An Up-to-Date Review on Alginate Nanoparticles and Nanofibers for Biomedical and Pharmaceutical Applications

Andrea Dodero,* Stefano Alberti, Giulia Gaggero, Maurizio Ferretti, Rodolfo Botter, Silvia Vicini, and Maila Castellano*

Alginate is a naturally occurring polysaccharide commonly derived from brown algae cell walls which possesses unique features that make it extremely promising for several biomedical and pharmaceutical purposes. Alginate biomaterials are indeed nowadays gaining increasing interest in drug delivery and tissue engineering applications owing to their intrinsic biocompatibility, nontoxicity, versatility, low cost, and ease of functionalization. Specifically, alginate-based nanostructures show enhanced capabilities with respect to alginate bulk materials in the targeted delivery of drugs and chemotherapies, as well as in helping tissue reparation and regeneration. Hence, it is not surprising that the number of scientific reports related to this topic have rapidly grown in the last decade. With these premises, the present review aims to provide a comprehensive state-of-the-art of the most recent advances in the preparation of alginate-based nanoparticles and electrospun nanofibers for drug delivery, cancer therapy, and tissue engineering purposes. After a short introduction concerning the general properties and uses of alginate and the concept of nanotechnology, the recent literature is then critically presented to highlight the main advantages of alginate-based nanostructures. Finally, the current limitations and the future perspectives and objectives are discussed in detail.

1. Introduction

Alginate is a marine-derived biopolymer with unique biological properties and it holds great promise in several industrial fields including the fabrication of novel materials for biomedical, pharmaceutical, food, and environmental purposes.[1,2] Alginate is one of the most abundant materials in nature and,

along with other polysaccharides (e.g., celluloses, chitosan, etc.), is indeed considered an extremely promising material in the viewpoint of circular economy and in substituting petroleum-derived polymers.[3] Among others, one of the reasons for alginate success is its unique capability to bind different cations leading to stable and tailor-made hydrogels.[4] Owing to its biocompatibility, biodegradability, and nontoxicity, in the past decades alginate has been vastly explored for drug and gene delivery, tissue engineering, and wound healing applications.[5] In this sense, the recent nanotechnological advances have allowed the fabrication and exploitation of alginate-based nanostructured materials with completely new capabilities. Thereby, it is not surprising that nowadays a broad variety of alginate-based nanomaterials with various shapes, sizes, and compositions are prepared via different approaches, including controlled gelation, electrospinning and electrospraying, self-assembly, phase-separation, and microfluidics., All these nanostructures hold the potential to interact with living organisms much more efficiently with respect to bulk systems, hence leading to specific functionalities at the same time avoiding the occurrence of toxicity issues.[6–8]

Despite the use of alginate-based nanomaterials has been reviewed in the past, the focus has been commonly pointed to their generic properties and applications. Conversely, this review attempts to provide a more specific and comprehensive summary limited to the most recent advances in the fabrication and use of two of the most common and promising alginate-based nanomaterials, namely nanoparticles (NPs) and electrospun nanofibers (NFs), with a focus on biomedical and pharmaceutical applications.

A. Dodero, S. Alberti, M. Ferretti, S. Vicini, M. Castellano
Department of Chemistry and Industrial Chemistry
Università degli Studi di Genova
Via Dodecaneso 31, Genoa 16146, Italy
E-mail: andrea.dodero@edu.unige.it; maila.castellano@unige.it
G. Gaggero, R. Botter
Department of Civil, Chemical and Environmental Engineering
Università degli Studi di Genova
Via All'Opera Pia 15, Genoa 16145, Italy

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/admi.202100809.

2. Alginate

2.1. Structure and Physical–Chemical Properties

Alginate (Alg) represents a class of naturally occurring anionic polysaccharides consisting of linear copolymers containing blocks of β-D-mannuronate (i.e., M units) and α-L-guluronate (i.e., G units) residues linked by β-glycosidic bonds (i.e., β—1,4

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
MATERIALS
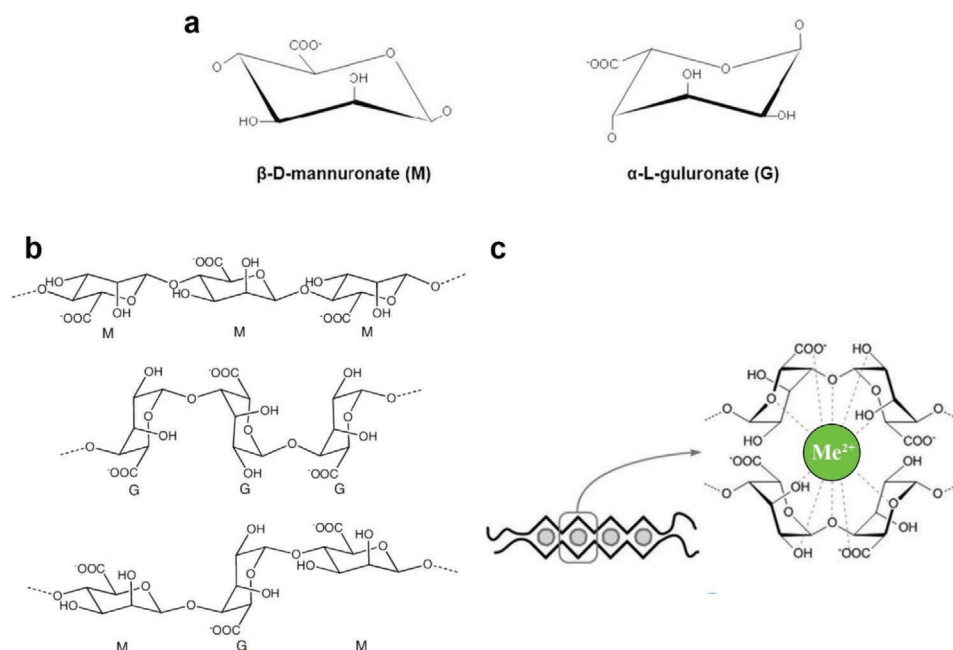INTERFACES**

www.advmatinterfaces.de

Figure 1. a) Alginate monomer structural units, b) alginate block distribution and chain conformation, and c) alginate egg-box gelation model with divalent cations.

linkages), as shown in **Figure 1**a.[5,9] Alginate is mainly found in the cell wall of brown algae (*Phaeophycea*), with the currently commercially available materials being commonly derived from *Laminaria hyperborean*, *Laminaria digitata*, *Laminaria japonica*, *Ascophyllum nodosum*, and *Macrocystis pyrifera* species. Alginate extraction is an uncomplicated but multi-step procedure, which is usually carried out via aqueous acid and alkali solution treatments, salt-induced precipitation, and subsequent purification.[10,11] However, it is noteworthy that the bacterial biosynthesis of alginate has been as well explored to produce products with controlled and tailor-made physical–chemical features.[12,13] As shown in Figure 1b, M and G units can be arranged either in consecutive homopolymer (i.e., MMM or GGG) or alternating heteropolymer blocks (i.e., MGM) depending on either the extraction procedure, the natural source, or the growth, the portion, and seasonal condition of the algae.[14] Additionally, such factors highly affect also the single block and the overall chain length (i.e., molecular weight) of alginate. Hence, it is not surprising that nowadays more than 200 different alginates presenting strongly dissimilar properties are produced.[15] Generally, the highest the content of G units, the greatest is the chain rigidity,[16,17] while the molecular weight usually varies between 30 and 400 kg mol^{-1}[18,19] playing a fundamental role in affecting alginate physical–chemical properties, including its biological activity.

Despite being soluble in water, the alginate capability to be solubilized strongly depends on its molecular weight and composition (i.e., M/G ratio), as well as on the pH value and ionic strength of the aqueous environment. One of the most intriguing properties of alginate, which, by the way, allows its wide industrial exploitation, consists in the capability to form gels via the coordination of divalent (e.g., Ca^{2+}, Sr^{2+}, Ba^{2+}, etc.) or trivalent cations (e.g., Al^{3+}, Fe^{3+}, etc.), as well as in acid conditions due to the polymer chain shrinkage.[20] Specifically,

such a mechanism is known as the egg-box model (Figure 1c) and it generally describes two antiparallel alginate chains that electrostatically interact with positively charged ions via their negatively charged carboxyl groups to form polyelectrolyte complexes (PECs).[4,21,22] Besides the strength of alginate-based gels depends on various factors (e.g., pH, temperature, ion type, etc.), M/G ratio is broadly considered the most important one. Indeed, only G units are believed to promote the intermolecular crosslinking of alginate chains via the egg-box mechanism hence playing a crucial role in affecting the resultant gel physical–chemical properties. Furthermore, also the molecular weight of alginate can markedly affect its gel-forming capabilities with longer chains presenting faster gelling rates, enhanced mechanical resistance, and higher elasticity.

Along with its native properties, owing to the modern-day chemical and biochemical advances, alginate can be enriched with new functionalities (e.g., hydrophobicity, the affinity for specific proteins, etc.) to meet specific needs.[23,24] By way of example, the hydroxyl groups can be modified by means of oxidation[25] and sulfation[26] reactions, whereas the carboxyl groups via esterification[27] and amidation[28] reactions. These chemical modifications can be exploited to fabricate "smart" alginate-based materials able to respond to external stimuli,[29,30] to enhance alginate capability to interact with cells controlling their growth and differentiation behavior,[31,32] or to increase the adsorption properties of alginate-based hydrogels for environmental applications.[33,34]

2.2. Biological Properties

Alginate is approved by the Food and Drug Administration (FDA)[35] and it possesses a variety of biological properties

2100809 (2 of 27)

that make him broadly exploited in the food, biomedical, and pharmaceutical industries.[5,36,37] It should be noted that, although the biocompatibility and immunogenicity of alginate have been extensively evaluated in vitro as well as in vivo, the impact of alginate composition is still controversial. Indeed, being alginate derived from natural sources, it can contain different impurities (e.g., heavy metals, endotoxins, proteins, and polyphenolic compounds) and so far this misunderstanding is most likely related to varying levels of purity in the alginate studied in different reports. However, alginate purified by multi-step extraction procedures does not usually induce any significant foreign body reaction.[38] Alginate is considered also a low or non-toxic natural polymer.[39,40] However, it is noteworthy that several studies have demonstrated that intravenous administrated alginate can be excreted by the renal system only for molecular weight lower than the renal clearance threshold, whereas longer macromolecules are retained in the circulation without accumulating in any tissue.[41] As a matter of fact, alginate cannot be degraded in mammals due to the lack of the specific enzyme (i.e., alginase), despite a potential approach to overcome such limitation consist of the partial oxidation of the polymer backbone.[42,43] Additionally, alginate has been often reported to display marked anti-oxidant, anti-inflammatory, and potential prebiotic activities.[44–46] A few studies also emphasize the anti-bacterial and anti-bacteriostatic properties of alginate-based materials explaining the mechanism either by taking into account the polymer backbone negative charges or chelation capabilities.[47–49] Yet, owing to the presence of free carboxyl and hydroxyl groups, alginate shows excellent mucoadhesive properties which play a topical role in mucosal delivery systems being able to enhance the efficiency and bioavailability of drugs.[50,51]

2.3. Industrial, Biomedical, and Pharmaceutical Applications of Alginate

Alginate unique characteristics, such as biocompatibility, high availability, biodegradability, water-solubility, low immunogenicity, versatility, relatively low cost, thickening properties, and gelling abilities, expanded its use in recent years in several industrial fields.[52] For instance, nowadays alginate finds broad usability in the food industry where it is also considered an important source of dietary fibers.[36] Specifically, alginate-based edible films and coatings can be applied onto food product surfaces, thereby acting as a protective barrier able to preserve food quality and flavors.[53,54] Additionally, alginate gelling and thickening properties make it suitable also as an additive for food products, cosmetics, and paints.[55–57] Again, the presence of the surface carboxyl and hydroxyl functional groups on the alginate backbone, as well as its high water adsorption capabilities, makes alginate interesting also for environmental-related applications. Alginate-based materials have indeed shown great promises in capturing several chemical species from polluted sources.[20,58,59] Another reason for alginate success is related to the possibility to combine this polysaccharide with other natural (i.e., anionic or cationic polysaccharides, proteins, etc.) and synthetic polymers, with organic and/or inorganic fillers, and with bioactive substances.[60] Among all these applications, the biomedical and pharmaceutical industries represent the

most important ones.[5,52] Indeed, the unique properties of alginate make it an extremely promising biomaterial that can be employed basically in any form (i.e., hydrogels, films, fibers, and beads), shape, and size for several purposes. For instance, in the past decade alginate has been vastly investigated as scaffolding material in tissue engineering applications.[61,62] Alginate biomaterials have been successfully employed in the treatment of bone and cartilage injuries as they can be implanted with poorly invasive surgical procedures,[62,63] in cardiac applications as substituting heart valves owing to their non-thrombotic behavior,[64] and in wound healing and dressing patches due to their capability to reproduce the native extracellular matrix.[65–67] Additionally, a variety of drug delivery systems (DDS) based on alginate, including microcapsules, microparticles, gel particles, pellets, and beads, have been developed as well and proved to be able to promote drug stabilization and longer release.[68,69] Alginate-based materials offer also great promises in the targeted treatment of cancer[70,71] and the development of specific biosensors.[72,73] A summary of the most common uses of alginate is reported in **Figure 2**.

3. Alginate-Based Nanostructures

3.1. General Principles

Nanotechnology consists of a multidisciplinary scientific field related to the fabrication of materials with dimensions in the nanometer scale (i.e., 1 nm = 10^{-9} m) and usually sized between 0.1 and 100 nm. Nanotechnology belongs to the borders between physics, chemistry, biology, and engineering sciences, and it is nowadays recognized as one of the most promising tools in solving a wide variety of modern-day issues, including environmental pollution, food spoilage and waste, and health-related diseases.[74–78] Its applications are countless and can generate both economic and social effects by reducing costs, increasing efficiency, and considerably improving the human quality of life.[79] In the near future, these beneficial impacts will likewise expand into any aspect of everyday life with particular emphasis on life and health sciences with the development of completely new therapeutic, diagnostic, and imaging techniques.[80–82] For example, nanotechnology offers the possibility to monitor and control serious metabolic disorders (e.g., diabetes),[83] to perform genetic tests,[84,85] to help tissue regeneration,[86,87] to fight against cancer,[88,89] and to develop completely innovative drug administration dosage forms.[90,91] With these premises, it is not surprising that nanomedicine, which comprises nanotechnology, nanoengineering, and nanoscience, is nowadays one of the most investigated worldwide research fields.[92] All these unique possibilities arise from the fact that, at the nanoscale level, the material surface undergoes significant changes and it generates unexpected physical, chemical, and biological features with respect to the macroscopic scale.[93] For instance, the extraordinary increase in the surface-to-volume ratio leads to the exposition of a considerable number of active sites on their surface making nanomaterials capable to specifically interact with other materials and even with biological tissue. Thereby, they show excellent characteristics that go well beyond the biomedical and pharmaceutical fields. However, it should be noted
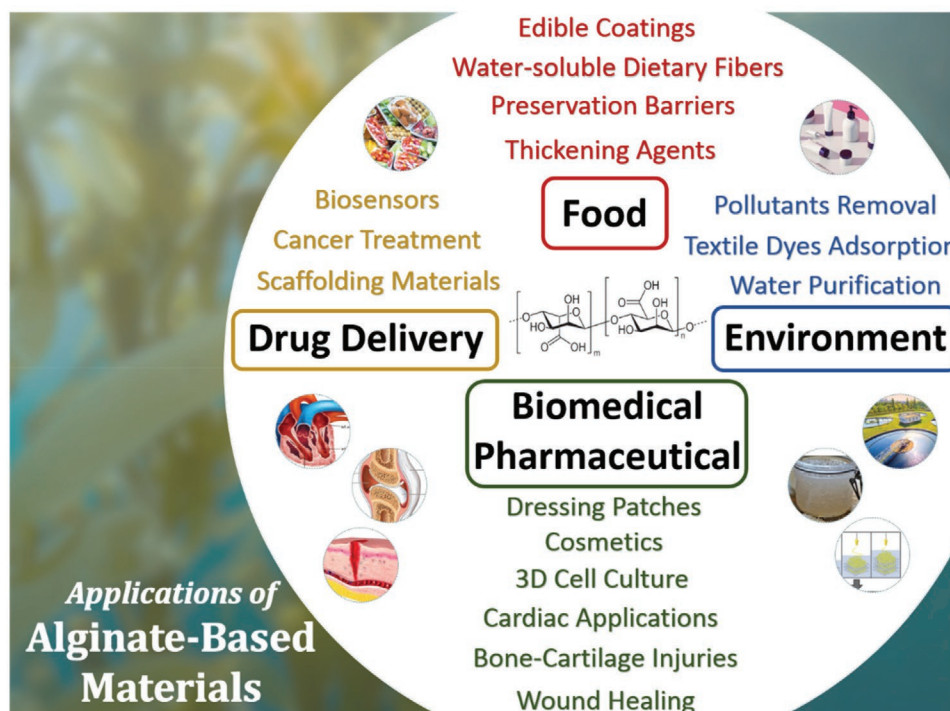
**ADVANCED
SCIENCE NEWS**
www.advancedsciencenews.com

**ADVANCED
MATERIALS
INTERFACES**
www.advmatinterfaces.de

Figure 2. Schematics of alginate applications.

that despite these unique properties offer many advantages, they may also cause serious side effects on the human body, and the health and environmental safety of modern nanotechnologies are still a contentious aspect.[94]

Nowadays nanostructures with different shapes and sizes can be obtained relatively easily, from both inorganic and organic materials due to the recent advances in nanofabrication techniques.[95] Among this variety of possibilities, alginate-based nanostructures have attracted a great deal of interest from both the academic and industry community due to their good biocompatibility and biodegradability, hence being considered safe to be applied in medicine.[8,96] Additionally, the great abundance, stability, and low cost make this and other polysaccharides extremely promising as raw materials to develop nanostructure for biomedical and pharmaceutical purposes. Specifically, some of the most important uses of alginate-based nanomaterials consist of, but are not limited to, antimicrobial products, drug and gene delivery, tissue engineering, cancer therapy, wound dressing, and biosensors.[15] In this sense, alginate is commonly employed to fabricate NPs, nanocapsules, NFs, and nanocoating, as well as nanostructured scaffolds, membranes, gels, beads, and sponge forms.[1] **Figure 3** schematically reports the most frequent applications of alginate-based nanostructures as biomedical and pharmaceutical products.

