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Archives of Gastroenterology Research Review Article

Advances in Functionalized Hybrid Biopolymer Augmented Lipid-based Systems: A Spotlight on Their Role in Design of Gastro Retentive Delivery Systems

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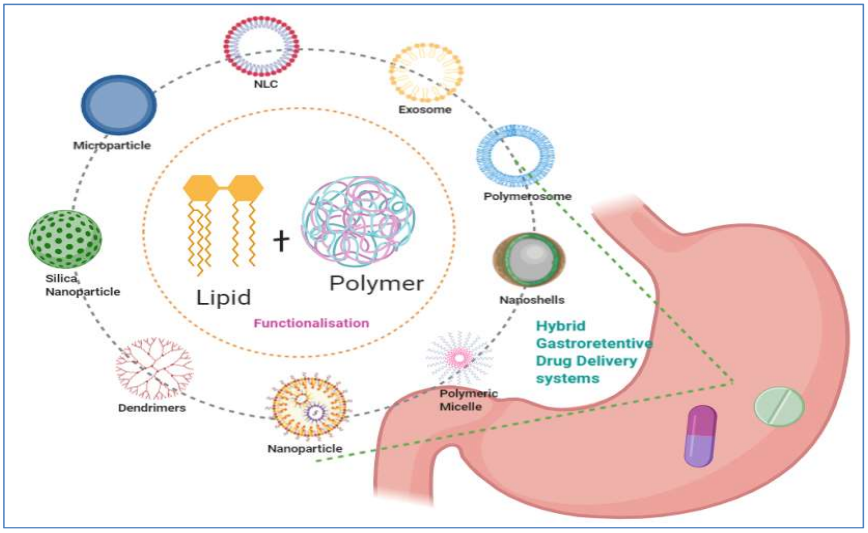
Abstract

Biopolymers are the polymers extracted from living organisms either from renewable plant or animal sources are gaining importance due to their better biodegradability, biocompatibility, less/no immunogenicity, less/no toxicity, and availability. Polysaccharides (e.g., chitosan, cellulose), polypeptides (e.g., collagen, silk), and polynucleotides are the important class of biopolymers that are finding multidisciplinary applications in biomedical fields. At the other end, lipid-based systems are having their special concern in drug delivery due to their advantages over other excipient systems. In this present review, various classes of biopolymers and their fusion with conventional lipids for amalgam entity using advanced techniques for futuristic biomedicine applications are outlined. The comprehensive focuses on upbringing the importance and types of functionalization techniques explored for designing deliverable for various unmet clinical needs. Along with recent trends, the scrutiny even addresses the future perspective of these hybrid systems impacting in addressing the pharceutical, formulational and clinical challenges in treating gasteroentric diseases.

Keywords: Lipid, Biopolymers, Functionalization, Drug delivery, Gastro retentive systems



Graphical abstract

Introduction

Biopolymers have earmarked their importance in the biomedical and pharmaceutical applications. Researchers are still working for the facilitation of better therapeutic effects and medical benefits. In this context, several strategies are on a play like functionalization of biopolymers with physicochemical modification, functionalization of lipids with biopolymers, development of composites or hybrid systems for bringing together the benefits of individual moieties/systems (e.g., a combination of polymers or combination of systems) and technical advancements. Different categories of biopolymers are well established physically, chemically, and biologically to let them useful in biomedical avenues. The drawbacks, if any, existing with the developed systems are being circumvented with the initiation of these composite/hybrid concepts with proven scientific responses worldwide. One such concept is the combined application of biopolymers with lipids and lipid-based systems [1]. Several lipid-based systems have gained wide-spread usage in the treatment and management of health. Examples include solid lipid nanoparticles, liposomes, micelles, and lipid hydrogels. These systems can provide controlled drug delivery, gene delivery, wound healing, and tissue engineering. Life-threatening diseases like cancer, immune disorders are being handled with such advanced lipid-based systems in addition to the particulate systems. However, they do suffer from certain drawbacks like low stability, less production feasibility, lack of hydrophilic properties, poor mechanical strength, and high processing costs [2,3]. To overcome the aforementioned drawbacks, the lipid systems are conjugated as composite systems with biopolymers to keep the hybrid composite stable, enhance the functionality, impart the properties of biopolymers and modulate the characteristics of the lipid system. Biopolymers are the polymers obtained from natural resources and are biocompatible, biodegradable, no or less antigenic, bioactive, easy to fabricate, comparatively stable, and supporting to cell growth and proliferation [3,4].

