



# Alginate-Based Interpenetrating Network Carriers for Biomedical Applications

Subhaseema Das and Usharani Subuddhi

## Abstract

With advances in modern medicine, there has been a constant need to develop a single material that caters to all demands such as high tensile strength, biocompatibility and biodegradability. The development of an interpenetrating polymer network (IPN) is both an outstanding innovation and contribution that has led to massive technological advances across a wide spectrum of applications in medicine. IPNs comprising natural and synthetic polymers are typically endowed with improved properties compared to monolithic materials and offer superior properties. Most importantly, synergism of properties has also been observed in most of the systems. This chapter discusses the potential of alginate-based IPN carriers for biomedical applications.

Alginate is a naturally occurring anionic polysaccharide widely employed in a broad spectrum of biomedical applications. The ability to assemble alginate with a diversity of polymers and to fabricate IPNs makes it a promising choice for various applications in biomedicine. This chapter discusses at length the various inherent properties of alginate that make it suitable as a biomaterial. The state-of-art applications of alginate IPNs in drug delivery, wound healing and tissue engineering have also been elaborated. The prospective of alginate in delivery of small molecule drugs as well as protein drugs has been presented. This chapter further focuses on the potential of alginate IPNs in wound dressings and regenerative medicine.

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S. Das

Department of Chemistry, Ravenshaw University, Cuttack, Odisha, India

U. Subuddhi (✉)

Department of Chemistry, NIT Rourkela, Rourkela, Odisha, India

e-mail: [subuddhiu@nitrkl.ac.in](mailto:subuddhiu@nitrkl.ac.in)

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**Keywords**

Alginate IPNs · Drug delivery · Protein delivery · Wound dressing · Tissue engineering

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## 4.1 Introduction

Utilization of naturally occurring polysaccharides towards the design of biomaterials for biomedical applications has blossomed into a promising approach owing to their biocompatibility and biodegradability. The diversity in the properties of these natural polysaccharides could be well ascribed to the presence of a large number of reactive groups, wide range of molecular weight and varying chemical composition (Prabaharan 2011). Due to the presence of various functional groups in their backbone, these polysaccharides are greatly suitable for chemical and biochemical modifications resulting in a wide range of derivatives (Prabaharan and Jayakumar 2009). In particular, their abundant resources in nature and low processing cost have fuelled up their utilities in pharmaceutical industries. In view of these magnificent attributes, alginate, a naturally occurring anionic polysaccharide, has carved a niche for itself for myriad biomedical applications. Alginate has been extensively investigated in biomedical utilities due to its natural abundance, relative low cost, biocompatibility and ease of fabrication of formulations (Gombotz and Wee 1998).

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## 4.2 Chemistry of Alginate

### 4.2.1 Sources and Extraction

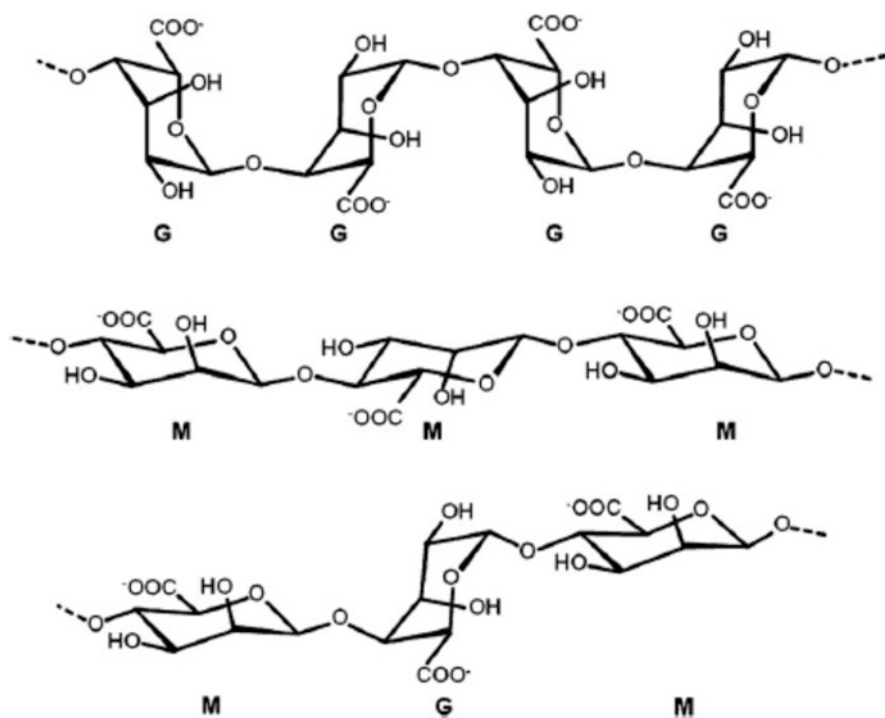
Alginate is a naturally occurring anionic polysaccharide primarily extracted from the species of brown seaweed viz. *Laminaria hyperborea*, *Laminaria digitata*, *Laminaria japonica*, *Ascophyllum nodosum* and *Macrocystis pyrifera* (Smidsrod and Skjak-Braek 1990). In all these algae, alginate constitutes almost 40% of dry weight (Sutherland 1991). Alginate is extracted from the dried algae after treatment with dilute mineral acid (mostly HCl) (Rinaudo 2008). Free alginic acid, thus obtained, is then converted to a salt, mostly the sodium salt, i.e. sodium alginate, which finds prominence in biomedical applications (Tonnesen and Karlsen 2002). Alginate also exists as mixed salts of various cations found in seawater such as  $Mg^{2+}$ ,  $Ca^{2+}$ ,  $Ba^{2+}$  and  $Na^{+}$ . To extract the alginate, the cations are exchanged for  $H^{+}$ . The alginate is then converted to its soluble sodium salt by addition of sodium carbonate while maintaining the pH below 10 (Sutherland 1991).

Bacterial alginates have also been isolated from *Azotobacter vinelandii* and several species of *Pseudomonas* (Smidsrod and Skjak-Braek 1990). The pathway for alginate biosynthesis mostly comprises of four decisive steps: (i) synthesis of precursor substrate, (ii) polymerization and cytoplasmic membrane transfer, (iii) periplasmic transfer and modification and, lastly, (iv) export through the outer membrane

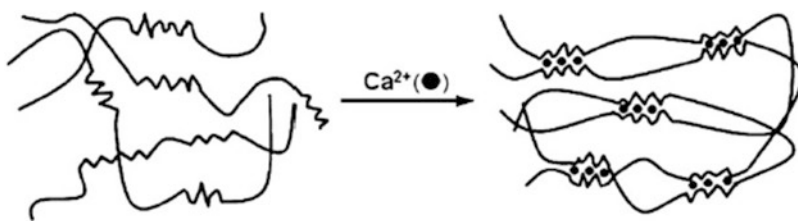
(Lee and Mooney 2012; Remminghorst and Rehm 2006). Further regulation and tailored development features in bacterial alginate biosynthesis could provide a new direction towards alginate production and its wide applications in biomedicine.

### 4.2.2 Chemical Structure

Alginates are a family of linear block copolymers comprising of 1,4'-linked  $\beta$ -D-mannuronic and  $\alpha$ -L-guluronic acid residues (George and Abraham 2006). The composition and properties of alginates are strongly dependent on the ratio of guluronate (G) to mannuronate (M) residues. Depending on the source of extraction, the contents of M and G vary and to date, more than 200 different alginates have been manufactured (Thakur et al. 2018). The blocks might be arranged with consecutive G residues, M residues and alternating G and M residues. Because of the difference in the mode of linkage between the G residues and M residues, the geometries of the G-block regions, M-block regions and the alternating regions are significantly different (Fig. 4.1a) (from Lee and Mooney 2012). The G-blocks are considered to be buckled shaped whereas M-blocks are often referred to as extended ribbons. The



**Fig. 4.1a** Chemical structures of G-block, M-block and alternating block in alginate. (Lee and Mooney 2012)



**Fig. 4.1b** Alginate hydrogels prepared by ionic crosslinking (egg-box model). (Lee and Mooney 2012)

specific arrangement of G residues results in diamond-shaped holes of suitable dimensions that are ideal for accommodating divalent cations such as  $\text{Ca}^{2+}$  to form stacked egg-box-like structures of the G residues resulting in gelation (Fig. 4.1b) (from Lee and Mooney 2012) (George and Abraham 2006). Thus, the composition (M/G ratio), the sequence and the G-block length are crucial factors that determine the physical properties of the alginate and its resultant formulations (George and Abraham 2006).

### 4.2.3 Molecular Weight and Viscosity

The molecular weights (MW) of commercially available Na-alginates mostly range between 32,000 and 400,000 g/mol (Rinaudo 1992). The intrinsic viscosity ( $[\eta]$ ) of alginate solution depends on its MW. According to Mark-Houwink relationship ( $[\eta] = KM_v^a$ ) the parameters are  $K = 2 \times 10^{-3}$  and  $a = 0.97$  for Na-alginate in 0.1 M NaCl and at 25 °C, where  $M_v$  is the viscosity average molecular weight (Rinaudo 1992). The viscosity of alginate solutions is also sensitive to the pH and it increases as the pH is lowered. A maximum viscosity is observed around pH 3–3.5 wherein the carboxylate groups in the polysaccharide become protonated and take part in hydrogen bonding (Berth 1992). It has also been demonstrated that alginate solutions with high MW become greatly viscous which is undesirable for further processing (LeRoux et al. 1999). Thus, judicious manipulation of MW can tailor the solution viscosity and render alginates with desired properties. Ideally, by employing a combination of high and low MW polymers, the viscosity of the resulting alginate gels could be adjusted (Kong et al. 2002).

