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REVIEW ARTICLE

Starch Functionalization and Coupling Reaction

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Abstract

Starch is a quite important edible carbohydrate resource for humans and critical raw material for food and light industry. It has been reviewed as one of the most promising candidates for future materials. But, some defects of starch restricting its use field was required to be overcome.

The grafting technology of starch is a way of chemical modification, which can confer multiple functions to the starch, such as emulsification, anti-bacterial, thickness, and absorption. Modification of starch by the coupling reaction can significantly expand the useful field of starch, including food processing, pharmacy, delivery of the nutrients and protection of environment. In the review article, the four main coupling agents used in grafting starch were discussed, and they were Polyethyleneimine (PEI), Isophorone diisocyanate (IPDI), N-N'- carbonyl diimidazole (CDI), and Epoxy choropropane (ECH). This review summarized the characteristics of these coupling agents, described the mechanisms of coupling reaction, and compared their application scene and reaction conditions.

PEI was suitable for coupling agent due to its active amine group, while IPDI was commonly used because of its two isocyanate groups. CDI was often used as an activator. Simultaneously, but it was also used as the coupling agent. ECH could also be used as a coupling agent in a certain place. Compared with PEI or ECH, the reaction conditions were harsher and more complex when IPDI and CDI were coupling agents, which were more difficult to be controlled. The costs of products were higher as well.

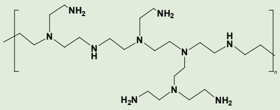
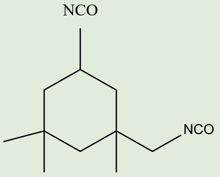
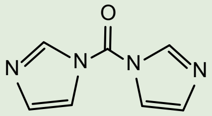
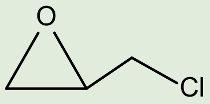
Keywords: Starch Functionalization; Modification; Coupling Reaction; Grafting

Introduction

Starch has been considered as one of the most promising candidates for future materials thanks to its biodegradability, low price, abundance, and thermoplastic behavior. It is a quite important edible carbohydrate resource for humans, and in the meantime. It is also very important raw material for food and light industry. However, native starch suffers from poor water-solubility and low adsorption efficiency, and the starch gel is low viscosity, elasticity, transparency, low water holding potential, and easily retrograded. So these drawbacks limit the industrial applications of starch.

To overcome these drawbacks, some modifications are necessary to improve properties of starch, which can extend the scope of application. In most of modification methods of starch, such as physical squeeze, enzyme hydrolysis, chemical modification, the grafting is a core technology belonged to chemical modification. By grafting functional compound on the starch, the properties of starch will be changed, and grafted starch will be used in more fields. In the grafting reaction, two methods would be expected to be adopted. The first one was that the starch was modified firstly, and then, the functional compound was polymerized. The second was coupling reaction, and the coupling agent connected functional compounds and starch. The former has been widely discussed for many years, and a lot of the results were obtained, but the latter was rarely studied. By grafting reaction, these were given a variety of functions, including emulsification, thickening, antimicrobial activity, and absorption.

The coupling agent was a type of compound with two functional groups of different properties, which could perform connection function. The most characteristic molecular structure was that it contained two activity groups with distinctive chemical properties. The one was a group of inorganic compounds which were easy to start chemical reaction on the inorganic surface, and the other was a group which was close to an organic compound. It could undergo chemical reaction with synthetic resins or other polymers, or generate hydrogen bond to dissolve in them. Coupling agent was mainly used in the field of polymer materials such as synthetic rubber to regulate the interface action between inorganic substances and organic substances [1]. Thus, it significantly improved the performance of composites. However, in the field of polysaccharide applications, such coupling agents were rarely used. In this review, we summarized four kinds of compounds which could act as a coupling agent and be more used in the modified field of polysaccharides. According to the chemical structure and composition, these coupling agents could be summarized into acid esters, diimidazole, polyethylene amine, and epoxy halogen replaced alkyl classes. The chemical structure and properties of the coupling agents were given in table 1. These kinds of coupling agents could be used not only in synthetic materials, but also in functional food and synthetic drugs.

Coupling agent	Molecular formula	Structural formula	Molecular weight	Hazard symbols	Reference
PEI	$(CH_2CH_2=NH)_n$		43n	T	(Wang, 2000)
IPDI	$C_{12}H_{18}N_2O_2$		222.32	T	(Wang, 2000)
CDI	$C_7H_6N_4O$		162.15	T	(Wang, 2000)
ECH	C_3H_5ClO		92.52	T	(Wang, 2000)

Note: PEI: Polyethyleneimine; IPDI: Isophorone isocynate; CDI: N-N'- carbonyl diimidazole; ECH:Epoxy choropropane; T: Toxic

Table 1: Chemical properties of some coupling agents used in polysaccharide modification

Polysaccharide is a class of high-molecular compounds composed of the combination of many monosaccharides, such as starch, glycogen, cellulose, and chitosan. They were similarly structured and rich in hydroxyl groups providing the basis for granting modification. However, chitosan had more energetic amine groups than starch [2]. Therefore, chitosan had superior chemical modification ability than starch. Compared with cellulose, starch was more hydrophilic and had less modified cost [3], which makes search a more suitable candidate for building hydrophilic composite adsorbent. Starch is composed of D-glucose groups connected by- (1→4) or-(1→6) of glycoside bonds [4]. The anhydroglucose units (AGU) in the starch chain have three active hydroxyl groups [5], and in most cases, one primary and two secondary hydroxyl groups provided possibilities for various modifications, including physical, chemical, biological, and compound modification. The active material was grafted on the starch by coupling agent, and the reaction belonged to a chemically modified type [6]. As a class of bio-macromolecules, starch had the advantages of wide sources, renewable, biodegradable and no cytotoxicity. Starch and its derivatives were widely used in many industrial fields, such as, food, textile, pharmaceutical, and chemical industry. For example, starch was often used as carrier in multivitamin tablets [7], preparation of antimicrobial starch particles [8], coatings of nutrition [9] and adhesives [10] and well performing composites. The detailed information was provided in table 2. Therefore, it has been a hot topic to make the starch function by grafting the active material in recent ten years.

Polysaccharides	**Coupling agent**	**Donor of activity group**	**Function**	**Application**	**Reaction conditions**	**Reference**
Wheat starch	IPDI	PHGH	Antibacterial	Medical devices and food packaging	T: 60℃ N_2 protected Oil bath	[8]
		PEI	Capture of acid fluorescent dye and excess electrophilic reagent.	Scavenger		[54]
Cellulose nano-crystals		Trifunctional poly-ether alcohol	Improve tensile properties	Catheters, sealants, or cardiovascular implants		[59]
		CTBN	Improve dispersion and enhance mechanical properties of polymers	Food packaging	T: 105℃ N_2 protected Oil bath	[63]
hydroxyethyl cellulose		Polybutadiene	Load transfer	Smart materials	T: 90℃ N_2 protected	[62]
Starch		PEI	Promote various reactions	Catalyst	T: 25℃	[58]
Starch		PEG	Improve hydrophobicity	Hydrophobic material	T: 90℃ N_2 protected Oil bath	[88]
High-amylose cornstarch		Alkanol	Improve hydrophobicity	Hydrophobic material	T: 80℃ N_2 protected Oil bath	[11]
Crosslinked chitosan microsphere	PEI	chitosan	Adsorb for SDBS	Adsorbent	T: 30℃	[74]
Cellulose		Polypropylene	Increase tensile strength and elongation at break	Composite materials with improved performance	T: 25℃	[73]
Cellulose		Benzyl	PH-responsive amphiphilicity	PH-responsive Pickering emulsion	T:25℃	[85]
Corn starch		AESO	Waterproof	Waterproof starch-based material	T: 25℃	[71]

