RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2023, **13**, 23087

Recent developments in natural biopolymer based drug delivery systems

Tanzeela Fazal,*[a] Bibi Nazia Murtaza,[b] Mazloom Shah,[c] Shahid Iqbal,*[d] Mujaddad-ur Rehman,[e] Fadi Jaber,[fg] Ayed A. Dera,[h] Nasser S. Awwad[i] and Hala A. Ibrahium[j]

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.

Received 20th May 2023
Accepted 24th July 2023

DOI: 10.1039/d3ra03369d

rsc.li/rsc-advances

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.

[a]*Department of Chemistry, Abbottabad University of Science and Technology, Pakistan. E-mail: tanzeelafazal@yahoo.com*
[b]*Department of Zoology, Abbottabad University of Science and Technology, Pakistan*
[c]*Department of Chemistry, Faculty of Science, Grand Asian University Sialkot, Pakistan*
[d]*Department of Chemistry, School of Natural Sciences (SNS), National University of Science and Technology (NUST), H-12, Islamabad 46000, Pakistan. E-mail: shahidgcs10@yahoo.com*
[e]*Department of Microbiology, Abbottabad University of Science & Technology, Pakistan*
[f]*Department of Biomedical Engineering, Ajman University, Ajman, UAE*
[g]*Center of Medical and Bio-Allied Health Sciences Research, Ajman University, Ajman, UAE*
[h]*Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Khalid University, Abha, Saudi Arabia*
[i]*Chemistry Department, Faculty of Science, King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia*
[j]*Biology Department, Faculty of Science, King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia*

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

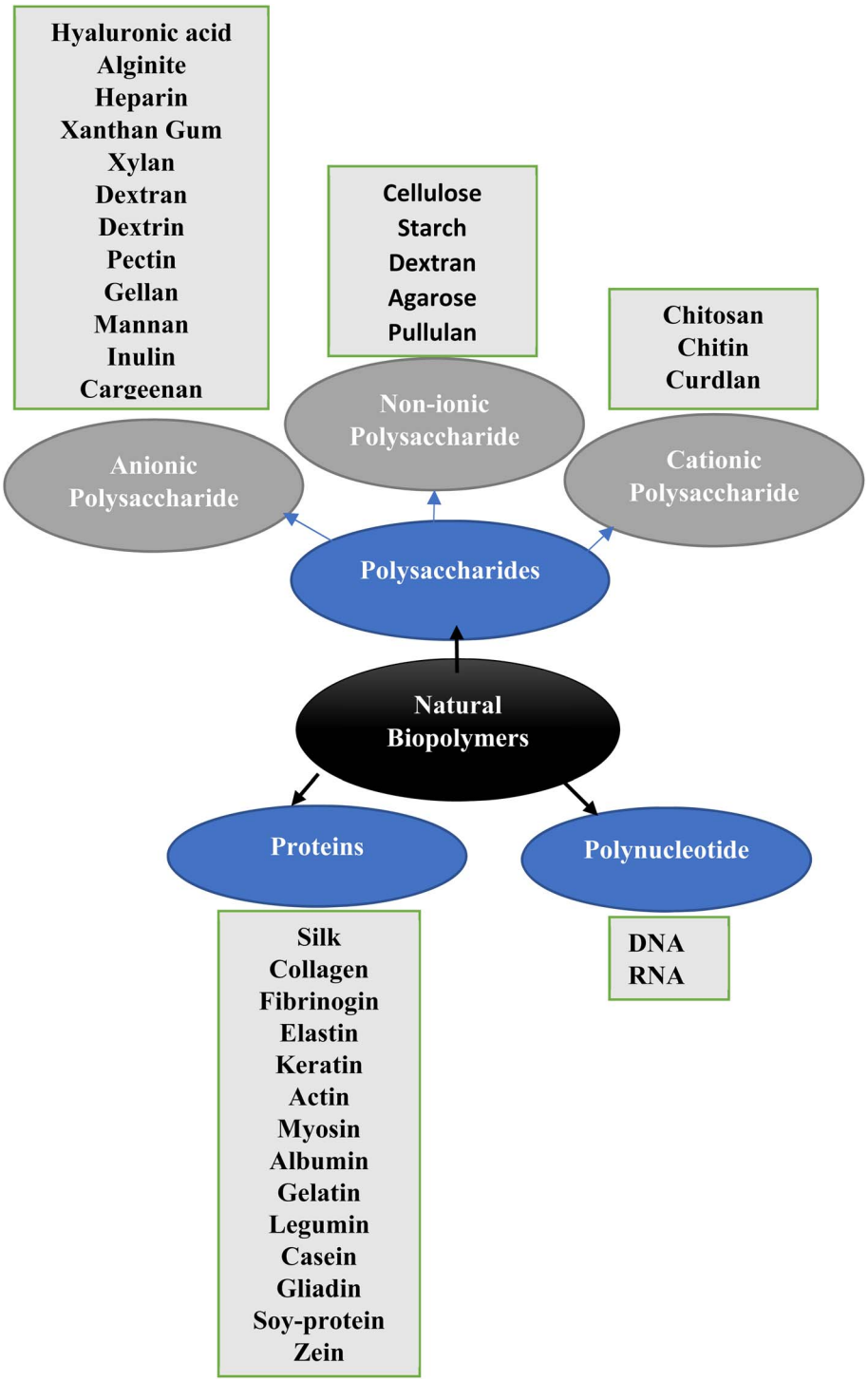

Fig. 1 Classification of different polysaccharide, protein and nucleotide-based biopolymers.

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
	As a carrier polymer for intragastric domperidone release	72
Poly(1-*O*-methacryloyl-β-dfructopyranose)-*block*-poly(methyl methacylate)	Paclitexal	73
Graphene oxide in bacterial cellulose	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] Fe_3O_4/chitosan nanocomposite has been employed for the intravenous supply of gemcitabine (an anticancer nucleoside analog).[83] Chitosan-encapsulated mesoporous Fe_3O_4/SiO_2 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 Fe_3O_4 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, Fe_2O_3 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 anticancer 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 once[112] 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 xenografts, 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 deliver

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
N-Octyl-*N* arginine chitosan	Insulin	153
Alginate–chitosan	Diclofenac sodium	154
Alginate–chitosan	Verapamil	155
Alginate–chitosan microparticles	Prednisolone	156
Chitosan-coated composite-sodium alginate microbeads	Amoxicillin	157
Blend of chitosan–sodium alginate and cloisite 30b	Curcumin	129
Chitosan	5-Fluorouracil, indomethacin	158
Chitosan/*N*-trimethyl azone	Testosterone	159
Chitosan eucalyptol, transcutol® P	Ondansetron hydrochloride	160
Chitosan, rhodamine, polydimethylsiloxane	Bovine serum albumin	161
Chitosan, SL (SoftCAT™), sodium deoxycholate	Lidocaine hydrochloride	162
Chitosan, hyaluronic acid, glyceryl monostearate, cetyltrimethylammonium bromide	Lidocaine	163
Chitosan, hyaluronic acid, glycidyl methacrylate	Lidocaine	164
Chitosan, b-CD, cineole, menthol, limonene, streptozotocin	Glimepiride	165
Hydrochloride chitosan, PLGA	Donepezil	166
Chitosan, oleic acid	Propranolol hydrochloride	167
Chitosan, *N*-vinyl caprolactam, azobisisobutyronitrile	Etoricoxib, paracetamol	168
Chitosan, cholesterol, deoxycorticosterone acetate	Carvedilol	169
Chitosan, triphenylphosphine	Aciclovir	170
Chitosan, lipoid S45, lipoid S100	Melatonin	171
Chitosan, hydroxypropyl methylcellulose, polyvinyl alcohol, polyamidoamine dendrimer, dibutyl phthalate	Meloxicam	172
L-*a*-Phosphatidylcholine, chitosan, cholestrol, triton X 100, dihexadecyl phosphate	Resveratrol	173
Chitosan oligosaccharide, cellulose nanocrystal, sodium tetraphenylborate	Procaine hydrochloride	174
Chitosan, azolectin	Curcumin, diclofenac and vitamin B12 chitosan	175
Chitosan, hydroxypropyl methylcellulose, dibutyl phthalate	Metformin hydrochloride	176
Chitosan, lactic acid	Lisinopril	177
Chitosan	Bovine serum albumin	178
Chitosan, bovine serum albumin, poly(sodium-4-styrene sulfonate)	Tetanus toxoid	179
Chitosan, mannitol, hydroxypropyl methylcellulose	Ketoprofen, chondroitin sulfate	180
Chondroitin sulfate	Methotrexate	181
	Chorine6	182
	Glycyl-prednisolone	183
	Quercetin	184
	Histamine	185
	Diacerein	186
Chitosan, *p*-nitrophenyl chloroformate and amino1-propanol, Pluronic F127	Curcumin	187
Chitosan, DMPC, lipiodol, D-glucose (dextrose)	Indocyanine green	188
Xanthan-*graft*-C16 alkyl chain	Glibenclamide	189
Chitin-*graft*-hexadecyl	DOX	190
Fucoidan-*graft*-octenyl succinic anhydride	Cur	191

with g-poly (*N* isoorpylacrylamide) 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.Paclitexal 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–curcumin 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/alginic 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
Hyaluronic acid ceramide	DOX	216
Hyaluronic acid-functionalized SLN	Paclitaxel	217
Hyaluronic acid-nanographene oxide	HA-conjugate NPs	218
Functionalized hyaluronic acid	Noisome	219
Hyaluronic acid-functionalized transferases	DOX	220
Hyaluronic acid-chitosan functionalized	PCL nanofiber scaffold	221
Hyaluronic acid polymeric micelle	Coenzyme Q10	222
Hyaluronic acid conjugate	Human growth hormone	223

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 paclitexal–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 delimotecan 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 Fe_3O_4 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 prodrug.[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*, *Emblica 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
Alginic 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	Aceclofeanc	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
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

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
Fructose	Curcumin	323
Cyclodextrin	Paclitaxel	324
Cyclodextrin	Dacarbazine	314
Dextran 5	Aminosalicylic acid	315
	Nalidixic acid	317
	Methotrexate	325
	Ibuprofen	316
	DOX and paclitaxel	326
Cyclodextrin	Camptothecin	327
β-cyclodextrin	Camptothecin	328
Carboxymethyl dextran	Delimotecan	329
Carboxymethyl dextran	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
Heparin-*graft*-α-tocopherol	Docetaxel	337
Heparin-*graft*-deocycholate	DOX	338
Pegylated heparin a	Pyropheophorbide-a	339
Heparin	Paclitaxel	340

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 polygonium	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.[423] Alginate hydrogels with composite collagen content have been described for medication administration to the eye.[425] 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-*graft*-polycaprolactone	Ciprofloxacin	371
Pullulan-*graft*-α-tocopherol	ε-Caprolactone	372
Pullulan–graft-SA	DOX	373
Pullulan-graft, biotin, and retinoic acid	DOX	374
Desaxycholic acid from pullulan grafts -*graft*-polyethyleneimine	DOX DNA	375
Pulullan-*graft*-retinoic acid	DOX	376
Dibutyl amino propyl carbamate-pululan-graft	DNA	377
Pullulan-*graft*-cholesterol	Methotrexate	378
Cysteine from heparin-*graft*-β-sitosterol	DOX	90
Pullulan	Polyethyleneimine, DOX, adriamycin	367 and 379
Schizophyllan-*graft*-styrene acrylonitrile	Paclitexal	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 corbonate 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 chemotherapeutics, growth factors, and cells.[438] 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-*graft*-acetic anhydride	Cur	411
Bletilla striata-*graft*-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
	Panobinostat	460
	Cabazitaxel, noscapine, mitoxantrone	407
		461
		462
Bovine serum albumin is a polymer made of oligo (ethylene glycol) methyl ether methacrylate	Sprouty 1 (C-12) (Spry1) protein	463
Human serum albumin	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/macrobeads, 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 swere also tabilized 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 benn 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 intragastrially 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.

Acknowledgements

The authors extend their appreciation to the Deanship of Scientific Research at King Khalid University for supporting this work through research groups program under grant number RGP.2/273/44.

References

1 J. Wróblewska-Krepsztul, *et al.*, Biopolymers for Biomedical and Pharmaceutical Applications: Recent Advances and Overview of Alginate Electrospinning, *Nanomaterials*, 2019, **9**, 404.
2 S. Talebian, *et al.*, Biopolymers for antitumor implantable DDS: recent advances and future outlook, *Adv. Mater.*, 2018, **30**(31), 1706665.
3 A. Gagliardi, *et al.*, Sodium deoxycholate-decorated zein nanoparticles for a stable colloidal drug delivery system, *Int. J. Nanomed.*, 2018, **13**, 601.
4 M. C. García, DDS based on nonimmunogenic biopolymers, in *Engineering of Biomaterials for DDS*, Elsevier, 2018, pp. 317–344.
5 X. Chen, *et al.*, Ultra-selective molecular-sieving gas separation membranes enabled by multi-covalent-crosslinking of microporous polymer blends, *Nat. Commun.*, 2021, **12**(1), 6140.
6 C. R. Lynch, *et al.*, Hydrogel biomaterials for application in ocular drug delivery, *Front. bioeng. biotechnol.*, 2020, **8**, 228.
7 E. Calzoni, *et al.*, Biocompatible polymer nanoparticles for drug delivery applications in cancer and neurodegenerative disorder therapies, *J. Funct. Biomater.*, 2019, **10**(1), 4.
8 A. Ali and S. Ahmed, A review on chitosan and its nanocomposites in drug delivery, *Int. J. Biol. Macromol.*, 2018, **109**, 273–286.
9 S. R. Jameela and A. Jayakrishnan, Glutaraldehyde cross-linked chitosan microspheres as a long acting biodegradable drug delivery vehicle: studies on the in vitro release of mitoxantrone and in vivo degradation of microspheres in rat muscle, *Biomaterials*, 1995, **16**(10), 769–775.
10 V. R. Sinha, *et al.*, Chitosan microspheres as a potential carrier for drugs, *Int. J. Pharm.*, 2004, **274**(1–2), 1–33.
11 L. Li, *et al.*, Effect of formulation variables on in vitro release of a water-soluble drug from chitosan–sodium alginate matrix tablets, *Asian J. Pharm. Sci.*, 2015, **10**(4), 314–321.
12 Y. Shao, *et al.*, Evaluation of chitosan−anionic polymers based tablets for extended-release of highly water soluble drugs, *Asian J. Pharm. Sci.*, 2015, **10**, 24–30.
13 A. M. Dyer, *et al.*, Nasal delivery of insulin using novel chitosan based formulations: a comparative study in two animal models between simple chitosan formulations and chitosan nanoparticles, *Pharm. Res.*, 2002, **19**(7), 998–1008.
14 A. G. Luque-Alcaraz, *et al.*, Preparation of chitosan nanoparticles by nanoprecipitation and their ability as a drug nanocarrier, *RSC Adv.*, 2016, **6**(64), 59250–59256.
15 J. Jacob, *et al.*, Biopolymer based nanomaterials in DDS: A review, *Mater. Today Chem.*, 2018, **9**, 43–55.
16 S. Mitra, *et al.*, Tumour targeted delivery of encapsulated dextran-DOX conjugate using chitosan nanoparticles as carrier, *J. Controlled Release*, 2001, **74**(1–3), 317–323.
17 S. Sanyakamdhorn and D. Agudelo, Encapsulation of Antitumor Drug DOX and Its Analogue by Chitosan Nanoparticles, *Biomacromolecules*, 2013, **14**, 557–563.
18 H. Katas, M. A. Raja and K. L. Lam, Development of Chitosan Nanoparticles as a Stable Drug Delivery System for Protein/siRNA, *Int. J. Biomater.*, 2013, **2013**, 146320.
19 K. A. Janes, *et al.*, Chitosan nanoparticles as delivery systems for DOX, *J. Controlled Release*, 2001, **73**(2–3), 255–267.
20 I. C. Kwon, Chitosan-based nanoparticles for cancer therapy; tumor specificity and enhanced therapeutic efficacy in tumor-bearing mice, *J. Controlled Release*, 2008, **132**(3), e69–e70.