## 4.3 Properties of Alginate Making It Suitable for Biomedical Applications

### 4.3.1 Gelation

The gel formation capacity or gelation property of alginate is of great importance in widespread applications of this polysaccharide in food and pharmaceutical industries. The ability of alginate to form two types of gels (i) pH dependent (acid gel)

and (ii) ionotropic gel confers unique advantages over neutral polysaccharides. Hydration of alginic acid, especially the high MW variants, leads to formation of high viscosity 'acid gels' due to strong intermolecular hydrogen bonding. These gels can entrap large amount of labile water molecules and are of great importance in many applications such as cell immobilization and encapsulation (Nahar et al. 2017). Alginate can form ionotropic gels with a variety of metal ions under mild conditions. Monovalent cations generally form soluble salt with alginate whereas divalent and multivalent cations often result in gelation. Ionic crosslinking mostly involves divalent cations such as  $\text{Ca}^{2+}$ ,  $\text{Ba}^{2+}$  and  $\text{Sr}^{2+}$ . The ionotropic gelation of alginate is mostly due to the ion-induced association of G-block regions in the polymer. Various functional properties such as porosity, swelling behaviour, stability, mechanical strength, biodegradability, immunological characteristics and biocompatibility of these gels are found to be greatly influenced by the chemical structure, MW, gel formation kinetics of the polysaccharide and the cation. Alginate gels can be prepared in various shapes and sizes among which alginate beads are largely explored.

Alginate beads have been prepared by extruding a solution of sodium alginate containing the desired protein or drug, as droplets, into divalent crosslinking solutions of  $\text{Ca}^{2+}$ ,  $\text{Ba}^{2+}$  and  $\text{Sr}^{2+}$  (Sutherland 1991). The viscosity of alginate solution and the diameter of the extruder are paramount in influencing the shapes and sizes of the resulting beads. Recent studies point to alginate gelation by covalent crosslinking (mostly esterification, carbodiimide, methacrylation, click chemistry) or by photo-crosslinking (Bidarra et al. 2014).

### 4.3.2 pH Sensitivity

Alginate is a well-known pH-responsive polymer due to its ionic nature. At low pH, (gastric environment) it shrinks into a porous insoluble matrix usually referred to as alginic acid skin but as soon as it experiences higher pH in the intestinal tract, the alginic acid skin converts to a soluble layer (Chen et al. 2004). The strong pH-dependent responsiveness of alginate could be accredited to the acidic  $\beta$ -D-mannuronic and  $\alpha$ -L-guluronic acid structural units on its backbone that get protonated in acidic environment (pH 1.2 of gastric fluid). In alkaline media (pH 7.4 of intestinal fluid) the repulsion between the deprotonated  $\text{COO}^-$  groups renders the alginate matrix a greater swellability (Kajjari et al. 2012). This pH-sensitive behaviour has been categorically exploited to customize drug release kinetics from alginate matrices. The various biomedical applications pertaining to pH sensitivity of alginate have been discussed in the later sections.

### 4.3.3 Mechanical Properties

Materials intended as extracellular matrices (ECMs) often require specific and reproducible elastic moduli that can be modulated in a controlled manner (Schneider et al. 2006). The mechanical properties of a polymer such as stiffness can mostly be

manipulated by physical factors like crosslinker type, crosslinking density, MWs and also by chemical modification of the polymer (Peppas 2004). Generally, in the case of high MW alginate, an increase in stiffness is observed upon increasing the polymer concentration. This, however, leads to a greatly viscous polymer solution that makes further processing difficult (Kong et al. 2003; Augst et al. 2006). To circumvent this hindrance, specifically formulated combination of high and low MW alginates is usually employed. In these formulations, the low MW chains reduce the physical interactions in solution while the high MW chains maintain the long-range interactions in the gel (Augst et al. 2006). Thus, the synergistic effects of these two factors tend to minimize the alginate gel brittleness.

Reinforcement of cationic polymers such polyethylene imine into alginate is also an effectual strategy to improve its mechanical strength (Kong and Mooney 2003). Gelling condition such as gelation time and type of crosslinker are pivotal that dramatically influence the swelling and mechanical properties of the alginate gel.

#### 4.3.4 Bioadhesiveness

Studies have revealed that polymers possessing a charge density serve as good mucoadhesive agents (Chickering and Mathiowitz 1995; Chang et al. 1985; George and Abraham 2006). More so, anionic polymers are more efficient bioadhesive candidates than their polycationic and nonionic counterparts. Literature reports have illustrated alginate with excellent bioadhesion characteristics (El-Kamel et al. 2002; Pinkas et al. 2017; Singh et al. 2017; Shtenberg et al. 2017; Hong et al. 2018;). Moreover, due to adherence of alginate to mucosal tissues, protein transit time is delayed and thus the drug is localized to the absorptive surfaces, thereby improving the drug bioavailability and efficacy (Szekalska et al. 2016). In a recent development, an oral mucoadhesive drug delivery system constituting alginate and liposomes were fabricated by Shtenberg and co-workers that displayed retention of around 80% of the biomaterial in the tongue tissues (Shtenberg et al. 2018).

#### 4.3.5 Biodegradation

Degradation of a biomaterial is often a key issue in tissue replacement and drug release. Ionically crosslinked alginates mostly dissolve in neutral pH by losing their divalent crosslinking cation (Augst et al. 2006). Gamma irradiation-assisted alginate degradation has also been reported at the optimum dose 100 kGy (Lee et al. 2003). Enzymic degradation of alginates is a well-known phenomenon (Gacesa 1992). Schaumann and Weide (1990) have explicitly detailed on alginase-mediated structural and molecular degradation of Na-alginate by marine fungi. The review article by Wong and co-authors (2000) particularly emphasizes on the enzyme characteristics of alginate lyase to engineer and fine-tune the degradation of alginate-based biomaterials. Recently, controlled degradation of alginate has also been achieved by crosslinked enzyme aggregates of alginate lyase (Kunjukunju et al.

2018). The study revealed that controlled degradation of alginate was obtained over a period of 28 days. These findings altogether suggest that it is possible to tailor the degradation kinetics of alginate and its derivatives with proper use of conditions.

### 4.3.6 Biocompatibility

The biocompatibility of alginate has been studied extensively by various authors *in vitro* as well as *in vivo*. However there still remains some debate about the varying levels of impurity particularly for commercially available alginates. Since crude alginates often contain contaminants such as proteins or endotoxins, it is desirable to properly purify the alginates to minimize the risk of an immune response. Tam et al. (2011) have studied the factors influencing the alginate gel biocompatibility and inferred that the mannuronate/guluronate content is the key factor. Orive and co-authors (2005) have presented a battery of *in vitro* techniques to access the biocompatibility of alginates with different compositions and purities. Their findings established that the differences in protein and polyphenol content amount to purified and non-purified alginates.

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## 4.4 Limitations of Pure Alginate

The foremost hindrance associated with pure alginate is its poor mechanical strength which usually warrants reinforcement (Li et al. 2005; Zineh et al. 2018). The application of alginate is further limited by its high moisture sensitivity (Jost and Reinelt 2018). Composite materials usually exhibit better tensile strength in comparison to monolithic materials and thus, alginate has been assimilated with a diversity of polymers to engineer composites of biomedical interest.

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## 4.5 Modifications of Alginate

In recent years multicomponent drug delivery systems have been developed for potential therapeutic and diagnostic applications and among these, semi-interpenetrating polymeric networks (semi-IPNs) and interpenetrating polymeric networks (IPNs) have emerged as innovative biomaterials for myriad biomedical applications (Dragan 2014). The network properties can be tailored by the type of polymer and its concentration, by the applied crosslinking method as well as by the overall procedure used for their preparation.

IPNs are ‘alloys’ of crosslinked polymers, at least one of them being synthesized and/or crosslinked within the immediate presence of the other, without any covalent bonds between them, which cannot be separated unless chemical bonds are broken (Dragan 2014). IPNs can be basically classified as simultaneous IPN and sequential IPN based on the preparation method. When the precursors of both networks are mixed and the two networks are synthesized at the same time, simultaneous IPN

results. A sequential IPN is typically performed by swelling of a single-network hydrogel into a solution containing the mixture of monomer, initiator and activator, with or without a crosslinker. In the presence of a crosslinker, a full IPN results while the absence of a crosslinker forms a semi-IPN (Matricardi et al. 2013; Dragan 2014; Lohani et al. 2014).

The high rates of success of IPNs and/or semi-IPNs used for biomedical and pharmaceutical applications could be attributed to the combination of favourable properties of each constituent polymer. Formation of IPNs leads to new systems with improved properties, which quite often are substantially different from those of the individual polymers. Most importantly, synergism of properties has also been observed in most of the IPNs (Matricardi et al. 2013). The combination and synergism of properties can be judiciously exploited to modify the characteristics of the resulting biomaterial to cater to specific needs, particularly in the biomedical and pharmaceutical fields. Development of IPNs has led to an assortment of architectures such as hydrogels, microspheres, microgels, nanoparticles, tablets, capsules and scaffolds, among others, to accomplish the biomedical objective (Lohani et al. 2014).

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## 4.6 IPNs of Alginate

Alginates have been assembled with a diversity of polymers for the fabrications of IPNs and/or semi-IPNs intended for biomedical applications in the form of films, microspheres, microgels, nanoparticles or depot matrices. They have also been designed as scaffolds in tissue engineering for bone, cartilage and soft tissue generation. Because of the high versatility and tailorable properties, IPNs of alginate are promising candidates in pharmacy. Alginates have often been taken in combination with synthetic polymers or with naturally occurring biopolymers for the generation of IPNs. Depending on the nature and the intrinsic properties of components, the resulting IPNs can be fine-tuned. Moreover, the range of reachable properties can be broadened substantially.

