journal of Pharmaceutical Sciences 2017; 12(6): 509-20.
10. Harris MR and Ghebre-Sellassie I: Aqueous polymeric coating for modified-release pellets. Aqueous polymeric coatings for pharmaceutical dosage forms. New York: Marcel Dekker 1989: 81-100.
11. Vyas SP and Khar RK: Controlled drug delivery concepts and advances. Vallabh Prakashan 2002; 1: 411-47.
12. Meka VS, Sing MK, Pichika MR, Nali SR, Kolapalli VR and Kesharwani P: A comprehensive review on poly-electrolyte complexes. Drug Discovery Today 2017; 22 (11): 1697-06.
13. Naidu VG, Madhusudhana K, Sashidhar RB, Ramakrishna S, Khar RK, Ahmed FJ and Diwan PV: Polyelectrolyte complexes of gum kondagogu and chitosan, as diclofenac carriers. Carbohydrate Polymers 2009; 76(3): 464-71.
14. Lankalapalli S and Kolapalli VR: Polyelectrolyte complexes: A review of their applicability in drug delivery technology. Indian Journal of Pharmaceutical Sciences 2009; 71(5): 481.
15. Dalmoro A, Sitenkov AY, Cascone S, Lamberti G, Barba AA and Moustafine RI: Hydrophilic drug encapsulation in shell-core microcarriers by two-stage polyelectrolyte complexation method. International Journal of Pharmaceutics 2017; 518(1-2): 50-8.
16. Insua I, Majok S, Peacock AF, Krachler AM and Fernandez-Trillo F: Preparation and antimicrobial evaluation of polyion complex (PIC) nanoparticles loaded