3.2. Alginate Nanoparticles

Among others, NPs are vastly the most explored alginate-based nanostructures in pharmaceutical applications.[101–104] Specifically, compared to the traditional dosage forms, NPs allow for the delivery of drugs and other substances (e.g., enzymes,

growth factors, vitamins, etc.) at the nanoscale level directly to the site of interest. Additionally, nanoparticle-based formulations can also help in enhancing the drug loading, thereby maximizing the pharmacological impact and minimizing the possible side effects.[105,106] To date, several approaches exist to fabricate alginate-based NPs. In this sense, the ion-induced gelation of alginate has been vastly exploited to fabricate carrier systems with a greater bioavailability of the traditional encapsulated drugs than other dosage forms.[107] Alternatively, also covalent crosslinking methodologies can be employed to prepare alginate-based NPs but may induce side reactions due to the high toxicity of common crosslinking agents (e.g., glutaraldehyde, epichlorohydrin, etc.).[108,109] Despite such approaches represent a simple and straightforward methodology to prepared drug-loaded NPs, they are generally coupled with other processing techniques in order to achieve better control of size, homogeneity, and drug loading. For example, the emulsification technique involves the deposition of an alginate layer on the surface of nanosized liquid droplets which contain the substance to be embedded. The obtained NPs are then stabilized via ionic and/or covalent crosslinking and then completely dried.[110,111] Another possibility is represented by the electrospraying technique, which comprises the application of an electric field to an alginate-based solution to induce the formation of NPs that are collected in a proper crosslinking medium.[112,113] Alternatively, alginate-based NPs can also be formed via a polyelectrolyte complexation phenomenon.[114] PECs are commonly prepared by mixing solutions of oppositely charged polyelectrolytes (e.g., alginate and chitosan), which then form nanostructures whose size and composition can be tuned by controlling the processing conditions.[115] In this sense, one of the most promising approaches to prepare alginate-based NPs consists
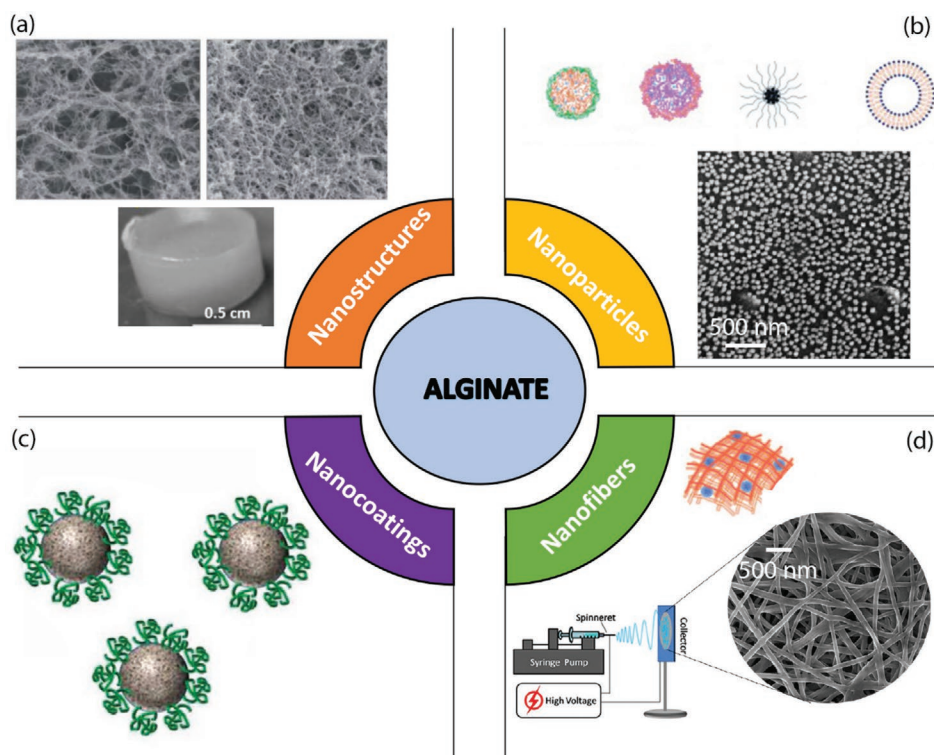
Figure 3. Schematics of the most common alginate-based nanomaterials. a) Nanostructured hydrogels. SEM micrographs on top: Reproduced under the terms of the CC-BY 3.0 license.[98] Copyright 2020, The Authors, published by Royal Society of Chemistry. Bottom image: Reproduced with permission.[97] Copyright 2015, Wiley Periodicals, Inc. b) Nanoparticles. Reproduced with permission.[99] Copyright 2012, Sharif University of Technology. Production and hosting by Elsevier B.V. c) Nanocoatings. Reproduced with permission.[100] Copyright 2014, Elsevier Ltd. d) Electrospun nanofibers. Reproduced with permission.[66] Copyright 2021, Elsevier B.V.

of the bottom-up layer-by-layer (LbL) self-assembly technology, which foresees the development of multilayer nanostructures (e.g., films, particles, scaffolds, foams, etc.) via the sequential use of aqueous solutions of oppositely charged polyelectrolytes.[116] Yet, the nanoparticle formation is also obtained via self-assembly methodologies by exploiting ad-hoc modified alginate in which hydrophobic moieties are covalently appended onto the polymer backbone.[117,118] These amphiphilic macromolecules can self-assemble into NPs via intra- and/or intermolecular hydrophobic interactions and hydrogen bonding under appropriate stimulation. Self-assembled nanostructures usually present unique characteristics, including the high biocompatibility of native alginate, and they may allow the encapsulation of hydrophobic substances.

Table 1 summarizes the main applications of alginate-based NPs along with the fabrication method, the encapsulated compounds, the presence of other organic or inorganic components, and the preferred administration route.

3.2.1. Drug Delivery

In the past years, Alg-NPs have been mostly investigated to prepare DDS for the treatment of various diseases as an alternative administration route with respect to oral intake and/or injection formulations.[102,119] As recently reviewed by Severino et al.,[101] coupling the unique biological properties of alginate with the capability of NPs to prolong drug half-life, improve the solubility of hydrophobic substances, and release the encapsulated compounds in a controlled manner may lead to a completely new class of pharmaceutical products. These concurrent features present a broad variety of advantages, including the possibility of modifications for site-specific targeting, biocompatibility, mucoadhesiveness, mechanical strength, gelation, and cell affinity. Additionally, the biodegradability of alginate represents a huge advantage when used as a nano-sized matrix for the development of DDS since it can be encapsulated, and eventually degraded, in the human tissues without any toxic effects during or after the release mechanism.[120,121] Noticeably, the unique ionic gelation capabilities of alginate have been hugely exploited to ensure the nanoparticle long-term stability in physiological-like conditions, despite covalent crosslinking approaches have been as well investigated.[107] In this regard, drug formulations based on alginate have been proven suitable for different drug types, such as metformin,[122] doxorubicin,[123] ethionamide,[124] and for various administration routes, such as pulmonary,[125] oral,[126] nasal,[127] intravenous,[128] and ocular.[129] For instance, miltefosine-loaded Alg-NPs were employed as alternative antifungal agents toward *Candida albicans, Cryptococcus neoformans,* and *Cryptococcus gatti* fungi aiming to reduce the drug-related toxicity.[39] Alginate NPs encapsulating peppermint-derived phenolic extracts, which are some of the most used functional ingredients in the food, pharmaceutical, and flavoring industries, were also reported.[130] Specifically, the phenolic compounds

Table 1. Summary of Alg-NPs applications together with the fabrication technique, the encapsulated compounds, the presence of other polymeric and/or inorganic components, and the preferred delivery form.

Application	Fabrication technique	Other polymeric or inorganic components	Encapsulated compounds	Delivery form	Reference
Drug delivery	Gelation method	–	Miltefosine	Oral	[39]
			Peppermint phenolic extract	Oral	[130]
			Grape pomace extract	Oral	[160]
			Glucosamine sulfate	Transdermal	[132]
			Immunoglobulin	Oral	[159]
			Lacticaseibacillus paracasei bacteriocins	Oral	[135]
			S-nitroso-mercaptosuccinic acid—silver nanoparticles	Parenteral	[136]
			Bovine serum albumin	Oral	[133]
			Transforming growth factor β1 and β3	Oral	[207]
			Neural proteins	Parenteral	[134]
			Farnesol	Parenteral	[212]
		Octaarginine	Insulin	Oral	[165]
		Pectin	Folic acid	Oral	[163]
		Starch—cellulose	Calcitonin—*Amaranthus retroflexcus L.* extracts	Parenteral	[138]
		Polysorbate 80	Curcumin	Parenteral	[140]
		Honey	Rifampicin	Oral	[107]
	Polyelectrolyte complexation	Chitosan	Crocin	Parenteral	[164]
			Furosemide	Oral	[146]
		Poly(3-acrylamidopropyl) trimethylammonium chloride	–	Parenteral	[153]
		Cationic polymethacrylate	Lysozyme	Parenteral	[154]
		Lecithin—pectin	Dexamethasone	Nasal	[127]
		Cetylpyridinium chloride	Ibuprofen	Parenteral	[155]
		Poly(acrylamido phenylboronic acid)	Insulin—glucose oxidase	Parenteral	[166]
	Gelation method/polyelectrolyte complexation	Chitosan	Liraglutide	Oral	[161]
			Curcumin diethyl diglutarate	Parenteral	[143]
			Pirfenidone	Transdermal	[142]
			Quercetin	Oral	[144]
			Curcumin	Paremteral	[145]
			Captopril—amlodipine—valsartan	Oral	[147]
			Growth factor derided peptide	Nasal	[149]
			Rifampicin—ascorbic acid	Pulmonal	[150]
			Bone morphogenetic protein-2	Parenteral	[151]
			Lovastatin	Parenteral	[152]
		Chitosan—oleic acid	Lutein	Ocular	[148]
		Succinylated chitosan	Quercetin	Oral	[162]
		Iron oxide nanoparticles—carboxymethyl chitosan	α-Amylase	Parenteral	[169]
		Polyethylene glycol—iron oxide nanoparticles—ZnO nanoparticles	Buprenorphine—rifampin	Oral	[213]
	Self-assembly	Polyarginine—chitosan—Eudragit 100—calcium carbonate nanoparticles	Curcumin	Oral	[172]
	Self-assembly/gelation method	Iron-doped hydroxyapatite	–	Parenteral	[167]

Table 1. Continued.

Application	Fabrication technique	Other polymeric or inorganic components	Encapsulated compounds	Delivery form	Reference
		Gold nanorods—porous silicon nanoparticles	–	Parenteral	[168]
		DNA	Vildagliptin	Oral	[185]
	Desolvation method	–	Curcumin	Parenteral	[131]
		Stearic acid-poly(ethylene glycol)	Zidovudine	Oral	[139]
	Spray drying	Gelatin	Metformin hydrochloride	Oral	[141]
Cancer therapy	Gelation method	–	Gadolinium	Parenteral	[197]
		Tween 80	Curcumin—resveratrol	Parenteral	[179]
		Gelatin—iron oxide nanoparticles—poly(vinyl alcohol)	Doxorubicin	Parenteral	[194]
		Arabic gum	Curcumin	Parenteral	[182]
		Hyaluronic acid—folic acid	Oxaliplatin	Oral	[184]
		Artemisia ciniformis extract	Paclitaxel	Parenteral	[181]
		Catechol	*Garcinia mangostana L.* extract	Parenteral	[183]
		Gold nanoparticles	Cisplatin	Parenteral	[195]
		Graphene oxide nanoplatelets	Doxorubicin	Parenteral	[196]
		Iron oxide nanoparticles	Doxorubicin	Parenteral	[198]
	Polyelectrolyte complexation	Chitosan	Doxorubicin	Parenteral	[186]
			Doxorubicin—paclitaxel	Pulmonal	[188]
		Cysteamine—disulphide—poly(allylamine hydrochloride)—poly(4-styrenesulfonic acid-co-maleic acid) sodium salt	Paclitaxel	Oral	[191]
		Hair keratin	Doxorubicin hydrochloride	Parenteral	[192]
		Chitosan—iron oxide nanoparticles	Curcumin	Parenteral	[199]
	Gelation method/polyelectrolyte complexation	Chitosan	Curcumin diglutaric acid	Oral/parenteral	[189]
			Amygdalin	Oral	[190]
		Chitosan—β-cyclodextrins	Curcumin—folic acid	Parenteral	[214]
	Self-assembly	–	Doxorubicin—curcumin	Parenteral	[180]
	Spray drying	TiO₂ nanoparticles	Temozolomide	Parenteral	[193]
Other applications	Gelation method	Tween 80—Span 80	Deactivated influenza virus	Nasal/parenteral	[206]
		–	Polydopamine or alginate dopamine	Parenteral	[208]
	Polyelectrolyte complexation	Phenylalanine ethyl ester—oleic acid	–	Parenteral	[209]
		ε-polylysine	Bovine serum albumin	Parenteral	[211]
		Polyethyleneimine	siRNA	Parenteral	[210]
	Self-assembly	–	Ovalbumin	Parenteral	[205]
	Electrospraying	–	Plasmid DNA	Parenteral	[204]

were used as the core material, whereas alginate was exploited both to overcome their instability drawbacks and improve their bioavailability. Again, curcumin-loaded alginate NPs with strong anti-carcinogenic properties toward *Streptococcus mutans* were prepared via a simple desolvation method and evaluated as dental decay fighting products.[131] Noticeably, Alg-NPs presented similar efficacy with respect to analogous chitosan- and starch-based NPs investigated in the same work. Similarly, alginate NPs loaded with farnesol were proposed as antifungal agents against *C. albicans*. Yet, a transdermal administration formulation of alginate NPs embedding glucosamine sulfate was reported for the treatment of osteoarthritis to overcome the limi-

tations in its oral delivery, including liver first-pass phenomenon and side effects.[132] The encapsulation in the nano-sized alginate matrix allowed to obtain a sustained and prolonged release with good results also in terms of skin permeation. Noticeably, the effect of several processing conditions on the release profile of alginate NPs loaded with bovine serum album was investigated.[133] In this sense, it was found that by increasing alginate concentration, crosslinking time, and drying time it was possible to considerably reduce the initial burst release in order to both obtain a prolonged therapeutic effect and avoid side effects. Again, alginate NPs were proved promising for the delivery of neural proteins.[134] Along with industrial drugs and natural
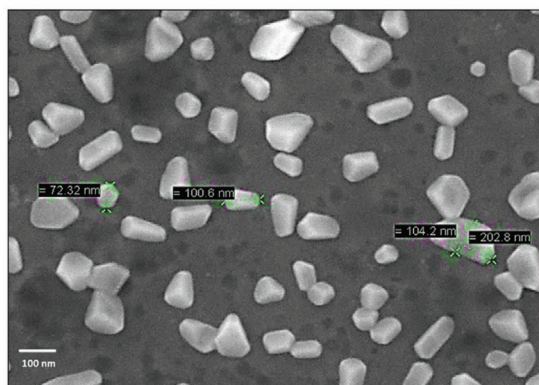
**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
MATERIALS
INTERFACES**

www.advmatinterfaces.de

Figure 4. Scanning electron microscopy image of alginate nanoparticles containing *Lacticaseibacillus paracasei*. Reproduced under the terms of the CC-BY 4.0 license.[135] Copyright 2020, The Authors, published by MDPI.

extracts, a novel class of bacteriocins produced by *Lacticaseibacillus paracasei* has also been successfully embedded within alginate NPs as shown in **Figure 4**.[135]

This nano-antibiotic formulation was found to display a much stronger and prolonger antibacterial activity against Gram-negative bacteria (e.g., *Escherichia coli*) with respect to free bacteriocins. Yet, Alg-NPs enriched with nitric oxide and/or ad-hoc synthesized green tea-derived silver NPs (AgNPs) were reported as potent antimicrobial nanocarriers against both Gram-negative and Gram-positive (e.g., *Staphylococcus aureus*) bacteria.[136] Interesting synergistic effects between nitric oxide and AgNPs were observed. In this sense, their minimum concentration required to show a marked antibacterial effect was not toxic at all to in vitro tested healthy model cells.

It is noteworthy that all the unique features of Alg-NPs can be easily tuned by combining alginate with other synthetic or natural polymers (e.g., poly(vinyl alcohol) (PVA), chitosan, pectin, etc.).[137] For instance, alginate-based NPs coated with a shell of starch and cellulose were explored for the delivery of calcitonin drug and/or *Amaranthus retroflexcus L.* extract in bone regeneration applications.[138] Noticeably, in vitro release studies in simulated body fluid and phosphate-buffered saline (PBS) showed the superior performances of the natural extract with respect to the industrial compound. Hybrid dendritic NPs comprised of alginate (i.e., core) and stearic acid-polyethylene glycol (i.e., shell) enriched with the anti-viral drug zidovudine were investigated showing good blood compatibility and nontoxicity in in vitro studies.[139] Yet, alginate-polysorbate 80 NPs were reported to enhance the encapsulation efficiency and bioavailability of curcumin, whose main release was observed in simulated colonic fluids.[140] Composite alginate-gelatin NPs loaded with metformin hydrochloride for the treatment of diabetic patients have also been prepared via nanospray drying technique.[141] The obtained NPs successfully displayed a sustained release profile of the drug in vitro, whereas in vivo rat model evaluations showed a significant reduction of blood glucose level over 24h.

Among others, NPs based on polymer-polymer PECs have been frequently studied for drug delivery and biomedical applications being able to encapsulate drugs and biologic components at a molecular level. They offer greater advantages compared to traditional dosage forms improving and altering physical–chemical properties such as stability, protection of bioactive substances, as well as controlling the release and thus pharmacological activity.[114,115] By way of example, composite alginate-chitosan NPs were prepared in order to overcome the limitations in the transdermal delivery of pirfenidone, an anti-inflammatory drug with strong antifibrotic effects broadly employed for the clinical treatment of pulmonary fibrosis, achieving a much higher skin penetration with respect to the correspondent liquid dosage form.[142] In a similar work, alginate-chitosan NPs displayed high stability and good protective properties toward UV and thermal exposure for the encapsulated curcumin diethyl diglutarate drug, whose in vitro digestibility and bio-accessibility considerably increased with respect to the free form in gastrointestinal conditions, as schematized in **Figure 5**.[143]

The safety profile and the antioxidant properties of oral administrated alginate-chitosan NPs loaded with quercetin were evaluated in vivo in an animal model.[144] Interestingly, increasing the chitosan amount in the NPs led to superior protective abilities toward iron/ascorbic acid-induced lipid peroxidation in microsomes and tert-butyl hydroperoxide oxidative stress in hepatocytes. Curcumin containing alginate-chitosan NPs also demonstrated to possess anticonvulsant and neuroprotective effects.[145] Specifically, the proposed NPs allowed to overcome the poor water solubility of curcumin and to reduce the side effects of pentylenetetrazol, hence being of significant value as an effective therapeutic approach in the treatment of epileptic patients. In another work, furosemide drug encapsulated within alginate-chitosan NPs showed prolonged release and enhanced mucus-permeability, which increased the overall drug therapeutic effect without showing cellular toxicity or inflammatory reaction in the gastrointestinal tissues.[146] Nanosized alginate-chitosan particles prepared via polyelectrolyte complexation have also shown promises in the encapsulation of hydrophobic antihypertensive drugs to be administered via oral forms.[147] Remarkably, the prepared formulations offered good encapsulation efficiency for captopril, valsartan, and amlodipine drugs, and their excellent retention corresponding to less than 8% of sustained drug release in vitro in 24 hat physiological pH. The ocular administration of alginate-oleic acid-chitosan NPs containing lutein, a hydrophobic carotenoid with well-known retinal and macular protection against oxidative stress, was as well explored.[148] The obtained results demonstrated higher solubility, bioavailability, thermal stability, and intracellular transport (40%) of lutein from the proposed NPs with respect to micellar lutein hence indicating them as a promising therapeutic tool to conquer macular degeneration and retinopathy. Alginate-chitosan NPs loaded with a small peptide derived from a neural growth factor have also shown promising abilities in the treatment of brain degenerative disorders, such as Alzheimer's disease, being able to promote the differentiation of stem cells into mature neurons.[149] The pulmonary administration of rifampicin and ascorbic acid coloaded alginate-chitosan NPs has also been reported, with the proposed nanocarriers showing strong and prolonged antibacterial properties against *S. aureus* due to the surface functionalization with chitosan.[150] Alginate-chitosan NPs have also been employed as nanosized delivery vehicles for human bone morphogenetic protein-2 showing favorable size, controlled release characteristics, and high loading efficiency.[151] Again, the use of
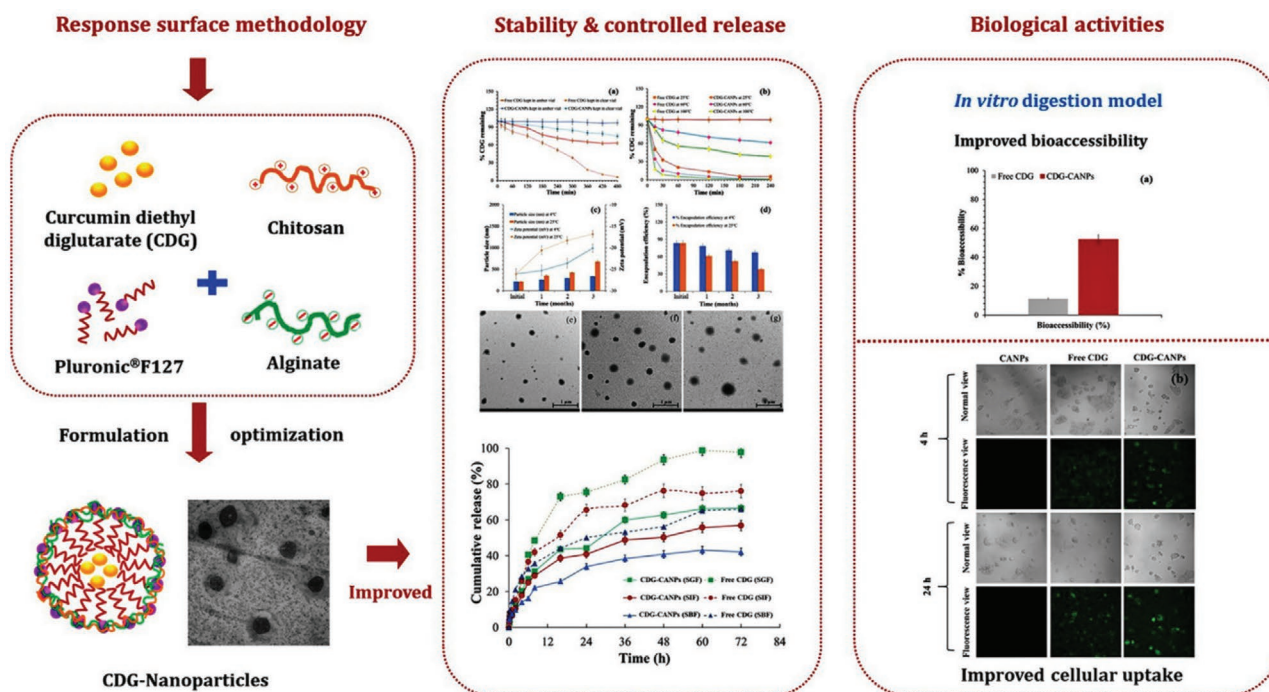
Figure 5. Schematic of alginate-chitosan nanoparticles preparation and characterization. Reproduced with permission.[143] Copyright 2019, Elsevier B.V.