Biopolymers

Biopolymers are the naturally arising polymeric materials from the living organisms either plant or animal or organism sources. They have predominant thrust in the pharmaceutical and biomedical fields of clinical application [5-7]. Biopolymers are classified as polysaccharides such as chitosan, cellulose, starch, xanthan, dextran, alginate; polypeptides such as collagen, gelatin, silk, zein, albumin; polynucleotides such as DNA, RNA and polyesters like polylactic acid, polyhydroxyalkanoates [1,8,9]. Physicochemical properties, structural factors, and composition of the biopolymer that defines its functional efficiency can be modulated to obtain the appropriate efficiency. For example, the electrical characteristics of the biopolymer influence the repulsion rate, aggregation, and interaction with other molecules [2,10]. Biopolymers obtained from renewable sources are easily biodegradable due to their structural backbone comprising of oxygen and nitrogen atoms. Upon biodegradation, biopolymers release water, carbon dioxide, biomass, humid mass, and some natural substances as metabolites that are naturally recycled by biological processes [11].

Polysaccharides

Polysaccharide based biopolymers are abundantly available and are highly used in pharmaceutical and biomedical fields. They are cheap, biocompatible, and show low or no toxicity. For tailoring of the functional attributes, the natural polysaccharides can be modulated by physical, chemical, or enzymatic alterations [12,13]. Different polysaccharides used as biopolymers are Agarose, Gum Arabic, Tragacanth, Alginate, Gellan gum, Chitin/Chitosan, Starch, Carrageenan, Dextran, Bacterial Cellulose, Nanocellulose, Xanthan gum.

Agarose: Agarose is a natural polysaccharide obtained from the Gelidium and Gracilario species of seaweed. Agarose hydrogel nanoparticles are potential systems for the delivery of protein and peptide drugs due to their high biocompatibility [14].

Gum arabic: Gum arabic is a complex exudate obtained from the stems and branches of Acacia senegal and Acacia seyal. It is highly used to cover the inflamed surfaces on the external application and for the treatment of intestinal mucosal inflammation on internal application. It is used as a promising agent in tissue engineering and drug delivery. Gum arabic is also tailorable to suit pH-responsive features and magnetic biomaterial development [1,15]. It is also claimed to have a gut, cardio, dental, nephron-protective effects along with antimicrobial and antioxidant properties [16].

Alginate: Alginate is one of the abundantly available biopolymers obtained from brown seaweed. This is a water-soluble exudate that has been extensively biosynthesized and used in the development of several drug delivery and biomedical systems. Alginate is an anionic charge biopolymer comprising of mannuronic acid and guluronic acid blocks [17-19]. Properties like solubility, hydrophobicity, and biological functionality are altered by modifying the availability of hydroxyl and carboxyl groups in its structure [20]. Alginate hydrogels are of high interest in the research area due to its unique properties of porosity, swelling nature, biocompatibility, biodegradability, non-antigenicity and is also useful in tissue engineering and regeneration. Alginates are also

having applications in dentistry [1]. Being approved by the U.S. Food and Drug Administration (FDA), alginate is used as a biomaterial in pharmaceutical, regenerative medicine, and biomedical applications. Alginate's ability to rapidly convert as a gel in the presence of divalent cations e.g., calcium made it a highly used biopolymer for nanoparticles and microparticles preparation through the ion-gelation method. The formation of polyelectrolyte complexes due to anionic charge of alginate and cationic charge of chitosan has been widely reported [21].

Carrageenan: Carrageenan, a gelling and viscous polysaccharide, is obtained from the seaweeds of the Rhodophyceae family [1]. It is a sulphated polygalactan showing 3 types (κ-, ι- and λ-) with varied percentage of ester sulfate content, 15-40 %. The difference in gelling properties of carrageenan is attributed to the variation in sulfate groups and anhydrous links [22].

