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Recent developments in natural biopolymer based drug delivery systems

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Targeted delivery of drug molecules to diseased sites is a great challenge in pharmaceutical and biomedical sciences. Fabrication of drug delivery systems (DDS) to target and/or diagnose sick cells is an effective means to achieve good therapeutic results along with a minimal toxicological impact on healthy cells. Biopolymers are becoming an important class of materials owing to their biodegradability, good compatibility, non-toxicity, non-immunogenicity, and long blood circulation time and high drug loading ratio for both macros as well as micro-sized drug molecules. This review summarizes the recent trends in biopolymer-based DDS, forecasting their broad future clinical applications. Cellulose chitosan, starch, silk fibroins, collagen, albumin, gelatin, alginate, agar, proteins and peptides have shown potential applications in DDS. A range of synthetic techniques have been reported to design the DDS and are discussed in the current study which is being successfully employed in ocular, dental, transdermal and intranasal delivery systems. Different formulations of DDS are also overviewed in this review article along with synthesis techniques employed for designing the DDS. The possibility of these biopolymer applications points to a new route for creating unique DDS with enhanced therapeutic qualities for scaling up creative formulations up to the clinical level.

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1 Introduction

Biopolymers are diverse and remarkably versatile class compounds derived from biological systems or synthesized from biological sources. Like other polymers, biopolymers are composed of similar repeating units (monomers) which are linked together.¹ Owing to the peculiar properties of biopolymers *e.g.* biodegradability, availability, and possibility of engineering the physicochemical characteristics, they are being engaged in innovative formulations. Particularly, while moving

towards a green sustainable life, biopolymers offer a platform that fits into the paradigm of achieving an eco-friendly environment. Recently biopolymers have received special attention for designing and fabricating DDS (DDS).² DDS is a tool to incorporate therapeutic agents to ensure the availability of a highly specific drug to target the diseased site with minimum side effects in the body.³ An ideal DDS can target as well as control release of the loaded drug. Drug delivery carriers act as a vehicle to protect the drugs from decomposition during transportation in the body before targeting the diseased site. DDS is intended to reduce side effects by virtue of being biocompatible and biodegradable. In order to provide the intended pharmacological response, it also modifies drug release at the target site. Both natural as well as synthetic polymers are recognized as potential candidate materials suitable for exploitation in designing the DDS.

Although natural polymers have shown remarkable contributions in developing the DDS but blending and functionalization of polymers through different physical and chemical means transfers into a state-of-the-art class of materials. Natural polymers having though good biocompatibility and biodegradability but their low mechanical and thermal properties as well as low solubilities restrict their applications.⁴ Blending as well as functionalization of polymer to fabricate innovative materials with resultant properties reflecting the parent compounds, that are not exhibited by individual ones.

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Functionalization of biopolymers through blends/composites by forming hybrid structures is an approach, widely used in DDS to launch the combined roles in the resultant hybrid system.^{3,4} By reducing the negative effects, the beneficial properties of each biopolymer are enhanced, which improves the effectiveness of the created DDS.⁵

Polymer–polymer or filler–polymer combinations may be used to create polymeric nano-biocomposites. Metal nanoparticles (NPs), hydroxyapatite, organic or inorganic clays, and other materials may be used as fillers. The highest amount of drugs can be loaded into a nano-composite system while using the smallest possible amounts of carrier. Drug loading is typically done *via* an impregnation or inclusion approach. While the integration approach includes drug trapping by nanocomposites at the time of manufacture, the impregnation involves drug entrapment by typically incubating the nanocomposites from a solution.⁶

In DDS, polymer–drug complexes are formed usually *via* hydrophobic interactions, van der Waals forces, hydrogen bonding and electrostatic attractions between opposite charges of the biopolymers. To get mechanical strength, aggregates are sometimes cross-linked with suitable linker(s) to enhance stability and integrity. A cavity-bearing supra-molecular aggregation is often necessary for the inclusion complexation procedure in order to serve as a host for an entering guest molecule (s). Nanoprecipitation, another worthwhile method is generally adopted for hydrophobic polymers. In the supercritical fluid method, another precipitation technique, involves the liquid or gas, and polymer(s)/drug(s) are solubilized together above their supercritical points. The selection of the preparative method is determined by a number of factors, such as the thermal and chemical stability of the bioactive components, the toxicity of the leftover chemicals after processing, particle sizes, release kinetic profiles, and finally the kind of delivery system. Two separate drying techniques are often used: freeze-drying and spray-drying. For freeze-drying, heat-sensitive materials have been selected, while for spray-drying, the nanoparticle solution is introduced into a stream of hot air, causing the solvent to quickly evaporate and the dried particles to aggregate.⁷

This review is also aimed to summarize the contribution of different natural biopolymers, particularly sugar-based polymers, amino-sugars and polynucleotide-based polymers. Fig. 1 gives the classification of different natural polymers which have been employed to design the DDS. Although almost all polymers have a prestigious role in DDS still their derivatives, functionalized composites are also in clinical trials in different formulations for designing the DDS. These encouraging biopolymer applications provide us a new route for creating unique DDS with enhanced therapeutic qualities for scaling up creative formulations to the clinical level.

2 Types of DDS

To improve the solubility of the pharmaceuticals for stable complex formation and their safety during delivery at the target location, many formulations of individual biopolymers and

their composites have been described, including powder, tablets, beads, films, fibres, meshes, membranes, and hydrogels.^{4,8}

2.1 Microspheres based DDS

The microsphere-based delivery method is often selected because of its long lifespan, control over drug release, and ability to distribute just certain types of medications. The interaction with counter ions, solvent evaporation, crosslinking, spray drying, ionic gelation, precipitation/coacervation, emulsion polymerization, and other processes may all be used to create microspheres^{17–20} Glutaraldehyde cross-linked microspheres by using mitoxantrone are also reported.^{9,10}

2.2 Tablets/capsules based DDS

DDS based on tablets or capsules is often created using the wet granulation method or just direct compression. Diltiazem's release behaviour from oral mucosal adhesive tablets manufactured with the direct compression method and a matrix of chitosan and alginate was evaluated, and it showed a noteworthy response. The chitosan–sodium alginate matrix system exhibited comparable characteristics.¹¹ Another study examined how different combinations of anionic polymers affected the release rate of chitosan.¹²

2.3 NPs based DDS

NPs are very effective in transferring macromolecules across the nasal, oral, tracheal, and ocular epithelium and improving pharmaceutical absorption *via* the nasal mucosa.¹³ For the production of biopolymer-based NPs, a number of techniques, including emulsion, nanoprecipitation coacervation, ionic gelation, reverse micellar approach, and sieving method, have been described.^{14,15} As the tumor-targeted carriers for the dextran–doxorubicin combination, chitosan nanoparticles (NPs).¹⁶ Similarly, it has been shown that chitosan nanoparticles can encapsulate DOX and *N*-trifluoroacetyl DOX.¹⁷ Significant anticancer activity of a photosensitizer meso-tetra (*N*-methyl-4-pyridyl) porphine tetra tosylated and encapsulated in antibody-targeted chitosan–alginate nanoparticles.¹⁷ Chitosan NPs are also reported as suitable stable delivery devices for siRNA and protein.¹⁸ Entrapment of DOX in chitosan NPs is also reported.¹⁹ Chitosan NPs loaded with paclitaxel illustrated superb tumor-homing.²⁰ The antiviral behavior of interferon-alpha *via* orally administered chitosan NPs is also evaluated.²¹

2.4 Nanofibers based DDS

To improve the properties like hydrophobicity, solubility, biological activity, biocompatibility *etc.* for widening their applications, chemical modification of biopolymers is an effectual tool. Another technique to increase the potential of biopolymer nanofibers for drug delivery applications is surface functionalization.²² For the announcement of controlled drugs, nanofibrous chitosan–polyethylene oxide was developed.²³ Electrospun membranes with ibuprofen-loaded poly(lactide-co-glycolide)/poly(ethylene glycol)-g-chitosan have been used in



