

Applications of food hydrocolloids in drug delivery system

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Received: 30 March 2022; Revised: 23 May 2022; Accepted: 27 May 2022

Abstract

Food hydrocolloids are multifunctional natural substances that are being exploited to create a new generation of functional foods that improve health and well-being. Pharmaceutical and culinary formulations play a crucial role in rheology, tribology, and intuition. According to current research, hydrocolloids have the potential to tailor nutritional value and deliver therapeutic benefits by lowering plasma cholesterol, postprandial glucose, glycemic response, insulin secretion, and preventing colon cancer by controlling meal transit, digestion, and gastric emptying. They also enhance the bioavailability of specific bioactive moieties and drugs by delivering them to the gastrointestinal tract in a regulated and targeted manner. The use of food hydrocolloids, particularly proteins and polysaccharides, as viscosity modifiers, gelling, coating, stabilizing agents, and emulsifiers in the drug delivery system and the nutraceutical potential utility of food colloids as functional components, are discussed in this article.

Keywords: excipients, bioavailability, nutritive value, polysaccharides

Introduction

Hydrocolloids are colloidal substances with a high-water affinity [1]. Some are water-soluble when exposed to water and form colloidal solutions, whereas others swell and spread due to shear forces [2]. Hydrocolloids form a colloid-like dispersion intermediate between a suspension and a real solution. They are now termed "hydrocolloids" [3]. Extracts from seaweeds or plants, tree exudates, sticky slimes created by fermentation processes, flours from seeds or grains, and other natural items were used to make them at first [4]. Hydrocolloids are a broad category of food polysaccharides that are abundant in nature.

Plant-derived hydrocolloids include terrestrial plants and seaweeds, whereas animal chitin and chitosan are frequently used in the food sector [5]. In pharmaceutical formulations, they are utilized as emulsifiers, coating agents, viscosity enhancers, stabilizing agents, and gelling agents [6]. In contrast to their therapeutic properties, innovative food hydrocolloids serve a significant role in food as new sources of dietary fibre. They also contain phytochemicals vital to human health [6]. Food hydrocolloids can be highly soluble, insoluble, or somewhat soluble in water and gastrointestinal fluids depending on their molecular properties, such as surface hydrophobicity, charge, and molecular weight [7]. On the surfaces of food hydrocolloids, non-polar, polar, cationic, and anionic functional groups can be found, with the degree, distribution, and type varying depending on the molecule. As a result, they bind to other molecules in their environment via various chemical interactions [8].

Proteins and polysaccharides are the most common types of functional dietary hydrocolloids. These hydrocolloids can be employed to change the nutritional fate of food in the gut in various ways [7]. Natural food hydrocolloids (proteins and polysaccharides) have been widely explored for their possible application in dietary therapy to improve health or prevent disease. By targeting the long

latent (silent) stage before clinical symptoms develop in the patient, this therapy can slow the progression of chronic non-communicable diseases (type 2 diabetes, cancer, cardiovascular diseases, and neurodegenerative diseases) [9]. Classification of food hydrocolloids and their functions are given in Table 1. This review focuses solely on proteins and carbohydrates.

Different hydrocolloids used in drug delivery system

Various types of food hydrocolloids are being used in pharmaceutical drug delivery systems, as shown in Figure 1.