lovastatin-loaded alginate-chitosan NPs allowed to considerably reduce the drug side effects in a rat animal model meanwhile improving its therapeutic efficiency.[152]

Despite alginate-chitosan NPs represent the most investigated ones, other polymer types have been employed as well. For example, the formation of alginate-poly(3-acrylamidopropyl) trimethylammonium chloride NPs was investigated with particular emphasis on understanding the effect of the processing parameters (i.e., pH, ionic strength, polymer concentration, and composition) on nanoparticle physical–chemical properties.[153] Yet, alginate-polymethacrylate polyelectrolyte complex NPs for the delivery of lysozyme, a biological drug with antibacterial properties, were prepared via the complexation between the anionic polysaccharide macromolecules and modified cationic polymethacrylate polymer.[154] Remarkably, controlling the synthesis conditions guaranteed a high control of the nanoparticle size and encapsulation efficiency, with the proposed NPs representing a versatile delivery platform. Alginate-lecithin NPs embedding dexamethasone, a corticosteroid drug vastly used in nasal delivery formulations, and dispersed in a pectin continuous phase were proposed as an in situ gelling system able to undergo a sol–gel transition triggered by Ca^{2+} present in the nasal mucosa.[127] Owing to the prolonged contact time with nasal mucosa upon gelation, such a delivery system provided a sustained therapeutic effect even at much lower drug concentrations with respect to the traditional dosages. Yet, complex nanostructured alginate-acetylpyridinium chloride NPs were reported for parenteral administration dosages of ibuprofen, with the surfactant being able to simultaneously increase the drug water solubility and crosslinking the polysaccharide.[155]

Several efforts have also been carried out by researchers to prepare advanced DDS based on Alg-NPs with stimuli-responsive properties. Such systems have indeed the huge advantage to release the encapsulated drugs after exposure to a proper external stimulation (e.g., pH and temperature variations, electric or magnetic field, light irradiation, etc.).[106,156,157] In this sense, alginate-based NPs, owing to their responsivity to pH, showed great potentialities in targeted intestinal delivery. Indeed, alginate tends to shrink at highly acidic pH values (i.e., stomach) thereby limiting the losses of encapsulated compounds, whereas it assumes an extended configuration in alkaline conditions.[158] By way of example, Alg-NPs were used to encapsulate chicken immunoglobulin, which is an antibacterial therapeutic agent highly sensitive to the severe conditions of the gastrointestinal tract.[159] In this regard, despite the quality and activity of immunoglobulin not changed, in vitro studies showed a release of 10% and 99.84% in simulated gastric fluids (i.e., pH = 1.2) and simulated intestine fluids (i.e., pH = 6.8). In a similar work, alginate NPs loaded with grape pomace extract, which is known for its beneficial effect on gastrointestinal health, were demonstrated to protect the bioactive compound toward digestion in the stomach, to increase the residence time in the intestine, and to enhance its bio-accessibility.[160]

Remarkably, composite alginate-based NPs have shown great promise in targeted drug delivery applications. For example, chitosan-coated alginate-based calcium-crosslinked NPs containing liraglutide manifested a great potential as gastrointestinal dosage form in the treatment of diabetic patients, with the chitosan coating helping in avoiding the drug leakage before the targeted site (i.e., intestine).[161] Similarly, core-shell-corona NPs comprised of water-soluble succinyl chitosan and alginate were also prepared for the targeted treatment of diabetes.[162] These composite NPs showed a remarkably high encapsulation efficiency (up to 95%) and a controlled release of quercetin
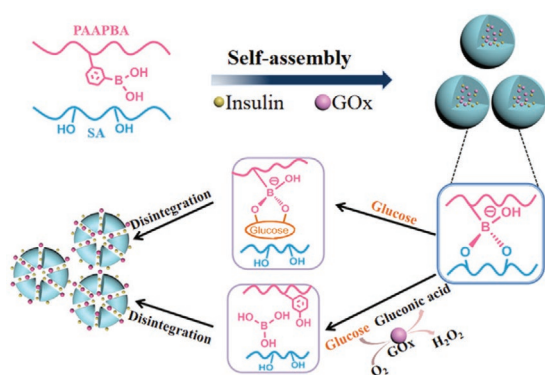
Figure 6. Fabrication and glucose-responsiveness mechanisms of insulin/GOx-loaded NPs. Reproduced with permission.[166] Copyright 2020, Elsevier B.V.

depending on the pH value guaranteeing a pronounced hypoglycemic effect and efficient maintenance of glucose homeostasis in diabetic rats compared to free oral administered quercetin. Yet, alginate-pectin NPs encapsulating folic acid displayed tailor-made release properties depending on the matrix composition.[163] Increasing the content of pectin in the polymeric matrix facilitated the release of the bioactive compound in highly acidic conditions (i.e., pH = 2), whereas increasing the alginate content allowed to preserve the drug for its release in neutral and basic conditions. Analogously, crocin-loaded alginate-chitosan NPs displayed sustained and controlled release in simulated gastrointestinal conditions, antioxidant activities, and anticancer properties.[164] Similarly, octaarginine-modified alginate NPs loaded with insulin were studied for colon targeted delivery, with the improvement of insulin intestinal uptake confirmed in vivo in a rat model.[165] Remarkably, alginate-poly(acrylamido phenylboronic acid) NPs containing insulin and glucose oxidase were reported as an innovative glucose-triggered insulin delivery system.[166] These biocompatible advanced nanocarriers were assembled via the formation of cycloborates and exploited the glucose/H_2O_2 dual-responsiveness to provide a faster release of insulin as reported in **Figure 6**, hence having strong clinical potential in diabetes treatment.

Natural benign substances have also been exploited in the development of alginate-based NPs for drug delivery applications with superior therapeutic effects. For instance, alginate-honey NPs containing rifampicin, a bactericidal drug, showed marked antioxidant and anti-inflammatory properties without toxic side effects.[107]

Hybrid alginate-based NPs with unique characteristics were developed in order to ensure the drug delivery remote activation. In this regard, highly biocompatible Alg-NPs containing an iron-doped hydroxyapatite nanophase were proposed as an innovative superparamagnetic pharmaceutical formulation with potential applicability in targeted drug delivery.[167] Also, conjugated gold nanorods and porous silicon NPs were successfully encapsulated in Alg-NPs in order to prevent their leakage and possible toxicity issues (**Figure 7**), hence showing great promises for photothermal combination therapy and other advanced biomedical applications.[168]

Superparamagnetic iron oxide NPs encapsulated in an alginate-carboxymethyl chitosan layer have been demonstrated highly promising for immobilizing α-amylase with the consequent increase in catalytic activity, slowdown of release rate, and improved reusable performances.[169] Also, advanced buprenorphine and rifampin coloaded alginate-polyethylene glycol nanocarriers functionalized with iron oxide and zinc oxide NPs have shown promising delivery capabilities in the treatment of intestinal inflammation.

Self-assembled alginate-based NPs have also been explored as nanocarrier DDS showing great advantages in targeted therapy and delivery.[170,171] These systems are usually comprised of amphiphilic block or graft copolymers that in aqueous solutions can form micelle-like particles consisting of an inner hydrophobic core and an outer hydrophilic shell. Additionally, stimuli-responsive multilayered nanocapsules for the colon targeted delivery of curcumin were fabricated as illustrated in **Figure 8**.[172] Specifically, these nanosized platforms were prepared by using calcium carbonate nanocores for the assembly of LbL of alginate, chitosan, Eudragit 100, and poly-L-arginine. Remarkably, release studies proved the potential for the proposed nanocapsules to be designed to protect the drug in the stomach and release it in the lower gastrointestinal tract.

3.2.2. Cancer Therapy

Cancer is a disease involving the fast, abnormal, and uncontrolled growth of tumor cells. Generally speaking, in order to prolong the patient life, any cancer therapy aims to prevent tumor growth, metastases formation, and relapse after removal.[173] Common cancer therapy methods include surgery, chemotherapy, and radiotherapy, with each method having its limitations hence being often not able to yield satisfactory therapeutic outcomes. To overcome such limits, nanocarriers have nowadays gained a great deal of interest for their capability to improve the aqueous solubility, pharmacodynamic, and pharmacokinetic profile of chemotherapy drugs meanwhile decreasing their concentration in non-targeted normal tissues.[174–176] However, nanocarriers are commonly associated with several drawbacks such as poor biodegradation, bioavailability, stability, tissue distribution, and toxicity, thus causing safety concerns especially for long-term cancer treatments. In this sense, among the broad variety of materials that can be used for this purpose, alginate, due to its unique physical–chemical and biological properties, has shown relevant promises in the development of highly effective chemotherapy nanocarriers.[71,177,178] By way of example, Alg-NPs loaded with curcumin and resveratrol were investigated for the treatment of prostate cancer showing marked cytotoxicity effect on tumor cells without producing hemolysis, hence being safe for intravenous administration.[179] Similarly, oxidized alginate NPs conjugated with doxorubicin and containing curcumin demonstrated lower toxicity toward health cells compared to analogous free drug formulations and pH-responsive delivery for the targeted treatment of breast cancer.[180] Yet, Alg NPs loaded with paclitaxel were added with *Artemisia ciniformis* extract aiming to reduce the drug side effects by reducing the cytotoxicity against healthy cells.[181] Composite alginate-based NPs have also been widely investigated in targeted cancer therapy due to their improved selectivity. For example, alginate-arabic gum

ADVANCED
SCIENCE NEWS
www.advancedsciencenews.com

ADVANCED
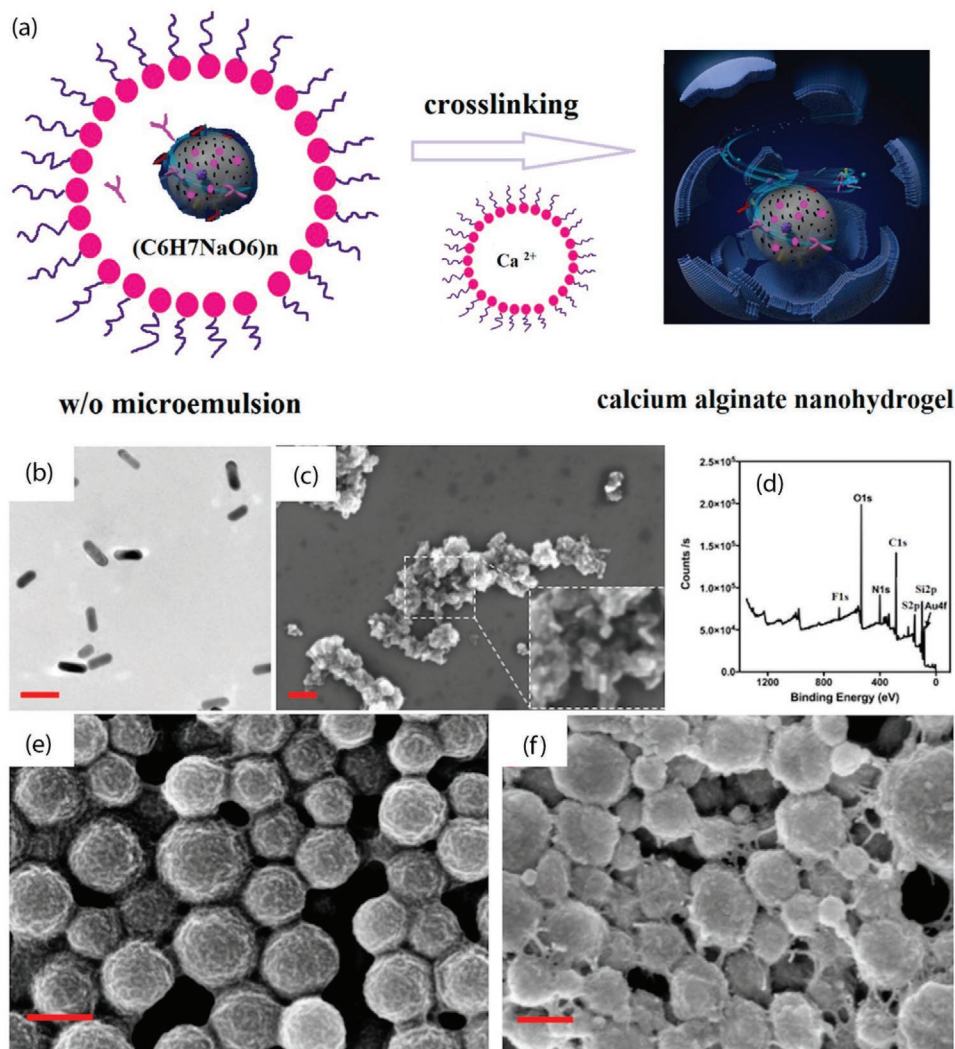**MATERIALS**
INTERFACES
www.advmatinterfaces.de

Figure 7. a) Formation of biocompatible gold nanorods conjugated porous silicon nanoparticles functionalized calcium alginate nanohydrogel using water-in-oil microemulsion templates through crosslinking as a versatile therapeutics co-delivery nanocarrier for photothermal therapy. b) TEM image of gold nanorods. The scale bar denotes 50 nm. c) SEM image of AuNRsPSiNPs. The scale bar denotes 100 nm. d) XPS spectrum of the gold nanorods conjugated porous silicon nanoparticles. e) SEM image of calcium alginate nanohydrogels. The scale bar denotes 100 nm. f) SEM image of the therapeutics co-loaded AuNRsPSiNPs functionalized calcium alginate nanohydrogels. The scale bar denotes 200 nm. a-f) Reproduced with permission.[168] Copyright 2018, American Chemical Society.

NPs embedding curcumin were studied for their growth inhibition capacity and anticancer activity against liver, colon, lung, and breast cancer.[182] Also, catechol-functionalized alginate NPs loaded with *Garcinia mangostana L.* extract were explored in the treatment of bladder cancer.[183] Remarkably, the surface functionalization with catechol guaranteed both excellent mucoadhesive properties and could prolong residence on the mucous tissues compared with unmodified Alg-NPs, thereby increasing the drug therapeutic effect. Alginate NPs coated with folate conjugated hyaluronic acid and enriched with oxaliplatin have been proposed to enhance antitumor and apoptosis efficacy on colorectal cancer cells compared to free drug formulation.[184] DNA cubes coated with alginate have also been proposed for the efficient release of vildagliptin in diabetic patients.[185] The formulated nanospheres attained size uniformity and better therapeutic outcomes in terms of reduced adverse events and

better control of glycemic levels with decreased dosages in an animal model.

Alg capability to form stable PECs was employed to fabricate alginate-chitosan NPs loaded with doxorubicin for the treatment of breast cancer.[186] The proposed NPs had indeed a concentration of drug sufficiently high to induce a therapeutic effect when used against the breast cancer cells in vitro. Yet, alginate-chitosan NPs loaded with the inclusion complexes between β-cyclodextrins and curcumin-folic acid were evaluated for the parenteral treatment of breast cancer.[187] Remarkably, a high amount of curcumin was effectively loaded within the prepared NPs, with folic acid being specifically employed to enrich chitosan with redox responsiveness and active targeting of tumor cell folate receptors aiming to enhance curcumin efficacy. Also, biodegradable alginate-chitosan hollow NPs were fabricated via a hard template methodology and investigated for
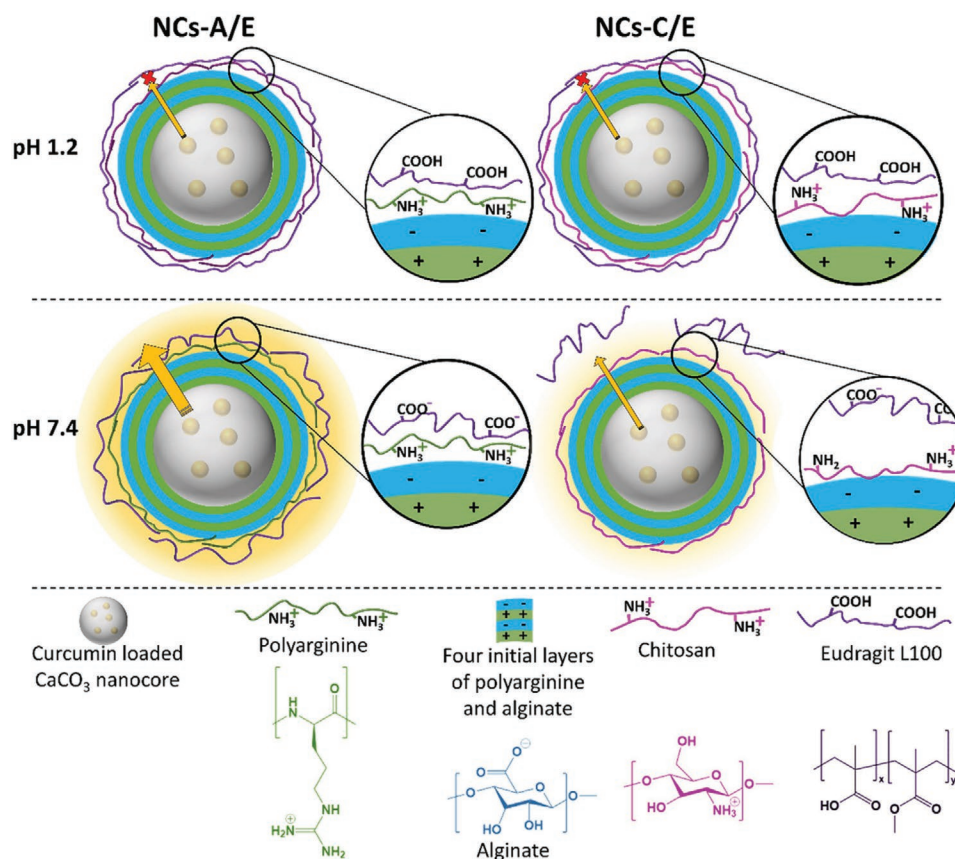
Figure 8. The pH-triggered release of curcumin from LbL coated nanoparticles. The figure illustrates the changes in the coating of the nanoparticles at pH 1.2 and pH 7.4. At pH 1.2 (mimic for conditions in the stomach) the outer coating of Eudragit L100 is protonated, insoluble in water, and will provide a barrier to the release of the curcumin entrapped in the nanocores for both NCs-A/E (polyarginine and Eudragit L100 as the outer two layers) and NCs-C/E (chitosan and Eudragit L100 as the outer two layers). At pH 7.4, (mimic for conditions in the intestine) the Eudragit L100 outer layer for both samples is deprotonated and anionic. However, the different behavior of the penultimate layer (polyarginine or chitosan) results in different curcumin release behavior for NCs-A/E and NCs-C/E. Reproduced with permission.[172] Copyright 2019, Elsevier B.V.

the co-delivery of doxorubicin and paclitaxel drugs in the treatment of lung cancer.[188] Drug release studies exhibited a sustained release effect, whereas cytotoxicity experiments proved the composite NPs as nontoxic carrier materials with the combination of the two drugs allowing a good inhibiting effect on cell proliferation. In a similar work, alginate-chitosan NPs containing curcumin diglutaric acid were explored for the treatment of colon, hepatic, and breast cancer.[189] These composite nanocarriers displayed better stability under UV radiation and in a simulated gastrointestinal environment, as well as a slower and prolonger release, with respect to the free drug in water. Alginate-chitosan NPs were also successfully employed to mitigate the side effects of amygdalin, which possesses strong antitumoral properties but requires particular attention due to the presence of the cyanide group.[190] Nano-sized alginate-based PECs were also fabricated via a LbL approach for the targeted treatment of colon cancer by using disulphide crosslinked oxidized alginate, cysteamine, poly(allylamine hydrochloride), and poly(4-styrenesulfonic acid-co-maleic acid) sodium salt.[191] The proposed NPs were loaded with paclitaxel and displayed high encapsulation efficiency, prolonger drug release in intestinal simulated conditions, and good biocompatibility. Yet, bioresponsive alginate-keratin nanogels loaded with doxorubicin

hydrochloride were proposed (**Figure 9**), with keratin offering the crosslinking structure and bio-responsive ability and alginate ameliorating the stability and drug loading capacity.[192] Specifically, the release of doxorubicin was triggered by specific markers (i.e., trypsin and glutathione) and allowed to achieve inhibition effect on cancer cells at 48 h in vitro.