21 C. Cánepa, *et al.*, Development of a Drug Delivery System Based on Chitosan Nanoparticles for Oral Administration of Interferon-α, *Biomacromolecules*, 2017, **18**(10), 3302–3309.
22 H. S. Yoo, T. G. Kim and T. G. Park, Surface-functionalized electrospun nanofibers for tissue engineering and drug delivery, *Adv. Drug Delivery Rev.*, 2009, **61**(12), 1033–1042.
23 R. Jayakumar, *et al.*, Novel chitin and chitosan nanofibers in biomedical applications, *Biotechnol. Adv.*, 2010, **28**(1), 142–150.
24 S.-H. Chen, *et al.*, Preparation and characterization of antiadhesion barrier film from hyaluronic acid-grafted electrospun poly(caprolactone) nanofibrous membranes for prevention of flexor tendon postoperative peritendinous adhesion, *Int. J. Nanomed.*, 2014, **9**, 4079–4092, DOI: **10.2147/ijn.s67931**.
25 R. Toshkova, *et al.*, Antitumor activity of quaternized chitosan-based electrospun implants against Graffi myeloid tumor, *Int. J. Pharm.*, 2010, **400**(1–2), 221–233.
26 A. C. Mendes, *et al.*, Hybrid electrospun chitosan-phospholipids nanofibers for transdermal drug delivery, *Int. J. Pharm.*, 2016, **510**(1), 48–56.
27 R. Barreiro-Iglesias, *et al.*, Preparation of chitosan beads by simultaneous cross-linking/insolubilisation in basic pH. Rheological optimisation and drug loading/release behaviour, *Eur. J. Pharm. Sci.*, 2005, **24**(1), 77–84.
28 V. H. Kulkarni, P. V. Kulkarni and J. Keshavayya, Glutaraldehyde-crosslinked chitosan beads for controlled release of diclofenac sodium, *J. Appl. Polym. Sci.*, 2007, **103**(1), 211–217.
29 A. K. Anal and W. F. Stevens, Chitosan-alginate multilayer beads for controlled release of ampicillin, *Int. J. Pharm.*, 2005, **290**(1–2), 45–54.
30 C. Tang, *et al.*, Preparation of ibuprofen-loaded chitosan films for oral mucosal drug delivery using supercritical solution impregnation, *Int. J. Pharm.*, 2014, **473**(1–2), 434–441.
31 C. Giovino, *et al.*, Development and characterisation of chitosan films impregnated with insulin loaded PEG-b-PLA nanoparticles (NPs): a potential approach for buccal delivery of macromolecules, *Int. J. Pharm.*, 2012, **428**(1–2), 143–151.
32 A. S. Can, *et al.*, Optimization and characterization of chitosan films for transdermal delivery of ondansetron, *Molecules*, 2013, **18**(5), 5455–5471.
33 V. F. Patel, F. Liu and M. B. Brown, Advances in oral transmucosal drug delivery, *J. Controlled Release*, 2011, **153**(2), 106–116.
34 A. S. Pedro, *et al.*, Chitosan: An option for development of essential oil delivery systems for oral cavity care?, *Carbohydr. Polym.*, 2009, **76**(4), 501–508.
35 J. Duan, *et al.*, High Strength Chitosan Hydrogels with Biocompatibility via New Avenue Based on Constructing Nanofibrous Architecture, *Macromolecules*, 2015, **48**.
36 A. K. Azab, *et al.*, Biocompatibility evaluation of crosslinked chitosan hydrogels after subcutaneous and intraperitoneal implantation in the rat, *J. Biomed. Mater. Res., Part A*, 2007, **83**(2), 414–422.
37 Y. N. Dai, *et al.*, Swelling characteristics and drug delivery properties of nifedipine-loaded pH sensitive alginate-chitosan hydrogel beads, *J. Biomed. Mater. Res., Part B*, 2008, **86**(2), 493–500.
38 C. Hu, *et al.*, Synergistic chemical and photodynamic antimicrobial therapy for enhanced wound healing mediated by multifunctional light-responsive nanoparticles, *Biomacromolecules*, 2019, **20**(12), 4581–4592.
39 G. R. Park, *et al.*, pH-sensitive gallol-rich chitosan hydrogel beads for on-off controlled drug delivery, *Int. J. Biol. Macromol.*, 2023, **240**, 124346.
40 H. Elmotasem, S. A. El-Marasy and A. L. Mohamed, Benzocaine mesoporous silica nanoparticles/bio polysaccharides-based hydrogels loaded cotton bandage as a platform for topical anesthesia, *Results Chem.*, 2023, **5**, 100830.
41 R. Lali Raveendran, M. Valsala and T. Sreenivasan Anirudhan, Development of nanosilver embedded injectable liquid crystalline hydrogel from alginate and chitosan for potent antibacterial and anticancer applications, *J. Ind. Eng. Chem.*, 2023, **119**, 261–273.
42 M. Jakubowski, *et al.*, Chitosan hydrogel modified with lanthanum as a drug delivery system for epigallocatechin gallate: Investigation of hydrogel – drug interaction by FT-IR and Raman spectroscopy, *Spectrochim. Acta, Part A*, 2023, **297**, 122748.
43 M. Rajaei, *et al.*, Chitosan/agarose/graphene oxide nanohydrogel as drug delivery system of 5-fluorouracil in breast cancer therapy, *J. Drug Deliv. Sci. Technol.*, 2023, **82**, 104307.
44 Y. Xiang, *et al.*, Highly efficient bacteria-infected diabetic wound healing employing a melanin-reinforced biopolymer hydrogel, *Chem. Eng. J.*, 2023, **460**, 141852.
45 I. Rani, S. G. Warkar and A. Kumar, Nano ZnO embedded poly (ethylene glycol) diacrylate cross-linked carboxymethyl tamarind kernel gum (CMTKG)/poly (sodium acrylate) composite hydrogels for oral delivery of ciprofloxacin drug and their antibacterial properties, *Mater. Today Commun.*, 2023, **35**, 105635.
46 E. Chiani, *et al.*, Synthesis and characterization of gelatin/lignin hydrogels as quick release drug carriers for Ribavirin, *Int. J. Biol. Macromol.*, 2023, **224**, 1196–1205.
47 S. A. Shah, *et al.*, Chitosan and carboxymethyl cellulose-based 3D multifunctional bioactive hydrogels loaded with nano-curcumin for synergistic diabetic wound repair, *Int. J. Biol. Macromol.*, 2023, **227**, 1203–1220.
48 M. Pourmadadi, *et al.*, pH-responsive polyacrylic acid (PAA)-carboxymethyl cellulose (CMC) hydrogel incorporating halloysite nanotubes (HNT) for controlled curcumin delivery, *Ind. Crops Prod.*, 2023, **197**, 116654.
49 M. Tanwar, R. K. Gupta and A. Rani, Natural gums and their derivatives based hydrogels: in biomedical, environment, agriculture, and food industry, *Crit. Rev. Biotechnol.*, 2023, 1–27.

50 H. Song, *et al.*, Folic acid-chitosan conjugated nanoparticles for improving tumor-targeted drug delivery, *BioMed Res. Int.*, 2013, **2013**, 723158.
51 H. Bao, *et al.*, Chitosan-functionalized graphene oxide as a nanocarrier for drug and gene delivery, *Small*, 2011, 7(11), 1569–1578.
52 C. Li, *et al.*, Highly biocompatible multi-walled carbon nanotube–chitosan nanoparticle hybrids as protein carriers, *Acta Biomater.*, 2011, 7(8), 3070–3077.
53 E. S. Lee, *et al.*, A feasibility study of a pH sensitive nanomedicine using DOX loaded poly(aspartic acid-graft-imidazole)-block-poly(ethylene glycol) micelles, *J. Mater. Chem. B*, 2014, **2**(9), 1152–1159.
54 W. S. Abo-Elseoud, *et al.*, Chitosan nanoparticles/cellulose nanocrystals nanocomposites as a carrier system for the controlled release of repaglinide, *Int. J. Biol. Macromol.*, 2018, **111**, 604–613.
55 T. Agarwal, *et al.*, Calcium alginate-carboxymethyl cellulose beads for colon-targeted drug delivery, *Int. J. Biol. Macromol.*, 2015, **75**, 409–417.
56 K. Hansen, *et al.*, Feasibility Investigation of Cellulose Polymers for Mucoadhesive Nasal Drug Delivery Applications, *Mol. Pharmaceutics*, 2015, **12**, 2732–2741.
57 J. T. Orasugh, *et al.*, Jute cellulose nano-fibrils/hydroxypropylmethylcellulose nanocomposite: a novel material with potential for application in packaging and transdermal drug delivery system, *Ind. Crops Prod.*, 2018, **112**, 633–643.
58 L. E. Low, *et al.*, Magnetic cellulose nanocrystal stabilized Pickering emulsions for enhanced bioactive release and human colon cancer therapy, *Int. J. Biol. Macromol.*, 2019, **127**, 76–84.
59 K. Prusty and S. K. Swain, Release of ciprofloxacin drugs by nano gold embedded cellulose grafted polyacrylamide hybrid nanocomposite hydrogels, *Int. J. Biol. Macromol.*, 2019, **126**, 765–775.
60 Z. Rao, *et al.*, Carboxymethyl cellulose modified graphene oxide as pH-sensitive drug delivery system, *Int. J. Biol. Macromol.*, 2018, **107**, 1184–1192.
61 L. Dai and C.-L. Si, Cellulose-graft-poly(methyl methacrylate) nanoparticles with high biocompatibility for hydrophobic anti-cancer drug delivery, *Mater. Lett.*, 2017, **207**, 213–216.
62 W. Qing, *et al.*, The modified nanocrystalline cellulose for hydrophobic drug delivery, *Appl. Surf. Sci.*, 2016, **366**, 404–409.
63 R. Wang, *et al.*, pH-Controlled drug delivery with hybrid aerogel of chitosan, carboxymethyl cellulose and graphene oxide as the carrier, *Int. J. Biol. Macromol.*, 2017, **103**, 248–253.
64 S. Javanbakht and H. Namazi, DOX loaded carboxymethyl cellulose/graphene quantum dot nanocomposite hydrogel films as a potential anticancer drug delivery system, *Mater. Sci. Eng. C*, 2018, **87**, 50–59.
65 C. J. Wijaya, *et al.*, Cellulose nanocrystals from passion fruit peels waste as antibiotic drug carrier, *Carbohydr. Polym.*, 2017, **175**, 370–376.
66 M. G. Bekaroğlu, Y. İşçi and S. İşçi, Colloidal properties and in vitro evaluation of Hydroxy ethyl cellulose coated iron oxide particles for targeted drug delivery, *Mater. Sci. Eng. C*, 2017, **78**, 847–853.
67 A. Solanki and S. Thakore, Cellulose crosslinked pH-responsive polyurethanes for drug delivery: α-hydroxy acids as drug release modifiers, *Int. J. Biol. Macromol.*, 2015, **80**, 683–691.
68 A. Melocchi, *et al.*, Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling, *Int. J. Pharm.*, 2016, **509**(1–2), 255–263.
69 J. Boetker, *et al.*, Modifying release characteristics from 3D printed drug-eluting products, *Eur. J. Pharm. Sci.*, 2016, **90**, 47–52.
70 A. Melocchi, *et al.*, 3D printing by fused deposition modeling (FDM) of a swellable/erodible capsular device for oral pulsatile release of drugs, *J. Drug Delivery Sci. Technol.*, 2015, **30**, 360–367.
71 K. Pietrzak, A. Isreb and M. A. Alhnan, A flexible-dose dispenser for immediate and extended release 3D printed tablets, *Eur. J. Pharm. Biopharm.*, 2015, **96**, 380–387.
72 X. Chai, *et al.*, Fused deposition modeling (FDM) 3D printed tablets for intragastric floating delivery of domperidone, *Sci. Rep.*, 2017, 7(1), 1–9.
73 D. Bhandari, *et al.*, A Review on Bioactive Peptides: Physiological Functions, Bioavailability and Safety, *Int. J. Pept. Res. Ther.*, 2020, **26**(1), 139–150.
74 H. Xiao, *et al.*, Acetylated starch nanocrystals: Preparation and antitumor drug delivery study, *Int. J. Biol. Macromol.*, 2016, **89**, 456–464.
75 R. Gul, *et al.*, Functionalised nanostructures for transdermal delivery of drug cargos, *J. Drug Targeting*, 2018, **26**(2), 110–122.
76 G. Garrait, E. Beyssac and M. Subirade, Development of a novel drug delivery system: chitosan nanoparticles entrapped in alginate microparticles, *J. Microencapsulation*, 2014, **31**(4), 363–372.
77 J. K. Patra, *et al.*, Nano based DDS: recent developments and future prospects, *J. Nanobiotechnol.*, 2018, **16**(1), 1–33.
78 J. R. Costa, *et al.*, Potential chitosan-coated alginate nanoparticles for ocular delivery of daptomycin, *Eur. J. Clin. Microbiol. Infect. Dis.*, 2015, **34**(6), 1255–1262.
79 G. Thakur, F. C. Rodrigues, and K. Singh, Crosslinking biopolymers for advanced drug delivery and tissue engineering applications, *Cutting-Edge Enabling Technologies for Regenerative Medicine*, 2018, pp. 213–231.
80 R. Sheshala, *et al.*, Investigation on solution-to-gel characteristic of thermosensitive and mucoadhesive biopolymers for the development of moxifloxacin-loaded sustained release periodontal in situ gels, *Drug Delivery Transl. Res.*, 2019, **9**(2), 434–443.
81 K. Bai, *et al.*, Selenium Nanoparticles-Embedded Chitosan Microspheres and Their Effects Upon Alcohol-Induced Gastric Mucosal Injury in Rats: Rapid Preparation, Oral Delivery, and Gastroprotective Potential of Selenium Nanoparticles, *Int. J. Nanomed.*, 2020, **15**, 1187–1203.

82 Y. Cong, *et al.*, Ureido-modified carboxymethyl chitosan-graft-stearic acid polymeric nano-micelles as a targeted delivering carrier of clarithromycin for Helicobacter pylori: Preparation and in vitro evaluation, *Int. J. Biol. Macromol.*, 2019, **129**, 686–692.
83 J. L. Arias, L. H. Reddy and P. Couvreur, Fe3O4/chitosan nanocomposite for magnetic drug targeting to cancer, *J. Mater. Chem.*, 2012, **22**(15), 7622–7632.
84 J. Wu, *et al.*, Synthesis and characterization of mesoporous magnetic nanocomposites wrapped with chitosan gatekeepers for pH-sensitive controlled release of DOX, *Mater. Sci. Eng. C*, 2017, **70**, 132–140.
85 J. Lin, *et al.*, Drug/Dye-Loaded, Multifunctional PEG-Chitosan-Iron Oxide Nanocomposites for Methotraxate Synergistically Self-Targeted Cancer Therapy and Dual Model Imaging, *ACS Appl. Mater. Interfaces*, 2015, **7**(22), 11908–11920.
86 Q. Yuan, S. Hein and R. D. K. Misra, New generation of chitosan-encapsulated ZnO quantum dots loaded with drug: Synthesis, characterization and in vitro drug delivery response, *Acta Biomater.*, 2010, **6**, 2732–2739.
87 M. Pooresmaeil, S. B. Nia and H. Namazi, Green encapsulation of LDH (Zn/Al)-5-Fu with carboxymethyl cellulose biopolymer; new nanovehicle for oral colorectal cancer treatment, *Int. J. Biol. Macromol.*, 2019, **139**, 994–1001.
88 Y. Ding, *et al.*, Chitosan-based magnetic/fluorescent nanocomposites for cell labelling and controlled drug release, *New J. Chem.*, 2017, **41**(4), 1736–1743.
89 S. Javanbakht, M. Pooresmaeil and H. Namazi, Green one-pot synthesis of carboxymethylcellulose/Zn-based metal-organic framework/graphene oxide bio-nanocomposite as a nanocarrier for drug delivery system, *Carbohydr. Polym.*, 2019, **208**, 294–301.
90 T. A. Debele, S. L. Mekuria and H.-C. Tsai, Synthesis and characterization of redox-sensitive heparin-β-sitosterol micelles: Their application as carriers for the pharmaceutical agent, DOX, and investigation of their antimetastatic activities in vitro, *Mater. Sci. Eng. C*, 2017, **75**, 1326–1338.
91 V. A. Kuznetsov, *et al.*, Graft copolymers of carboxymethyl cellulose with N-vinylimidazole: synthesis and application for drug delivery, *Polym. Bull.*, 2019, **76**(10), 4929–4949.
92 X. Sun, *et al.*, pH-sensitive ZnO/carboxymethyl cellulose/chitosan bio-nanocomposite beads for colon-specific release of 5-fluorouracil, *Int. J. Biol. Macromol.*, 2019, **128**, 468–479.
93 C. W. Hsiao, *et al.*, Photothermal tumor ablation in mice with repeated therapy sessions using NIR-absorbing micellar hydrogels formed in situ, *Biomaterials*, 2015, **56**, 26–35.
94 J. Shi, *et al.*, Schiff based injectable hydrogel for in situ pH-triggered delivery of DOX for breast tumor treatment, *Polym. Chem.*, 2014, **5**(21), 6180–6189.
95 M. M. Silva, *et al.*, Chitosan Nanoparticles as a Mucoadhesive Drug Delivery System for Ocular Administration, *Mar. Drugs*, 2017, **15**(12).
96 S. Pistone, *et al.*, Formulation of polysaccharide-based nanoparticles for local administration into the oral cavity, *Eur. J. Pharm. Sci.*, 2017, **96**, 381–389.
97 S. Liu, S. Yang and P. Ho, Intranasal Administration of Carbamazepine-loaded Carboxymethyl Chitosan Nanoparticles for Drug Delivery to the Brain, *Asian J. Pharm. Sci.*, 2018, **13**, 72–81.
98 L. Yu, *et al.*, A new hybrid nanocomposite prepared by graft copolymerization of butyl acrylate onto chitosan in the presence of organophilic montmorillonite, *Radiat. Phys. Chem.*, 2004, **69**, 467–471.
99 J.-M. Shen, *et al.*, A novel carboxymethyl chitosan-based folate/Fe3O4/CdTe nanoparticle for targeted drug delivery and cell imaging, *Carbohydr. Polym.*, 2012, **88**(1), 239–249.
100 Y. Ding, *et al.*, Design and construction of polymerized-chitosan coated Fe3O4 magnetic nanoparticles and its application for hydrophobic drug delivery, *Mater. Sci. Eng., C*, 2015, **48**, 487–498.
101 X. Wang, Y. Du and J. Luo, Biopolymer/montmorillonite nanocomposite: preparation, drug-controlled release property and cytotoxicity, *Nanotechnology*, 2008, **19**(6), 065707.
102 B. Liu, *et al.*, Alginate/quaternized carboxymethyl chitosan/clay nanocomposite microspheres: preparation and drug-controlled release behavior, *J. Biomater. Sci., Polym. Ed.*, 2013, **24**(5), 589–605.
103 U. Parida, *et al.*, Synthesis and Characterization of Chitosan-Polyvinyl Alcohol Blended with Cloisite 30B for Controlled Release of the Anticancer Drug Curcumin, *J. Biomater. Nanobiotechnol.*, 2011, **02**, 414–425.
104 S. A. Agnihotri, S. S. Jawalkar and T. M. Aminabhavi, Controlled release of cephalexin through gellan gum beads: effect of formulation parameters on entrapment efficiency, size, and drug release, *Eur. J. Pharm. Biopharm.*, 2006, **63**(3), 249–261.
105 M. Xie, *et al.*, Non-covalent modification of graphene oxide nanocomposites with chitosan/dextran and its application in drug delivery, *RSC Adv.*, 2016, **6**(11), 9328–9337.
106 C.-L. Huang, *et al.*, Application of paramagnetic graphene quantum dots as a platform for simultaneous dual-modality bioimaging and tumor-targeted drug delivery, *J. Mater. Chem. B*, 2015, **3**(4), 651–664.
107 F. Abedini, *et al.*, Overview on natural hydrophilic polysaccharide polymers in drug delivery, *Polym. Adv. Technol.*, 2018, **29**(10), 2564–2573.
108 A. C. F. Patta, *et al.*, Polyionic complexes of chitosan-N-arginine with alginate as pH responsive and mucoadhesive particles for oral drug delivery applications, *Int. J. Biol. Macromol.*, 2020, **148**, 550–564.
109 S. Kumar, J. Ali, and S. Baboota, Polysaccharide nanoconjugates for drug solubilization and targeted delivery, *Polysaccharide Carriers for Drug Delivery*, 2019, pp. 443–475.
110 P. Chanphai and H. A. Tajmir-Riahi, DNA binding to folic acid-chitosan nanoconjugates, *J. Biomol. Struct. Dyn.*, 2018, **36**(10), 2746–2751.

