Review

A Review on Hydrophobically Associated Alginates: Approaches and Applications

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ABSTRACT: Alginates are linear anionic polysaccharides, which are well-known for their biocompatible, nontoxic, and biodegradable nature. The polymer consists of alternating units of β-$(1 \rightarrow 4)$-linked D-mannuronic acid (M) and α-$(1 \rightarrow 4)$-linked L-guluronic acid (G) that have hydroxyl and carboxyl groups as the main functional groups. As a large number of free carboxyl and hydroxyl groups are present in the polymeric chain, the polymer is predominantly hydrophilic. The food and pharmaceutical industries have been the most extensive utilizers of alginates to produce gelling and thickening agents. However, by imparting hydrophobicity to alginates, the range of applications can be widened. Although there are reviews on alginate and its chemical modifications, reviews focusing on hydrophobically associated alginates have not been presented. The commonly used chemical modifications to incorporate hydrophobicity include esterification, Ugi reaction, reductive amination, and graft copolymerization. The hydrophobically modified alginates play an important role in delivery of hydrophobic drugs and pesticides as the modification increases the affinity toward hydrophobic components and helps in their sustained release. Due to their nontoxic and edible nature, they find use in the food industry as emulsion stabilizer to stabilize oil-in-water emulsions and to improve creaming ability. Further, alginate-based materials such as membranes, aerogels, and films are hydrophobically modified to improve their functionality and applicability to water treatment and food packaging. This Review aims to highlight the important chemical modifications and methods that are done to impart hydrophobicity to alginate, and the applications of hydrophobically modified alginates in different sectors ranging from drug delivery to food packaging are discussed.
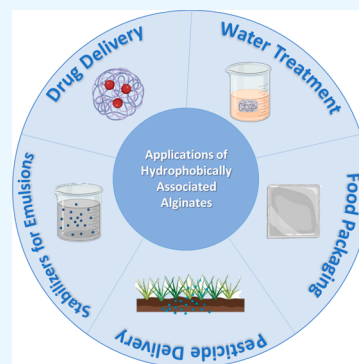
1. INTRODUCTION

Alginate is a binary heteropolysaccharide comprising 1,4-linked β-D-mannuronic (M) and α-L-guluronic acid (G), isolated from brown seaweeds (Phaeophyceae) in the form of their sodium salts.[1] Alginates are increasingly gaining the attention of industries and researchers as seaweeds pave the way for a sustainable future since they act as a carbon sink, improve marine biodiversity, and do not require land and high maintenance.[2] There are eight different species of the Phaeophyceae family from which alginates are extracted, and the industrially important species are *Laminaria hyperborea*, *Laminaria digitata*, *Macrocystis pyrifera*, and *Ascophyllum nodosum*.[3] The polyuronide is secreted as an exopolysaccharide by certain bacterial species like *Pseudomonas aeruginosa*[4] and *Azotobacter*.[5] Alginate exists as a block copolymer constituted of homopolymeric β-D-mannuronic and α-L-guluronic acids, denoted as M- and G-units, interspersed with alternating structural sections as MG units.[6] Due to their inert, biocompatible, nonimmunogenic and biodegradable nature alginates are widely used in biomedical applications,[7] packaging,[8] water treatment,[9] as emulsifiers,[10] binders,[11] thickening and gelling agents,[12] storage materials for heat and energy.[13,14] In this brief Review, the hydrophobic modifications of alginate and its applications are addressed and discussed.

1.1. Extraction. The industrial extraction of alginate from seaweed comprises five major steps. First, the ground seaweed, containing insoluble alginate salts is treated with formaldehyde or formalin followed by acidification using mineral acids.[15] The pretreatment with formaldehyde is done primarily for depigmentation of alginate, wherein the algal pigments are made insoluble with the action of formaldehyde with the phenolic compounds present in them.[16] Acidification converts the alginate salts to alginic acids, which are converted to sodium salts by alkaline treatment with sodium carbonate. During acidification, residual chemicals from depigmentation, salts, lipids, polysaccharides like fucoidan, laminarian, and other nontarget compounds are removed. The sodium alginate is separated from the residues of seaweed, precipitated, and dried. Alkaline treatment is the crucial step in the extraction process which breaks the cell wall of alginate and converts alginic acid to its soluble alginate salt at a pH of 9−10.[17] After
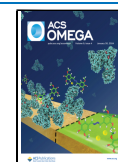
Table 1. Nonconventional Methods for the Extraction of Alginate - Advantages and Disadvantages

S. No	Type of extraction	Advantages	Disadvantages	ref
1	Ultrasound	Reduction in extraction time, Less usage of chemicals	High frequency ultrasound can lead to decomposition; Considerable reduction of molecular weight.	22, 23
2	Microwave assisted	Simple, efficient, less solvent usage, and energy due to better heat distribution, high yield compared to the conventional chemical treatment, exhibits higher antioxidant property.	Requires higher selectivity to be used solely for polysaccharide fractionation, therefore requiring the coupling of other methods/solvents to selectively extract the target compound	24, 17
3	Enzymatic treatment	Ecofriendly, highly pure, reduced solvent usage, food compatible extraction method, energy consumption, and extraction time, exhibits higher antioxidant property than chemically extracted alginates.	Expensive,selectivity and specificity of enzymes influenced by reaction conditions pH, temperature, and concentration	25

the alkaline treatment, the alginates are precipitated and dried. Processing time, concentration of acid, alkali, and pH during the extraction steps influences the rheology and yield of alginate obtained. Currently, the industrial production of alginates is done only through seaweed and efficient biosynthetic pathways for extraction through bacterial sources is still being developed.[18] Other nonconventional methods of alginate extraction such as enzymatic treatments,[19] ultrasound[20] and microwave assisted methods[21] are also reported (Table 1).

1.2. Alginate − Structure, Physical, and Chemical Properties. *1.2.1. Structure.* The structure of alginates was determined using ^{13}C NMR, ^{1}H NMR, FT-IR, and the polymer is composed of β-(1,4) linked D-mannuronic acid with $^{4}C_{1}$ ring conformation and α-(1,4)-linked L-guluronic acid with $^{1}C_{4}$ ring conformation, where L-guluronic acid is the C-5 epimer of D-mannuronic acid.[26] The ratio of mannuronic and guluronic acid units is found to vary according to the species, age and parts of seaweed, geographical location, and climatic conditions.[27,28] The GG units are axially linked which results in a rigid polymer backbone, and the MM units are equatorially linked forming linear domains.[1] The conformation alignment of G units creates a cavity that helps in binding of cross-linker ions. Bacterial alginates show a slight structural dissimilarity from the seaweed extracted alginates as the hydroxyl groups in the mannuronic acid are acetylated at C2 and/or C3 position (Figure 1).[29]
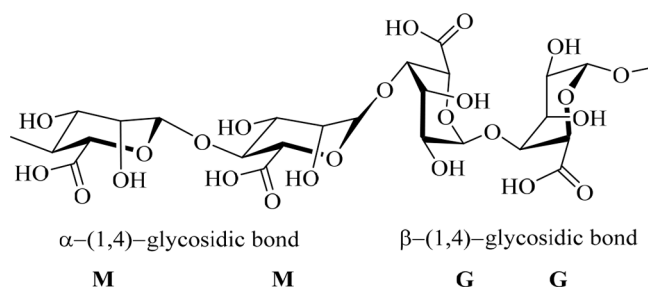

Figure 1. Structural depiction of monomers of alginate: M representing β-D-mannuronic acid units and G representing α-L-guluronic acid.

1.2.2. Physical Properties. Alginic acid is insoluble in water, and its monovalent salts (sodium, potassium, and ammonium alginate) are soluble in water. The solubility of alginate depends on pH, ionic strength, cosolvents and chelating ions in the medium.[30] Due to the abundance of hydroxyl groups in alginate, they are predominantly hydrophilic and form hydrocolloids with water and hydrogels via ionotropic gelation when cross-linking ions are present.[7] Alginates are insoluble in organic solvents but can be made soluble in polar aprotic

organic solvents like DMSO and DMF, when counterions (tetrabutylammonium (TBA)) and dissolution promoters (tetrabutylammonium fluoride (TBAF)) are present.[30] The addition of TBAF to the TBA-Alg is required for the complete dissolution of the TBA-Alg, and the solubility of TBA-Alg can be improved by increasing the degree of substitution of TBA-alginate by optimizing the reaction conditions for the synthesis of the modified alginate derivate.[31] The viscosity of alginates varies considerably according to the pH, ionic strength, cross-linking ions, temperature, and amount of G and M units in the alginate.[32−34] Further, the interchain electrostatic repulsive forces present in the alginate polymeric backbone can cause chain extension, which also affects the viscosity of the alginate. The viscosities of dilute solutions of sodium alginate tend to decrease with increase of temperature. Sodium alginate has been reported to exhibit the polyelectrolyte effect as its dilute solutions show the upward bending phenomenon of reduced viscosity.[35]

