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Review Article

A REVIEW ON IONOTROPIC GELATION METHOD: NOVEL APPROACH FOR CONTROLLED GASTRORETENTIVE GELISPHERES

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ABSTRACT

The purpose of this review is to compile the recent literature with special focus on the method of preparation i.e. Ionotropic gelation method to achieve a pharmaceutical product with desired characteristics. Ionotropic gelation is based on the ability of polyelectrolytes counter ions to cross link to form hydrogels. Naturally occurring polysaccharides use as biopolymers has been increased in the novel area such as hydrogel sustained release formulation, thus providing an ecofriendly pharmaceutical product development process.

This review focused on recent developments of multiple-unit floating drug delivery system approaches based on Ionotropic gelation method, polymers used and factors affecting on method of ionotropic gelation.

Keywords: Ionotropic gelation, Gelispheres, Gastroretentive multiparticulate system.

INTRODUCTION

The basic rationale of controlled release drug delivery system is to optimize the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug administered by the most suitable route to achieve its maximum utility, to control condition within shortest possible time by using smallest quantity of drug. It also provides constant drug level in the blood with reduced dosing frequency and reduced side-effects, thus increasing patient compliance and decreasing adverse drug effects[1].

Controlled release or Extended-release dosage forms with prolonged residence times in the stomach is highly desirable for drugs which are:

1. Has an absorption window in the stomach
2. Targeted at sites in the upper GI tract
3. Imbalancing, irritating, or unsafe in the lower GI region
4. More effective when plasma levels are more constant
5. Locally active in the stomach
6. Unstable in the intestinal or colonic environment
7. Low solubility at high pH values

Generally Multiparticulate drug delivery systems are intended for oral, parentral and topical formulations and approaches include formulations in the form of pellets, granules, beads, gelispheres, microcapsules, microspheres, liposphere, microparticles and nanoparticles[2]. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with selective diameter range. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet.

Considerable research efforts have been spent on oral controlled release multiparticulate drug delivery system due to its advantages over monolithic dosage forms as[3,4,5]:

1) Less inter and intra subject variations in gastric transit time.
2) Taste masking.
3) No risk of dose dumping.
4) Less local irritation.
5) Increased solubility or dispersibility, hence quick diffusion, leading to a more rapid drug release and better absorption, as having large surface area.
6) Avoid risk of toxicity since they have ability to spread uniformly throughout gastrointestinal tract.
7) Improves patient compliance by decreasing dosing frequency.
8) Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
9) Increased therapeutic efficiency.
10) Improved stability.

In this present review, an attempt was made to discuss the different natural polymers used in ionotropic gelation method and their mechanism to form cross-linked gelispheres with suitable counter ions present on respective polyelectrolyte. Here, it was also tried to explain the importance of ionotropic gelation and recent advances in the methods of ionotropic gelation, as these methods show great promise as a tool for the development of encapsulation process.

Approaches for gastroretention of gelispheres

1. Effervescent systems

- Volatile liquid containing systems
- Gas-generating Systems

2. Non-effervescent systems

- Colloidal gel barrier systems
- Micro-porous Compartment System
- Hollow microspheres
- Mucoadhesive systems

Fig. 1: It shows the types of Gastroretention of gelispheres[6]

Ionotropic gelation method

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogel beads also called as gelispheres. Gelispheres are spherical crosslinked hydrophilic polymeric entity capable of extensive gelation and swelling in simulated biological fluids and the release of drug through it controlled by polymer relaxation. 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 crosslinked moiety. Biomolecules can also be loaded into these gelispheres under mild conditions to retain their three dimensional structure[7,8].

