REVIEW ARTICLE

Polysaccharides Based Novel and Controlled Released Multiparticulate Systems for Colon-specific Delivery: Contemporary Scenario and Future Prospects

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Abstract

In our noble pharmaceutical field, polysaccharides were become an indispensable part during dosage form development for the last few decades. The matrix polysaccharides that were utilizing for dosage form were mostly hydrophilic in nature that gets swell and form a viscous gel-like mass upon contact with dissolution fluids or gastrointestinal fluids. The polymeric properties were successfully exploited in the development of novel polyelectrolyte complexes based multiparticulate delivery systems based on ionic gelation techniques. These complex systems have awaken as an emerging need to deliver the drug(s) into the target site of action for possible controlling and sustaining the drug release properties and thereby affecting the pharmacological responses other than those traditional dosage forms. Site-specific deliveries to the colon were confirmed for providing enzymatic digestion of those polysaccharides. Furthermore, in the present review, an attempt was made to describe the significance of the physicochemical properties of those polysaccharides for defining its possible mechanism of actions.

Key words: Chitosan, Colon drug delivery, Ionic gelation, Multiparticulates, Pectin, Polyelectrolyte complex, Sodium alginate

MULTIPARTICULATE (MP) SYSTEM

Development of MP systems had gained much fame over the single unit systems for oral drug delivery applications as per reports during the last few decades. It has proved to be a most preferred potential system due to numerous reasons, namely, predictable gastric emptying, reduced risk of toxicity, reduced dose dumping, reduced local irritation, reduced inter-intra subject variability, increased bioavailability, improved stability, etc. MPs mostly used for oral routes include nanoparticles, microspheres, beads, granules, and microparticles that ensure for unique release profiles, uniform drug dispersion, and absorption into the gastrointestinal tract (GI tract). These systems were mostly having particle diameter range from few micrometers to millimeter (except nanoparticles) consists of active medicaments in a multiplicity of small discrete units or typically plurality of independent subunits. It is formulated either as a reservoir or matrix type based on polysaccharides (polymer) that exhibiting some desirable novel physicochemical properties. Recently, MPs were mostly using for colon-specific targeting of medicament as compared to single-unit dosage systems, since due to its smaller particle sizes, it uniformly disperses

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and reaches to colon promptly. In addition, it gets easily pass through numerous assaults (acidic and alkaline secretions) of GI tract and arrived into the colonic targeted region within a stipulated lag time and retained there for a relatively prolonged period of time for desirable sustained local or systemic drug absorptions, especially for shorter half-life drug candidates.[1]

Even though tremendous advancements taken place in various types of oral drug delivery systems, but those MPs had acquired a specific role in the terrain of pharmaceutical research and development program. It had so far opened tremendous opportunities and frontier for achieving the delayed and sustained release controlled formulations. This system offers and ensures in terms of novelty, stability (physical and chemical), design flexibility, and clinical benefits in comparison to those single-unit systems. Numerous other technological and therapeutic returns are offered with maximum patient compliances, minimized adverse drug effects, reduced peak plasma variations, and effective drug absorption (local or systemic) benefits. So far, several methods had been reported for the preparation of those MPs using variable processing conditions of distinct characteristics for the purpose to achieve desired and modified drug release profiles. Among those methods were falling under, namely, ionic gelation (polyelectrolyte complexes), granulation, pelletization, spray drying, congealing, etc.[2,3]

Designing and development of MPs

Various approaches had been reported for the successful designing of those MPs that include, namely, pH dependent, time dependent, microbial dependent (polysaccharide based), or combination of two approaches. The designed and developed formulation ensures reliability in terms of that there are very lesser chances for shifting of drug release profiles or formulation performances due to any variation of multiple subunits systems. The *in vitro* and *in vivo* performance of those systems was reported by various researchers as better than single-unit systems. For the reasons of its smaller size that enables it to spread out entirely all along the GI tract passages, it causes lesser irritation and enhanced drug release profiles. The occurrence of GI tract's pH variation and unambiguous presence of bacterial populations of colon had comprehensively explored to design MPs based on colon-specific drug delivery.

Rationale behind designing of MPs

Recent reports and reviews suggested that MPs are endowed with a promising platform for delivery of numerous drug candidates (both existing as well as newer molecules) at the targeted site with desired modified release profiles. It offers powerful tools to those researchers to optimize therapy with greater flexibility, adaptability, and efficiency over the single-unit systems. The individual subunit particles easily transit through the upper GI tract and shown reproducible absorption and pharmacokinetic release profile than any other conventional drug delivery systems. With respect to the technological point of view, overall, those MPs have so far better performed in terms of numerous merits, namely, stability, safety, lesser intra-inter subject variability, and bioavailability.

Merits of MPs

MPs offer several advantages over the conventional drug delivery system with respect to foreseeable gastric emptying, abridged risk of local irritation, negligible systemic toxicity, improved drug bioavailability, and patient comfort and compliances. Due to its flexibility in design and technology, it leads to lesser subject-to-subject variability, compressed adverse effects, and thereby improved acceptability as well. Entirely, there is no risk of dose dumping, modified release profile, improved product stability were also reported and documented.[4]

Shortcomings of MPs

In simulation to other delivery systems, these systems also suffer from fewer demerits such as the requirement of various process variables and advanced technology resulted into expensive production cost. In addition, highly trained and skilled staff likely to be needed during development and production processes.

Polyelectrolyte complex

The physicochemical properties of polysaccharides had been successfully exploited in the development of novel polyelectrolyte complexes based on modified sustained and controlled drug delivery systems using ionic gelation techniques over the last few decades. Polyelectrolyte complexes are the gel formation process in which oppositely charged cationic type polyions (polybases) associate electrostatically with those anionic type polyions (polyacids) in an aqueous media. It results into three-dimensional "Egg-box-junction" like structures bearing repeating units of ionic or ionizable positively and negatively charged electrolyte groups. Entirely, this depends on effective cross-linking of those polycations and anions type polysaccharides with or without using counter ions that develop into ionically cross-linked lattices hydrogel networks. These solitary polymeric complex systems based dosage form have aroused as an emerging needs to deliver those drug(s) candidates into the target site of action effectively. Such a system helps for controlling and sustaining the drug release properties and thereby having overall better-appealing properties, namely, improved pharmacotherapeutic responses, biocompatibility, biodegradability, lesser toxic, and lower production cost in comparison to those conventional dosage forms. There are

significant roles of those abundant natural and synthetic polysaccharides for formations of polyelectrolyte complexes and its applications during designing of various matrix-based potential dosage forms such as nanoparticles, microparticles, beads, and sponges. The mechanically strong complexes dissociate completely at reasonable pH solutions since due to its reversible electro statistic properties. These complexes were combined with unique physicochemical properties that were widely used as matrix carriers for various drug moieties and made it easier for drug targeting to specific sites.