1.2.3. Chemical Properties - Gel Formation and Cross-Linking. The sol−gel transition of alginates occurs in the presence of di, tri and tetravalent cations of Al, Pb, Cu, Cd, Ba, Sr, Ca, Co, Ni, Zn and Mn.[36] Due to their inert nature, calcium ions are used as the go-to cross-linker for alginates.[37] Conventional methods of gel formation include external diffusion of cross-linker ions into the alginate sol and internal setting wherein slow release of ions into the alginate solution occurs. For the internal setting, the D-glucono-δ-lactone (GDL) and CaCO$_3$ system is used, which facilitates slow release of calcium ions into the alginate as the hydrolysis of the lactone occurs, forming a homogeneous gel.[38] The gels formed via diffusion are found to have a nonhomogeneous composition, which is attributed to the rapid chelation of ions to the alginate. Alginate gels with a capillary like structure can also be formed by external diffusion of ions and this typical morphology in the alginate gel is exploited in tissue engineering due to their structural resemblance to tissues.[39] Apart from diffusion and internal setting with cross-linking ions, carbon dioxide induced gelation, cryogelation, nonsolvent induced phase separation, covalent cross-linking, drying (freeze-drying, evaporative drying, supercritical drying) and organic acids (oxalic, maleic, tartaric, glutaric and citric acids) are used for the gelation of alginate.[40] At low pH, alginate forms stable hydrogels, while at higher pH, the stability of the polymer sharply declines. This is because, the carboxyl group ionizes at pH above 4.4 leading to an increase of electrostatic repulsive forces causing chain extension and while at low pH, ionization of carboxyl group does not occur leading to an insoluble structure.[41,42] The gels formed in acidic conditions were found to be stabilized by intramolecular hydrogen bonding.[43] Variation in the amount of monomer units has been observed from one species to the other, which
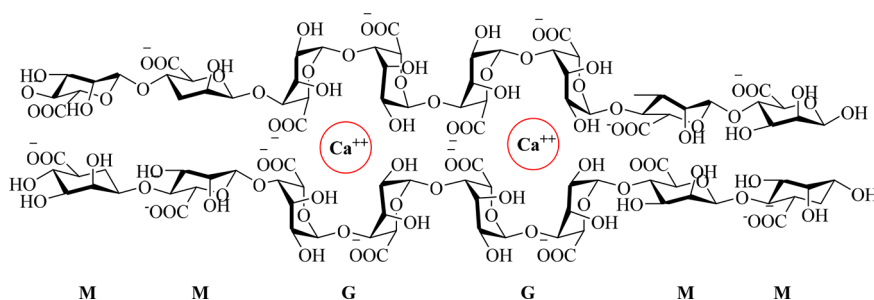
Figure 2. Egg-box model of calcium ions cross-linking with G units of alginate.

significantly influences the physical, chemical, and mechanical properties of alginates.[5] An important factor that decides the strength of the hydrogel is the number of G units that are present in the polymer as they are known to form the strongest cross-linking points in the polymeric chain.[44] Chain strength is reported to increase in the order of MG < MM < GG units, and the affinity of poly M, poly G and poly MG uronic units toward chelating ions differs.[45] The gelling of alginate through ionic cross-linking forms a unique egg box like chelation where the cross-linking ions are accommodated between the two polymeric chains of the alginate.[46] The axially linked GG units are reported to chelate the metal ions rather than the equatorially linked MM units.[47] By tuning the cross-linker concentration and other factors like pH, temperature, the sol–gel transition can be made reversible or irreversible (Figure 2).[48]

2. Hydrophobic Modification. As a result of the availability of hydroxyl and carboxyl groups, alginates are predominantly hydrophilic molecules. The introduction of hydrophobic groups to the polymer backbone is a direct method to impart hydrophobic character, which usually involves the formation of ester and amide derivatives of alginates. The chemical modification of alginate could be achieved mostly at the two secondary hydroxyl positions (C-2 and C-3) or at the carboxyl (C-6) position.[49] However, intramolecular hydrogen bonding between the hydroxyl and carboxyl groups makes the polymer chain rigid and tends to reduce the reactivity of the two groups, requiring the addition of catalysts and coupling agents to improve the reactivity. The hydroxyl groups can be modified by oxidation, sulfation, reductive amination, while the esterification and amidation reactions preferably take place in the carboxyl group.[50] Attempts in which the hydroxyl group undergoes esterification are also reported in the literature.[49]

Moreover, alginates are extremely sensitive to harsh reaction conditions which involve high temperature, concentrations of acids, bases, and even reducing agents. The polymer chain degrades causing it to lose its stability, its molecular weight and thus its characteristics when treated in such conditions.[30] Moreover, alginates are susceptible to chain degradation even with sterilization techniques like autoclaving, γ radiation, heat and ethylene oxide treatment.[51,52] Therefore, chemical modification of alginates is preferably done in mild environments and in green solvents. Thus, care must be taken while synthesizing alginate derivatives, as there is a possibility of chain degradation, side reactions, and unwanted byproducts.

Once a hydrophobic group is introduced to the alginate backbone, there are now two opposite forces: the electrostatic repulsive force from the carboxylate and the attractive force between the hydrophobic and hydrophilic moieties.[53] When the attractive force dominates, aggregation of the polymeric chain occurs leading to increase in molecular weight and collapse of the chain, while chain extension occurs when the repulsive forces dominate. There is also a prevalence of intermolecular interaction between the alginate chains, which facilitates chain aggregation once a certain concentration is reached. This property of forming high molecular aggregates is exploited in encapsulation of drugs, pesticides for their loading and controlled delivery.[54,55]

Apart from modifying the carboxyl and hydroxyl groups using chemical reactions, alginate hydrogels, films, and aerogels can be imparted with hydrophobicity using techniques like chemical vapor deposition followed by silanization, freeze-drying, cross-linking, alkyl grafting, incorporation of essential oils, etc. This Review encompasses the major chemical modifications and methods that are done to reduce the hydrophilicity of alginate which are applied to the field of biomedical, food packaging, water treatment, emulsion stabilizers. Modification on alginate was already published by a few researchers (Table S1). This Review is specifically focused on hydrophobically modified alginates for some specific applications (Figure 3).

2.1. Esterification. Esterification is one of the common methods and earliest chemical modifications to introduce a hydrophobic alkyl chain to the alginate backbone.[56] Alginate
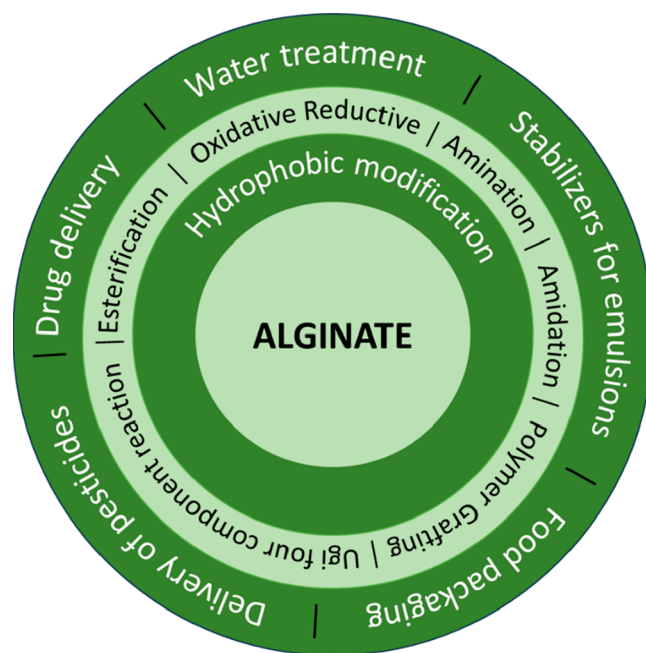

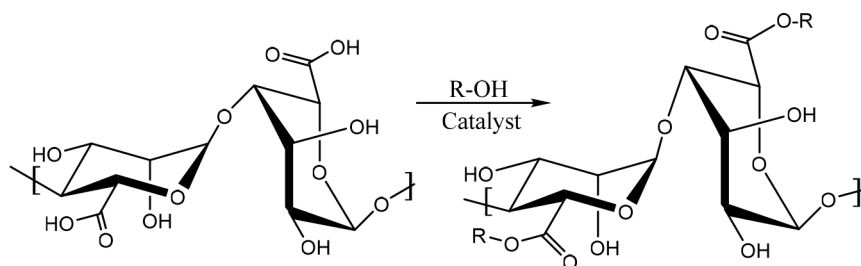**Figure 3.** Hydrophobically associated alginates and their applications.
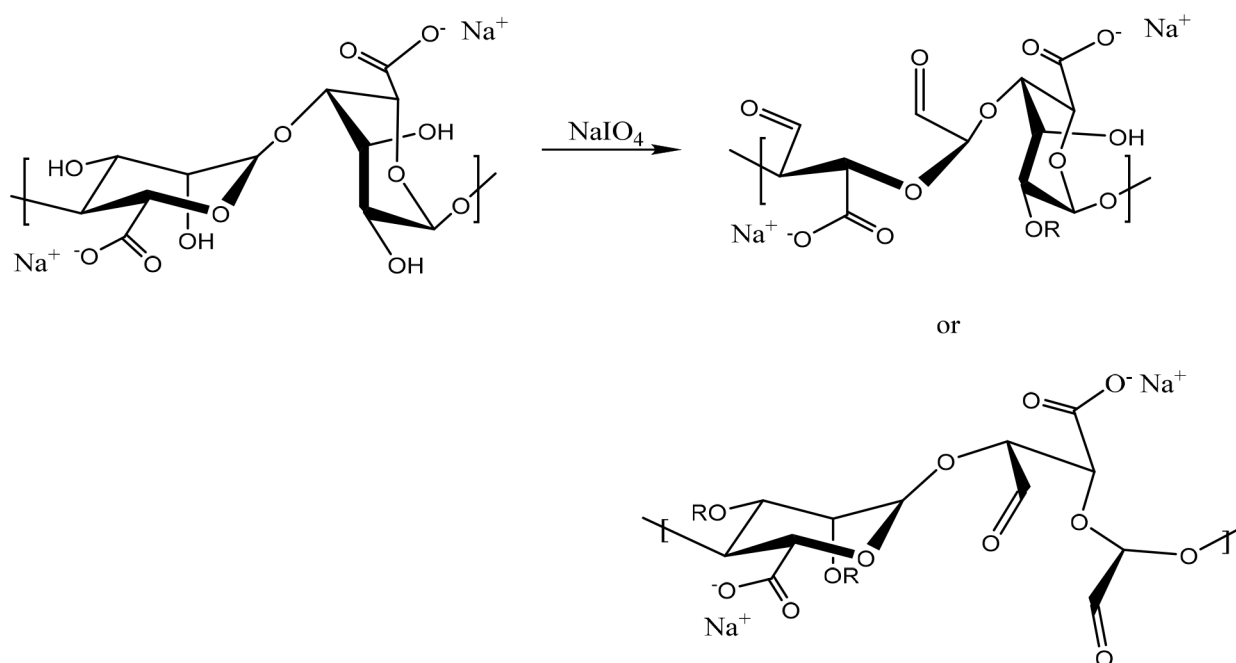
Figure 4. Esterification of alginate.