cellulose	CDI	ECH	Functional materials	Degradable film	T: Proper temperatue N_2 protected	[64]
Cellulose		Aliphatic amines	Amine functionalization	Adsorbent	T: 60℃ N_2 protected	[89]
Starch		PEI	Gene delivery	Diagnostic agent	T: 37℃	[67]
Corn starch		Caffeic-acid	Antioxidant	Antioxidant agent	T: 30℃ N_2 protected	[90]
starch		Quercetin	Antioxidant	Antioxidant agent	T: 70℃ N_2 protected	[90]
Cellulose		Organophosphorus hydrolase enzyme	Enzyme immobilization	Biodegradation of organophosphate compounds		[82]
Corn starch		Ferulic acid	Antioxidant dietary fiber for food and drink industries	Antioxidant agent	T: 60℃ N_2 protected	[91]
Starch	ECH	Crylic acid	Functionalized aerogel	Aerogel adsorbent	T: 70℃	[92]
chitosan		PEI	Functionalized aerogel			[76]
Cellulose		PEI	Adsorbing materials	Sorbent	T: 70℃	[93]
Starch		p-Tert-butyl-calix-[n]arene (n = 4, 6, 8)	Adsorbing dye wastewater	Adsorbent	T: 50℃	[94]
Starch		Amine	Removal of anionic organic pollutants from water	Biosorbent	T: 95℃	[95]
Cassava starch		Fluorescein	Nano fluorescent starch	Biomedicine	T: 50-60℃	[84]
Corn starch		GODAC	Flocculants over a wide range of pH	Flocculant	T: 25℃	[96]
Starch		CdS particles	Photocatalytic degradation	Degradation of organic dyes	T: 50-60℃	[97]
Starch nanocrystals	Glutaraldehyde	PEI	Removal of methyl blue dye	Biosorbent	T: 25℃	[75]

Note: IPDI：Isophorone isocynate; PHGH：Polyhexamethylene guanidine hydrochloride; CTBN：Carboxyl-terminated butadiene-acrylonitrile rubber; PEG：Polyethylene glycol; SDBS： Sodium dodecyl benzene sulfonate; AESO：Acrylated epoxidized soybean oil; ECH：Epoxy choropropane; GODAC：Glycidyloctyl dimethylammonium chloride; CDI: N-N'- carbonyl diimidazole

Table 2: Different coupling agents and its application in the polysaccharides modification

Starch functionalization

In order to functionalize the starch, Function of Starch and Modified Methods were shown in Figure 1. Chemical grafting from four modified method was mainly exposition in this section.

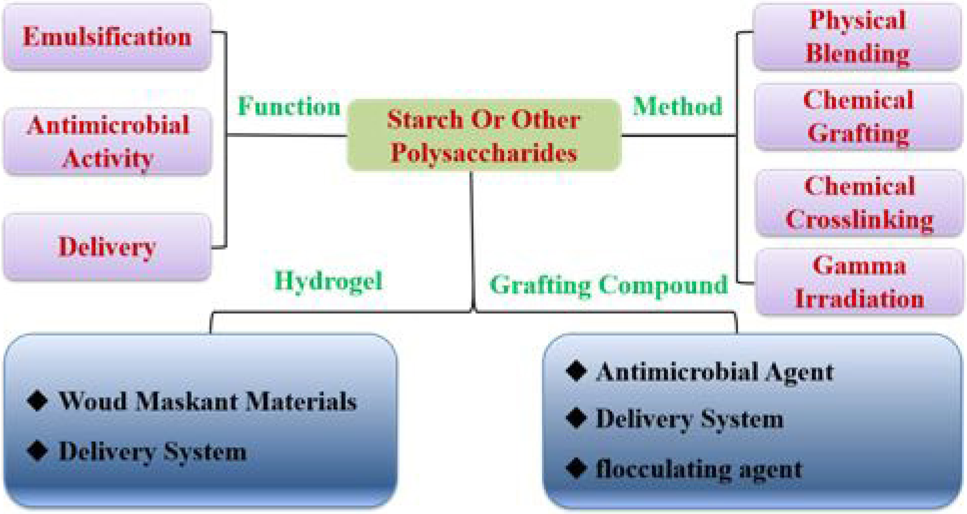


Figure 1: Function of Starch and Modified Method

Emulsified starch

Hydrophobic modification of starch

Methods of hydrophobic modification were included chemical substitution, physical mixing, and chemical grafting. Chemical substitution was that the hydroxyl group in starch was substituted with hydrophobic compound. The hydrophobic compounds mainly included alkyl succinate anhydrate, alkyl acyl chloride, epoxyalkane, isocyanate and silanes [11]. Physical mixing was that hydrophobic compounds and starch were bonded through different intermolecular forces to make starch hydrophobic [12]. Chemical grafting was that hydrophobic compounds were grafted on starch by using coupling agent making starch hydrophobic. Chemical substitution is currently the most commonly used for the hydrophobic modification of starch. For example, the esterification reaction was to substitute the hydroxyl group on the starch with the ester group, but usually the substitution degree was not high, so the hydrophobic modification of the starch was not very ideal [13]. While during the physical remixing, mixing the hydrophobic material and hydrophilic starch was problematic due to significant differences in their polarity resulting in inhomogeneous reaction products. Moreover, hydrophobic modification of grafting polymerization had some problems such as strict reaction conditions, low grafting efficiency, and complex graft homopolymers. Therefore, hydrophobic modification of most starch could first esterify the primary starch reducing its hydrophilicity, and then further physically mix hydrophobic substances or chemically graft hydrophobic groups.

In methods of hydrophobic modification, chemical grafting could also be classified into two methods. The first one was grafting hydrophobic substances on starch by coupling agent or a crosslinking agent. And the second was tantamount to modify the starch and then the modified starch was associated with the hydrophobic substances without the addition of the coupling agent in this chemical reaction process. Both methods could attach hydrophobic substances to starch, thus effectively improving the hydrophilic nature of starch.

Hydrophilic modification of starch

The common method for starch hydrophilic modification was chemical grafting. For instance, acrylic acid, acrylamide and other hydrophilic monomers and some hydrophilic amino acids were grafted on starch, so that starch had more hydrophilic. The percent grafting was usually used to react the hydrophilic degree of starch. The higher the grafting rate, the more hydrophilic monomers attached to the starch, and the hydrophilic of grafted starch was stronger. In grafting reactions with hydrophilic-modified starch, some reactions would happen using a cross-linking agent, while others did not. Currently, starch hydrophilic modification was used in the preparation of super absorbent materials for sanitary products. The demand for highly absorbent polymer materials for desert control, soil erosion prevention, afforestation and wastewater treatment was also increasing.

Emulsified starch

Through the hydrophobic and hydrophilic modification of starch, starch had amphipathy, which played an important role in stabilizing the emulsion and had the potential to prepare an excellent stabilizer of Pickering emulsion. The preparation method mainly esterified the hydrophilic starch to make the starch amphiphilic. For example, the wax-based corn starch with pulsed electric field (PEF) -assisted octenyl succinic anhydride (OSA) modified by Bo-Ru Chen et al [13]. Guantian Li et al found that nonenyl succinic anhydride (NSA) modification could serve as a substitute for octenyl succinic anhydride (OSA) modification of starch [14]. And modified corn starch using C-3 octenyl succinic anhydride was studied by Wei Gao et al [15]. In addition to the shared OSA modification, the NSA-modified starch had the potential to become an effective Pickering emulsion stabilizer. Both Octenyl succinylation reaction and particle size [16] had important effects on the emulsification properties of starch particles as Pickering stabilizer [17]. Emulsification ability of the OSA-modified starch depended largely on the number of the hydrophobic groups attached, which was called the degree of substitution (DS) [13]. Moreover, OSA-modified starch was a universal method to stabilize Pickering emulsifier, but the toxicity after its modification remained to be studied [17].