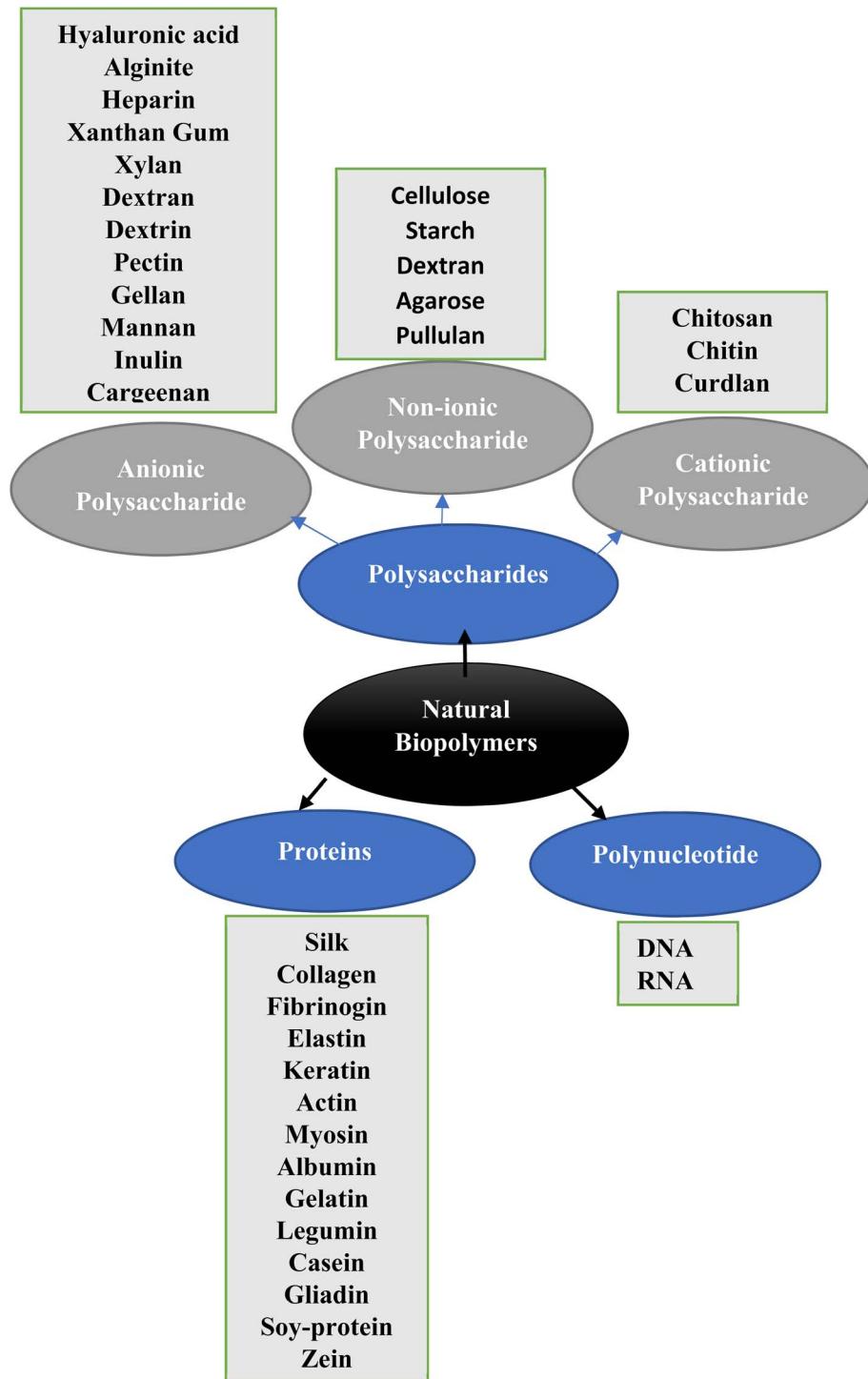


Fig. 1 Classification of different polysaccharide, protein and nucleotide-based biopolymers.

controlled drug delivery applications.²⁴ Quaternary electrospun polymers containing DOX showed enhanced cytotoxicity against the graffiti tumor cells.²⁵ Chitosan and phospholipids hybrid nanofiber has been employed for transdermal drug delivery.²⁶

2.5 Beads-based DDS

Crosslinked beads are an important form of biopolymers exploited broadly in delivery systems.²⁷ The controlled release of

diclofenac sodium from glutaraldehyde crosslinked polymeric beads were also evaluated.²⁸ Multi-layered alginate and chitosan beads directed controlled gastrointestinal passage of ampicillin, which is a low molecular weight compound.²⁹

2.6 Films-based DDS

Biopolymeric thin films find numerous applications in DDS. Mostly, casting methods are preferred to deposit thin films. In

comparison to their parent material, hybrid materials have notably better characteristics. Drug delivery systems using biopolymeric crosslinked films have been researched in a number of applications, such as oral mucosal delivery,³⁰ buccal delivery,³¹ transdermal delivery,³² sublingual delivery,³³ and periodontal delivery.³⁴ For oral mucosal administration, super critical solution impregnation technique films filled with ibuprofen have been studied.³⁰

2.7 Hydrogels-based DDS

Three-dimensional crosslinked polymeric networks called hydrogels may absorb a lot of water without dissolving.³⁵ Through implantation, the biocompatibility of crosslinked biopolymeric hydrogels is assessed.³⁶ Swell behaviour and delivery in a pH-dependent manner. The development of sensitive alginate–chitosan hydrogel beads loaded with nifedipine is also being studied.³⁷ For the purpose of promoting wound healing, photosensitive cationic NPs based hydrogels of hyaluronic acid and chitosan, with chlorin e6 and quaternary ammonium salt, were described.³⁸ Gallic acid conjugated with chitosan hydrogel beads are reported to be employed for the loading of rhodamine B.³⁹ The mechanical characteristics of the treated cotton gauze were evaluated on drug-loaded silica during an *ex vivo* drug penetration research *via* isolated rat skin, and bio polysaccharides-based hydrogels were studied using the culture count technique.⁴⁰ The injectable administration of the anticancer medication doxycycline hydrochloride has been reported to use Schiff base alginate–chitosan hydrogels with nanosilver incorporated in them.⁴¹ Epigallocatechin gallate has been found to be transported using lanthanum-modified chitosan hydrogel.⁴² 5-Fluorouracil is delivered using chitosan/agarose/graphene oxide nanohydrogel in the treatment of breast cancer.⁴³ Melaninin incorporated polysaccharide hydrogels of chitosan and oxidized β -glucanis has been reported for treating the bacterially infected diabetic wounds.⁴⁴ Carboxymethyl cellulose based hydrogels have been reported for colon-specific delivery of gentamicin. For the administration of ciprofloxacin, composite hydrogels with ZnO embedded in polyethylene glycol diacrylate and cross-linked carboxymethyl tamarind kernel gum have been reported.⁴⁵ Gelatin/lignin hydrogels have been utilized drug carriers for ribavirin.⁴⁶ Three dimensional chitosan and carboxymethyl cellulose-based hydrogels, loaded with nano-curcumin for synergistic diabetic wounds have been very well reported.⁴⁷ Polyacrylic acid–carboxymethyl cellulose hydrogel incorporating halloysite nanotubes have been reported for curcumin delivery release.⁴⁸ Natural gums and their derivatives based hydrogels have also drug delivery potential.⁴⁹

2.8 Conjugates-based DDS

It has been claimed that the development of nano-conjugates allows for both passive and active delivery of medicinal substances to the desired region. Using DOX hydrochloride, foliate-chitosan conjugated NPs improved tumour target selectivity without causing any harm.⁵⁰ Polymers by functionalization with graphene oxide were employed as nanocarriers for

camptothecin.⁵¹ Multi-walled carbon nano tubes have also been employed for the functionalization of biopolymers and showed good biocompatibility against HeLa cells and protein immobilization.⁵² Biopolymeric–biopolymeric functionalization *i.e.* alginate with chitosan is a combination reported with enhanced behavior.⁸

3 Formulations of biopolymers and their composites

Currently, natural polymers are revealing remarkable contributions in developing the DDS through physical and chemical means by blending and functionalization of polymers in different forms. In this review article, designs of different DDS made from natural biopolymer building blocks at nano and micro scale levels are tried explored and discussed individually. Fig. 1 classifies the natural biopolymers into different classes.

3.1 Polysaccharides based DDS

Polysaccharides are monosaccharides units attached by glycosidic linkages. They have properties *i.e.* bioactivity, biodegradability and processability, which make them promising biomaterials for developing the DDS under complex biological environments. Especially recent developments by using polysaccharides-derived functional biomaterials.⁵³ The role of different cationic, anionic and neutral polysaccharides, their composites and derivatives for DDS is discussed.

3.1.1 Cellulose. The most common non-ionic polysaccharide that is found naturally is cellulose. It has also been used to release repaglinide orally using cellulose and chitosan nanoparticles (NPs).⁵⁴ Specifically developed to target colon diseased sites, calcium alginate beads with carboxymethylcellulose loaded with 5-fluoroalkyl.⁵⁵ These four cellulose derivatives—methylcellulose, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and cationic hydroxyethyl cellulose—have been used as DDS in the nasal mucosa.⁵⁶ The impact of hydroxy propyl methylcellulose-based nanocomposites with cellulose nanofibrils for drug release in the form of thin films was explored.⁵⁷ As magnetic-responsive drug carriers for *in vitro* anti-colon cancer treatment, Fe3O4 loaded at cellulose containing curcumin has been used.⁵⁸ For use in *in vitro* ciprofloxacin drug release, cellulose–polyacrylamide hydrogel nanocomposite with gold nanoparticles has been developed.⁵⁹ Table 1 lists some other instances of the use of cellulose and its mixtures for medication delivery.

3.1.2 Chitosan. The most prevalent naturally occurring cationic amino polysaccharide after cellulose is chitosan. Chitosan was discovered and discussed by Rouget in 1859 for the first time and entered the pharmaceuticals field in 1990 owing to the versatility of its active amino groups.⁸ Chitosan, a cationic polysaccharide derivative of chitin has been employed in different routes of administration including nasal, ocular, intravenous, oral, mucosal, *etc.* The nasal absorption of peptide medicines as an enhancer is one of its many biological uses that merits highlighting. Peptide pharmaceuticals are often employed as an adjuvant in immunotherapy, a carrier for



Table 1 Cellulose and its composites in drug delivery

Polymer	Bioactive agent	References
Carboxymethyl cellulose	DOX	60
Cellulose	Betulinic acid	61
Microcrystalline cellulose	Luteolin and luteoloside	62
Carboxymethyl cellulose	5-Fluorouracil	63
Carboxymethyl cellulose	DOX	64
Passion fruit peel cellulose	Tetracycline	65
Hydroxy ethyl cellulose	DOX	66
Cellulose	Felodipine	67
Ethylcellulose	Multilayer layer coatings that allow for instant or customised release	68
Hydroxypropyl methylcellulose acetate succinate	For creating capsules and coating layers for instantaneous or regulated release	68
Hydroxypropyl methylcellulose	The release of nitrofurantoin might be impacted by the HPMC fraction of 0– 40%	69
Hydroxypropyl methylcellulose	For printing capsules and coating layers for immediate or modified release, barrier material	68
Hydroxypropylcellulose	Design of the capsule and pulsatile drug release	70
Hydroxypropylcellulose	Serving as a polymer carrier for theophylline release	71
Poly(1-O-methacryloyl-β-dfructopyranose)-block-poly(methyl methacrylate)	As a carrier polymer for intragastric domperidone release	72
Graphene oxide in bacterial cellulose	Paclitaxel	73
	Nanocarrier of ibuprofen	74

siRNA/DNA and gene therapy, as anticancer drugs, and as a scaffold in the healing of wounds. Functionalization is a viable method to accomplish unattainable therapeutic objectives in order to fully realise the promise of nanomedicines.⁷⁵ Chitosan along with amaranth red and microencapsulation with alginate released the intestinal and gastric fluids for the protection of molecules, after oral administration for intestinal release.^{76,77} It has also been claimed that chitosan-alginate nanocomposites improve the delivery of daptomycin to the ocular epithelium for antibacterial activities.⁷⁸ Chitosan that has been functionalized to release catechol has been tried as a buccal medication delivery method for lidocaine.⁷⁹