Figure 5. Oxidation of alginate.

Figure 6. Reductive amination of oxidized alginate.
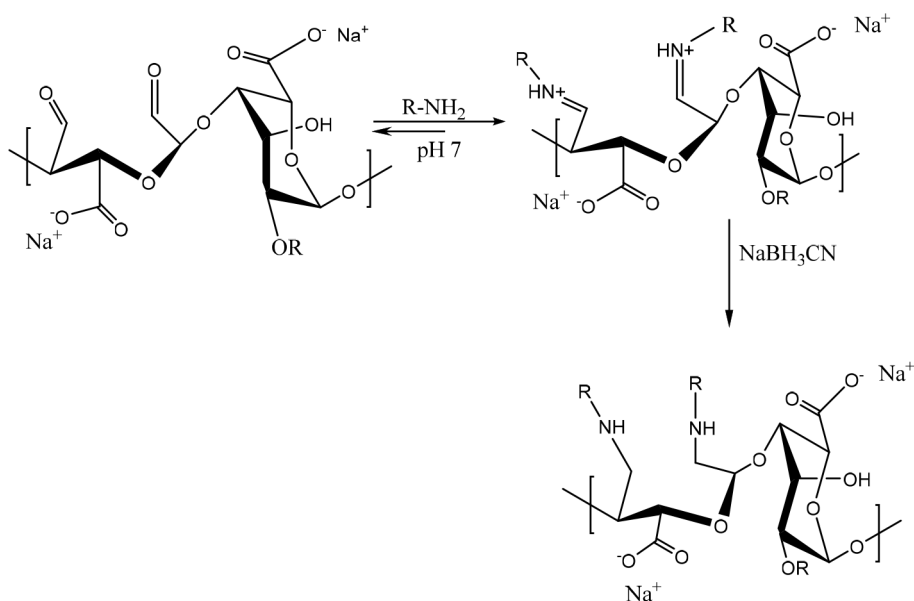
esters can be derived from a simple chemical reaction of the two functional groups hydroxyl and carboxyl groups with acids or alcohols. In most cases, it is the carboxyl group that forms an ester when treated with alcohol. The esterified alginates are found to have better swelling capabilities than the unmodified alginates.[57] Alginate esters can be formed via carbodiimide
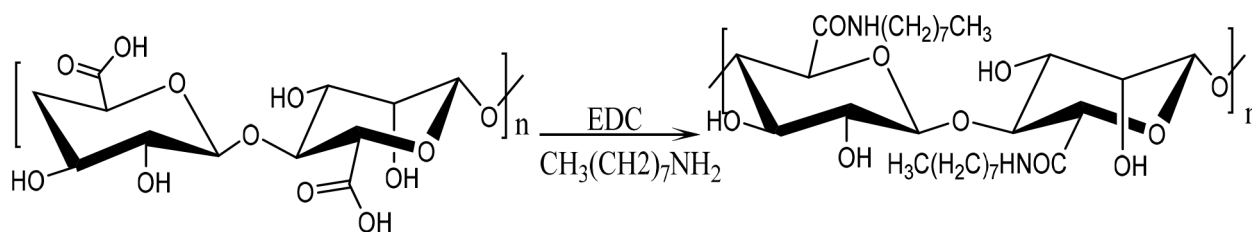
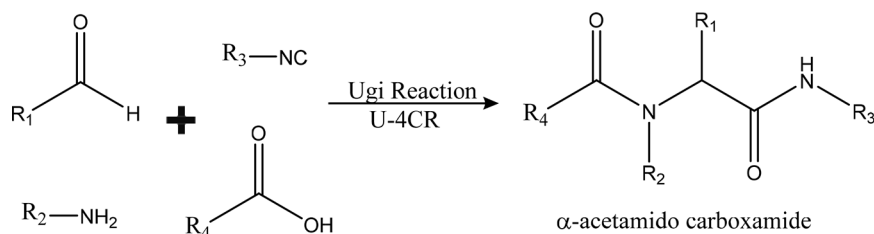**Figure 7.** Amidation of alginate by using EDC-NHS.

Figure 8. General Ugi four-component reaction.

coupling, which is preferred for the incorporation of long chain alkyl groups to the alginate polymeric network, and the reaction can be carried out in aqueous media. The conversion of sodium alginates to tetrabutylammonium (TBA) salt of alginic acid has opened doors for chemical modifications of alginates in organic media. A strategy that could allow alginates to react in organic media with other reactants without loss of stability was devised, which involved the use of two component polar aprotic solvent system and tetrabutylammonium fluoride (TBAF) and chemoselective alginate esters can be formed from this method (Figure 4).[58]

2.2. Oxidation Reductive Amination Reaction. Alginates can be covalently attached to amine groups through the oxidative reductive amination of alginates. For the alginates to undergo amination, they must first be oxidized so that the carbonyl groups can be converted to amines easily. While sodium periodate is predominantly used for oxidizing alginates, other oxidizing agents like potassium permanganate and hydrogen peroxide have also been reported for the oxidation process.[59] During oxidation, ring opening of alginate occurs as the carbon–carbon bond joining the cis diols of alginate gets cleaved and dialdehyde alginate is formed. This ring opening tends to reduce the rigidity of the alginates, which increases the rate of degradability. Oxidized alginates are prone to degradation in aqueous media, compared to alginate salts; thus, the oxidized derivatives are only used when there is a need to improve the degradation rate of alginates. The carbonyl groups in the dialdehyde alginate can be treated with amine, alkoxyamine, and hydrazine to form the corresponding derivatives. In the case of reductive amination, when treated with an amine, the oxidized alginates form a Schiff base, which reduces to a stable secondary amine.[49] Often, the hazardous sodium cyanoborohydride (NaCNBH₃) is preferred for the selective reduction of imine intermediate formed during the reaction (Figures 5 and 6).[14]

2.3. Polymer Grafting/Copolymerization. Polymer grafting or graft copolymerization is a facile method to introduce hydrophobic alkyl chains to the alginate backbone. Poly(methyl methacrylate) (PMMA),[60] poly(acrylonitrile) (PAN),[4] PNIPAM (Poly(N-isopropylacrylamide)[61,62] are commonly used polymers that impart amphiphilic properties to alginate.[63] Redox, electron beam, microwave irradiation and

gamma ray irradiation are used for grafting of alginates while redox remains the most common method.[64] For the free radical graft polymerization, an initiator is added for the polymerization to occur, and the pyran ring of the alginate might open in the course of the reaction. The grafted polymer can form interpenetrating networks if the chain length is longer.

2.4. Amidation. Amidation can also influence the hydrophilicity of alginates and for the synthesis of alginate amides, coupling agents like EDC-NHS are used for reactions in aqueous media and 2-chloro-1-methylpyridinium iodide (CMPI) for reactions in organic solvents.[49] For CMPI coupling, sodium alginate is treated with TBA and dissolved in an organic solvent after which CMPI is added to activate the carboxyl groups of alginates. The amide derivative is obtained when a diamine and triethylamine catalysts are added. The alginate amide derivatives are widely used for conjugation, tailoring of peptides and has gained much attention in tissue engineering applications (Figure 7).[65]

2.5. Ugi Reaction. Ugi reaction belongs to the class of isocyanide based multicomponent reaction which requires a primary amine, aldehyde or ketone, a carboxylic acid, and an isocyanide.[66] A variety of bisamides, pseudopeptides having suitable biological activity can be derived from the four component Ugi reaction as four different functional groups take part in the reaction.[67] Moreover, the atom economy and efficiency of the reaction is high, and it can be carried out in mild organic solvents and water, which makes it attractive to the pharmaceutical industries for exploiting the reaction for large-scale production of biologically active compounds.[68] Using an Ugi reaction, alginates can be converted to amphiphilic bisamides suitable for pharmaceutical applications especially for hydrophobic drug delivery and sustained drug release (Figures 8 and 9).[66]

3. APPLICATIONS

Figure 10 gives an overview of the different application areas of the hydrophobically modified alginate.