with polymyxin B. European Polymer Journal 2017; 87: 478-86.
17. Berger J, Reist M, Mayer JM, Felt O and Gurny R: Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. European Journal of Pharmaceutics and Biopharmaceutics 2004; 57(1): 35-52.
18. Tsuchida E: Formation of polyelectrolyte complexes and their structures. Journal of Macromolecular Science-Pure and Applied Chemistry 1994; 31(1): 1-5.
19. Weinbreck F, De Vries R, Schrooyen P and De Kruif CG: Complex coacervation of whey proteins and gum arabic. Biomacromolecules 2003; 4(2): 293-03.
20. Kudlay A and Olvera de la Cruz M: Precipitation of oppositely charged polyelectrolytes in salt solutions. The Journal of Chemical Physics 2004; 120(1): 404-12.
21. Gamzazade AI and Nasibov SM: Formation and properties of polyelectrolyte complexes of chitosan hydrochloride and sodium dextran sulfate. Carbohydrate Polymers 2002; 50(4): 339-43.
22. Shiratori SS and Rubner MF: pH-dependent thickness behavior of sequentially adsorbed layers of weak polyelectrolytes. Macromolecules 2000; 33(11): 4213-9.
23. Liu P and Krishnan TR: Alginate-pectin-poly-L-lysine particulate as a potentially controlled release formulation. Journal of Pharmacy and Pharmacology 1999; 51(2): 141-9.
24. Torre ML, Giunchedi P, Maggi L, Stefli R, Machiste EO and Conte U: Formulation and characterization of calcium alginate beads containing ampicillin. Pharmaceutical Development and Technology 1998; 3(2): 193-8.
25. Lin SY and Ayres JW: Calcium alginate beads as core carriers of 5-aminosalicylic acid. Pharmaceutical Research 1992; 9(9): 1128-31.
26. Gombotz WR, Healy MS and Brown LR: US patent. 1991; 5, 400.
27. Skjåk-Bræk G and Martinsen AN: Applications of some algal polysaccharides in biotechnology. Seaweed resources in Europe: Uses and Potential 1991: 219-57.
28. Abe K, Ohno H, Nii A and Tsuchida E: Calorimetric study on the formation of polymer complexes through electrostatic interaction and hydrogen bonding. Die Makromolekulare Chemie: Macromolecular Chemistry and Physics 1978; 179(8): 2043-50.
29. Mok H and Park TG. Functional polymers for targeted delivery of nucleic acid drugs. Macromolecular Bioscience 2009; 9(8): 731-43.
30. Andrianov AK, Marin A and Roberts BE: Polyphosphazene polyelectrolytes: a link between the formation of noncovalent complexes with antigenic proteins and immunostimulating activity. Biomacro-molecules 2005; 6(3): 1375-9.
31. Farhat TR and Schlenoff JB: Ion transport and equilibria in polyelectrolyte multilayers. Langmuir 2001; 17(4): 1184-92.
32. Gujarathi NA, Rane BR and Patel JK: pH sensitive polyelectrolyte complex of O-carboxymethyl chitosan and poly (acrylic acid) cross-linked with calcium for sustained delivery of acid susceptible drugs. International Journal of Pharmaceutics 2012; 436(1-2): 418-25.
33. Hemalatha K: Formulation and evaluation of metoclopramide hydrochloride microbeads by ionotropic gelation method. International Journal of Pharmaceutical & Biological Archive 2011; 2(3): 921-25.
34. Patil JS, Kamalapur MV, Marapur SC and Kadam DV: Ionotropic gelation and polyelectrolyte complexation: the novel techniques to design hydrogel particulate sustained, modulated drug delivery system: a review. Digest Journal of Nanomaterials and Biostructures 2010; 5(1): 241-8.
35. Al-Kassas RS, Al-Gohary OM and Al-Faadhel MM: Controlling of systemic absorption of gliclazide through incorporation into alginate beads. International Journal of Pharmaceutics 2007; 341(1-2): 230-7.
36. Takka S, Ocak ÖH and Acartürk F: Formulation and investigation of nicardipine HCl-alginate gel beads with factorial design-based studies. European Journal of Pharmaceutical Sciences 1998; 6(3): 241-6.
37. Silva CM, Ribeiro AJ, Figueiredo IV, Gonçalves AR and Veiga F: Alginate microspheres prepared by internal gelation: Development and effect on insulin stability. International J of Pharmaceutics 2006; 311(1-2): 1-10.
38. Szekalska M, Winnicka K, Czajkowska-Kosnik A, Sosnowska K and Amelian A: Evaluation of Alginate Microspheres with Metronidazole Obtained by the Spray Drying Technique. Acta Poloniae Pharmaceutica 2015; 72(3): 569-78
39. Jamshidi P, Birdi G, Williams RL, Cox SC and Grover LM: Modification of gellan gum with nanocrystalline hydroxyapatite facilitates cell expansion and spontaneous osteogenesis. Biotechnology and bioengineering, 2015; 113(7): 1568-76.
40. Moxon SR and Smith AM: Controlling the rheology of gellan gum hydrogels in cell culture conditions. International Journal of Biological Macromolecules 2015; 84: 79-86.
41. Henao E, Delgado E, Contreras H and Quintana G: Polyelectrolyte Complexation versus Ionotropic Gelation for chitosan-based hydrogels with carboxy methyl cellulose, carboxymethyl starch, and alginic acid. International J of Chemical Engineering 2018; 2018: 1-12.
42. Bernabe P, Peniche C and Argüelles-Monal W: Swelling behavior of chitosan/pectin polyelectrolyte complex membranes. Effect of thermal cross-linking. Polymer Bulletin 2005; 55(5): 367-75.
43. Miran W, Nawaz M, Jang J and Lee DS: Conversion of orange peel waste biomass to bioelectricity using a mediator-less microbial fuel cell. The Science of the Total Environment 2016; 547: 197-05.
44. Boppana R, Kulkarni RV, Setty CM and Kalyane NV: Carboxymethylcellulose-aluminum hydrogel microbeads for prolonged release of simvastatin. Acta Pharmaceutica Sciencia 2010; 52(2): 137-43.
45. Huei GO, Muniyandy S, Sathasivam T, Veeramachineni AK and Janarthanan P: Iron cross-linked carboxymethyl cellulose-gelatin complex coacervate beads for sustained drug delivery. Chemical Papers 2016; 70(2): 243-52.
46. Patil JS, Kamalapur MV, Marapur SC and Kadam DV: Ionotropic gelation and polyelectrolyte complexation: the novel techniques to design hydrogel particulate sustained, modulated drug delivery system: a review. Digest Journal of Nanomaterials and Biostructures 2010; 5(1): 241-8.
47. Anal AK and Stevens WF: Chitosan-alginate multilayer beads for controlled release of ampicillin. International Journal of Pharmaceutics 2005; 290(1-2): 45-54.
48. Sullad AG, Manjeshwar LS and Aminabhavi TM: Microspheres of carboxymethyl guar gum for *in-vitro* release of abacavir sulfate: preparation and characterization. Journal of Applied Polymer Science 2011; 122(1): 452-60.
49. Singh DJ, Parmar JJ, Hegde DD, Lohade AA, Soni PS, Samad A and Menon MD: Development and evaluation of dry powder inhalation system of terbutaline sulphate for better management of asthma. International Journal of Advances in Pharmaceutical Sciences 2010; 1(2): 138-50.

50. Han J, Guenier AS, Salmieri S and Lacroix M: Alginate and chitosan functionalization for micronutrient encapsulation. Journal of Agricultural and Food Chemistry 2008; 56(7): 2528-35.
51. Pillay V and Danckwerts MP: Textural profiling and statistical optimization of crosslinked calcium-alginate-pectinate-cellulose acetophthalate gelisphere matrices. J of Pharmaceutical Sciences 2002; 91(12): 2559-70.
52. Ma L and Liu C: Preparation of chitosan microspheres by ionotropic gelation under a high voltage electrostatic field for protein delivery. Colloids and Surfaces B: Biointerfaces 2010; 75(2): 448-53.
53. Han J, Guenier AS, Salmieri S and Lacroix M: Alginate and chitosan fictionalization for micronutrient encapsulation. Journal of Agricultural and Food Chemistry 2008; 56(7): 2528-35.
54. Gerez CL, Font de Valdez G, Gigante ML and Grosso CR: Whey protein coating bead improves the survival of the probiotic *Lactobacillus rhamnosus* CRL 1505 to low pH. Letters in Applied Microbiology 2012; 54(6): 552-6.

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