Hyaluronic acid: Hyaluronic acid, a biocompatible and biodegradable mucoadhesive biopolymer of polysaccharide category, is a U.S. FDA approved material and is present in the extracellular matrix and joints of mammals [23]. It shows a negative charge and is used in polyelectrolyte complex formation with other opposite charged polymers. It is also used as a copolymer for better drug delivery. It is known for several applications like wound healing, tissue regeneration, ophthalmic treatment, intraarticular injections, etc [24-27]. Modified hyaluronic acid has been reported for its application as a dental implant, ocular lenses, catheters, dermal regeneration, etc [1,28,29].

Gellan gum: Gellan gum a biopolymer obtained from Pseudomonas elodea (or Sphingomonas elodea). It is used in colon-specific drug delivery as it is stable over the upper GI environment. It is preferred for better application in combination with other biopolymers like xanthan gum and chitosan [12,30-33].

Inulin: Inulin is a natural substance obtained from vegetables and is recognized for its probiotic effect. It is applicable for colon targeted delivery due to its stable nature in the stomach and intestine on partial hydrolysis [12].

Chitosan: Chitosan, a cationic polysaccharide is a derivative of chitin which is initially isolated from the mushroom. Chitin is insoluble and its deacetylated form chitosan is water-soluble. After cellulose, chitin is the most abundant biopolymer obtained from different sources like yeast, fungi, insects, crustaceans (e.g., crabs, lobsters, shrimps), shellfish, and nematodes. Chitosan has gained its importance in several biomedical and pharmaceutical applications and also reported with some therapeutic actions (anti-bacterial, anti-acid, dental). Its electrostatic properties are favorable for the development of hybrid systems. The availability of chitosan in different molecular grades and degree of acetylation enable it for the fabrication of biocomposites [1,12,34-44].

Glucans: Glucan is a natural abundant homopolymer mainly obtained from the yeast *Saccharomyces cerevisiae*. In addition to its use as a biopolymer, glucan is reported for several therapeutic advantages like anti-viral, anti-tumor, and anti-infective actions [34,45-47].

Cellulose: Cellulose is the most abundant polysaccharide biopolymer of glucose available as the main constituent of plants and natural fibers like cotton and linen. Chemically identical cellulose is also obtained from bacterial sources like Acetobacter xylinum however there are some differences in macromolecular structure and physical properties [48]. Cellulose comprises of linear chains of β (1→4) linked D-glucose units ranging from hundreds to thousands [49]. Biomedically relevant cellulose fibers in use are natural cotton fibers, regenerated cellulose fibers like modal, viscose, and lyocell [50]. Cellulose is a resource for the development of several other derivatives like methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, cellulose acetate phthalate, etc. which are very popular in many pharmaceutical and biomedical applications [1].

Xylan: Xylan, another abundant biopolymer, is a hemicellulose polysaccharide predominantly available in plants and cereals. It is of high consideration in the development of colonic drug delivery systems because colonic microflora produces enzymes that can cause its biodegradation. Hence, xylan issued as a colonic specific biopolymer [51]. Xylans are also reported for their physiological effects like the bulking effect of feces, lowering of blood cholesterol, decreasing of postprandial glucose, and immune responses [1].

Starch: Starch is the cheap and abundant biopolymer available in nature and is obtained from plant sources (e.g., cereals/grains/tubers/legumes/roots/fruits) with cereals being the main source [52-55]. It contains two polysaccharides namely amylose (linear) and amylopectin (branched). Starch is suitable for physical, chemical, or enzymatic modifications to achieve specific functional characteristics as modified starch that suit the biomedical and pharmaceutical applications [12]. Starch is widely used in targeted as well as controlled delivery of drugs and bioactive through its fabrication as nanoparticles, microparticles, inclusion complexes, composites, etc. [56-58]. Thermoplastic starch is blended with fatty acids of a long-chain component to enhance its compatibility [59].

Xanthan: Xanthan gum is another natural biopolymer of the polysaccharide category that is obtained from *Xanthomonas campestris* bacteria. It has a thickening

ability and shows pseudoplastic flow [1].

Dextran: Dextran is a polysaccharide biopolymer of neutral hydrophilic nature. Modification of dextran is possible due to its huge number of hydroxyl moieties which may alter the characteristics like solubility [12,60-62].