3.1. As Stabilizing Agent in Emulsions. The introduction of hydrophobic alkyl chains to the alginate backbone makes the polymer an amphiphilic moiety. As a result, they can be used as emulsifiers in the food and pharmaceutical
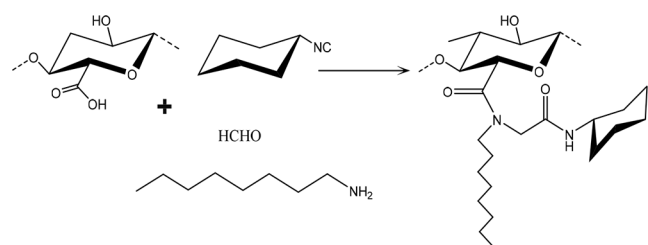
Figure 9. Ugi 4-Component reaction involving alginate, formaldehyde, cyclohexyl isocyanide, and octylamine.
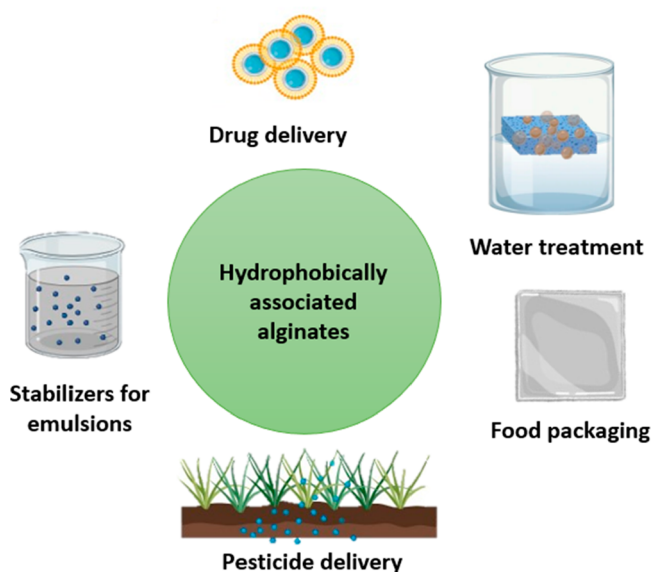

Figure 10. Applications of hydrophobically associated alginates.

industries as alginates (calcium, sodium, potassium, ammonium salts) and the alginic acid ester. Generally, emulsifiers stabilize emulsions by absorbing at the oil−water interface, forming a layer around the oil droplets, which helps to prevent aggregation. The hydrophobically associated alginates form a viscoelastic interfacial film at the oil−water interface, which makes the modified alginates suitable for emulsifiers.[69]

Dodecyl glycidyl ether was introduced to the polymeric chain as a result of nucleophilic substitution between the alginate and the alkyl ether. The hydrophobic interactions between the alkyl groups formed the hydrophobic core of micelles in water. The micelles exhibited a low poly dispersity index of 0.384, high zeta potential of about −80 mV, decreased surface tension and increased the solubility of the hydrophobic Sudan IV dye which was used as a model for lipophilic molecules.[69] A switchable surfactant for liquid paraffin, responsive to CO_2 and N_2, was developed using hydrophobically modified alginate.[70] The modified alginate was prepared through the esterification pathway, and the hexyl diethyl tertiary amine (HDEA) alkyl chain was grafted on the polymeric backbone, with the grafting ratio being 12.8% (HDEA: Alginate). HDEA was formed when the polymer reacted with (6-bromo-hexyl)-diethyl-amine (BHDEA) in the presence of tetrabutyl ammonium bromide (TBAB) as the phase transfer catalyst. In the presence of the modified alginate, the emulsion lost its stability when CO_2 was bubbled at 5 °C for 30 min and completely separated into oil and water. The emulsion was reformed when N_2 passed into the solution at 50 °C for 30 min, indicating its sensitivity to both the gases. A

succinylated alginate emulsifier with succinylation degree of 33.9% provided better creaming ability and prevented lipid oxidation in a 30% fish oil in water emulsion.[71] About 79% reduction in the formation of secondary oxidants was observed with alginate esterified with dodecenyl succinic anhydride (SAC12). The modified alginate exhibited interfacial properties and reduced the surface tension of the interface by adsorbing to the oil/water interface, which formed a protective oil coating around it. In a similar way, dodecanol alginate (DA) (0.8−1.2 wt %) acted as an emulsifier for the oil in water system, with DA reducing the surface tension by adsorbing to the oil−water interface. The dodecanol alginate was formed as a result of ester linkage when the protonated sodium alginate and dodecanol reacted in the presence of carbodiimide hydrochloride (EDC-HCl) as the coupling reagent and 4-(N,N-dimethylamino) pyridine for 45 °C for 30 h.[72]

3.2. Drug Delivery. Being biocompatible, biodegradable, nontoxic, and mucoadhesive, the polymer shines as an ideal candidate for drug delivery systems wherein the hydrophobic modification plays a crucial role in the delivery of hydrophobic drugs.[18] But before administering them for drug delivery, their poor stability, hydrophilic nature and fast drug release need to be addressed.[73] Although calcium alginate exists as stable gels in water, it can undergo chelation when placed in a release medium containing metal ions and biological buffers.[74] An important factor which promotes the transfer of ions is the porous nature of hydrogel which also limits the efficient release of drug molecules.[75] Thus, to overcome these drawbacks, alginates are modified with hydrophobic alkyl groups, or coated with other stable polymers.[76] Hydrophobic modification helps in the efficient encapsulation and controlled release of drugs. The amphiphilic alginate derivatives modified by introducing hydrophobic groups onto its hydrophilic backbone could enhance its affinity for the hydrophobic drug. The modified alginate based micelles, microspheres, capsules loaded with drugs provide a promising mode of drug delivery for variety of anticancer, antiviral and antibacterial drugs.[77]

Hydrophobically modified alginate micelles loaded with Doxorubicin (DOX) possessing pH and enzyme responsive properties were developed for the efficient delivery of the anticancer drug.[78] Highly ordered spherical micelles were found to form above the critical micellar concentration after the modification with dodecyl glycidyl ether. The anticancer drug was loaded by the further self-assembly of the modified alginate. This facilitated the carrier of Doxorubicin, with a drug release of 80% and aided in enzyme and pH triggered release of the drug. The DOX loaded hydrophobically modified alginate micelles exhibited high toxicity toward HepG2 cells, which can be promoted by the overexpression of AFU in the HepG2 cells. The HMA-DOX micelles also inhibited the growth of the Hela cells. Controlled release of bovine serum albumin was achieved by grafting of polybutyl methacrylate facilitated by EDC-NHS coupling and the methacrylate was polymerized prior to the coupling by free radical polymerization in the presence of 2-amino-ethanethiol as a chain transfer agent. The modified alginate was mixed with the protein, and the solution was added dropwise to calcium chloride solution to form the microspheres. The bovine serum albumin loaded microspheres exhibited a prolonged release of the protein. In the in vitro drug release studies, it was found that for 20 days, only 58% of the protein was released from the modified microspheres where the unmodified alginate carrier all the protein was lost in the same time period.[79] In another