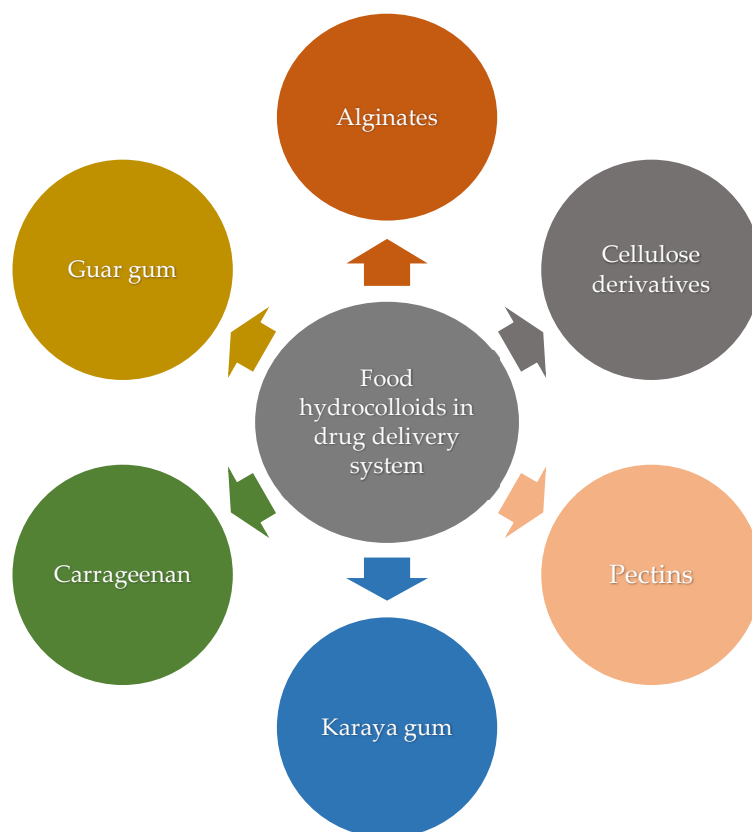


Figure 1. Important food hydrocolloids in drug delivery systems.

Alginates

Brown seaweeds such as *Laminaria digitata* (Hudson) J.V.Lamouroux, 1813 and *Laminaria japonica* contain structural polysaccharides called alginates. *Laminaria hyperborean* (Gunnerus) Foslie, 1884, *Macrocystis Pyrifera* (Linnaeus) C. Agardh, and *Ascophyllum nodosum* (Linnaeus) Le Jolis, 1863 [4]. J.E. Areschoug, *Laminaria hyperborean* (Gunnerus) Foslie, 1884, *Macrocystis Pyrifera* (Linn They are unbranched copolymers made up of (1→4)-linked β -D-mannuronic acid (M) and α -L-guluronic acid (G) residues [1]. With alginate, monovalent metal ions form soluble salts, but divalent and multivalent cations (with the exception of Mg^{2+}) form gels or precipitates. Alginates rich in guluronic acid blocks form substantially stronger gels than alginates rich in mannuronate blocks because guluronic acid residues have a more significant attraction for divalent ions than mannuronate residues [10]. Alginate is a biocompatible, cost-effective, readily available food or medical-grade polymer. Alginate has long been utilized as a tablet disintegrant and gelling agent in the pharmaceutical sector. Alginate has been widely used in various biological treatments, including drug administration, tissue engineering, and some formulations to reduce gastrointestinal reflux due to its biodegradability, chelating ability, biocompatibility, and non-antigenicity [11].

Applications in drug delivery

Encapsulation of drugs using alginates

Alginate is combined with natural polymers like chitosan and pectin to encapsulate drugs into nanoparticles or microparticles. Alginate-chitosan encapsulated prednisolone and inulin nanoparticles in colon administration are two examples. Indomethacin nanoparticles encapsulated in alginate-mesoporous silica are used for long-term medication delivery [12].

Alginates in dentistry for drug delivery

Lan et al. developed a dental implant ring made of alginate and polycaprolactone for metronidazole-controlled release [12].

Alginates in refilling drug delivery

Specific binding to complementary oligodeoxynucleotides carrying alginate gels in vitro and injected gels in vivo was achieved using oligodeoxynucleotides attached to alginate strands. When combined with a drug payload, sequence tailored refilling of an intratumor hydrogel delivery depot reduced tumour development. The minimally invasive refill of a drug delivery device in vivo with new drug payloads through the blood. In this paradigm, the injectable delivery mechanism is altered to bind refills delivered into the circulation. Drug payloads injected into a patient's blood extravasate to the desired locations and are connected to the device, allowing long-term drug release at the targeted area [13].