Pectin: Pectin is a natural heteropolysaccharide present in the cell walls of the primary level in terrestrial plants (almost all non-woody parts). The major component of pectin includes galacturonic acids. Pectin has multiple biomedical and pharmaceutical applications in combination with other polymers. The modified pectin shows altered gelation, degradation, and physical characteristics based on the degree of esterification. Pectin is of prime importance in developing colon-specific drug delivery systems, tissue engineering, and controlled release systems [1,12,63,64].

Pullulan: Pullulan is a water-soluble biopolymer obtained from fungus Aurobasidium pullulans. Its main component is maltotriose. It shows solubility in organic solvents, unlike other polysaccharides. Pullulan is having pharmaceutical and biomedical applications with modifications and composite forms (e.g., antitumor, anti-cancer effects, and medical devices) [65-70].

Polypeptides

Polypeptide biopolymers are of emerging filed in addition to polysaccharides for biomedical and pharmaceutical applications. Polypeptides are of natural origin and can be modified to alter the functional attributes by physical, chemical, or enzymatic changes. These are biodegradable, biocompatible, and ensures wide applications in the fields of medicine and pharmacy. However, more stability concern is required for polypeptides (e.g., environments like varying pH, ionic strength, temperature) [12,71-76].

Animal-derived proteins

Albumin: Albumin is the animal-derived protein with functional groups like carboxylic acid, thiol, and amino groups which allows addition/entrapment of active substances. Albumin is a water-soluble globular protein with slight solubility in salt solutions [12,72].

Casein: Casein is the natural protein obtained from milk and is used in combination with other biopolymers for its biomedical and pharmaceutical applications [12].

Collagen: Collagen is the most abundant mammalian protein and is the primary structural material of vertebrates. Its contribution counts for about 20-30% of the total body proteins. It has very low antigenicity in addition to properties like biodegradability, biocompatibility, non-toxicity and is also easily absorbable in the body due to its high affinity towards water [1,77-80].

Gelatin: Gelatin is a cheap and water-soluble protein obtained from collagen (derived from skin, bones, connective tissues of animals like sheep, pig, cattle, and fish) upon acidic or alkaline hydrolysis. It is available with varying strengths, isoelectric points and can undergo cross-linking with glutaraldehyde or formaldehyde which shows a decrease in dissolution or solubility for controlled release of the encapsulated agent favoring prolonged therapeutic effect. It is also used in combination with other biopolymers [1,81].

Fibroin: Fibroin is one of the widely used biopolymers in the biomedical field due to its thermal stability in addition to biocompatibility and biodegradability. It has also been reported for its anti-microbial properties. It is also used in combination with other biopolymers like albumin to fabricate the particular systems [12,82].

Whey protein: Whey protein is also commonly used for the formation of biopolymer particulate systems through thermal treatments like denaturation or cold-set gelation. It is used for the encapsulation of probiotics. It is also used in combination with other biopolymers like alginate to develop carriers for the delivery of bioactive compounds [83].

Plant-derived proteins: Plant-derived proteins show the lesser risk of contamination and infection in comparison with animal-derived proteins and also these are cheaper. These proteins gain values in vegetarian or vegan products. Zein and gliadin are the best examples for water-insoluble, biodegradable, and biocompatible plant-derived proteins that are useful in the development of biopolymer particles for encapsulation of active ingredients. These systems are further stabilized by emulsifiers to have good physical stability across varying pH conditions [84-90].

Soy protein and pea legumin: These proteins derived from plants are also useful in the development of biopolymer particles. Combinations of these substances with other biopolymers are also reported for the fabrication of certain particulate systems to deliver active ingredients like nutraceuticals [12,91-93].

Silk sericin: Silk sericin is the natural protein biopolymer obtained from silkworm namely *Bombyx mori*. It surrounds two fibroin filaments and keeps them together in a cocoon. The sericin discarded by the textile industry has been noted for recovery and reuse in scientific applications like the biomedical field, food, and cosmetic industry. It is known as a biomaterial for its wound healing, tissue engineering, cell proliferation, drug delivery, and some therapeutic effects [94-100].

Polynucleotides

Polynucleotides like DNA and RNA (comprising of 13 or even more nucleotide monomers) are also a part of biopolymers that have applications in the biomedical field [1].