There is a wider augmentation for the use of natural and chemically modified polysaccharides in the last few decades for potential dosage form development and work area interest for many researchers. Those polyelectrolytes and ionic gelatin-based hydrogels systems had gained significant interest for the development of various novels, sustained and controlled bead systems.[5,6] The MP based bead systems were of smaller particle size due to which it has numerous advantages over single-unit dosage forms in many respects, namely, avoidance of inter and intrasubject variations, more uniform GI tract dispersion, easy transit, and absorptions. Whereas, these were have longer retention or residence and more bioavailability upon arrival into the targeted colonic region. The matrix of beads system consisting of three dimensional polymeric cross-linked networks structures. That cross-linked matrix has greater potential for carrying out large quantities of biological fluids and drug particles into it. On the basis of those natural, chemically modified or synthetic types of polysaccharides, these polyelectrolytes are classified as polycations or polyanions types. These charged molecular groups, sometimes also called as poly salts, dissociate as cations and/or anions upon contact into an aqueous medium that plays an essential role in determining structural and molecular assemblies and stability of these systems. Usually, this polymeric hydro-gel-complex or compact precipitate gets produced when solutions of two oppositely charged polycation and anion are mixed together. Polyelectrolytes complexes are usually self-assembly or spontaneous associations due to reversible strong electrostatic links that formed between oppositely charged cations and anions of polysaccharides. These reversible electrostatic links are due to the factors of either electrostatic force of attraction, hydrogen/hydrophobic bonding, or ion-dipole forces between those charged polymeric chains.[1,7] Those association complexes are biocompatible and sensitive for environmental conditions on the other hand. These properties play a significant role in the preparation and development of advantageous novel drug delivery systems.[4,8] Various factors affecting the formation and stability of those polyelectrolyte complexes, namely, molecular weights, degree of ionization, mixing ratio, order and duration of time of interaction, pH of the reaction media and its temperature, density of charge distribution, concentration, and nature of ionic groups and ionic strength.[2,9-12]

Commonly used polysaccharides in Ionotropic gelation method

Alginates

Alginate also called algin or alginic acid is anionic high-molecular-mass natural polysaccharides or poly acids extracted from the cell wall of brown marine algae and some species of bacteria that were non-toxic, highly biocompatible, biodegradable, pH-sensitive and swellable, porosity, and ease of manipulation nature. It is a linear copolymer composed of altering compositions and arrangements of (1,4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) monomers having significant affinity to form insoluble aqueous gel meshwork in the presence of divalent or polyvalent cations (NH_2^+, Ca^{2+}, Cu^{2+}, Sr^{2+}, Br^{2+}, Zn^{2+}, Al^{3+}, Fe^{3+}, Pb^{3+}). The G and M monomeric blocks are joined together into mainly three types, namely, homopolymeric G-blocks at junction of the G (GG), homopolymeric M-blocks (MM), and heteropolymeric sequentially alternating M/G-blocks (MG). The average chain length of the G-blocks is directly responsible for affinity toward divalent cations and capacity for subsequent gel formation [Figure 1]. Those alginates containing the highest G-G fractions possess the strongest ability to form gels which can be explained by the so-called "egg-box-junctions" in which divalent cation binds to two carboxylic groups on the adjacent alginate molecules.[13] A stable polyelectrolytes or scaffolds formed when negatively charged carboxylic acid (COO^-) groups of mannuronic and guluronic acid units in alginate interact electrostatically with the positively charged divalent metal ions or polyvalent cations that were easily to manipulate both mechanical and drug release properties. A spherical gel or alginate beads with regular size and shape are commonly prepared in the laboratory when an aqueous dispersion of sodium alginate is added dropwise into the aqueous solution containing cationic Ca^{2+} ion typically made from calcium chloride bath at room temperature. Alginate

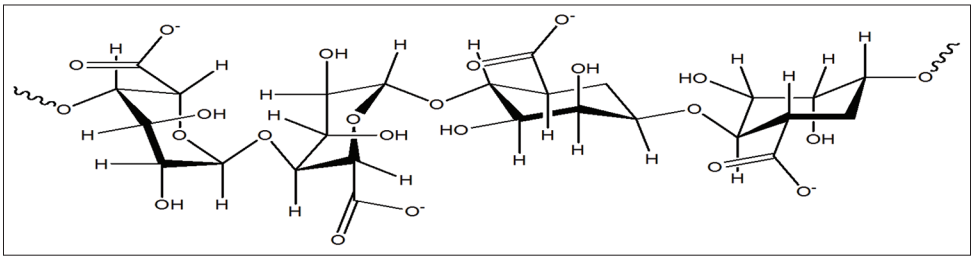

Figure 1: Chemical structure of sodium alginate polysaccharide

beads were extensively used as immobilization matrix or encapsulation for food, cosmetics, pharmaceuticals, and biomedical industries. It is advantageous for the delivery of various pH and enzymatic sensitive drug candidates, proteins, hormones, living cells, etc., into the localized area.[14,15] Another significant feature of alginate gels is that it was stable at lower pH while re-swelling capacity in weak or higher pH gastrointestinal region. This feature of susceptible to the environmental pH is utilized for acid-labile drugs loaded within the beads can be protected from the acidic gastric environment.[16] It had been reported that the physicochemical properties of alginate beads were affected by viscosity and concentration grades of alginate, proportion of glucuronic acid-mannuronic acid, charge concentration, gelling time, size and formulation compositions, etc.[17] Taha *et al*., 2005, reported that alginate beads have been used as excellent drug carriers into controlled release formulations for protein drugs, metoclopramide, cisapride, diclofenac, indomethacin, propranolol, gentamicin, gene transfection agent, etc.[18] Alginate beads due to its mucoadhesion property were exploited for site-specific drug delivery to intestinal mucosal for prolonged release of various molecules and macromolecules as investigated by.[19] Furthermore, into his study, he had undertaken to develop controlled release formulations of antidiabetic drug-using alginate beads that were compared with that of marketed conventional tablet formulation. Pongjanyakul and Puttipipatkhachorn 2008 investigated for the incorporation of wax materials and magnesium aluminum silicate could able to modify the physical properties of calcium-alginate beads while increasing the hydrophobic nature that in turn improves the drug entrapment efficiency and retarded drug release properties.[20] Tapia *et al*., 2004 reported that the electrostatic interaction of alginates with other chitosan, carrageenan, etc., for providing prolonged drug release profile of drugs.[21]