Chitosan nanoparticles have been discovered to significantly increase medication absorption through nasal mucosa and to transfer macromolecules across the nasal, ocular epithelium oral and tracheal.¹³ Chitosan NPs that were paclitaxel-loaded demonstrated excellent tumor-homing.²⁰ Interferon-alpha administered by chitosan nanoparticles' antiviral efficacy is also evaluated.²¹ In the quest to search the thermosensitive and mucoadhesive biopolymers, moxifloxacin-loaded sustained release periodontal showed that poloxamer-and chitosan-based formulations sustained the drug release for 8 h with low initial burst release.⁸⁰ Chitosan microspheres embedded with selenium NPs are reported to express gastroprotective potential.⁸¹ Amoxicillin is degraded by the acidic pH of the stomach, and was encapsulated in a biopolymer functionalized with lipids.⁸² Fe₃O₄/chitosan nanocomposite has been employed for the intravenous supply of gemcitabine (an anticancer nucleoside analog).⁸³ Chitosan-encapsulated mesoporous Fe₃O₄/SiO₂ nanocomposite is tested and shown to be adequate for the controlled release of DOX.⁸⁴

A composite made of polyethylene glycol, chitosan, and iron oxide that also contains cyanin dye, a near-infrared fluorescent, and has paramagnetic, targeting, fluorescent, and anticancer

properties is described for self-targeted curative drug delivery.⁸⁵ It is also claimed that chitosan plus zinc oxide make an excellent medication delivery system.⁸⁶ Iron oxide and cadmium telluride functionalized on zinc sulfide quantum dots with carboxymethyl chitosan have been employed for cell labeling and drug release.^{64,87,88} 5-Fluorouracil encapsulated carboxymethyl chitosan for colon cancer therapy.⁸⁹ Chitosan, cyclodextrin, and carboxymethyl chitosan were combined to create pH-sensitive magnetic hydrogels for the controlled release of the medication.⁹⁰ The effect of the incorporation of Fe₃O₄ NPs was also explored on carboxymethyl chitosan, cyclodextrin, and chitosan hydrogel to deliver methotrexate.⁹¹ pH-sensitive chitosan and carboxymethyl chitosan biopolymers have also been used for colon-targeting medication delivery.⁹² Using carboxymethyl chitosan, cyclodextrin, and chitosan, Fe₂O₃ hydrogels sensitive to pH were created, and they have been employed for the controlled release of medications.⁹⁰ The effect of the incorporation of iron oxide NPs was also explored on carboxymethyl chitosan, cyclodextrin, and chitosan hydrogel to deliver methotrexate.⁹¹ pH-sensitive chitosan and carboxymethyl chitosan biopolymers for colon-targeting drug delivery have also been reported.⁹²

Chitosan-chondroitin sulfate is being used for transporting the lornoxicam as a gastroretentive delivery system.¹²³ Hollow and bio-adhesive microspheres composed of ethyl cellulose and glyceryl monooleate have been fabricated and had proved to extend the drug retention time in the stomach.¹²⁵ For an 8 hour continuous release of loratadine, oil-entrapped floating microbeads were developed as a gastro retentive controlled release device. Chitosan derivative with polyaniline side chain for effective suppression of tumor growth is also reported.⁹³ An injectable succinate chitosan and oxidized alginate for *in vitro* release of DOX for inhibition of tumor growth breast cancer have been formulated.⁹⁴ In order to transport the antibiotic



ceftazidime to the eye, the effectiveness of hydroxypropyl methylcellulose containing chitosan, sodium tripolyphosphate, and hyaluronic acid NPs is assessed.⁹⁵ For the oral delivery of medications, chitosan, alginate, and pectin NPs have shown promise.⁹⁶ It is widely known that carboxymethyl chitosan may release intra-nasal carbamazepine by evading the blood–brain barrier membrane.⁹⁷ Through γ -ray irradiation polymerization, poly(butyl acrylate) modified chitosan-organophilic nanocomposite has been devised for DDS.⁹⁸ Through folate, conjugation of doped carboxymethyl chitosan-ferro-ferric oxide with cadmium telluride quantum dots a DDS has been synthesized.⁹⁹ Hybrid polysaccharides composites with crosslinked chitosan with carboxymethyl- β -cyclodextrin grafted on Fe_3O_4 have been reported for the transportation of 5-fluorouracil.¹⁰⁰ Using the drug's controlled release in *N*-(2-hydroxyl) propyl-3-trimethyl ammonium chitosan chloride was similarly successful.¹⁰¹ Alginate nanocomposites with quaternized carboxymethyl chitosan clay are tested for their drug release characteristics.¹⁰² When combined with cloisite 30B, chitosan-polyvinyl alcohol effectively administers curcumin release.¹⁰³ DOX release was observed using electrospun nanofibrous scaffolds made of polyethylene, chitosan, and graphene oxide.¹⁰⁴

Chitosan and dextran were tested as carriers for the anti-cancer medication DOX after being modified with graphene oxide.¹⁰⁵ Chitosan-alginate nanoblends with cloisite 30B have been evaluated for the controlled release of curcumin.¹⁰⁶ Graphene/gold nanocomposite films for glucose biosensing are also reported. Commercially accessible, water-soluble derivatives of glycol chitosan have been utilised to deliver drugs like paclitaxel and DOX.¹⁰⁷ Protonated chitosan with ionized alginate shows prolonged retention of the structures in the intestinal mucosa.^{108,109} *In vitro*, study revealed the ability to deliver DNA by folic acid–chitosan conjugates.¹¹⁰ Hyaluronan–cisplatin fabricated the nanoconjugates to target colon cancer.¹¹¹ A chitosan-based hydrogel containing latanoprost eye drops was discovered in the aqueous humour seven days after the system had been applied topically only once¹¹² and A polymer made of poly (*N*-isopropylacrylamide) and chitosan was used to administer timolol topically over a 12 hour period.¹¹³ Additionally, sustained drug release patterns were shown using carboxymethyl chitosan and a poloxamer made of polyethylene oxide, polypropylene oxide, and polyethylene oxide.¹¹⁴

Several conjugates with mitomycin C, exhibited good *in vitro* antitumor activities against sarcoma, melanoma, murine leukemias, hepatic cell carcinoma, and metastatic liver cancer.¹¹⁵ DOX-chitosan conjugates showed suppress tumor growth against breast cancer,¹¹⁶ melanoma,¹¹⁷ and mesothelioma cells.¹¹⁸ Paclitaxel-chitosan nanoconjugates, showed appreciable inhibition of murine melanoma when applied for oral administration.¹¹⁹ For the purpose of developing the DDS, docetaxel-chitosan conjugates also shown desirable features, such as bioavailability, decreased acute toxicity, and *in vivo* effective anticancer activity.¹²⁰ Targeted anticancer drug delivery and photothermal treatment have both been achieved using chitosan/sodium alginate functionalized magnetised graphene oxide nanocomposites.¹²¹ Silver NPs were physically crosslinked in chitosan to form hydrogel beads for application as DDSs.¹²²

Chitosan supported ciprofloxacin Tween-80/tripolyphosphate along with bovine serum albumin are reported to target the site.¹²³ Hydrogel nanocomposite of Fe_3O_4 NPs with acrylic acid/*N*-isopropyl acrylamide and chitosan for controlled release of DOX.¹²⁴ Chitosan composite with mesoporous aluminosilicate thin films was employed for the delivery of metformin.¹²⁵ Chitosan NP with Fe_2O_3 modification was created to regulate the distribution of DOX and cell imaging,⁸⁸ for simultaneous cancer imaging and therapy using methotrexate and gemcitabine administration.^{83,126} Chitosan-alginate constructs have also been employed for delivering anticancer,^{127,128} ocular,¹²⁹ pulmonary and asthma,¹³⁰ and anti-inflammatory drugs.¹³¹ Chitosan-hyaluronic acid systems were also employed for ocular applications^{132,133} and for treating asthma and osteoarthritis.^{134,135} For sustained drug release in the intestine chitosan and xanthan gum-based tablets showed excellent results.^{136,137}

The optimum encapsulation characteristics of benzalkonium chloride inside mesoporous silica/polysaccharide hybrid materials increase the amount of the drug release by improving the dispersion of the MSN and permitting enhanced drug diffusion.¹³⁸ The prolonged administration of medications to the eye is improved by chitosan and gelatin hydrogels.¹³⁹ Crosslinked chitosan with embedded Fe_3O_4 NPs showed good rational drug administration.¹⁴⁰ Chitosan microspheres loaded with 5-fluorouracil to DDS were developed in order to understand *in vitro* cytotoxicity and *in vivo* efficacy for the treatment of colon cancer.¹⁴¹

Fe_3O_4 NPs functionalized with 3-amino propyl, triethoxy silane were covered in tragacanth gum and chitosan to create capsules for the medicine curcumin.¹⁴² Zinc oxide composites with chitosan have also been used as drug delivery platforms.¹⁴³ Effective drug carriers for cancer treatment with improved absorption are pH-sensitive fluorinated carboxymethyl chitosan nanoparticles.¹⁴⁴ In colorectal cancer treatment efficiency of 5-fluorouracil was seen to be enhanced *via* nanoencapsulation.¹⁴⁵ Table 1 provides some other instances of the use of chitosan and its mixtures in medication administration.