Lipids and Biopolymer Functionalization

Type of lipids used in biopolymer composites

Being natural resources, the application of lipids has been enormously growing in the area of biomedical and pharmaceutical applications. The main reason for the interest shown by the researchers is that lipids play a key role in cellular construction and functions. Hence, the biocompatibility of lipid biopolymers is well appreciable with less toxicity. Different categories of lipids include simple, compound, and derived lipids are presented in (Figure 1) [59].

Functionalization concept

Searching for or synthesizing a new material is always a tedious and cumbersome strategy to meet the desired properties. Rather, it is comparatively better to tailor the properties of existing and established materials to achieve the expected outcomes. In a scientific sense, it can be called "functionalization", which means adding new properties, functions, features, or capabilities to the existing material by modulating the physical, chemical or biological parameters of the material. Sometimes a compromising achievement can be obtained by such a concept. In the present chapter, functionalization through physical and chemical means of blends/composites by forming hybrid structures will be discussed, with more emphasis on biopolymer-lipid based systems. The main aim of using composites of different polymers is to establish combined functions in the hybrid system. The positive features of each polymer will be combined to the system thereby neutralizing or minimizing the undesired functions, hence, increasing the performance of the developed system. For example, the addition of polyethylene glycol chains to liposomes renders them sterically stable and increases the circulation times for prolonged therapy.

Biopolymer-biopolymer functionalization

Polysaccharide with polysaccharide composite: Alginate composite with chitosan is a well-reported

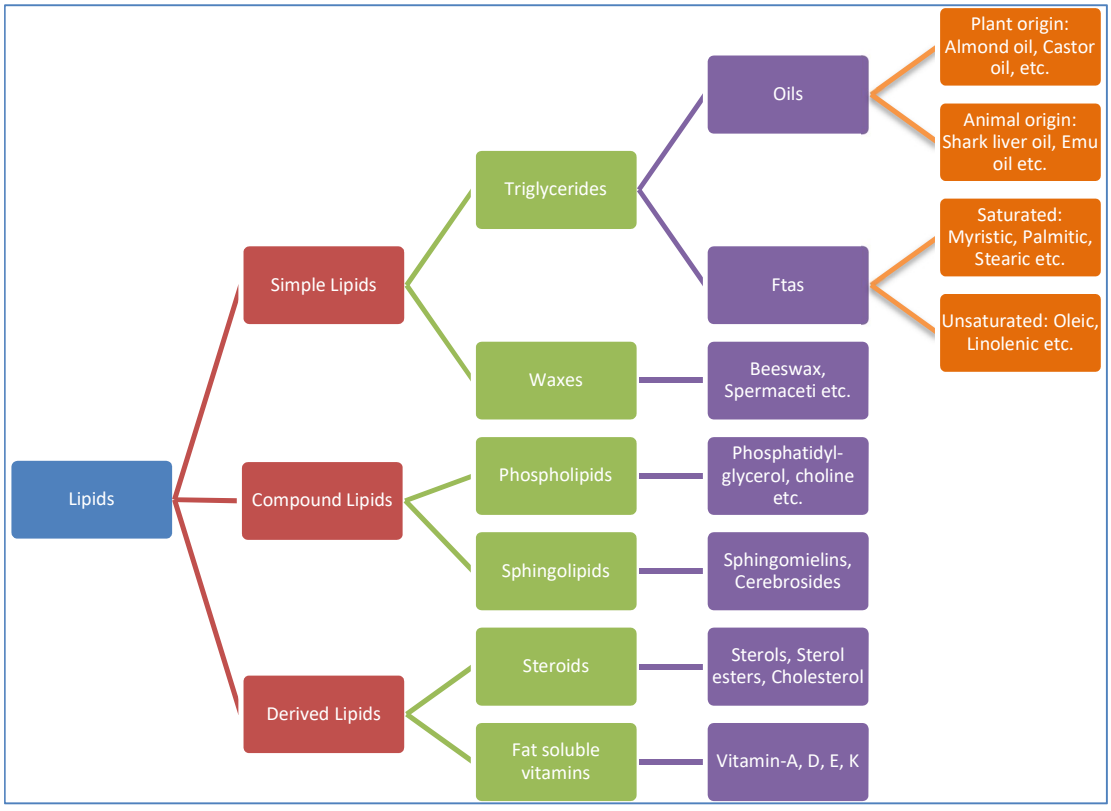


Figure 1: Scheme of lipid classification with examples [59].

combination of biopolymers for improved properties of the system. This composite is used for bone tissue repair. The cationic chitosan combines with the anionic alginate forming a polyelectrolyte complex showing improved mechanical properties and cell proliferation. The concentration of alginate in the composite defines the pore size of the alginate-chitosan scaffold [101].