Chitosan

Chitosan is the most widely used natural polysaccharide available on the earth obtained through deacetylation of chitin that is found particularly in the shells of crustaceans such as crab and shrimp, cuticles of insects and cell wall of fungi. Such poly ions or poly cations were not digested in the upper GI tract by human digestive enzymes having excellent characteristics of non-toxic, biocompatible, mucoadhesion, and easily biodegradable in nature. It is a copolymer consisting of β-1,4-linked glucosamine (deacetylated units) and N-acetyl-D-glucosamine (acetylated units) residues as shown in Figure 2. The repeating glucopyranose units of chitosan consist of cationic amino groups ($-NH_2$) on the C-2 position that can electrostatically interact with the anionic carboxylic acid (COO^-) groups of other synthetic and natural poly ions such as carrageenan, sodium alginate, xanthan gum, carboxymethyl cellulose, pectin, chondroitin sulfate, hyaluronic acid, dextran sulfate, poly acrylic acids, polyphosphoric acid, poly (L-lactide), urea formaldehyde, glutaraldehyde, and tripolyphosphate to form polyelectrolyte

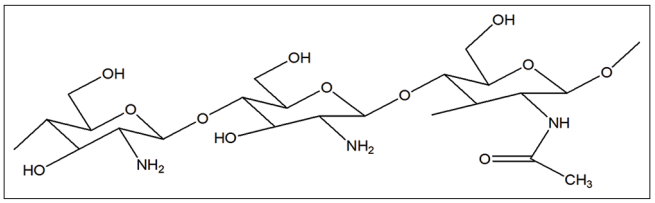

Figure 2: Chemical structure of chitosan polymer

complexes.[22] It is having unique properties of gel and film forming due to which it is used in pharmaceutical industries as potential carriers for development of various controlled drug delivery systems especially for protein and peptide drugs.[23]. Recently, chitosan has drawn attention for its potential to achieve colon-specific delivery as it is susceptible to glycosidic hydrolysis by microbial enzymes present in the colon similar to those of other enzymatically depolymerized polysaccharides. These poly ions on arrival to the colon undergo degradation by microorganism's enzymes or break down, leading toward a subsequent reduction in molecular weight and mechanical strength due to that no more able to hold the drug candidate and thereafter released the drug abruptly into the bio environments. Various studies reported for numerous applications of that chitosan polymer for colon targeting.[24] Chitosan complexes are mostly used for protein delivery, enzyme, drug and cell transplantation, immobilization, etc. Along with these complexes, chitosan-alginate complex may be the most considerable drug delivery among those hydrogel systems. Chitosan poly anion complexes have many 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 poly anion complexes used as biosensors, scaffolds in tissue engineering, for waste-water treatment, and for drug delivery in various forms. Albarghouthi *et al*. investigated about chitosan that was utilized for protein immobilization by covalent coupling of the enzyme β-glucosidase to glutaraldehyde activated chitosan.[25] The immobilized enzymes were more stable into chitosan beads than the free enzymes while effectively maintaining enzyme activities.

Pectin

Among the heterogeneous linear polysaccharides, pectin is one of the natural anionic type poly ions having wider applications in biomedical sciences due to its unique properties of inexpensive, water-soluble, non-toxic, acid stable, highly biocompatible and biodegradable extracted from citrus peels, sugar beetroots, apple pomaces, etc. In food and pharmaceutical industries, it has been used as food additive, thickener, gelling agent, and excipient for drug delivery systems.[26] Pectin also known as pectic polysaccharides are rich in galacturonic acid consists mainly of linear chains of α-1,4 D-galacturonic acid and 1,2 D-rhamnose with D-galactose and D-arabinose side chains having lower viscosities than other plant gums[27] as presented in Figure 3. During last few decades, pectin has been reported to possessing gelling properties to form

hydrogel beads due to ionotropic interaction between anionic carboxylic acid (COO^-) groups with the cationic divalent and trivalent metal ions, namely, Ba^{2+}, Zn^{2+}, Ca^{2+}, Al^{3+}, etc. As due to these properties, it has been extensively investigated in the designing of various oral drug delivery systems.[28,29] On the basis of degree of methylation pectin can be categorized into two as (1) low methoxy pectin or amidated pectin (LMP_C, with 25–5.0% degree of methylation) and (2) high methoxy pectin (HMP_C, with 50–80% degree of methoxylation) that influences the solubility and gelation properties effectively. The two groups of pectin are gelled by different mechanisms due to their different degree of methylation. HMP_C required minimum concentration of soluble solid and pH values to form gelling mass. While, LMP_C required controlled amount of divalent cations and can form gel matrix through ionotropic interactions of the carboxyl groups with cross-linking cations that induces the formation of the so-called "egg-box" structure. Auriemma *et al*. also informed that amidated LMP_C has been suggested for gel beads formulations due to its high hydrophobic interactions of internal hydrogen bonding between amide groups and pectin chain.[30] Gelation by the "egg-box" model is slightly resembles from behavior of those alginates and that is used as an effective vehicle for formulating various drug delivery systems.[31] Pectin is utilized to formulate colon-specific drug delivery systems for several drugs.[32] But some time, pectin based colon delivery formulation suffers from development problems due to its high water solubility that causes easily swelling and release of the entrapped drug into the upper GI tract through diffusion. However, this problem was overcome by the controlled choice of pectin type and additives selections or use of ethylcellulose (hydrophobic polymer), chitosan, etc., in combination other than single-use of pectin polymer alone. For the last few decades, ionotropically gel beads of calcium pectinate have been exhaustively investigated and utilized as a carrier in controlled and sustained release drug delivery for many drugs or for targeting to the colon. However, some report says that these pectinate beads experienced with disadvantages of low percent drug entrapment and premature drug release of drugs.[33] To overcome the limitations, several modifications of calcium pectinate beads have been researched as introducing mucoadhesive polymer-blend with LMPc, ionotropically gelled calcium pectinate mucoadhesive beads for controlled release, etc., by various researchers.[34,35] In addition, calcium pectinate is not degraded or broken down by gastric or intestinal enzymes, but due to various enzymes secreted by microbial populations that are present in human colonic regions.[36]