### 4.6.1 IPNs with Synthetic Polymers

A combination of synthetic polymers with alginate further widens the window of pharmaceutical and biomedical utilities. Synthetic polymers such as polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyacrylic acid (PAA), polyacrylamide (PAAm), poly(N-isopropylacrylamide) (PNIPAAm), polycaprolactone (PCL), polylactic acid (PLA), polyvinyl pyrrolidone (PVP), etc., have been taken in conjugation with alginate to form IPNs.

Table 4.1 reviews the IPNs of alginate with various synthetic polymers and their potential applications in biomedicine.



**Table 4.1** IPNs of alginate with synthetic polymers and their biomedical applications

Polymer	IPN component	Formulation	Biomedical applications	References
PVA	PVA-g-PAA	Semi-IPN hydrogels	Controlled release of loxoprofen sodium	Khalid et al. (2018)
	PVA-graphene nanosheet	Fibres	Scaffolds for engineering neural construct	Golafshan et al. (2017)
	PVA	Hydrogels	Controlled release of tramadol	Anwar et al. (2017)
	PVA	Hydrogel	Controlled delivery of carbidopa	Tareq (2016)
	PVA	Semi-IPN and IPN hydrogels	Cardiac tissue engineering	Thankam et al. (2013)
	PVA	Hydrogel	Controlled release of prazosin HCl	Kulkarni et al. (2010)
PNIPAAm	PNIPAAm	Hydrogels	Wound dressing	Li et al. (2018)
	PNIPAAm/acryloyl phenylalanine	Hydrogels	Controlled release of imatinib mesylate	Jalababu et al. (2018)
	PNIPAAm	Semi-IPN microspheres	Controlled delivery of 5-fluorouracil	Reddy et al. (2008)
	PNIPAAm	Semi-IPN beads	Sustained release of indomethacin	Shi et al. (2006)
PAA	PAA	Hydrogel	Controlled release of diclofenac potassium to the colon	Jalil et al. (2016)
	Starch-g-PAA	Hydrogel	Controlled release of diclofenac sodium in pH 7.4	Chang (2015)
	PAA	Microgels	Controlled release of Ibuprofen	Babu et al. (2006)
PAAm	PAAm-graphene oxide-gelatin	Hydrogels	Scaffolds for nerve tissue engineering application	Zhao et al. (2018)
	PAAm	Hydrogels	Cartilage replacement	Arjmandi et al. (2018a, b)
	PAAm-montmorillonite platelets	Hydrogels	Aquatic load-bearing materials for artificial tissues, actuators, agriculture, etc.	Su and Chen (2018)
	PAAm-gum ghatti	Microbeads	Ketoprofen delivery	Boppana et al. (2015)
	PAAm	Semi-IPN hydrogels	Acetaminophen release	Samanta and Ray (2014)
	PAAm	Hydrogels	Biomaterials	Darnell et al. (2013)

(continued)

**Table 4.1** (continued)

Polymer	IPN component	Formulation	Biomedical applications	References
PEG	PNIPAAm-PEG-co-poly( $\epsilon$ -aprolactone)	Hydrogel	Oral delivery of BSA	Zhao et al. (2010)
	PEG acrylate	Hydrogel	Encapsulation of islets of Langerhans	Desai et al. (2000)
	PEG	Hydrogel	Drug-eluting stents	Livnat et al. (2005)
	PEG	Fibres	Controlled delivery of salicylic acid	Wang et al. (2007)
	Chitosan-PEG	Microcapsule	Controlled delivery of hirudin in pH 7.4	Chandy et al. (1998)
PVP	PVP	Beads	Controlled delivery of ibuprofen	Yigitoglu et al. (2014)
Pluronic	PF68	Nanoparticles	Sustained release of zidovudine in pH 7.4	Joshy et al. (2017)
	Au nanoparticle-loaded F127	Microparticles	Controlled release of FITC-dextran	Park et al. (2017)
	Chitosan-Pluronic	Nanoparticles	Sustained delivery of meloxicam	Fattahpour et al. (2015)
	Chitosan-Pluronic	Nanoparticles	Enhanced biological activity of nisin	Bernela et al. (2014)
PCL	PCL	Scaffolds	Tissue regeneration	Hu and Ting (2019)
	PCL nanofibers	Scaffolds	In situ transfection	Hu et al. (2018a)
	PCL	Scaffolds	Improved cellular responses	Kim and Kim (2014)
PLA	Ciprofloxacin-loaded poly(lactic-co-glycolic acid)	Microparticles	Wound dressings	Liu et al. (2018a, b)
	Doxorubicin-loaded poly(lactic-co-glycolic acid)	Hydrogels	Antitumor applications	Chai et al. (2017)
	PLA nanofibers	Hydrogels	Bioink for 3D bioprinting of constructs	Narayanan et al. (2016)

#### 4.6.2 IPN with Biopolymers

Biopolymers such as chitosan, guar gum, cellulose, pectin, soya protein and others have been integrated with alginate and explored for manifold biomedical applications. Table 4.2 enlists the recent advances in the IPNs of alginates with various biopolymers and their diverse pharmaceutical applications.

**Table 4.2** IPNs of alginate with biopolymers and their biomedical applications

Biopolymer	IPN component	Formulation	Biomedical applications	References
Chitosan and its derivatives	Chitosan	Hydrogel scaffolds	Tissue engineering	Kolanthai et al. (2018) and Naghizadeh et al. (2018)
	Chitosan/ $\beta$ -cyclodextrin	Polyelectrolyte complexes	Piroxicam release	Hardy et al. (2018)
	Chitosan/gelatin	Gel	Sustained release of ranitidine	Belhadji et al. (2018)
	Chitosan	Hydrogels	Controlled delivery of deferoxamine	Rassu et al. (2016)
	Chitosan	Hydrogel	Cell growth applications	Baysal et al. (2013)
	Chitosan	IPN scaffolds	Cartilage tissue engineering	Tigli and Gumusderelioglu (2009)
	Chitosan-g-(PAA/ attapulgate/ Na-alginate)	Hydrogel beads	Controlled delivery of diclofenac sodium to intestine	Wang et al. (2009)
	Chitosan-coated alginate beads containing PNIPAAm	Beads	pH-/temperature-sensitive controlled delivery system for indomethacin	Shi et al. (2008)
	Chitosan	Fibrous scaffolds	Intervertebral disc tissue engineering	Shao and Hunter (2007)
	Carboxymethyl chitosan	Beads	Intestinal delivery of BSA	Lin et al. (2005)
	Chitosan	IPN scaffolds	Cartilage tissue engineering	Li and Zhang (2005)
Chitosan	IPN scaffolds	Bone tissue engineering	Li et al. (2005)	
Guar gum and its derivatives	Guar gum	Hydrogel	Controlled delivery of BSA	George and Abraham (2007)
	Carboxymethyl cellulose/guar gum	Fibres	Antibacterial activity	Riaz et al. (2018)
	Guar gum succinate	Beads	Colon-specific delivery of ibuprofen	Seeli et al. (2016)
	Guar gum-garose	Hydrogels	Entrapment of ginger peroxidase	Ali and Husain (2018)
	Carboxymethyl guar gum	Beads	Oral delivery of drugs along GIT	Bajpai et al. (2006)

(continued)

**Table 4.2** (continued)

Biopolymer	IPN component	Formulation	Biomedical applications	References
Cellulose and its derivatives	Polypyrrole-TEMPO-oxidized microfibrillated cellulose	Hydrogels	Excellent swelling and biocompatibility	Lin et al. (2019)
	Rifampicin-loaded cellulose nanocrystal hybrids	Nanoparticles	Potential for treatment against <i>M. tuberculosis</i>	Thomas et al. (2018)
	Bacterial cellulose	Nanofibers	Drug delivery carriers	Shi et al. (2014)
Gelatin and its derivatives	Gelatin-agar	Scaffolds	Improved growth of microbial cells	Aljohani et al. (2018)
	Gelatin	Hydrogels	Oral delivery of hydrophobic drugs	Bhutani et al. (2016)
	Gelatin	Nanogels	Controlled delivery of curcumin to cancer cells	Sarika et al. (2016)
	Methacrylamide-modified gelatin	Hydrogels	Suitable cell carriers	Graulus et al. (2015)
Pectin	Cefazolin-loaded pectin	Nanoparticles	Wound dressing agents	Shahzad et al. (2019)
	Pectin	Hydrogels	Optimized delivery of anthocyanins	Guo et al. (2018)
	Pectin	Microgels	Controlled release of antacids	Chen et al. (2018a)
	Pectin	Hydrogels	Treatment of gastro-oesophageal reflux disorders	Hanif and Abbas (2018)
Xanthan gum	Xanthan gum	Hydrogels	Inhibition of <i>H. pylori</i> infection	Vega-Sagardia et al. (2018)
	Xanthan gum reinforced with cellulose nanocrystals and halloysite nanotubes	Scaffolds	Bone tissue engineering	Kumar et al. (2017)
	Xanthan gum- $\beta$ -cyclodextrin	Hydrogels	Cholesterol reducing potential	Fareez et al. (2017)

(continued)