Alginate for protein delivery and cell encapsulation

The ovalbumin (OVA) peptide has been encapsulated in alginate and discovered to act as a carrier and adjuvant for cancer immunotherapy. To optimize stomach retention time and regulate release, curcumin-loaded self-micro emulsifying drug delivery devices with alginate-based composite sponges as carriers were developed (CurSMEDDS). Davis et al. created and evaluated liposomal bupivacaine sustained release delivery formulation encapsulated in alginate to see how it altered the production of three key Mesenchymal stromal cells (MSC) regulators: interleukin 6 (IL-6), prostaglandin E2 (PGE2), and transforming growth factor-beta 1 (TGF-1) [14].

Carrageenans

Rhodophyceae, a family of marine red algae, contains structural polysaccharides called carrageenans. *Chondrus crispus* Stackhouse, 1797; *Gigartina skottsbergi* Setchell & Gardner, 1936; *Euchema cottonii* Weber-van Bosse, 1913; and *Iradaealaminarioides* Bory de Saint-Vincent, 1828 are the most widely used sources [15]. They're all sulfated and non-sulfated high-molecular-weight linear hydrophilic polysaccharides with repeating galactose and 3,6-anhydrous-galactose disaccharide units linked by alternating α -(1 \rightarrow 3)- and β -(1 \rightarrow 4) glycosidic linkages. Its significant fractions are κ -, λ -, and ι -carrageenans (kappa, lambda, and iota, respectively) [16].

Applications in drug delivery

- Polowsky et al. [17] encapsulated eugenol neutraceutical in sodium and calcium salts of iota-carrageenan to safely deliver eugenol neutraceutical to the target site.
- Because of their physicochemical properties, such as increased viscosity, larger molecular weight, and gelling, carrageenans can make extended-release tablets, although with limited drug loading [15].
- Carrageenan polymers absorb water, increasing the solubility of the drug and enhancing the oral bioavailability of weakly water-soluble drugs. As a result, carrageenan could be used as a replacement for microcrystalline cellulose (MCC) pellets or gelatin capsules [16].

- Because of the high swelling ratio and formation of stronger gels, carrageenan combined with magnetic nanoparticles is used to aid in the delivery of medications [18].
- Gram-positive and Gram-negative bacteria are inhibited by oxidized kappa-carrageenan, which damages the bacterial cell wall and cytoplasmic membrane [19].
- Intranasal poloxamer-carrageenan-based in situ hydrogel systems have been created, which remain liquid and gel in situ during injection or instillation. Carrageenan improves drug stability, retention, and release time when conjunction with poloxamer [20].

Pectins

Pectins are a complex family of heteropolysaccharides that make up the main cell walls of many dicotyledons. The most critical structural elements of pectic polysaccharides are the homogalacturonan (HG) and type I rhamnogalacturonan (RG-I) regions, which are typically defined in simple terms as "smooth" and "hairy," respectively [21]. Apple pomace, sugar beet pulp, citrus peel, and other vegetable sources make pectin for commercial use [22]. In pure water, pectins are very soluble. Monovalent cation (alkali metal) salts of pectin and pectic acid are common water-soluble; divalent and trivalent cation salts are moderately soluble or insoluble [23].

The carboxyl groups in pectin, which regulate the polysaccharide chain's charge reactivity, can be modified with amide groups and methyl esters [24]. High methoxyl pectin (HMP) is pectin with a degree of methyl esterification (DE) greater than 50%, while low methoxyl pectin (LMP) is pectin with a lower DE (LMP). Smaller changes in DE and charge distributions impact pectin function [25].