3.1.3 Cellulose. Cellulose is a non-ionic polysaccharide. Cellulose and chitosan NPs are also employed for the oral release of repaglinide is also practiced.⁵⁴ Targeting colon diseased cites, calcium alginate beads with carboxymethylcellulose loaded with 5-fluoroalkyl.⁵⁵ These four cellulose derivatives—methylcellulose, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and cationic hydroxyethyl cellulose—have been used as DDS in the nasal mucosa.⁵⁶ The impact of hydroxy propyl methylcellulose-based nanocomposites with cellulose nanofibrils for drug release in the form of thin films was explored.⁵⁷ For *in vitro* anti-colon cancer treatment, magnetic-responsive drug carriers loaded at cellulose containing curcumin were utilised instead of Fe_3O_4 .⁵⁸ *In vitro* drug release of ciprofloxacin with a 96.6 percent success rate over a 5 hour period using gold nanoparticles with cellulose grafted polyacrylamide hydrogel.⁵⁹ Colon cancer treatment with 5-fluorouracil-encapsulated carboxymethyl chitosan is widely documented.⁸⁹ Chitosan, cyclodextrin, and carboxymethyl chitosan were combined to create pH-sensitive magnetic hydrogels for the controlled release of the medication.⁹⁰ In order to



distribute methotrexate, the impact of including Fe_3O_4 NPs on carboxymethyl chitosan, cyclodextrin, and chitosan hydrogel was also investigated.⁹¹ pH-sensitive chitosan and carboxymethyl chitosan biopolymers have also been used for colon-targeting medication delivery.⁹² Table 2 lists some other instances of the use of cellulose and its mixtures for medication delivery.

3.1.4 Hyaluronic acid. Different forms of cancer, such as breast cancer, lung cancer, and colon cancer, have been treated using a variety of hyaluronic acid (anionic polysaccharide) and

its derivatives combined with paclitaxel.¹⁰⁹ They are proved prospective carriers for butyric acid to treat Lewis lung, melanoma, and leukaemia and have undergone significant research for the transport of analgesics, siRNA, proteins, antibiotics and anticancer medicines.¹⁹² In human ovarian carcinoma xeno-grafts, hyaluronic acid (HA) alone and in conjugation with DOX demonstrated targeted toxicity *in vitro* and potent anticancer action *in vivo*¹⁹³ and bladder carcinoma respectively.¹⁹⁴ HA functionalized by adipic dihydrazide or methacrylic anhydride showed an appreciable DD profile.¹⁹⁵ Hyaluronic acid coupled

Table 2 Chitosan and its composites in drug delivery

Polymer	Bioactive agent	References
Polyurethane-alginate/chitosan	A model antigen	146
Chitosan-alginate	Silver	147
	Crocin	148
	Naringenin	149
	Quercetin	150
	Insulin	151
	DOX	152
	Insulin	153
	Diclofenac sodium	154
	Verapamil	155
	Prednisolone	156
	Amoxicillin	157
	Curcumin	129
	5-Fluorouracil, indomethacin	158
	Testosterone	159
	Ondansetron hydrochloride	160
	Bovine serum albumin	161
	Lidocaine hydrochloride	162
	Lidocaine	163
	Lidocaine	164
	Glimepiride	165
	Donepezil	166
	Propranolol hydrochloride	167
	Etoricoxib, paracetamol	168
	Carvedilol	169
	Aцикловир	170
	Melatonin	171
	Meloxicam	172
	Resveratrol	173
	Procaine hydrochloride	174
	Curcumin, diclofenac and vitamin B12	175
	chitosan	
	Metformin hydrochloride	176
	Lisinopril	177
	Bovine serum albumin	178
	Tetanus toxoid	179
	Ketoprofen, chondroitin sulfate	180
	Methotrexate	181
	Chorine6	182
	Glycyl-prednisolone	183
	Quercetin	184
	Histamine	185
	Diacerein	186
	Curcumin	187
	Indocyanine green	188
	Glibenclamide	189
	DOX	190
	Cur	191
Chitosan, <i>p</i> -nitrophenyl chloroformate and amino1-propanol, Pluronic F127		
Chitosan, DMPC, lipiodol, $\text{D}-\text{glucose}$ (dextrose)		
Xanthan- <i>graft</i> -C16 alkyl chain		
Chitin- <i>graft</i> -hexadecyl		
Fucoidan- <i>graft</i> -octenyl succinic anhydride		



with g-poly (*N* isoropylacrylamide) has high drug-loading capabilities. Another system for loading cyclosporine A showed results comparable to commercially available DDS.¹⁹⁶ Zhong *et al.* did extensive study on reversible crosslinked hyaluronic acid nanoparticles to address medicine resistance (NPs).¹⁹⁷ Crosslinked hyaluronic acid composite hydrogels and nano-carriers have been used to deliver drugs to the eyes.¹⁹⁵ The modified hyaluronic macromers were crosslinked with matrix metalloprotease peptides to allow for a sustained release of the growth hormones.¹⁹⁸

The creation and subsequent loading of an injectable hydrogel based on the chemical bonds between hyaluronic acid and adipic acid dihydrazide and hyaluronic acid aldehyde. Paclitaxel comes in micelle and microparticulate forms.¹⁹⁹ Results revealed a significant tumor reduction. Cho *et al.* developed platinum-incorporated HA NPs to inhibit tumor growth.²⁰⁰ Ueda *et al.* developed an injectable interferon-alpha containing hyaluronic acid-tyramine that was subsequently combined with sorafenib in a kidney cancer xenograft mice model (a tyrosine kinase inhibitor).²⁰¹ Ferrocenium tetradecyl coated with HA was used for the delivery of the DOX drug.^{94,202} An enhanced therapeutic effect was shown by a nanocomposite comprised of fluorochrome indocyanine green, carboxyl terminated dendrimer, HA and DOX.²⁰³ Iron oxide NPs with dopamine-modified Hyaluronic acid have been reported.²⁰⁴ For lung cancer treatment, an injectable alginate-calcium hydrogel containing dendrimer-encapsulated platinum NPs was used.²⁰⁵ Table 3 lists some further instances of hyaluronic acid and its compounds being used for medication delivery.

3.1.5 Xylan. Another prevalent cationic polysaccharide biopolymer, xylan is mostly found in plants and grains and is hemicellulose. Due of colonic microflora's ability to generate enzymes that may lead to biodegradation, it is a crucial factor in the development of colonic DDS. Thus, xylan was approved as a biopolymer that is only used in the colon.²²⁴ A sort of illness connected to the colon area is colorectal cancer. The activation

of the carboxylic acid was employed by Sauraj and his collaborators to create xylan-5-fluorouracil-1-acetic acid conjugates, which they found to be more effective than the medicine when administered alone.²²⁵ Additionally, xylan-curdumin conjugates for the therapy of cancer have been described.²²⁶ These systems are described for the delivery of peptides and proteins, as well as for the treatment of Chron's disease and ulcerative colitis, in addition to having shown promise for colon medication delivery.²²⁷

3.1.6 Alginate/alginate acid. Alginate composites, conjugates, and derivatives with a variety of therapeutically active components have been described and are offered in the market commercially.²²⁸ Active compounds, ranging from microscopic drug molecules to macromolecular proteins, may be released from alginate gels in a controlled manner depending on the kind and cross-linking procedure. Their applications in the pharmaceutical sector are expanded by the fact that they may also be administered orally or through injection.²²⁸ HT-29 cells were used as the test subject for the *in vitro* cytotoxicity of capecitabine-loaded interpenetrating polymeric network created by the ionotropic gelation process employing the polymers locust bean gum and sodium alginate. Results showed that cell proliferation has been significantly reduced.²²⁹ For the treatment of depression, alginate NPs have been used to release venlafaxine through intranasal delivery.²³⁰ Moxifloxacin hydrochloride is effectively delivered over time using sodium alginate.²³¹ Anti-inflammatory medications have also been administered to the eye using sodium alginate hydrogels. Another such very effective formulation is created.²³² Román *et al.* developed alginate microcapsules containing epidermal growth factor linked to its exterior section to precisely target the non-small cell lung cancer cells.²³³ Additionally put in the NPs was cisplatin. To increase the penetration of daptomycin into the ocular epithelium in an effort to have an antibacterial impact, chitosan-coated alginate NPs were used.⁷⁸

Table 3 Drug delivery using hyaluronic acid and its composites

Polymer	Bioactive agent	References
Adipic dihydrazole hyaluronic acid	Quercetin	206
Hyaluronic acid	Curcumin	207
Hyaluronic acid	Curcumin	208
Dithiodipropionic acid hyaluronic acid	Quercetin curcumin	209
Hyaluronic acid	Paclitaxel	210
	Butyric acid	211
	Cisplatin	212
	Cisplatin	213
	Paclitaxel	214
	Paclitaxel	215
	DOX	216
	Paclitaxel	217
	HA-conjugate NPs	218
Hyaluronic acid ceramide	Noisome	219
Hyaluronic acid-functionalized SLN	DOX	220
Hyaluronic acid-nanographene oxide	PCL nanofiber scaffold	221
Functionalized hyaluronic acid	Coenzyme Q10	222
Hyaluronic acid-functionalized transferases	Human growth hormone	223
Hyaluronic acid-chitosan functionalized		
Hyaluronic acid polymeric micelle		
Hyaluronic acid conjugate		



To create drug delivery systems, alginate nanoaggregates of 250 to 850 nm may be coupled with chitosan and glycol chitosan.²³⁴ Alginate nano aggregates have been used to deliver DNA, antisense oligonucleotides, insulin, cisplatin, and DOX.¹⁰⁷ Using galactosylated chitosan graft dextran, DNA complexes have been delivered to the liver.²³⁵ Chitosan/hyaluronic acid microparticles were used to load the DOX hydrochloride drug.²³⁶ To deliver 5-fluorouracil for colon cancer therapy and blood drug concentration, a mesoporous silica-alginate/folic acid-conjugated O-carboxymethyl chitosan-gelatin nanocomposite was developed.²³⁷ By avoiding the burst release, sodium alginate-ZnO hydrogel beads improved the release of curcumin.²³⁷ Films made of calcium alginate loaded with diclofenac sodium and other hydrophilic polymers performed well.²³⁸ Ca-alginate composite films are used in clinical therapeutic applications.²³⁹ Table 4 lists some other instances of the use of alginate and its mixtures for medication administration.