Along with all-polymer NPs, hybrid alginate-TiO_2 NPs loaded with temozolomide were proposed for improving the treatment of neuroblastoma.[193] In this regard, these hybrid nanocarriers displayed higher cytotoxicity toward tumor cells but less inhibitory activity toward healthy neuronal cells, also showing antioxidant and anti-inflammatory activities. Similarly, dual-layer magnetic NPs comprised of a doxorubicin-loaded core and an alginate shell functionalized with Fe_3O_4 NPs were investigated for the targeted treatment of breast cancer.[194] Embedding doxorubicin in the gelatin core guaranteed a high encapsulation efficiency, whereas the magnetic outer layer ensured the targeting to the tumor tissues providing controlled drug release. Again, alginate NPs co-loaded with cisplatin and in situ synthesized Au-NPs were proposed for the combined photothermal therapy and chemotherapy in the colorectal tumor treatment as schematized in **Figure 10**.[195] The in vivo results indicated that the tumors treated with the NPs received a dramatically higher
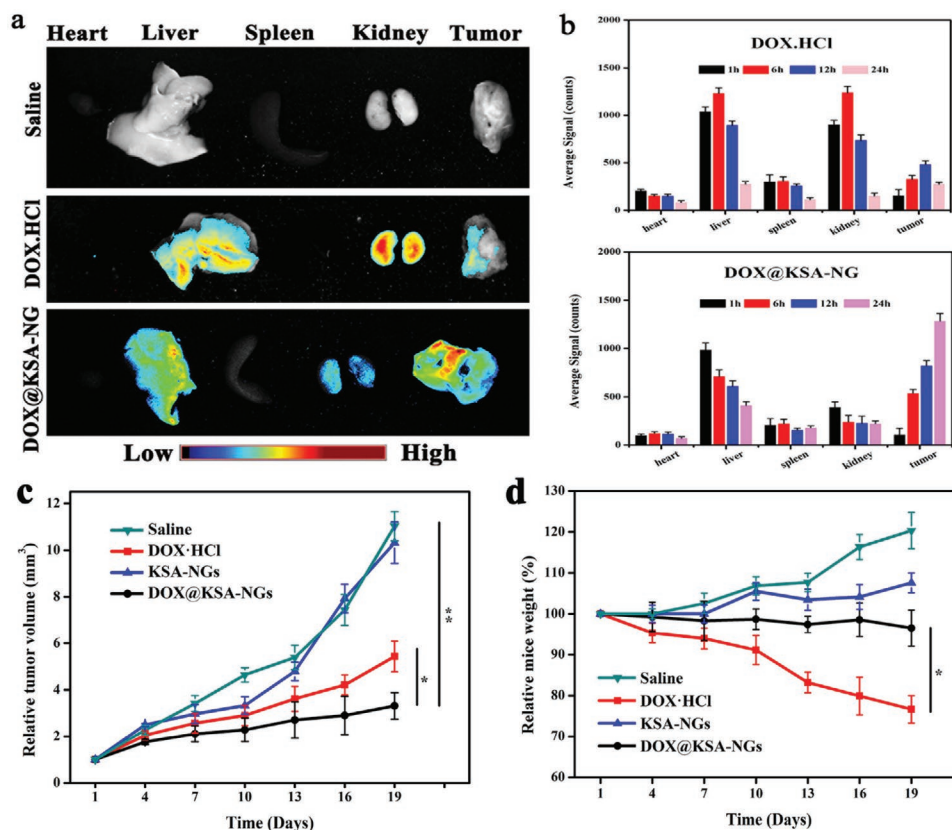
Figure 9. a) Ex vivo DOX biodistribution in major organs and tumors examined 24 h post administration. b) Semi-quantitative of DOX and DOX@KSA-NG distribution in major organs and tumors post intravenous injection for different time points. c) Relative tumor volume. d) Body weight changes. ($n = 5$, data expressed as average ± standard error, $*p < 0.05$, $**p < 0.01$ compared to other group using the Tukey's post-test). a-d) Reproduced with permission.[192] Copyright 2017, Elsevier Ltd.
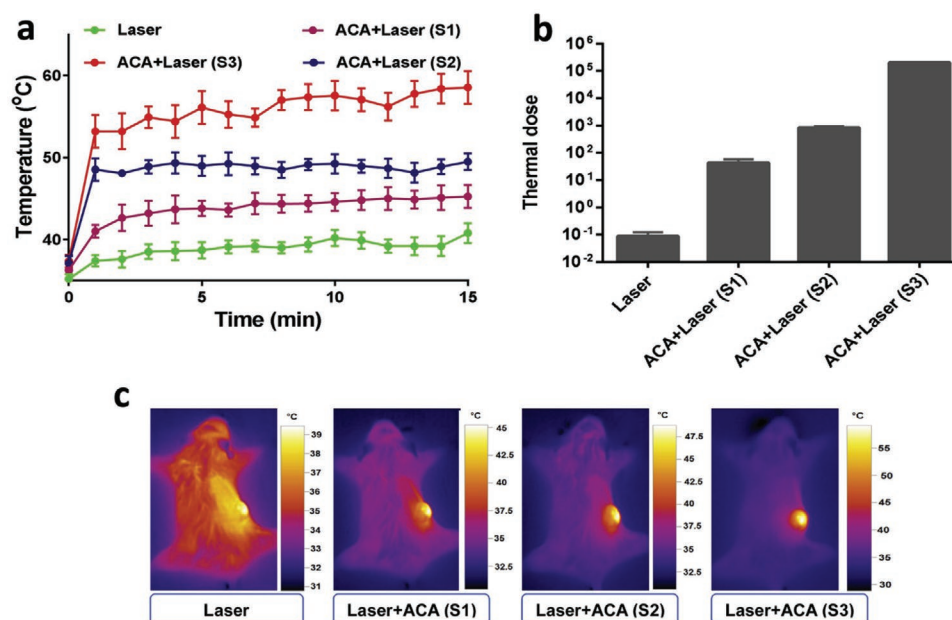

Figure 10. a) Temperature rise profile of the tumor under 15 min laser irradiation. b) Values of the thermal dose received by the tumors treated with laser alone (the average of the three sessions) and ACA+laser (at different sessions). c) Representative infrared thermal image of the tumor bearing mice upon laser irradiation at different sessions. a-c) Reproduced with permission.[195] Copyright 2019, Elsevier Ltd.
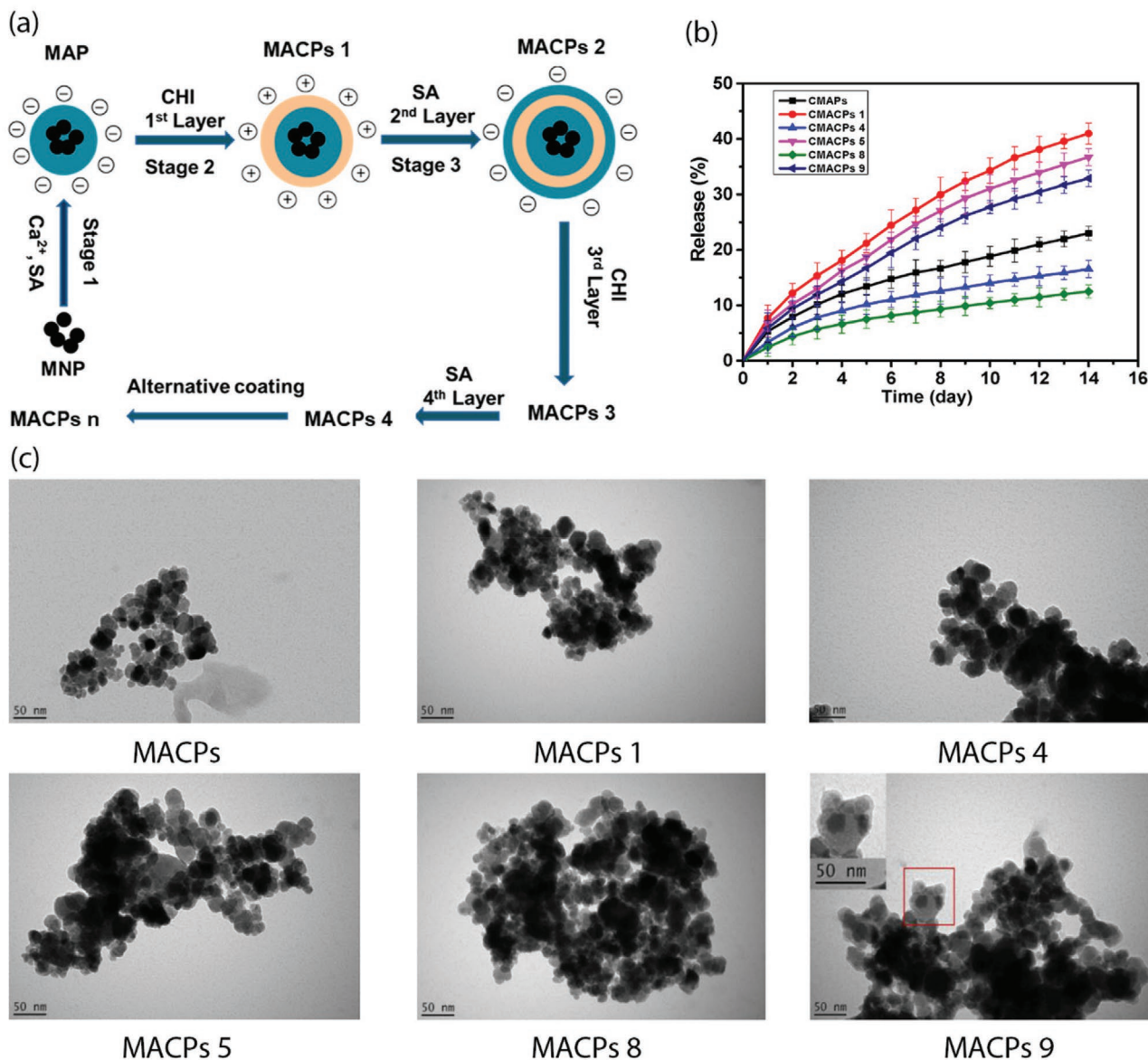
**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
MATERIALS
INTERFACES**

www.advmatinterfaces.de

Figure 11. a) Schematic illustration for the preparation of MAPs and MACPs. MAPs were fabricated by coating crosslinked alginate on MNPs using Ca^{2+} as the crosslinker. MACPs were prepared by alternatively depositing CHI and sodium alginate (SA) on MAPs based on the electrostatic interaction between the two biopolymers. The alternative coating was repeated until MACPs with the desired number of layers were obtained (Stages 2 and 3). MACPs 1, 2, 3, 4, and n represent CMACPs that possess 1, 2, 3, 4, and n layers of polymers coated on MNPs respectively. b) Curcumin release profile of CMAPs and CMACPs (layer number: 1 and 4) in PBS buffer at pH 7.4 and pH 5.6. c) TEM images of MAPs and MACPs with the layer numbers of 1, 4, 5, 8, and 9. Reproduced under the terms of the CC-BY 4.0 license.[199] Copyright 2018, The Authors, published by MDPI.

thermal dose due to the optical absorption properties of AuNPs, hence being able to suppressed tumor growth up to 95% of control and markedly prolonged the animal survival rate.

In a similar work, Alg-NPs embedding graphene oxide nanoplatelets and doxorubicin were developed.[196] These hybrid nanocarriers showed improved stimulative delivery controllability, faster release of the encapsulated drug, and photothermal effect in adenocarcinoma cells. Yet, gadolinium alginate NPs were successfully prepared for theranostic applications.[197] Alginate-based magnetic nanogels were as well proposed for oncotheranostics.[198] Specifically, these NPs displayed magnetic-targeted characteristics, high drug loading content, co-triggered

release behavior, high toxicity to tumor cells, low side effects to normal cells, and magnetic resonance imaging functions. In a similar work, magnetic alginate-chitosan NPs containing iron oxide were developed for the targeted release of curcumin in breast cancer treatment as shown in **Figure 11**.[199]

3.2.3. Other Applications

Alginate NPs have also been proposed for other biomedical and pharmaceutical applications, including gene therapy, nano-vaccines, tissue engineering, and wound healing. Among

others, gene and cellular delivery have shown great promise in future medical applications. Since the development of modern medicine, scientists have hypothesized that introducing exogenous DNA into the human genome could be an effective treatment for a broad number of genetic and inherited human diseases.[200] In this sense, nowadays gene therapy is considered a revolutionary approach to mitigate or even resolve most of the genetically related diseases, including cancer, by a single treatment.[201,202] However, it is noteworthy that significant efforts and technological advances are still needed to overcome several barriers to the effective application of gene delivery. In this sense, viral vectors, while efficient, pose safety issues, despite the continuous efforts of virologists to minimize their immunogenicity and side effects. On the contrary, polymer delivery systems have recently gained an increasing deal of interest because of their low toxicity, targeted delivery capacity, long-term stability, lack of immunogenicity, and relatively low production costs.[203] Additionally, macromolecular polyelectrolyte can be conjugated with genetic material via electrostatic attraction at physiological pH, thereby facilitating and controlling gene delivery. Alginate, owing to its unique properties and capabilities, has also been to some extent explored for this purpose. By way of example, electrosprayed Alg-NPs loaded with two different clustered regularly interspaced short palindromic repeats plasmids showed outstanding encapsulation efficiency, cytocompatibility, and targeted delivery into mammalian cells.[204] Mannose-modified alginate NPs functionalized with ovalbumin were then reported for the targeted antigen delivery to dendritic cells as a potent nano-vaccine for cancer immunotherapy.[205] Yet, alginate NPs were explored for nasal immunization in rabbits toward the influenza virus.[206] These new nanocarriers increased the immune response likewise being able to increase the residence time in mucosal tissues. Alg-NPs loaded with the transforming growth factor β1 and β3 showed also great promise in promoting chondrogenesis for tissue engineering applications.[207] Hybrid alginate NPs containing polydopamine or dopamine were investigated for bioimaging purposes via magnetic resonance.[208] Additionally, self-assembled polyelectrolyte complex oleoyl modified alginate-phenylalanine ethyl ester NPs were assessed for their cellular delivery capacity showing a promising cellular uptake efficiency of 60% within 4 h.[209] Also, alginate-polyethyleneimine NPs were proved able to adhere to and condense siRNA to form toroidal complexes without showing cytotoxicity issues.[210] Remarkably, these NPs were completely degraded by autophagy via direct (i.e., formation of autophagosome and amphisome) and indirect (i.e., maintaining viability and survival of the cells) pathways. Alginate-ε-polylysine NPs loaded with bovine serum albumin were also proposed as potential candidates for vaccine delivery.[211] In this sense, the prepared NPs displayed in vitro sustained release behavior and no cytotoxicity.

3.3. Alginate-Based Electrospun Nanofibers

Polymeric NFs hold great potentialities in many biomedical and pharmaceutical fields, such as tissue engineering, wound healing, and drug delivery.[215] NFs are commonly defined as solid fibers with a submicrometer dimension. The main advantages of nanofibrous structures are their high surface-to-volume ratio and porosity, as well as the greater and simpler handleability with respect to polymeric NPs.[216–218] In the past decades, several fiber-forming techniques have been proposed, including electrospinning, solution blowing, force spinning, phase separation, and template synthesis. Among these, the electrospinning technique, which induces the formation of solid NFs via the application of a strong electric field to a polymeric solution or melt, presents many advantages and it is nowadays considered one of the most promising nanotechnologies due to its simplicity, low cost, scalability, and versatility.[219–221] Additionally, electrospun NFs can be easily enriched with unique and specific functionalities in order to meet the specific requirements for the application of interest, and can be prepared in a variety of biomimetic structures.[222–226] For instance, electrospun mats are able to mimic the native extracellular matrix (ECM) thereby representing the ideal environment to foster cell viability allowing gas exchange and nutrient transport.[227] Also, due to the fact that drugs, NPs, and other various substances can be efficiently encapsulated within the NFs, electrospun nanomaterials find great applicability in delivery applications.[228,229] Despite any existing polymer can be potentially electrospun, as far as it can be solubilized or melted, petroleum-derived materials show much greater processability with respect to natural-derive ones (e.g., polysaccharides and proteins) and the mass production of highly pure alginate-based NFs is still unsolved.[230] Indeed, pure alginate solutions are extremely difficult to be electrospun due to the high number of hydrogen bonds, the great viscosity, and the lack of sufficient chain entanglements. The common approach to prepare alginate-based NFs via electrospinning comprises the employment of co-spinning agents and surfactants able to enhance the mixture processability. Thereby, it is not surprising that alginate nanofibrous materials were rarely employed in biomedical products and pharmaceutics. However, it is noteworthy that alginate NFs possess several properties, namely biocompatibility, biodegradability, nontoxicity, that make them extremely promising in medical applications with particular significance in the fabrication of engineered scaffolds for soft and hard tissues, of wound dressing products, and of DDS.[2]

Table 2 summarizes the main applications of alginate-based NFs along with the type of electrospinning method, the presence of additional polymers and/or co-spinning agents, the encapsulated compounds, and the crosslinking agent.

3.3.1. Tissue Engineering and Wound Healing

Tissue engineering foresees to use and integrate the basic principle of medicine, biology, and engineering to design biological substitutes to restore, maintain, and/or enhance the functionalities of native tissues by reproducing the structural and physicochemical features of natural tissues.[231,232] Generally speaking, engineered structures must mimic the ECM, ensure the cells with gas and nutrient circulation, and remove metabolic wastes. Moreover, they must possess high biocompatibility, nontoxicity, and good cell adhesion capabilities. Nowadays, the recent advances in nanotechnology offer the possibility to meet all the above-mentioned requirements in order to fabricate versatile,

Table 2. Summary of Alg-NFs applications together with the fabrication technique, the presence of other polymers, the type of co-spinning or template agent, the encapsulated compounds, and the crosslinker type.

Application	Fabrication method	Other polymers	Co-spinning/template polymeric agent	Crosslinker	Bioactives and other substances	Reference
Tissue engineering and wound healing	Solution electrospinning	–	PVA or PEO	Ca^{2+}	–	[236,237]
			PVA	–	–	[238,240]
			PVA	Ca^{2+}	–	[239]
			PEO	Adipic acid dihydrazide	–	[241]
			PEO	Trifluoroacetic acid	Curcumin	[242]
			PVA or PEO	Glutaraldehyde	Lipase	[243]
			PVA	Glutaraldehyde	Honey	[244]
			PVA	Glutaraldehyde	Purple cabbage anthocyanins	[245]
			PVA	–	Spider silk	[246]
			PVA	–	Layered silicate	[253]
			PEO	–	Fluorescent carbon dots	[252]
			PEO	–	Hydrated iron oxide nano-clays	[256]
			PEO	Ba^{2+}	Silver nanoparticles	[254]
			PEO	Ca^{2+}	Chitosan-coated silver nanoparticles	[255]
			PEO	Ca^{2+}, Sr^{2+}, and Ba^{2+}	ZnO nanoparticles	[259,260]
		Chitosan	PEO	Ca^{2+}	–	[247]
			PEO	Ca^{2+}—glutaraldehyde	Chitosan-coated silver nanoparticles	[257]
			PEO	–	Chitin nano-whiskers	[250]
		Carboxymethyl chitosan	PEO	Ca^{2+}—glutaraldehyde	–	[248]
		Methacrylate gelatin	PEO	Ca^{2+}—Irgacure 2959	–	[249]
		PCL	PVA	Ca^{2+}	–	[251]
			PEO	Sr^{2+}	ZnO nanoparticles	[261]
		PLA	PEO	Ca^{2+}—glutaraldehyde	Hydroxyapatite nano-crystals	[258]
	Coaxial solution electrospinning	–	PEO	Ca^{2+}	–	[263]
		Chitosan	PEO	–	–	[264]
		PCL	–	N,N'-disuccinimidyl carbonate	–	[266]
		Poly-3-hydroxybutyric acid	PVA	–	Arginine—bacitracin nano-clays	[265]
	Emulsion electrospinning	–	PLA	Ca^{2+}	–	[269]
		–	PLA	–	Tricalcium phosphate nano-clays	[270]
		Carboxymethyl chitosan	PCL	–	–	[268]
	Free surface electrospinning	Pullulan	–	Ca^{2+}	–	[271]
	3D printing/solution electrospinning	–	PEO	Ca^{2+}	Angiogenic factors	[274]
		–	PCL	Ca^{2+}	–	[272,273]
	Near-field electrospinning	–	PEO	Ca^{2+}	–	[267]
Drug delivery	Solution electrospinning	–	PEO	Sr^{2+}	–	[299]
			PEO	–	Sodium ibuprofen	[283]

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
MATERIALS
INTERFACES**

www.advmatinterfaces.de

Table 2. Continued.