Applications in drug delivery

- Pectins have long been used as a gelling agent, but there has recently been a rise in the use of pectin gels in controlled drug delivery [25].
- Pectin is a natural remedy to cation poisoning caused by harmful ions. It has been found to help remove lead and mercury from the gastrointestinal tract (GI) and respiratory organs [26].
- Pectin has been discovered to inhibit enzyme-mediated proteolysis. As a result, before being digested by the colonic microbiota, the pectin-stabilized polypeptide drug remains intact in the small intestine and stomach, resulting in drug molecule release. As a result, pectin is used as a carrier in transporting drugs to the colon [26].
- In tablet formulations and controlled release matrix tablet formulations, pectin hydrogels have been employed as a binding agent [27].
- Calcium pectinate as an insoluble hydrophilic gel coat for interfacial complexation-based sustained release delivery. It is utilized as an insoluble hydrophilic gel coat for gastro-retentive drug delivery. Coated pellet medication release profiles show a lag time when the gel coat hydrates and swells, followed by zero-order release [28].
- Chitosan/pectin polyelectrolyte complexes can be used to make mucoadhesive nasal inserts with variable drug release characteristics [29].

Guar gum

Guar gum (GG) is a seed gum produced from the conserved embryos of *Cyamopsis tetragonolobus* (Linnaeus.) Taubert of the Leguminosae family. In a linear chain, it is made up of (14)-d-mannopyranosyl units connected by (16) links to -d- galactopyranosyl units. GG comprises Galactomannan, water, protein, acidic insoluble ash, ash, and fat. It's used in pharmaceutical formulations as a binding, disintegrant, suspending, thickening, and stabilizing agent [30]. Because guar gum is anionic, it maintains its stability and viscosity over a wide pH range. The pH range of 6-9 has the highest viscosity, while the pH range of 3.5 has the lowest [31]. GG generates hydrogen

bonding in the aquatic environment due to numerous hydroxyl groups along the chain. The mannose structure and galactose branches significantly enhance the number of available hydroxyl groups [32].

Applications in drug delivery

- For regulated oral delivery, metoprolol tartrate, which is generally used to treat angina and hypertension, was developed as a tablet formulation with three layers of GG matrix [33].
- Castro et al. integrated an antihypertensive peptide (AAP) generated from whey protein with polymeric nanoparticles for the first time. They combined a poly (lactic-co-glycolic acid) (PLGA) nanoparticle formulation with a GG film matrix to make a peptide carrier. Due to the gradual release of the GG film, the peptide can make more intimate and long-lasting contact with the buccal epithelium [34].
- Antigen (Ag85A)-loaded GG nanoparticles (NPs) were developed to administer a tuberculosis vaccine orally [35].
- Kaur et al. also used a precipitation process to make GG porous nanoaggregate particles to deliver antitubercular drugs (rifampicin and isoniazid) [36].
- Gowda et al. developed 5-fluorouracil-containing cross-linked GG-based microparticles for drug delivery in the colon. Using trisodiumtrimetaphosphate as a cross-linking agent, microparticles were produced using an emulsification method [37].
- A grafted nanocarrier based on GG was developed to deliver ketoprofen using microwave irradiation techniques [38].

Table 1. Classification of food hydrocolloids.

Source	Hydrocolloids	Function
Cellulose and derivatives	Microcrystalline cellulose	Emulsion stabilizer, Foam stabilizer
	Carboxymethylcellulose	Viscosity modifier, Emulsion stabilizer
	Methylcellulose and its derivatives	Thickener, Emulsifier
	Galactomannans –	
	Locust bean gum	Film forming property
	Guar gum	Thickener
	Senna gum	Thickener
	Guar gum	Thickener
Plant tissue extracts	Pectins	Gelling agent
	Glucans	Gelling agent
Exudate gums	Gum arabic	Foaming agent, emulsifier
	Gum tragacanth	Adhesive
	Gum karaya	Adhesive
	Gum ghatti	Adhesive
Mucilage gums	Psyllium gum	Gelling agent
	Flaxseed mucilage	Thickener, Stabilizer
Seaweed hydrocolloids	Alginates	Gelling agent
	Carrageenans	Thickener
	Agar	Gelling agent
Microbial hydrocolloids	Xanthan gum	Viscosity modifier, Stabilizer
	Gellan gum	Gelling agent
Animal hydrocolloids	Chitin and chitosan	Gelling agent, Antimicrobial
	Gelatin	Gelling agent