Polysaccharide with protein composite: Alginate has been chemically modified (by methacrylate) to obtain control over the degradation rate, mechanical and swelling properties. It is further combined with the collagen to develop hydrogels demonstrating higher mechanical moduli, improved cell proliferation, osteogenic differentiation, decreased swelling ratios on comparison with pure methacrylated alginate hydrogel [101-103]. The gelatin in combination with sodium alginate as scaffolds for bone tissue engineering has shown better cell proliferation, mineral modules formation, and type 1 collagen expression [104]. Cell adhesion and proliferation of the chemically developed sodium alginate-gelatin scaffolds (using a saturated ethanolic solution of calcium chloride) were found to be better than with conventionally developed scaffolds. So, the preparation method of systems also influences performance [101,105]. Alginate covalently cross-linked with heparin (by using ethylenediamine) has produced a new matrix that has shown a controlled release of active basic fibroblast growth factor for 1 month in cell-based experiments [106]. Microcrystalline cellulose-silk fibroin composite films were developed for improved tensile strength which is 5 times more than that of films prepared by cellulose alone or fibroin alone [107].

Biopolymer-synthetic polymer functionalization: Chitosan in combination with biodegradable polymers, polylactic acid (PLA), and keratin has been used for the development of a novel composite as a PLA matrix for tissue engineering and artificial bone reconstruction. The combination of chitosan with PLA matrix has shown improved Young modulus, increased hardness, and decreased tensile strength of PLA. Keratin incorporation resulted in enhancement of impact strength, increased hardness, decreased tensile properties, and increased resistance to degradation. In addition to these mechanical properties, the biological assessment using a cell line (human osteosarcoma) also revealed that there area good viability and proliferation outcome. So, it is proved that the composite of chitosan-PLA-keratin has shown improved mechanical behavior and in vitro osteoblast response [108]. Adding synthetic polymer to the biopolymer normally increases the mechanical strength of the composite system. For example, a combination of poly(N-isopropylacrylamide) with aminated alginate has produced a thermosensitive copolymer showing biocompatibility with mesenchymal stem cells [109].

Biopolymer-bioglass functionalization: Bioglass is a bioactive osteoconductive material (allogenic and alloplastic bone graft substitutes) that shows osteoproductive effects. The drawback of the bioglass material is lack of cohesiveness. Hence, the composite formation of bioglass with biopolymers has been augmented. One such development is the combination of bioglass with medium molecular weight dextran which shown putty consistency and improved handling features without any adverse influence on the bioactive functions of bioglass or bone regeneration [110].

Biopolymer-ceramic functionalization: Scaffolds for tissue and bone engineering are developed in a combination with biopolymer with ceramic materials due to their biocompatibility and osteoconductive properties. Since alginate scaffolds alone have poor mechanical strength, the combination of alginate with inorganic substances has shown improved properties. Alginate mixed with hydroxyapatite is one such combination that has shown excellent applications in bone tissue engineering, cell delivery, growth factor delivery, and wound healing in biomedicine. Thus, the obtained composite scaffold can provide suitable optimal conditions for new bone tissue generation via cell proliferation, mechanical strength, and surface morphology [111,112].