3.1.7 Dextran. The microbially produced dextran is a complex branching poly-*d*-glucoside with variable-length glycosidic linkages. On a group of human tumour xenografts and colon cancer, a dextran-camptothecin combination demonstrated strong anticancer efficacy *in vivo*.¹⁹² A combination of dextran and exatecan demonstrated substantial therapeutic effectiveness against a panel of murine solid tumours and human xenografts.³⁰⁷ Compared to the free medication, methotrexate to dextran combination demonstrated enhanced activity against human tumour xenograft models.³⁰⁸ Multiple colon cancer cell lines exposed to paclitaxel-carboxymethyl-dextran ester conjugates shown strong anticancer activity *in vivo*.³⁰⁹ In a Lewis lung cancer rat model, an imine conjugation of DOX to Ox-dextran shown greater therapeutic effectiveness.¹⁹² Additionally, a clinical investigation for a CM-dextran combination with deliomotecan has begun.³¹⁰ Dextran nanogels that have been PEGylated have been used for gene therapy using short interfering RNA,³¹¹ which, in human hepatoma and glioblastoma, have effectively accomplished gene knockdown. Drug-resistant cancer cell lines may be treated using Dextran nanogels that carry siRNA to silence the genes that cause multidrug resistance.¹⁹² Fast-dissolving oral medication administration was achieved by electrospinning metronidazole/hydroxypropyl- β -cyclodextrin inclusion complex nanofibrous webs.³¹²

For complexation, cyclodextrins are most often used. Examples include budesonide (for pulmonary drug delivery), acetazolamide (for ocular drug administration), and buserelin (nasal drug delivery).³¹³ To overcome drug resistance, a gold-paclitaxel nanoconjugate was developed using -cyclodextrin.³¹⁴ Additionally, diisocyanate-modified Fe₃O₄ and cyclodextrin were used to create magnetic nanoconjugates of dacarbazine.³¹⁵ Methotrexate was conjugated with dextran to lower the dosage and lessen unwanted effects.³¹⁶ Dextran and 5-aminosalicylic acid conjugates have been utilised to carry drugs to the small intestine and stomach. The prodrug of the azo-coupled dextran-salicylic acid combination regulated the drug's release into the colon.³¹⁷ Since nalidixic acid alone is pH sensitive, dextran-nalidixic acid ester conjugate is used as a colon-specific drug.³¹⁸ When used to treat human ovarian cancer cells, dextran

nanocomposites with paclitaxel and DOX shown encouraging results for more tumour mass penetration and less side effects than the pure medication.²¹⁰ Curcumin- and curcumin- γ -hydroxypropyl cyclodextrin-loaded nanoconjugates were shown to be more efficient than the pure medication for delivering genetic material in cancer cells.³¹⁹ Table 5 lists some further instances of dextran and its compounds being used for medication delivery.

3.1.8 Heparin. A member of the glycosaminoglycan family, heparin is a sulfated polysaccharide containing a linear anionic unit composition that is mostly composed of 2-O-sulfo-*iduonic acid* and 2-deoxy-2-sulfamino-6-O-sulfo-*d*-glucose, with trace quantities of 2-acetamido-2-deoxy-*d*-glucose. DDS also came into contact with heparin anionic polysaccharides. All-trans-retinoic acid and DOX were combined to form a system that Zhang and colleagues created. It was coupled to low molecular weight heparin, and DOX was physically loaded.¹⁰⁹ A heparin/DOX complex-containing composite system was described. To create self-assembled NPs encapsulating docetaxel, a polymer in the coupling of stearyl amine with low molecular weight heparin was employed. The research examined the NPs' effects on human breast cancer cell lines.³³² Table 6 lists some further instances of the use of heparin and its mixtures in medication administration.

3.1.9 Xanthan gum. A polysaccharide, xanthan gum is often used as a food ingredient in industry. It has been reported that the drug release mechanism from binary composition tablets made of quetiapine fumarate, xanthan, and tragacanth gum (anionic polysaccharide) obtained a drug control release similar to that of the commercial product.^{341,342} A successful report of ibuprofen-loaded xanthan gum microsphere.³⁴³ When combined with xanthan gum, *Terminalia chebula*, *Glycyrrhiza glabra*, *Emblia Officinalis*, *Terminalia belerica*, and *Turbinella rapa* herbal extracts shown increased efficacy.³⁴⁴ Lamivudine microsphere made from xanthan and guar gum revealed a slower release rate and continuous release for up to 24 hours.³⁴⁵ Metformin hydrochloride mucoadhesive microspheres produced with various XG and guar gum concentrations have been reported.³⁴⁶ A carbamazepine mucoadhesive nanoemulgel for targeting the brain *via* the olfactory mucosa is also disclosed.³⁴⁷ For effective transport of curcumin to the brain through the nose, xanthan gum-coated mucoadhesive liposomes were studied. The ability to effectively carry medication into the brain through the nasal route using xanthan gum-coated liposomes or other nanocarriers has been shown.³⁴⁸ Drug release from formulations including xanthan gum and carbopol 934 was maintained for 8 hours.³⁴⁹

3.1.10 Pectin. The major goal of the work was to alter specific pectin characteristics by adding thiol moieties to the polymer *via* the construction of pectin (anionic polysaccharide)-cysteine conjugates.¹⁰⁹ Pectin-cysteine beads with zinc added showed increased stability in simulated gastrointestinal settings, but their insulin release profile was identical to that of unaltered zinc pectinate beads.¹⁰⁹ To administer paclitaxel, a pectin-conjugated magnetic graphene oxide composite was created.¹⁰⁹ Methotrexate-conjugated pectin nanoparticles (NPs) were developed for the delivery of a cytotoxic drug to



Table 4 Drug delivery using alginate and its composites

Polymer	Bioactive agent	References
Alginate	Zidovudine	240
Alginate	DOX loaded liposomes	241
Sodium-alginate	Indomethacin	242
	Retinoic acid	243
	DOX	244
	5-Fluorouracil	245
Alginate	Ibuprofen	246
Sodium-alginate	Ketoprofen	247
Algic acid	DOX	248
Alginate-calcium phosphate NPs	Glucocerebrosidase	249
Alginate-montmorillonite NPs	Vitamin B1 and B6	250
Alginate-magnesium stearate NPs entrapped in oil	Ibuprofen	251
Alginate gel entrapped in oil-	Risperidone	252
Alginate tamarind gum magnesium stearate buoyant NPs	Metronidazole	253
Alginate-calcium silicate effervescent beads	Alfuzocin HCl	254
Alginate-calcium silicate muco adhesive NPs	5-Fluorouracil	255
Glass-alginate-samarium composite	DOX and paclitaxel	256
Alginate-calcium carbonate hybrid NPs	DOX	257
Alginate-strontium-substituted hydroxyapatite nanocomposites	Vancomycin	258
Montmorillonitealginate composites	Diclofenac sodium	259
Composite of calcium alginate and methyl cellulose	Gliclazide	260
Microbeads made of polyvinylpyrrolidone and calcium alginate	Diclofenac sodium	261
Alginate-polysaccharide beads made of linseed	Diclofenac sodium	262
Okra gum with zinc alginate beads	Diclofenac sodium	263
Mucilage-alginate mucoadhesive beads made from paghula husk	Gliclazide	264
NPs made of ispaghula husk and alginate	Glibenclamide	265
Microspheres made of tamarind seed polysaccharide that are mucoadhesive	Gliclazide	266
Polysaccharide-alginate mucoadhesive beads made with tamarind seeds	Metformin HCl	267
Microspheres of esterified gellan gum and alginate	Aceclofenac	268
Lipid/alginate	Dexamethasone	269
Calcium/alginate	Hector (Aah), attenuated androctonus australis venom	270
Graphene conjugated sodium alginate	Carrier of DOX hydrochlorid	271
Carboxymethyl cellulose and sodium alginate protected silver NPs	Nanomedicine	272
Polyurethane-alginate	Insulin	229
Poly vinyl alcohol-alginate	Metformin	273
Lipid/alginate	Dexamethasone	269
Calcium/alginate	Attenuated Androctonus australis hector (Aah) venom	270
Alginate	Curcumin	274 and 275
Galactosylated alginate	Curcumin	276
Sterculia gum-alginate floating beads with oil entrapment	Aceclofeneac	277
Mucilage-alginate mucoadhesive beads made from fenugreek seeds	Metformin HCl	278
Tamarind seed polysaccharide-alginate floating beads that have been emulsion-gelled	Diclofenac sodium	279
Microbeads of zinc alginate-carboxymethyl cashew gum	Isoxsuprine HCl	280
Sodium alginate	Theophylline	247
	Diltiazem HCl	281
	Metronidazole	282
	Gliclazide	283
	Sulindac	284
	Ampicillin	285
	Diclofenac sodium	286
	Furosemide	287
	Diclofenac sodium	288
	Aceclofenac	289
	Glipizide	290
	Aceclofenac	268
	Diclofenac sodium	291
	Diclofenac sodium	292
	Glibenclamide	293
	Pantoprazole	294
	Glibenclamide	293
Alginate-locust bean gum		
Alginate-pectinate		
Alginate-gellan gum		
Alginate-gellan gum		
Alginate-xanthan gum		
Alginate, guar gum, locust bean gum, and xanthan gum		
Alginate-gum Arabic		
Sterculia gum-alginate		
Gum Arabic-alginate		



Table 4 (Contd.)