111 S. W. Tsai, *et al.*, Hyaluronan-cisplatin conjugate nanoparticles embedded in Eudragit S100-coated pectin/alginate microbeads for colon drug delivery, *Int. J. Nanomed.*, 2013, **8**, 2399–2407.

112 Y.-H. Cheng, *et al.*, Thermosensitive chitosan-based hydrogel as a topical ocular drug delivery system of latanoprost for glaucoma treatment, *Carbohydr. Polym.*, 2016, **144**, 390–399.

113 Y. Cao, *et al.*, Poly(N-isopropylacrylamide)-chitosan as thermosensitive in situ gel-forming system for ocular drug delivery, *J. Controlled Release*, 2007, **120**(3), 186–194.

114 S. Yu, *et al.*, A novel pH-induced thermosensitive hydrogel composed of carboxymethyl chitosan and poloxamer cross-linked by glutaraldehyde for ophthalmic drug delivery, *Carbohydr. Polym.*, 2017, **155**, 208–217.

115 H. S. Adhikari and P. N. Yadav, Anticancer Activity of Chitosan, Chitosan Derivatives, and Their Mechanism of Action, *Int. J. Biomater.*, 2018, **2018**, 2952085.

116 F. Q. Hu, *et al.*, Synthesis and antitumor activity of DOX conjugated stearic acid-g-chitosan oligosaccharide polymeric micelles, *Biomaterials*, 2009, **30**(36), 6955–6963.

117 J. Hyung Park, *et al.*, Self-assembled nanoparticles based on glycol chitosan bearing hydrophobic moieties as carriers for DOX: in vivo biodistribution and anti-tumor activity, *Biomaterials*, 2006, **27**(1), 119–126.

118 Y. J. Son, *et al.*, Biodistribution and anti-tumor efficacy of DOX loaded glycol-chitosan nanoaggregates by EPR effect, *J. Controlled Release*, 2003, **91**(1), 135–145.

119 E. Lee, *et al.*, Conjugated chitosan as a novel platform for oral delivery of paclitaxel, *J. Med. Chem.*, 2008, **51**(20), 6442–6449.

120 E. Lee, *et al.*, In vivo antitumor effects of chitosan-conjugated docetaxel after oral administration, *J. Controlled Release*, 2009, **140**(2), 79–85.

121 M. Xie, *et al.*, Layer-by-layer modification of magnetic graphene oxide by chitosan and sodium alginate with enhanced dispersibility for targeted drug delivery and photothermal therapy, *Colloids Surf., B*, 2019, **176**, 462–470.

122 M. Yadollahi, S. Farhoudian and H. Namazi, One-pot synthesis of antibacterial chitosan/silver bio-nanocomposite hydrogel beads as DDS, *Int. J. Biol. Macromol.*, 2015, **79**, 37–43.

123 Y. K. Manea, *et al.*, Ciprofloxacin-supported chitosan/polyphosphate nanocomposite to bind bovine serum albumin: Its application in drug delivery, *J. Mol. Liq.*, 2019, **292**, 111337.

124 S. Hosseinzadeh, *et al.*, Synthesis of stimuli-responsive chitosan nanocomposites via RAFT copolymerization for DOX delivery, *Int. J. Biol. Macromol.*, 2019, **121**, 677–685.

125 Z. Shariatinia and Z. Zahraee, Controlled release of metformin from chitosan-based nanocomposite films containing mesoporous MCM-41 nanoparticles as novel DDS, *J. Colloid Interface Sci.*, 2017, **501**, 60–76.

126 M. Jia, *et al.*, Development of both methotrexate and mitomycin C loaded PEGylated chitosan nanoparticles for targeted drug codelivery and synergistic anticancer effect, *ACS Appl. Mater. Interfaces*, 2014, **6**(14), 11413–11423.

127 Q. S. Zhao, *et al.*, Preparation of alginate coated chitosan hydrogel beads by thermosensitive internal gelation technique, *J. Sol-Gel Sci. Technol.*, 2010, **54**(2), 232–237.

128 M. Tavakol, E. Vasheghani-Farahani and S. Hashemi-Najafabadi, The effect of polymer and CaCl(2) concentrations on the sulfasalazine release from alginate-N,O-carboxymethyl chitosan beads, *Prog. Biomater.*, 2013, **2**(1), 10.

129 V. K. Malesu, D. Sahoo and P. Nayak, Chitosan–sodium alginate nanocomposites blended with cloisite 30B as a novel drug delivery system for anticancer drug curcumin, *Int. J. Appl. Biol. Pharm. Technol.*, 2011, 162176.

130 A. A. Elzatahry, *et al.*, Evaluation of alginate–chitosan bioadhesive beads as a drug delivery system for the controlled release of theophylline, *J. Appl. Polym. Sci.*, 2009, **111**(5), 2452–2459.

131 T. W. Wong, *et al.*, Design of controlled-release solid dosage forms of alginate and chitosan using microwave, *J. Controlled Release*, 2002, **84**(3), 99–114.

132 M. de la Fuente, B. Seijo and M. J. Alonso, Novel hyaluronic acid-chitosan nanoparticles for ocular gene therapy, *Invest. Ophthalmol. Visual Sci.*, 2008, **49**(5), 2016–2024.

133 L. Contreras-Ruiz, *et al.*, Ocular tolerance to a topical formulation of hyaluronic acid and chitosan-based nanoparticles, *Cornea*, 2010, **29**(5), 550–558.

134 F. A. Oyarzun-Ampuero, *et al.*, Chitosan-hyaluronic acid nanoparticles loaded with heparin for the treatment of asthma, *Int. J. Pharm.*, 2009, **381**(2), 122–129.

135 H. D. Lu, *et al.*, Novel hyaluronic acid-chitosan nanoparticles as non-viral gene delivery vectors targeting osteoarthritis, *Int. J. Pharm.*, 2011, **420**(2), 358–365.

136 M. Fukuda, N. A. Peppas and J. W. McGinity, Properties of sustained release hot-melt extruded tablets containing chitosan and xanthan gum, *Int. J. Pharm.*, 2006, **310**(1), 90–100.

137 T. Phaechamud and G. C. Ritthidej, Sustained-release from Layered Matrix System Comprising Chitosan and Xanthan Gum, *Drug Dev. Ind. Pharm.*, 2007, **33**(6), 595–605.

138 A. M. Pandele, *et al.*, New biocompatible mesoporous silica/polysaccharide hybrid materials as possible DDS, *Materials*, 2019, **12**(1), 15.

139 Y. Song, *et al.*, In situ formation of injectable chitosan-gelatin hydrogels through double crosslinking for sustained intraocular drug delivery, *Mater. Sci. Eng. C*, 2018, **88**, 1–12.

140 J. Wei, *et al.*, Multi-Stimuli-Responsive Microcapsules for Adjustable Controlled-Release, *Adv. Funct. Mater.*, 2014, **24**(22), 3312–3323.

141 K. Ganguly, A. R. Kulkarni and T. M. Aminabhavi, In vitro cytotoxicity and in vivo efficacy of 5-fluorouracil-loaded enteric-coated PEG-crosslinked chitosan microspheres in colorectal cancer therapy in rats, *Drug Delivery*, 2015, 1–14.

142 S. Shafiee, H. A. Ahangar and A. Saffar, Taguchi method optimization for synthesis of Fe3O4 @chitosan/Tragacanth Gum nanocomposite as a drug delivery system, *Carbohydr. Polym.*, 2019, **222**, 114982.

143 M. Yadollahi, *et al.*, Facile synthesis of chitosan/ZnO bio-nanocomposite hydrogel beads as DDS, *Int. J. Biol. Macromol.*, 2016, **82**, 273–278.
144 X. Cheng, *et al.*, Surface-fluorinated and pH-sensitive carboxymethyl chitosan nanoparticles to overcome biological barriers for improved drug delivery in vivo, *Carbohydr. Polym.*, 2019, **208**, 59–69.
145 F. Luo, *et al.*, pH-responsive stearic acid-O-carboxymethyl chitosan assemblies as carriers delivering small molecular drug for chemotherapy, *Mater. Sci. Eng. C*, 2019, **105**, 110107.
146 C. Zhang, *et al.*, Targeted antigen delivery to dendritic cell via functionalized alginate nanoparticles for cancer immunotherapy, *J. Controlled Release*, 2017, **256**, 170–181.
147 J. Venkatesan, *et al.*, Antimicrobial and anticancer activities of porous chitosan-alginate biosynthesized silver nanoparticles, *Int. J. Biol. Macromol.*, 2017, **98**, 515–525.
148 S. Rahaiee, *et al.*, Nanoparticles based on crocin loaded chitosan-alginate biopolymers: Antioxidant activities, bioavailability and anticancer properties, *Int. J. Biol. Macromol.*, 2017, **99**, 401–408.
149 S. Maity, *et al.*, Alginate coated chitosan core-shell nanoparticles for efficient oral delivery of naringenin in diabetic animals—An in vitro and in vivo approach, *Carbohydr. Polym.*, 2017, **170**, 124–132.
150 D. Aluani, *et al.*, Evaluation of biocompatibility and antioxidant efficiency of chitosan-alginate nanoparticles loaded with quercetin, *Int. J. Biol. Macromol.*, 2017, **103**, 771–782.
151 P. Mukhopadhyay, *et al.*, pH-sensitive chitosan/alginate core-shell nanoparticles for efficient and safe oral insulin delivery, *Int. J. Biol. Macromol.*, 2015, **72**, 640–648.
152 N. P. Katuwavila, *et al.*, Chitosan-alginate nanoparticle system efficiently delivers DOX to MCF-7 cells, *J. Nanomater.*, 2016, **2016**, 3178904.
153 Z.-H. Zhang, *et al.*, N-Octyl-N-Arginine Chitosan Micelles as an Oral Delivery System of Insulin, *J. Biomed. Nanotechnol.*, 2013, **9**(4), 601–609.
154 M. L. González-Rodriguez, *et al.*, Alginate/chitosan particulate systems for sodium diclofenac release, *Int. J. Pharm.*, 2002, **232**(1), 225–234.
155 G. Pasparakis and N. Bouropoulos, Swelling studies and in vitro release of verapamil from calcium alginate and calcium alginate-chitosan beads, *Int. J. Pharm.*, 2006, **323**(1–2), 34–42.
156 S. Wittaya-areekul, J. Kruenate and C. Prahsarn, Preparation and in vitro evaluation of mucoadhesive properties of alginate/chitosan microparticles containing prednisolone, *Int. J. Pharm.*, 2006, **312**(1), 113–118.
157 S. C. Angadi, L. S. Manjeshwar and T. M. Aminabhavi, Novel composite blend microbeads of sodium alginate coated with chitosan for controlled release of amoxicillin, *Int. J. Biol. Macromol.*, 2012, **51**(1), 45–55.
158 L. Gao, *et al.*, Evaluation of genipin-crosslinked chitosan hydrogels as a potential carrier for silver sulfadiazine nanocrystals, *Colloids Surf., B*, 2016, **148**, 343–353.
159 K. Sharma, V. Mahalwal and A. Arora, Natural biodegradable polymers as matrices in transdermal drug delivery, *Int. J. Drug Dev. Res.*, 2011, **3**, 85–103.
160 M. Sano, *et al.*, Chitosan Gel for Transdermal Delivery of Morphine Hydrochloride, *Iryo Yakugaku*, 2007, **33**(6), 515–519.
161 H. Dureja, A. K. Tiwary and S. Gupta, Simulation of skin permeability in chitosan membranes, *Int. J. Pharm.*, 2001, **213**(1), 193–198.
162 V. H. Kulkarni, *et al.*, Transdermal delivery of antiasthmatic drug through modified chitosan membrane, *Indian J. Pharm. Sci.*, 2005, **67**, 544–547.
163 J. R. Fried, *Polymer science and technology*, Pearson Education, 2014.
164 S. Chen, *et al.*, Intestinal glucuronidation protects against chemotherapy-induced toxicity by irinotecan (CPT-11), *Proc. Natl. Acad. Sci. U. S. A.*, 2013, **110**(47), 19143–19148.
165 T. S. Anirudhan, S. S. Nair and A. S. Nair, Fabrication of a bioadhesive transdermal device from chitosan and hyaluronic acid for the controlled release of lidocaine, *Carbohydr. Polym.*, 2016, **152**, 687–698.
166 A. J. Shinde, A. L. Shinde and H. N. More, Design and evaluation of transdermal drug delivery system of gliclazide, *Asian J. Pharm.*, 2014, **4**(2), 201–211.
167 S. F. Taveira, A. Nomizo and R. F. V. Lopez, Effect of the iontophoresis of a chitosan gel on DOX skin penetration and cytotoxicity, *J. Controlled Release*, 2009, **134**(1), 35–40.
168 J. J. Escobar-Chávez, *et al.*, Transdermal nortriptyline hydrocloride patch formulated within a chitosan matrix intended to be used for smoking cessation, *Pharm. Dev. Technol.*, 2011, **16**(2), 162–169.
169 G. Banche, *et al.*, Antimicrobial chitosan nanodroplets: new insights for ultrasound-mediated adjuvant treatment of skin infection, *Future Microbiol.*, 2015, **10**(6), 929–939.
170 S. Indulekha, *et al.*, Thermoresponsive polymeric gel as an on-demand transdermal drug delivery system for pain management, *Mater. Sci. Eng. C*, 2016, **62**, 113–122.
171 H.-N. Huang, *et al.*, Transdermal immunization with low-pressure-gene-gun mediated chitosan-based DNA vaccines against Japanese encephalitis virus, *Biomaterials*, 2009, **30**(30), 6017–6025.
172 L. Sadhasivam, *et al.*, Transdermal patches of chitosan nanoparticles for insulin delivery, *Int. J. Pharm. Pharm. Sci.*, 2015, **7**, 84–88.
173 J.-g. Gao, *et al.*, Preparation of chitosan microspheres loading of 3,5-dihydroxy-4-i-propylstilbene and in vitro release, *J. Polym. Res.*, 2011, **18**(6), 1501–1508.
174 J. Kim, A. Lund and C. Dombrowski, Telling the story in big data, *Interactions*, 2013, **20**(3), 48–51.
175 N. Charernsriwilaiwat, *et al.*, Preparation of Chitosan-Thiamine Pyrophosphate/Polyvinyl Alcohol Blend Electrospun Nanofibers, *Adv. Mater. Res.*, 2012, **506**, 118–121.
176 R. V. N. Gundloori, A. Singam, and N. Killi, Chapter 19 – Nanobased Intravenous and Transdermal DDS, in *Applications of Targeted Nano Drugs and Delivery Systems*, ed. S.S. Mohapatra, et al., Elsevier, 2019, pp. 551–594.