**Table 4.2** (continued)

Biopolymer	IPN component	Formulation	Biomedical applications	References
Carrageenan	Carrageenan-gelatin	Hydrogels	Tissue engineering	Vignesh et al. (2018)
	Carrageenan-carboxymethyl cellulose-grapefruit seed extract	Hydrogels	Antibacterial applications	Shankar and Rhim (2018)
	$\kappa$ -Carrageenan	Hydrogel beads	Controlled delivery of oral insulin	Lim et al. (2017)
	$\kappa$ -Carrageenan	Microparticle	Mucosal delivery of ketoprofen and quercetin	Goncalves et al. (2016)
Locust bean gum	Locust bean gum	Microbeads	Controlled delivery of capecitabine for treatment of colon cancer	Upadhyay et al. (2018)
	Locust bean gum	Microspheres	Sustained release of aceclofenac	Jana et al. (2015)
	Locust bean gum	Microcapsule	Controlled release of <i>Lactobacillus rhamnosus</i> probiotic cells	Cheow et al. (2014)
Soy protein isolates	Soy protein isolates	Beads	Thyme oil encapsulation for intestinal delivery	Volic et al. (2018)
	Soy protein isolates	Scaffolds	Tissue engineering	Noeaid et al. (2017)
	Soy protein isolates	Hydrogels	Tissue regeneration and wound healing materials	Tansaz et al. (2017)
Acacia gum	Acacia gum	Beads	Oral delivery of diclofenac sodium to intestine	Benfattoum et al. (2018)
	ZnO nanoparticle-loaded acacia gum	Hydrogels	Antibacterial and wound healing effects	Raguvaran et al. (2017)

## 4.7 Biomedical Applications of IPN of Alginate

Owing to its biocompatible, non-immunogenic, non-toxic, mucoadhesive and biodegradable features, applications of alginate are manifold in biomedical field. Alginate biocompatibility has been affirmed *in vivo* after ocular (Lin et al. 2004), nasal (Sarei et al. 2013), topical (Coskun et al. 2014), vascular (Rottensteiner et al. 2014; Amirian et al. 2017) and oral (Nunamaker et al. 2007; Thomas et al. 2018; Yang et al. 2018a, b) administration. Alginate has been greatly studied for pharmaceutical applications like targeted drug delivery, protein delivery, tissue engineering and wound healing purposes. The following sections explore the biomedical wonders of alginates in greater details.

### 4.7.1 Pharmaceutical Applications

Oral formulations are currently the most frequent and preferred mode for pharmaceutical applications (Nahar et al. 2017). The design of oral dosage forms usually follows any one of these two principles: (i) the entire drug dose is in the same physical unit or (ii) the dose is encapsulated in an assembly of small subunits (Nahar et al. 2017). In the latter case, the subunits are further compressed into tablets which, thereby, experience a ‘barrier’ that is pivotal to provide a controlled release profile. In particular, hydrocolloids like alginates undergo an immediate hydration to create a high viscosity layer around themselves which act as diffusion barrier, thereby decreasing the migration of small chemical drugs, thus sustaining the delivery. Additionally, the intrinsic pH responsivity of alginates makes them wonderful agents for colon-specific drug delivery. Alginates are widely used as delivery vehicles due to their ability to encapsulate and release a wide range of drugs in a gentle and biocompatible manner.

#### 4.7.1.1 Delivery of Small Chemical Drugs

Alginate hydrogels may be broadly useful for the sustained and localized delivery of traditional small chemical drugs. Conventional approaches to drug delivery (oral mostly) usually lead to burst release of drugs and poor targeting to the site of interest causing side effects and inefficacy. The release kinetics of low MW drugs from alginate gels can be controlled by regulating drug-alginate interactions. When there are no chemical interactions between the drug and the polymer, the release depends largely on the charge polarization of the molecule; i.e. hydrophilic molecules may diffuse very quickly while hydrophobic drugs diffuse slowly through the gel pores (Augst et al. 2006).

#### pH-Sensitive Alginate Hydrogels in Drug Delivery

A plethora of alginate-based IPN formulations have been developed towards the controlled delivery of drug molecules to the target. pH-sensitive composite hydrogel beads of Ca-alginate and agar have been developed towards controlled drug

delivery (Yin et al. 2018). Biodegradable and biocompatible semi-IPN hydrogels of Na-alginate and poly(methacrylic acid) have been utilized for controlled delivery of theophylline to colon (Ganguly et al. 2018). Upadhyay and co-workers (2018) have optimized capecitabine-loaded IPN beads of locust bean gum and Na-alginate by ionotropic gelation method and investigated their controlled drug delivery features. In vitro drug release studies indicated sustained delivery for 12 h. More so, cytotoxicity assay against HT-29 cells revealed significant reduction in cell growth, validating their worth towards the treatment of colon cancer. IPN hybrid hydrogels comprising Ca-alginate and peptide Fmoc-tyrosine have been constructed with an aim to achieve a controlled release drug profile for small molecules (Chen et al. 2018b). The IPN hydrogels exhibited enhanced storage moduli and fracture energy in comparison to Ca-alginate and revealed minimal drug release at acidic pH and sustained release at intestinal pH. Basu et al. (2017) have developed silver nanocomposite semi-IPN hydrogels of Na-alginate and acrylamide and explored their drug delivery features. The results demonstrated sustained release of ciprofloxacin for colonic delivery. Anwar and co-authors (2017) constructed Na-alginate and PVA hydrogels by free radical polymerization using 2-cyanoamido-2-methylpropane-sulfonic acid. The hydrogels exhibited prolonged delivery of tramadol HCl with improved entrapment efficiency.

Samanta and Ray (2014) synthesized various grades of Na-alginate-acrylamide IPN hydrogels using  $N,N'$ -methylenebisacrylamide as crosslinker and studied the release of acetaminophen. It was observed that the IPN with 6 wt% Na-alginate content was the best of the lot in terms of optimum swelling, drug entrapment and controlled release drug profile at physiological pH. Na-alginate has also been assimilated with carrageenan to formulate pH-responsive IPN hydrogel beads (Mohamadnia et al. 2007). The beads displayed sustained release profile for betamethasone acetate at pH 7.4. Literature reports pertaining to carrageenan and alginate-based IPN suggest their utility as colon-targeted controlled drug delivery systems (Mohamadnia et al. 2008; Kulkarni et al. 2011; Kulkarni et al. 2012; Mahdavinia et al. 2014).

In situ forming IPN hydrogels of Ca-alginate and hydroxyethyl-methacrylate-derivatized dextran have been prepared by Pescosolido and co-workers (2011) and bovine serum albumin (BSA) was loaded as a model drug to evaluate the drug delivery efficacy of the hydrogels. Surprisingly the drug release spanned approximately for 15 days. Treenate and Monvisade (2017) investigated the release profile of paracetamol from hydroxyethylacryl chitosan and Na-alginate IPN hydrogels cross-linked by ionic crosslinkers such as  $Ca^{2+}$ ,  $Zn^{2+}$  and  $Cu^{2+}$ . The comprehensive results of the study demonstrated their potential in the applications of site-specific oral drug delivery to the intestine and colon. Na-alginate-carboxymethyl cellulose hydrogel beads have been prepared in ferric chloride solution that showed excellent pH responsivity and controlled delivery features for metformin in pH 7.4 (Swamy and Yun 2015). IPN hydrogel membranes of Na-alginate and PVA prepared by Kulkarni et al. (2010) by solvent casting method were explored for prolonged transdermal delivery of antihypertensive drug prazosin hydrochloride.

### Temperature-Sensitive Alginate Hydrogels in Drug Delivery

Thermo-sensitive smart polymers are one of the most common classes of smart polymers studied in drug delivery research. Two major classifications of thermo-responsive IPNs can be categorized as:

1. IPNs that exhibit an upper critical solution temperature (UCST) that show a transition from gel to sol state above this temperature
2. IPNs that exhibit a lower critical solution temperature (LCST) that show a transition from gel to sol state below this temperature

Temperature-sensitive smart IPN hydrogels of alginate have often been prepared by taking in combination with one of the most commonly used thermo-responsive polymers, poly(N-isopropylacrylamide) (PNIPAAm) that has its phase transition near body temperature ( $\sim 33$  °C). The use of PNIPAAm in interpenetrating architectures has been particularly investigated for tailoring the release of drugs. Integrating alginates with PNIPAAm result in a special class of dual stimuli-sensitive composites with responsiveness to both pH and temperature.

Doxorubicin-loaded alginate-g-PNIPAAm IPN hydrogels demonstrated a sustained release profile of drug in physiological pH and were found to be effective in cancer therapy (Liu et al. 2017). Alginate-g-PNIPAAm injectable temperature-sensitive hydrogels with potential for localized and sustained delivery of stem cells and bioactive molecules have been successful and are ready to serve their purpose (Pentlavalli et al. 2017). Temperature-sensitive alginate beads synthesized via microwave-assisted graft copolymerization were found to prolong the delivery rate of indomethacin (Isiklan and Kucukbalci 2016). Muniz and co-workers studied the effect of temperature on the mechanical properties and permeability of PNIPAAm-Ca-alginate semi-IPNs and IPNs (Guilherme et al. 2002; de Moura et al. 2005; Guilherme et al. 2005). The authors evaluated the IPN hydrogel strength and observed a synergism of the mechanical performances of the polymers both below and above the LCST. The effect was more pronounced above LCST where the uniaxial compressive modulus of the hydrogel was much higher than individual components. More so, sustained release of drug was observed above LCST, which is attributed to the tighter structure of the hydrogel matrices with smaller pore sizes.

Ju and co-workers (2002) prepared semi-IPN hydrogels of alginate and amine-terminated PNIPAAm using calcium chloride as crosslinker. Also, they reported that semi-IPN hydrogel exhibited a remarkable sensitivity to temperature, pH and ionic strength of swelling. Li et al. (2018) employed Ca-alginate-PNIPAAm IPN onto cotton fibre surfaces using 1,2,3,4-butanetetracarboxylic acid crosslinking. The cotton fibre-supported hydrogels exhibited stiffer mechanical properties and controlled drug release characteristics at 37 °C. The in vitro drug release of anticancer drug 5-fluorouracil from semi-IPN networks of Na- alginate-PNIPAAm microspheres was reported by Reddy and co-workers (2008). The drug release at 25 °C and 37 °C confirmed about the thermo-responsive nature of the microspheres.