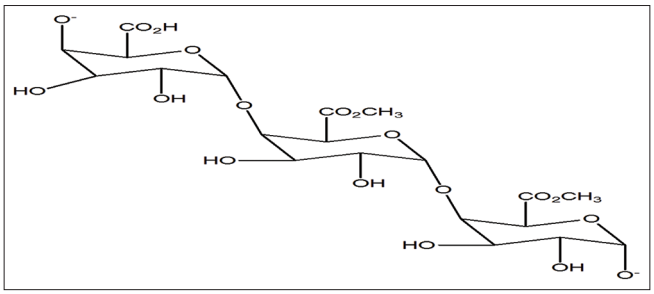

Figure 3: Typical chemical structure of pectin

Gellan gum

Gellan gum is a water-soluble anionic bacterial exopolysaccharide obtained commercially by anaerobic submerged fermentation of microorganism called Pseudomonas elodea. Food and Drug Administration in its 21 CFR 172.665 approved the gellan as safe and may be used as a direct food additive for human consumption. Gellan is consisting of linear structure of repeating tetrasaccharide units of glucose, glucuronic acid, and rhamnose 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→] as residues [Figure 4]. Gellan beads were evaluated for the effect of various divalent cations on percent entrapment efficiencies with constant factors of polymer concentration and ionotropic medium. Coviello *et al*. informed for the type of cations and its atomic number that affects the drug solubility and loading efficiency of gelled beads.[6] The higher the atomic number of polycations, the higher the ionotropic gelation, and thereby increased loading efficiencies occur. Such polysaccharide has been investigated for the controlled and sustained release of a various drug candidate(s) as its unique ability to form ionotropic hydrogel beads in the presence of monovalent (Na^+ and K^+) or divalent (Ca^{2+} and Mg^{2+}) cations. It has been reported that the Gellan beads are stable in lower gastric pH condition, but swell abruptly in higher pH condition due to which the beads allow faster drug release at alkaline pH condition suitable for colon-specific delivery.

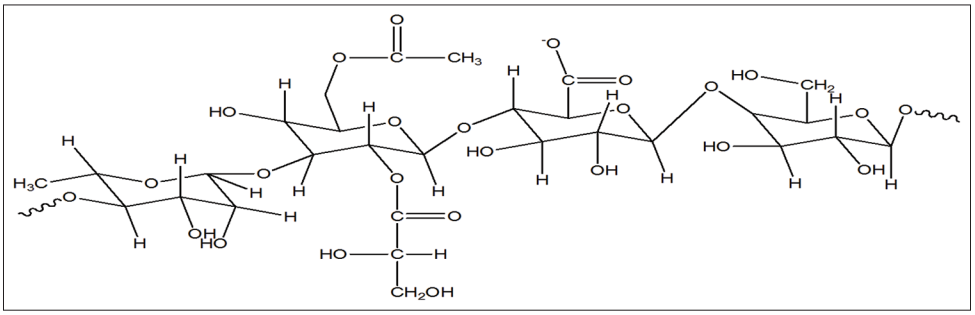

Figure 4: Chemical structure of gellan gum polymer

Xanthan gum

Xanthan gum is an extracellular polysaccharide secreted by the bacterium *Xanthomonas campestris*, commonly used as a food additive and rheology modifier, stabilizer in cosmetic products, and additives in numerous oral drug delivery systems. The gum consisting of a primary chain of β-D-(1,4)-glucose backbone, having branching of trisaccharides side-chain comprised of β-D-(1,2)-mannose attached to β-D-(1,4)-glucuronic acid, which terminates in β-D-mannose [Figure 5]. Many researchers had investigated the gum for oral and topical formulations, preparation of pellets,[37] sustained released tablet dosage form, etc. Pongjanyakul and Puttipipatkhachorn investigated on xanthan-alginate composite gel beads and suggested that xanthan gum could modulate physicochemical properties and drug release of drug-loaded calcium-alginate beads, which in turn is based on the existence of molecular interaction between xanthan and sodium alginate.[38] The ionic gelation of xanthan gum can be induced by a change in temperature, ionic strength of the solution, the pH, and type of electrolytes (Na^+, K^+, $NH4^+$, Ba^{2+}, Mg^{2+}, Ca^{2+}) used. An investigation was carried by Argin-Soysal *et al*. prepared microcapsules from a combination of chitosan-xanthan gum polyelectrolyte complexes.[39] It designated that the extent of cross-linking was mutually dependent on the concentration of xanthan and chitosan and pH of chitosan solution. Furthermore, it was reported that chitosan-xanthan microcapsules can be used as a matrix for enzyme immobilization and to improve the dissolution of water-insoluble drugs, namely, ursodeoxycholic acid, fenofibrate, indomethacin, and nifedipine.[6,3]

Carboxymethyl cellulose

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 multivalent metal ions can be primarily stabilized by the electrostatic interactions. In addition, the stability and the water insolubility of these polyelectrolyte complex may be due to the interactions between the –OH groups of the polymer and with the metal ions, as depicted in Figure 6. For the preparation of biodegradable hydrogel beads, the CMC mainly cross-linked with aluminum/ferric salt.[40]

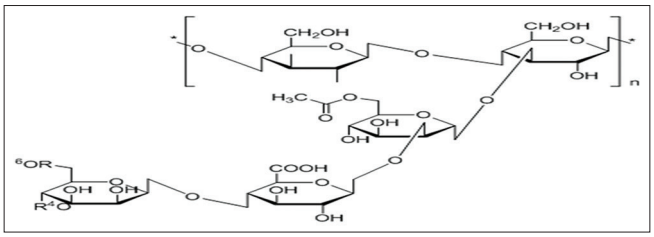

Figure 5: Chemical structure of xanthan gum polysaccharide

Carrageenan

Carrageenan is an anionic high molecular weight sulfated ester polysaccharides extracted from marine red edible seaweeds consisting of an alternative copolymer of 1,4-α and 1,3-β-D-galactopyranose and 3,6-anhydro-D-galactopyranose units. It is a linear heteropolysaccharide basically classified into three types which differ in their degree of sulfate ion, namely, Kappa carrageenan (κ) has one sulfate group per disaccharide, Iota carrageenan (i) has two sulfate groups per disaccharide, and Lambda carrageenan (λ) has three sulfate groups per disaccharide. As per the degree of sulphation, k–Carrageenan and i-Carrageen are widely used their gelling properties while λ-Carrageenan is used for its thickening and stabilizing properties. Carrageenan has been used as a sustained release formulation due to its properties of gelling, viscosity-enhancing, and proven safety reasons. Polyelectrolyte complexes using combined use of κ-, ι -, λ-carrageenan, and chitosan to form controlled release systems. The formed polyelectrolyte complex between chitosan and κ-carrageenan showed high encapsulation efficiencies that were able to protect encapsulates against degradation into upper GI acidic pH conditions. Use of κ-carrageenan to prepare a blend hydrogel system with two natural agar and gelatin polymers and found that drug release mechanisms were related to the network structure of gelatin-κ-carrageenan.[41,42]