177 R. T. Allena, *et al.*, Preparation and evaluation of transdermal patches of metformin hydrochloride using natural polymer for sustained release, *Int. J. Pharm. Pharm. Sci.*, 2012, **4**(3), 297–302.

178 V. Bhat, *et al.*, *Influence of blending of chitosan and pullulan on their drug release behavior: an in-vitro study research article*, 2012.

179 Y. Xie, B. Xu and Y. Gao, Controlled transdermal delivery of model drug compounds by MEMS microneedle array, *Nanomed.: Nanotechnol. Biol. Med.*, 2005, **1**(2), 184–190.

180 K. Siddhapura, H. Harde and S. Jain, Immunostimulatory effect of tetanus toxoid loaded chitosan nanoparticles following microneedles assisted immunization, *Nanomed.: Nanotechnol. Biol. Med.*, 2016, **12**(1), 213–222.

181 X. Ling, *et al.*, Synthesis and characterization of hyaluronic acid–platinum(iv) nanoconjugate with enhanced antitumor response and reduced adverse effects, *RSC Adv.*, 2015, **5**(99), 81668–81681.

182 F. Li and K. Na, Self-Assembled Chlorin e6 Conjugated Chondroitin Sulfate Nanodrug for Photodynamic Therapy, *Biomacromolecules*, 2011, **12**(5), 1724–1730.

183 H. Onishi, Y. Isoda and M. Matsuyama, In vivo evaluation of chondroitin sulfate-glycyl-prednisolone for anti-arthritic effectiveness and pharmacokinetic characteristics, *Int. J. Pharm.*, 2013, **456**(1), 113–120.

184 C. Yu, *et al.*, Redox-responsive shell-sheddable micelles self-assembled from amphiphilic chondroitin sulfate-cholesterol conjugates for triggered intracellular drug release, *Chem. Eng. J.*, 2013, **228**, 290–299.

185 C. Yu, *et al.*, Facile preparation of pH-sensitive micelles self-assembled from amphiphilic chondroitin sulfate-histamine conjugate for triggered intracellular drug release, *Colloids Surf., B*, 2014, **115**, 331–339.

186 A. Jain, *et al.*, Targeting of diacerein loaded lipid nanoparticles to intra-articular cartilage using chondroitin sulfate as homing carrier for treatment of osteoarthritis in rats, *Nanomed.: Nanotechnol. Biol. Med.*, 2014, **10**(5), e1031–e1040.

187 A. Nawaz and T. W. Wong, Quantitative characterization of chitosan in the skin by Fourier-transform infrared spectroscopic imaging and ninhydrin assay: application in transdermal sciences, *J. Microsc*, 2016, **263**(1), 34–42.

188 Y. Ramesh and V. Sireesha, Transdermal patch of ramipril loaded chitosan nanoparticles dispersed in carbopol gel, *J. Drug Delivery Ther.*, 2017, **7**, 56–65.

189 S. Maiti and S. Mukherjee, Controlled drug delivery attributes of co-polymer micelles and xanthan-O-carboxymethyl hydrogel particles, *Int. J. Biol. Macromol.*, 2014, **70**, 37–43.

190 N. Peng, *et al.*, Amphiphilic hexadecyl-quaternized chitin micelles for DOX delivery, *Int. J. Biol. Macromol.*, 2019, **130**, 615–621.

191 C. Cao, *et al.*, Correlation between Drug Loading Content and Biological Activity: The Complexity Demonstrated in Paclitaxel-Loaded Glycopolymer Micelle System, *Biomacromolecules*, 2019, **20**(4), 1545–1554.

192 J. D. Schneible, M. A. Daniele, and S. Menegatti, Natural and Synthetic Biopolymers in Drug Delivery and Tissue Engineering, *Biopolymers for Biomedical and Biotechnological Applications*, 2021, pp. 265–356.

193 S. Cai, *et al.*, Localized DOX chemotherapy with a biopolymeric nanocarrier improves survival and reduces toxicity in xenografts of human breast cancer, *J. Controlled Release*, 2010, **146**(2), 212–218.

194 I. M. Montagner, *et al.*, Paclitaxel-hyaluronan hydrosoluble bioconjugate: Mechanism of action in human bladder cancer cell lines, *Urol. Oncol.: Semin. Orig. Invest.*, 2013, **31**(7), 1261–1269.

195 L. K. Widjaja, *et al.*, Hyaluronic acid-based nanocomposite hydrogels for ocular drug delivery applications, *J. Biomed. Mater. Res., Part A*, 2014, **102**(9), 3056–3065.

196 Y. Wu, *et al.*, Enhanced and sustained topical ocular delivery of cyclosporine A in thermosensitive hyaluronic acid-based in situ forming microgels, *Int. J. Nanomed.*, 2013, **8**, 3587–3601.

197 Y. Zhong, *et al.*, Reversibly crosslinked hyaluronic acid nanoparticles for active targeting and intelligent delivery of DOX to drug resistant CD44+ human breast tumor xenografts, *J. Controlled Release*, 2015, **205**, 144–154.

198 J. L. Holloway, *et al.*, Modulating hydrogel crosslink density and degradation to control bone morphogenetic protein delivery and in vivo bone formation, *J. Controlled Release*, 2014, **191**, 63–70.

199 G. Bajaj, *et al.*, Hyaluronic acid-based hydrogel for regional delivery of paclitaxel to intraperitoneal tumors, *J. Controlled Release*, 2012, **158**(3), 386–392.

200 E. J. Cho, *et al.*, Intraperitoneal delivery of platinum with in-situ crosslinkable hyaluronic acid gel for local therapy of ovarian cancer, *Biomaterials*, 2015, **37**, 312–319.

201 K. Ueda, *et al.*, Growth inhibitory effect of an injectable hyaluronic acid–tyramine hydrogels incorporating human natural interferon-α and sorafenib on renal cell carcinoma cells, *Acta Biomater.*, 2016, **29**, 103–111.

202 H. L. Mao, *et al.*, Delivery of DOX from Hyaluronic Acid-Modified Glutathione-Responsive Ferrocene Micelles for Combination Cancer Therapy, *Mol. Pharm.*, 2019, **16**(3), 987–994.

203 P. Wu, *et al.*, Enhanced anti-tumor efficacy of hyaluronic acid modified nanocomposites combined with sonochemotherapy against subcutaneous and metastatic breast tumors, *Nanoscale*, 2019, **11**(24), 11470–11483.

204 G. Wang, *et al.*, Theranostic Hyaluronic Acid–Iron Micellar Nanoparticles for Magnetic-Field-Enhanced in vivo Cancer Chemotherapy, *ChemMedChem*, 2018, **13**(1), 78–86.

205 Z. Pan, H. Ye and D. Wu, Recent advances on polymeric hydrogels as wound dressings, *APL Bioeng.*, 2021, **5**(1), 011504.

206 X. Pang, *et al.*, Hyaluronic acid-quercetin conjugate micelles: Synthesis, characterization, in vitro and in vivo evaluation, *Colloids Surf., B*, 2014, **123**, 778–786.

207 J. Li, *et al.*, Modified curcumin with hyaluronic acid: Combination of pro-drug and nano-micelle strategy to

address the curcumin challenge, *Food Res. Int.*, 2015, **69**, 202–208.

208 C. Tian, *et al.*, The effect of the molecular weight of hyaluronic acid on the physicochemical characterization of hyaluronic acid-curcumin conjugates and in vitro evaluation in glioma cells, *Colloids Surf., B*, 2018, **165**, 45–55.

209 Z. Cheng, *et al.*, Preparation and characterization of dissolving hyaluronic acid composite microneedles loaded micelles for delivery of curcumin, *Drug Delivery Transl. Res.*, 2020, **10**(5), 1520–1530.

210 S. C. Abeylath and M. M. Amiji, 'Click' synthesis of dextran macrostructures for combinatorial-designed self-assembled nanoparticles encapsulating diverse anticancer therapeutics, *Bioorg. Med. Chem.*, 2011, **19**(21), 6167–6173.

211 E. M. Kemper, *et al.*, Increased penetration of paclitaxel into the brain by inhibition of P-Glycoprotein, *Clin. Cancer Res.*, 2003, **9**(7), 2849–2855.

212 D. Coradini, *et al.*, Hyaluronic acid as drug delivery for sodium butyrate: Improvement of the anti-proliferative activity on a breast-cancer cell line, *Int. J. Cancer*, 1999, **81**(3), 411–416.

213 S. Cai, *et al.*, Phase I-II clinical trial of hyaluronan-cisplatin nanoconjugate in dogs with naturally occurring malignant tumors, *Am. J. Vet. Res.*, 2016, **77**(9), 1005–1016.

214 P. F. Bassi, *et al.*, Paclitaxel-Hyaluronic Acid for Intravesical Therapy of Bacillus Calmette-Guérin Refractory Carcinoma In Situ of the Bladder: Results of a Phase I Study, *J. Urol.*, 2011, **185**(2), 445–449.

215 A. Rosato, *et al.*, HYTAD1-p20: A new paclitaxel-hyaluronic acid hydrosoluble bioconjugate for treatment of superficial bladder cancer, *Urol. Oncol.: Semin. Orig. Invest.*, 2006, **24**(3), 207–215.

216 Y. J. Jin, *et al.*, Hyaluronic acid derivative-based self-assembled nanoparticles for the treatment of melanoma, *Pharm. Res.*, 2012, **29**(12), 3443–3454.

217 H. Shen, *et al.*, Coating Solid Lipid Nanoparticles with Hyaluronic Acid Enhances Antitumor Activity against Melanoma Stem-like Cells, *Theranostics*, 2015, **5**(7), 755–771.

218 H. S. Jung, *et al.*, Nanographene Oxide–Hyaluronic Acid Conjugate for Photothermal Ablation Therapy of Skin Cancer, *ACS Nano*, 2014, **8**(1), 260–268.

219 M. Kong, *et al.*, Construction of hyaluronic acid noisome as functional transdermal nanocarrier for tumor therapy, *Carbohydr. Polym.*, 2013, **94**(1), 634–641.

220 L. Hou and M. Kong, Enhanced transdermal lymphatic drug delivery of hyaluronic acid modified transfersome for tumor metastasis therapy, *J. Controlled Release*, 2015, **213**, e77.

221 P. Lee, *et al.*, Influence of chondroitin sulfate and hyaluronic acid presence in nanofibers and its alignment on the bone marrow stromal cells: cartilage regeneration, *J. Biomed. Nanotechnol.*, 2014, **10**(8), 1469–1479.

222 D. Šmejkalová, *et al.*, Hyaluronan polymeric micelles for topical drug delivery, *Carbohydr. Polym.*, 2017, **156**, 86–96.

223 J.-A. Yang, *et al.*, Transdermal delivery of hyaluronic acid – Human growth hormone conjugate, *Biomaterials*, 2012, **33**(25), 5947–5954.

224 A. Ebringerová and Z. Hromádková, Xylans of Industrial and Biomedical Importance, *Biotechnol. Genet. Eng. Rev.*, 1999, **16**(1), 325–346.

225 S. U. Kumar, P. Gopinath and Y. S. Negi, Synthesis and bio-evaluation of xylan-5-fluorouracil-1-acetic acid conjugates as prodrugs for colon cancer treatment, *Carbohydr. Polym.*, 2017, **157**, 1442–1450.

226 S. U. Kumar, *et al.*, pH-responsive prodrug nanoparticles based on xylan-curcumin conjugate for the efficient delivery of curcumin in cancer therapy, *Carbohydr. Polym.*, 2018, **188**, 252–259.

227 S. C. da Costa Urtiga, *et al.*, Xylan in drug delivery: a review of its engineered structures and biomedical applications, *Eur. J. Pharm. Biopharm.*, 2020, **151**, 199–208.

228 P. Severino, *et al.*, Alginate nanoparticles for drug delivery and targeting, *Curr. Pharm. Des.*, 2019, **25**(11), 1312–1334.

229 M. Upadhyay, *et al.*, Development of biopolymers based interpenetrating polymeric network of capecitabine: a drug delivery vehicle to extend the release of the model drug, *Int. J. Biol. Macromol.*, 2018, **115**, 907–919.

230 S. Haque, *et al.*, Development and evaluation of brain targeted intranasal alginate nanoparticles for treatment of depression, *J. Psychiatr. Res.*, 2014, **48**(1), 1–12.

231 S. Mandal, *et al.*, Formulation and evaluation of an in situ gel-forming ophthalmic formulation of moxifloxacin hydrochloride, *Int. J. Pharm. Invest.*, 2012, **2**(2), 78–82.

232 D. Bharathi, *et al.*, Long acting ophthalmic formulation of indomethacin: Evaluation of alginate gel systems, *Indian J. Pharm. Sci.*, 2007, **69**(1), 37.

233 J. V. Román, M. A. Galán and E. M. M. del Valle, Preparation and preliminary evaluation of alginate crosslinked microcapsules as potential drug delivery system (DDS) for human lung cancer therapy, *Biomed. Phys. Eng. Express*, 2016, **2**(3), 035015.

234 M. Rajaonarivony, *et al.*, Development of a new drug carrier made from alginate, *J. Pharm. Sci.*, 1993, **82**(9), 912–917.

235 I. K. Park, *et al.*, Galactosylated chitosan-graft-dextran as hepatocyte-targeting DNA carrier, *J. Controlled Release*, 2000, **69**(1), 97–108.

236 J. Wei, *et al.*, Hollow hydroxyapatite/polyelectrolyte hybrid microparticles with controllable size, wall thickness and drug delivery properties, *J. Mater. Chem. B*, 2015, **3**(41), 8162–8169.

237 T. S. Anirudhan, C. Sekhar V and S. S. Nair, Polyelectrolyte complexes of carboxymethyl chitosan/alginate based drug carrier for targeted and controlled release of dual drug, *J. Drug Delivery Sci. Technol.*, 2019, **51**, 569–582.

238 K. Ghosal, *et al.*, Synthesis and characterization of interpenetrating polymeric networks based bio-composite alginate film: A well-designed drug delivery platform, *Int. J. Biol. Macromol.*, 2019, **130**, 645–654.

239 H. Yan, *et al.*, Entrapment of bacterial cellulose nanocrystals stabilized Pickering emulsions droplets in

alginate beads for hydrophobic drug delivery, *Colloids Surf., B*, 2019, **177**, 112–120.

240 K. S. Joshy, *et al.*, Encapsulation of zidovudine in PF-68 coated alginate conjugate nanoparticles for anti-HIV drug delivery, *Int. J. Biol. Macromol.*, 2018, **107**, 929–937.

241 Y. Shtenberg, *et al.*, Mucoadhesive alginate pastes with embedded liposomes for local oral drug delivery, *Int. J. Biol. Macromol.*, 2018, **111**, 62–69.

242 Z.-C. Yin, Y.-L. Wang and K. Wang, A pH-responsive composite hydrogel beads based on agar and alginate for oral drug delivery, *J. Drug Delivery Sci. Technol.*, 2018, **43**, 12–18.

243 F. Wang, S. He and B. Chen, Retinoic acid-loaded alginate microspheres as a slow release drug delivery carrier for intravitreal treatment, *Biomed. Pharmacother.*, 2018, **97**, 722–728.

244 M. Xie, *et al.*, Surface modification of graphene oxide nanosheets by protamine sulfate/sodium alginate for anti-cancer drug delivery application, *Appl. Surf. Sci.*, 2018, **440**, 853–860.

245 B. Zhang, *et al.*, A colon targeted drug delivery system based on alginate modificated graphene oxide for colorectal liver metastasis, *Mater. Sci. Eng. C*, 2017, **79**, 185–190.