Application	Fabrication method	Other polymers	Co-spinning/template polymeric agent	Crosslinker	Bioactives and other substances	Reference
			PEO	–	Lavender oil	[284]
			PEO	Ca^{2+}	Ciprofloxacin hydrochloride	[286]
			PEO	Glutaraldehyde	Vitamin C	[294]
			PVA	–	Probiotic bacteria	[288]
			PVA	–	Gatifloxacin	[287]
			PVA	–	Growth factors	[290]
			PVA	Glutaraldehyde	Moxifloxacin hydrochloride	[282]
			PVA	Glutaraldehyde—boric acid	Lutein	[285]
			PVA	Glutaraldehyde	Dexpanthenol	[295]
			PVA	Glutaraldehyde	Moxifloxacin hydrochloride	[282]
			PVA—PEO	Ca^{2+}	Gabapentin—acetaminophen	[296]
		Chitosan	–	Glutaraldehyde	Gentamicin	[292]
		Zein	–	–	Betanin—TiO_2 nanoparticles	[298]
		Soy protein isolated	PEO	Ca^{2+}	Vancomycin	[291]
		Inulin	PVA	–	Probiotic bacteria	[289]
		Carboxymethyl cellulose	PVA	Ca^{2+}	Lidocaine	[293]
	Emulsion electrospinning	PVA	–	Ca^{2+}	Artemisia argyi oil—laponite nano-clays	[297]

tailor-made, and advanced tissue-engineered scaffolds.[86,233] In this sense, owing to their unique properties, in the past decade electrospun NFs have vastly served in the fabrication of nanofibrous scaffolds for different tissue regeneration applications.[227,234] Despite it is associated with several drawbacks (e.g., low processability, poor reproducibility, slow production rate, etc.), the electrospinning of alginate and other natural-derived biopolymers to produce scaffolds is currently a highly investigated research topic.[2,235] It is noteworthy that due to its high water solubility, alginate-based NFs must be subjected to suitable crosslinking treatments, either ionic or covalent, aiming to increase their long-term stability in physiological conditions. The physical–chemical properties of the resultant nanofibrous scaffolds can be finely tailored by controlling the processing parameters, the composition and the presence of nanofillers, and the 3D organization opening the way to the fabrication of highly versatile structures for both soft and hard tissues. For instance, alginate NFs prepared using PVA or PEO as co-spinning agents, water as the unique solvent, and Ca^{2+} ions as crosslinker were proved to be highly biocompatible and suitable for long-lasting scaffolding materials.[236–239] It is noteworthy that the mass production of alginate NFs via electrospinning has been demonstrated by decreasing intramolecular hydrogen bonding of Alg via a simple sulfonation reaction.[240] Additionally, the effect of alginate dialdehyde chemical modification on the chain flexibility and electrospinning process was also explored.[241] This research suggested that increasing periodate-oxidation reaction time dramatically broadened the spinnable concentration range of alginate solutions, at the same time better promoting cell adhesion and proliferation.

Alg-NFs can easily be functionalized with bioactive substances, drugs, and even nano-sized inorganic structures in order to meet specific requirements. For example, alginate-based NFs containing curcumin and crosslinked with trifluoro-acetic acid were proposed for various possible applications, including tissue engineering owing to their high biocompatibility.[242] Yet, alginate NFs were investigated as a promising platform for immobilizing lipase, an enzyme holding great potential in bone regeneration, being able to preserve its activity for up to 14 days.[243] Honey was also incorporated into Alg-NFs to fabricate an efficient wound dressing material with enhanced antioxidant activity, strong antibacterial properties toward Gram-positive and Gram-negative bacteria, non-cytotoxicity, and good biocompatibility as reported in **Figure 12**a–d.[244] pH-responsive alginate NFs able to monitor pH changes in open wounds were also reported.[245] These NFs exploited the colorimetric sensing capability of purple cabbage anthocyanins ensuring the monitoring of wound status in real-time during the healing period, hence having a usage potential for wound dressing applications.

Electrospinning technique offers also the prospect to prepare easily composite NFs in order to exploit the strengths of different specific materials. For example, alginate NFs were combined with natural spider silk and assessed as wound dressing materials by comparing their physical–chemical and biological properties with commercially available products.[246] In this sense, these composite NFs accelerated the rate of wound healing by improving the collagen formation rate and proliferative cell activity, as well as by decreasing the inflammatory cell amount as reported in Figure 12e. The unique complexation capability of alginate and chitosan has also been exploited to fabricate in situ crosslinked stable electrospun NFs.[247] Specifically, due to the avoidance of toxic crosslinking agents, the proposed NFs showed great potential for guiding cell behavior in tissue
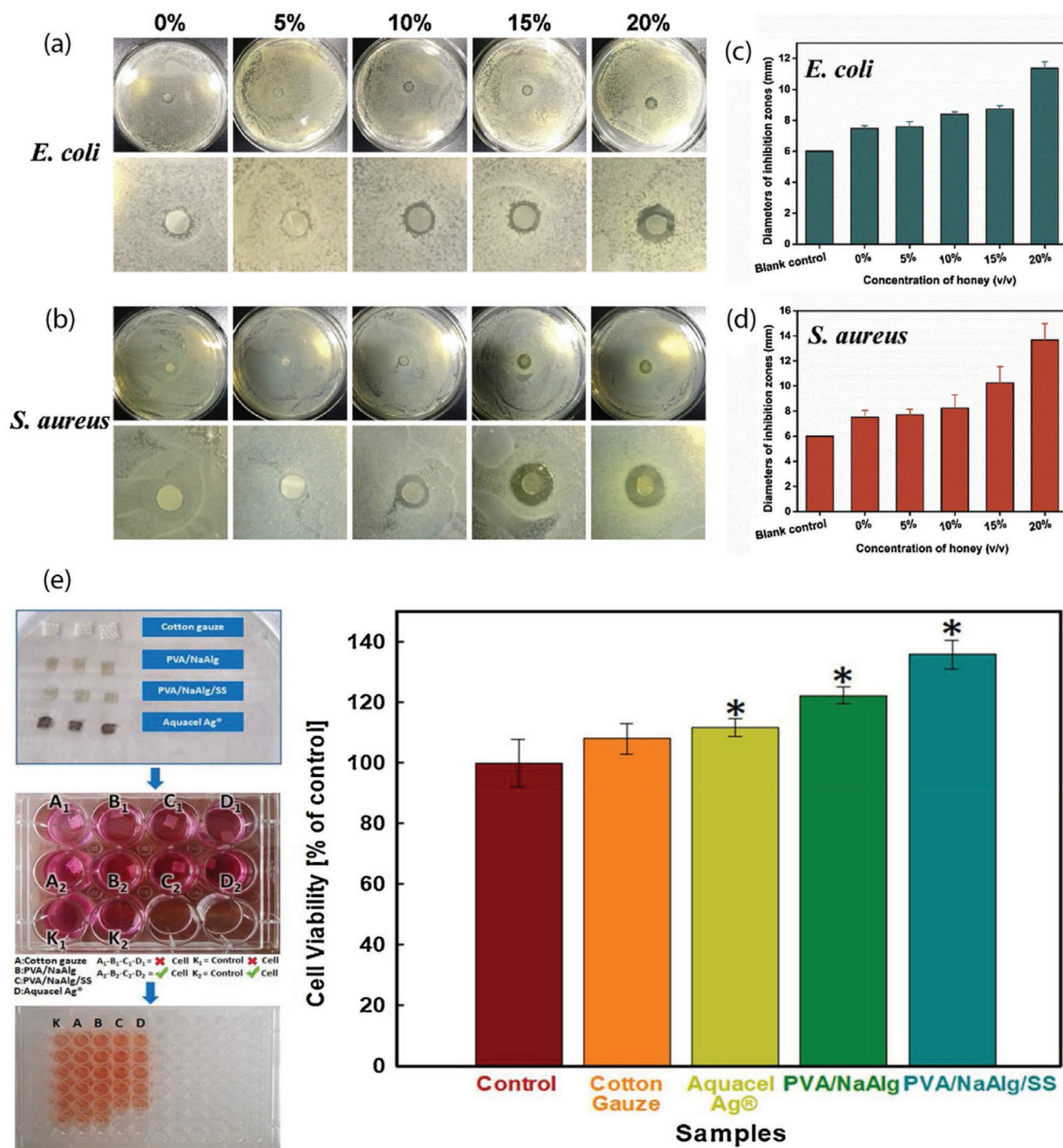
ADVANCED
Science News

www.advancedsciencenews.com

ADVANCED
MATERIALS
INTERFACES

www.advmatinterfaces.de

Figure 12. Antibacterial activity of the honey/SA/PVA nanofibrous membranes with varying honey content (0%, 5%, 10%, 15%, and 20%) evaluated by disc diffusion assay. a,b) Photographs of the inhibition zone against *E. coli* and *S. aureus*. c,d) Size of the inhibition zone against *E. coli* and *S. aureus*. a-d) Reproduced with permission.[244] Copyright 2019, Elsevier Ltd. e) Cell viability diagram by XTT assay (*$p < 0.05$). Reproduced with permission.[246] Copyright 2020, Elsevier Ltd.

regeneration applications. Yet, alginate-carboxymethyl chitosan NFs were prepared for bone tissue engineering applications.[248] Specifically, alginate was partially oxidized aiming to enhance the crosslinking efficiency, with the obtained nanofibrous scaffold maintaining structural integrity after immersion in PBS for up to 15 days and promoting the adhesion, proliferation,

and alkaline phosphatase activity of bone marrow stromal cells. Moreover, alginate-gelatin electrospun NFs have been proposed for 3D cell cultures.[249] The fabricated macroporous scaffold was obtained via a wet collector approach and presented low cytotoxicity as well as marked capability to foster mesenchymal stem cell viability over 5 weeks.

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
MATERIALS
INTERFACES**

www.advmatinterfaces.de

Additionally, multilayered alginate-based electrospun structures have also been fabricated in order to better satisfy the requirements for the regeneration of hard tissues. For example, a bilayer scaffold consisting of chitosan and alginate-chitin nano-whiskers electrospun NFs was found to promote mesenchymal stem cell proliferation at the same time ensuring antibacterial properties.[250] Yet, a multilayered nanofibrous scaffold consisting of a sandwich-like structure comprised of two hydrophobic PCL nanofibrous layers and a hydrophilic alginate-based one was investigated for bone tissue regeneration.[251] The effect of multilayer deposition of NFs was observed in terms of an increase in the water absorption, a slower degradation rate, and improved mechanical properties together with marked ability to foster cell viability.

Hybrid alginate-based NFs containing inorganic nanosized fillers have also been explored as advanced tissue engineering scaffolds. In this sense, fluorescent carbon dots were found to significantly increase the spinnability of highly concentrated alginate solutions.[252] Remarkably, these hybrid NFs inherited the fluorescence properties of the used carbon dots and displayed non-toxicity and good biocompatibility. Yet, Alg-NFs containing a layered modified silicate were fabricated as potential scaffolding materials with antibacterial properties.[253] Similarly, alginate NFs embedding in situ synthesized silver NPs with strong antibacterial properties and promises in tissue engineering applications have been reported.[254] Chitosan-coated Ag-NPs were also successfully embedded within alginate NFs, and the resultant nanofibrous structure was found appropriate for wound dressing treatment.[255] Yet, multifunctional alginate NFs enriched with hydrated iron oxide nano-clays presenting strong antibacterial activity and good mechanical properties were prepared.[256]

Chitosan-coated alginate NFs containing silver NPs and prepared in a double-step procedure were also reported.[257] This multifunctional nanofibrous structure displayed strong antibacterial activity against both Gram-negative and Gram-positive bacteria due to the double action of chitosan and Ag-NPs. Again, an alginate-PLA nanofibrous scaffold was prepared via double nozzle electrospinning and its surface was mineralized with hydroxyapatite nano-crystals.[258] This functionalization considerably increased the stem cell adhesion and growth, as well as their osteogenic differentiation, hence indicating the fabricated hybrid scaffold suitable for bone tissue engineering applications. Alg-NFs enriched with ZnO NPs showing strong antibacterial properties and promises in wound healing applications were also reported.[259,260] These hybrid nanofibrous structures displayed good mechanical properties, high water vapor permeability, hydrophilicity, good biocompatibility, and the marked capacity to foster fibroblast and keratinocyte cell viability. Furthermore, Alg-NFs containing ZnO-NPs were coupled with a PCL electrospun scaffold in order to obtain a multilayered structure able to provide both the ideal environment to foster cell viability and protective action against the external environment.[261]

Along with the traditional electrospinning solution methodology, other approaches have been reported for fabricating alginate-based biomedical products.[228,262] By way of example, coaxial electrospinning was employed to fabricate core-shell alginate-PEO NFs able to promote fibroblasts cells attachment and proliferation.[263] Coaxial alginate-chitosan NFs were also reported, with the polycomplexation occurring between the anionic polysaccharide and the cationic one guaranteeing the fiber water stability without the need of a crosslinking treatment.[264] Yet, coaxial electrospinning was explored to prepare core-shell NFs to be employed for wound healing purposes and consisting of an inner structure of poly-3-hydroxybutyric acid enriched with bacitracin nano-clays and an outside layer of alginate loaded with arginine.[265] Likewise, core-shell PCL-alginate electrospun NFs were proposed as substitutes for peripheral nerves.[266] These composite NFs promoted water absorption and biological activity of the neural precursors, leading to fast-tracking of the sciatic nerve repair in a rat model. The near-field electrospinning of alginate was also demonstrated.[267] This approach based on the direct-writing of alginate patterns allowed to spatially control cell alignment thereby opening the way to the development of 3D scaffolds with specific structural organization depending on the targeted tissue. Yet, emulsion electrospinning was exploited to develop polycaprolactone (PCL) NFs containing alginate and carboxymethyl chitosan to be used for periosteal tissue engineering.[268] Similarly, poly-lactic acid NFs enriched with Ca^{2+} crosslinked alginate were prepared to show a beneficial effect for cell proliferation and differentiation.[269] In another work, emulsion electrospinning was used to develop alginate-PLA NFs enriched with tricalcium phosphate nano-clays derived from the orange oyster shell.[270] These hybrid NFs displayed a smooth and bead-less surface, superior mechanical properties, biocompatibility, and good capability to foster bone cell viability. Again, alginate-pullulan NFs were fabricated via free surface electrospinning without the use of any co-spinning agent and undesirable organic solvents, hence showing promises for biomedical purposes.[271]

Electrospun alginate NFs have also been investigated in combination with other scaffold-forming techniques aiming to develop hierarchical structures with superior performances.[272] For example, alginate- PCL NFs were coupled with a 3D-printed PCL scaffold (**Figure 13**) with enhanced mechanical properties, hydrophilic behavior, water absorption, and in vitro cellular responses (i.e., cell viability and proliferation) and osteogenic differentiation activity compared to those of a pure PCL fibrous scaffold.[273]

Yet, bio-printed alginate structures and electrospun alginate NFs were coupled to develop a complex hierarchical structure containing angiogenic factors with strong potentialities in stem cell therapy.[274]

3.3.2. Drug Delivery

To achieve and maximize the desired therapeutic effect, drugs require to be embedded within a suitable delivery system to ensure a specific release profile. Among others, electrospun NFs are considered one of the most promising nanotechnologies in overcoming the current challenges and drawbacks of modern DDS.[275,276] Generally speaking, polymeric NFs can be used for several routes of administration, including oral, topical, transdermal, and transmucosal and can protect a drug from decomposition in the body prior to arrival at the required target.[277–279] The release of drugs from electrospun NFs can
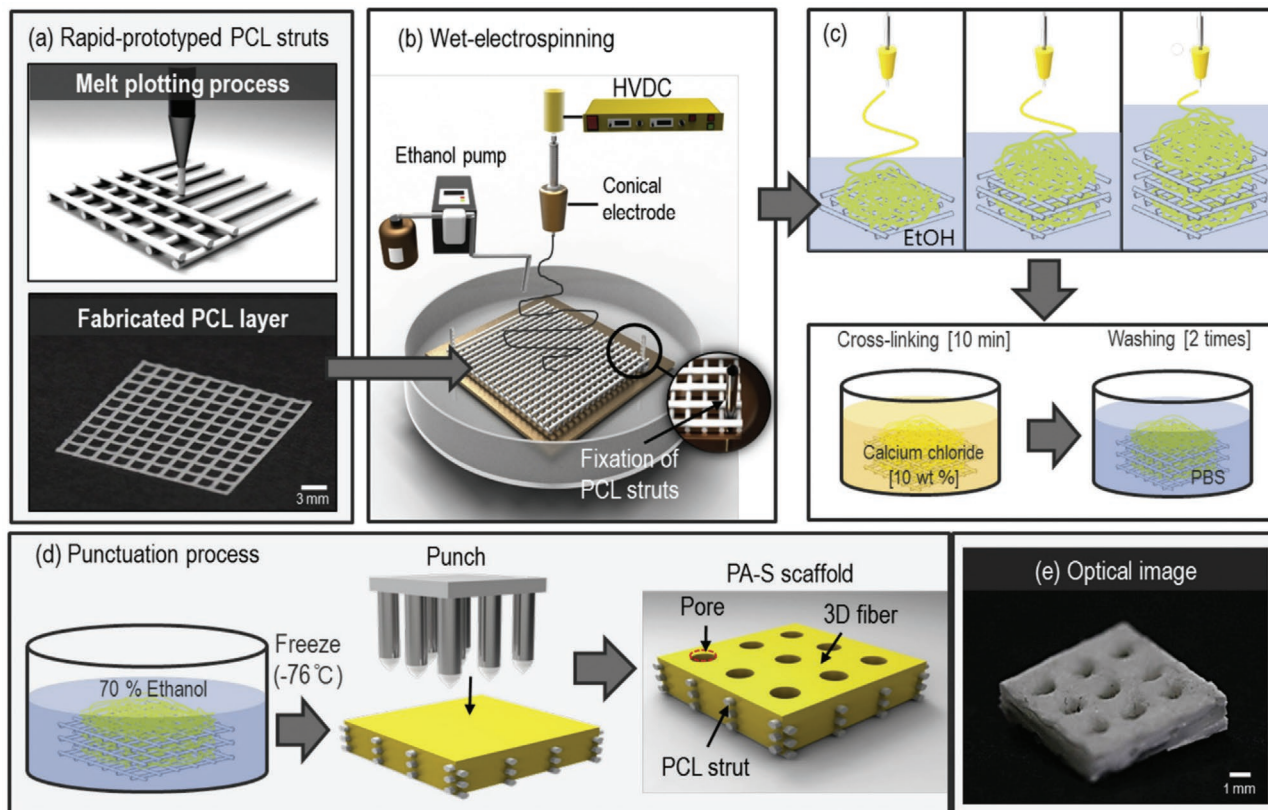
**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
MATERIALS
INTERFACES**

www.advmatinterfaces.de

Figure 13. Schematic of fabrication of a PCL/alginate fibrous scaffold with inserted PCL micro-struts. a) Rapid-prototyping process for fabrication of micro-sized PCL struts, b) wet-electrospinning process, c) layer-by-layer structure consisting of PCL/alginate fibers and layers of perpendicular PCL struts, d) punching process to produce micro-sized pores, and e) an optical image of the final PCL/alginate (PA-S) scaffold with layered PCL struts. a-e) Reproduced with permission.[273] Copyright 2014, Elsevier Ltd.

be attributed to dissolution, desorption, subsequent diffusion through water-filled pores, and polymer degradation control. Therefore, the properties of the specific drug (i.e., hydrophilic or hydrophobic), drug loading type (i.e., physical, chemical, or physical and chemical adsorption), drug loading methods (i.e., coating, embedding, encapsulating), and carrier polymer (i.e., synthetic or natural) can influence the final drug release profiles. Hence, they can be designed for different kinetics allowing to obtain both immediate and modified release profiles.[280,281] With these premises, owing to properties including biocompatibility, the ability to entrap biomolecules, and the possibility of achieving different sizes and shapes have made alginate-based systems appropriate for DDS.[2] For example, Alg-NFs loaded with moxifloxacin hydrochloride were explored as potential antibacterial wound dressing systems.[282] As much as 80% of the encapsulated drug was released from the electrospun NFs after 10 h of incubation at 37 °C, a higher drug concentration was proved to exhibit a greater antibacterial effect as well as to accelerate the rate of wound regeneration in an animal model. Similarly, sodium ibuprofen was embedded within alginate NFs.[283] Interestingly, it was observed that at pH = 6.8 (i.e., reminiscent of the intestinal tract) the NFs dissolved very rapidly freeing the entire embedded drug. Conversely, at pH = 3 (i.e., reminiscent of the stomach tract) a rapid burst release, followed by a period where no further drug was released for 2–3 h and a final stage of release freeing the remainder of

the drug, was observed. Remarkably, all the release stages could be finely controlled by varying the nanofiber composition. Yet, Alg-NFs containing lavender oil (i.e., linalool, caryophyllene, and caryophyllene oxide), a potent antibacterial and anti-inflammatory natural agent, were reported.[284] Even after 24 and 48 h the amount of linalool released was appreciable, therefore confirming the activity of NFs for more than 2 days. Again, lutein-loaded alginate NFs were prepared and showed a sustained release up to 48 h.[285] Alg-NFs were also used to encapsulate ciprofloxacin hydrochloride,[286] a potent antibiotic with low water solubility, gatifloxacin,[287] and moxifloxacin hydrochloride.[282] Along with traditional drugs, alginate NFs were used to encapsulate probiotics and tested for their delivery in simulated gastrointestinal conditions and kefir.[288] It has been proved that the electrospinning process did not influence the stability and metabolism of the loaded cells, which retained their survival/viability, and improved the survival of the strain in simulated gastric juice. Specifically, the in situ and in vitro studies demonstrated that this nanoencapsulation approach enhanced the strain survival in simulated gastric juice and improved its viability/survival in kefir. In a similar work, Alg-NFs were enriched with inulin in order to increase the probiotic bacteria encapsulation efficiency.[289] Remarkably, along with an increment of the nanofiber mat tensile strength and elongation at break, the addition of inulin improved cell viability against simulated gastric and intestinal fluids. Yet, the delivery of

growth factors from alginate electrospun NFs was explored.[290] Specifically, sulfonated alginate was exploited to ensure specific binding and controlled release of a heparin-like growth factor (i.e., transforming growth factor-β1).