Biopolymer-lipid functionalization: The combination of biopolymers with lipids has been emerged as a novel concept a decade ago and still a promising area for improvements in the field of biomedical and pharmaceutical applications (Fig.2). Lipids contribute their positive factors to the biopolymers and the biopolymers enhance the properties of lipids which in total result in the functionalization of the composite for better performance. Not only with biopolymers, but it is also the case with synthetic polymers too. For example, unsaturated polyester resin, a synthetic polymer is of thermosetting nature which is abundantly available, cheap, easy to process, and shows good mechanical, chemical, and electrical properties, however, it suffers from the problem of being hard in nature. To gain flexibility in that synthetic polymer, it is mixed with lipid (e.g., castor oil) [59,113]. Another example from the biopolymer category is starch, which is a thermoplastic natural polymer (thermoplastic starch) obtained by extrusion of native starch using water, sorbitol, or glycerol as plasticizers). [114] The drawback of such thermoplastic starch utility in bioplastics is its hydrophilicity and strong brittle nature. Upon the formation of starch triacetate, the hydrophobic nature is obtained but the brittleness problem became still worse even after adding plasticizers [115]. Hence, esterification of the starch with fatty acids was attempted and got successful with the result of strong hydrophobicity, flexibility with low glass transition temperature, film formability, even in

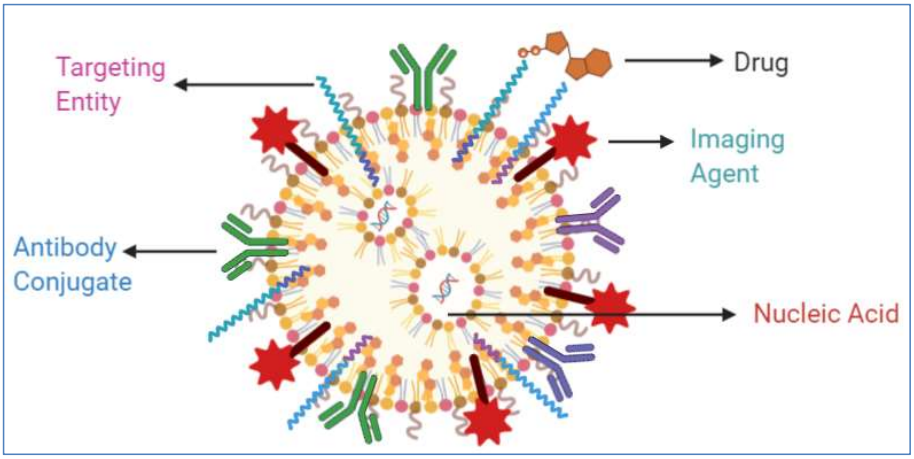


Figure 2: Hybrid conjugate formed after functionalization of lipid and biopolymer indicating the scope of ligands for targeted delivery.

the absence of plasticizers [116,117]. In the above example, properties of the polymer are modulated by mixing with lipids. As a vice versa strategy, here is an example. Chitosan can be added to olive oil emulsion films to obtain stable olive oil emulsion with homogeneous, thin, and translucent films formation as reported by Pereda et al. The enhanced properties were confirmed by examination of its tensile properties like tensile strength, Young modulus, and maximum elongation. The emulsifying property of chitosan resulted in stability enhancement of emulsion [118].

Spotlight on Biopolymer-Lipid Functionalised Carriers Designed for Gastro Retentive Drug Delivery Systems

Selenium (Se) is recognised for gastroprotection and in a recent study Selenium nanoparticles embedded chitosan microspheres (SeNPs-CM) were developed and their gastroprotective potential was evaluated. SeNPs with a nanosize range of 60 nm were loaded into CS-microspheres sucessfully and Se released from the microspheres was confirmed in gastric conditions. SeNPs-CM pre-treatment significantly attenuate the ethanol-induced gastric mucosal damage, based on histological evaluation. Further reduction in lipid peroxidation, the augmentation in antioxidant enzymatic activity as well as decreasing aggressive nitric oxides (NO) were even observed [119]. In another study, amoxicillin that is most commonly used for H.pylori infection is often degrdaded by acidic pH of stomach, therefore to prevent his amoxicillin was encapsulated in biopolymer functionalised with lipid for more retention at site of infection and protect from stomach acids. ween 80 and linolenic acid were used as potential therapeutic adjuvants and dioleoylphosphatidylethanolamine as a targeting agent to *Helicobacter pylori*. The optimised formulation was found to be stable for at least 6 months at 4°C. *In vitro* release studies revealed a high resistance to harsh conditions, including acidic pH and physiologic temperature as well. The studies even confirmed that these nanoparticles have a low cytotoxicity effect in both fibroblasts and gastric cell lines, and indicated potential to be retained at the gastric mucosa [120]. In another study, a polymeric nano-micelle was prepared to prevent antibiotic clarithromycin degradation against *H.pylori* infection. The conjugate is carboxymethyl chitosan (CMCS) that was hydrophobically modified with stearic acid (SA), and the obtained CMCS-g-SA co-polymers was further conjugated with urea to acquire U-CMCS-g-SA co-polymers. The conjugate showed no cell toxicity to AGS cells and was able to maintain a stable particle size for 6h in simulated gastric fluid and for 24h in PBS. The grafted ureido groups conferred effective targeting to *H. pylori* and *in vitro* inhibitory assay indicated enhanced anti-*H. pylori* activity by using the developed nano-micelle [121].