246 S. M. H. Dabiri, *et al.*, New in-situ synthetized hydrogel composite based on alginate and brushite as a potential pH sensitive drug delivery system, *Carbohydr. Polym.*, 2017, **177**, 324–333.

247 P. Bonilla, *et al.*, Influence of crosslinked alginate on drug release from highly concentrated emulsions, *Colloids Surf., A*, 2018, **536**, 148–155.

248 S. M. Tawfik, *et al.*, Naturally modified nonionic alginate functionalized upconversion nanoparticles for the highly efficient targeted pH-responsive drug delivery and enhancement of NIR-imaging, *J. Ind. Eng. Chem.*, 2018, **57**, 424–435.

249 C. C. Ribeiro, C. C. Barrias and M. A. Barbosa, Calcium phosphate-alginate microspheres as enzyme delivery matrices, *Biomaterials*, 2004, **25**(18), 4363–4373.

250 B. D. Kevadiya, *et al.*, Montmorillonite-Alginate Nanocomposites as a Drug Delivery System: Intercalation and In Vitro Release of Vitamin B1 and Vitamin B6, *J. Biomater. Appl.*, 2010, **25**(2), 161–177.

251 J. Malakar and A. K. Nayak, Formulation and statistical optimization of multiple-unit ibuprofen-loaded buoyant system using 23-factorial design, *Chem. Eng. Res. Des.*, 2012, **90**(11), 1834–1846.

252 H. Bera, *et al.*, Alginate gel-coated oil-entrapped alginate–tamarind gum–magnesium stearate buoyant beads of risperidone, *Int. J. Biol. Macromol.*, 2015, **78**, 102–111.

253 Y. Javadzadeh, *et al.*, Evaluation of drug release kinetics and physico-chemical characteristics of metronidazole floating beads based on calcium silicate and gas-forming agents, *Pharm. Dev. Technol.*, 2010, **15**(4), 329–338.

254 R. H. Fahmy, Statistical Approach for Assessing the Influence of Calcium Silicate and HPMC on the Formulation of Novel Alfuzosin Hydrochloride Mucoadhesive-Floating Beads as Gastroretentive DDS, *AAPS PharmSciTech*, 2012, **13**(3), 990–1004.

255 F. F. Azhar and A. Olad, A study on sustained release formulations for oral delivery of 5-fluorouracil based on alginate–chitosan/montmorillonite nanocomposite systems, *Appl. Clay Sci.*, 2014, **101**, 288–296.

256 Y. Zhang, *et al.*, A DOX delivery system: Samarium/mesoporous bioactive glass/alginate composite microspheres, *Mater. Sci. Eng. C*, 2016, **67**, 205–213.

257 J.-L. Wu, *et al.*, Multi-drug delivery system based on alginate/calcium carbonate hybrid nanoparticles for combination chemotherapy, *Colloids Surf., B*, 2014, **123**, 498–505.

258 H. Li, *et al.*, Bioactive apatite incorporated alginate microspheres with sustained drug-delivery for bone regeneration application, *Mater. Sci. Eng. C*, 2016, **62**, 779–786.

259 B. D. Kevadiya, *et al.*, Montmorillonite-Alginate Composites as a Drug delivery System: Intercalation and In vitro Release of Diclofenac sodium, *Indian J. Pharm. Sci.*, 2010, **72**(6), 732–737.

260 D. Pal and A. K. Nayak, Development, Optimization, and Anti-diabetic Activity of Gliclazide-Loaded Alginate–Methyl Cellulose Mucoadhesive Microcapsules, *AAPS PharmSciTech*, 2011, **12**(4), 1431–1441.

261 A. Nayak, *et al.*, Development of alginate-PVP K 30 microbeads for controlled diclofenac sodium delivery using central composite design, *Daru, J. Fac. Pharm.*, 2011, **19**, 356–366.

262 M. S. Hasnain, *et al.*, Isolation and characterization of Linum usitatisimum polysaccharide to prepare mucoadhesive beads of diclofenac sodium, *Int. J. Biol. Macromol.*, 2018, **116**, 162–172.

263 P. Sinha, *et al.*, Alginate-okra gum blend beads of diclofenac sodium from aqueous template using ZnSO4 as a cross-linker, *Int. J. Biol. Macromol.*, 2015, **79**, 555–563.

264 A. K. Nayak, *et al.*, Mucoadhesive beads of gliclazide: Design, development, and evaluation, *ScienceAsia*, 2010, **36**(1), 319–325.

265 A. K. Nayak, D. Pal and K. Santra, Plantago ovata F. Mucilage-alginate mucoadhesive beads for controlled release of glibenclamide: development, optimization, and in vitro-in vivo evaluation, *J. Pharm*, 2013, **2013**, 151035.

266 D. Pal and A. K. Nayak, Novel tamarind seed polysaccharide-alginate mucoadhesive microspheres for oral gliclazide delivery: in vitro–in vivo evaluation, *Drug Delivery*, 2012, **19**(3), 123–131.

267 A. K. Nayak, D. Pal and K. Santra, Swelling and drug release behavior of metformin HCl-loaded tamarind seed polysaccharide-alginate beads, *Int. J. Biol. Macromol.*, 2016, **82**, 1023–1027.

268 S. Jana, *et al.*, Aceclofenac-loaded unsaturated esterified alginate/gellan gum microspheres: In vitro and in vivo assessment, *Int. J. Biol. Macromol.*, 2013, **57**, 129–137.

269 B. J. Dukovski, *et al.*, Lipid/alginate nanoparticle-loaded in situ gelling system tailored for dexamethasone nasal delivery, *Int. J. Pharm.*, 2017, **533**(2), 480–487.

270 F. A. N. Mohamed and F. Laraba-Djebari, Development and characterization of a new carrier for vaccine delivery based on calcium-alginate nanoparticles: Safe immunoprotective approach against scorpion envenoming, *Vaccine*, 2016, **34**(24), 2692–2699.

271 S. Gopi, *et al.*, Biopolymers and their composites for drug delivery: a brief review, in *Macromolecular Symposia*, Wiley Online Library, 2018.

272 Z. Shariatinia and Z. Zahraee, Controlled release of metformin from chitosan–based nanocomposite films containing mesoporous MCM-41 nanoparticles as novel DDS, *J. Colloid Interface Sci.*, 2017, **501**, 60–76.

273 S. Kumar, *et al.*, Metformin-loaded alginate nanoparticles as an effective antidiabetic agent for controlled drug release, *J. Pharm. Pharmacol.*, 2017, **69**(2), 143–150.

274 S. Dey and K. Sreenivasan, Conjugation of curcumin onto alginate enhances aqueous solubility and stability of curcumin, *Carbohydr. Polym.*, 2014, **99**, 499–507.

275 P. R. Sarika, N. R. James, P. R. Anil Kumar, D. K. Raj, *et al.*, Galactosylated alginate-curcumin micelles for enhanced delivery of curcumin to hepatocytes, *Int. J. Biol. Macromol.*, 2016, **86**, 1–9.

276 D. Lachowicz, *et al.*, Blood-compatible, stable micelles of sodium alginate – Curcumin bioconjugate for anti-cancer applications, *Eur. Polym. J.*, 2019, **113**, 208–219.

277 P. R. Guru, A. K. Nayak and R. K. Sahu, Oil-entrapped sterculia gum–alginate buoyant systems of aceclofenac: development and in vitro evaluation, *Colloids Surf., B*, 2013, **104**, 268–275.

278 A. K. Nayak, *et al.*, Fenugreek seed mucilage-alginate mucoadhesive beads of metformin HCl: Design, optimization and evaluation, *Int. J. Biol. Macromol.*, 2013, **54**, 144–154.

279 A. K. Nayak, D. Pal and J. Malakar, Development, optimization, and evaluation of emulsion-gelled floating beads using natural polysaccharide-blend for controlled drug release, *Polym. Eng. Sci.*, 2013, **53**(2), 238–250.

280 B. Das, *et al.*, Zinc alginate-carboxymethyl cashew gum microbeads for prolonged drug release: development and optimization, *Int. J. Biol. Macromol.*, 2014, **70**, 506–515.

281 A. El-kamel, O. Al-Gohary and E. Hosny, Alginate-diltiazem hydrocloride beads: Optimization of formulation factors, in vitro and in vivo availability, *J. Microencapsulation*, 2003, **20**, 211–225.

282 Y. L. Patel, P. Sher and A. P. Pawar, The effect of drug concentration and curing time on processing and properties of calcium alginate beads containing metronidazole by response surface methodology, *AAPS PharmSciTech*, 2006, **7**, 86, DOI: **10.1208/pt070486**.

283 R. S. Al-Kassas, O. M. Al-Gohary and M. M. Al-Faadhel, Controlling of systemic absorption of gliclazide through incorporation into alginate beads, *Int. J. Pharm.*, 2007, **341**(1–2), 230–237.

284 B. A. Yegin, *et al.*, Sulindac loaded alginate beads for a mucoprotective and controlled drug release, *J. Microencapsulation*, 2007, **24**(4), 371–382.

285 M. L. Torre, *et al.*, Formulation and Characterization of Calcium Alginate Beads Containing Ampicillin, *Pharm. Dev. Technol.*, 1998, **3**(2), 193–198.

286 M. Morshed, *et al.*, Effect of Barium Chloride as A Cross Linking Agent on the Sodium Alginate Based Diclofenac Sodium Beads, *Bangladesh Pharm. J.*, 2012, **15**, 53–57.

287 M. K. Das and P. C. Senapati, Furosemide-loaded Alginate Microspheres Prepared by Ionic Cross-linking Technique: Morphology and Release Characteristics, *Indian J. Pharm. Sci.*, 2008, **70**(1), 77–84.

288 V. Deshmukh, *et al.*, Formulation, Optimization and Evaluation of Controlled Release Alginate Microspheres Using Synergy Gum Blends, *Res. J. Pharm. Technol.*, 2008, **2**.

289 D. S. Chakraborty, *et al.*, Preparation, in vitro and in vivo evaluation of algino-pectinate bioadhesive microspheres: An investigation of the effects of polymers using multiple comparison analysis, *Acta Pharm.*, 2010, **60**, 255–266.

290 J. Raja Kumar and S. Muralidharan, Formulation and In vitro Evalution of Gellan Gum/Carbopol and Sodium Alginate based Solution to Gel Depot of Ketotifen Fumarate System, *J. Pet. Sci. Res.*, 2012, **4**, 1973–1977.

291 T. Pongjanyakul and S. Puttipipatkhachorn, Xanthan-alginate composite gel beads: molecular interaction and in vitro characterization, *Int. J. Pharm.*, 2007, **331**(1), 61–71.

292 A. K. Nayak and D. Pal, Formulation optimization and evaluation of jackfruit seed starch–alginate mucoadhesive beads of metformin HCl, *Int. J. Biol. Macromol.*, 2013, **59**, 264–272.

293 A. K. Nayak, B. Das and R. Maji, Calcium alginate/gum Arabic beads containing glibenclamide: Development and in vitro characterization, *Int. J. Biol. Macromol.*, 2012, **51**(5), 1070–1078.

294 B. Singh, V. Sharma and D. Chauhan, Gastroretentive floating sterculia–alginate beads for use in antiulcer drug delivery, *Chem. Eng. Res. Des.*, 2010, **88**(8), 997–1012.

295 A. K. Nayak, D. Pal and K. Santra, Development of calcium pectinate-tamarind seed polysaccharide mucoadhesive beads containing metformin HCl, *Carbohydr. Polym.*, 2014, **101**, 220–230.

296 A. K. Nayak and D. Pal, Development of pH-sensitive tamarind seed polysaccharide-alginate composite beads for controlled diclofenac sodium delivery using response surface methodology, *Int. J. Biol. Macromol.*, 2011, **49**(4), 784–793.

297 A. Nayak, D. Pal and K. Santra, Tamarind seed polysaccharide–gellan mucoadhesive beads for controlled release of metformin HCl, *Carbohydr. Polym.*, 2014, **103**, 154–163.

298 A. Nayak, B. Mohanty and K. Sen, Comparative evaluation of in vitro diclofenac sodium permeability across excised mouse skin from different common pharmaceutical vehicles, *Int. J. PharmTech Res.*, 2010, **2**, 920–930.

299 D. P. Maurya, *et al.*, Formulation and optimization of alkaline extracted ispaghula husk microparticles of isoniazid – in vitro and in vivo assessment, *J. Microencapsulation*, 2011, **28**(6), 472–482.

300 V. Kumar and A. Bhattacharya, Release of Metformin Hydrochloride from Ispaghula-Sodium Alginate Beads Adhered on Cock Intestinal Mucosa, *Indian J. Pharm. Educ. Res.*, 2008, **42**(4).

301 H. Sharma, B. Sarangi and S. P. Pradhan, Preparation and in-vitro evaluation of mucoadhesive microbeads containing timolol maleate using mucoadhesive substances of Dillenia indica L, *Arch. Pharm. Sci. Res.*, 2009, **1**, 181–188.

302 R. Raparla and T. E. G. K. Murthy, Preparation and evaluation of mucoadhesive microcapsules of glipizide formulated with gum kondagogu: In vitro and in vivo, *Acta Pharm. Sci.*, 2010, **52**, 335–344.

303 R. Justin, *et al.*, Biodegradable and conductive chitosan–graphene quantum dot nanocomposite microneedles for delivery of both small and large molecular weight therapeutics, *RSC Adv.*, 2015, **5**(64), 51934–51946.

304 P. R. Guru, *et al.*, Aceclofenac-Loaded Plantago ovata F. Husk Mucilage-Zn+2-Pectinate Controlled-Release Matrices, *Starch – Stärke*, 2018, **70**(3–4), 1700136.

305 A. K. Nayak, D. Pal and K. Santra, Ispaghula mucilage-gellan mucoadhesive beads of metformin HCl: development by response surface methodology, *Carbohydr. Polym.*, 2014, **107**, 41–50.

306 A. K. Nayak, D. Pal and K. Santra, Artocarpus heterophyllus L. seed starch-blended gellan gum mucoadhesive beads of metformin HCl, *Int. J. Biol. Macromol.*, 2014, **65**, 329–339.

307 J. A. Posey, *et al.*, Phase 1 study of weekly polyethylene glycol-camptothecin in patients with advanced solid tumors and lymphomas, *Clin. Cancer Res.*, 2005, **11**(21), 7866–7871.

308 Y. Chau, *et al.*, Antitumor efficacy of a novel polymer-peptide-drug conjugate in human tumor xenograft models, *Int. J. Cancer*, 2006, **118**(6), 1519–1526.

309 S.-i. Sugahara, *et al.*, Complete regression of xenografted human carcinomas by a paclitaxel–carboxymethyl dextran conjugate (AZ10992), *J. Controlled Release*, 2007, **117**(1), 40–50.

310 S. A. Veltkamp, *et al.*, Clinical and pharmacologic study of the novel prodrug delimotecan (MEN 4901/T-0128) in patients with solid tumors, *Clin. Cancer Res.*, 2008, **14**(22), 7535–7544.

311 B. Naeye, *et al.*, PEGylation of biodegradable dextran nanogels for siRNA delivery, *Eur. J. Pharm. Sci.*, 2010, **40**(4), 342–351.

312 A. Celebioglu and T. Uyar, Metronidazole/Hydroxypropyl-β-Cyclodextrin inclusion complex nanofibrous webs as fast-dissolving oral drug delivery system, *Int. J. Pharm.*, 2019, **572**, 118828.

313 P. Yousefpour, *et al.*, Targeted delivery of DOX-utilizing chitosan nanoparticles surface-functionalized with anti-Her2 trastuzumab, *Int. J. Nanomed.*, 2011, **6**, 1977–1990.

314 F. Li, *et al.*, Reducing Both Pgp Overexpression and Drug Efflux with Anti-Cancer Gold-Paclitaxel Nanoconjugates, *PLoS One*, 2016, **11**(7), e0160042.

315 A. Solanki, *et al.*, β-Cyclodextrin based magnetic nanoconjugates for targeted drug delivery in cancer therapy, *RSC Adv.*, 2016, **6**(101), 98693–98707.

316 W. Dang, *et al.*, Covalent coupling of methotrexate to dextran enhances the penetration of cytotoxicity into a tissue-like matrix, *Cancer Res.*, 1994, **54**(7), 1729–1735.

317 T. F. Vandamme, *et al.*, The use of polysaccharides to target drugs to the colon, *Carbohydr. Polym.*, 2002, **48**(3), 219–231.

318 J. S. Lee, *et al.*, Synthesis and properties of dextran–nalidixic acid ester as a colon-specific prodrug of nalidixic acid, *Drug Dev. Ind. Pharm.*, 2001, **27**(4), 331–336.

319 A. Popat, *et al.*, Curcumin-cyclodextrin encapsulated chitosan nanoconjugates with enhanced solubility and cell cytotoxicity, *Colloids Surf., B*, 2014, **117**, 520–527.