Polymer	Bioactive agent	References
Tamarind gum-alginate	Gliclazide	266
Tamarind gum-alginate	Metformin HCl	267
Tamarind gum-pectinate	Metformin HCl	295
Tamarind gum-alginate	Diclofenac sodium	296
Tamarind gum-gellan gum	Metformin HCl	297
Gum-alginate of okra	Diclofenac sodium	263
Alginate from okra	Glibenclamide	263
Linseed polysaccharide-alginate	Diclofenac sodium	262
Seed mucilage-alginate of fenugreek	Metformin HCl	265
Mucilage-alginate from the ispaghula husk	Glibenclamide	298
	Gliclazide	298
	Isoniazid	299
	Metformin HCl	300
Fruit gum-alginate from dellinia	Timolol maleate	301
Kondagogu-alginate gum	Glipizide	302
Mucilage-alginate from fenugreek seeds	Metformin HCl	265
Alginate	Zidovudine	240
Alginate	DOX loaded liposomes	241
Sodium-alginate	Indomethacin	242
	Retinoic acid	243
	DOX	244
	5-Fluorouracil	245
Alginate	Ibuprofen	246
Sodium-alginate	Ketoprofen	247
Alginic acid	DOX	248
Chitosan, sodium alginate	Rabeprazole sodium	303
Alginate-locust bean gum	Diclofenac sodium	288
Alginate-pectinate	Aceclofenac	289
Alginate-gellan gum	Glipizide	290
Alginate-gellan gum	Aceclofenac	268
Alginate-xanthan gum	Diclofenac sodium	291
Alginate, guar gum, locust bean gum, and xanthan gum	Diclofenac sodium	292
Alginate-gum Arabic	Glibenclamide	293
Sterculia gum-alginate	Pantoprazole	294
Gum Arabic-alginate	Glibenclamide	293
Tamarind gum-alginate	Gliclazide	266
Tamarind gum-alginate	Metformin HCl	267
Tamarind gum-pectinate	Metformin HCl	295
Tamarind gum-alginate	Diclofenac sodium	296
Gellan gum with tamarind gum	Metformin HCl	297
Gum-alginate of okra	Diclofenac sodium	263
Gum-alginate of okra	Glibenclamide	263
Linseed polysaccharide-alginate	Diclofenac sodium	262
Seed mucilage-alginate of fenugreek	Metformin HCl	265
Mucilage-alginate from the ispaghula husk	Glibenclamide	298
Mucilage-alginate made from spigola husk	Gliclazide	298
Mucilage-pectinate from the ispaghula husk	Aceclofenac	304
Spaghula husk mucilage-pectinate	Metformin HCl	305
Mucilage-gellan gum made from spaghetti husk	Metformin HCl	306

hepatic cancer cells.³⁵⁰ Pectin-adriamycin conjugates' potential for lymphatic targeting was investigated.³⁵¹ Using pectin matrices coated with eudragit 100, the release of 5-fluorouracil in the colon was examined. Pectin formulation reduced cytotoxicity concentration in cells by 50% in human colon cancer cells.³⁵² Some other examples of pectin in drug delivery are reported in Table 7.

3.1.11 Polyarginine. This sugar containing molecules also made its space for designing DDS. Because of its capacity to

permeate membranes, polyarginine is often employed in DDS as a cell-penetrating peptide.³⁶¹ For the delivery of quantum dots, arginine-rich peptides have been widely used.³⁶² Role of arginine peptides in drug delivery is reported in Table 8.

3.1.12 Pullulan. A polysaccharide made of maltotriose trimers is pullulan. A neutral polysaccharide called pullulan has been researched for non-viral gene delivery techniques.¹⁰⁷ In order to explore their potential for usage in gene delivery applications, Rekha and colleagues produced



Table 5 Drug delivery using dextran and its compounds

Polymer	Bioactive agent	References
Dextran	Curcumin	320
	Indomethacin	321
	Indomethacin	322
	Curcumin	323
	Paclitaxel	324
	Dacarbazine	314
	Aminosalicylic acid	315
	Nalidixic acid	317
	Methotrexate	325
	Ibuprofen	316
Cyclodextrin	DOX and paclitaxel	326
	Camptothecin	327
	Camptothecin	328
	Delimotecan	329
	Exatecan	330
Dextran	DOX	331

polyethyleneimine-conjugated pullulans.³⁶⁷ Utilizing pullulan-deoxycholic acid conjugated for medication administration in cancer patients, Na and colleagues created a self-organized nano gel of DOX. The effective transfer of plasmid DNA to the liver was made possible by serine pullulan samples.³⁶⁸ DNA could be quantitatively loaded into pullulan microspheres using 1,2-chloro-2,3-epoxypropane without DNA degradation.³⁶⁹ Pullulan nanoparticles disulfide-cross-linked with folic acid for antitumoral hepatic drug delivery.³⁷⁰ In order to functionalize nanocarriers for targeted medication delivery in the treatment of cancer, heparin has been widely researched for its anticancer action.¹⁰⁹ Table 9 lists some further instances of pullulan and its mixtures being used for medication delivery.

3.1.13 Starch. Starch is a non-ionic carbohydrate. Occurring *in situ* during the formation of CuO NPs, oxidised starch-CuO nanocomposite hydrogels allowed for the measurement of extended drug release for the CuO NPs containing oxidised starch that was elevated by increasing the CuO amount. In a separate study, two controlled-release drug carriers for the medicine methylprednisolone were developed as silver-starch nanocomposite beads.¹²¹ Table 10 lists some other instances of the use of starch and its composites for medication delivery.

3.1.14 Guar gum. To assess their potential for drug delivery, neutral and cationic guar gum nanocomposites

Table 7 Role of Pectin in drug delivery

Polymer	Bioactive agent	References
Pectin	Indomethacin	353
	Rutin	354 and 355
	Theophylline	356
	Ketoprofen	357
	Cisplatin	358
	Insulin	359
	Paclitaxel	360
	Methotrexate	350
	Adriamycin	351
	5-Flourouracil	352

containing montmorillonite-loaded ibuprofen have been studied.⁴⁰⁰ Guar gum-*graft*-acrylic acid was synthesized by an L-alanine crosslinker for hydrophilic drug delivery.⁴⁰¹ Guar-gum-polyacrylamide incorporated with diltiazem hydrochloride has been reported.⁴⁰² Acrylamide-grafted-guar-gum blended with chitosan as DDS has been evaluated.⁴⁰³ For the transdermal distribution of the medication diclofenac sodium, carboxymethyl guar gum containing nano silica was created.⁴⁰⁴ Guar-gum nanocomposite hydrogels and multiwalled carbon nanotubes have been utilised to administer the drug diclofenac sodium.⁴⁰⁵

Target-specific crosslinked hydrogels based biopolymers for the controlled release of cephradine.⁴⁰⁶ For the *in vitro* release of cephradine, chitosan/guar gum hydrogels were created by mixing with PEG. Results indicated that 85 percent of the cephradine was released in 130 minutes. Gelatin is a linear polypeptide made up of 18 distinct kinds of amino acids and a hydrophilic biopolymer. To treat resected primary/metastatic bone locations, zoledronic acid-containing nanocomposites of gelatin and beta-tricalcium phosphate were created.¹⁵⁰ The biocompatible gelatin was filled with methotrexate.¹⁵¹ Zinc oxide was synthesised *in situ* to create antibacterial chitosan/zinc oxide nanocomposite hydrogels that were used as naproxen drug delivery systems.¹⁵² Table 11 lists further instances of gelatin being used for medication delivery.

The local administration of anticancer medications using injectable chitosan-based gels has shown significant potential. For instance, liposomal DOX was loaded into a thermosensitive injectable hydrogel with chitosan and -glycerophosphate that released DOX *in vitro* in a pH-dependent manner.²¹⁷ Some other

Table 6 Drug delivery using heparin and its blends

Polymer	Bioactive agent	References
Heparin	DOX	333
	DOX and all trans retinoic acid	334
	A peptide-modified DOX	335
	Retinoic acid	336
	Docetaxel	337
	DOX	338
Heparin- <i>graft</i> - α -tocopherol	Pyropheophorbide-a	339
Heparin- <i>graft</i> -deoxycholate	Paclitaxel	340
Pegylated heparin a		
Heparin		



Table 8 Role of Polyarginine in drug delivery

Polymer	Bioactive agent	References
Polyarginine	Cyclosporin A	363
	NLC encapsulated spantide II and ketoprofen	364
	Liposomes encapsulated curcumin	365
	Liposomes encapsulated polygonum	366

examples of gum and its composites in drug delivery are reported in Table 12.

3.2 Protein-based DDS

Natural poly(amino acids), a kind of biodegradable ionic polymers, has only one type of amino acid. The biomaterials that are examined the most often are poly(γ -glutamic acid) and poly(L-lysine). The glutamic acid polymer Because of the polymer's reactive side carboxylate centres, other functional groups and medications may be attached covalently.⁴ Antibiotics, vaccines, DNA, and proteins have all been explored to be transported using poly(γ -glutamic acid)-based particles. A poly(glutamic acid)-based carrier that contains paclitaxel is a well-known cancer product. In biomedical applications, it has been employed as a carrier to increase the effectiveness of several interferon inducers, antiviral medications, and anticancer medications. Biomedical uses for polynucleotides like DNA and RNA exist.⁴¹⁸ The role of individual proteinaceous polymers is discussed below:

3.2.1 Collagen. Collagen, the primary element of connective tissues, is the most abundant protein in the human body. Due to their diverse qualities, which include mechanical strength and biocompatibility-degradability, 29 distinct kinds of collagen have been identified and are being intensively explored for use in the fabrication of the DDS.⁷⁹ Low-molecular-weight pharmaceuticals may be transported well by collagen; gentamicin-loaded collagen-based delivery systems are one example of this. Numerous different collagen and synthetic polymer composite systems are being described as DDS.^{79,419} Polylactic-co-glycolic acid and alginate microparticles containing collagen have been produced for continuous administration of recombinant human bone morphogenetic protein 2, making them an effective controlled delivery vehicle of the pro-

osteogenic factor.⁴²⁰ Additionally, collagen/polyvinyl alcohol is being tested for the continuous administration of salicylic acid.⁴²¹ To combat bacterial infections, collagen scaffolds crosslinked with hexamethylene diisocyanate and containing cefaclor have been created.⁴²² Collagen bandage contact lenses to lubricate the eye along with active ingredients are reported.⁴²³ It has been reported to use collagen-alginate microspheres to deliver medications to the eyes.⁴²⁴ In order to lubricate the eye, collagen bandage contact lenses containing active substances and a coating of collagen have been used.⁴²⁵ Alginate hydrogels with composite collagen content have been described for medication administration to the eye.⁴²⁶ Table 13 discusses the few applications of collagen and its composite.