Polyelectrolyte solution

[Sodium Alginate (-)/Gellan gum (-)/CMC (-)/Pectin (-)/ Chitosan (+) + Drug]

↓

Added drop wise under magnetic stirring by needle

↓

Counter ion solution

[Calcium chloride solution (+)/Sodium tripolyphosphate (-)]

↓

Gelispheres

Fig. 2: It shows the basic technique of Gelispheres praparation[8]

Table 1: Polyelectrolytes used in Ionotropic gelation

Natural polymers	Synthetic monomers/polymers	Multivalent Cations
Chitosan	Hydroxyethylmethacryate (HEMA)	Calcium (Ca^{+2})
Alginate	*N*-(2-Hydroxy propyl)methacrylate (HPMA)	Potassium (K^{+})
Fibrin	*N*-Vinyl-2-pyrrolidone (NVP)	Ferric (Fe^{+2}), Barium (BA^{+2}) Sodium (Na^{+}) Magnesium(Mg^{+2})
Collagen	*N*-Isopropylacrylamide (NIPAMM)	Aluminium (Al^{+3})
Gelatin	Vinyl acetate (VAc)	Zinc (Zn^{+2})
Hyaluronic acid	Acryolic acid (AA)	
Dextran	Methacrylic acid (MAA)	
	Polyethylene glycol acrylate/methacrylate (PEGA/PEGMA)	
	Polyethylene glycol diacrylate/dimethacrylate (PEGDA/PEGDMA)	

In Ionotropic gelation technique, there has been a growing interest in the use of natural polymers as drug carriers due to their biocompatibility and biodegradability. The natural or semisynthetic polymers i.e. Alginates, Gellan gum, Chitosan, Pectin and Carboxymethyl cellulose are widely use for the encapsulation of drug by this technique[9]. These natural polyelectrolytes contain certain anions/cations on their chemical structure, these anions/cations forms meshwork structure by combining with the counter ions and induce gelation by cross linking. In spite of having a property of coating on the drug core these natural polymers also acts as release rate retardant.

Natural polymers used in ionotropic gelation method

Alginates[10, 11]

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. 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.

Gellan gum[12]

Gellan gum is a bacterial exopolysaccharide prepared commercially by aerobic submerged fermentation of Sphingomones Eloda. 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), thus giving a thermo-reversible hydrogel.

Chitosan[13]

Chitosan is natural poly-(aminosaccharide), having structural characteristics similar to glycosaminoglycans, is non-toxic and easily bioabsorbable[32]. Chitosan due to its antacid and antiulcer characteristics prevents or weakens drug irritation in the stomach[33]. 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. Among these, complexes, chitosan-alginate complex may be the most important drug delivery hydrogel system.

Carboxymethyl cellulose[5, 14]

The cellulose, a plant product on carboxymethylation process, can be modified as carboxymethylcellulose (CMC). 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.

Pectin[15]

Pectin is an inexpensive, non-toxic polysaccharide extracted from citrus peels or apple pomaces, and has been used as a food additive, a thickening agent and a gelling agent. Basically, it is a polymer of a-D-galacturonic acid with 1-4 linkages.

Factors affecting ionotropic gelation method

1) Polymer and crosslinking electrolyte concentration

Polymer and electrolyte concentration have major effect on formulation of beads by ionotropic gelation method. Concentration of both should in the ratio calculated from number of crosslinking units. Percent entrapment efficiency varies from the type of electrolytes and also the concentration of electrolytes.

2) Temperature

Temperature also plays imp role on size of beads formed by ionotropic gelation method and also on the curing time i.e. time required for crosslinking.

3) pH of crosslinking solution

pH of crosslinking solution also considerable factor during the formulation as it shows effect on reaction rate, shape and size of beads.

4) Drug concentration

Drug to be entrapped in the beads should be in the proper ratio with the polymer, as the drug concentration greatly affects the entrapment efficiency, if drug: polymer ratio exceeds the range then bursting effect may observe, density of gelispheres enhances and the size and shape of gelispheres also increases.

5) Gas forming agent concentration

Gas forming agents such as calcium carbonate, sodium bicarbonate added in to the formulation to develop porous gelispheres, which tremendously affect the gelispheres size and shape. As gas forming agent forms porous gelispheres, breaks the lining of gelispheres and results into the irregular surface.

Advances in Ionotropic gelation

1) Polyelectrolyte complexation technique/ Ionotropic pre-gelation[8]

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 gelispheres. For instance, addition of polycations allows a membrane of polyelectrolyte complex to form on the surface of alginate gelispheres.