In addition, starch emulsion was willing to stabilize the Pickering emulsion by physical mixing. For example, a novel emulsifier was prepared by mixing potato starch and soybean protein in an acidic environment by Die Dong et al [18]. Liang Huang et al prepared starch fatty acid complexes utilizing solid encapsulation methods and applied them to stabilize Pickering emulsion, a novel way of hydrophobic modified starch [12].

Wax corn starch, potato starch, corn starch, quinoa starch which is relatively low in amylose content [14] and high amylose starches [17] were used as a modified starch raw material. The species of starch could be chosen according to the content of the specific research. The OSA-modified starch chain had the ability to stabilize the oil-water interface and that amylopectin was more stable under long-term conditions as showed in the results of Madai Lopez-Silva et al [19]. Therefore, esterification modification usually selected for starch with high branched chain content.

Antimicrobial starch

Methods for preparing antibacterial starch included physical mixing and chemical grafting. Among them, physical mixing was to mix antibacterial compounds with starch, and the whole compound was used as an antibacterial agent. Chemical grafting was to branch antibacterial compounds to starch. The advantage of chemical grafting was that the immobilization of antibacterial substances was well achieved, so that the antibacterial substances were retained on the starch for a long time to achieve antibacterial persistence.

For example, Ewomazino Ojogbo et al prepared the antimicrobial starch by applying the antibacterial agent PHGH to the starch by a coupling agent [8]. Jin et al. prepared zinc (II) and functionalized L-phenylalanine in situ grafted starch. The antibacterial principle of this experiment was to substitute Boc group by zinc (II) complexes with antibacterial effect [20]. Poly (N-vinyl imidazole) (PVI) has been grafted onto carboxymethyl starch (CMS) in aqueous solution [21]. Mu Huang et al. prepared quaternary ammonium salt grafted starch as flocculant, and starch-graft-poly (2-methacryloyloxyethyl) trimethyl ammonium chloride (St-g-PDMC) showed good inhibition against E. coli [22]. Subhadip Das et al. first chemically modified the primary starch to hydroxy ethyl starch (HES), and then applied methylacrylate (MA) to the modified starch to successfully prepare antibacterial starch. Antibacterial starch had inhibitory effect on B. cereus and Bacillus subtilis [23]. In the study of hypromellose-graft-chitosan-based polyelectrolyte complex film, chitosan has been known that it has antibacterial activity, so CDI was used as a coupling agent to connect hypromellose with chitosan to prepare antibacterial film [24]. A novel bead of modified starch for encapsulating 2,4-dichlorophenoxy acetate (2,4 DA) was made from natural rubber-graft-cassava starch (NS) and sodium alginate (SA) in a water-based system [25]. Bionanocomposite films were prepared by crosslinking starch with cellulose nanofibres to evaluate antibacterial properties of film against four different food pathogens [26]. Quaternarized N-halamine-grafted graphene oxide (GO) showed strong speedy bactericidal activity against Escherichia coli (E.coli) and Staphylococcus aureus (S. aureus) (99%) [27]. Roman Sarder et al reviewed copolymers of starch in biomedical applications which concluded grafting starch used as antimicrobial agents and drug delivery system [6]. Starch was modification by quaternary ammonium and then glutaraldehyde (GA) was used as cross-linker to prepare antibacterial cross-linked blend film [28]. A hybrid flocculant with antibacterial activity was made by grafting cinnamic acid on N-(2-hydroxy)-propyl-3-trimethylammonium chitosan chloride (HTCC), which had better inhibiting effect on Escherichia coli [29]. A kind of starch-based macroporous sponge (KR-Sps) immobilized covalently with antimicrobial peptide KR12 was developed by Xiao Yang et al [30], which were believed to be an excellent hemostatic and antimicrobial product. The urea group was included in the starch to have antioxidant, antifungal, and antibacterial activities [31]. Citric acid-crosslinked rice starch was developed and then calcium oxide (CaO) was mixed in this copolymer to make this polymer antibacterial property [32].

From these studies, operative groups were grafted on starch or other polysaccharides. Some reactions realized without coupling agents, but other compounds were bonded by crosslinking-agents or other activating agents. The above chemical grafting methods for preparing antimicrobial starch was divided into two categories. One was that the coupling agent served as an intermediate link to connect antibacterial compounds with starch. The other type was that starch was chemically modified firstly, and then the polymerization with antibacterial compounds was achieved. It showed good antibacterial activity against both Bacillus subtilis and E. coli. Functional substances were grafted to starch through chemical grafting reaction. The modified starch not only maintained the original properties, but also was endowed with additional functions making the application of starch more widely used. From these examples, most application fields were preparing bioactive starch-based film to inhibit food borne microorganisms. The materials used in food packaging were safe and non-toxic. So most chemical grafting reactions were designed using organic reagent which cannot be used in food packaging. However, coating or other material fields can be permitted.

Using lemongrass extract to produce a modified starch was used in combination with alum in order to enhance the removal of TSS and E. coli from untreated water [33]. Wing-Fu Lai et al reported food-grade polyelectrolyte complex film generated via electrostatic interactions between two cellulose-based agents [24]. There was a physical novel method to make starch copolymer. Simultaneous gamma irradiation was used to synthesize Starch/acrylamide/allyl triphenyl phosphorus bromide (St/AM/TP) copolymers to against S. aureus [34]. Antibacterial modification methods of pure polysaccharides hydrogels were reviewed by Rong Zhang et al [35]. Hydrogel materials, because of their retained water ability, and a porous structure, have better met the conditions required for wound healing.

Delivery function of modified starch

There was for two methods of starch delivery system formation. They were physical and chemical methods. First, the chemical method was to modify the raw starch to change its original properties, so that it had a delivery function. Second, the instinctive method was mainly to achieve the starch and other compounds self- assembly, in which the starch itself did not react. Resistant starch microparticles (SMP) were emerged as promising biocarrier because of its good chemical and thermal stability as well as high resistance to digestive enzymes in the human gastrointestinal tract. It can encapsulate hydrophilic molecules without chemical modification and crosslinking reactions. However, compared to chemical grafting, its encapsulated objects had limitations, and lipid-soluble objects cannot be encapsulated. In general, choosing a suitable coupling agent and the grafting monomer was a convenient way to prepare a suitable delivery material according to the experimental purpose. Starch hydrogel which also had the function of delivery was also a kind of resistant starch and belonged to RS III. Since starch hydrogel had a 3D network structure through cross-linking, porous structures and it was similarity to the extracellular matrix, it was a more appropriate choice for the drug delivery system. A material that was prepared for a drug delivery system after chemical modification of starch, including oxidation, acid lysis, enzymatic lysis, crosslinking, and etherification, was reviewed by Paulo Vitor França Lemos et al [36]. Therefore, chemical grafting for delivery was also an essential method.

Poly (ethylene phthalate) was grafted on gelatinous substance to prepare a drug delivery system by Hooshang Hamidian et al. Mucoadhesive starch-graft-poly (acrylic acid) copolymers have been synthesized by Mehmet Koray Gök et al [37]. Fucoxanthin (Fx), a model hydrophobic bioactive, was encapsulated within starch-based microparticle (SMP), which could be useful in designing an effective drug carrier for delivering several hydrophobic bioactives to different parts of the intestine. Starch-graft-poly (acrylic acid) copolymers (S-g-PAA) were synthesized to prepare a vaginal mucoadhesive hormone delivery system. Grafting copolymers of methyl methacrylate (St-g-PMMA and Ast-g-PMMA) on starch and acetylated starch to prepare controlled release tablets of salbutamol sulphate (SS) was studied by Pankaj Kumar et al [38]. Zeinab Karami Ghaleseiedi et al studied and prepared starch-based dual amphiprotic grafting copolymer as a new pH-sensitive multidrug co-delivery system [39]. Hydrolyze polyacrylamide grafted maize starch based micro beads were used in pH responsive drug delivery [40]. To the best of our knowledge, grafted copolymers of starch and acrylic monomers have been demonstrated their ability to control drug release [41]. Grafting poly-glutamic acid (PGA) on waxy maize starch was prepared in an aqueous solution using microwave irradiation by Jingyuan Xu et al [42]. Hypromellose -graft- chitosan (CS) was prepared by Wing-Fu Lai et al. In this study, CDI was used as a coupling agent to connect the hypromellose with CS [43]. These studies showed grafted starch can be used as delivery systems. The most materials were used in drug delivery system, and the reactions were complicated including reaction conditions.