Glucomannan

Glucomannan is a high molecular weight water-soluble polysaccharide extracted from tubers of *Amorphophallus konjac* plant commonly named as konjac glucomannan. Glucomannan is mainly a straight-chain polymer, with a small amount of branching consisting of the component sugars are β-(1→4)-linked D-mannose and D-glucose in a ratio of 1.6:1, respectively. The degree of branching is about 8% through β-(1→6)-glucosyl linkages. Glucomannan with α-(1→6) linked galactose units in side branches is called galactoglucomannan [Figure 7]. The polysaccharide is not digested at the upper GI tract, similar to pectin. These

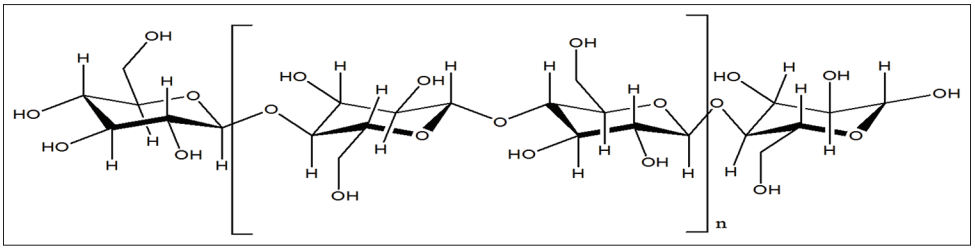

Figure 6: Chemical structure of carboxymethyl cellulose

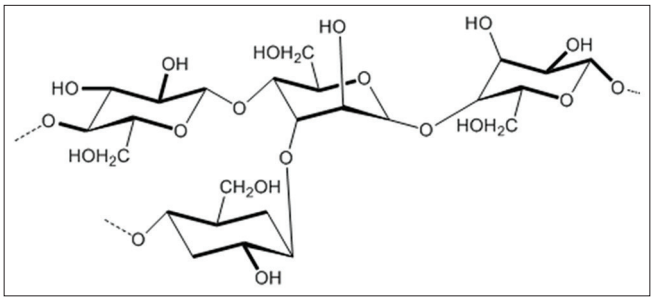

Figure 7: Chemical structure of glucomannan polymer

were recognized for the preparation of delivery systems to prevent the risk of diabetes and heart diseases. When the polymeric solution of glucomannan is heated with mild alkali or in the presence of a higher amount of salt could result into strong, elastic, and heat-stable glucomannan gel that is used as a carrier for drug delivery systems. Due to heating, the interaction takes place between acidic moieties of glucomannan with alkalies that facilitate the formation of hydrogen bonding and hydrophobic interactions between the glucomannan chains leading to the formation of gel networks. The gelation is affected by some parameters such as degree of acetylation, temperature, molecular weight, concentration of the polymer, and alkali additions. Gelation of glucomannan with carrageenan, alginate, chitosan, xanthan gum, and gellan gum had been reported by various researchers for the preparation of promising drug delivery systems using model drug.[43]

Hyaluronan

Hyaluronan or hyaluronic acid (HA) is a non-sulfated glycosaminoglycan consists of 2500–25,000 repeating long-chain disaccharide units of D-glucuronic acid (GlcA) and D-N-acetyl-glucosamine (GlcNAc), linked through alternating β-1,4 and β -1,3 glycoside bonding. These glycosaminoglycans are associated with the glucuronate unit that carries an anionic charge and also a carboxylate group that carries negative charges at physiological pH. It is found in the mammalian extracellular matrix throughout the bone marrow and connective tissues, as well as skin, vitreous humor of the eye, cartilage, and umbilical cord tissue. These are produced for commercial purposes through extraction from rooster combs, synovial fluids, umbilical cords, or vitreous humor bacterial or by fermentation of *Streptococcus* species. HA is a naturally occurring, high molecular mass (ranging from 10^3 to 10^4 kDa), and linear anionic polysaccharide possessed with excellent physicochemical properties such as biocompatibility, biodegradability, and non-immunogenicity and highly hydrophilic under physiological conditions. During the last few decades, its physical and biochemical properties in hydrogel form have extremely secured a widespread range of applications in various drug deliveries, tissue engineering, viscosupplementation, cosmetics, tissue engineering, plastic filling, wound dressing, bio-printing, and other pharmaceutical and biomedical uses. Hydrogels prepared from HA are particularly striking suitable to its excellent high water retention capacity, viscoelastic properties, and biodegradable properties. These were designed with chitosan-hyaluronic acid PEC scaffold cross-linked with genipin systematically as a template for controlled BMP-2 delivery for bone tissue engineering. It was found that BMP-2 was immobilized in the chitosan-hyaluronic acid PEC by the electrostatic attraction that has potential in drug and protein delivery and bone and soft tissue engineering.[6,11]

Kondagogu

Gum kondagogu, a "novel natural biopolymer" form collected by tribal by tapping from the tree of *Cochlospermum gossypium* (Family: Bixaceae), is also recognized as "good emulsifying agent even at low concentration." Gum kondagogu (*C. gossypium*), an exudates tree gum, was explored for its potential to decontaminate toxic metals such as Pb^{2+} and Cd^{2+}. The presence of optimum biosorption of metals was determined by investigating the contact time, pH, initial concentration of metal ions, and biosorbent dose at define temperature. Kondagogu is an anionic polysaccharide belonging to the class of substituted rhamnogalacturonans. It has unique, including its morphological, physicochemical, structural, rheological, pharmaceutical, and emulsifying properties. Physicochemical properties consisted of high soluble fiber, high volatile acidity, and water binding capacity. The structural analysis of kondagogu biopolymer contains sugars such as rhamnose, arabinose, glucose, mannose, galactose, glucuronic acid, and galacturonic acid and other major functional groups identified in the gum were hydroxyl, acetyl, carbonyl, and carboxylic groups. These polymer-metal complexes are employed in a different field and mainly used for the synthesis organic catalysts, hydrometallurgy, environmental remediating agents, sensing, and biomedical fields. The principal mechanisms involved in metallic cation sequestration, the formation of complexes between a metal ion and functional groups (carboxyl, carbonyl, amino, sulfonate, amido, phosphate, etc.) Different binding mechanisms involved such as physical adsorption, ion exchange, complexation, chemisorption, and microprecipitation are proposed in metal binding processes by an adsorbent.[44]