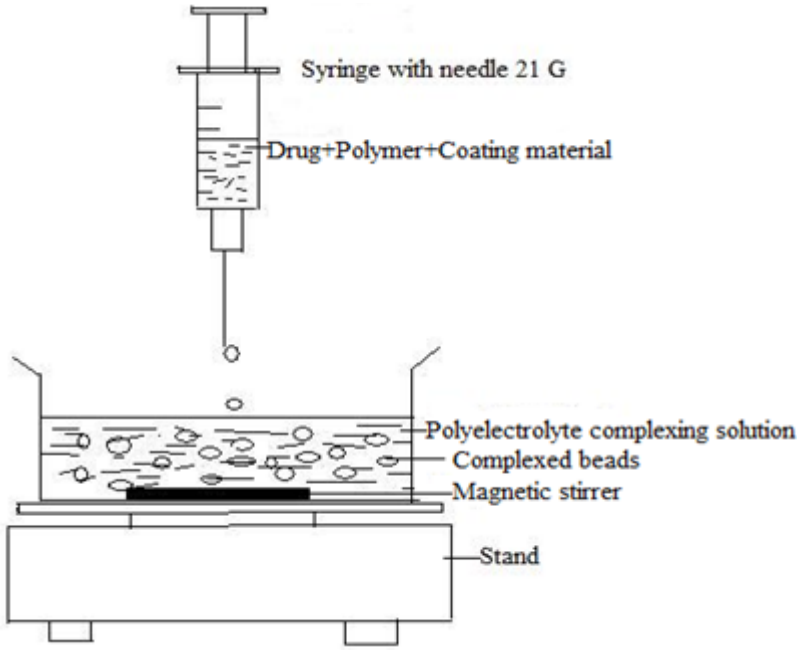

Fig. 3: It shows the diagrammatical presentation of Gelispheres preparation by polyelectrolyte complexation technique[8]

Authors Anil K. Anal, Willem F. Stevens reported a method for polyelectrolyte beads of ampicillin prepared by ionotropic gelation method. Authors selected alginate and chitosan for complexation and reported enhancement in encapsulation efficiency and improved properties of controlled release of formed multilayer ampicillin[16].

2) Ionotropic gelation under a high voltage electrostatic field[17]

Authors Lihua Ma and Changsheng Liu reported a modified ionotropic gelation method by combining it with a high voltage electrostatic field to prepare protein-loaded chitosan microspheres. This is new method for sustain delivery of Bovine Serum Albumin (BSA) by encapsulating in chitosan microsphere also reported that the microspheres exhibited good sphericity and dispersibility when the mixture of sodium tripolyphosphate (TPP) and ethanol was applied as coagulation solution. The results from the literature survey suggest that ionotropic gelation method combined with a high voltage electrostatic field is an effective method for sustained delivery of protein by gelispheres.

3) Emulsion-internal ionotropic gelation

It is the advanced method in ionotropic gelation with the incorporation 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 Span 85 (0.5% w/v) to form a w/o emulsion. After 20 minutes of mechanical stirring, 15 mL of 1N sodium hydroxide solution was added at the rate of 5mL per min at 15min intervals. Stirring speed

of 2000 to 2200 rpm was continued for 2.5 hours. The microspheres were separated by filtration and subsequently washed with petroleum ether, followed by distilled water and then air dried[18]. Also Anita G. Sullad, Lata S. Manjeshwar and Tejraj M. Aminabhav developed microspheres of Abacavir sulfate by w/o emulsion method using Carboxy methyl guar gum, an anionic synthetic derivative[19].