Fe_3O_4 nanoparticles were mixed with starch at 50°C, and then the gelatinous substance would be formed [44]. Dicarboxylic acid modified starch was combined with clay as carriers for pesticide delivery [45]. Amylose is in a position to forming an inclusion complex for the encapsulation [46]. According to these reports, physical mixed method was convenient to make the delivery system. Compared to chemical methods, the disadvantage might be that physically modified starch was unsound.

Specifically, microparticles, nanoparticles, nanocrystals, hydrogels, and scaffolds used these materials which were hydrophilic and hydrophobic starch derivatives as drug delivery systems [36]. For example, Starch hydrogels can be used as targeted colonic drug delivery vehicles because hydrogel structures abled to resist small intestinal digestion [47]. A novel starch-based stimuli-responsive magnetite nanohydrogel (MNHG) was successfully developed for targeted delivery of doxorubicin (DOX) as an anticancer drug [48]. Starch-based hydrogel drug delivery system was intended to improve the release rate of quercetin as a poorly water-soluble drug [49]. In a study by Abhijit Sarkar et al, starch was combined with poly (vinyl alcohol) (PVA) and achieved gelatinization [50]. Then clay minerals were grafted on starch/PVA to prepare encapsulated controlled release fertilizers. New pH-responsive nanoparticles for controlled delivery of anticancer drug doxorubicin (Dox) were designed by Alireza Shalviri et al, and then poly (methacrylic acid) and polysorbate 80 were grafted on starch [51]. Fernando G. Torres et al reviewed modified starch nanoparticles as drug delivery systems [52]. In this structure, delivery system performance can be enhanced by enhancing the properties of the starch hydrogel.

Coupling structure and mechanism of action

Properties of PEI and mechanism of coupling reaction

The structure of PEI molecule (Polyethyleneimine) contains linear and branching regions, and its primary amine group is terminal unit, secondary amine group is linear unit, and dendritic unit is comprised of tertiary amine group [53]. PEI was a polymer without uniform repeating unit [54], and it was a water-soluble polyamine. The polyamine structure had high activity of a chemical reaction. Because its amine group was partially protonated under acidic or neutral pH conditions, PEI was positive and a cationic polyelectrolyte and could easily bind to a negatively charged surface [55]. The addition of the cationic polyelectrolyte which neutralized the dispersed anionic charges in the colloids promoted the solidification and retention of the colloidal particles and improved the separation from the liquid phase [56]. The mechanism of action was that the primary amine and secondary amine groups on PEI molecules could be directly coupled as active groups to the medium, and it was synthesized the ion exchange medium and thus the coupling reaction happened was shown in Figure 2. The other end could be attached to other substances. Since PEI had abundant active group amine groups, the grafting reaction conditions were mild relative, such as lower reaction temperature, normal pressure, and without inert gas protection.

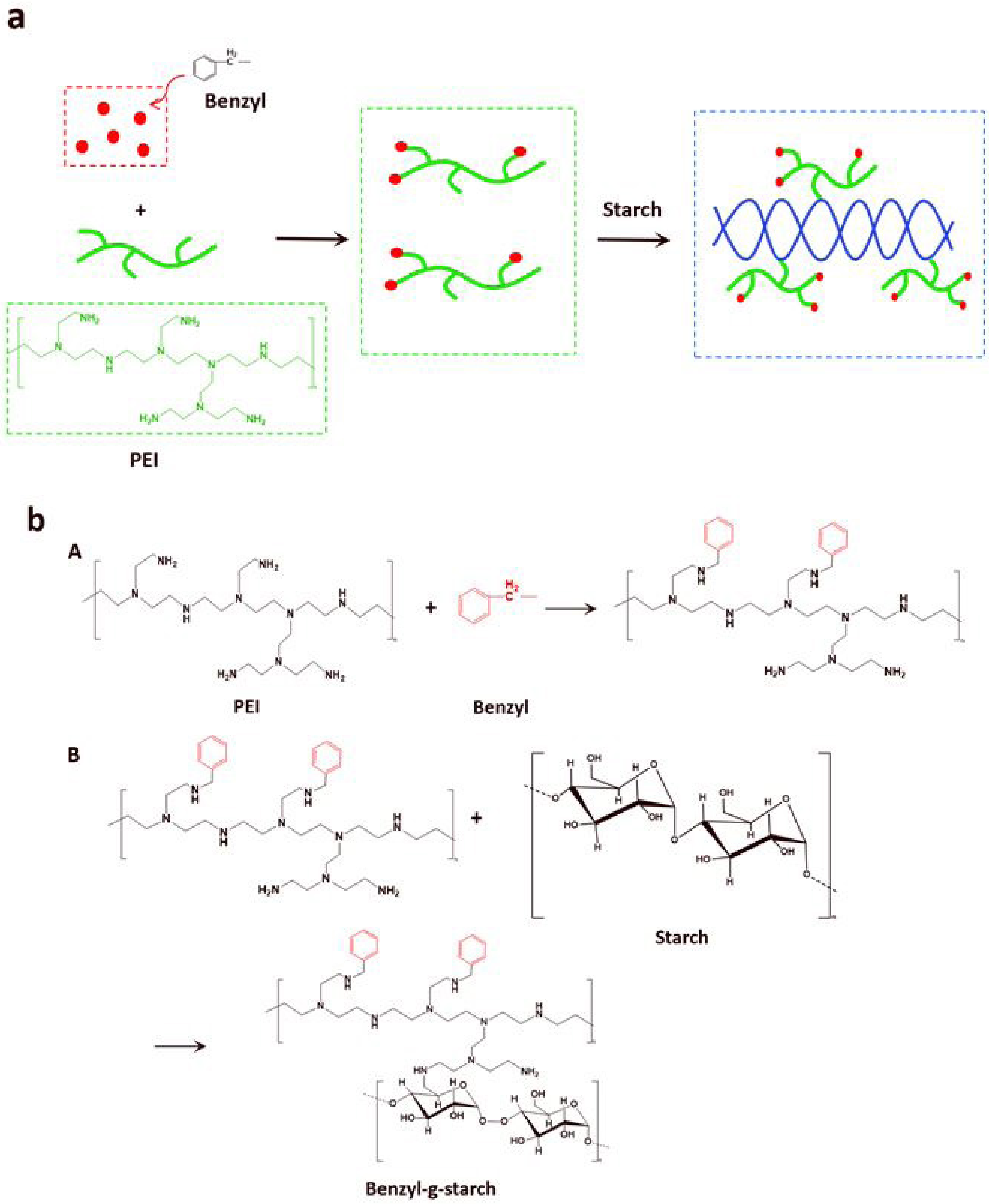
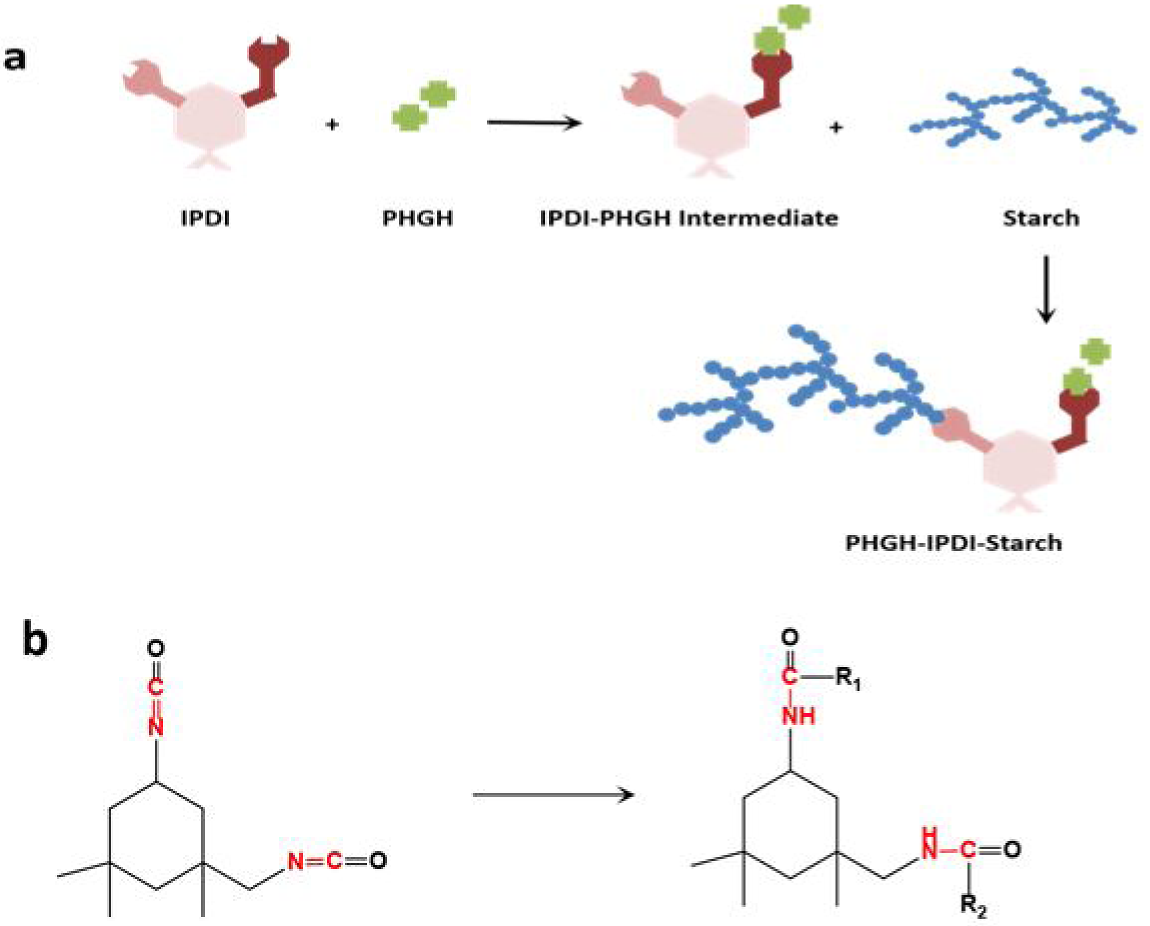