Pullulan gum

Pullulan is a natural polysaccharide generated from starch by cultivating black yeast *Aureobasidium pullulans*. The gum is odorless, tasteless, white color, and water-soluble. Pullulan polymer consisting of maltotriose units, also known as α-1,4- and α-1,6-glucan. In these three glucose units in maltotriose are connected by an α-1,4 glycosidic bond, whereas consecutive maltotriose units are connected to each other by an α-1,6 glycosidic bond. The average molecular weight of pullulan is 2,00,000 daltons and has admirable film-forming qualities. Mainly commercial use of pullulan is in the manufacture of edible films that are used in various breath fresheners or oral hygiene products formulation. Pullulan polysaccharide may be used as a

coating and packaging material, as a sizing agent for paper, in plywood manufacturing, and in dielectric condensers, as a starch replacer in low-calorie food formulations, in cosmetic emulsions, and in other industrial and medicinal applications. It is mainly used by the cell to resist against desiccation and predation, the presence of this polysaccharide also facilitates diffusion of molecules both into and out of the cell. Due to all those properties, it is very useful for the delivery of drug through diffusion or erosion mechanism from dosage forms.[6]

Colon-specific delivery utilizing multiparticulate systems

Colon-specific drug delivery has acquired enough importance for the oral route for last few decades. It provides a friendlier environment for various drug candidates, including those protein, peptides, oligonucleotides vaccines, and growth hormones than the hostile upper GIs. The colon is proved to be beneficial for local treatment of a number of pathologies such as colorectal cancer, Crohn's disease, inflammatory bowel disease, and amebiasis as per reports. To achieve successful colon drug delivery, any drug needs to be protected from degradation, release and/or absorption in the upper portion of gastrointestinal (GI) tract and then ensure for abrupt or sustained and controlled release upon arrival into the proximal colon region. Colon targeting is usually advised because of several advantages, namely, predictable gastric emptying, reduced risk of toxicity, reduced dose dumping, reduced local irritation, reduced inter-intra subject variability, increased bioavailability, improved stability, etc. Colon as a site offers distinct advantages on account of a near-neutral pH, a much longer transit time, reduced digestive enzymatic activity, and much greater responsiveness to absorption enhancers. Colonic drug delivery is also reported for local or systemic absorption of various drug candidates, especially protein and peptide types, because of the less hostile environment as compared with the stomach and/or small intestine.

It has been reported by many researchers that few conventional dosage forms were inefficient for delivering drug to the colon in appropriate concentration due to the reason of being absorption or degradation (assaults) of upper GI. However, drug targeting to colon would be promising for both local and systemic drug delivery.[45-50] Literature review suggested that various targeting approaches have been utilized to achieve colon-specific drug delivery, including, namely, (a) time-dependent delivery, (b) pH-sensitive polymer coatings, (c) microbially triggered enzymatic degradation by colonic bacteria, (d) prodrug approach based delivery, and (e) pressure controlled release system. Among all those systems developed, the use of combinations of pH-dependent systems and microbially triggered approaches together are reported for more practical significances and promising for colon-specific delivery.[51-53]

The use of such natural, synthetic, or semi-synthetic type polymers in the design and development of colon delivery systems has gained much attention owing to their excellent biocompatibility and biodegradability properties only. Biodegradable and biocompatible type polysaccharides such as chitosan, pectin, inulin, alginate, and guar gum have been extensively explored for colon targeting potentials. Among several polymers, those pH-sensitive sodium alginate, pectin, and chitosan were have been widely used by various researchers and proved to be promising matrix carriers for those MPs based dosage forms. It has been well documented by many researchers that the microflora present in the colonic region is considered surely as triggering component for that site-specific drug releases out from dosage forms. The colon consists of more than 400 bacterial species, namely, Bacteroides, Eubacterium, Lactobacillus, Bifidobacterium, etc., having a population of 10^{11}–10^{12} CFU/ml were only highly responsible for the fermentation and degradation of polysaccharides (polymers) for dietary sources. Those specific bacterial enzymes responsible that were acting as triggering components for polymeric degradation are including B-xylosidase, β-D-glucosidase, β-D-galactosidase, and β-D-fucosidase. The matrix polysaccharides of dosage forms are mostly hydrophilic in nature that gets swells and form a viscous gel-like mass upon contact with dissolution fluids or gastrointestinal fluids. The alginate-chitosan based polymeric beads prepared by either single cross-linking or dual cross-linking beads had been widely investigated by those researchers.[54,55] In our pharmaceutical field, the polysaccharides are now a day became an indispensable excipient for the development of colon-specific dosage form developments. It has wider utilization in terms of that, able to sustain or control the drug release profile out from the system, act as potential carriers, as well as highly susceptible to degradation by the colonic microflora, etc. In addition, it has been well established that for the purpose of evaluations of colon-specific delivery systems, the cecal content of rodents is utilizing more commonly as an alternative dissolution medium to overcome certain limitations of conventional USP dissolution testing. Since that cecal content is found to have similarity with human colonic microflora and fermentation of polysaccharides, such an approach could avoid the limitations during the designing of pH-dependent and microbial triggered delivery systems.[56-60]

CONCLUSIONS AND PROSPECTS

An ample range of research had been done on the polyelectrolyte complexes based MP systems during the last few decades which state that it had gained much importance in our modern pharmaceutical technology. The current scenario also emphasizes that it is one of the promising tools in the development of biocompatible, novel controlled and sustained drug delivery systems for a range of drug candidates. Polyelectrolyte complexes are having the ability to merge the unique properties of those matrix polysaccharides and also potential in encapsulating the drug without losing their stability and biocompatibility. Polysaccharides and

polyelectrolyte complexes based systems were yet to have numerous other potentials and applications in the future for our field of pharmaceutical technology regarding the designing of novel and controlled drug delivery system for colon delivery. These techniques are proved to be successful by altering some of the physicochemical parameters of polysaccharides for modified drug release rate while retaining their structural integrity on the other hand. As per advancement into the area of polymer chemistry, these demands were rising day by day. Also that, due to the development of polyelectrolyte complexes, the intensive utilization of expensive and toxic organic solvents in the microencapsulation process has been reduced abruptly. Polyelectrolyte complexes based on ionic gelation were confirm to provide biocompatible and eco-friendly pharmaceutical product development, of which it is anticipated to have multiple applications and scope in the near future.