Karaya gum

Gum karaya, or sterculia gum, is a branched acidic polysaccharide derived from the exudates of the Indian tree *Sterculia urens* Roxb. of the Sterculiaceae family's *Sterculia urens*. The backbone chain of rhamnogalacturonan is composed of (1→4)- linked D-galacturonic acid and α -(1→2)- linked-L-

rhamnosyl residues [1]. Galactose, rhamnose, protein, and other sugars are found in commercial karaya gum. Gum karaya has an acetyl group content of 8% and a uronic acid residue content of 40%. It is widely used in various industries [39] due to moisture absorption, adhesiveness, gel, and film-forming properties.

Applications in drug delivery

- Singh and Chauhan used the ionotropic gelation process and BaCl₂ as a cross-linker to develop pantoprazole-loaded alginate and sterculia gum (SG)-based gastroretentive floating systems [40].
- SG-based microflora-triggered drug delivery systems (MCDDS) were developed by Nath and Nath to deliver azathioprine to the colon, reducing systemic toxicity [41].
- Singh et al. developed sterculia gum-alginate beads and floating sterculia gum-alginate beads containing the antiulcer medication pantoprazole using calcium chloride (CaCl₂) as an ionotropic cross-linker [42].
- Gangadharappa et al. developed a single-unit gastric floating medication delivery system for verapamil hydrochloride using hydroxypropyl methylcellulose (HPMC) and karaya gum as polymers. The viability of karaya gum in the development of a floating drug delivery system was investigated by evaluating the developed dosage forms for drug content, swelling index, sustained release, in vitro buoyancy, and in vitro drug release [43].
- In contrast to the well-studied HPMC, Moin and Shivakumar developed diltiazem hydrochloride (DTZ) matrix tablets for sustained release using natural gums such as Karaya gum and locust bean gum as unique Hydrophilic matrix systems. Direct compression was used to make DTZ matrix tablets with the various drug: polymer ratios. The findings show that tablets containing only locust bean gum cannot control the drug's release. Compared to locust bean gum, karaya gum has a higher drug-resistance rating [44].
- To make glipizide microcapsules with an alginate and gum karaya coating, Rama Krishna et al. used the ionic gelation and emulsification ionotropic gelation methods. The emulsification ionotropic gelation approach has been proven effective for glipizide release over a prolonged period [45].

Cellulose derivatives

Cellulose, a polysaccharide, is the most prevalent carbohydrate on the planet. It is the most important structural polysaccharide in the cell walls of higher plants [45]. Cellulose derivatives are produced via ethylation/esterification of cellulose with inorganic or organic acids or by Michael addition under heterogeneous or homogeneous conditions [46]. In the pharmaceutical and cosmetic sectors, extended and controlled release matrices, osmotic drug delivery systems, bioadhesives, binders, gelling agents, thickening agents, and other semisynthetic cellulose derivatives are frequently employed. The most often used cellulose-based polymers are given in Figure 2 [47].

Cellulose ethers

To make cellulose ethers, the hydroxyl groups of cellulose are nucleophilically combined with electrophiles such as alkyl halides or epoxides. Food, medications, personal care products, construction, paper, adhesives, oil field chemicals, batteries, and textiles all employ them as thickeners, binders, lubricants, emulsifiers, rheology modifiers, and film formers. Cellulose ethers are employed in oral, transdermal, and transmucosal systems in a variety of medicinal applications [48].