### **pH/Temperature Dual-Sensitive Alginate Hydrogels in Drug Delivery**

Several studies have also focused on the development of pH and temperature dual stimuli-sensitive smart alginate hydrogels. The properties of alginate-PNIPAAm semi-IPNs or IPNs were found to be strongly affected not only by pH but also by temperature. Shi et al. (2006) studied the effect of pH and temperature on the release of indomethacin from semi-IPN beads of Ca-alginate and PNIPAAm. At pH 2.1 and 37 °C, the drug release was slow and less than 10% of drug was released in 7 h while the release completed in 3 h at pH 7.4. Temperature-dependant drug release was also observed from the same gel, leading to a faster release at 37 °C than 25 °C. An overview of the properties and performances of alginate-based smart IPNs for drug delivery applications has been elucidated in the review article by Matricardi and co-authors (2013).

### **Alginate Microparticles in Drug Delivery**

Alginate-based microparticles have been fabricated by various groups and are found to be quite efficacious towards oral targeted drug delivery. The microparticles have been formulated mostly by the conventional shredding method in a commercial food processor or by a water/oil (w/o) emulsion and external gelation method. Chitosan-reinforced alginate microparticles for sustained release of antineoplastic drugs have been successfully synthesized and drug delivery potential has been explored (Yu et al. 2008). The same authors have also developed composite microparticle drug delivery systems composed of alginate, chitosan and pectin for site-specific delivery via oral route (Yu et al. 2009). Moebus et al. (2009) illustrated the efficacy of alginate-poloxamer microparticles for controlled drug delivery to mucosal tissues. The recently published review article by Agüero and co-authors (2017) summarizes the utility of alginate microparticles as oral colonic drug delivery devices with greater precision.

### **Alginate Nanoparticles in Drug Delivery**

The development of nanoparticles has proven to be a boon to the pharmaceutical sector. The idea of IPN nanoparticles as drug delivery agents may be utilized to modify or control the drug distribution at the tissue, cellular or subcellular levels (Lohani et al. 2014). Chitosan-alginate nanoparticles as delivery systems for  $\epsilon$ -polylysine were designed and a sustained release profile was achieved (Liu et al. 2018a, b, c). In another report of the above nanoparticulate systems by Motwani and co-workers (2008), prolonged ocular delivery of the ophthalmic antibiotic gatifloxacin was revealed for a period of 24 h. Hybrid nanoparticles of alginate and stearic acid-polyethylene glycol were loaded with an antiviral drug, zidovudine (Joshy et al. 2017). The optimized formulations were stable up to a period of six months and represented potential carrier for the drug by enhancing its efficiency.

### **Alginate Microgels in Drug Delivery**

Microgels offer unique advantages for polymeric drug delivery systems in terms of high degree of control over properties such as stability for prolonged circulation in

blood stream, control over particle size and biodegradability for sustained release of drugs. The potential of alginate microgels as sustained drug delivery agents is well-established. Chen and co-authors (2018a) have demonstrated the controlled release of an antacid (magnesium hydroxide) from alginate-pectin microgels. Microgels of varying dimensions were formed using either a handheld syringe or a vibrating nozzle encapsulation device with different nozzle sizes. The slowest antacid releasing features was observed from the microgel containing 80% alginate and 20% pectin. The authors inferred that the role of alginate was crucial for the design of microgels for the release of antacids in stomach. In another study by Wang and Newby (2018), coating of poly(allylamine) and poly(styrene sulfonate) was deposited layer by layer on alginate microgels and evaluated for sustained release of two hydrophilic drugs, sodium benzoate and zosteric acid. The results revealed that a prolonged release of the drugs could be achieved from the microgels spanning from hours to at least three days. Na-alginate microgel spheres encapsulated with tea polyphenol were designed for the treatment of bone infection (Chen et al. 2018d). The drug loading efficiency was reported to be 92.96% and the polyphenol release was therapeutic. Apart from exhibiting excellent antibacterial activity against *S. aureus*, the microgels promoted proliferation and differentiation of osteoblasts. Microgel suspensions of alginate have been developed for controlled release of vascular endothelial growth factor (VEGF)-encoding lentivectors (Madrigal et al. 2018). Babu and co-workers (2005) have reported IPN microgels of Na-alginate-acrylic acid prepared by w/o emulsion technique for the controlled release of ibuprofen. The developed systems showed pH responsivity and prolonged the drug delivery at physiological pH.

#### 4.7.1.2 Protein Delivery

The various inimitable features of alginate have enabled it to be used as a matrix for encapsulation and delivery for a variety of protein drugs. These features include (Gombotz and Wee 2006):

1. An almost inert aqueous environment within the matrix
2. An encapsulation process devoid of any organic solvents that proceeds at room temperature
3. A high gel porosity which allows for high diffusion rates for macromolecules
4. Ease of controlling the porosity with simple procedures
5. Biodegradation of the system under normal physiological conditions

Proteins encapsulated in alginate matrices are essentially released by two mechanisms: (i) diffusion of the protein through the pores of the polymer network and (ii) degradation of the polymeric network (George and Abraham 2006). In order to achieve a sustained release profile for protein drugs, the matrix degradation may not be the suitable method since it usually results in the rapid release of the protein. Therefore, for protein delivery, it is apt that the matrix remains intact and the protein diffuses out through the pores. Numerous reports have been published on the encapsulation and release of proteins from alginate matrices.

In a recently published article by Lima et al. (2018), pH-responsive alginate hydrogels have been evaluated for oral delivery of bovine serum albumin (BSA) in acidic and alkaline environments. The hydrogels were found to be compatible with living cells and higher BSA release was observed at pH 7.4, thereby validating them to be ideal for oral protein delivery. In another study utilizing Na-alginate-glycerol dressings for the delivery of therapeutic proteins to wounds, the authors found that the protein release was sustained for more than 72 h (Momoh et al. 2015). The films also showed ideal moisture content that is required for protein conformation and exhibited a good balance of flexibility and toughness.

Rahmani and Sheardown (2018) have explored the potential of protein-alginate complexes as pH-/ion-sensitive carriers for protein delivery. The authors used cytochrome C, lysozyme, myoglobin, chymotrypsin and BSA as model proteins for preparing the complexes. They observed that the proteins could be complexed with alginate in the absence of a cation and the complexes displayed decreased release rates. Furthermore, the protein release was facilitated by environmental triggers such as pH and ionic strength. Reports pertaining to protein encapsulation in alginate hydrogel beads also point to the utility of alginate for controlled protein delivery. Whey protein was encapsulated in Ca-alginate beads using an extrusion device (Zhang et al. 2016). The results suggested that hydrogel beads were suitable for encapsulation and the pH-triggered release of proteins was monitored. L-arginine-g-alginate beads were synthesized by Eldin et al. (2015) to be utilized as carriers for BSA. The grafting of alginate improved its release profile. The preliminary results clearly suggested that the Arg-g-alginate hydrogel may be a potential candidate for polymeric carrier for oral delivery of protein. IPN hydrogel beads composed of Na-alginate-carboxymethyl chitosan have shown great potential towards the oral delivery of BSA (Hu et al. 2016).

Injectable pH-/thermo-responsive hydrogels of poly(ethylene glycol) methacrylate, N-isopropylacrylamide and methacrylated alginate were prepared by Zhao and co-workers (2014). BSA as a model protein drug was encapsulated in situ in the hydrogel. BSA release results indicated that these hydrogels, as carriers, have great potential for long-term localized protein release.

A study by Pescosolido et al. (2011) demonstrated the potential of in situ forming IPN hydrogels based on a physical network of Ca-alginate, interpenetrated with a chemical one based on hydroxyethyl-methacrylate-derivatized dextran (dex-HEMA). BSA was gradually released from the IPNs over approximately 15 days. In situ semi-IPN hydrogels of Ca-alginate and dextran methacrylate (Dex-MA) were obtained by a dispersion of Dex-MA chains into a Ca-alginate hydrogel (Matricardi et al. 2008). The release of protein from these hydrogels validated their efficacy as sustained protein delivery systems.

### 4.7.2 Wound Dressing

An ideal dressing should always protect the wound from bacterial infection as well as promote healing. Hydrogels have received widespread applications as wound

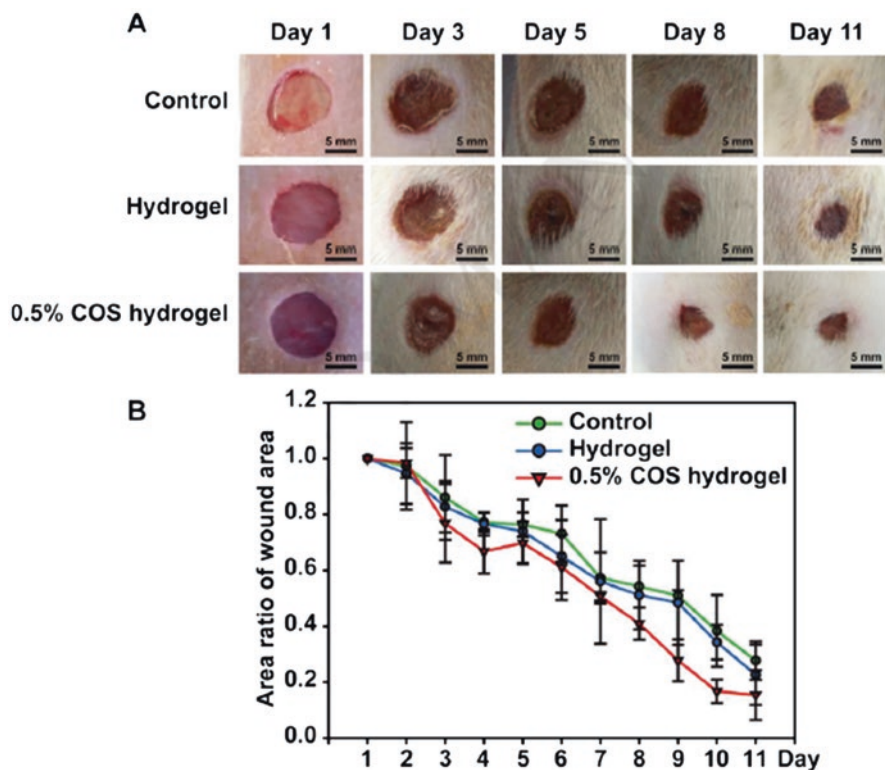
healing agents because they provide a moist environment, accelerate wound healing capacity, allow gaseous exchange and protect against bacterial infection. Moreover, they are non-toxic and have suitable mechanical and water vapour retention capabilities that can facilitate the healing process. Alginate-based formulations have been used in an array of wound healing applications. Bakhshayesh et al. (2018) reviewed that alginate-based wound dressing formulations such as sponges, hydrogels and electrospun mats are promising candidates for wound healing and have numerous advantages in terms of haemostatic capability and gel-forming ability upon absorption of wound exudates.