3.2.2 Natural rubber. Natural rubber is a very elastic polymer with a strongly crosslinked structure that is an intriguing biomaterial for DDS for proteins, antitumoral drugs, and antimicrobial chitosan.⁴ Pilocarpine was released from gelatin hydrogels created by Natu *et al.* during an 8 hour period at a rate ranging from 29 to 99 percent.⁴³⁶ Human elastin-like polypeptides were included into the creation of bioactive molecules, which showed how therapeutic compounds may be delivered in response to proteolytic stimuli.⁴³⁷ In order to combine the best qualities of two materials that may be employed for therapeutic molecule administration, a composite matrix made of human elastin-like polypeptide hydrogel and electrospun poly-L-lactic acid was created.^{438,439} Some examples of starch and its composites in drug delivery are reported in Table 14.

3.2.3 Keratin. In clinical medicine, the administration of anticancer drugs may be possible using keratin, which is a highly practical and affordable protein for biomedical purposes.^{418,444} Han *et al.* used keratin for drug release of rhBMP-2, rhIGF-1, and ciprofloxacin, as well as simple alkylation on keratin for regulated release of gel G, which

Table 9 Drug delivery using pullulan and its composites

Polymer	Bioactive agent	References
Pullulan- <i>graft</i> -polycaprolactone	Ciprofloxacin	371
Pullulan- <i>graft</i> - α -tocopherol	ϵ -Caprolactone	372
Pullulan- <i>graft</i> -SA	DOX	373
Pullulan- <i>graft</i> , biotin, and retinoic acid	DOX	374
Desoxycholic acid from pullulan grafts - <i>graft</i> -polyethyleneimine	DOX DNA	375
Pulullan- <i>graft</i> -retinoic acid	DOX	376
Dibutyl amino propyl carbamate-pululan- <i>graft</i>	DNA	377
Pullulan- <i>graft</i> -cholesterol	Methotrexate	378
Cysteine from heparin- <i>graft</i> - β -sitosterol	DOX	90
Pullulan	Polyethyleneimine, DOX, adriamycin	367 and 379
Schizophyllan- <i>graft</i> -styrene acrylonitrile	Paclitaxel	380



Table 10 Starch and its Composites in drug delivery

Polymer	Bioactive agent	References
Hydroxyethyl starch	Curcumin	381
Starch coated onto the Fe_3O_4	Magnetic carrier	272
Pectinate–high amylase starch	Diclofenac sodium	382
Tapioca starch–alginate	Metoprolol tartrate	383
Potato starch–alginate	Tolbutamide	384
Potato starch–alginate	Ibuprofen	385
Assam bora rice starch–alginate	Metformin HCl	386
Jackfruit seed starch–alginate	Pioglitazone	279
Jackfruit seed starch–pectinate	Metformin HCl	387
Jackfruit seed starch–alginate	Metformin HCl	388
Jackfruit seed starch–gellan gum	Metformin HCl	389
Starch	DOX, hydroxycamptothecin, chlorpheniramine maleate	390
Aminated starch	Curcumin	391
Starch	Tungstophosphoric acid	392
Carboxymethyl starch	Mesalamine	393
PEGylated starch	DOX	394
Starch acetate	Cisplatin	395
Commercial glycerin latex, glutinous starch, rice, and potatoes	Lidocaine	396
Alginate–starch beads	Aceclofenac	397
Alginate beads made from jackfruit seed	Pioglitazone	398
Alginate–starch beads made of jackfruit seeds	Metformin HCl	292
Particles made of soluble starch composites with Ca21–Zn21–alginate	Aceclofenac	399
Rice–starch–alginate beads from Assam	Metformin HCl	386
Particles made of soluble starch composites with Ca21–Zn21–alginate	Aceclofenac	399

Table 11 Examples of Gealtin in drug delivery

Polymer	Bioactive agent	References
Gelatin	Tizanidine hydrochloride	407
		408
	Gatifloxacin	409
	Fluconazole	410

demonstrated no toxicity.⁴⁴⁵ As a model drug, rhodamine B dye release from films made of keratin and polyvinyl alcohol that were crosslinked with starch was studied.⁴⁴⁶ DOX-loaded keratin NPs are also well reported.⁴⁴⁷

3.2.4 Albumin. Proteins are water-soluble, three-dimensional folded structures, made up of amino acids joined together by amide bonds.³⁵ Different drug binding sites are found in albumin, allowing a range of medicines to be loaded.⁴⁴⁸ The most potent drug ever developed, albumin paclitaxel nanoparticle, is the first DDS approved by the FDA for the treatment of metastatic breast cancer. Levemir, created by Novo Nordisk, is another medication with albumin that is

authorised for use in the treatment of type 1 and type 2 diabetes. A human insulin derivative that binds to albumin is present. Additionally, Herceptin and Avastin, which are NPs for the antibodies trastuzumab and bevacizumab, respectively, have been studied to learn more about their potential.⁴⁴⁹ An *N*-lysinal-*N'*-succinyl chitosan and poly (*N*-isopropylacrylamide) hydrogel was enclosed within a crosslinked bovine serum albumin shell in order to function as an effective carrier of chemotherapeutic drugs.⁴⁵⁰ Calcium carbonate hybrid particles with bovine serum albumin along with polydopamine showed good DDS applications.⁴⁵¹ Table 15 lists some further instances of albumin and its mixtures being used for medication delivery.

3.2.5 Fibrin. The protein substance known as fibrin is often rigid and organised into long fibrous threads. Numerous fibrin matrices come in different forms that enable the controlled release and/or targeted administration of therapeutics, growth factors, and cells.⁴⁵² The organic protein biopolymer called silk sericin is derived from silkworms. Because of its abilities to promote cell growth, distribute drugs, heal wounds, and have certain therapeutic benefits, it is referred to as a biomaterial.⁴¹⁸ Additionally, the kinetics of physically

Table 12 Some examples of Gum and its composites in drug delivery

Polymer	Bioactive agent	References
Guar gum galactomannan- <i>graft</i> -acetic anhydride	Cur	411
Bletilla striata- <i>graft</i> -SA	DOX	412
Phthalated cashew gum	Benznidazole	413
Gellan gum	Amoxicillin, amoxicillin trihydrate, cephalexin	414 and 415
Fenugreek seed mucilage–pectinate	Metformin HCl	416
Fenugreek seed mucilage–gellan gum	Metformin HCl	417



Table 13 Collagen and its composites in drug delivery

Polymer	Bioactive agent	References
Collagen	DOX	426
Hydrolyzed collagen	Hydrocortisone	8
Collagen	DOX	427
	Chloramphenicol	428
	Ibuprofen	429
	Fludarabine/epirubicin	430
	Cardamom extract	431
	5-Fluorouracil	432
	Econazole nitrate	433
	Ciprofloxacin	434
Hydroxyapatite-collagen alginate composites	Bone morphogenetic protein	435

crosslinked silk films carrying the medicines crizotinib and DOX are evaluated.⁴⁶⁵ Core-shell silk fibroin hydrogels incorporated with albumin for drug delivery are also designed.⁴⁶⁶ Silk NPs that are DOX-loaded exhibit better NP cell uptake and promote cytotoxicity against cancer cells.⁴⁶⁷ Insulin was employed as a growth factor in silk NPs by Wenk *et al.*, who demonstrated that the release was constant for 7 weeks.⁴⁶⁸ Some other examples of silk fibroin and its composites in drug delivery are reported in Table 16.

3.2.6 Soy protein and pea legumin. Soy and pea proteins are very protein-dense with around 90% protein content while soy protein is widely-known for its abundance of essential amino acids, pea protein is gaining ground for its vegan-friendly profile. Combinations of proteins (soy protein and pea legumin) substances with other biopolymers are also reported to be engaged in DDS to deliver active ingredients like nutraceuticals.⁴¹⁸ Legumin was employed to deliver methylene blue as a model drug.⁴⁹² Soy proteins was used to deliver the timolol maleate.⁴⁹³ Soy protein-based films by glycerol and gelatin are also reported.⁴⁹⁴ Various formulations *e.g.* micro and nano hydrogel, tablet and electrospun fibers were reported.⁴¹⁹ Soy protein is a well-characterized resource for the production of nanogel-based drug delivery and nutraceutical delivery applications.⁴⁹⁵ The enzymes pepsin and pancreatin are capable of degrading soy protein compositions. Additional reports of soy protein hydrogel and tablets containing riboflavin are available.⁴⁹⁶

3.2.7 Zein. Zein, a hydrophobic protein abundant in prolamine and present in the endosperm of the maize kernel, is often employed in films and coatings. Zein is typically extracted

by aqueous alcohol at 60 °C from corn gluten meal. Zein NPs coated with sodium deoxycholate are stable, biocompatible colloidal carriers that may be utilised as effective DDS.^{3,438} The bioavailability of carvedilol was improved by up to 7 times by NPs made from casein-silk fibroin.⁴⁹⁷ *In vivo* tests on rats using NPs created by crosslinking silk fibroin and casein revealed enhanced bioavailability.⁴⁹⁸ Rutin was enclosed by pectin-casein NPs in simulated gastric and intestinal settings, extending the period of release and sustaining release.⁴⁹⁹ Casein NPs with alfuzosin hydrochloride loaded on them showed persistent alfuzosin hydrochloride release for 24 hours.⁵⁰⁰ Whey proteins, synthetic and biopolymers, and electrospun fibres and microspheres were used to create a number of different compositions.⁴¹⁹ Due to matrix degradation, riboflavin-loaded whey proteins and alginate NPs showed pH-sensitive drug release.⁵⁰¹ Some other examples of protein and its composites in drug delivery are reported in Table 17.