Table 2. Hydrophobically Modified Alginates for Drug Delivery

| S. No	Components	Type	Drug, Pharmaceutical agent	Type of drug	Performance	ref
1	Dodecyl glycidyl ether	Micelle	Doxorubicin	Anticancer	80% DOX was released; drug loading efficiency: 65.4%; DOX-HMA effectively taken up by Hela and HepG2 cells	78
2	Butyl methacrylate - coupling reaction of poly(butyl methacrylate) with alginate in the presence of EDC and NHS	Microsphere	Bovine serum albumin	Protein	58% of bovine serum albumin released after 20 days	79
3	Sodium palmitate, N-isopropylacrylamide, polyelectrolyte layer of chitosan and alginate, calcium ions	Membrane	Indomethacin	Nonsteroidal anti-inflammatory drug (NSAID)	60% within 12 h	61
4	Oleic acid attached Magnetic iron MNP@OA nanoparticle coated on Hydrazine oleate grafted alginate dialdehyde (AlgOA)	Core shell magnetic nanoparticle–pH sensitive alginate outer shell, hydrophobic magnetic inner core	Paclitaxel, Doxorubicin	Anticancer	Drug release in acidic medium; Paclitaxel release - after 72 h in acidic medium. Toxic for MCF-7 and HeLa cells	82
5	Alkyl chains (C12)linked to the alginate backbone via esterification	Microparticles	Bovine serum Albumin, human hemoglobin (Hb), or of a vaccine protein (*Helicobacter pylori* (H. pylori) urease)	Protein	Encapsulation yield: 70–100%;	83
6	Oleoyl alginate ester	Nanoparticle	Vitamin D$_3$	Vitamin	Increased absorption of VD$_3$	84
7	PBMA-NH$_2$ grafted thiolated sodium alginate	Plasmonic magnetic nanocomposites	Paclitaxel (PTX)	Anticancer	10% more efficacy against PLC/PRF/5 cells than unmodified carrier	85
8	Octyl alginate ester, hexyl alginate ester, lauryl alginate ester derivative	Microcapsules	Ibuprofen	Nonsteroidal anti-inflammatory drug (NSAID)	Controlled the release rate of ibuprofen; low cytotoxicity to the murine macrophage RAW264.7 cells	57
9	C8 alkyl chains	Microparticle	Sulindac	Nonsteroidal anti-inflammatory drug (NSAID)	pH-sensitive release; zero-order release of drug	86
10	Octylamine	Micelles	Kaempferol	Flavonoid antioxidant	encapsulation efficiency: 70.4%, sustained release of kaempferol up to 80 h	87
11	Poly(N-isopropylacrylamide)	Micelles	Doxorubicin	Anticancer	Encapsulation efficiency: 60%	88
12	Sodium alginate, cyclohexyl isocyanide, octylamine and propionaldehyde	Micelles	Ibuprofen	Nonsteroidal anti-inflammatory drug (NSAID)	Controlled release of Ibuprofen	89
13	Octylamine, oxidized sodium alginate, acetic acid and tosylmethyl isocyanide (TOSMIC)	Micelles	Ibuprofen	Nonsteroidal anti-inflammatory drug (NSAID)	pH responsive release of Ibuprofen	81
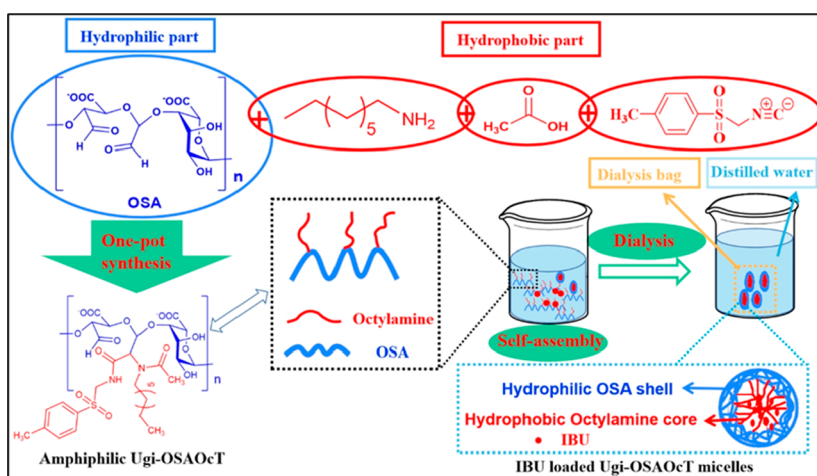
Figure 11. One-pot synthesis of amphiphilic alginate derivative via Ugi reaction with octylamine as the primary amine. The Ugi-Alginate derivative is used for the encapsulation of ibuprofen, reproduced with permission from 81 under Creative Common Attribution (CC BY) license).

study, pH and thermoresponsive release of indomethacin was carried out by sodium palmitate incorporated biomineralized alginate. Initially, a membrane made of *N*-isopropylacrylamide, known for its thermoresponsive nature along with alginate and Indomethacin, was developed. It was then subjected to biomineralization, formation of a polyelectrolyte layer, and cross-linking with calcium ions. The biomineralization, incorporation of sodium palmitate and the polyelectrolyte layer of chitosan and alginate all together reduced the hydrophilicity of the membrane, which leads to sustained release of the encapsulated drug.[61] Ibuprofen loaded alginate microcapsules having an average hydrodynamic diameter of 277 nm were constructed using octylamine grafted alginate. The octylamine grafting on alginate was achieved by oxidative reductive amination with a degree of substitution of 28%. The encapsulation efficiency of the modified alginates was 87.6%, and in vitro drug release studies showed sustained release of the hydrophobic drug.[80] In a different study, the Ugi reaction was employed to modify alginate for the pH responsive release of Ibuprofen, suitable for oral drug delivery. The Ugi alginate derivative was synthesized using octylamine, oxidized sodium alginate, acetic acid, and tosylmethyl isocyanide (TOSMIC) and the formed amphiphilic derivative (Ugi-OSAOcT) self-assembled into stable micelles (CMC range of 0.30−0.085 mg/mL), within which the ibuprofen drug molecules were incorporated by dialysis. The drug loading capacity and encapsulation efficiency of the Ibuprofen loaded Ugi-OSAOcT micelles (IBU/Ugi-OSAOcT = 3:10) were as high as $10.9 \pm 0.4 - 14.6 \pm 0.3$% and $40.8 \pm 1.6 - 57.2 \pm 1.3$% (Table 2, Figures 11 and 12).[81]

3.3. Water Treatment. In the past several decades, many oil/water separation techniques involving physical adsorbents, filtration membranes have been explored for removal of oil spills from ocean and oil-based effluents from industries. Three-dimensional porous hydrophobic aerogels, present as convenient sorbents for oil removal, and retention of contaminated water than powder-based adsorbents.[90] The porous architecture, large available surface area, and low density make them superior oil-absorptive materials. Further, alginate-based adsorbents are exploited for the removal of toxic metal ions from water.[91] Typically, for the hydrophobic transition of aerogels, silanization,[92,93] pyrolysis[94−96] plasma treatment[97−99] are the commonly sought out routes. Alginate

based aerogels offer a facile and inexpensive way of fabrication due to their ease of hydrogel formation with ionic cross-linkers. Alginate hydrogels are easily converted to aerogels by freeze-drying which is then hydrophobically modified.[9]

A dual ionic cross-linking approach was utilized to produce highly porous alginate foams that exhibited high adsorptive capabilities (11.2−25.9 g/g) for oils and a wide range of organic solvents. The foams prepared by freeze-drying were subjected to calcium chloride crosslinking and then treated with zirconium oxy chloride. For each cross-linking, the foams were impregnated with the respective solutions, calcium chloride and zirconium oxychloride for about 4 h and were thoroughly washed with distilled water once the process is over. The introduction of zirconium ions reduced the surface energy, thereby increasing the water contact angle up to 140°. The foams showed reusability up to six cycles, and after each adsorption cycle is completed, they were squeezed and washed with ethanol.[100] Cellulose nanofibers reinforced sodium alginate foams possessing parallel lamellar microstructures was prepared by bidirectional freezing, which exhibited high elasticity and mechanical strength. Once formed, the foams were subjected to ionic cross-linking by divalent calcium ions followed by treatment with MTCS (methyl trichlorosilane) by thermal chemical vapor deposition. After the silane treatment, the water contact angle reached 148.7 °C and the oil contact angle was nearly 0 °C. To make this method economically viable for the removal of oil spills, a vacuum assisted removal strategy was devised in which the aerogel was connected to a thin tube connected to a vacuum pump, which when turned on, collected the oil from the pores of the aerogel. During this process, there was absence of water in the tube, which ensured the high hydrophobic nature of the aerogel.[101] A composite aerogel containing zinc nanoparticles, graphene oxide, and alginate exhibited antibacterial activity against *Staphylococcus aureus* and absorbed high amounts of oil in the presence of sunlight. The photothermal conversion efficiency of the graphene oxide in the aerogel was responsible for the high intake of oil in the presence of sunlight.[102] A composite foam of an alginate-hydroxyl aluminum stearate oil gelator with tunable porosity showed a promising potential for the removal of oil from water. The oil gelator imparts hydrophobicity to the foam, gels oils and improves oil retention, while the polymer network helps in faster absorption of oils.[103] Calcium alginate
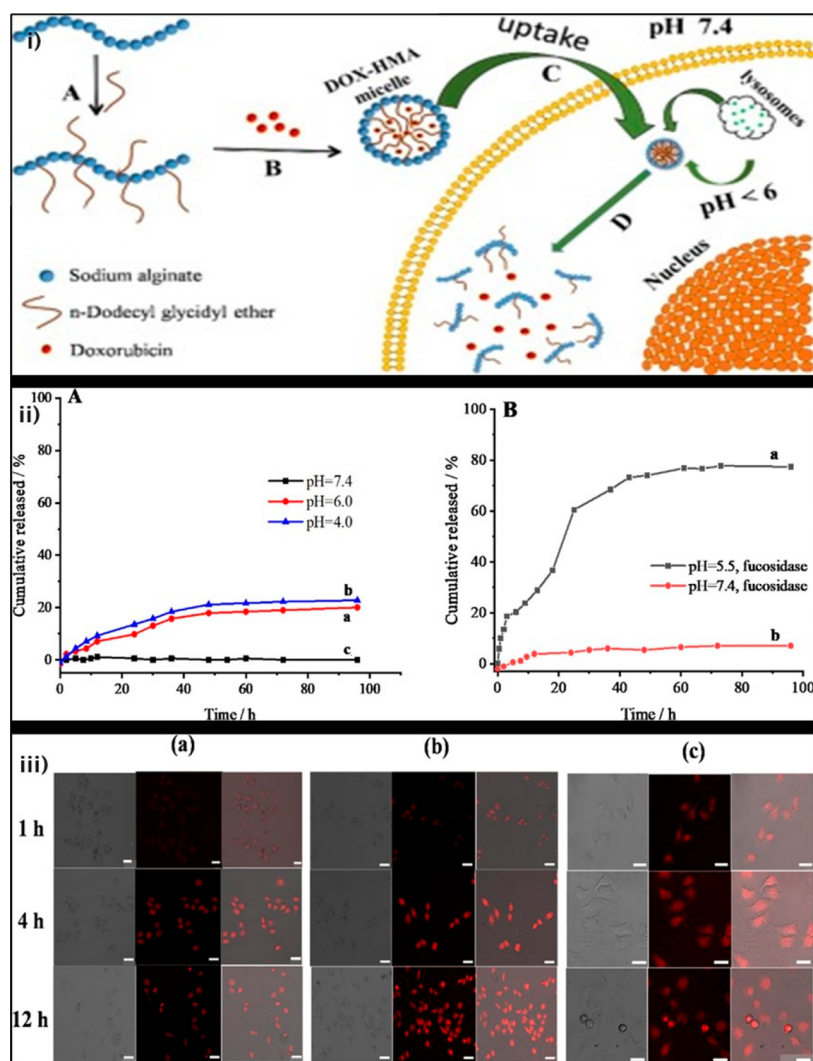
Figure 12. (i) Schematic representing Doxorubicin loaded hydrophobically modified micelles: (A) dodecyl glycidyl ether modified alginate, (B) Doxorubicin encapsulated into HMA micelles, (C) Doxorubicin-loaded hydrophobically modified alginate micelles accumulated into tumor cells, and (D) intracellular stimuli-responsive degradation and release of Doxorubicin. (ii) In vitro release of Doxorubicin loaded hydrophobically modified micelles in A) PBS solution B) in the presence of AFU (iii) Confocal laser scanning microscopy images of Hela cells (a and b) and HepG2 cells (c) incubated with free Doxorubicin (a) or Doxorubicin loaded hydrophobically modified micelles (b and c) at 37 °C for 1 h, 4 and 12 h In vitro cytotoxicity of HMA against Hela cells and HepG2 cells (a) Cytotoxicity of free Doxorubicin (b) Doxorubicin loaded hydrophobically modified micelles (c) toward Hela cells or HepG2 cells incubated for 24 or 48 h. Scale: 30 μm, reproduced with permission from ref 78. Copyright 2020 Elsevier.