Figure 2: Schematic diagram of PEI grafted with starch (a) and molecular structure diagrams of coupling reaction (b) (PEI: Polyethylene-imine)

The two parts of the grafting were that the first part was polysaccharide with active hydroxyl groups, such as chitosan, starch, cellulose and other polysaccharide, and the other part was a small molecular material containing the aldehyde group or the active hydroxyl group. If the other part was a substance containing the aldehyde group, the amine group of PEI would take off two H, and the aldehyde group would take off one O to generate H_2O, and then the rest of structures were connected. If the other part contained the active hydroxyl group, the grafting mechanism would be that the amine group of PEI removed one H which connected one H of the functional hydroxyl group to generate H_2, and the rest of structures were connected.

Properties of IPDI and mechanism of coupling reaction

sophorone diisocyanate (IPDI) is an aliphatic isocyanate containing equally reactive primary and secondary isocyanate groups [57], which connect two compounds like two I”handles” for coupling purposes. In the isocyanate group (-NCO) because the electronegativity of O was greater than ones of N, the electron pair migrated from C=O to C=N, the C=N double bond was more likely to break in the –NCO structure. Thus the addition reaction was that C was connected to another compound while N added H to form the amine group and this reaction was given in figure 3.



R_1: starch, cellulose,or other polysaccaride; R_2: something with amine group, hydroxyl group, or other functional groups;

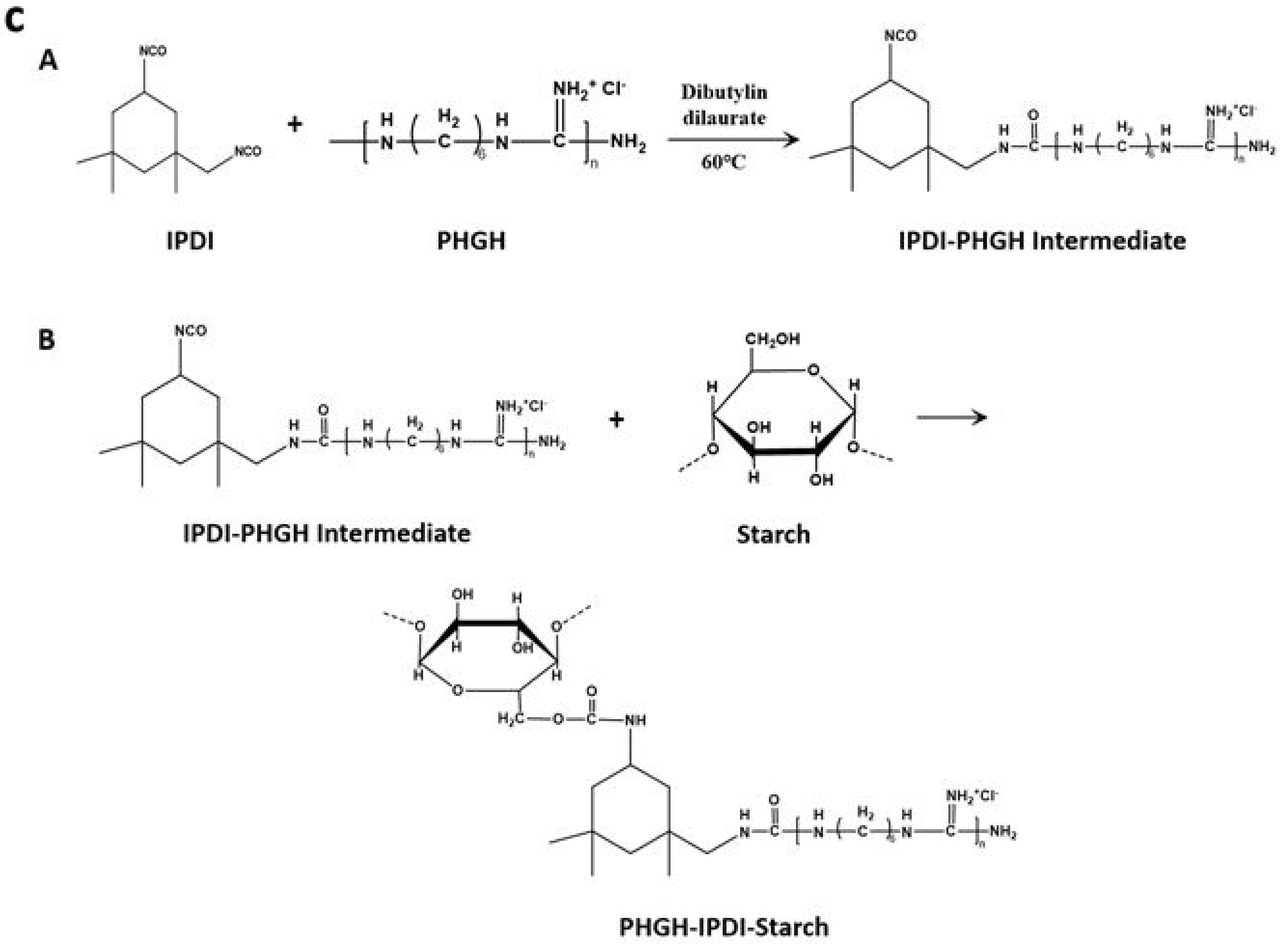


Figure 3: Schematic diagram of PHGH-IPDI-Starch (a), the structure of IPDI (b) and molecular structure diagram of coupling reaction (c) [8] (PHGH: Polyhexamethylene guanidine hydrochloride; IPDI: Isophorone isocynate)