Author Deepak singh and his colleagues developed Dry Powder Inhalation system of Terbutaline sulfate for management of Asthma and the microspheres of Terbutaline sulfate prepared 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 oil phase (100-200ml) consisting of dichloromethane and light liquid paraffin (LLP) 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 and glucose 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 previously 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 same speed, and finally centrifuged on a high-speed centrifuge at 10000 rpm for 10 min, in order to separate the microspheres. The sediment was dispersed in diethyl ether to remove the oil, and this dispersion was again centrifuged for 3 min at the same speed. Washing with diethyl ether was repeated three more times in a similar manner to remove traces of oil. The sediment thus obtained was dried in oven at 50°-60°C, passed through 100-mesh sieve and stored[20].

w/o/w emulsion solvent evaporation containing ionotropic gelation is the modified technique involving multiphase. This method draws more attention nowadays, as the method is useful for encapsulation of water-soluble drugs, proteins, DNA or antigens into microsphere or nanosphere as effective delivery carriers.

4) Ionotropic gelation followed by coacervation[21,22]

Jaejoon Han, Anne-sophie Guenier and colleagues successfully developed a new encapsulation method involving two polymers (alginate and chitosan) and using methods of functionalization (acylation) and ionotropic gelation followed coacervation to improve the stability and physicochemical properties of beads. Beads were formed by ionotropic gelation via calcium cross-linking and by alginate-chitosan complex coacervation. The main difference between native and functionalized beads consisted in the presence of fatty acid chains in the core (palmitoylated alginate) and external layer (palmitoylated chitosan) of beads. Hence, alginate cross-links improved insolubility of beads by ionotropic gelation and alginate-chitosan coacervation, which led to polyionic links between the core bead and the external layer. Functionalization increases hydrophobic interactions into polymeric matrix involving structural changes also improves the polymers barrier property by decreasing water uptake and Water vapour pressure. Functionalized polymers did not improve their mechanical properties and stability of micronutrients encapsulated in native and functionalized beads. Authors also demonstrated that encapsulation had an excellent capacity to protect bioactive molecules against temperature, humidity, and acidic conditions and allowed a controlled 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 improve the survival rate of *Lactobacillus rhamnosus* in Gastric fluid.

5) Alginate-Poly(ethylene glycol) Hybrid Gelispheres[23]

A new type of hydrogel microspheres was synthesized by Redouan Mahou and Christine Wandrey, according to them the combination of electrostatic interaction of calcium ions with sodium alginate and the chemical reaction of vinyl sulfone-terminated poly (ethylene glycol) (PEG-VS) with Threo-1,4-dimercapto-2,3-butanediol (DTT). A one-step extrusion process under physiological conditions yielded calcium alginate-poly (ethylene glycol) hybrid microspheres (Alg-PEG-M), an interpenetrating network with well-controllable physical properties. It was mentioned that the permeability of the hydrogel can be tailored by adequate choice of the arm length of PEG-VS, while the swelling degree can be tuned by varying the PEG-VS concentration and/or by liquefaction of Calcium-alginate. It was also given that dissolution of Calcium alginate has no significant impact on the mechanical resistance of the obtained Poly (ethylene glycol) microspheres (PEG-M). Overall, important physical properties of the hydrogel spheres are obtainable in the range desired for biotechnological, biomedical, and pharmaceutical applications.

6) Multi-polyelectrolyte gelispheres[24]

Viness Pillay, Michael P. Danckwerts statistically developed and evaluated calcium-alginate-pectinate-cellulose acetophthalate gelisphere. Authors focus on the the complex dynamics associated with the three key textural parameters namely matrix resilience, fracture energy, and matrix hardness which were significantly influenced by the degree of crosslinking achieved under various conditions of reaction.

In this technique the polymer solution for crosslinking 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. To facilitate dissolution of cellulose acetophthalate, the solution was magnetically stirred at 658°C, taking precautions not to introduce air bubbles. Thereafter, sodium alginate and pectin (1.5% w/v each) was added to this solution. This multicomponent solution was then made up to volume 100 mL with deionized water. The crosslinking solution was prepared by dissolving 150mL of glacial acetic acid in 1000 mL of deionized water. To this acidified solution, 2% w/v calcium chloride was incorporated. Gelispheres were formed by titration of the polymer suspension at 2 mL/min with the crosslinking solution using flat-tip 19-guage opening. The gelispheres formed were allowed to cure for period of 24 hour at 218°C, then the crosslinking solution decanted and gelispheres washed and dried for 48 hour at 218°C under extractor.