Also, composite alginate-soy protein isolated electrospun NFs were loaded with vancomycin and their release behavior was broadly investigated.[291] These NFs guaranteed a slower release of vancomycin in the initial stage followed by a constant release over a longer time compared to pure Alg-NFs, hence providing strong antibacterial activity against Gram-positive bacteria as well as good biocompatibility and non-cytotoxicity. Alginate-chitosan electrospun NFs containing gentamicin were also prepared and explored as anti-bacterial wound patches.[292] These composite NFs displayed both growth inhibition against bacteria and tissue regeneration capabilities being able to promote fibroblast cell adhesion. Additionally, alginate-carboxymethyl cellulose electrospun NFs loaded with lidocaine were explored as an anesthetic delivery system.[293] Noticeably, the lidocaine release profile was finely controlled by tuning the alginate crosslinking degree with the resultant mats displaying also marked anti-adhesion properties. Core-shell alginate-PEO NFs were investigated for the delivery of vitamin C in the treatment of skin disorders,[294] whereas core-shell alginate-chitosan NFs loaded with dexpanthenol were proposed as a transdermal delivery system, with the addition of chitosan ensuring a better-enhanced control over the drug release.[295] A double-layer nanofibrous mat consisting of a PEO and an Alg-based electrospun patches was loaded with gabapentin and acetaminophen, two essential oils used in the treatment of burn wounds.[296] Such a multi-layer structure was specially developed in order to ensure the burst release of gabapentin, to provide a pain killer action, and the sustained release of acetaminophen, to ensure anti-inflammatory activity and tissue regeneration action. Yet, hybrid Alg-NFs enriched with artemisia argyi oil and laponite nano-clays were explored as a delivery platform with potent antibacterial properties.[297] Similarly, alginate NFs co-loaded with betanin and TiO_2 NPs were investigated as potential antibacterial dressings.[298] Alginate electrospun NFs and containing ad-hoc synthesized ZnO NPs with strong antibacterial properties were also proposed as an innovative drug delivery platform.[299] Noticeably, the release profile was found to be finely tunable by simply changing the chemical structure of the encapsulated drug model molecule.

4. Concluding Remarks and Future Perspectives

Nowadays, naturally occurring polymers are being employed in several application fields with particular emphasis on the biomedical and pharmaceutical industries where their unique biological properties play a fundamental role. To this purpose, alginate-based nanomaterials hold extreme promises owing to their superior biocompatibility, mucoadhesive properties, non-toxicity, hydrophilicity, bioavailability, relatively low cost, and possible mass production. Hence, it is not surprising that in recent years tremendous efforts have been devoted to the fabrication of different alginate nanostructures that can be integrated into a wide range of applications, including drug and gene delivery, cancer therapy, tissue engineering, wound

dressing, and biosensors. Among others, based on the present literature, alginate-based NPs and electrospun NFs represent the most promising ones for drug delivery and tissue engineering purposes. Specifically, alginate NPs and their derivates offer several advantages compared to traditional DDS. By way of example, they can enhance the water solubility of hydrophobic substances leading to previously unreachable loading efficiency acting at the same time as protective agents, they are suitable for several administration routes minimizing possible side reaction and as drug release controller depending on the specific purpose. Additionally, the latest advances in polymer chemistry and nanotechnology made it possible to enrich Alg-NPs with stimuli-responsive properties opening the way to their proficient use in targeted delivery applications. Thereby, these unique nanostructures are gaining an increasing deal of interest in cancer therapy where their drug-triggered release may reduce the adverse effects of commercial chemotherapies. Similarly, alginate electrospun NFs hold great potentialities in both tissue engineering and drug delivery applications. Indeed, nanofibrous scaffolds are capable of resembling the microstructure of the native ECM presenting a high surface-to-volume ratio and porosity, hence providing the ideal environment to foster cell viability and promote tissue regeneration. Remarkably, the physical–chemical properties of these structures can be finely tuned either by controlling the composition and spatial organization of the NFs or by adding bioactive substances and/or inorganic nanostructures with specific properties. It is noteworthy that the mild processing conditions of electrospinning even allow the efficient encapsulation of sensible molecules without occurring in degradation processes, thus allowing the preparation of electrospun scaffold presenting both cell adhesion and drug delivery capabilities. Due to such versatility, it is not surprising that alginate-based nanofibrous scaffolds have shown great promises in substituting and/or repairing both soft and hard tissues, including bones, cartilage, nerves, and skin.

Despite the great advantages displayed by alginate NPs and alginate electrospun NFs and the fact that their applicability for biomedical and pharmaceutical purposes has been demonstrated by several proof-of-concept studies, their use on a large scale is far from being achieved. As a matter of fact, such nanostructures present several drawbacks and limitations which, to date, hinder the translation of laboratory-scale studies on effective clinical applications. First, being alginate naturally derived, it presents an intrinsically variable structure able to affect the material physical–chemical features, which may be further influenced by the extraction and processing procedures. In addition, despite the overall biocompatibility of pure alginate seems to be not dependent on its composition, the presence of impurities in industrially derived materials could lead to unexpected side reactions in the human body. Consequently, in the near future, it is of topical importance to develop standardized extraction and purification procedures, as well as laboratory quality tests, to ensure the repeatability of either the raw or the processed material features. Second, another great challenge in the large-scale use of alginate-based nanostructures is the considerably low production rate with respect to synthetic polymers. Indeed, even if the great environmental availability of alginate, along with the possibility to use water as the unique

processing solvent, makes such a material a promising candidate to substitute petroleum-derived products not only in the biomedical and pharmaceutical industry, its processability via common techniques is lacking. Specifically, the electrospinning of pure alginate solutions cannot be performed due to the polysaccharide tendency to form hydrogen bonds and polyelectrolyte nature, whereas surfactants are usually required in the fabrication of Alg-NPs to ensure nano-sizing, good homogeneity, and result reproducibility. Consequently, since mass production approaches are missing, the beneficial biological properties of alginate can be reduced, eliminated, or even inverted during the nanostructure fabrication. With these premises, further investigations are essential to overcome alginate current processing limitations with the continuous technological advances offering promising solutions. Another key aspect in the use of alginate-based nanostructures for biomedical and pharmaceutical purposes is connected to the long-term safety concerns, especially in the case of hybrid systems containing nano-sized inorganic materials whose leakage from the polymeric matrix may lead to their accumulation in specific tissues with related inflammatory or potentially fatal adverse reactions. Additionally, since only low molecular weight alginate can be completely eliminated via the renal system, long macromolecules could be retained in the circulatory system inducing unexpected effects. Unfortunately, the lack of extensive literature concerning long-term in vivo tests of alginate-based nanomaterials leaves, to date, the safety question open. In this regard, it is noteworthy that the in vitro and in vivo responses of alginate-based nanostructures may significantly differ. For example, it is well known that the majority of delivery system mechanisms excel the in vitro studies but completely fail the in vivo ones, especially when the purpose comprises targeted delivery. Additionally, the immune response may considerably vary between individuals, which possibly hinders the development of alginate-based biomedical and pharmaceutical devices for a broad number of patients. The stability of alginate NPs and alginate NFs under physiological like conditions still poses significant doubts, especially when the bivalent ion gelation method is used. Indeed, despite such an approach ensure good biocompatibility and non-toxicity, it is most likely not able to provide long-term stability and resistance to alginate-based nanostructures. Conversely, chemical crosslinkers may be associated with cytotoxicity issues and stronger side effects but can generally ensure much greater stability. Thereby, it is important to correctly evaluate the expected lifetime of Alg-NPs and Alg-NFs in the human body to design them with the capability to last for a sufficient time to completely exhibit their function. For all these reasons, more extensive in vivo evaluation is warranted to better understand the actual behavior of alginate-based nanomaterials.

Due to the great promises held by alginate biomaterials and the great academic and industrial interest showed by its nanomaterials, it is likewise that the above-discussed challenges will be solved soon. In this sense, future development could be represented by the enrichment of alginate-based nanostructures with smart and even personalized functionalities. Indeed, several authors have already reported the use of alginate-based nanocarriers able to respond to both chemical and physical stimuli in order to deliver the encapsulated drug with accurate time and specific sites. However, except in some specific cases, such an effect is obtained by combining alginate with other polymers and/or inorganic nanofillers, which are the true responsible for this stimuli-responsive behavior but often present limitations in terms of biocompatibility, costs, and large-scale exploitation. A much more promising but to date scarcely investigated alternative consists of the chemical modification of alginate macromolecules with specific functional groups able to confer and enrich the resultant nanomaterials with unique, specific, and even personalized features. Such a possibility may indeed easily lead to the fabrication of intrinsically biocompatible alginate nanomaterials able to deliver a certain drug or a chemotherapy agent to a targeted site or at a specific time, hence making it possible to considerably improve the life quality of patients affected by chronic diseases and tumors. Enriching alginate-based nanomaterials with tailor-made stimuli-responsive properties may also allow the development of a new class of scaffolds capable to better induce cell differentiation, which will eventually lead to their exchangeable use for different tissues, including organs and neural zones.

Conflict of Interest

The authors declare no conflict of interest.

[1] S. Anand, P. S. Rajinikanth, in *Biopolymer-Based Nanomaterials in Drug Delivery*, Elsevier, Amsterdam **2021**, p. 339.

[2] M. A. Taemeh, A. Shiravandi, M. A. Korayem, H. Daemi, *Carbohydr. Polym.* **2020**, *228*, 115419.

[3] R. A. Sheldon, M. Norton, *Green Chem.* **2020**, *22*, 6310.

[4] L. Cao, W. Lu, A. Mata, K. Nishinari, Y. Fang, *Carbohydr. Polym.* **2020**, *242*, 116389.

[5] K. Y. Lee, D. J. Mooney, *Prog. Polym. Sci.* **2012**, *37*, 106.

[6] A. E. Stoica, C. Chircov, A. M. Grumezescu, *Molecules* **2020**, *25*, 2699.

[7] H. Choukaife, A. A. Doolaanea, M. Alfatama, *Pharmaceuticals* **2020**, *13*, 335.

[8] P. Manivasagan, J. Oh, *Int. J. Biol. Macromol.* **2016**, *82*, 315.

[9] M. Rinaudo, *TIP* **2014**, *17*, 92.

[10] K. I. Draget, in *Handbook of Hydrocolloids*, 2nd ed., Elsevier Inc., Amsterdam **2009**, p. 807.

[11] M. Rinaudo, *Polym. Int.* **2008**, *57*, 397.

[12] U. Remminghorst, B. H. A. Rehm, *Biotechnol. Lett.* **2006**, *28*, 1701.

[13] V. Urtuvia, N. Maturana, F. Acevedo, C. Peña, A. Díaz-Barrera, *World J. Microbiol. Biotechnol.* **2017**, *33*, 198.

[14] H. Hecht, S. Srebnik, *Biomacromolecules* **2016**, *17*, 2160.

[15] I. P. S. Fernando, W. W. Lee, E. J. Han, G. Ahn, *Chem. Eng. J.* **2020**, *391*, 123823.

[16] A. Can Karaca, I. G. Erdem, M. M. Ak, *LWT* **2018**, *92*, 297.

[17] A. Dodero, S. Vicini, M. Alloisio, M. Castellano, *Rheol. Acta* **2020**, *59*, 365.

[18] C. L. Okolie, B. Mason, A. Mohan, N. Pitts, C. C. Udenigwe, *Food Biosci.* **2020**, *37*, 100672.

[19] A. Dodero, S. Vicini, M. Castellano, *Food Hydrocolloids* **2020**, *109*, 106128.

[20] S. Thakur, B. Sharma, A. Verma, J. Chaudhary, S. Tamulevicius, V. K. Thakur, *J. Cleaner Prod.* **2018**, *198*, 143.

[21] C. Hu, W. Lu, A. Mata, K. Nishinari, Y. Fang, *Int. J. Biol. Macromol.* **2021**, *177*, 578.

[22] A. Dodero, L. Pianella, S. Vicini, M. Alloisio, M. Ottonelli, M. Castellano, *Eur. Polym. J.* **2019**, *118*, 586.

[23] S. N. Pawar, in *Seaweed Polysaccharides: Isolation, Biological and Biomedical Applications*, Elsevier, Amsterdam **2017**, p. 111.

[24] L. Szabó, S. Gerber-Lemaire, C. Wandrey, *Polymers* **2020**, *12*, 919.

[25] C. G. Gomez, M. Rinaudo, M. A. Villar, *Carbohydr. Polym.* **2007**, *67*, 296.

[26] J. Yang, Y. Zhao, Y. Fang, *Carbohydr. Res.* **2008**, *343*, 719.

[27] S. N. Pawar, K. J. Edgar, *Carbohydr. Polym.* **2013**, *98*, 1288.

[28] J. S. Yang, Y. J. Xie, W. He, *Carbohydr. Polym.* **2011**, *84*, 33.

[29] M. Liu, X. Song, Y. Wen, J. L. Zhu, J. Li, *ACS Appl. Mater. Interfaces* **2017**, *9*, 35673.

[30] X. Gao, Z. Yu, B. Liu, J. Yang, X. Yang, Y. Yu, *Eur. Polym. J.* **2020**, *133*, 109779.

[31] H. W. Ooi, C. Mota, A. Tessa Ten Cate, A. Calore, L. Moroni, M. B. Baker, *Biomacromolecules* **2018**, *19*, 3390.

[32] J. M. Silva, J. R. García, R. L. Reis, A. J. García, J. F. Mano, *Acta Biomater.* **2017**, *51*, 279.

[33] Y. Zhuang, F. Yu, J. Ma, J. Chen, *J. Colloid Interface Sci.* **2017**, *507*, 250.

[34] R. G. Huamani-Palomino, C. R. Jacinto, H. Alarcón, I. M. Mejía, R. C. López, D. de Oliveira Silva, E. T. G. Cavalheiro, T. Venâncio, J. Z. Dávalos, A. C. Valderrama, *Int. J. Biol. Macromol.* **2019**, *129*, 1056.

[35] CFR—Code of Federal Regulations Title 21, https://www.fda.gov/medical-devices/medical-device-databases/code-federal-regulations-title-21-food-and-drugs (accessed: May 2021).

[36] Y. Qin, J. Jiang, L. Zhao, J. Zhang, F. Wang, in *Biopolymers for Food Design*, Elsevier Inc., Amsterdam **2018**, p. 409.

[37] J. Liu, S. Yang, X. Li, Q. Yan, M. J. T. Reaney, Z. Jiang, *Compr. Rev. Food Sci. Food Saf.* **2019**, *18*, 1859.

[38] G. Orive, S. Ponce, R. M. Hernández, A. R. Gascón, M. Igartua, J. L. Pedraz, *Biomaterials* **2002**, *23*, 3825.

[39] C. C. Spadari, F. W. M. S. de Bastiani, L. B. Lopes, K. Ishida, *Int. J. Nanomed.* **2019**, *14*, 5187.

[40] M. M. Alsmadi, R. M. Obaidat, M. Alnaief, B. A. Albiss, N. Hailat, *AAPS PharmSciTech* **2020**, *21*, 191.

[41] A. Liberski, N. Latif, C. Raynaud, C. Bollensdorff, M. Yacoub, *Glob. Cardiol. Sci. Pract.* **2016**, *2016*, 1.

[42] T. Distler, K. McDonald, S. Heid, E. Karakaya, R. Detsch, A. R. Boccaccini, *ACS Biomater. Sci. Eng.* **2020**, *6*, 3899.

[43] S. Reakasame, A. R. Boccaccini, *Biomacromolecules* **2018**, *19*, 3.

[44] Z. H. Kelishomi, B. Goliaei, H. Mahdavi, A. Nikoofar, M. Rahimi, A. A. Moosavi-Movahedi, F. Mamashli, B. Bigdeli, *Food Chem.* **2016**, *196*, 897.

[45] D. Bi, Q. Lai, N. Cai, T. Li, Y. Zhang, Q. Han, Y. Peng, H. Xu, J. Lu, W. Bao, Q. Liu, X. Xu, *J. Agric. Food Chem.* **2018**, *66*, 2083.

[46] M. V. Alvarez, M. F. Bambace, G. Quintana, A. Gomez-Zavaglia, M. del Rosario Moreira, *LWT* **2021**, *137*, 110483.

[47] J. Li, J. He, Y. Huang, *Int. J. Biol. Macromol.* **2017**, *94*, 466.

[48] J. Kurczewska, M. Cegłowski, P. Pecyna, M. Ratajczak, M. Gajęcka, G. Schroeder, *Mater. Lett.* **2017**, *201*, 46.

[49] D. M. S. A. Salem, M. A. E. Sallam, T. N. M. A. Youssef, *Bioorg. Chem.* **2019**, *87*, 103.

[50] Y. Shtenberg, M. Goldfeder, H. Prinz, J. Shainsky, Y. Ghantous, I. Abu El-Naaj, A. Schroeder, H. Bianco-Peled, *Int. J. Biol. Macromol.* **2018**, *111*, 62.

[51] F. Tentor, G. Siccardi, P. Sacco, D. Demarchi, E. Marsich, K. Almdal, S. Bose Goswami, A. Boisen, *J. Mater. Sci.: Mater. Med.* **2020**, *31*, 25.

[52] R. Gheorghita Puscaselu, A. Lobiuc, M. Dimian, M. Covasa, *Polymers* **2020**, *12*, 2417.

[53] M. S. Abdel Aziz, H. E. Salama, M. W. Sabaa, *LWT* **2018**, *96*, 455.

[54] T. Senturk Parreidt, K. Müller, M. Schmid, *Foods* **2018**, *7*, 170.

[55] Y. Jiang, J. A. De La Cruz, L. Ding, B. Wang, X. Feng, Z. Mao, H. Xu, X. Sui, *Int. J. Biol. Macromol.* **2020**, *148*, 811.

[56] S. R. Derkach, D. S. Kolotova, N. G. Voron'ko, E. D. Obluchinskaya, A. Y. Malkin, *Polymers* **2021**, *13*, 743.

[57] G. Gaggero, M. Delucchi, G. Allegretta, S. Vicini, R. Botter, *Prog. Org. Coat.* **2021**, *151*, 106016.

[58] B. Wang, Y. Wan, Y. Zheng, X. Lee, T. Liu, Z. Yu, J. Huang, Y. S. Ok, J. Chen, B. Gao, *Crit. Rev. Environ. Sci. Technol.* **2019**, *49*, 318.

[59] A. Dodero, P. Lova, S. Vicini, M. Castellano, D. Comoretto, *Chemosensors* **2020**, *8*, 37.

[60] T. Ramdhan, S. H. Ching, S. Prakash, B. Bhandari, *Trends Food Sci. Technol.* **2020**, *106*, 150.

[61] P. Rastogi, B. Kandasubramanian, *Biofabrication* **2019**, *11*, 042001.

[62] M. Farokhi, F. Jonidi Shariatzadeh, A. Solouk, H. Mirzadeh, *Int. J. Polym. Mater. Polym. Biomater.* **2020**, *69*, 230.

[63] B. Sarker, A. R. Boccaccini, *Alginates and Their Biomedical Applications*, Springer, Singapore **2018**, pp. 121–155.

[64] Z. Xu, M. T. Lam, *Alginates and Their Biomedical Applications*, Springer, Singapore **2018**, pp. 185–212.

[65] K. Varaprasad, T. Jayaramudu, V. Kanikireddy, C. Toro, E. R. Sadiku, *Carbohydr. Polym.* **2020**, *236*, 116025.

[66] A. Dodero, I. Donati, S. Scarfì, S. Mirata, S. Alberti, P. Lova, D. Comoretto, M. Alloisio, S. Vicini, M. Castellano, *Mater. Sci. Eng. C* **2021**, *124*, 112067.

[67] S. Vicini, M. Mauri, S. Vita, M. Castellano, *J. Appl. Polym. Sci.* **2018**, *135*, 46390.

[68] D. M. Hariyadi, N. Islam, *Adv. Pharmacol. Pharm. Sci.* **2020**, *2020*, 8886095.

[69] N. T. T. Uyen, Z. A. A. Hamid, N. X. T. Tram, N. Ahmad, *Int. J. Biol. Macromol.* **2020**, *153*, 1035.

[70] B. Reig-Vano, B. Tylkowski, X. Montané, M. Giamberini, *Int. J. Biol. Macromol.* **2021**, *170*, 424.

[71] L. He, Z. Shang, H. Liu, Z. X. Yuan, *Biomed Res. Int.* **2020**, *2020*, 1487259.

[72] Z. Shokri, F. Seidi, S. Karami, C. Li, M. R. Saeb, H. Xiao, *Carbohydr. Polym.* **2021**, *262*, 117963.