320 A. Hinz, *et al.*, Analysis of toxicity and anticancer activity of micelles of sodium alginate-curcumin, *Int. J. Nanomed.*, 2019, **14**, 7249–7262.

321 W. Ji, *et al.*, Chemosensitizing indomethacin-conjugated dextran-based micelles for effective delivery of paclitaxel in resistant breast cancer therapy, *PLoS One*, 2017, **12**(7), e0180037.

322 X. Zeng, *et al.*, Indomethacin-grafted and pH-sensitive dextran micelles for overcoming inflammation-mediated multidrug resistance in breast cancer, *Carbohydr. Polym.*, 2020, **237**, 116139.

323 S. Wong, *et al.*, Just add sugar for carbohydrate induced self-assembly of curcumin, *Nat. Commun.*, 2019, **10**(1), 582.

324 D. Agudelo, *et al.*, Transporting antitumor drug tamoxifen and its metabolites, 4-hydroxytamoxifen and endoxifen by chitosan nanoparticles, *PLoS One*, 2013, **8**(3), e60250.

325 J. S. Lee, *et al.*, Synthesis and properties of dextran-nalidixic acid ester as a colon-specific prodrug of nalidixic acid, *Drug Dev. Ind. Pharm.*, 2001, **27**(4), 331–336.

326 A. O. Abioye and A. Kola-Mustapha, Controlled Electrostatic Self-Assembly of Ibuprofen-Cationic Dextran Nanoconjugates Prepared by low Energy Green Process – a Novel Delivery Tool for Poorly Soluble Drugs, *Pharm. Res.*, 2015, **32**(6), 2110–2131.

327 G. J. Weiss, *et al.*, First-in-human phase 1/2a trial of CRLX101, a cyclodextrin-containing polymer-camptothecin nanopharmaceutical in patients with advanced solid tumor malignancies, *Invest. New Drugs*, 2013, **31**(4), 986–1000.

328 M. E. Davis, Design and development of IT-101, a cyclodextrin-containing polymer conjugate of camptothecin, *Adv. Drug Delivery Rev.*, 2009, **61**(13), 1189–1192.

329 S. A. Veltkamp, *et al.*, Clinical and Pharmacologic Study of the Novel Prodrug Delimotecan (MEN 4901/T-0128) in Patients with Solid Tumors, *Clin. Cancer Res.*, 2008, **14**, 7535–7544.

330 O. Soepenberg, *et al.*, Phase I and pharmacokinetic study of DE-310 in patients with advanced solid tumors, *Clin. Cancer Res.*, 2005, **11**(2), 703–711.

331 S. Danhauser-Riedl, *et al.*, Phase I clinical and pharmacokinetic trial of dextran conjugated DOX (AD-70, DOX-OXD), *Invest. New Drugs*, 1993, **11**(2–3), 187–195.

332 K. Park, *et al.*, Preparation and Characterization of Self-Assembled Nanoparticles of Heparin-Deoxycholic Acid Conjugates, *Langmuir*, 2004, **20**(26), 11726–11731.
333 K. Park, *et al.*, Heparin–deoxycholic acid chemical conjugate as an anticancer drug carrier and its antitumor activity, *J. Controlled Release*, 2006, **114**(3), 300–306.
334 T. Zhang, *et al.*, Combination chemotherapy of DOX, all-trans retinoic acid and low molecular weight heparin based on self-assembled multi-functional polymeric nanoparticles, *Nanotechnology*, 2015, **26**(14), 145101.
335 N. U. Khaliq, *et al.*, DOX/heparin composite nanoparticles for caspase-activated prodrug chemotherapy, *Biomaterials*, 2016, **101**, 131–142.
336 T. H. Tran, *et al.*, Heparin-folate-retinoic acid bioconjugates for targeted delivery of hydrophobic photosensitizers, *Carbohydr. Polym.*, 2013, **92**(2), 1615–1624.
337 J. Emami, *et al.*, Novel pH-triggered biocompatible polymeric micelles based on heparin–α-tocopherol conjugate for intracellular delivery of docetaxel in breast cancer, *Pharm. Dev. Technol.*, 2020, **25**(4), 492–509.
338 Y. Wu, *et al.*, Tumor microenvironment-responsive PEGylated heparin-pyropheophorbide-a nanoconjugates for photodynamic therapy, *Carbohydr. Polym.*, 2021, **255**, 117490.
339 L. Mei, *et al.*, Antitumor and Antimetastasis Activities of Heparin-based Micelle Served As Both Carrier and Drug, *ACS Appl. Mater. Interfaces*, 2016, **8**(15), 9577–9589.
340 X. Wang, *et al.*, HFT-T, a Targeting Nanoparticle, Enhances Specific Delivery of Paclitaxel to Folate Receptor-Positive Tumors, *ACS Nano*, 2009, **3**(10), 3165–3174.
341 C. H. Salamanca, *et al.*, Natural gum-type biopolymers as potential modified nonpolar drug release systems, *Carbohydr. Polym.*, 2018, **189**, 31–38.
342 L. I. Atanase, Micellar DDS based on natural biopolymers, *Polymers*, 2021, **13**(3), 477.
343 B. Devrim, A. Bozkir and K. Canefe, Formulation and evaluation of reconstitutable suspensions containing ibuprofen-loaded Eudragit microspheres, *Acta Pol. Pharm.*, 2011, **68**(4), 593–599.
344 G. Roopa, R. S. Bhat and M. S. Dakshina, Formulation and evaluation of an antacid and anti-ulcer suspension containing herbal drugs, *Biomed. Pharmacol. J.*, 2015, **3**(1), 01–06.
345 M. Chaturvedi, *et al.*, Recent development in novel DDS of herbal drugs, *Int. J. Green Pharm.*, 2011, **5**(2), 363–371.
346 R. Nethaji, *et al.*, Formulation and evaluation of metformin hydrochloride loaded mucoadhesive microspheres, *Int. J. Pharm., Chem. Biol. Sci.*, 2016, **6**(2).
347 O. Samia, R. Hanan and E. T. Kamal, Carbamazepine mucoadhesive nanoemulgel (MNEG) as brain targeting delivery system via the olfactory mucosa, *Drug Delivery*, 2012, **19**(1), 58–67.
348 S. Samudre, *et al.*, Xanthan gum coated mucoadhesive liposomes for efficient nose to brain delivery of curcumin, *Drug Delivery Lett.*, 2015, **5**(3), 201–207.
349 R. Saudagar and K. Badhe, Development and evaluation of ph dependent in situ nasal gel of loratadine, *Eur. J. Biomed. Pharm. Sci.*, 2016, **1**(3), 233–238.
350 C. Chittasupho, M. Jaturanpinyo and S. Mangmool, Pectin nanoparticle enhances cytotoxicity of methotrexate against hepG2 cells, *Drug Delivery*, 2013, **20**(1), 1–9.
351 M. Cheng, *et al.*, [Preparation and lymphatic targeting research of targeting antitumor drug: pectin-adriamycin conjugates], *Shengwu Yixue Gongchengxue Zazhi*, 2009, **26**(3), 569–574.
352 R. K. Dev, V. Bali and K. Pathak, Novel microbially triggered colon specific delivery system of 5-Fluorouracil: Statistical optimization, in vitro, in vivo, cytotoxic and stability assessment, *Int. J. Pharm.*, 2011, **411**(1), 142–151.
353 J. T. Chung and Z. Zhang, Mechanical characterization of calcium pectinate hydrogel for controlled drug delivery, *Hem. Ind.*, 2003, **57**, 611–616.
354 A. Assifaoui, O. Chambin and P. Cayot, Drug release from calcium and zinc pectinate beads: Impact of dissolution medium composition, *Carbohydr. Polym.*, 2011, **85**(2), 388–393.
355 C. Lara-Espinoza, *et al.*, Pectin and pectin-based composite materials: Beyond food texture, *Molecules*, 2018, **23**(4), 942.
356 P. Sriamornsak, *et al.*, Effect of drug loading method on drug content and drug release from calcium pectinate gel beads, *AAPS PharmSciTech*, 2010, **11**(3), 1315–1319.
357 I. El-Gibaly, Oral delayed-release system based on Zn-pectinate gel (ZPG) microparticles as an alternative carrier to calcium pectinate beads for colonic drug delivery, *Int. J. Pharm.*, 2002, **232**(1), 199–211.
358 K. A. Verma and K. Sachin, Novel Hydrophilic Drug Polymer Nano-Conjugates of Cisplatin Showing Long Blood Retention Profile - Its Release Kinetics, Cellular Uptake and Bio-Distribution, *Curr. Drug Delivery*, 2008, **5**(2), 120–126.
359 S. Majzoob, *et al.*, Pectin-cysteine conjugate: synthesis and in-vitro evaluation of its potential for drug delivery, *J. Pharm. Pharmacol.*, 2010, **58**(12), 1601–1610.
360 N. A. Hussien, N. Işıklan and M. Türk, Pectin-conjugated magnetic graphene oxide nanohybrid as a novel drug carrier for paclitaxel delivery, *Artif. Cells, Nanomed., Biotechnol.*, 2018, **46**(sup1), 264–273.
361 F. A. Oyarzun-Ampuero, *et al.*, A new drug nanocarrier consisting of polyarginine and hyaluronic acid, *Eur. J. Pharm. Biopharm.*, 2011, **79**(1), 54–57.
362 A. Villaverde, *Nanoparticles in translational science and medicine*, Academic Press, 2011.
363 J. B. Rothbard, *et al.*, Conjugation of arginine oligomers to cyclosporin A facilitates topical delivery and inhibition of inflammation, *Nat. Med.*, 2000, **6**(11), 1253–1257.
364 P. P. Shah, *et al.*, Enhanced skin permeation using polyarginine modified nanostructured lipid carriers, *J. Controlled Release*, 2012, **161**(3), 735–745.
365 S. Patra, E. Roy and R. Madhuri, The next generation cell-penetrating peptide and carbon dot conjugated nano-liposome for transdermal delivery of curcumin, *Biomater. Sci.*, 2015, **4**, 418–429.

366 S. S. Kwon, *et al.*, Cell penetrating peptide conjugated liposomes as transdermal delivery system of Polygonum aviculare L. extract, *Int. J. Pharm.*, 2015, **483**(1–2), 26–37.
367 M. R. Rekha and C. P. Sharma, Hemocompatible pullulan–polyethyleneimine conjugates for liver cell gene delivery: In vitro evaluation of cellular uptake, intracellular trafficking and transfection efficiency, *Acta Biomater.*, 2011, **7**(1), 370–379.
368 M. Dionísio, *et al.*, Pullulan-based nanoparticles as carriers for transmucosal protein delivery, *Eur. J. Pharm. Sci.*, 2013, **50**(1), 102–113.
369 J. M. Pereira, M. Mahoney and K. J. Edgar, Synthesis of amphiphilic 6-carboxypullulan ethers, *Carbohydr. Polym.*, 2014, **100**, 65–73.
370 L. Huang, *et al.*, Versatile redox-sensitive pullulan nanoparticles for enhanced liver targeting and efficient cancer therapy, *Nanomedicine*, 2018, **14**(3), 1005–1017.
371 R. Garhwal, *et al.*, Sustained Ocular Delivery of Ciprofloxacin Using Nanospheres and Conventional Contact Lens Materials, *Invest. Ophthalmol. Visual Sci.*, 2012, **53**(3), 1341–1352.
372 J. Wang, *et al.*, Tocopheryl pullulan-based self assembling nanomicelles for anti-cancer drug delivery, *Mater. Sci. Eng. C*, 2014, **43**, 614–621.
373 L. Chen, *et al.*, New bifunctional-pullulan-based micelles with good biocompatibility for efficient co-delivery of cancer-suppressing p53 gene and DOX to cancer cells, *RSC Adv.*, 2015, **5**(115), 94719–94731.
374 F. Hassanzadeh and J. Varshosaz, Biotin-encoded Pullulan-Retinoic Acid Engineered Nanomicelles: Preparation, Optimization and In Vitro Cytotoxicity Assessment in MCF-7 Cells, *Indian J. Pharm. Sci.*, 2016, **78**, 557–565.
375 L. Chen, *et al.*, Biocompatible cationic pullulan-g-desoxycholic acid-g-PEI micelles used to co-deliver drug and gene for cancer therapy, *Mater. Sci. Eng. C*, 2017, **70**, 418–429.
376 F. Hassanzadeh, *et al.*, Novel NGR anchored pullulan micelles for controlled and targeted delivery of DOX to HeLa cancerous cells, *Iran. Polym. J.*, 2018, **27**(4), 263–274.
377 M. Constantin, *et al.*, Novel cationic and hydrophobic pullulan derivatives as dna nanoparticulate carriers, *Cellul. Chem. Technol.*, 2019, **53**, 695–707.
378 H. Yuan, *et al.*, Preparation of Cholesteryl-Modified Aminated Pullulan Nanoparticles to Evaluate Nanoparticle of Hydrophobic Degree on Drug Release and Cytotoxicity, *J. Nanomater.*, 2020, **2020**, 7171209.
379 K. Na, *et al.*, Self-organized pullulan/deoxycholic acid nanogels: Physicochemical characterization and anti-cancer drug-releasing behavior, *Biotechnol. Bioprocess Eng.*, 2006, **11**(3), 262.
380 G. Shu, *et al.*, Fucoidan-based micelles as P-selectin targeted carriers for synergistic treatment of acute kidney injury, *Nanomed.: Nanotechnol. Biol. Med.*, 2021, **32**, 102342.
381 S. Chen, *et al.*, Nano-micelles based on hydroxyethyl starch-curcumin conjugates for improved stability, antioxidant and anticancer activity of curcumin, *Carbohydr. Polym.*, 2020, **228**, 115398.
382 G. A. Soares, *et al.*, Blends of cross-linked high amylose starch/pectin loaded with diclofenac, *Carbohydr. Polym.*, 2013, **91**(1), 135–142.
383 N. Biswas and R. K. Sahoo, Tapioca starch blended alginate mucoadhesive-floating beads for intragastric delivery of Metoprolol Tartrate, *Int. J. Biol. Macromol.*, 2016, **83**, 61–70.
384 J. Malakar, *et al.*, Potato starch-blended alginate beads for prolonged release of tolbutamide: Development by statistical optimization and in vitro characterization, *Asian J. Pharm.*, 2013, **7**, 43–51.
385 A. Jha and A. Bhattacharya, Preparation and evaluation of sweet potato starch-blended sodium alginate microbeads, *Asian J. Pharm.*, 2009, **4**, 122–128.
386 N. Sachan and A. Bhattacharya, Feasibility of Assam bora rice based matrix microdevices for controlled release of water insoluble drug, *Int. J. Pharm. Pharm. Sci.*, 2009, **1**, 96–102.
387 A. K. Nayak and D. Pal, Blends of jackfruit seed starch-pectin in the development of mucoadhesive beads containing metformin HCl, *Int. J. Biol. Macromol.*, 2013, **62**, 137–145.
388 A. K. Nayak and D. Pal, Ionotropically-gelled mucoadhesive beads for oral metformin HCl delivery: Formulation, optimization and antidiabetic evaluation, *J. Sci. Ind. Res.*, 2013, **72**, 15–22.
389 A. Nayak, D. Pal and K. Santra, Development of pectinate-ispagula mucilage mucoadhesive beads of metformin HCl by central composite design, *Int. J. Biol. Macromol.*, 2014, **66**.
390 K. Liu, *et al.*, A facile one-pot synthesis of starch functionalized graphene as nano-carrier for pH sensitive and starch-mediated drug delivery, *Colloids Surf., B*, 2015, **128**, 86–93.
391 C. Saikia, *et al.*, Effect of crosslinker on drug delivery properties of curcumin loaded starch coated iron oxide nanoparticles, *Int. J. Biol. Macromol.*, 2016, **93**, 1121–1132.
392 H. Hamidian and T. Tavakoli, Preparation of a new Fe3O4/starch-g-polyester nanocomposite hydrogel and a study on swelling and drug delivery properties, *Carbohydr. Polym.*, 2016, **144**, 140–148.
393 M. M. Friciu, *et al.*, Carboxymethyl starch and lecithin complex as matrix for targeted drug delivery: I. Monolithic Mesalamine forms for colon delivery, *Eur. J. Pharm. Biopharm.*, 2013, **85**(3), 521–530.
394 C. Wu, *et al.*, Redox-responsive core-cross-linked mPEGylated starch micelles as nanocarriers for intracellular anticancer drug release, *Eur. Polym. J.*, 2016, **83**, 230–243.
395 V. Raj and G. Prabha, Synthesis, characterization and in vitro drug release of cisplatin loaded Cassava starch acetate–PEG/gelatin nanocomposites, *J. Assoc. Arab Univ. Basic Appl. Sci.*, 2016, **21**, 10–16.
396 L.-K. Zhang, *et al.*, Bacterial cellulose based composites enhanced transdermal drug targeting for breast cancer treatment, *Chem. Eng. J.*, 2019, **370**, 749–759.
397 J. Malakar, A. K. Nayak and A. Das, Modified starch (cationized)–alginate beads containing aceclofenac:

Formulation optimization using central composite design, *Starch – Stärke*, 2013, **65**(7–8), 603–612.