DECLARATION OF INTEREST

The authors declare that there are no conflicts of financial interest or financial conflict with the subject matter or materials discussed in the manuscript.

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REFERENCES

1. Wang F, Yang Y, Ju X, Udenigwe CC, Han R. Polyelectrolyte complex nanoparticles from chitosan and acylated rapeseed cruciferin protein for curcumin delivery. J Agric Food Chem 2018;66:2685-93.
2. Etrych T, Leclercq L, Boustta M, Vert M. Polyelectrolyte complex formation and stability when mixing polyanions and polycations in salted media: A model study related to the case of body fluids. Eur J Pharm Sci 2005;25:281-8.
3. Asghar LF, Chandran S. Multiparticulate formulation approach to colon specific drug delivery: Current perspectives. J Pharm Pharm Sci 2006;9:327-38.
4. Berger J, Reist M, Mayer JM, Felt O, Peppas NA, Gurny R. Structure and interactions in covalently and ionically crosslinked chitosan hydrogels for biomedical applications. Eur J Pharm Biopharm 2013;57:19-34.
5. Tomme VSR, Storm G, Hennink WE. *In situ* gelling hydrogels for pharmaceutical and biomedical applications. Int J Pharm 2008;355:1-18.
6. Coviello T, Matricardi P, Marianecci C, Alhaique F. Polysaccharide hydrogels for modified release formulations. J Control Release 2007;119:5-24.
7. Mark HF, Bikales NM, Overberger CG, Menges G. Encyclopedia of Polymer Science and Engineering. 2nd ed. New York: Willey Interscience Publisher; 1987. p. 739.
8. Berger J, Reist M, Maye JM, Felt O, Gurny R. Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. Eur J Pharm Biopharm 2004;57:35-52.
9. Bhattarai N, Gunn JJ, Zhang M. Chitosan-based hydrogels for controlled, localized drug delivery. Adv Drug Deliv Rev 2010;62:83-99.
10. Park JH, Saravanakumar G, Kim K, Kwon IC. Targeted delivery of low molecular drugs using chitosan and its derivatives. Adv Drug Deliv Rev 2010;62:28-41.
11. Hamman JH. Chitosan based polyelectrolyte complexes as potential carrier materials in drug delivery systems. Mar Drugs 2010;8:1305-22.
12. Lankalapalli S, Kolapalli VR. Polyelectrolyte complexes: A review of their applicability in drug delivery technology. Indian J Pharm Sci 2009;71:481-7.
13. Sankalia MG, Mashru RC, Sankalia JM, Sutariya VB. Papain entrapment in alginate beads for stability improvement and site-specific delivery: Physicochemical characterization and factorial optimization using neural network modeling. AAPS PharmSciTech 2005;6:E209-22.
14. Gao C, Liu M, Chen S, Jin S, Chen J. Preparation of oxidized sodium alginate-graft-poly((2-dimethylamino) ethyl methacrylate) gel beads and *in vitro* controlled release behavior of BSA. Int J Pharm 2009;371:16-24.
15. Pongjanyakul T, Puttipipatkhachorn S. Modulation of drug release from glyceryl palmitostearate-alginate beads via heat treatment. Int J Pharm 2006;319:20-8.
16. Tamponnet C, Lievremont M. Production of proteoglycans by immobilized chodryocytes: Effect of divalent cations. Biotechnol Tech 1991;5:69-72.
17. Lee BJ, Min GH. Preparation and release characteristics of polymer-reinforced and coated alginate beads. Arch Pharm Res 1995;18:183-8.
18. Taha MO, Aiedeh KM, Al-Hiari Y, Al-Khatib H. Synthesis of zinc-crosslinked thiolated alginic acid beads and their *in vitro* evaluation as potential enteric delivery system with folic acid as model drug. Pharmazie 2005;60:736-42.
19. Nayak D, Lahiri S. Biosorption of toxic, heavy, no-carrier-added radionuclides by calcium alginate beads. J Radioanal Nucl Chem 2006;267:59-65.
20. Pongjanyakul T, Puttipipatkhachorn S. Alginate-magnesium aluminum silicate composite films: Effect of film thickness on physical characteristics and permeability. Int J Pharm 2008;346:1-9.
21. Tapia C, Escobar Z, Costa E, Sapag-Hagar J, Valenzuela F, Basualto C, *et al*. Comparative studies on polyelectrolyte complexes and mixtures of chitosan-alginate and chitosan-carrageenan as prolonged diltiazem clorhydrate release systems. Eur J Pharm Biopharm 2004;57:65-75.
22. Pandey S, Mishra A, Raval P, Patel H, Gupta A, Shah D. Chitosan-pectin polyelectrolyte complex as a