[73] W. Zheng, C. Gao, L. Shen, C. Qu, X. Zhang, L. Yang, Q. Feng, R. Tang, *Sensors* **2020**, *20*, 4831.

[74] P. Shende, P. Kasture, R. S. Gaud, *Artif. Cells, Nanomed., Biotechnol.* **2018**, *46*, 413.

[75] M. Thiruvengadam, G. Rajakumar, I. M. Chung, *3 Biotech* **2018**, *8*, 74.

[76] K. Pathakoti, M. Manubolu, H. M. Hwang, in *Handbook of Nanomaterials for Industrial Applications*, Elsevier, Amsterdam **2018**, p. 894.

[77] M. Naslahzadeh, S. M. Sajadi, M. Sajjadi, Z. Issaabadi, in *Interface Science and Technology*, Elsevier B.V., Amsterdam **2019**, p. 1.

[78] S. Kargozar, M. Mozafari, *Mater. Today: Proc.* **2018**, *5*, 15492.

[79] J. J. Ramsden, *Applied Nanotechnology: The Conversion of Research Results to Products*, Elsevier, Amsterdam **2018**.

[80] S. Bayda, M. Adeel, T. Tuccinardi, M. Cordani, F. Rizzolio, *Molecules* **2019**, *25*, 112.

[81] M. Mozafari, *Mol. Ther.* **2018**, *26*, 2085.

[82] S. Chen, X. J. Liang, *Sci. China: Life Sci.* **2018**, *61*, 371.

[83] P. Kesharwani, B. Gorain, S. Y. Low, S. A. Tan, E. C. S. Ling, Y. K. Lim, C. M. Chin, P. Y. Lee, C. M. Lee, C. H. Ooi, H. Choudhury, M. Pandey, *Diabetes Res. Clin. Pract.* **2018**, *136*, 52.

[84] C. G. Yao, P. N. Martins, *Transplantation* **2020**, *104*, 682.

[85] P. Valentini, A. Galimberti, V. Mezzasalma, F. De Mattia, M. Casiraghi, M. Labra, P. P. Pompa, *Angew. Chem., Int. Ed.* **2017**, *56*, 8094.

[86] R. Kumar, K. R. Aadil, S. Ranjan, V. B. Kumar, *J. Drug Delivery Sci. Technol.* **2020**, *57*, 101617.

[87] N. Z. Laird, T. M. Acri, J. L. Chakka, J. C. Quarterman, W. I. Malkawi, S. Elangovan, A. K. Salem, *Eur. J. Pharm. Biopharm.* **2021**, *161*, 15.

[88] M. S. Goldberg, *Nat. Rev. Cancer* **2019**, *19*, 587.

[89] W. Song, A. C. Anselmo, L. Huang, *Nat. Nanotechnol.* **2019**, *14*, 1093.

[90] M. Saeedi, M. Eslamifar, K. Khezri, S. M. Dizaj, *Biomed. Pharmacother.* **2019**, *111*, 666.

[91] M. A. Dos Santos Ramos, P. B. Da Silva, L. Spósito, L. G. De Toledo, B. vidal Bonifácio, C. F. Rodero, K. C. Dos Santos, M. Chorilli, T. M. Bauab, *Int. J. Nanomed.* **2018**, *13*, 1179.

[92] B. Pelaz, C. Alexiou, R. A. Alvarez-Puebla, F. Alves, A. M. Andrews, S. Ashraf, L. P. Balogh, L. Ballerini, A. Bestetti, C. Brendel, S. Bosi, M. Carril, W. C. W. Chan, C. Chen, X. Chen, X. Chen, Z. Cheng, D. Cui, J. Du, C. Dullin, A. Escudero, N. Feliu, M. Gao, M. George, Y. Gogotsi, A. Grünweller, Z. Gu, N. J. Halas, N. Hampp, R. K. Hartmann, et al., *ACS Nano* **2017**, *11*, 2313.

[93] Y. Wang, Z. Zhou, M. Chen, Y. Huang, C. Wang, W. L. Song, *Appl. Surf. Sci.* **2018**, *439*, 176.

[94] H. N. Cheng, L. J. Doemeny, C. L. Geraci, D. G. Schmidt, in *Nanotechnology: Delivering the Promise*, Vol. 2, American Chemical Society, Washington **2016**, p. 1.

[95] G. Rius, A. Baldi, B. Ziaie, M. Z. Atashbar, in *Springer Handbooks*, Springer, Berlin **2017**, p. 51.

[96] Y. Zeng, Y. Xiang, R. Sheng, H. Tomás, J. Rodrigues, Z. Gu, H. Zhang, Q. Gong, K. Luo, *Bioact. Mater.* **2021**, *6*, 3358.

[97] D. Shahriari, J. Koffler, D. A. Lynam, M. H. Tuszynski, J. S. Sakamoto, *J. Biomed. Mater. Res., Part A* **2016**, *104*, 611.

[98] P. Paraskevopoulou, I. Smirnova, T. Athamneh, M. Papastergiou, D. Chriti, G. Mali, T. Čendak, G. Raptopoulos, P. Gurikov, *RSC Adv.* **2020**, *10*, 40843.

[99] H. Daemi, M. Barikani, *Sci. Iran.* **2012**, *19*, 2023.

[100] K. Hu, D. J. McClements, *Food Hydrocolloids* **2015**, *44*, 101.

[101] P. Severino, C. F. da Silva, L. N. Andrade, D. de Lima Oliveira, J. Campos, E. B. Souto, *Curr. Pharm. Des.* **2019**, *25*, 1312.

[102] M. S. Hasnain, A. K. Nayak, M. Kurakula, M. N. Hoda, in *Alginates in Drug Delivery*, Elsevier, Amsterdam **2020**, p. 129.

[103] A. Raza, F. B. Sime, P. J. Cabot, F. Maqbool, J. A. Roberts, J. R. Falconer, *Drug Discovery Today* **2019**, *24*, 858.

[104] M. Lopes, B. Abrahim, F. Veiga, R. Seiça, L. M. Cabral, P. Arnaud, J. C. Andrade, A. J. Ribeiro, *Expert Opin. Drug Delivery* **2017**, *14*, 769.

[105] M. Cheraghi, B. Negahdari, H. Daraee, A. Eatemadi, *Biomed. Pharmacother.* **2017**, *86*, 316.

[106] D. Lombardo, M. A. Kiselev, M. T. Caccamo, *J. Nanomater.* **2019**, *2019*, 3702518.

[107] D. Thomas, K. KurienThomas, M. S. Latha, *Int. J. Biol. Macromol.* **2020**, *154*, 888.

[108] S. I. Somo, K. Langert, C. Y. Yang, M. K. Vaicik, V. Ibarra, A. A. Appel, B. Akar, M. H. Cheng, E. M. Brey, *Acta Biomater.* **2018**, *65*, 53.

[109] E. Kim, M. H. Kim, J. H. Song, C. Kang, W. H. Park, *Int. J. Biol. Macromol.* **2020**, *154*, 989.

[110] R. Delshadi, A. Bahrami, D. J. McClements, M. D. Moore, L. Williams, *J. Controlled Release* **2021**, *331*, 30.

[111] P. Shrimal, G. Jadeja, S. Patel, *Chem. Eng. Res. Des.* **2020**, *153*, 728.

[112] S. Bin Bae, H. C. Nam, W. H. Park, *Int. J. Biol. Macromol.* **2019**, *133*, 278.

[113] W. C. Wu, S. H. Wang, S. T. Ou, Y. W. H. Liu, B. H. Liu, F. G. Tseng, *Nanomedicine* **2020**, *15*, 1067.

[114] B. C. Mohanta, M. N. Javed, M. S. Hasnain, A. K. Nayak, in *Alginates in Drug Delivery*, Elsevier, Amsterdam **2020**, pp. 297–321.

[115] V. S. Meka, M. K. G. Sing, M. R. Pichika, S. R. Nali, V. R. M. Kolapalli, P. Kesharwani, *Drug Discovery Today* **2017**, *22*, 1697.

[116] E. Guzmán, R. G. Rubio, F. Ortega, *Adv. Colloid Interface Sci.* **2020**, *282*, 102197.

[117] Y. Hu, A. S. Mao, R. M. Desai, H. Wang, D. A. Weitz, D. J. Mooney, *Lab Chip* **2017**, *17*, 2481.

[118] R. Zhang, J. Lv, C. Zhang, R. Yang, X. Sun, B. Song, C. P. Wong, *Colloids Surf., A* **2018**, *542*, 15.

[119] S. Jana, K. Kumar Sen, A. Gandhi, *Curr. Pharm. Des.* **2016**, *22*, 3399.

[120] M. Xing, Q. Cao, Y. Wang, H. Xiao, J. Zhao, Q. Zhang, A. Ji, S. Song, *Mar. Drugs* **2020**, *18*, 144.

[121] S. Boi, N. Rouatbi, E. Dellacasa, D. Di Lisa, P. Bianchini, O. Monticelli, L. Pastorino, *Int. J. Biol. Macromol.* **2020**, *156*, 454.

[122] F. Martínez-Gómez, J. Guerrero, B. Matsuhiro, J. Pavez, *Carbohydr. Polym.* **2017**, *155*, 182.

[123] N. S. Elbialy, N. Mohamed, *Int. J. Biol. Macromol.* **2020**, *154*, 114.

[124] S. Abdelghany, M. Alkhawaldeh, H. S. AlKhatib, *J. Drug Delivery Sci. Technol.* **2017**, *39*, 442.

[125] T. Athamneh, A. Amin, E. Benke, R. Ambrus, C. S. Leopold, P. Gurikov, I. Smirnova, *J. Supercrit. Fluids* **2019**, *150*, 49.

[126] L. Agüero, D. Zaldivar-Silva, L. Peña, M. Dias, *Carbohydr. Polym.* **2017**, *168*, 32.

[127] B. J. Dukovski, I. Plantić, I. Čunčić, I. Krtalić, M. Juretić, I. Pepić, J. Lovrić, A. Hafner, *Int. J. Pharm.* **2017**, *533*, 480.

[128] A. A. Karpov, N. A. Anikin, A. M. Mihailova, S. S. Smirnov, D. D. Vaulina, L. A. Shilenko, D. Y. Ivkin, A. Y. Bagrov, O. M. Moiseeva, M. M. Galagudza, *Int. J. Mol. Sci.* **2021**, *22*, 1149.

[129] F. S. Y. Wong, K. K. Tsang, A. M. W. Chu, B. P. Chan, K. M. Yao, A. C. Y. Lo, *Biomaterials* **2019**, *201*, 53.

[130] S. Mokhtari, S. M. Jafari, E. Assadpour, *Food Chem.* **2017**, *229*, 286.

[131] A. Maghsoudi, F. Yazdian, S. Shahmoradi, L. Ghaderi, M. Hemati, G. Amoabediny, *Mater. Sci. Eng. C* **2017**, *75*, 1259.

[132] A. S. El-Houssiny, A. A. Ward, D. M. Mostafa, S. L. Abd-El-Messieh, K. N. Abdel-Nour, M. M. Darwish, W. A. Khalil, *Eur. J. Nanomed.* **2017**, *9*, 105.

[133] F. Yasmin, X. Chen, B. Eames, *J. Funct. Biomater.* **2019**, *10*, 42.

[134] X. Wei, H. Xiong, D. Zhou, X. Jing, Y. Huang, *Carbohydr. Polym.* **2018**, *186*, 45.

[135] Y. Belguesmia, N. Hazime, I. Kempf, R. Boukherroub, D. Drider, *Int. J. Mol. Sci.* **2020**, *21*, 8654.

[136] A. L. Urzedo, M. C. Gonçalves, M. H. M. Nascimento, C. B. Lombello, G. Nakazato, A. B. Seabra, *Mater. Sci. Eng. C* **2020**, *112*, 110933.

[137] S. Hadiya, R. Radwan, M. Zakaria, T. El-Sherif, M. A. Hamad, M. Elsabahy, *Pharm. Dev. Technol.* **2021**, *26*, 30.

[138] A. Esmaeili, S. Behzadi, *Colloids Surf., B* **2017**, *158*, 556.

[139] K. S. Joshy, A. George, J. Jose, N. Kalarikkal, L. A. Pothen, S. Thomas, *Int. J. Biol. Macromol.* **2017**, *103*, 1265.

[140] R. Govindaraju, R. Karki, J. Chandrashekarappa, M. Santhanam, A. K. K. Shankar, H. K. Joshi, G. Divakar, *Pharm. Nanotechnol.* **2019**, *7*, 39.

[141] T. M. Shehata, M. M. Ibrahima, *Drug Dev. Ind. Pharm.* **2019**, *45*, 1907.

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

**ADVANCED
MATERIALS
INTERFACES**

www.advmatinterfaces.de

[142] M. Abnoos, M. Mohseni, S. A. J. Mousavi, K. Ashtari, R. Ilka, B. Mehravi, *Int. J. Biol. Macromol.* **2018**, *118*, 1319.

[143] F. N. Sorasitthiyanukarn, P. Ratnatilaka Na Bhuket, C. Muangnoi, P. Rojsitthisak, P. Rojsitthisak, *Int. J. Biol. Macromol.* **2019**, *131*, 1125.

[144] D. Aluani, V. Tzankova, M. Kondeva-Burdina, Y. Yordanov, E. Nikolova, F. Odzhakov, A. Apostolov, T. Markova, K. Yoncheva, *Int. J. Biol. Macromol.* **2017**, *103*, 771.

[145] M. Hashemian, D. Anisian, M. Ghasemi-Kasman, A. Akbari, M. Khalili-Fomeshi, S. Ghasemi, F. Ahmadi, A. A. Moghadamnia, A. Ebrahimpour, *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2017**, *79*, 462.

[146] S. E. S. Radwan, M. S. Sokar, D. A. Abdelmonsif, A. H. El-Kamel, *Int. J. Pharm.* **2017**, *526*, 366.

[147] T. Niaz, H. Nasir, S. Shabbir, A. Rehman, M. Imran, *Int. J. Biol. Macromol.* **2016**, *91*, 180.

[148] V. Toragall, N. Jayapala, B. Vallikannan, *Int. J. Biol. Macromol.* **2020**, *150*, 578.

[149] M. A. Lauzon, B. Marcos, N. Faucheux, *Carbohydr. Polym.* **2018**, *181*, 801.

[150] I. R. Scolari, P. L. Páez, M. M. Musri, J. P. Petiti, A. Torres, G. E. Granero, *Drug Delivery Transl. Res.* **2020**, *10*, 1403.

[151] M. Zohri, H. A. Javar, T. Gazori, M. R. Khoshayand, S. H. Aghaee-Bakhtiari, M. H. Ghahremani, *Int. J. Nanomed.* **2020**, *15*, 8345.

[152] H. Thai, C. Thuy Nguyen, L. Thi Thach, M. Thi Tran, H. Duc Mai, T. Thi Thu Nguyen, G. Duc Le, M. Van Can, L. Dai Tran, G. Long Bach, K. Ramadass, C. I. Sathish, Q. Van Le, *Sci. Rep.* **2020**, *10*, 909.

[153] S. Amani, Z. Mohamadnia, *Int. J. Biol. Macromol.* **2019**, *135*, 163.

[154] S. Sepúlveda-Rivas, H. Fritz, C. Valenzuela, C. Santiviago, J. Morales, *Pharmaceutics* **2019**, *11*, 103.

[155] J. Mirtič, A. Paudel, P. Laggner, S. Hudoklin, M. E. Kreft, J. Kristl, *Int. J. Pharm.* **2020**, *580*, 119199.

[156] E. Galbis, N. Iglesias, R. Lucas, E. Tinajero-Díaz, M. V. De-Paz, S. Munoz-Guerra, J. A. Galbis, *ACS Omega* **2017**, *3*, 375.

[157] D. Liu, F. Yang, F. Xiong, N. Gu, *Theranostics* **2016**, *6*, 1306.

[158] V. Rahmani, H. Sheardown, *Int. J. Pharm.* **2018**, *535*, 452.

[159] M. Bakhshi, F. Ebrahimi, S. Nazarian, J. Zargan, F. Behzadi, D. S. Gariz, *Biologicals* **2017**, *49*, 69.

[160] J. R. Costa, M. Xavier, I. R. Amado, C. Gonçalves, P. M. Castro, R. V. Tonon, L. M. C. Cabral, L. Pastrana, M. E. Pintado, *Mater. Sci. Eng. C* **2021**, *119*, 111551.

[161] F. Shamekhi, E. Tamjid, K. Khajeh, *Int. J. Biol. Macromol.* **2018**, *120*, 460.

[162] P. Mukhopadhyay, S. Maity, S. Mandal, A. S. Chakraborti, A. K. Prajapati, P. P. Kundu, *Carbohydr. Polym.* **2018**, *182*, 42.

[163] G. Pamunuwa, N. Anjalee, D. Kukulewa, C. Edirisinghe, F. Shakoor, D. N. Karunaratne, *Carbohydr. Polym. Technol. Appl.* **2020**, *1*, 100008.

[164] S. Rahaie, M. Hashemi, S. A. Shojaosadati, S. Moini, S. H. Razavi, *Int. J. Biol. Macromol.* **2017**, *99*, 401.

[165] M. Li, Y. Sun, C. Ma, Y. Hua, L. Zhang, J. Shen, *J. Pharm. Sci.* **2021**, *110*, 268.

[166] Z. Chai, H. Dong, X. Sun, Y. Fan, Y. Wang, F. Huang, *Int. J. Biol. Macromol.* **2020**, *159*, 640.

[167] E. Campodoni, A. Adamiano, S. M. Dozio, S. Panseri, M. Montesi, S. Sprio, A. Tampieri, M. Sandri, *Nanomedicine* **2016**, *11*, 2119.

[168] H. Zhang, Y. Zhu, L. Qu, H. Wu, H. Kong, Z. Yang, D. Chen, E. Mäkilä, J. Salonen, H. A. Santos, M. Hai, D. A. Weitz, *Nano Lett.* **2018**, *18*, 1448.

[169] J. Jiang, Y. Chen, W. Wang, B. Cui, N. Wan, *Carbohydr. Polym.* **2016**, *151*, 600.

[170] J. P. Paques, E. Van Der Linden, C. J. M. Van Rijn, L. M. C. Sagis, *Adv. Colloid Interface Sci.* **2014**, *209*, 163.

[171] S. Yadav, A. K. Sharma, P. Kumar, *Front. Bioeng. Biotechnol.* **2020**, *8*, 127.

[172] N. M. Elbaz, A. Owen, S. Rannard, T. O. McDonald, *Int. J. Pharm.* **2020**, *574*, 118866.

[173] H. Jin, C. Wan, Z. Zou, G. Zhao, L. Zhang, Y. Geng, T. Chen, A. Huang, F. Jiang, J. P. Feng, J. F. Lovell, J. Chen, G. Wu, K. Yang, *ACS Nano* **2018**, *12*, 3295.

[174] R. Pushpalatha, S. Selvamuthukumar, D. Kilimozhi, *J. Drug Delivery Sci. Technol.* **2017**, *39*, 362.

[175] M. Sohail, W. Guo, Z. Li, H. Xu, F. Zhao, D. Chen, F. Fu, *Curr. Med. Chem.* **2020**, *27*, 3753.

[176] R. Ahuja, N. Panwar, J. Meena, M. Singh, D. P. Sarkar, A. K. Panda, *Environ. Chem. Lett.* **2020**, *18*, 2021.

[177] J. R. Lakkakula, P. Gujarathi, P. Pansare, S. Tripathi, *Carbohydr. Polym.* **2021**, *259*, 117696.

[178] K. T. Jin, Z. B. Lu, J. Y. Chen, Y. Y. Liu, H. R. Lan, H. Y. Dong, F. Yang, Y. Y. Zhao, X. Y. Chen, *J. Nanomater.* **2020**, *2020*, 9184284.

[179] P. Saralkar, A. K. Dash, *AAPS PharmSciTech* **2017**, *18*, 2814.

[180] C. Gao, F. Tang, G. Gong, J. Zhang, M. P. M. Hoi, S. M. Y. Lee, R. Wang, *Nanoscale* **2017**, *9*, 12533.

[181] M. Rahimivand, F. Tafvizi, H. Noorbazargan, *Int. J. Biol. Macromol.* **2020**, *158*, 338.

[182] A. Hassani, S. Mahmood, H. H. Enezei, S. A. Hussain, H. A. Hamad, A. F. Aldoghachi, A. Hagar, A. A. Doolaanea, W. N. Ibrahim, *Molecules* **2020**, *25*, 2244.

[183] N. Sahatsapan, T. Ngawhirunpat, T. Rojanarata, P. Opanasopit, P. Patrojanasophon, *AAPS PharmSciTech* **2020**, *21*, 212.

[184] P. M. Shad, S. Z. Karizi, R. S. Javan, A. Mirzaie, H. Noorbazargan, I. Akbarzadeh, H. Rezaie, *Toxicol. In Vitro* **2020**, *65*, 104756.