hydrogel esterified with maleic anhydride exhibited an amphiphilic nature, which facilitated the adsorption of oils. The esterified calcium alginate beads were found to be an effective biosorbent, the adsorbent capacity of which increased with the ionic strength of the solution containing oil showing high adsorbent capacities at pH 5 and 9.[104] Low density aerogels were developed using reinforced alginates which were subjected to gelation by the $CaCO_3$-GDL cross-linking system. The compressive strength of alginate foams was improved by the addition of reinforcing agents: N,N-methylenebis-(acrylamide) or carboxy-methylcellulose which formed hydrogen bonds with alginate. After the aerogel formation they were subjected to carbon tetra chloride plasma treatment for hydrophobic modification after which the aerogels acted as oil- absorptive materials (Table 3, Figures 13 and 14).[105]

3.4. Delivery of Pesticides. Pesticides are an integral part of agricultural production systems to preserve the crop yield. Usually, pesticides are sprayed over the plants, which does not ensure efficient delivery of the biocide and causes direct exposure to pesticides which may lead to potential health hazards. Therefore, delivery of pesticides in the form of polymer encapsulated micro/nanoparticles, controlling its release, has opened new frontiers in pesticides delivery. Hydrophobic alkyl chain grafted alginate microparticles encapsulated with pesticides provide a suitable choice for efficient delivery of pesticides and reduce the toxicity due to direct exposure.

Most of the pesticides are organic molecules that are hydrophobic. Alginate hydrogels provide an effective method for the delivery of pesticides to the soil. In a study, a series of cholesteryl esters of sodium alginate were synthesized differing in the molecular weight of alginate for the encapsulation and release of the pesticide acetamiprid. The hydrophobic interactions between the cholesteric groups facilitate the self-assembly of the polymeric chain. Encapsulation efficiency was increased by the action of ionic cross-linking by divalent

Table 3. Hydrophobically Modified Alginates for the Removal of Oil and Organic Impurities

| S. No	Adsorbent/Absorbent	Strategies	Performance	Adsorbate	Adsorption/Absorbent capacity/Removal efficiency	ref
1	Sodium alginate- Calcium – Zirconium foam (SA–Ca-Zr)	Freeze-drying, dip coating, ion induced cross-linking by Zr ions	Hydrophobic, porous, oleophilic, Recyclability	Oil and organic solvents	11.2–25.9 g/g	100
2	Sodium alginate/Cellulose nanofibers aerogel	Freeze casting (bidirectional)/calcium ion cross-linking/silane modification	Superelastic; recyclable compressibility; hydrophobic and super oleophilic	Oil and organic solvents	17 to 34 times its mass (mass-based oil absorption capacity)	101
3	Alginate, zinc nanoparticles, graphene oxide and Aerogel	Freeze-drying/silane modification	Antibacterial activity against *Staphylococcus aureus*, high porosity (95.2%),	Crude oil	Common oil: 11–34 g g^{-1}; Highly viscous oil: 12 g g^{-1}	102
4	Alginate-hydroxyl aluminum stearate oil gelator foam	Freeze-drying/silanization using Heptadecafluorodecyltrimethoxysilane/oil gelator	Tunable porosity, high oil absorption and oil retention	Oil and organic solvents	32–63 g/g	103
5	Calcium alginate bead esterified with maleic anhydride	Esterification with maleic anhydride	High adsorption at low temperature; high ionic strength	oil	143.0 mg/g (BET model)	104
6	Alginate/N,N-methylene bis(acrylamide) aerogel and Alginate/carboxy-methyl cellulose aerogel	Plasma surface modification by CCl$_4$	Low density; High compressive strength	Peanut oil, Methyl silicone oil, Vacuum pump oil, liquid paraffin	Peanut oil-13–14 g/g, Methyl silicone oil-10–11 g/g, Vacuum pump oil-12 g/g, liquid paraffin- 10–13 g/g	105
7	Alginate/Kapok fibers aerogel	Directional freeze-drying/silanization using CVD	High oil capturing efficiency; super hydrophobicity; neurovascular network-like aerogel	oil	99.39–99.68% removal efficiency of oil from oil-in water emulsion	106
8	Sodium alginate-Polyacrylamide copolymers -SAG-g-PAM, SAG-g-PDMA, SAG-g-poly(AM-co-DMA), SAG-g-poly(NMA-co-DMA) and SAG-g-poly(AM-co- NMA)	Graft copolymerization with Polyacrylamide (PAM)	All the five grafted polymers were capable of removing Pb^{2+} ions	Pb^{2+}	Maximum adsorption occurs at 0.048 g	91
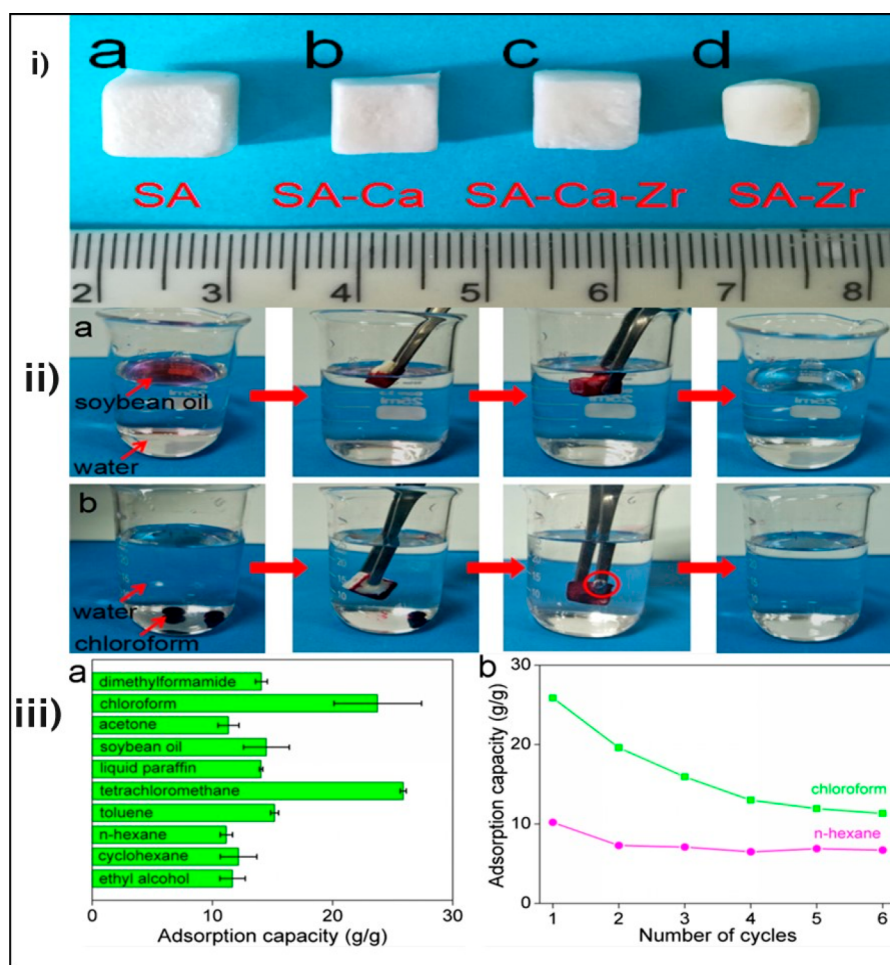
Figure 13. i) Aerogel of a) sodium alginate (SA) b), calcium alginate (SA- Ca) c), Calcium alginate - Zr ions cross-linked (SA−Ca-Zr) d) Zr ions-cross-linked alginate aerogel (SA-CA-Zr) (ii) Adsorption of a) soybean oil b) Chloroform by SA-CA-Zr aerogel (iii) Adsorption Characteristics of SA-CA-Zr aerogels a) and b), reproduced with permission from ref 100. Copyright 2019 Elsevier.