carrier for colon targeted drug delivery. J Young Pharm 2013;5:160-6.
23. Wu C, Lo SL, Boulaire J, Hong ML, Beh HM, Leung DS, *et al*. A peptide-based carrier for intracellular delivery of proteins into malignant glial cells *in vitro*. J Control Release 2008;130:140-5.
24. Jain SK, Jain A, Gupta Y, Ahirwar M. Design and development of hydrogel beads for targeted drug delivery to the colon. AAPS PharmSciTech 2007;8:E34-41.
25. Albarghouthi M, Fara DA, Saleem M, El-Thaher T, Matalka K, Badwan A. Immobilization of antibodies on alginate-chitosan beads. Int J Pharm 2000;206:23-34.
26. Nayak AK, Pal D. Blends of jackfruit seed starch-pectin in the development of mucoadhesive beads containing metformin HCl. Int J Biol Macromol 2013;62:137-45.
27. Wong TW, Colombo G, Sonvico G. Pectin matrix as oral drug delivery vehicle for colon cancer treatment. AAPS PharmSciTech 2010;12:201-14.
28. Munarin F, Petrini P, Tanzi MC, Barbosa MA, Granja PL. Biofunctional chemically modified pectin for cell delivery. Soft Matter 2012;8:4731-9.
29. Patil JS, Kamalapur MV, Marapur SC, Kadam DV. Ionotropic gelation and polyelectrolyte complexation: The novel techniques to design hydrogel particulate sustained, modulated drug delivery system: A review. Dig J Nanomater Biostruct 2010;5:241-8.
30. Auriemma G, Mencherini T, Russo P, Stigliani M, Aquino RP, Gaudio PD. Prilling for the development of multi-particulate colon drug delivery systems: Pectin vs. pectin-alginate beads. Carbohydr Polym 2013;92:367-73.
31. Das RK, Kasoju N, Bora U. Encapsulation of curcumin in alginate-chitosan-pluronic composite nanoparticles for delivery to cancer cells. Nanomedicine 2010;6:153-60.
32. Oliveira MA, Ciarlini PC, Feitosa JP, De Paula RC, Paul HC. Chitosan/"angico" gum nanoparticles: Synthesis and characterization. Mater Sci Eng C 2009;29:448-51.
33. Lee MH, Chun MK, Cho HK. Preparation of Carbopol/ Chitosan interpolymer complex as a controlled release tablet matrix; effect of complex formation medium on drug release characteristics. Arch Pharm Res 2008;31:932-7.
34. Chakraborty S, Khandai M, Sharma A, Khanam N, Patra CN, Dinda SC. Preparation, *in vitro* and *in vivo* evaluation of algino-pectinate bioadhesive microspheres: An investigation of the effects of polymers using multiple comparison analysis. Acta Pharm 2010;60:255-66.
35. De Castro LI, Soares RA, Saldiva PH, Ferrari RA, Miguel AM, Almeida CA, *et al*. Amaranth oil increased fecal excretion of bile acid but had no effect in reducing plasma cholesterol in hamsters. Lipids 2013;48:609-18.
36. Chambin O, Dupuis G, Champion D. Colon-specific drug delivery: Influence of solution reticulation properties upon pectin beads performance. Int J Pharm 2006;321:86-93.
37. Santos H, Veiga F, Pina ME, Sousa JJ. Compaction, compression and drug release characteristics of xanthan gum pellets of different compositions. Eur J Pharm Sci 2004;21:271-81.
38. Pongjanyakul T, Puttipipatkhachorn S. Xanthan-alginate composite gel beads: Molecular interaction and *in vitro* characterization. Int J Pharm 2007;331:61-71.
39. Argin-Soysal S, Kofinas P, Lo YL. Effect of complexation conditions on xanthan-chitosan polyelectrolyte complex gels. Food Hydrocoll 2009;23:202-9.
40. Kulkarni RV, Setty B, Kalyane NV. Carboxymethylcellulose-aluminum hydrogel microbeads for prolonged release of simvastatin. Acta Pharma Sci 2010;52:137-43.
41. Shumilina EV, Shchipunov YA. Chitosan-carrageenan gels. Colloid J 2002;64:372-8.
42. Briones AV, Sato T. Encapsulation of glucose oxidase (GOD) in polyelectrolyte complexes of chitosan-carrageenan. React Funct Polym 2010;70:19-27.
43. Jain A, Gupta Y, Jain SK. Perspectives of biodegradable natural polysaccharides for site-specific drug delivery to the colon. J Pharm Pharm Sci 2007;10:86-128.
44. Friend DR, Chang GW. A colon-specific drug-delivery system based on drug glycosides and the glycosidases of colonic bacteria. J Med Chem 1984;27:261-6.
45. Watts P, Lllum L. Colonic drug delivery. Drug Dev Ind Pharm 1997;23:893-913.
46. Fell JT. Targeting of drugs and delivery systems to specific sites in the gastrointestinal tract. J Anat 1996;189:517-9.
47. Rubinstein A. Approaches and opportunities in colon-specific drug delivery. Crit Rev Ther Drug Carrier Syst 1995;12:101-49.
48. Kumar LS, Singh JS. Development and *in-vitro* drug release studies of methotrexate from modified pulsatile release guar gum based enteric coated capsules for colon specific delivery. Indian J Pharm Educ 2008;42:154-60.
49. Gazzaniga A, Iamartino P, Maffione G, Sangalli ME. Oral delayed-release system for colonic specific delivery. Int J Pharm 1994;108:77-83.
50. Sinha VR, Kumria R. Coating polymers for colon specific drug delivery: A comparative *in vitro* evaluation. Acta Pharm 2003;53:41-7.
51. Peeters R, Kinget R. Film-forming polymers for colonic drug delivery: I. Synthesis and physical and chemical properties of methyl derivatives of Eudragit S. Int J Pharm 1993;94:125-34.
52. Van Den Mooter G, Samyn C, Kinget R. *In vivo* evaluation of a colon-specific drug delivery system: An absorption study of theophylline from capsules coated with azo polymers in rats. Pharm Res 1992;12:244-7.
53. Bansal AK, Pande V. Development and evaluation of dual cross-linked pulsatile beads for chronotherapy of rheumatoid arthritis. J Pharm (Cairo) 2013;2013:906178.
54. Xu Y, Zhan C, Fan L, Wang L, Zheng H. Preparation of dual crosslinked alginate-chitosan blend gel beads and *in vitro* controlled release in oral site-specific drug delivery system. Int J Pharm 2007;336:329-37.

55. Gorbach SL. Intestinal microflora. Gastroenterology 1971;60:1110-29.
56. Macfarlane GT, Cummings JH, Philips SF, Pemberton JH, Shorter RG. The colonic flora fermentation and large bowel digestive function. In: The Large Intestine: Physiology, Pathophysiology and Diseases. New York: Raven Press; 1991. p. 51-92.
57. Prasad YV, Krishnaiah YS, Satyanarayana S. *In vitro* evaluation of guar gum as a carrier for colon-specific drug delivery. J Control Release 1998;51:281-7.
58. Yang L, Chu J, Fix J. Colon-specific drug delivery: New approaches and *in vitro*/*in vivo* evaluation. Int J Pharm 2002;235:1-15.
59. Kumar S, Jeet K, Baldi A. Recent technological advancements in multiparticulate formulations: The smart drug delivery systems. Asian J Pharm 2015;9:S13-25.
60. Ramesh KV, Yadav HK, Usman S, Elmarsafawy TS. Studies on the influence of formulation and processing factors on the drug release from multiparticulate systems. Asian J Pharm 2020;14:17-25.

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