7) Ionotropic gelation followed by compression[25]

Yahya E. Choonara and colleagues developed a new method for Alginate-Hydroxyethylcellulose Gelispheres for Controlled Intrastriatal Nicotine Release in Parkinson's disease. Hydroxyethylcellulose was incorporated as a reinforcing protective colloidal polymer to induce interactions between the free carboxyl groups of alginate with Hydroxyethylcellulose monomers. Further to prolong the release of nicotine, Gelispheres were compressed within an external poly(lactic-co-glycolic acid) (PLGA) matrix.

Evaluation parameters for gelispheres

1) Size and shape of gelispheres
2) Drug content and Entrapment efficiency
3) Swelling properties
4) Water uptake by gelispheres
5) In-vitro drug release
6) Floating time and lag floating time
7) Flow properties
8) Density
9) IR of gelisphere
10) DSC
11) Stability studies

Table 2: Various drugs and excipients used in Ionotropic gelation process

Drug	Cross-linking polymer	Drug delivery system	Reference No.
Prednisone	Chitosan, pectin-calcium chloride	Controlled release beads	4
Simvastatin	Sodium CMC-aluminium chloride	Controlled release microbeads	5
Gliclazide	Sodium alginate-calcium chloride	Controlled release beads	9
Nicardipine HCl	Sodium alginate-calcium chloride	Controlled release beads	10
Ibuprofen	Chitosan-tripolyphosphate	Controlled release beads	26
Piroxicam	Chitosan-tripolyphosphate	Controlled release beads	27
Metronidazole	Alginate containing chitosan-calcium pantothenate	Gastroretentive sustained release microbeads	30
Pindolol	Sodium alginate-calcium chloride	Controlled release beads	31
Cefadroxil	Sodium alginate-calcium chloride	Controlled release beads	32
Metronidazole	Sodium alginate-calcium chloride	Gastroretentive sustained release beads	33
Riboflavin	Sodium alginate-calcium chloride	Gastroretentive sustained release beads	34,35
Theophylline	Sodium alginate-calcium chloride	Gastroretentive sustained release microbeads	36
Captopril	Sodium alginate-calcium chloride	Gastroretentive sustained release microbeads	37
Acyclovir	Sodium alginate-calcium chloride	Gastroretentive drug delivery beads	38
Indomethacin	Calcium pectinate gel-calcium chloride	Controlled release beads	39
Glipizide	Gellan gum-Al^{+3} ion	Controlled release beads	40
Propranolol	Gellan gum- calcium chloride	Controlled release beads	41
Bovine serum albumin (BSA)	Sodium alginate, chitosan-calcium chloride	Controlled release beads	43
Ambroxol HCl	Pectin-calcium chloride, Pectin-zinc acetate	Gastroretentive drug delivery beads	44
Pantoprazole	Sodium alginate-calcium chloride	Gastroretentive drug delivery beads	45
Ampicillin	Chitosan, sodium alginate-polyphosphate	Controlled release beads	46
Shark liver oil	Sodium alginate, chitosan-calcium chloride	Controlled release capsules	47
Piperine	Sodium alginate-calcium chloride	Sustained release beads	48
Pancreatin	Pectin, chitosan-calcium chloride	Controlled release beads	49

CONCLUSION

Ionotropic gelation is promising tool in the development of biocompatible novel sustained and targeted controlled drug delivery systems as naturally occurring polysaccharides functioning as biopolymers are capable to encapsulate large number of micro and macro therapeutic molecules in their hydrogel meshwork structure. 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 utilization of expensive and toxic organic solvents in the microencapsulation process has been drastically reduced due to evolution of ionotropic gelation and hence provides an eco friendly pharmaceutical product development process in the preparation of gelispheres. To overcome the lacunas of ionotropic gelation technique certain advances carried out in the conventional method, which are one step ahead in gaining desired drug delivery system. The modified technique has gaining more acceptability in delivery of most sensitive macromolecules such as proteins and peptides since 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. Multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development.

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