calcium ions. Increase in the molecular weight of the alginate chains increased the loading of acetamiprid, and a shift from non-Fickian to Fickian drug release mechanism was followed as the molecular weight decreased.[107] In an attempt to facilitate sustained release of pesticides into soil, nanocomposites containing hydrophobically modified alginate was developed. A four-component Ugi reaction comprising octylamine, formaldehyde, cyclohexyl isocyanide, and sodium alginate was used for the development of hydrophobic alginate derivative (Ugi-SA). The Ugi-SA was first cross-linked by free-radical cross-link polymerization using acrylamide (AM) followed by ionic cross-linking with calcium sulfate. For the free radical cross-linking, the Ugi-SA was treated with ammonium persulfate (APS), which acts as an initiator for cross-linking, *N*,*N*-methylene-bis(acrylamide) (MBAA) and TEMED for accelerated cross-linking of polyacrylamide (PAM). Nanocomposite hydrogel developed using the Ugi-SA incorporated with Polyacrylamide (PAM), and montmorillonite (MMT) was studied for the sustained release of the hydrophobic pesticide *λ*-cyhalothrin. The hydrogel with 5% MMT exhibited the lowest cumulative release percentage about 6.68% up to 87 h.[108] In another study, alginate was hydrophobically modified using EDC-HCl which introduced amide connections between octylamine molecules and the carboxylate group of alginates. The amide derivative of alginate

efficiently encapsulated *λ*-cyhalothrin, and the alginate microspheres were formed by an emulsification-gelation method. Further by changing the degree of substitution of the amide derivative, the pesticide release from the microspheres could be controlled (Figure 15).[109]

3.5. Food Packaging. Alginate is known for its excellent film forming abilities, yet the unmodified alginate films are moisture sensitive, which limits its application to packaging of food products. The hydrophilic nature of the films can be reduced by the incorporation of hydrophobic plasticizers, cross-linkers, essential oils, copolymers, plant extracts, and coating of a hydrophobic layer over the alginate films. Alginate films are cross-linked externally by calcium chloride which decreases its water solubility and water vapor permeability. The moisture sensitivity of alginates is a major drawback when it comes to intelligent food packaging, especially those that involve colorimetric change in response to a stimulus.

In a study, cellulose nanocrystals were used to reduce the moisture sensitivity of the alginate films. A reduction in the surface hydrophilicity and water vapor permeability was observed for the alginate films containing 5% w/w of cellulose nanofibers. The crystallinity of nanocellulose and hydrogen bonding between the alginate and nanocellulose was attributed to the increase in water contact angle (80 °C) of the nanocomposite films.[110] To improve surface hydrophobicity of
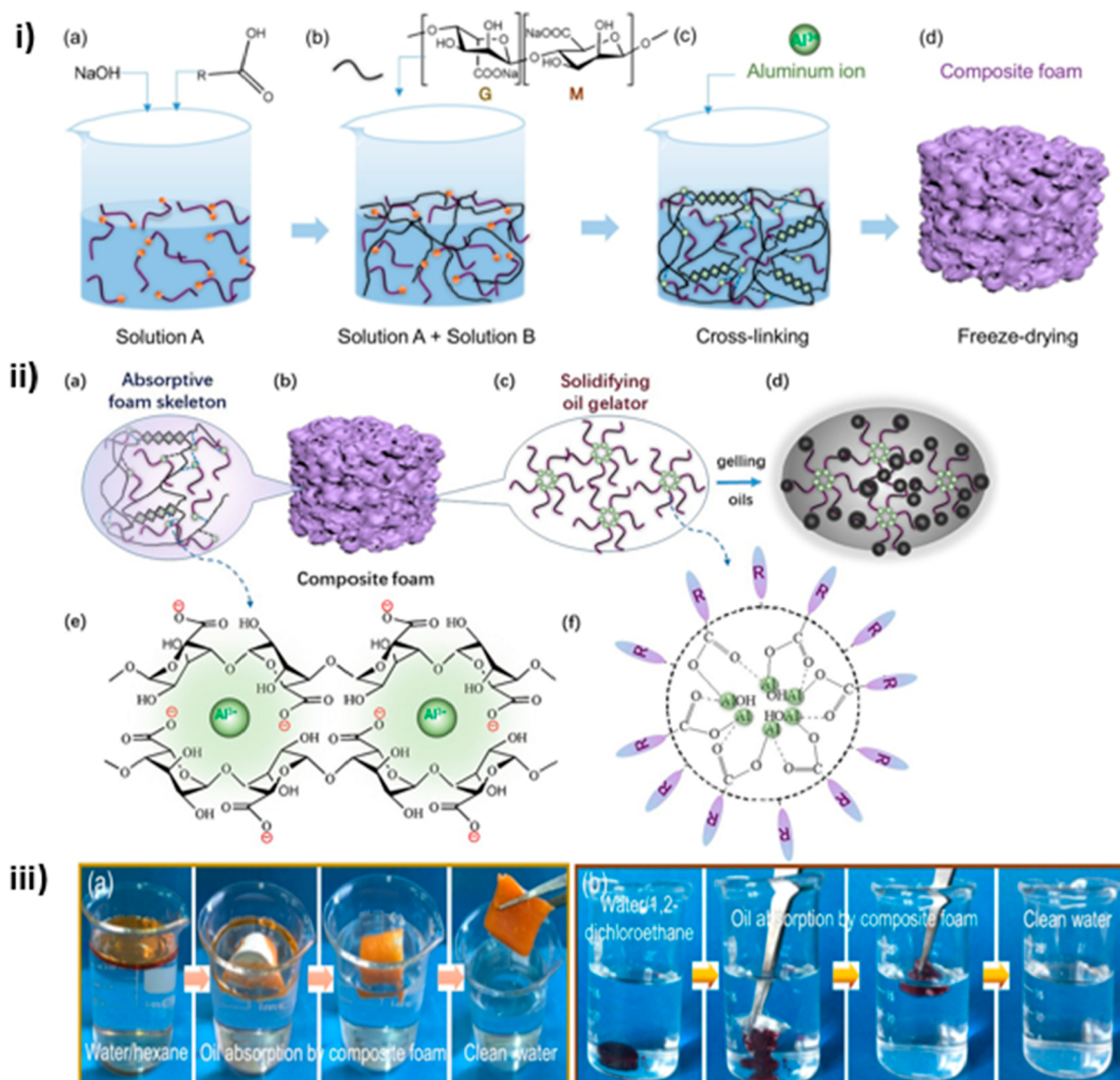
Figure 14. Alginate-oil gelator composite foam for effective oil spill treatment. (ii) Proposed mechanism of composite foam oil absorbent. (i) Schematic illustration of the fabrication process of composite foam oil absorbent. (b). Cross-linking structure includes absorptive foam skeleton (a, e) and solidifying oil gelator (c, d, f). (iii) Selective absorption of oils from water surface (a) and underwater (b). Oil absorption capacity for different oils and organic solvents, reprinted with permission from ref 103. Copyright 2022 Elsevier.

alginates and expand its applications to intelligent packaging, a beeswax coating was applied on the surface of alginate films incorporated with pH sensitive anthocyanins and cellulose nanocrystals. The films had a water contact angle of 111.5° at 5% concentration of the beeswax and was stable at 100% relative humidity for about 10 days.[111] The effect of six different plasticizers and chestnut extract on the physiochemical nature of alginate was evaluated by Janik and co-workers.[112] Glycerol, epoxidized soybean oil and palm oil, (i) esters of propylene glycol with acetic acid, (ii) esters of propylene glycol with oleic acid and succinic acid, and (iii) epoxidized esters based on propylene glycol, oleic acid, and succinic acid were used, and the films were prepared by dissolving alginate in chestnut extract, followed by the plasticizers, cross-linking with calcium ions, and casting. The films containing epoxidized ester as plasticizer only showed a significant reduction in hydrophilicity compared to the other plasticizers. While plant extracts have phenolic compounds which can impart antioxidant ability to the alginate films and form hydrophobic interactions which alginate, they tend to fall

short in reducing the hydrophilicity of alginate. In a study, the effects of various ionic cross-linking agents ($CaCl_2$, $FeCl_2$, $FeCl_3$, and $FeSO_4$) on the characteristics of alginate hydrogel films were investigated and the water vapor permeability was lowest in the $FeSO_4$-cross-linked film. It was concluded that $FeSO_4$ had the highest potential to replace $CaCl_2$ in the production of food packaging materials (Figure 16).[113]