[185] M. M. F. A. Baig, M. Abbas, M. Naveed, S. A. Kassim, G. J. Khan, M. Sohail, S. Ullah, M. Hasnat, K. Shah, M. T. Ansari, *J. Food Drug Anal.* **2019**, *27*, 805.

[186] J. G. Rosch, H. Winter, A. N. DuRoss, G. Sahay, C. Sun, *Colloid Interface Sci. Commun.* **2019**, *28*, 69.

[187] E. Afzali, T. Eslaminejad, S. E. Yazdi Rouholamini, M. Shahrokhi-Farjah, M. Ansari, *Int. J. Nanomed.* **2021**, *16*, 579.

[188] L. Tao, J. Jiang, Y. Gao, C. Wu, Y. Liu, *Biomed Res. Int.* **2018**, *2018*, 4607945.

[189] F. N. Sorasitthiyanukarn, C. Muangnoi, P. Ratnatilaka Na Bhuket, P. Rojsitthisak, P. Rojsitthisak, *Mater. Sci. Eng. C* **2018**, *93*, 178.

[190] R. Sohail, S. R. Abbas, *Int. J. Biol. Macromol.* **2020**, *153*, 36.

[191] A. D. Ayub, H. I. Chiu, S. N. A. Mat Yusuf, E. Abd Kadir, S. H. Ngalim, V. Lim, *Artif. Cells, Nanomed., Biotechnol.* **2019**, *47*, 353.

[192] Z. Sun, Z. Yi, H. Zhang, X. Ma, W. Su, X. Sun, X. Li, *Carbohydr. Polym.* **2017**, *175*, 159.

[193] J. Zhao, L. Yao, S. Nie, Y. Xu, *Int. J. Biol. Macromol.* **2021**, *167*, 921.

[194] C.-H. Huang, T.-J. Chuang, C.-J. Ke, C.-H. Yao, *Polymers* **2020**, *12*, 1747.

[195] M. Mirrahimi, Z. Abed, J. Beik, I. Shiri, A. Shiralizadeh Dezfuli, V. P. Mahabadi, S. Kamran Kamrava, H. Ghaznavi, A. Shakeri-Zadeh, *Pharmacol. Res.* **2019**, *143*, 178.

[196] X. Xu, J. Wang, Y. Wang, L. Zhao, Y. Li, C. Liu, *Nanomed.: Nanotechnol. Biol. Med.* **2018**, *14*, 2387.

[197] K. Podgórna, K. Szczepanowicz, M. Piotrowski, M. Gajdošová, F. Štěpánek, P. Warszyński, *Colloids Surf., B* **2017**, *153*, 183.

[198] N. Peng, X. Ding, Z. Wang, Y. Cheng, Z. Gong, X. Xu, X. Gao, Q. Cai, S. Huang, Y. Liu, *Carbohydr. Polym.* **2019**, *204*, 32.

[199] W. Song, X. Su, D. Gregory, W. Li, Z. Cai, X. Zhao, *Nanomaterials* **2018**, *8*, 907.

[200] C. E. Dunbar, K. A. High, J. K. Joung, D. B. Kohn, K. Ozawa, M. Sadelain, *Science* **2018**, *359*, eaan4672.

[201] C. C. Ma, Z. L. Wang, T. Xu, Z. Y. He, Y. Q. Wei, *Biotechnol. Adv.* **2020**, *40*, 107502.

[202] M. Riley, W. Vermerris, *Nanomaterials* **2017**, *7*, 94.

[203] R. Rai, S. Alwani, I. Badea, *Polymers* **2019**, *11*, 745.

2100809 (25 of 27)

[204] B. Alallam, S. Altahhan, M. Taher, M. H. Mohd Nasir, A. A. Doolaanea, *Pharmaceuticals* **2020**, *13*, 158.

[205] C. Zhang, G. Shi, J. Zhang, H. Song, J. Niu, S. Shi, P. Huang, Y. Wang, W. Wang, C. Li, D. Kong, *J. Controlled Release* **2017**, *256*, 170.

[206] S. Dehghan, M. T. Kheiri, K. Abnous, M. Eskandari, M. Tafaghodi, *Microb. Pathog.* **2018**, *115*, 74.

[207] Z. Mahmoudi, J. Mohammadnejad, S. Razavi Bazaz, A. Abouei Mehrizi, M. Saidijam, R. Dinarvand, M. Ebrahimi Warkiani, M. Soleimani, *Carbohydr. Polym.* **2020**, *229*, 115551.

[208] K. D. Addisu, B. Z. Hailemeskel, S. L. Mekuria, A. T. Andrgie, Y. C. Lin, H. C. Tsai, *ACS Appl. Mater. Interfaces* **2018**, *10*, 5147.

[209] P. Zhang, S. Zhao, Y. Yu, H. Wang, Y. Yang, C. Liu, *Molecules* **2019**, *24*, 555.

[210] G. d. Wang, Y.-z. Tan, H.-j. Wang, P. Zhou, *Int. J. Nanomed.* **2017**, *12*, 6661.

[211] J. Yuan, L. Guo, S. Wang, D. Liu, X. Qin, L. Zheng, C. Tian, X. Han, R. Chen, R. Yin, *Colloids Surf., B* **2018**, *171*, 406.

[212] F. Nikoomanesh, S. Roudbarmohammadi, M. Khoobi, F. Haghighi, M. Roudbary, *Artif. Cells, Nanomed., Biotechnol.* **2019**, *47*, 64.

[213] S. Masoumi, A. Esmaeili, *Int. J. Biol. Macromol.* **2020**, *159*, 204.

[214] L. N. Dang, S. L. Hoang, M. Malin, J. Weisser, T. Walter, M. Schnabelrauch, J. Seppälä, *Eur. Polym. J.* **2016**, *81*, 129.

[215] T. Grafe, K. Graham, *Int. Nonwovens J.* **2003**, *os-12*, 1558925003os.

[216] S. Nemati, S. jeong Kim, Y. M. Shin, H. Shin, *Nano Convergence* **2019**, *6*, 36.

[217] S. Thakkar, M. Misra, *Eur. J. Pharm. Sci.* **2017**, *107*, 148.

[218] S. Alberti, M. Ferretti, S. Vicini, M. Castellano, V. Caratto, *J. Mater. Sci.* **2019**, *54*, 1665.

[219] J. Xue, J. Xie, W. Liu, Y. Xia, *Acc. Chem. Res.* **2017**, *50*, 1976.

[220] J. Xue, T. Wu, Y. Dai, Y. Xia, *Chem. Rev.* **2019**, *119*, 5298.

[221] A. Dodero, M. Castellano, P. Lova, M. Ottonelli, E. Brunengo, S. Vicini, M. Alloisio, *Polymers* **2021**, *13*, 1604.

[222] J. Han, L. Xiong, X. Jiang, X. Yuan, Y. Zhao, D. Yang, *Prog. Polym. Sci.* **2019**, *91*, 1.

[223] L. Zhao, G. Duan, G. Zhang, H. Yang, S. He, S. Jiang, *Nanomaterials* **2020**, *10*, 150.

[224] A. Dodero, E. Brunengo, M. Alloisio, A. Sionkowska, S. Vicini, M. Castellano, *Carbohydr. Polym.* **2020**, *235*, 115976.

[225] A. Dodero, S. Scarfi, S. Mirata, A. Sionkowska, S. Vicini, M. Alloisio, M. Castellano, *Polymers* **2021**, *13*, 831.

[226] A. Dodero, E. Brunengo, M. Castellano, S. Vicini, *Polymers* **2020**, *12*, 1524.

[227] M. Rahmati, D. K. Mills, A. M. Urbanska, M. R. Saeb, J. R. Venugopal, S. Ramakrishna, M. Mozafari, *Prog. Mater. Sci.* **2020**, *117*, 100721.

[228] P. Vass, E. Szabó, A. Domokos, E. Hirsch, D. Galata, B. Farkas, B. Démuth, S. K. Andersen, T. Vigh, G. Verreck, G. Marosi, Z. K. Nagy, *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.* **2020**, *12*, e1611.

[229] D. R. Madhukiran, A. Jha, M. Kumar, G. Ajmal, G. V. Bonde, B. Mishra, *Expert Opin. Drug Delivery* **2021**, *18*, 25.

[230] A. D. Juncos Bombin, N. J. Dunne, H. O. McCarthy, *Mater. Sci. Eng. C* **2020**, *114*, 110994.

[231] M. Jafari, Z. Paknejad, M. R. Rad, S. R. Motamedian, M. J. Eghbal, N. Nadjmi, A. Khojasteh, *J. Biomed. Mater. Res., Part B* **2017**, *105*, 431.

[232] F. Asghari, M. Samiei, K. Adibkia, A. Akbarzadeh, S. Davaran, *Artif. Cells, Nanomed., Biotechnol.* **2017**, *45*, 185.

[233] S. Nobile, L. Nobile, *Polym. Eng. Sci.* **2017**, *57*, 644.

[234] T. Jiang, E. J. Carbone, K. W. H. Lo, C. T. Laurencin, *Prog. Polym. Sci.* **2015**, *46*, 1.

[235] T. C. Mokhena, M. J. Mochane, A. Mtibe, M. J. John, E. R. Sadiku, J. S. Sefadi, *Materials* **2020**, *13*, 934.

[236] W. Shen, Y. L. Hsieh, *Carbohydr. Polym.* **2014**, *102*, 893.

[237] A. Dodero, S. Vicini, M. Alloisio, M. Castellano, *J. Mater. Sci.* **2019**, *54*, 8034.

[238] K. K. Aloma, S. Sukaryo, N. I. Fahlawati, K. Dahlan, S. Oemar, *Macromol. Symp.* **2020**, *391*, 1900199.

[239] A. Covelo, S. Rodil, E. O. López-Villegas, C. A. Álvarez, M. Hernandez, *Surf. Interface Anal.* **2020**, *52*, 1128.

[240] H. Daemi, M. Mashayekhi, M. P. Modaress, *Carbohydr. Polym.* **2018**, *198*, 481.

[241] S. Wang, J. Ju, S. Wu, M. Lin, K. Sui, Y. Xia, Y. Tan, *Carbohydr. Polym.* **2020**, *230*, 115665.

[242] J. Gutierrez-Gonzalez, E. Garcia-Cela, N. Magan, S. S. Rahatekar, *Mater. Lett.* **2020**, *270*, 127662.

[243] Y. İspirli Doğaç, İ. Deveci, B. Mercimek, M. Teke, *Int. J. Biol. Macromol.* **2017**, *96*, 302.

[244] Y. Tang, X. Lan, C. Liang, Z. Zhong, R. Xie, Y. Zhou, X. Miao, H. Wang, W. Wang, *Carbohydr. Polym.* **2019**, *219*, 113.

[245] A. Pakolpakçıl, B. Osman, G. Göktalay, E. T. Özer, Y. Şahan, B. Becerir, E. Karaca, *J. Polym. Res.* **2021**, *28*, 50.

[246] K. E. Öksüz, N. K. Özkaya, Z. D. Ş. İnan, A. Özer, *Mater. Today Commun.* **2021**, *26*, 101942.

[247] S. I. Jeong, M. D. Krebs, C. A. Bonino, J. E. Samorezov, S. A. Khan, E. Alsberg, *Tissue Eng., Part A* **2011**, *17*, 59.

[248] X. Zhao, S. Chen, Z. Lin, C. Du, *Carbohydr. Polym.* **2016**, *148*, 98.

[249] S. S. Majidi, P. Slemming-Adamsen, M. Hanif, Z. Zhang, Z. Wang, M. Chen, *Int. J. Biol. Macromol.* **2018**, *118*, 1648.

[250] V. A. Petrova, A. S. Golovkin, A. I. Mishanin, D. P. Romanov, D. D. Chernyakov, D. N. Poshina, Y. A. Skorik, *Biomedicines* **2020**, *8*, 305.

[251] N. A. Pattanashetti, D. D. Achari, A. I. Torvi, R. V. Doddamani, M. Y. Kariduraganavar, *Materialia* **2020**, *12*, 100826.

[252] J. Yu, Z. Zhao, J. Sun, C. Geng, Q. Bu, D. Wu, Y. Xia, *Nanomaterials* **2020**, *10*, 565.

[253] W. Li, X. Li, Y. Chen, X. Li, H. Deng, T. Wang, R. Huang, G. Fan, *Carbohydr. Polym.* **2013**, *92*, 2232.

[254] M. Castellano, M. Alloisio, R. Darawish, A. Dodero, S. Vicini, *J. Therm. Anal. Calorim.* **2019**, *137*, 767.

[255] T. C. Mokhena, A. S. Luyt, *Carbohydr. Polym.* **2017**, *165*, 304.

[256] S. Moon, J. Lee, *Polym. Eng. Sci.* **2013**, *53*, 1321.

[257] T. C. Mokhena, A. S. Luyt, *J. Cleaner Prod.* **2017**, *156*, 470.

[258] M. Ataie, I. Shabani, E. Seyedjafari, *J. Biomed. Mater. Res., Part A* **2019**, *107*, 586.

[259] A. Dodero, M. Alloisio, S. Vicini, M. Castellano, *Carbohydr. Polym.* **2020**, *227*, 115371.

[260] A. Dodero, S. Scarfi, M. Pozzolini, S. Vicini, M. Alloisio, M. Castellano, *ACS Appl. Mater. Interfaces* **2020**, *12*, 3371.

[261] A. Dodero, M. Alloisio, M. Castellano, S. Vicini, *ACS Appl. Mater. Interfaces* **2020**, *12*, 31162.

[262] C. Zhang, F. Feng, H. Zhang, *Trends Food Sci. Technol.* **2018**, *80*, 175.

[263] G. Ma, D. Fang, Y. Liu, X. Zhu, J. Nie, *Carbohydr. Polym.* **2012**, *87*, 737.

[264] S. V. G. Nista, J. Bettini, L. H. I. Mei, *Carbohydr. Polym.* **2015**, *127*, 222.

[265] P. J. Shiny, M. Vimala Devi, S. J. G. Felciya, G. Ramanathan, P. Fardim, U. T. Sivagnanam, *Int. J. Biol. Macromol.* **2021**, *168*, 46.

[266] N. Askarzadeh, M. H. Nazarpak, K. Mansoori, M. Farokhi, M. Gholami, J. Mohammadi, F. Mottaghitalab, *Macromol. Biosci.* **2020**, *20*, 2000149.

[267] Y. K. Fuh, Y. C. Wu, Z. Y. He, Z. M. Huang, W. W. Hu, *Mater. Sci. Eng. C* **2016**, *62*, 879.

[268] F. Tao, Y. Cheng, H. Tao, L. Jin, Z. Wan, F. Dai, W. Xiang, H. Deng, *Mater. Des.* **2020**, *194*, 108849.

[269] W. Xu, R. Shen, Y. Yan, J. Gao, *J. Mech. Behav. Biomed. Mater.* **2017**, *65*, 428.

[270] S. Cesur, F. N. Oktar, N. Ekren, O. Kilic, D. B. Alkaya, S. A. Seyhan, Z. R. Ege, C. C. Lin, S. E. Kuruca, G. Erdemir, O. Gunduz, *J. Aust. Ceram. Soc.* **2020**, *56*, 533.

[271] Q. Xiao, L. T. Lim, *Int. J. Biol. Macromol.* **2018**, *112*, 809.

[272] H. J. Lee, G. H. Kim, *J. Colloid Interface Sci.* **2014**, *430*, 315.

[273] M. S. Kim, G. Kim, *Carbohydr. Polym.* **2014**, *114*, 213.

[274] J. S. Lee, S. J. Chae, D. Yoon, D. Yoon, W. Chun, G. H. Kim, *Biofabrication* **2020**, *12*, 045028.

[275] S. Kajdič, O. Planinšek, M. Gašperlin, P. Kocbek, *J. Drug Delivery Sci. Technol.* **2019**, *51*, 672.

[276] J. Nanomed, A. Akhgari, Z. Shakib, S. Sanati, *Nanomed. J.* **2017**, *4*, 197.

[277] S. Parham, A. Z. Kharazi, H. R. Bakhsheshi-Rad, H. Ghayour, A. F. Ismail, H. Nur, F. Berto, *Materials* **2020**, *13*, 2153.

[278] F. Aavani, S. Khorshidi, A. Karkhaneh, *J. Med. Eng. Technol.* **2019**, *43*, 38.

[279] A. Dodero, G. Schlatter, A. Hébraud, S. Vicini, M. Castellano, *Carbohydr. Polym.* **2021**, *264*, 118042.

[280] H. Cheng, X. Yang, X. Che, M. Yang, G. Zhai, *Mater. Sci. Eng. C* **2018**, *90*, 750.

[281] B. Ghafoor, A. Aleem, M. Najabat Ali, M. Mir, *J. Drug Delivery Sci. Technol.* **2018**, *48*, 82.

[282] R. Fu, C. Li, C. Yu, H. Xie, S. Shi, Z. Li, Q. Wang, L. Lu, *Drug Delivery* **2016**, *23*, 818.

[283] A. Y. A. Kaassis, N. Young, N. Sano, H. A. Merchant, D. G. Yu, N. P. Chatterton, G. R. Williams, *J. Mater. Chem. B* **2014**, *2*, 1400.

[284] H. Hajiali, M. Summa, D. Russo, A. Armirotti, V. Brunetti, R. Bertorelli, A. Athanassiou, E. Mele, *J. Mater. Chem. B* **2016**, *4*, 1686.

[285] X. Han, P. Huo, Z. Ding, P. Kumar, B. Liu, *Pharmaceutics* **2019**, *11*, 449.

[286] A. Kyzioł, J. Michna, I. Moreno, E. Gamez, S. Irusta, *Eur. Polym. J.* **2017**, *96*, 350.

[287] S. Arthanari, G. Mani, J. H. Jang, J. O. Choi, Y. H. Cho, J. H. Lee, S. E. Cha, H. S. Oh, D. H. Kwon, H. T. Jang, *Artif. Cells, Nanomed., Biotechnol.* **2014**, *44*, 847.

[288] M. T. Yilmaz, O. Taylan, C. Y. Karakas, E. Dertli, *Carbohydr. Polym.* **2020**, *244*, 116447.

[289] D. Duman, A. Karadag, *Int. J. Food Sci. Technol.* **2021**, *56*, 927.

[290] S. Mohammadi, S. Ramakrishna, S. Laurent, M. A. Shokrgozar, D. Semnani, S. Dadeghi, S. Bonakdar, M. Akbari, *J. Biomed. Mater. Res., Part A* **2019**, *107*, 403.

[291] R. Wongkanya, P. Chuysinuan, C. Pengsuk, S. Techasakul, K. Lirdprapamongkol, J. Svasti, P. Nooeaid, *J. Sci.: Adv. Mater. Devices* **2017**, *2*, 309.

[292] H. R. Bakhsheshi-Rad, Z. Hadisi, A. F. Ismail, M. Aziz, M. Akbari, F. Berto, X. B. Chen, *Polym. Test.* **2020**, *82*, 106298.

[293] S. Baek, H. Park, Y. Park, H. Kang, D. Lee, *Polymers* **2020**, *12*, 618.

[294] S. Rezaei, A. Valipouri, S. A. Hosseini Ravandi, M. Kouhi, L. G. Mobarakeh, *Polym. Adv. Technol.* **2019**, *30*, 2447.

[295] M. Najafiasl, S. Osfouri, R. Azin, S. Zaeri, *J. Drug Delivery Sci. Technol.* **2020**, *57*, 101708.

[296] S. Abid, T. Hussain, A. Nazir, A. Zahir, N. Khenoussi, *Polym. Bull.* **2019**, *76*, 6387.

[297] T. T. Li, J. Li, Y. Zhang, J. L. Huo, S. Liu, B. C. Shiu, J. H. Lin, C. W. Lou, *J. Mater. Res. Technol.* **2020**, *9*, 13450.

[298] S. Amjadi, H. Almasi, M. Ghorbani, S. Ramazani, *Food Packag. Shelf Life* **2020**, *24*, 100504.

[299] A. Dodero, S. Vicini, P. Lova, M. Alloisio, M. Castellano, *Int. J. Biol. Macromol.* **2020**, *165*, 1939.

Andrea Dodero received his M.Sc. in Materials Science and Engineering in 2017 from the University of Genoa where he is currently enrolled as a Doctoral student in Sciences and Technologies of Chemistry and Materials at the Department of Chemistry and Industrial Chemistry. His research activity includes the characterization and application of polysaccharide materials for biomedical and pharmaceutical products and the development of polymeric and polymeric-inorganic composite nanofibers via the electrospinning technique.

Maila Castellano received her Ph.D. in Chemical Science in 1999 from the University of Genoa. Since 2005, after concluding her postdoctoral activity, she is an assistant professor at the Department of Chemistry and Industrial Chemistry, University of Genoa. Her current research interests concern the development of composite materials for energy applications, the characterization and the exploitation of polysaccharide-based products with several potential purposes, with great attention in the use of the electrospinning technique to prepare nanofibrous membranes for biomedical and pharmaceutical applications.