The antibacterial and wound healing properties of Na-alginate-PAAm hydrogels have been reported by Zhou et al. (2018). The influence of different divalent ion crosslinking (Cu, Zn, Sr and Ca) on the efficacy of the hydrogels has been explored. In vitro and in vivo study results showed that Zn-crosslinked hydrogel has a spectrum of advantages such as antibacterial activities, cell viability, better mechanical strength and higher ability of wound closure. Studies comprising chitosan-alginate-collagen have also proven them to be quite effective wound dressing materials (Xie et al. 2018). In another study, ZnO nanoparticle-loaded Na-alginate-gum acacia hydrogels displayed excellent wound healing effect on fibroblast cells (Raguvaran et al. 2017).

Summa et al. (2018) studied the in vitro biocompatibility and the efficiency of Na-alginate and povidone iodine (PVPI) polymeric composite in a mouse model for wound healing features. The hydrogel exhibited outstanding wound healing properties of alginates with the bactericidal and fungicidal properties of PVPI, providing a controlled release of antiseptic; thus, it is a good candidate for reduction in inflammatory response both in human foreskin fibroblasts and in rodents after wound induction. The synthesis of ciprofloxacin-loaded electrospun hydrophobic poly(lactic-co-glycolic acid) (PLGA) fibrous mats modified by Na-alginate microparticles was reported by Liu et al. (2018b). The results revealed that alginate improved the wettability and water absorption capacity and improved the release rate of ciprofloxacin from the PLGA fibrous mats and reduced the stiffness of the mats for better protection of the injured area. Furthermore, the burst release of ciprofloxacin which resulted from the addition of alginate could offer an improved antibacterial effect to the PLGA mats.

Alginate crosslinked by calcium gluconate crystals deposited in poly( $\epsilon$ -caprolactone)-b-poly(ethylene glycol)-b-poly( $\epsilon$ -caprolactone) porous microspheres was developed by Liao et al. (2018) for skin wound healing. The porous structure of the microspheres offered additional anchor points for fibroblast attachment and growth, enhancing the cell growth in the hybrid hydrogel.

N-Carboxymethyl chitosan and alginate-based hydrogels were prepared by electrostatic interaction and divalent chelation with epidermal growth factor (EGF) by Hu et al. (2018b) for cell proliferation and wound healing activities. Their investigation suggested that the loading of EGF did not depreciate the mechanical properties of hydrogels. Moreover, the porous 3D structure of the hydrogels permitted sufficient loading and release of EGF and improved cell proliferation indicating that the hydrogel is an excellent candidate for wound healing applications. Carboxymethyl



**Fig 4.2** Photographs at each time point of 10 mm diameter wounds (a) and wound closure curves (b) demonstrating the accelerated healing for wounds treated with CMCS/alginate hydrogel and CMCS/alginate hydrogel with 0.5% COS. (Lv et al. 2018)

chitosan (CMCS)-alginate and CMCS-alginate-chitosan oligosaccharide (COS) hydrogels were synthesized by Lv et al. (2018) for in situ wound healing treatment. CMCS-alginate and CMCS-alginate-COS hydrogels demonstrated faster wound contraction, while the healing speed of CMCS-alginate-COS hydrogels was faster as compared with CMCS-alginate. At 11 days of treatment, both the hydrogels showed remarkable increase in thickness and integrity of epidermal tissue and increased construction of collagen fibres (Fig. 4.2.) (Wound healing and cytotoxicity from Lv et al. 2018).

Akbar and co-authors (2018) evaluated the in vivo anti-diabetic and wound healing potential of curcumin-loaded chitosan-alginate-maltodextrin-pluronic-based mixed polymeric micelles. They reported that after 2 weeks of treatment of wound with different formulations, effective wound healing responses in rats were observed. Shahzad et al. (2018) studied the wound healing activity of cefazolin nanoparticles of chitosan loaded into Na-alginate/pectin films crosslinked by calcium chloride. Their finding suggested that after 7 days the films were fairly protective against the growth of the secondary bacterial infections at the wound area. Kamoun et al. (2018)

have demonstrated Na-alginate/PVA hydrogels containing sodium ampicillin as an ideal candidate in wound care. It has also been reported that alginate- and gelatin-based biocomposite wafers containing silver sulfadiazine have a potential wound healing application (Boateng et al. 2015).

The main problem associated with chronic non-healing wounds is drug-resistant infection as the skin barrier functionality reduced. Also, biofilm formation due to the existence of aerobic and anaerobic bacteria produces a drug-resistant infection that escapes the host immune response. Tarusha and co-workers (2018) fabricated alginate hydrogels loaded with hyaluronic acid-lactose-modified chitosan and silver nanoparticles to stimulate wound healing and to regulate bacterial contamination of non-healing wounds. In vitro investigation revealed that hyaluronic acid released by the membrane is able to stimulate the wound healing whereas the silver nanoparticle exploits an effectual antibacterial activity against both planktonic bacteria and biofilms.

Amniotic fluid (AF) is enriched with a varied range of growth factors such as fibroblast growth factor (FGF), epidermal growth factor (EGF) and transforming growth factor beta 1 (TGF-  $\beta$ 1) that are ideal to promote cellular response and wound healing. AF has specified functions and applications like cell proliferation, migration and differentiation which have enormous effect on improvement of the wound healing process. Moreover, AF has revealed to enhance healing in bone, regeneration in tendon tissue and prevention of scar formation in nerve cells. Ghalei and co-workers (2018) fabricated alginate hydrogel-electrospun silk fibroin fibres to deliver AF to the wound site. Fibroblast culturing on the fabricated dressings demonstrated that cellular proliferation, spreading and secretion of collagen enhanced with increasing AF. Taken together, the results provided a novel bioactive dressing with great potentials for speeding up the healing process in severe wounds.

### 4.7.3 Tissue Engineering

Tissue engineering has emerged as a viable approach to treat disease or repair damage in tissues and organs. The ideal paradigm in tissue engineering is introduction of tissue grafts native to the wounded areas to facilitate the regenerative process. Tissue engineering mostly involves the in vitro seeding and proliferation of cells in a scaffold-based or injectable supports. To ensure that adequate cells reach the target tissue, it is important to have effective cell transplantation process that is capable of sustaining the survival of implanted cells while maintaining their function and improving their adhesion with the host (Sun and Tan 2013). The delivery of cells with the help of a biocompatible material has emerged as an efficient strategy. In this regard, alginate is a classic example because of its versatility and tunability. The potential of alginate as an artificial three-dimensional cellular matrix in a diversity of applications in regenerative medicine has been elucidated beautifully by Giri et al. (2012) and Sun and Tan (2013).

### 4.7.3.1 Bone Tissue Regeneration

Bone is a complex tissue that comprises of hydroxyapatite and collagen. Bone defects or fractures occur under various medical conditions such as osteoporosis, arthritis, neoplasm, congenital defects, etc. The current standard treatment is based on the use of autograft, allograft and xenograft. Despite the introduction of several augmentation techniques and bone graft materials, bone regeneration still remains a subject of clinical challenge. Autografts and allografts are inevitably associated with certain shortcomings such as donor site morbidity, risk of immune reaction and post-operative pain and infection (Venkatesan et al. 2015). Therefore, there has been a constant need for development of biomaterials that apart from restoring/repairing the damaged bone should also be structurally, functionally and mechanically equivalent to a healthy bone and favour cell adhesion, proliferation and differentiation for bone tissue regeneration. In this regard, alginate has been appraised as a promising biomaterial because of its biocompatibility, non-immunogenicity and biodegradability. A broad overview of alginate composites, their preparation and subsequent applications in bone tissue engineering has been vividly provided by Venkatesan et al. (2015) in their review article.

Over the years, natural polymer-ceramic composites have evolved to be a promising bone graft substitute. While the ceramic provide strength and osteoconductivity, the polymer imparts flexibility and resorbability. Recently, R. A. Popescu et al. (2018) have combined bioactive glass-ceramics with alginate-pullulan hydrogel for the synthesis of new biocompatible hydrogels for in vivo bone tissue regeneration. The proliferation rates for the fibroblast and osteoblast cell viability assays were excellent for the composites. Additionally, the histopathological results displayed good biocompatibility, thus validating their worth in bone regeneration applications. In another report by Tohamy et al. (2018), alginate-hydroxyethyl cellulose-hydroxyapatite composite scaffolds were potentially explored for enhanced in vitro bone regeneration. The authors witnessed higher protein adsorption, cell proliferation and cell viability for human mesenchymal cells. X. Zhang and co-workers (2018) prepared composite hydrogels of Na-alginate-akermanite-glutamate to promote irregular bone regeneration through stem cell recruitment. Their findings revealed no cytotoxicity and higher gene expressions in human bone marrow stromal cells after culturing with hydrogel extracts. The implanted hydrogel also assisted bone mesenchymal stem cell migration to the injured area via CXCR4 (C-X-C chemokine receptor type 4) elevation and stimulated osteogenic differentiation of these cells through the MAPK pathway. This study validated the hydrogels as competent materials for the regeneration of irregular bone cavities.