The coupling mechanism of IPDI was as followed: an asymmetrical diisocyanate group formed a carbamate bond with the active compound, so that the IPDI was anchored on the surface of the polysaccharide. And another isocyanate group which still served as a further decorated reaction site [58] could react with other dynamic compound. Therefore, the coupling of IPDI could be utilized to prepare prepare structurally diverse functional polymers. The surface of the starch had number of chemically modified hydroxyl groups that could be coupled to the diisocyanate group, and another binding site of IPDI could connect other compounds.

As a coupling agent, IPDI had numerous advantages. First, due to the nature of the addition reaction, no byproducts were formed during the reaction. Second, polyurethane bond between the isocyanate group and the hydroxyl group of the starch was very stable against hydrolysis cutting. Third, the IPDI ring contained methyl groups to facilitate dissolution in various solvents. In addition, two distinct reactive isocyanate functional groups of IPDI could meet the selective coupling reaction during the two-step coupling reaction [59]. Finally, the unreacted IPDI could be easily removed from the synthesized polymer production by reprecipitation [60].

Since the isocyanate groups had chemical reactions with various nucleophiles, such as hydroxyl, ammonia, and thiol compounds, the reaction conditions to be noted in the actual grafting reaction were listed:

1. The reagents to dissolve IPDI were anhydrous acetonitrile, such as N, N-Dimethylformamide, tert-Butyl peroxybenzoate (TBPB), chloroform, etc. [8, 10].

2. The starch was to be dried at a temperature of 105°C–110°C for 6–9h. Dry starch was first dissolved with dimethylsulphoxide

(DMSO), and the starch was dissolved with 40°C -60°C [61].

3. The IPDI grafted starch reaction usually performed under inert gas protecting, and it occurred at a reaction temperature of 60°C -120°C. [8, 62].

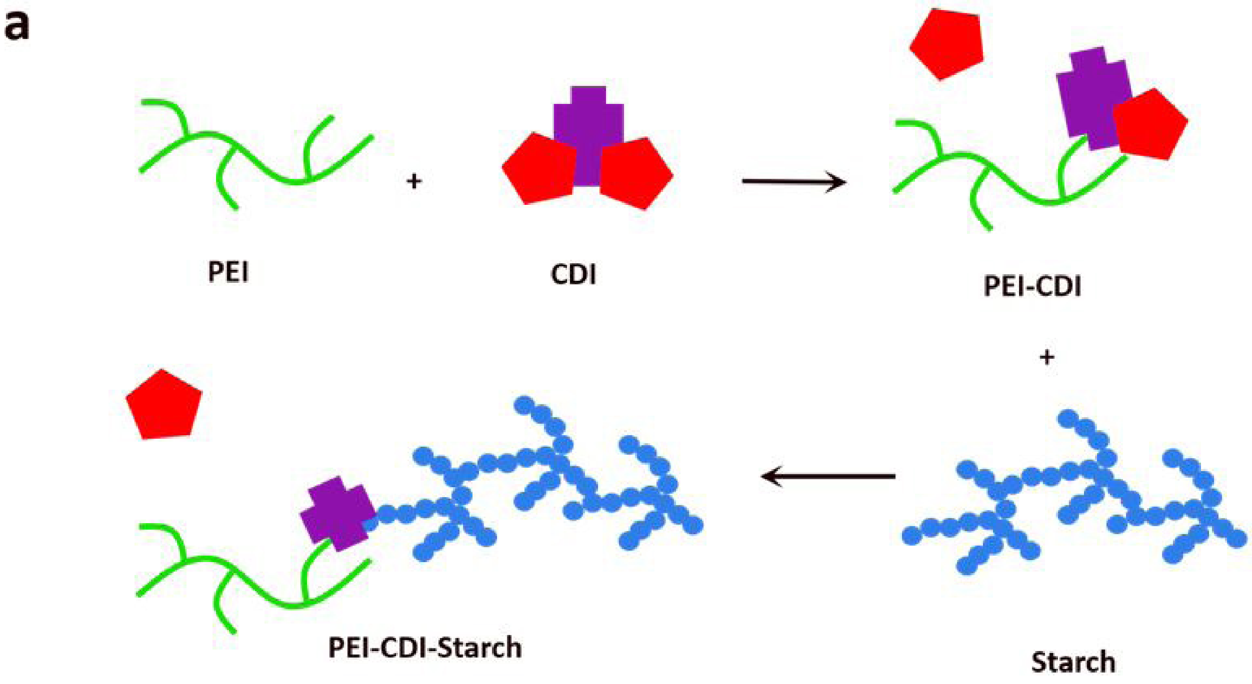
4. Reaction containers generally used three-necked or four-necked round-bottomed flask supported by mechanical stirrers, condensers, drop funnels, and inert gas entrances [8,61, 63].

From these reaction conditions, compared to the test conditions for grafting starch, IPDI grafted cellulose was similar with starch and reaction conditions varied depending on the degree of grafting. When preparing hydroxyethyl cellulose copolymer-modified urethane bionanocomposites [62], the reaction condition required N_2 protection probably because compared with the native cellulose, hydroxyethyl group of hydroxyethyl cellulose replaced hydroxyl group [62] reducing the binding site of active hydroxyl group, and the reaction conditions were slightly more difficult. When branched starch, it might also need to be protected to use inert gas. Owing to these complex reaction conditions the cost of experience might be more expensive and it might be difficult to conduct this grafting experience.

The two parts of grafting were usually that the one part was chitosan, starch, cellulose or other polysaccharide with active hydroxy group, and the other part was compound with active amine or hydroxyl group.

Properties of CDI and mechanism of coupling reaction

The N-N'-carbonyl diimidazole (CDI) structure has a closed large π bond [64]. The chemical structure of CDI is axisymmetric structure, and the π-π conjugate is formed by left N- heterocycle and double bond, and the right is same. The coupling mechanism was as followed: because the density of heterocyclic electron cloud was larger than the double bond, electrons were biased to N- heterocycle. So the bond between C-N and C-N' was not difficult to break. N- heterocycle was usually removed during the coupling process and the C was connected to other activist groups as showed in figure 4.