Sodium carboxy methyl cellulose (NaCMC)

It is a water-soluble polyanionic cellulose derivative that is commercially available and physiologically inert. NaCMC is used as a thickening, stabilizer, disintegration agent, bioadhesive material, and film-former in pharmaceutical formulations. Croscarmellose, a cross-linked NaCMC, is extensively used in tablet and capsule formulations as a super disintegrant [49].

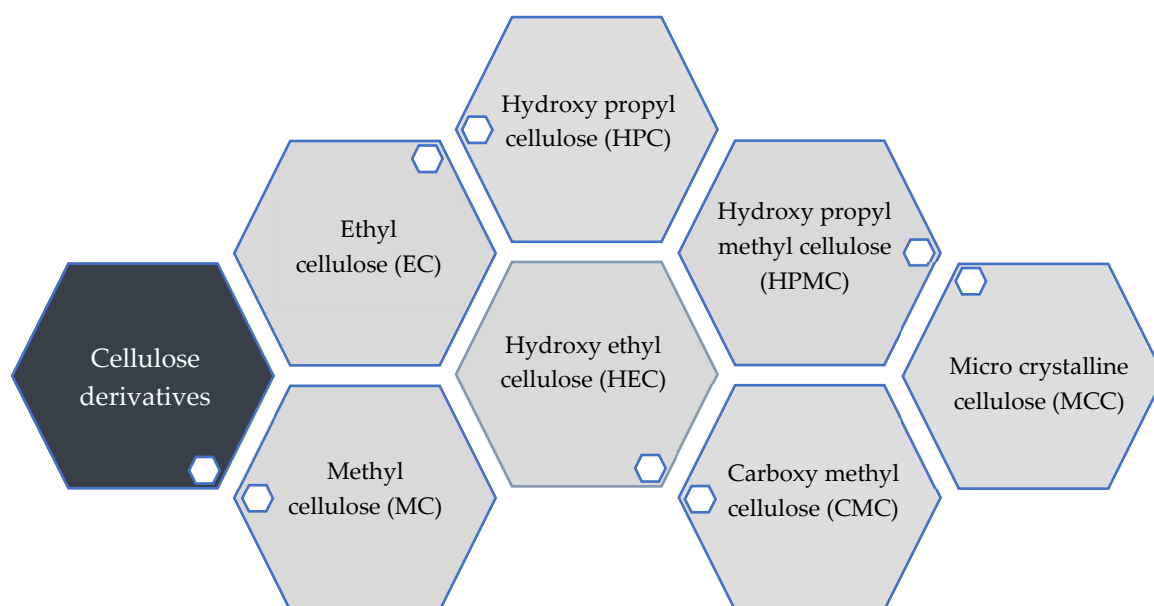


Figure 2. Examples of Cellulose-based polymers.

MC

It is commercially formed by reacting alkali cellulose (cellulose treated with sodium hydroxide) with methyl chloride as an electrophile in a Williamson ether synthesis. A unique property of aqueous MC solutions is thermo-reversible gelation. When heated to roughly 55°C, the gel forms and then dissipates when cooled [50]. The US Food and Drug Administration (FDA) defines MC as Generally Recognized as Safe (GRAS), allowing it to be used in oral formulations up to 183 mg, buccal formulations up to 4 mg, vaginal formulations up to 102 mg, and ocular formulations up to 0.5% (v/v) [51].

EC

Williamson ether synthesis, which is identical to the process used to make MC, is used to make EC. Thermal extrusion makes it simple to extrude EC into films or drug matrices. In medicinal applications, EC is employed in a variety of ways. It has been utilized as a binder, film-forming agent, or coating material in drug delivery systems [52]. According to the US FDA, the daily maximum permitted dose for EC is 308 mg for oral, 80 mg for transdermal, and 50 mg for vaginal applications [51].

HPC

Alkali cellulose and propylene oxide are combined at high temperatures and pressures to produce HPC. HPC is an amphiphilic, non-ionic cellulose ether that is soluble in both aqueous and polar organic solvents [53].