Conjugates with insulin released the payload for several hours in the intestine hence, controls the blood glucose levels effectively by increasing its bioavailability.⁵³⁰ DOX-loaded nanospheres functionalized showed great promise against breast and ovarian cancers with targeting antibodies.³¹³ Deoxycholic acid NPs that have been crosslinked with chitosan and are filled with plasmid DNA successfully transfect COS-1 cells. Chitosan NPs delivered tumor-suppressing interleukin receptor B, siRNA and DOX to inhibit the migration of breast cancer cells. Gal-1 expression in tumor-bearing mice was significantly reduced by chitosan NPs, which were created to carry siRNA against a brain tumour.¹⁹² It was shown that chitosan conjugates with CdS might function as adaptable nanoplatforms for

Table 14 Natural rubber and its composites in drug delivery

Polymer	Bioactive agent	References
Polyethylene glycol, natural rubber, carbazole, ammonium persulfate, 2-methyl-4-(methylthio)-2-morpholino propiophenone	Indomethacin	440
Hevea brasiliensis' isolated natural rubber latex	Diclofenac potassium	441
Natural rubber latex	Ketoprofen natural	442
3-Mercaptopropionate, 2-methyl-4-(methylthio)-2-morpholinopropiophenone, and natural rubber	Ibuprofen	443



Table 15 Albumin and its composites in drug delivery

Polymer	Bioactive agent	References
Albumin	Paclitaxel, warfarin, silibinin, diazepam	452
Bovine serum albumin	Curcumin	453
Albumin	Vancomycin	454
HAS	5-Aminosalicylic acid	455
Bovine serum albumin	Dimethylcurcumin	456
Bovine serum albumin	Curcumin	457
Albumin	Ibuprofen	458
	Irinotecan	459
Bovine serum albumin is a polymer made of oligo (ethylene glycol) methyl ether methacrylate	Panobinostat	460
Human serum albumin	Cabazitaxel, noscapine, mitoxantrone	407
		461
		462
	Sprouty 1 (C-12) (Spry1) protein	463
	Adriamycin	464

the creation of *in vivo* and *in vitro* cancer treatments.⁵³¹ Using chitosan-DOX nanoconjugates for targeted administration, ovarian and breast cancer outcomes were favourable.³¹³

A variety of therapeutic molecules *e.g.* proteins and vaccines are delivered by zein microsphere, particularly for drugs with low solubility in water in oral delivery.¹⁹² Zein films showed proven biocompatibility by successfully culturing in the mice fibroblasts and liver cells of human.²⁰² According to reports, it is also used as a covering material for tablets because of its exceptional resistance to abrasion, heat, and humidity. Ivermectin, coumarin, and 5-fluorouracil will be delivered *via* Zein.^{407,532} Zein (core) and pectin (shell) are also reported to

deliver encapsulated curcumin.⁵³³ Electrospun woven fibres made of zein and hydroxyapatite showed improved calcium phosphate mineralization in simulated bodily fluid and were shown to be biocompatible with adipose-derived stem cells.¹⁹⁶ Hyaluronic acid has been combined with mesoporous based-silica nanoconjugates for cell-specific regulated and targeted drug release for the enzymes at target location.⁵³⁴

3.2.8 Gellan gum. Gellan gum is an anionic, water-soluble polymer that is produced by the bacterium *Sphingomonas elodea*. Gellan gum-based nano-hydrogel systems have been widely documented for use in ophthalmic, gastric, and nasal drug administration applications. These systems take the shape

Table 16 Silk fibroin and its composites in drug delivery

Polymer	Bioactive agent	References
Silk fibroin	5-Fluorouracil	469
Methacrylated silk fibroin	Mouse articular chondrocytes	470
Silk fibroin or gelatin	Ibuprofen	471
	Ibuprofen	472
	Curcumin	473
	DOX	474
	Ciprofloxacin	475
	DOX	476
	DOX	477
Silk NPs	FITC	478
Silk microcapsules	FITC labeled dextrans	479
Silk NPs	FITC	480
Silk	DOX	481
	5-Fluorouracil	469
	DOX, indocyanine green	482
	3-Mercapto propionic acid coated CdTe quantum dots	483
	Rhodamine B	484
	Methylene blue	485
	Recombinant human insulin	486
	FITC dextran	487
	Insulin	488
	Tetracycline	489
	Ibuprofen	490
	Antibiotics	491



Table 17 Protein and its composites in drug delivery

Polymer	Bioactive agent	References
Milk protein casein	DOX indocyanine green	502
Lactoferrin and glycomacropeptide	Nanocarrier for curcumin	503
Gliadin	Carbazole	504 and 505
Whey protein	Ndomethacin	506
	Investigational new drug	507
	Carvedilol	508
	Folic acid	509
	Fenofibric acid	510
	Curcumin	511
	Saffron	512
	Vitamin E	513
	Resveratrol and naringenin	514
	Curcumin	515
	Theophylline	516
	Riboflavin	517
	Insulin	518
	Curcumin	519
	Proguanil hydrochloride, chloroquine diphosphate	520
	Daidzein	521
	Lycopene	522
	Zinc citrate	523
	Zinc	524
	Theophylline	525
	Puerarin 5	526
	Indomethacin, carvedilol, and furosemide	527
Whey protein isolate	Curcumin	528
Curcumin with amylase	Encapsulated curcumin	272
ABD035 peptide	Paclitaxel	529

of micro/microbeads, films, hydrogels, fibres, granules, particles, pellets, spheres, and spheroids. It has been reported that paclitaxel and prednisolone are put onto gellan gum.⁵³⁵ To explore gold nanoparticles stabilised by gellan gum, human glioma cell lines and mouse embryonic fibroblast cells were employed.⁵³⁶ Gellan gum were also loaded with DOX hydrochloride.⁵³⁷ Along with gold, silver NPs were also stabilized with the help of gellan gum for testing the cytotoxic activity and for intercellular drug delivery and imaging in mouse embryonic fibroblast cells.⁵³⁸ Hydrocolloid bead based gellan gum was also evaluated for slow drug release applications.⁵³⁹ For applications in mucoadhesive and gastroretentive drug administration, ofloxacin-loaded gellan gum and polyvinyl alcohol nanofibers.⁵⁴⁰ Resveratrol loaded chitosan/gellan gum nanofibers have also been reported for gastrointestinal delivery system.⁵⁴¹ Sericin (natural protein)-chitosan doped maleate gellan gum composites have also been reported to cure *Mycobacterium tuberculosis*.⁵⁴² It has been reported that gellan gum in the form of hydrogels combined with LAPONITE® clay makes an effective medication delivery mechanism.⁵⁴³ Gellan gum composites with sericin and rice bran albumin has also been employed as a drug carrier DOX.⁵⁴² For the buccal delivery of aceclofenac, composites of gellan gum-amino methacrylate has been employed.⁵⁴⁴ There have also been reports of gellan gum derivatives for the controlled release of ciprofloxacin.⁵⁴⁵ Metformin HCl was delivered intragastrically under regulated conditions using gellan gum hydrogel composites with olive oil-

incorporated pectin that had been modified by diethanolamine.⁵⁴⁶

3.2.9 Gum acacia/gum Arabic. Gum acacia is an environmentally benevolent and biodegradable natural polymer. Gum arabic has reportedly been used to construct multiple-unit DDS, such as beads, microparticles, NPs, etc. for sustained drug release for a variety of medicines.⁵⁴⁷ It has been utilized for the release of bisphosphonate drugs.⁵⁴⁸ Gum acacia-hydroxyapatite nanocomposite was utilized to deliver the naringenin drug.⁵⁴⁹ Additionally, it has been used as a controlled release method for antiprotozoal medications including curcumin and derivatives of the 4-aminoquinoline ring.⁵⁵⁰ When prednisone was delivered using polyvinyl alcohol/gum acacia/titania nanocomposites, it was revealed that the release of the medication was pH-responsive.¹³⁶ Acacia-carbopol-polyvinyl imidazole hydrogel loaded with gentamicin and lidocaine has also been reported.⁵⁵¹

4 Conclusions and future perspectives

Natural biopolymers and their derivatives play a remarkable role in improving the biosafety of medication cargo and targeted delivery while reducing adverse effects. The above-discussed promising uses for biopolymers point the way to a new technique for creating unique DDS with enhanced therapeutic benefits for scaling up novel formulations to the clinical



level. Above discussion also revealed that since properties and hence applications of the resultant biopolymer composites are dictated by the composition of the constituents, reaction parameters and synthetic techniques, therefore it is very crucial to optimize the biopolymeric formulations for any specific application. Another important consideration is the polymeric carrier's bioacceptability, which is influenced by the shape, size and physicochemical characteristics of both the polymer and the medication. The above discussion reviewed here motivates to devise the of engineered biopolymer-based materials with optimized properties by composites and functionalization fabrication. But there are still some things to think about before using these nanocarrier systems for therapeutic purposes. One of these entails improving biosafety even further, as well as the effects of repeated doses at the intended spot. Important issues that need additional research are chemical and structural stability during application and storage, as well as the interpretation of drug delivery design from an experimental to a commercial development perspective.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

The manuscript was written with the contributions of all authors. All authors have approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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