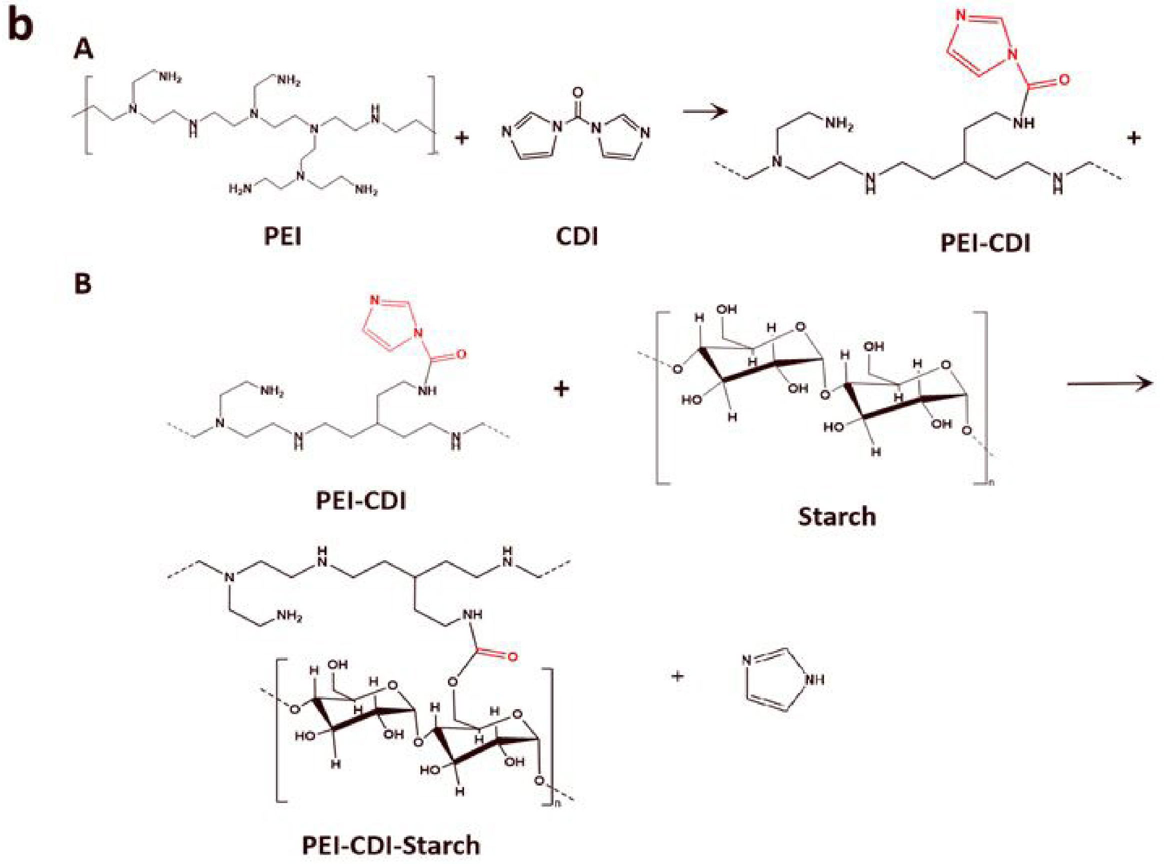


Figure 4: Schematic diagram of PEI-CDI-Starch coupling reaction (a) and molecular structure coupling reaction (b) (PEI: Polyethyleneimine; CDI: N-N'-carbonyl diimidazole)

CDI could react with functional groups such as ammonia, alcohol, and acid, so CDI was easily linked to starch that was abundant in active hydroxyl groups. And CDI was a multifunctional reagent with excellent water resistance and good activity against polysaccharides such as dextran, chitosan and cellulose. Similar to the coupling reaction of IPDI, the coupling reaction conditions of CDI were summarized as followed:

1. Nitrogen protection was required during the reaction [65, 66, 67].
2. The end point of the reaction process was that CO_2 was no longer released [68].
3. Dialysis was required, and it was longer, usually ranging from 24h to 96h [69].
4. The CDI grafting reaction time was longer [68, 70].

The condition of CDI was similar with IPDI, and the cost of experience might be expensive, and the operation of grafting experience was complicated. The two parts usually grafted were that the part one was starch, chitosan, hyaluronic acid, dextran or other polysaccharide, and the other part could be organic acids such as caffeic acid, or small molecular compounds containing active hydroxyl groups such as poly (acetic acid).

Properties of ECH and mechanism of coupling reaction

The structure of epoxy choropropane (ECH) was shown in Table 1, an alkyl group is composed of epoxy groups and chlorine atoms. The mechanism of preparing cross-linked starch by ECH was as followed: ECH removed chloride atoms firstly, and cross-linked them with starch to produce an ether bond. Then the epoxy group opened the ring and connected another molecule of glucose unit through the oxygen bridge bond to form cross-linked starch. Eventually, ECH was cross-linked to the starch molecules by two ether bonds. Similarly, the mechanism of ECH as coupling agent coupling starch to other substances was that because the electron cloud was concentrated on the oxygen atoms, the oxygen atoms were very activevigorous, and the hydroxyl group in the starch-replaced Cl in the coupling process. Then the epoxy group opened the ring and connected to another substance. As showed in Figure 5, ECH was coupled with starch and diethylenetriamine (DETA). ECH can graft starch, cellulose, chitosan, or other polysaccharides. Compared to the coupling reaction conditions of IPDI and CDI, the ECH-grafting process did not require nitrogen protection, but had a longer reaction time, and the reaction conditions were relatively placid.

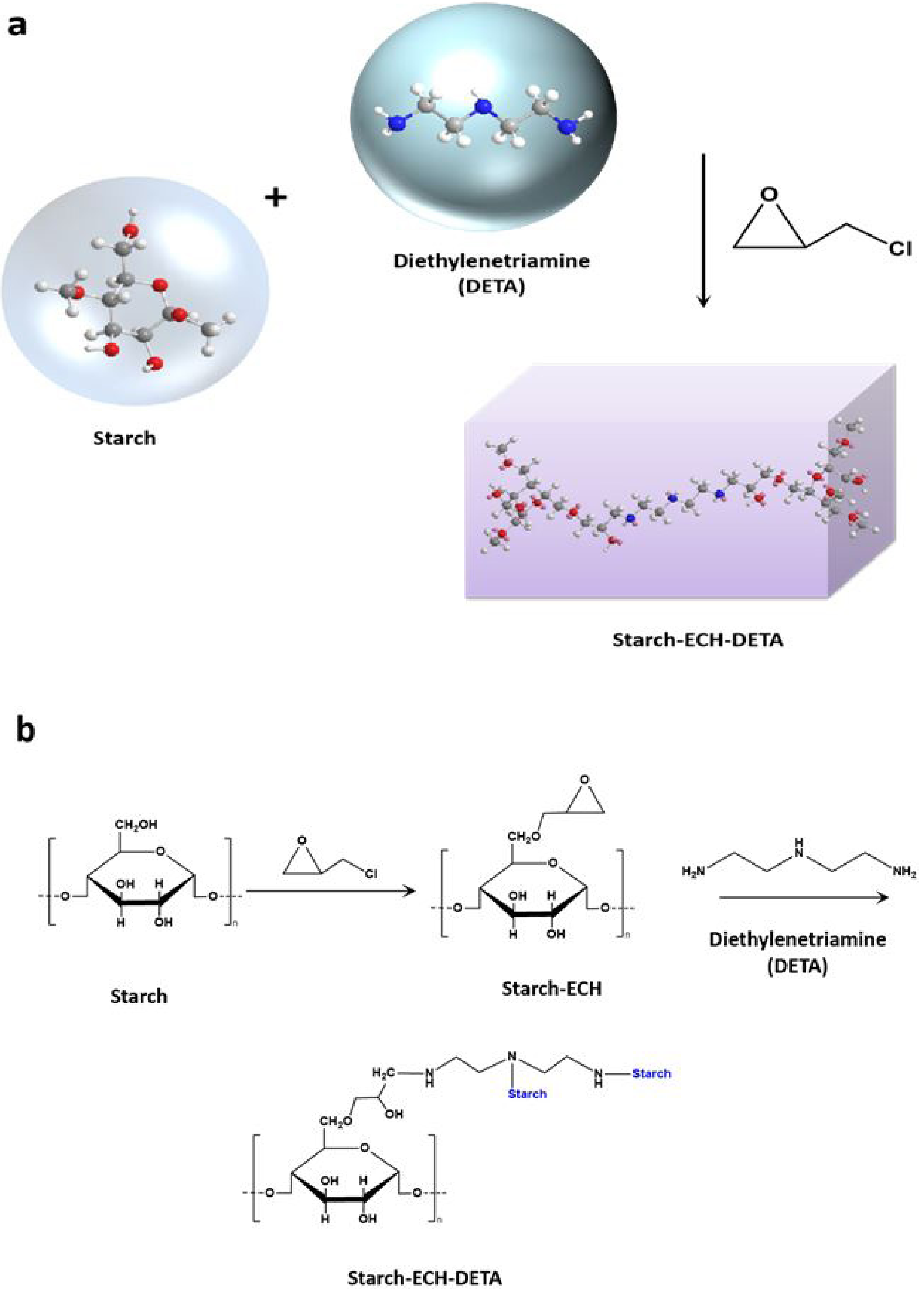


Figure 5: Schematic diagram of ECH grafted with starch (a) and molecular structure diagrams of coupling reaction (b) (ECH: Epoxy choropropane)