Using a liquid multi-layering process, floating and bioadhesive drug delivery system was designed and composed of a hollow spherical shell, a waterproof layer (Stearic acid), a drug layer (Ofloxacin), a release retarding film (the novel blended coating materials) and a bioadhesive layer (Carbomer 934P) was prepared. The formulation was suceesful and solved the problem of the initial burst release of the formulation and indicated sustained release with a retention in stomach for more than 6 h [122]. In a different study, novel composite sponges of chitosan (CH)-chondroitin sulfate (CS) as a low-density gastroretentive delivery system for lornoxicam (LOR) was reported. The triple anti-inflammatory therapy-loaded matrices was able to expand and float upon contact with gastric fluids for prolonged time upto 12 h. Further, the magnetite-loaded sponges was monitored in healthy volunteers via

MRI proving their gastroretentivity for at least 5h [123]. To enhance the oral bioavailability of atorvastatin and protect from incomplete intestinal absorption and gut wall extraction, a optimised tablet formulation containing hypromellose, sodium bicarbonate, polyethylene oxide, docusate sodium, mannitol, crosscarmellose sodium, and magnesium stearate was prepared. The tablet gave floating lag time of 56 ± 4.16 s and good matrix integrity with in vitro dissolution of 98.2% in 12 h. The *in-vivo* rabbit studies revealed that floating tablets showed 1.6 times more bioavailability in comparison to the conventional tablet (Storvas® 80 mg tablet) [124]. Hollow and bioadhesive microspheres composed fo ethylcellulose (matrix), Eudragit and glyceryl monooleate (GMO) as polymer in-situ were developed and had proved lengthen drug retention time in the stomach. The microspshere showed strong mucoadhesive properties with good buoyancy both *in vitro* and *in vivo* indicating advantageous in the treatment of stomach diseases [125]. Oil entrapped floating microbeads as gastro retentive controlled release system composed of polymer ratio of 2.5:1.5 (pectin/ sodium alginate) by mass, 15% (m/V) of oil (mineral oil or castor oil) and 0.45 mol L(-1) calcium chloride solution was prepared for loratadine. In vitro drug release in the fed state conditions demonstrated sustained release of loratadine for 8 h, which best fitted the Peppas model with n<0.45 [126].

Future Prospects

With the existing reports and successful journey, there is a lot of scope for future progress utilizing the probabilities of a combination of biopolymer and lipid systems for better therapeutic efficiency with minimized or no adverse effects in treatment of gastric diseases. There is a need to understand the complete mechanism for the enhanced properties and optimization strategies. Applying the existing concepts in different routes of administration and different disease conditions has yet to be explored to identify the best-synchronized applications. The utilization of the novel analytical methods for a better understanding of the influence of formulation parameters on the performance of the hybrid systems has to be established well. Even with the high-end technologies available today, there is the least commercialization of the products which indicates that the research needs gear up in the right path that reaches the patient.

Conclusion

Biopolymer-lipid-based systems have shown remarkable applications in the pharmaceutical fields covering several areas drug delivery, and gene delivery. The reasons for the versatility of these hybrid systems include biocompatibility, biodegradability, improved stability, combined advantages of individual systems, well-defined control over drug release, prolonged residence, and targeted delivery especially for gastric diseases. With the advancements in the technology and availability of abundant biopolymers and lipids, this area has more scope for the development of novel systems with commercializing features.

Conflict of Interest

The authors declare no conflicts of interest.

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