HPMC

HPMC is a cellulose ether produced from cellulose, methyl chloride, and propylene oxide in a base-catalyzed heterogeneous process [54]. HPMC is soluble in water or water/solvent mixtures and can be dissolved in nonaqueous solvents with medium to high polarity [55]. The FDA has classified HPMC as GRAS, based on toxicity assessments using oral and intraperitoneal delivery methods. HPMC can be found at concentrations of up to 670 mg in oral, 24 mg in buccal, 54 mg in vaginal, and 2.25% in ophthalmic solution formulations in FDA-approved drug products [48]. It is used as a

film coating agent, thickening agent, hydrophilic matrix material, and tablet binder in the pharmaceutical industry. It also has bioadhesive properties and is resistant to microbial attack [56].

Cellulose ether esters

Carboxymethyl cellulose acetate butyrate (CMCAB)

CMCAB has the potential to be utilized as a film-forming binder or matrix in the administration of water-soluble and poorly water-soluble drugs [57].

Hydroxypropyl methyl cellulose acetate succinate (HPMCAS)

HPMCAS is a complex co-polymer made by reacting HPMC with the anhydrides of acetic and succinic acid. It is widely deployed in amorphous solid dispersions with hydrophobic medicines because of its amphiphilic nature [48]. Health benefits of food hydrocolloids is mentioned in Table 2.

Applications in drug delivery

- To coat extended-release formulations, aqueous ethylcellulose dispersions, such as Aquacoat® (FMC BioPolymer), Surelease® (Colorcon), or its organic solutions can be used [58].
- Due to its crystallisation inhibitory activity, NaCMC was employed to synthesise amorphous drug-polyelectrolyte nanoparticle complex (nanoplex), an efficient solubility improvement strategy for weakly basic, poorly soluble medicines like ciprofloxacin [59].
- The nanoprecipitation approach was used to produce nanoparticulated targeted delivery vehicles based on CMC and rosin gum, demonstrating promising results in the targeted release of 5-aminosalicylic acid in the upper GI tract [59].
- To control the release of tolmetin sodium, matrix-type transdermal patches infused with eucalyptus oil for improved penetration were used with EC/HPMC combinations [59].
- MCC can be used as a strong dry binder, lubricant, diluent, absorbent, tablet disintegrant, and anti-adherent in wet granulation and direct compression procedures in oral tablet and capsule formulations [60].

Table 2. Health benefits of food hydrocolloids.

Hydrocolloids	Health aspects	Reference
Alginate	Reduces heavy chemicals and cholesterol, wound dressings, lowers hypertension	[61]
Pectins	Prebiotic, reduces glucose and cholesterol absorption, improves physical bowel function	[62]
Guar gum	Lowers TC and LDL-C levels	[63]
Karaya gum	Laxative	[64]
Cellulose derivatives	Positive effect on gastrointestinal physiology, hypolipidemic effects, anti-obesity effect, wound healing, blood purification	[65], [66]

Conclusion

Hydrocolloids have been used in foods and beverages for decades as technologically bioactive components as a thickening, emulsifying, gelling, and stabilizing agents. Hydrocolloids have been investigated as potential therapeutic agents in preventing and treating diseases such as hypertension, cancer, colon health, and others. Hydrocolloids are functional in extended-release, controlled release, targeted release, and oral drug delivery. It can improve drug molecules' solubility, bioavailability, and permeability, allowing oral delivery without digestive degradation. These characteristics make it suitable for application in the delivery of drugs.

Authors Contribution

All the authors have contributed equally.

Funding

This work has not received any funds from national and international agencies.

Conflict of interest

The authors declare no conflict of interest.

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How to cite this article:

Tamkeen J, Kukati L, Rahman A, Reddi P, Gundlapalli SP. Applications of food hydrocolloids in drug delivery system. *German J Pharm Biomaterials.* 2022;1(2):4-14.