398 K. A. Nayak, D. Pal and S. M. Hasnain, Development, Optimization and in vitro-in vivo Evaluation of Pioglitazone- Loaded Jackfruit Seed Starch-Alginate Beads, *Curr. Drug Delivery*, 2013, **10**(5), 608–619.

399 A. K. Nayak, *et al.*, Soluble starch-blended Ca2+-Zn2+-alginate composites-based microparticles of aceclofenac: Formulation development and in vitro characterization, *Future J. Pharm. Sci.*, 2018, **4**(1), 63–70.

400 J. Dziadkowiec, *et al.*, Preparation, characterization and application in controlled release of Ibuprofen-loaded Guar Gum/Montmorillonite Bionanocomposites, *Appl. Clay Sci.*, 2017, **135**, 52–63.

401 S. Sharma, *et al.*, l-Alanine induced thermally stable self-healing guar gum hydrogel as potential drug vehicle for sustained release of hydrophilic drug, *Mater. Sci. Eng., C*, 2019, **99**, 1384–1391.

402 K. Dutta, *et al.*, An ex situ approach to fabricating nanosilica reinforced polyacrylamide grafted guar gum nanocomposites as an efficient biomaterial for transdermal drug delivery application, *New J. Chem.*, 2017, **41**(17), 9461–9471.

403 P. B. Kajjari, L. S. Manjeshwar and T. M. Aminabhavi, Novel interpenetrating polymer network hydrogel microspheres of chitosan and poly (acrylamide)-grafted-guar gum for controlled release of ciprofloxacin, *Ind. Eng. Chem. Res.*, 2011, **50**(23), 13280–13287.

404 A. Giri, *et al.*, Tailoring carboxymethyl guargum hydrogel with nanosilica for sustained transdermal release of diclofenac sodium, *Carbohydr. Polym.*, 2012, **87**(2), 1532–1538.

405 A. Giri, *et al.*, Polymer hydrogel from carboxymethyl guar gum and carbon nanotube for sustained trans-dermal release of diclofenac sodium, *Int. J. Biol. Macromol.*, 2011, **49**(5), 885–893.

406 A. Butt, *et al.*, Controlled release of cephradine by biopolymers based target specific crosslinked hydrogels, *Int. J. Biol. Macromol.*, 2019, **121**, 104–112.

407 W. Lohcharoenkal, *et al.*, Protein Nanoparticles as Drug Delivery Carriers for Cancer Therapy, *BioMed Res. Int.*, 2014, **2014**, 180549.

408 M. Foox and M. Zilberman, Drug delivery from gelatin-based systems, *Expert Opin. Drug Delivery*, 2015, **12**(9), 1547–1563.

409 E. J. Lee, *et al.*, Studies on the characteristics of drug-loaded gelatin nanoparticles prepared by nanoprecipitation, *Bioprocess Biosyst. Eng.*, 2012, **35**(1), 297–307.

410 A. O. Elzoghby, Gelatin-based nanoparticles as drug and gene delivery systems: reviewing three decades of research, *J. Controlled Release*, 2013, **172**(3), 1075–1091.

411 G. Zhang, *et al.*, DOX-loaded folate-mediated pH-responsive micelle based on Bletilla striata polysaccharide: Release mechanism, cellular uptake mechanism, distribution, pharmacokinetics, and antitumor effects, *Int. J. Biol. Macromol.*, 2020, **164**, 566–577.

412 A. C. d. J. Oliveira, *et al.*, Microwave-initiated rapid synthesis of phthalated cashew gum for DDS, *Carbohydr. Polym.*, 2021, **254**, 117226.

413 Z. Negahban, S. A. Shojaosadati and S. Hamedi, A novel self-assembled micelles based on stearic acid modified schizophyllan for efficient delivery of paclitaxel, *Colloids Surf., B*, 2021, **199**, 111524.

414 R. J. Babu, *et al.*, Formulation of controlled release gellan gum macro beads of amoxicillin, *Curr. Drug Delivery*, 2010, **7**(1), 36–43.

415 M. Narkar, P. Sher and A. Pawar, Stomach-specific controlled release gellan beads of acid-soluble drug prepared by ionotropic gelation method, *AAPS PharmSciTech*, 2010, **11**(1), 267–277.

416 H. Bera, S. Boddupalli and A. K. Nayak, Mucoadhesive-floating zinc-pectinate–sterculia gum interpenetrating polymer network beads encapsulating ziprasidone HCl, *Carbohydr. Polym.*, 2015, **131**, 108–118.

417 A. Nayak, D. Pal and K. Santra, Development of calcium pectinate-tamarind seed polysaccharide mucoadhesive beads containing metformin HCl, *Carbohydr. Polym.*, 2014, **101**, 220–230.

418 P. Basim, S. Gorityala and M. Kurakula, Advances in Functionalized Hybrid Biopolymer Augmented Lipid-based Systems: A Spotlight on Their Role in Design of Gastro Retentive Delivery Systems, *Arch. Gastroenterol. Res.*, 2021, **2**(1), 35–47.

419 S. Nagarajan, *et al.*, Overview of Protein-Based Biopolymers for Biomedical Application, *Macromol. Chem. Phys.*, 2019, **220**(14), 1900126.

420 E. Quinlan, *et al.*, Development of collagen–hydroxyapatite scaffolds incorporating PLGA and alginate microparticles for the controlled delivery of rhBMP-2 for bone tissue engineering, *J. Controlled Release*, 2015, **198**, 71–79.

421 X. Zhang, K. Tang and X. Zheng, Electrospinning and Crosslinking of COL/PVA Nanofiber-microsphere Containing Salicylic Acid for Drug Delivery, *J. Bionic Eng.*, 2016, **13**(1), 143–149.

422 E. K. Tsekoura, *et al.*, Battling bacterial infection with hexamethylene diisocyanate cross-linked and Cefaclor-loaded collagen scaffolds, *Biomed. Mater.*, 2017, **12**(3), 035013.

423 R. Khan and M. H. Khan, Use of collagen as a biomaterial: An update, *J. Indian Soc. Periodontol.*, 2013, **17**(4), 539–542.

424 W. Liu, M. Griffith and F. Li, Alginate microsphere-collagen composite hydrogel for ocular drug delivery and implantation, *J. Mater. Sci.: Mater. Med.*, 2008, **19**(11), 3365–3371.

425 Z. Liu, *et al.*, Study of an alginate/HPMC-based in situ gelling ophthalmic delivery system for gatifloxacin, *Int. J. Pharm.*, 2006, **315**(1–2), 12–17.

426 S. Anandhakumar, *et al.*, Preparation of collagen peptide functionalized chitosan nanoparticles by ionic gelation method: An effective carrier system for encapsulation and release of DOX for cancer drug delivery, *Mater. Sci. Eng. C*, 2017, **70**, 378–385.

427 D. Choi, *et al.*, Nano-film coatings onto collagen hydrogels with desired drug release, *J. Ind. Eng. Chem.*, 2016, **36**, 326–333.
428 G. T. Tihan, *et al.*, Chloramphenicol collagen sponges for local drug delivery in dentistry, *C. R. Chim.*, 2015, **18**(9), 986–992.
429 G. T. Tihan, *et al.*, Collagen-based biomaterials for ibuprofen delivery, *C. R. Chim.*, 2016, **19**(3), 390–394.
430 G. Voicu, *et al.*, Synthesis, characterization and bioevaluation of drug-collagen hybrid materials for biomedical applications, *Int. J. Pharm.*, 2016, **510**(2), 474–484.
431 H. Nejat, *et al.*, Preparation and characterization of cardamom extract-loaded gelatin nanoparticles as effective targeted drug delivery system to treat glioblastoma, *React. Funct. Polym.*, 2017, **120**, 46–56.
432 A. Salerno, *et al.*, Hybrid gelatin-based porous materials with a tunable multiscale morphology for tissue engineering and drug delivery, *Eur. Polym. J.*, 2018, **99**, 230–239.
433 L. S. Dolci, *et al.*, Non-equilibrium atmospheric pressure plasma as innovative method to crosslink and enhance mucoadhesion of econazole-loaded gelatin films for buccal drug delivery, *Colloids Surf., B*, 2018, **163**, 73–82.
434 R. Brito-Pereira, *et al.*, Silk fibroin-magnetic hybrid composite electrospun fibers for tissue engineering applications, *Composites, Part B*, 2018, **141**, 70–75.
435 S. Sotome, *et al.*, Synthesis and in vivo evaluation of a novel hydroxyapatite/collagen–alginate as a bone filler and a drug delivery carrier of bone morphogenetic protein, *Mater. Sci. Eng. C*, 2004, **24**(3), 341–347.
436 M. V. Natu, *et al.*, Controlled release gelatin hydrogels and lyophilisates with potential application as ocular inserts, *Biomed. Mater.*, 2007, **2**(4), 241–249.
437 A. Bandiera, *et al.*, Stimuli-induced release of compounds from elastin biomimetic matrix, *Biomacromolecules*, 2014, **15**(1), 416–422.
438 S. Nagarajan, *et al.*, Overview of Protein-Based Biopolymers for Biomedical Application, *Macromol. Chem. Phys.*, 2019, **220**(14), 1900126.
439 A. Bandiera, *et al.*, Composite of Elastin-Based Matrix and Electrospun Poly(L-Lactic Acid) Fibers: A Potential Smart Drug Delivery System, *Front. Bioeng. Biotechnol.*, 2018, **6**, 127.
440 S. H. Park, H. S. Shin and S. N. Park, A novel pH-responsive hydrogel based on carboxymethyl cellulose/2-hydroxyethyl acrylate for transdermal delivery of naringenin, *Carbohydr. Polym.*, 2018, **200**, 341–352.
441 M. Khamrai, *et al.*, Curcumin entrapped gelatin/ionically modified bacterial cellulose based self-healable hydrogel film: An eco-friendly sustainable synthesis method of wound healing patch, *Int. J. Biol. Macromol.*, 2019, **122**, 940–953.
442 A. Anderson, *et al.*, Electrochemically Controlled Dissolution of Nanocarbon–Cellulose Acetate Phthalate Microneedle Arrays, *ACS Appl. Mater. Interfaces*, 2019, **11**(39), 35540–35547.
443 W. Simchareon, *et al.*, Characterization of Natural Rubber Latex Film Containing Various Enhancers, *Procedia Chem.*, 2012, **4**, 308–312.
444 M. Rahim, M. R. H. M. Haris and N. U. Saqib, An overview of polymeric nano-biocomposites as targeted and controlled-release devices, *Biophys. Rev.*, 2020, 1–9.
445 S. Han, *et al.*, Alkylation of human hair keratin for tunable hydrogel erosion and drug delivery in tissue engineering applications, *Acta Biomater.*, 2015, **23**, 201–213.
446 Y. Dou, *et al.*, Keratin/Polyvinyl Alcohol Blend Films Cross-Linked by Dialdehyde Starch and Their Potential Application for Drug Release, *Polymers*, 2015, **7**(3), 580–591.
447 Y. Li, *et al.*, Preparation and characterization of DOX loaded keratin nanoparticles for pH/GSH dual responsive release, *Mater. Sci. Eng., C*, 2017, **73**, 189–197.
448 A. O. Elzoghby, W. M. Samy and N. A. Elgindy, Albumin-based nanoparticles as potential controlled release DDS, *J. Controlled Release*, 2012, **157**(2), 168–182.
449 B. Elsadek and F. Kratz, Impact of albumin on drug delivery — New applications on the horizon, *J. Controlled Release*, 2012, **157**(1), 4–28.
450 C. Ju, *et al.*, Sequential intra-intercellular nanoparticle delivery system for deep tumor penetration, *Angew. Chem., Int. Ed. Engl.*, 2014, **53**(24), 6253–6258.
451 M. L. P. Vidallon, F. Yu and B. M. Teo, Controlling the Size and Polymorphism of Calcium Carbonate Hybrid Particles Using Natural Biopolymers, *Cryst. Growth Des.*, 2020, **20**(2), 645–652.
452 Y. Okamoto, *et al.*, Albumin-Encapsulated Liposomes: A Novel Drug Delivery Carrier With Hydrophobic Drugs Encapsulated in the Inner Aqueous Core, *J. Pharm. Sci.*, 2018, **107**(1), 436–445.
453 S. Perteghella, *et al.*, Stem cell-extracellular vesicles as DDS: New frontiers for silk/curcumin nanoparticles, *Int. J. Pharm.*, 2017, **520**(1), 86–97.
454 M. J. de Jesús Valle, *et al.*, Development and In Vitro Evaluation of a Novel Drug Delivery System (Albumin Microspheres Containing Liposomes) Applied to Vancomycin, *J. Pharm. Sci.*, 2016, **105**(7), 2180–2187.
455 Y. Iwao, *et al.*, Inflamed site-specific drug delivery system based on the interaction of human serum albumin nanoparticles with myeloperoxidase in a murine model of experimental colitis, *Eur. J. Pharm. Biopharm.*, 2018, **125**, 141–147.
456 R. P. Das, *et al.*, Tuning the binding, release and cytotoxicity of hydrophobic drug by Bovine Serum Albumin nanoparticles: Influence of particle size, *Colloids Surf., B*, 2017, **158**, 682–688.
457 H. Nosrati, *et al.*, Bovine Serum Albumin (BSA) coated iron oxide magnetic nanoparticles as biocompatible carriers for curcumin-anticancer drug, *Bioorg. Chem.*, 2018, **76**, 501–509.
458 M. Benkő, *et al.*, Bovine serum albumin-sodium alkyl sulfates bioconjugates as DDS, *Colloids Surf., B*, 2015, **130**, 126–132.
459 N. Taneja and K. K. Singh, Rational design of polysorbate 80 stabilized human serum albumin nanoparticles