Clinically used supraphysiological dose of bone morphogenetic protein-2 (BMP-2) usually carries the risk of adverse effects. Thus, an injectable hydrogel composed of BMP-2-loaded recombinant collagen-based microspheres and alginate were developed by Mumcuoglu et al. (2018). BMP-2 doses of 10 µg, 3 µg and 1 µg per implant (50 µg/mL, 15 µg/mL and 5 µg/mL, respectively) were effectively injected subcutaneously in rats in a time- and dose-dependent manner for both ectopic and calvarial rat defect models. Lin et al. (2018) reported about the implantation of alginate fibre with diclofenac and bone cells coated with chitosan for bone regeneration

during inflammation. The outcome revealed that on days 7 and 10, when diclofenac was consumed and the concentrations of inflammatory compounds surged, the coating efficiently blocked the harmful compounds and protected the bone cells within the fibres. In another study by Chen and co-authors (2018c) the effect of an IPN of sodium hyaluronate-Na-alginate scaffold combined with berberine on osteochondral repair was investigated in vivo. The authors explored the mechanism of the osteochondral repair and found that the IPN could simultaneously regenerate not only the cartilage but also the subchondral bone and hence is a promising material for osteochondral defect regeneration. Hydrogels comprising of chitosan-alginate-hydroxyapatite have also been successfully designed and efficaciously utilized for bone tissue engineering therapies with amazing biocompatibility and proliferation with osteoblast cells (Kim et al. 2015; Sharma et al. 2016).

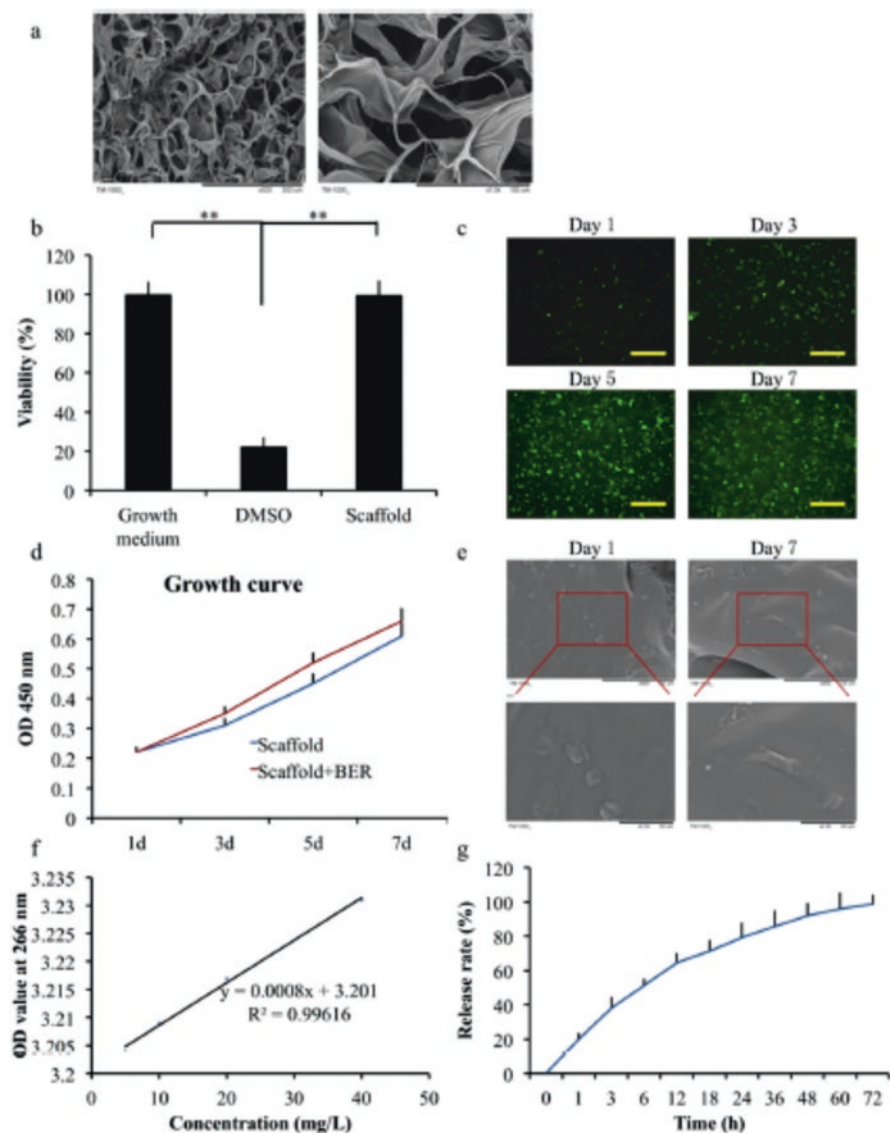
#### 4.7.3.2 Cartilage Regeneration

Despite intensive research, regeneration of [articular cartilage](#) largely remains an unresolved medical concern due to their very limited reparative capacity. For cartilage treatment in tissue engineering, the implantation of autologous chondrocytes and stem cells have been explored in the pursuit of cartilage repair (Bidarra et al. 2014). There have been many recent examples where alginate has been employed for cartilage tissue regeneration.

Ruvinov and co-authors (2018) assessed the feasibility and long-term efficiency of a bilayered injectable acellular affinity-binding alginate hydrogel in a mini pig model of osteochondral defects and the outcomes were evaluated after 6 months. Macroscopical and histological evaluation of the defects treated with the hydrogel revealed about the effective reconstruction of articular cartilage layer, glossy surface and cellular organization hyaline tissue associated with noticeable deposition of proteoglycans and type II collagen. The authors concluded that the model showed promising potential of an injectable acellular growth factor-loaded affinity-binding candidate for effective repair and regeneration of articular hyaline cartilage (Fig. 4.3) (Chen et al. 2018c).

Three-dimensional cell printing is a unique technique that enables free-form fabrication of cell-laden hydrogel scaffolds with controllable features and interconnected pores for tissue engineering applications. Thus, bioink materials that are able to offer good printability and favourable cellular interaction are highly desirable. Recent literature has pointed towards the surge of 3D bioprinted alginate scaffolds for cartilage engineering. Yang et al. (2018a, b) constructed printed cartilage tissue using collagen type I or agarose mixed with Na-alginate to serve as 3D bioprinting bioinks by incorporating chondrocytes. The Na-alginate/collagen scaffold could noticeably facilitate cell adhesion and proliferation and improved the expression of cartilage-specific genes such as *Acan*, *Col2a1* and *Sox9* than Na-alginate/agarose. The authors further observed that Na-alginate/collagen scaffold effectively suppressed the differentiation of chondrocytes and preserved the phenotype and hence is a promising biomaterial in cartilage tissue engineering. In a study by Markstedt and co-workers (2015), 3D bioprinted human chondrocytes with nanocellulose/alginate bioink for cartilage tissue engineering were developed. The bioinks enabled





**Fig. 4.3** Preparation and characterization of sodium hyaluronate and sodium alginate IPN scaffold. (a) Microscopic structure of the scaffold. (b) Cell viability in the presence of the scaffold. (c) Live-dead cell staining. Scale bars = 200  $\mu\text{m}$ . (d) Cell proliferation assay. (e) SEM micrographs of BMSCs on the scaffold. (f) Standard curve of BER. (g) Controlled release profile of BER. (Chen et al. 2018c)

the printing of both 2D grid-like structures and 3D constructs. Additionally, the human chondrocytes bioprinted in the bioink exhibited a cell viability of 86% even after seven days of culture. This study established the efficacy of nanocellulose/alginate bioinks for 3D bioprinting of living tissues. Kundu et al. (2015) have developed 3D cell-printed scaffolds using layer-by-layer deposition of polycaprolactone and chondrocyte cell-encapsulated alginate hydrogel. The 3D cell-printed scaffolds were then implanted in the dorsal subcutaneous spaces of female nude mice. After 4 weeks, the retrieved implants revealed much enhanced cartilage tissue formation in the scaffold.

Several studies have also demonstrated the use of injectable hydrogels for cartilage regeneration purposes because of the ease of handling and complete filling of defect area through minimally invasive surgical instruments. In a study by Liao et al. (2017) an injectable 3D alginate hydrogel crosslinked by calcium gluconate-loaded porous microspheres was assessed for cartilage regeneration features. The authors reported that the defects could be completely healed by 18 weeks and the repaired chondrocytes regained a normal tissue structure. A series of injectable in situ self-crosslinking poly(L-glutamic acid)-alginate hydrogels were fabricated and rabbit chondrocytes were encapsulated in them (Yan et al. 2014). The results affirmed the injectability and rapid in vivo gel formation along with mechanical stability, cell growth and ectopic cartilage formation.

#### 4.7.3.3 Cardiac Tissue Regeneration

Heart failure is one of the most common causes of death globally. Majority cases of heart failure have been due to myocardial infarction (MI) associated with the left ventricle. Since the adult heart lacks regenerative capacity, loss of myocardium is irreversible and ultimately leads to failure. Existing heart failure therapies aim to compensate for the insufficient and low intrinsic regenerative ability of the adult heart. In order to repopulate the areas of cell loss in the damaged hearts, cell regeneration has gained thrust (Bidarra et al. 2014). Alginate has been identified as one building block to accomplish the therapeutic regeneration of cardiomyocytes.