4. CHALLENGES AND COMMERCIAL ASPECTS

Although alginate has several advantages, the cost of the biopolymer is relatively higher than that of conventional synthetic polymers. Still, due to its biocompatible and inert nature, it holds a place among food industry and drug delivery. However, even in these sectors, the commercial availability of modified alginates is very low. The esterified alginate derivate propylene glycol alginate (PGA) is approved by the FDA as GRAS (Generally Regarded As Safe) for food grade alginate under Title 21 of the Code for Federal Regulations (CFR) and approves its use for emulsifiers, stabilizers, thickeners, and gelling agents. For water treatment, the modification of
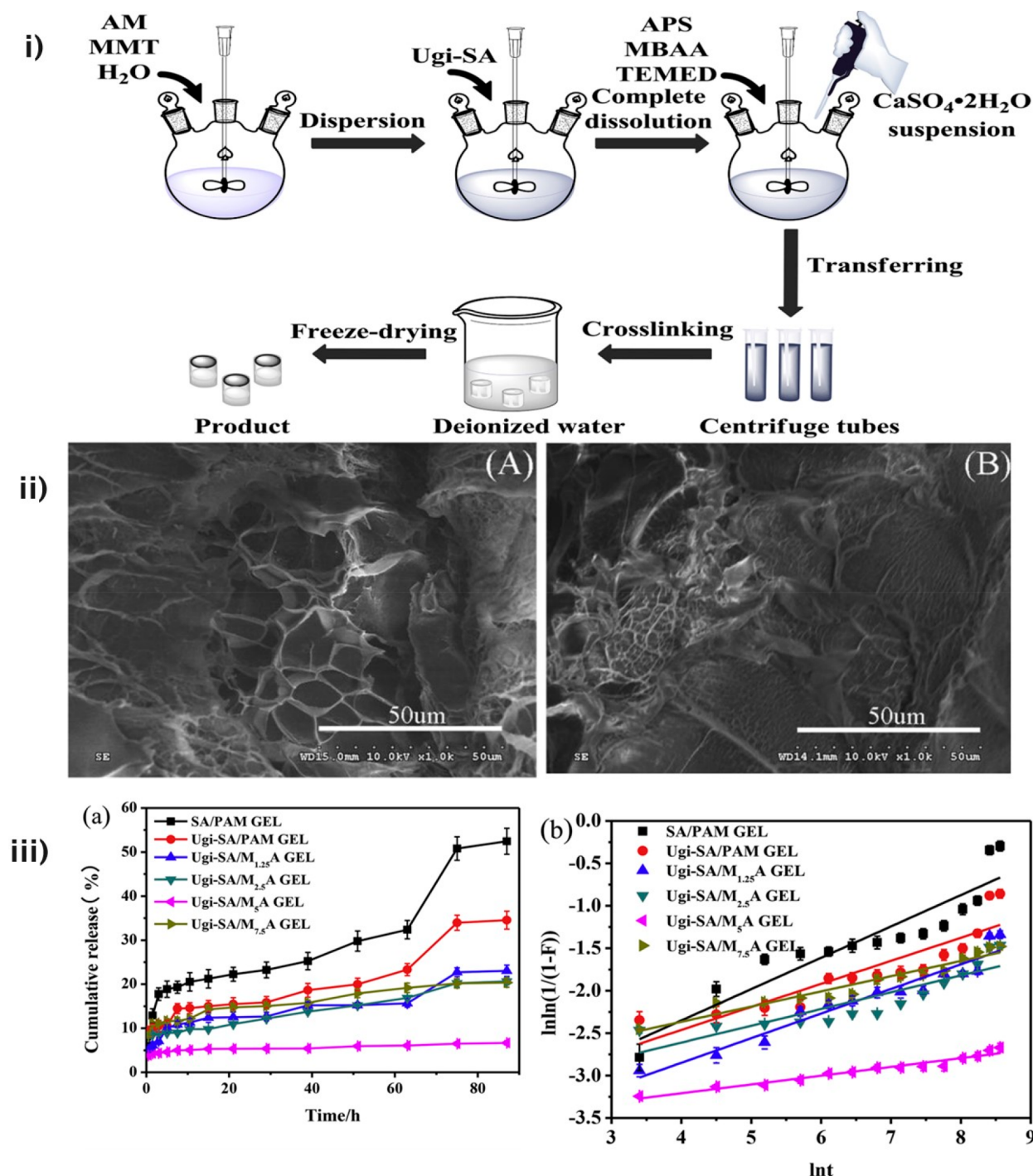
Figure 15. i) Schematic representing the nanocomposite hydrogel containing modified sodium (ii) SEM images of the nanocomposite hydrogel (iii) a) and b) Cumulative release pattern of the pesticide λ-cyhalothrin, reproduced with permission from ref 108. Copyright 2019 Elsevier.

alginate aerogels involves the use of hazardous chemicals that can leach out as secondary pollutants. Therefore, to ensure the practical applicability of the modified alginate aerogels, the modifying and cross-linking agents used should not leach any toxic components as it can pose a threat to aquatic life. Compared to chemically modified hydrophobic aerogels, magnetically modified aerogels are preferred due to their low toxicity and ease of recovery of the pollutants. The cost of alginate remains higher than the synthetic polymers, and further modification will increase the overall cost of the food packaging material.

5. CONCLUSION

This Review provides a brief perspective on hydrophobic modified alginates and its usage in different areas like drug delivery, water treatment, food packaging, and agriculture. Minimizing the side reactions that can occur during modifications and choosing the appropriate reaction environment are important aspects to consider while performing any kind of modification to the alginate due to their sensitivity to heat and harsh chemicals. When it comes to the food packaging sector, many companies have come forward to expand the use of this biodegradable polymer, as stringent
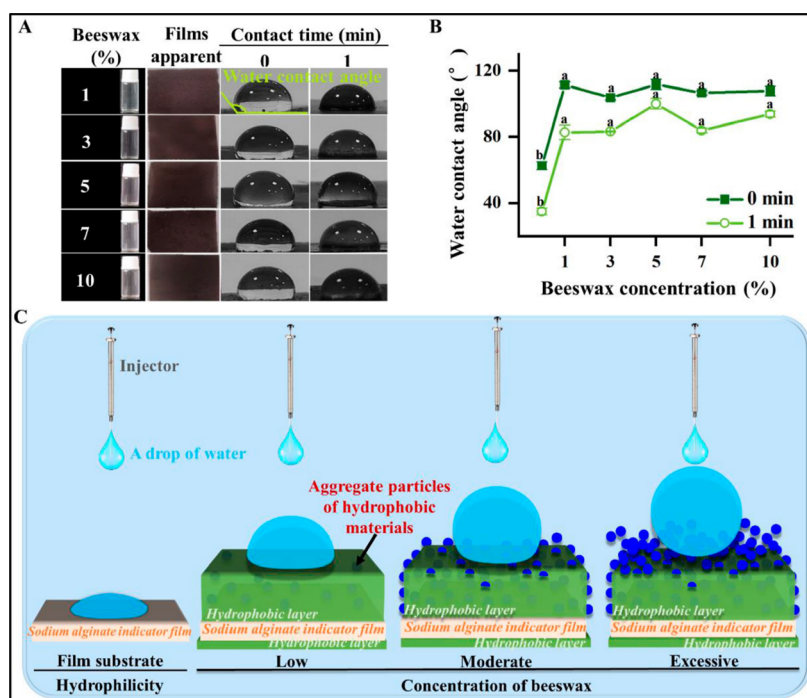
Figure 16. Improved hydrophobicity of the beeswax coated alginate-cellulose nanocrystal and anthocyanin incorporated film A) Contact angle with increase in amount of beeswax concentration and after 5% it starts to decrease. B) Maximum contact angle of 111.5° was observed for 5% beeswax coating. C) Effect of beeswax concentration on water barrier properties of the film, reproduced with permission from ref 111. Copyright 2023 Elsevier.

rules have started to be imposed upon the production and consumption of petroleum-based polymers. Modified alginates can serve as a matrix for the incorporation of functional material in intelligent packaging. In the case of drug delivery, the hydrophobically modified alginates not only provide a plant-based alternative to gelatin but also act as good drug carriers when it comes to controlled drug release for the delivery of hydrophobic drugs. Further, the modified alginates capable of added capabilities along with drug delivery, MRI imaging and stimuli responsiveness will play a major role in development and delivery of hydrophobic drugs. Alternate sterilization techniques for alginates like low energy electron beam sterilization and combined supercritical carbon dioxide treatment are being developed to overcome the sensitivity of alginates to conventional methods, which would increase the use of the biopolymer for biomedical applications. Successful attempts have been made in the development of super-hydrophobic and flame-retardant fabrics which can provide a sustainable alternative to protective equipment made from synthetic polymers.[114]

ASSOCIATED CONTENT

Supporting Information

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Notes

The authors declare no competing financial interest.

ABBREVIATION:

CVD - Chemical Vapor Deposition
DOX - Doxorubicin
HMA - Hydrophobic modified alginate
MMT - Montmorillonite
TEMED - Tetramethylethylenediamine
AFU - α-L-fucosidase

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