tailored for high drug loading and entrapment of irinotecan, *Int. J. Pharm.*, 2018, **536**(1), 82–94.
460 A. A. A. Smith, *et al.*, Albumin–Polymer–Drug Conjugates: Long Circulating, High Payload Drug Delivery Vehicles, *ACS Macro Lett.*, 2016, **5**(10), 1089–1094.
461 G. Zhou, *et al.*, Human serum albumin nanoparticles as a novel delivery system for cabazitaxel, *Anticancer Res.*, 2016, **36**(4), 1649–1656.
462 S. Sebak, *et al.*, Human serum albumin nanoparticles as an efficient noscapine drug delivery system for potential use in breast cancer: preparation and in vitro analysis, *Int. J. Nanomed.*, 2010, **5**, 525–532.
463 Y. Jiang, *et al.*, PEGylated Albumin-Based Polyion Complex Micelles for Protein Delivery, *Biomacromolecules*, 2016, **17**(3), 808–817.
464 L. Chen, *et al.*, A Redox-Sensitive Micelle-Like Nanoparticle Self-Assembled from Amphiphilic Adriamycin-Human Serum Albumin Conjugates for Tumor Targeted Therapy, *BioMed Res. Int.*, 2015, **2015**, 987404.
465 F. P. Seib, *et al.*, Focal therapy of neuroblastoma using silk films to deliver kinase and chemotherapeutic agents in vivo, *Acta Biomater.*, 2015, **20**, 32–38.
466 L. P. Yan, *et al.*, Core-shell silk hydrogels with spatially tuned conformations as drug-delivery system, *J. Tissue Eng. Regener. Med.*, 2017, **11**(11), 3168–3177.
467 L. Xiao, *et al.*, Direct formation of silk nanoparticles for drug delivery, *ACS Biomater. Sci. Eng.*, 2016, **2**(11), 2050–2057.
468 E. Wenk, *et al.*, Silk fibroin spheres as a platform for controlled drug delivery, *J. Controlled Release*, 2008, **132**(1), 26–34.
469 B. Mao, *et al.*, Cyclic cRGDfk peptide and Chlorin e6 functionalized silk fibroin nanoparticles for targeted drug delivery and photodynamic therapy, *Biomaterials*, 2018, **161**, 306–320.
470 Y. Zhou, *et al.*, Photopolymerized maleilated chitosan/methacrylated silk fibroin micro/nanocomposite hydrogels as potential scaffolds for cartilage tissue engineering, *Int. J. Biol. Macromol.*, 2018, **108**, 383–390.
471 M. A. Marin, R. R. Mallepally and M. A. McHugh, Silk fibroin aerogels for drug delivery applications, *J. Supercrit. Fluids*, 2014, **91**, 84–89.
472 Y. Dong, *et al.*, Fabrication and characterization of silk fibroin-coated liposomes for ocular drug delivery, *Eur. J. Pharm. Biopharm.*, 2015, **91**, 82–90.
473 K.-L. Mao, *et al.*, Skin-penetrating polymeric nanoparticles incorporated in silk fibroin hydrogel for topical delivery of curcumin to improve its therapeutic effect on psoriasis mouse model, *Colloids Surf., B*, 2017, **160**, 704–714.
474 B. Subia, *et al.*, Folate conjugated silk fibroin nanocarriers for targeted drug delivery, *Integr. Biol.*, 2014, **6**(2), 203–214.
475 A. K. M. M. Alam and Q. T. H. Shubhra, Surface modified thin film from silk and gelatin for sustained drug release to heal wound, *J. Mater. Chem. B*, 2015, **3**(31), 6473–6479.
476 H. Zhang, *et al.*, Multifunctional iron oxide/silk-fibroin (Fe3O4–SF) composite microspheres for the delivery of cancer therapeutics, *RSC Adv.*, 2014, **4**(78), 41572–41577.
477 S. Wang, *et al.*, Colloidal Stability of Silk Fibroin Nanoparticles Coated with Cationic Polymer for Effective Drug Delivery, *ACS Appl. Mater. Interfaces*, 2015, **7**(38), 21254–21262.
478 S. Cao, *et al.*, Shape-dependent biodistribution of biocompatible silk microcapsules, *ACS Appl. Mater. Interfaces*, 2019, **11**(5), 5499–5508.
479 H. Wang, *et al.*, Fabrication of silk microcapsules by layer-by-layer desolvation, *Mater. Lett.*, 2019, **237**, 109–112.
480 J. Kundu, *et al.*, Silk fibroin nanoparticles for cellular uptake and control release, *Int. J. Pharm.*, 2010, **388**(1–2), 242–250.
481 T. Wongpinyochit, *et al.*, PEGylated silk nanoparticles for anticancer drug delivery, *Biomacromolecules*, 2015, **16**(11), 3712–3722.
482 D. Hu, *et al.*, Self-stabilized silk sericin-based nanoparticles: In vivo biocompatibility and reduced DOX-induced toxicity, *Acta Biomater.*, 2018, **74**, 385–396.
483 J. Wu, *et al.*, Control of silk microsphere formation using polyethylene glycol (PEG), *Acta Biomater.*, 2016, **39**, 156–168.
484 Q. Wang, *et al.*, Facile fabrication of silk fibroin microspheres via electrostatic assembly, *Mater. Res. Express*, 2018, **5**(7), 075401.
485 Z. Cao, *et al.*, The preparation of regenerated silk fibroin microspheres, *Soft Matter*, 2007, **3**(7), 910–915.
486 X. Wang, *et al.*, Injectable silk-polyethylene glycol hydrogels, *Acta Biomater.*, 2015, **12**, 51–61.
487 Z. Yin, *et al.*, Swellable silk fibroin microneedles for transdermal drug delivery, *Int. J. Biol. Macromol.*, 2018, **106**, 48–56.
488 S. Wang, *et al.*, Insulin-loaded silk fibroin microneedles as sustained release system, *ACS Biomater. Sci. Eng.*, 2019, **5**(4), 1887–1894.
489 K. Tsioris, *et al.*, Fabrication of silk microneedles for controlled-release drug delivery, *Adv. Funct. Mater.*, 2012, **22**(2), 330–335.
490 S. S. Silva, *et al.*, Fabrication and characterization of Eri silk fibers-based sponges for biomedical application, *Acta Biomater.*, 2016, **32**, 178–189.
491 E. M. Pritchard, *et al.*, Antibiotic-releasing silk biomaterials for infection prevention and treatment, *Adv. Funct. Mater.*, 2013, **23**(7), 854–861.
492 T. Mirshahi, *et al.*, Adaptive Immune Responses of Legumin Nanoparticles, *J. Drug Targeting*, 2002, **10**(8), 625–631.
493 A. González, *et al.*, Crosslinked soy protein films and their application as ophthalmic drug delivery system, *Mater. Sci. Eng. C*, 2015, **51**, 73–79.
494 P. Guerrero, *et al.*, Functional properties of films based on soy protein isolate and gelatin processed by compression molding, *J. Food Eng.*, 2011, **105**(1), 65–72.
495 M. Maviah, *et al.*, Food Protein-Based Nanodelivery Systems for Hydrophobic and Poorly Soluble Compounds, *AAPS PharmSciTech*, 2020, **21**, 101.

496 A. Maltais, G. E. Remondetto and M. Subirade, Tabletted soy protein cold-set hydrogels as carriers of nutraceutical substances, *Food Hydrocolloids*, 2010, **24**(5), 518–524.

497 M. A. Farooq, *et al.*, Whey protein: A functional and promising material for DDS recent developments and future prospects, *Polym. Adv. Technol.*, 2019, **30**(9), 2183–2191.

498 S. Kumar and S. K. Singh, In silico-in vitro-in vivo studies of experimentally designed carvedilol loaded silk fibroin-casein nanoparticles using physiological based pharmacokinetic model, *Int. J. Biol. Macromol.*, 2017, **96**, 403–420.

499 J. Zhu, Bioactive modification of poly(ethylene glycol) hydrogels for tissue engineering, *Biomaterials*, 2010, **31**(17), 4639–4656.

500 A. O. Elzoghby, *et al.*, Swellable floating tablet based on spray-dried casein nanoparticles: near-infrared spectral characterization and floating matrix evaluation, *Int. J. Pharm.*, 2015, **491**(1–2), 113–122.

501 L. Chen and M. Subirade, Alginate–whey protein granular microspheres as oral delivery vehicles for bioactive compounds, *Biomaterials*, 2006, **27**(26), 4646–4654.

502 G. M. Tavares, *et al.*, Milk proteins as encapsulation devices and delivery vehicles: Applications and trends, *Trends Food Sci. Technol.*, 2014, **37**(1), 5–20.

503 A. Mohandas, *et al.*, Chitosan based metallic nanocomposite scaffolds as antimicrobial wound dressings, *Bioact. Mater.*, 2018, **3**(3), 267–277.

504 M. A. Arangoa, *et al.*, Bioadhesive potential of gliadin nanoparticulate systems, *Eur. J. Pharm. Sci.*, 2000, **11**(4), 333–341.

505 C. Duclairoir, *et al.*, Evaluation of gliadins nanoparticles as DDS: a study of three different drugs, *Int. J. Pharm.*, 2003, **253**(1), 133–144.

506 W. He, *et al.*, Formulating food protein-stabilized indomethacin nanosuspensions into pellets by fluid-bed coating technology: physical characterization, redispersibility, and dissolution, *Int. J. Nanomed.*, 2013, **8**, 3119.

507 W. He, *et al.*, Food proteins as novel nanosuspension stabilizers for poorly water-soluble drugs, *Int. J. Pharm.*, 2013, **441**(1–2), 269–278.

508 T. Geng, *et al.*, Comparative study on stabilizing ability of food protein, non-ionic surfactant and anionic surfactant on BCS type II drug carvedilol loaded nanosuspension: Physicochemical and pharmacokinetic investigation, *Eur. J. Pharm. Sci.*, 2017, **109**, 200–208.

509 E. Assadpour, S.-M. Jafari and Y. Maghsoudlou, Evaluation of folic acid release from spray dried powder particles of pectin-whey protein nano-capsules, *Int. J. Biol. Macromol.*, 2017, **95**, 238–247.

510 W. He, *et al.*, Food protein-stabilized nanoemulsions as potential delivery systems for poorly water-soluble drugs: preparation, in vitro characterization, and pharmacokinetics in rats, *Int. J. Nanomed.*, 2011, **6**, 521.

511 M. Li, Y. Ma and J. Cui, Whey-protein-stabilized nanoemulsions as a potential delivery system for water-insoluble curcumin, *LWT–Food Sci. Technol.*, 2014, **59**(1), 49–58.

512 A. F. Esfanjani, S. M. Jafari and E. Assadpour, Preparation of a multiple emulsion based on pectin-whey protein complex for encapsulation of saffron extract nanodroplets, *Food Chem.*, 2017, **221**, 1962–1969.

513 S. Parthasarathi and C. Anandharamakrishnan, Enhancement of oral bioavailability of vitamin E by spray-freeze drying of whey protein microcapsules, *Food Bioprod. Process.*, 2016, **100**, 469–476.

514 Z. Fang, *et al.*, Partition and digestive stability of α-tocopherol and resveratrol/naringenin in whey protein isolate emulsions, *Int. Dairy J.*, 2019, **93**, 116–123.

515 W. Liu, *et al.*, On enhancing the solubility of curcumin by microencapsulation in whey protein isolate via spray drying, *J. Food Eng.*, 2016, **169**, 189–195.

516 H. Hsein, *et al.*, Atomization of denatured whey proteins as a novel and simple way to improve oral drug delivery system properties, *Int. J. Biol. Macromol.*, 2017, **105**, 801–809.

517 E. Déat-Lainé, *et al.*, Efficacy of mucoadhesive hydrogel microparticles of whey protein and alginate for oral insulin delivery, *Pharm. Res.*, 2013, **30**(3), 721–734.

518 G. J. O'Neill, *et al.*, In vitro and in vivo evaluation of whey protein hydrogels for oral delivery of riboflavin, *J. Funct. Foods*, 2015, **19**, 512–521.

519 F. Alavi, *et al.*, Cold gelation of curcumin loaded whey protein aggregates mixed with k-carrageenan: Impact of gel microstructure on the gastrointestinal fate of curcumin, *Food Hydrocolloids*, 2018, **85**, 267–280.

520 S. Owonubi, *et al.*, Characterization and in vitro release kinetics of antimalarials from whey protein-based hydrogel biocomposites, *Int. J. Ind. Chem.*, 2018, **9**(1), 39–52.

521 L. Lv, *et al.*, Thermally-induced whey protein isolate-daidzein co-assemblies: Protein-based nanocomplexes as an inhibitor of precipitation/crystallization for hydrophobic drug, *Food Chem.*, 2019, **275**, 273–281.

522 A. Jain, *et al.*, Lycopene loaded whey protein isolate nanoparticles: An innovative endeavor for enhanced bioavailability of lycopene and anti-cancer activity, *Int. J. Pharm.*, 2018, **546**(1–2), 97–105.

523 F. H. MAE, Preparation and Characterization of Sustained Released Zinc Citrate Encapsulated in Whey Protein Nanoparticles, *Pak. J. Biol. Sci.*, 2018, **21**(9), 448–453.

524 S. Shao, X. Shen and M. Guo, Zinc-loaded whey protein nanoparticles prepared by enzymatic cross-linking and desolvation, *Int. J. Food Sci. Technol.*, 2018, **53**(9), 2205–2211.

525 H. Hsein, *et al.*, Denatured whey protein powder as a new matrix excipient: design and evaluation of mucoadhesive tablets for sustained drug release applications, *Pharm. Res.*, 2017, **34**(2), 365–377.

526 R. Zhang, *et al.*, Succinylated whey protein isolate as a sustained-release excipient of puerarin derivative oral tablets: Preparation, optimization and pharmacokinetics, *Asian J. Pharm. Sci.*, 2018, **13**(4), 383–394.

527 J. Mishra, *et al.*, Whey proteins as stabilizers in amorphous solid dispersions, *Eur. J. Pharm. Sci.*, 2019, **128**, 144–151.
528 M. Mohammadian, *et al.*, Enhancing the aqueous solubility of curcumin at acidic condition through the complexation with whey protein nanofibrils, *Food Hydrocolloids*, 2019, **87**, 902–914.
529 Y. Zhang, *et al.*, Endogenous albumin-mediated delivery of redox-responsive paclitaxel-loaded micelles for targeted cancer therapy, *Biomaterials*, 2018, **183**, 243–257.
530 E. Lee, J. Lee and S. Jon, A Novel Approach to Oral Delivery of Insulin by Conjugating with Low Molecular Weight Chitosan, *Bioconjugate Chem.*, 2010, **21**(10), 1720–1723.
531 A. A. P. Mansur, S. M. de Carvalho and H. S. Mansur, Bioengineered quantum dot/chitosan-tripeptide nanoconjugates for targeting the receptors of cancer cells, *Int. J. Biol. Macromol.*, 2016, **82**, 780–789.
532 S. Lee, N. S. A. Alwahab and Z. M. Moazzam, Zein-based oral drug delivery system targeting activated macrophages, *Int. J. Pharm.*, 2013, **454**(1), 388–393.
533 K. Hu, *et al.*, Core–shell biopolymer nanoparticle delivery systems: Synthesis and characterization of curcumin fortified zein–pectin nanoparticles, *Food Chem.*, 2015, **182**, 275–281.
534 Z. Chen, *et al.*, Bioresponsive Hyaluronic Acid-Capped Mesoporous Silica Nanoparticles for Targeted Drug Delivery, *Chem. - Eur. J.*, 2013, **19**(5), 1778–1783.
535 T. Muthukumar, J. E. Song and G. Khang, Biological Role of Gellan Gum in Improving Scaffold Drug Delivery, Cell Adhesion Properties for Tissue Engineering Applications, *Molecules*, 2019, **24**(24), 4514.
536 S. Dhar, *et al.*, Biocompatible gellan gum-reduced gold nanoparticles: cellular uptake and subacute oral toxicity studies, *J. Appl. Toxicol.*, 2011, **31**(5), 411–420.
537 S. Dhar, *et al.*, Natural gum reduced/stabilized gold nanoparticles for drug delivery formulations, *Chem. – Eur. J.*, 2008, **14**(33), 10244–10250.
538 S. Vieira, *et al.*, Gellan gum-coated gold nanorods: an intracellular nanosystem for bone tissue engineering, *RSC Adv.*, 2015, **5**(95), 77996–78005.
539 A. Gal and A. Nussinovitch, Hydrocolloid carriers with filler inclusion for diltiazem hydrochloride release, *J. Pharm. Sci.*, 2007, **96**(1), 168–178.
540 P. Vashisth, *et al.*, Ofloxacin loaded gellan/PVA nanofibers-Synthesis, characterization and evaluation of their gastroretentive/mucoadhesive drug delivery potential, *Mater. Sci. Eng. C*, 2017, **71**, 611–619.
541 M. Rostami, *et al.*, Development of resveratrol loaded chitosan-gellan nanofiber as a novel gastrointestinal delivery system, *Int. J. Biol. Macromol.*, 2019, **135**, 698–705.
542 M. Arjama, *et al.*, Sericin/RBA embedded gellan gum based smart nanosystem for pH responsive drug delivery, *Int. J. Biol. Macromol.*, 2018, **120**, 1561–1571.
543 S. Pacelli, *et al.*, Design of a tunable nanocomposite double network hydrogel based on gellan gum for drug delivery applications, *Eur. Polym. J.*, 2018, **104**, 184–193.
544 E. Elmowafy, *et al.*, In situ composite ion-triggered gellan gum gel incorporating amino methacrylate copolymer microparticles: a therapeutic modality for buccal applicability, *Pharm. Dev. Technol.*, 2019, **24**(10), 1258–1271.
545 O. Novac, *et al.*, Antibacterial quaternized gellan gum based particles for controlled release of ciprofloxacin with potential dermal applications, *Mater. Sci. Eng. C*, 2014, **35**, 291–299.
546 H. Bera, S. Kumar and S. Maiti, Facile synthesis and characterization of tailor-made pectin-gellan gum-bionanofiller composites as intragastric drug delivery shuttles, *Int. J. Biol. Macromol.*, 2018, **118**(Pt A), 149–159.
547 Q. Liang, *et al.*, A gum Arabic assisted sustainable drug delivery system for adult Drosophila, *Biol. Open*, 2020, **9**(6), 052241.
548 B. A. Aderibigbe, *et al.*, Kinetic release studies of nitrogen-containing bisphosphonate from gum acacia crosslinked hydrogels, *Int. J. Biol. Macromol.*, 2015, **73**, 115–123.
549 V. P. Padmanabhan, R. Kulandaivelu and S. Nellaiappan, New core-shell hydroxyapatite/Gum-Acacia nanocomposites for drug delivery and tissue engineering applications, *Mater. Sci. Eng., C*, 2018, **92**, 685–693.
550 B. Aderibigbe, *et al.*, Controlled dual release study of curcumin and a 4-aminoquinoline analog from gum acacia containing hydrogels, *J. Appl. Polym. Sci.*, 2015, **132**(10), 41613.
551 B. Singh and A. Dhiman, Design of Acacia Gum–Carbopol–Cross-Linked-Polyvinylimidazole Hydrogel Wound Dressings for Antibiotic/Anesthetic Drug Delivery, *Ind. Eng. Chem. Res.*, 2016, **55**(34), 9176–9188.