Liberski et al. (2016) have reviewed the current applications of alginate in cardiac regeneration and valve replacement techniques. In another review article by Ruvinov and Cohen (2016), the authors have summarized the versatile applications of alginate as a supporting cardiac implant after acute MI to its employment as delivery vehicles for stem cells and other bioactive molecules and/or regenerative factors to the heart. The preclinical and first-in-man clinical trials using alginate hydrogels leading to myocardial repair and tissue regeneration have been discussed in greater details.

Recently, Sondermeijer et al. (2018) reported the development of a porous, bio-compatible 3D alginate scaffold covalently modified with RGDfK (Arg-Gly-Asp-D-Phe-Lys) peptide. Following implantation in the abdominal rectus muscles in rats, the authors observed that the scaffolds seeded with human mesenchymal precursor cells and patched to the epicardial surface of infarcted myocardium induced myocardial neoangiogenesis and significantly improved cardiac function. The

authors established this biomaterial as a potential strategy to deliver cells to myocardial infarct areas to improve neovascularization and cardiac function.

Rosellini and co-workers (2018) have lately fabricated a new class of porous scaffolds by integrating a protein (collagen or gelatin) with alginate for mimicking native ECM for cardiac tissue engineering applications. The gelatin-alginate scaffolds better mimicked the native tissues and exhibited superior mechanical properties. A high viability of the resulting cardiac constructs was observed from the scaffolds after culturing with neonatal rat cardiomyocytes. The authors strongly proposed the protein-alginate scaffolds as viable substitutes for application in cardiac tissue regeneration.

Cardiac stem cells (CSC) are a heterogenic group of cells concentrated in particular areas of heart such as the atria or pericardium. CSCs represent a logical cell type to be explored as a regenerative treatment option for tissues damaged due to MI. Since the isolation of CSCs is time consuming and expensive, O'Neill and co-authors (2018) proposed the incorporation of growth factor-eluting alginate microparticles into collagen-based scaffolds to promote the recruitment and expansion of CSCs. The alginate microparticles were encapsulated with two types of proteins, hepatocyte growth factor and insulin-like growth factor-1, and subsequently incorporated into the collagen matrix. The *in vitro* assays with isolated CSCs demonstrated that the sustained protein release (which extended up to 15 days) from the scaffolds resulted in motogenic and proliferative effect.

#### 4.7.3.4 Liver Tissue Regeneration

Liver tissue engineering basically deals with the possibility of reproducing in total or in part the functions of the liver in order to treat acute or chronic liver disorders and, ultimately, create a fully functional organ to be transplanted or used as an extracorporeal device. The technological strategies in this direction are based on allocating hepatocytes/hepatocyte-like cells within a 3D structure to ensure their survival and maintain their functional phenotype. The recently published review article by Mazza et al. (2018) elucidates liver tissue engineering with precision in terms of implantable liver tissues to whole organ engineering.

A recent study carried out by Liu and co-authors (2018c) employed Ca-alginate gel sheets, embedded with liver cells (RLC-18) with the intention to imitate liver lobule tissue. The Ca-alginate sheets having hepatic lobule-shaped patterns were deposited onto a microelectrode device using electrodeposition and the viability of embedded cells exceeded 80%. The cell sheets were removed from the electrode substrate and stacked onto a 3D multilayered structure to mimic the morphology of liver lobule tissue. The authors concluded that the developed method could provide a new bottom-up paradigm to build 3D macroscopic liver tissue similar to that *in vivo*.

Developing 3D cell culture systems is necessary for investigating the mechanism of hepatocellular carcinoma (HCC) metastasis and screen therapeutic drugs. Sun et al. (2018) constructed decellularized liver matrix-alginate (DLM-ALG) hybrid gel beads for the 3D culture of HCC cells. DLM-ALG beads exhibited better activity of matrix metalloproteinases (MMPs) of HCCLM3 cells, including MMP2 and

MMP9 and urokinase plasminogen activator system. The findings of this study established DLM-ALG beads as potential in HCC research and subsequently in liver tissue engineering.

Injectable hydrogels synthesized from glycyrrhizin, alginate and calcium for 3D cell culture in liver tissue engineering has been reported by Tong et al. (2018). The hydrogels showed good biocompatibility and could maintain the viability, proliferation and liver function for longer periods of time. Moreover, the hydrogels enhanced the mRNA expression of cytochrome P450, which were key enzymes to the metabolism of hepatocytes and could be a potential 3D cell culture system for liver tissue engineering.

#### 4.7.3.5 Nerve Tissue Regeneration

Neural regeneration research is designed to develop strategies for therapy for nerve damage incurred by disease or injury. In order to fabricate fully functional and biomimetic nerve substitutes, various kinds of polymeric-based scaffolds have been proposed. Artificial nerve grafts need to mimic the native extracellular matrix both structurally and mechanically in order to provide the appropriate environment for the neotissues. Furthermore, artificial nerve grafts need to be electrically conductive to support the electrical conduction of injured nerve during regeneration and enhance regeneration. The biomaterial further needs to induce appropriate chemical and physical signalling cues, which transduce into intracellular biochemical responses to moderate the cellular function. Alginate being a negatively charged polysaccharide has been widely applied to develop artificial constructs for peripheral nerve tissues (Prang et al. 2006).

Bioprinting Schwann cell-encapsulated scaffolds using alginate, fibrin, hyaluronic acid and/or RGD peptide were synthesized by Ning et al. (2018) for nerve tissue engineering. The printed scaffolds enhanced the alignment of Schwann cells inside scaffolds and provided haptotactic cues to direct the extension of dorsal root ganglion neurites, which has potential applications in nerve tissue engineering. A composite hydrogel of PAAm-graphene oxide-gelatin-Na-alginate for accelerating peripheral nerve regeneration was fabricated through in situ free radical polymerization (Zhao et al. 2018). The hydrogel displayed remarkable adhesion and proliferation of cultured Schwann cells. The results of this study validated the hydrogel for neural tissue engineering applications by promoting Schwann cell growth. In another study, Golafshan and co-workers (2017) developed graphene-Na-alginate-PVA scaffolds for engineering neural constructs. The scaffolds displayed superior electrical and mechanical properties with enhanced PC12 cell interaction. Overall, the developed scaffolds were promising devices for peripheral nerve regeneration. Wu et al. (2017) studied about the neural tissue engineering through chitosan-poly lactide-alginate fibres. Nerve growth factor (NGF)-induced neurite extension of PC12 cells confirmed about the bioactivity of NGF released from fibres was well retained. Bu and co-authors (2018) have synthesized a conductive polymer of Na-alginate-carboxymethyl chitosan crosslinked with  $\text{Ca}^{2+}$  ions. The conductivity of the hydrogel was implemented by doping with polypyrrole. The conductive

hydrogel exhibited excellent biocompatibility and repair features as a bioactive biomaterial and is potent for neural tissue engineering applications.

In a novel methodology, Buyukoz et al. (2018) utilized a combined strategy of thermally induced phase separation and porogen leaching to create interconnected macropores and nanofibrous structures. Gelatin scaffolds integrated with nerve growth factor-loaded alginate microspheres were prepared by the aforementioned strategy. The scaffolds had good topologic and mechanical properties similar to brain tissue and pore structure suitable for cell growth and differentiation and can have potential applications in brain tissue engineering.

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## 4.8 Conclusion and Future Perspectives

To summarize, alginate has been extensively utilized in drug/protein delivery or as building blocks for tissue repair and regeneration. Owing to their versatility, alginate IPNs have been tailored with the desired structures, properties and functions. Alginate-based biomaterials are promising substrates for tissue engineering applications with the advantage that both drugs and cells can be readily integrated into the scaffolding matrix. The surge in alginate bioinks in 3D bioprinting points to the greater utility and success of the biopolymer in tissue engineering. Successful exploitation of alginate-based biomaterials in different tissues and organs such as bone, cartilage, cardiac, liver and nerve suggests their promising future for repair and regeneration applications. The applications of alginate IPNs as wound healing dressings are manifold. Alginate has rendered itself as a hugely potent wound dressing agent.

Engineering of more alginate-based biomaterials endowed with precisely designed physical, chemical and biological properties should be carried out to mimic the environment of natural tissues. The design of such alginate IPNs could further revolutionize the applicability of alginate IPNs in the world of biomedicine.

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**Dr. Subhraseema Das** completed her Ph.D. from the Department of Chemistry, National Institute of Technology, Rourkela, and is currently serving as Asst. Prof. (Faculty-on-Contract) in the Department of Chemistry, Ravenshaw University, Cuttack, Odisha. Her research interests focus on cyclodextrin inclusion complexes, design of polymeric materials towards biomedical applications, non-thermal plasma functionalization of polymers and plasma-assisted synthesis of polymeric biomaterials. She has 11 research papers in international journals, 15 conference proceedings and participation in 10 workshops/training programs to her credit.

**Dr. Usharani Subuddhi** completed her Ph.D. from the Department of Chemistry, IIT Madras, in 2006 in the field of Physical Photochemistry and Fluorescence Spectroscopy. She received post-doctoral fellowship from the Canadian Institute of Health Research and worked in the Department of Biological Sciences at the University of Alberta, Canada. She joined NIT Rourkela in July 2009 as an assistant professor. Currently she is working on various research projects. Her research interest mostly spans the following areas: physical photochemistry and fluorescence spectroscopy, spectroscopic investigations of biological and biomimetic systems, and design and study of novel drug delivery systems. She has guided several masters theses and two Ph.D. theses and is continuing guidance of Ph.D. and M.Sc. students. She has around 22 publications in international journals to her credit.