The two parts grafted were usually that one part was starch, chitosan, cellulose or other polysaccharides, and the other part was quaternary ammonium salt, or compound containing active hydroxyl or amine groups. It was worth noting that if the quaternary ammonium salt was grafted through ECH. The mechanism will be that the Cl of ECH would transfer to quaternary ammonium salt as negative ions of chlorine. And then it could be electric neutrality to communicate with ECH. After the epoxy ring opened, it could be combined with the reactive hydroxyl group of polysaccharides.

Current application of coupling agent in carbohydrates

Polyvinyl imines take PEI an example

PEI has been widely used in the past decades to control colloidal stability and surface properties, such as coatings, adhesives, water treatment, cosmetics, CO_2 capture, DNA transporter, and manufacturing of food packaging films because of the advantages of low toxicity, easy separation, biodegradable, lack of odor [71].

Benzyl-polyethyleneimine modified cellulose nanocrystals (Ben-PEI-CNCs) were prepared by PEI grafting from cellulose nan crystals [72], and PEI grafted benzyl in cellulose nanocrystals had a good pH response making Pickelin emulsion emulsifier which has green and recyclable pH response [72]. Besides, PEI was used as a coupling agent to improve the interface adhesion of cellulose-reinforced polypropylene composites (M.U. dela Orden et al). On the one hand, the amine group of PEI reacted with the cellulose carboxyl group to form imides and amides, on the other hand, PEI formed a stable compound with polypropylene. The coupling reaction markedly enhanced the tensile strength and fracture elongation of the composite material [73]. W. Liu et al also used PEI to improve adhesion between hydrophilic starch and hydrophobic coatings with biomass correlated specialized soybean oil (AESO). PEI effectively interacted with the starch membrane by hydrogen bonding and chemically bound to AESO by the Michael addition reaction enabling a significant improvement in the interface adhesion of the starch and AESO coating after PEI treatment In these studies above, the similar part was that PEI was used for grafting cellulose or starch with functional compounds like benzyl or AESO. From the study of Jing Yingjun et al, it was understood that the protonation occurred on the PEI in a wide range of pH values, and then PEI was positively charged. The electrostatic interactions could occur with the negatively charged material, which can reversibly adsorb anionic dye [74]. PEI was grafted onto starch nanocrystals (SNCs), and then a novel SNCs-PEI biosorbent was successfully prepared, which had good adsorption properties for the anionic dye methyl blue (MB) [75]. In the field of biomedical research, PEI-DNA was a suitable candidate for a gene delivery vector, and it had good security profile (Yamada et al., 2014). The PEI was also a very useful drug carrier [58] at the same time. The PEI could also remove heavy metal ions in the aqueous solution by chemically modifying grafting onto natural polysaccharides such as starch, cellulose, and chitosan [58]. For example, PEI could be grafted into the aerogel due to its rich amine group and spatial branched chain structure, which could not only enhance the mechanical strength of the aerogel in the three-dimensional porous network mechanism, but also the protonation amine group (NH^{3+}) of PEI under acidic conditions can fix Cr^{3+} and Cr^{6+} through electrostatic action and coordination action respectively [76].

From the applications above, PEI coupling to further compound was commonly used to alter the interfacial properties of the composites. By adding PEI, compounds with fresh properties were introduced to the polysaccharides. In most instances, PEI rarely used as coupling agent, and the possible reason was that PEI had complicated structure because of its larger molecular weight than IPDI, CDI, or ECH, so the degree of polymerization was difficult to control, which could difficultly connect other compound and polysaccharide. If PEI was as coupling agent, lower molecule and suitable degree of polymerization would be thought about, which made PEI be extensively utilized.

Acid esters take IPDI as an example

According to GreenBio Institute et al, Lysine diisocyanate (LDI) and Hexamethylene diisocyanate (HDI) belonged to the aliphatic isocyanates class like IPDI. The addition of isocyanates improved the interface adhesion between the polymer matrix and the corn starch packing, and the tensile property of the composite was also improved [77]. Although LDI and HDI had isocyanate groups, their two isocyanate groups were symmetrical. So the two isocyanate groups had no difference in the chemical reaction. IPDI was suitable for grafting because of its asymmetrical diisocyanate group, and the activity of the isocyanate group in the branched chain was better than that of the benzene ring. E. Ojogbo et al. used IPDI as a coupling agent to chemically graft antibacterial molecules on starch to form antimicrobial polymers. Antibacterial starch microparticles were established by grafting the PHGH, an antimicrobial agent [78], to the starch [8]. In contemporary studies, antimicrobial materials were made by grafting starch and cellulose to act as effective polymeric biocides [79]. L. Fu et al prepared isocyanate -functionalized polysaccharides. The principle was that isocyanate functionalized starch was prepared with symmetrical diisocyanate as bridging block. PEI was paired with starch, cellulose or chitosan by IPDI, which was used to remove heavy metal ions [58]. Cannabis cellulose was coupled with biomass correlated specialized soybean oil by IPDI to improve the performance of lower viscosity and curing temperature of soybean oil and hemp fiber composites [80]. M. A. Javaid et al. synthesized wax corn starch modified polyurethane elastomers by step growth polymerization reaction of the -NCO- terminated pre-polymer of IPDI with chain extenders (1, 4-butanadiol/ starch) for biodegradable polyurethane of the biomedical system [7]. Xiaojian Chen et al. grafted glycidyl methacrylate (GMA) into starch by polyaryl polymethylene isocyanate (PAPI) to enhance the hydrophobicity of starch to prepare efficient and environmentally friendly adhesives.

From these applications above, IPDI played two roles in the composite namely as cross-linking agent [77] or coupling agent [63]. Both effects make a significant contribution to improve some of the physico-chemical properties of the composites. At the same time, many studies showed that the properties of grafting starch would also be changed due to graft different compounds by IPDI.

Diimidazole take CDI as an example

Since the native starch-based materials were hydrophilic and its mechanical properties decreased with increasing water intake. To overcome its limitations, starch was coupled with other materials with CDI to prepare degradable and machinable starch polyester [81]. CDI as the chemical coupling agent, Meisam Sharifi et al. fixed organophosphorus hydrolase (OPH) by covalently attaching to cellulose microfibers to prepare efficiently and low toxic chitosan nonverbal carriers [82]. The hydroxyl group on the surface of nanocellulose was activated with CDI, and then for a grafting reaction. Grafting activated group could expand the application scope of nanocellulose. CDI as coupling agent, Novel modified caffeate-grafted starch was prepared by grafting caffeic acid to starch [83]. In order to award starch the antioxidant activity, quercetin grafted to starch by CDI has significantly improved the thermal stability, resistant starch content, and antioxidant activity of starch [84]. For the adsorption and degradation of persistent organic pollutants in aqueous solution, CDI was as a coupling agent, Desheng Liu et al studied a novel magnetic bifunctional-cyclodextrin nanocomposite (Fe_3O_4@ -CD-CDI) based on metal coordination [85]. In addition, CDI can also act as an imidazole ligand that can bind to metal ions (Cu^{2+}, Zn^{2+}, Co^{2+}, Fe^{3+}, and Fe^{2+}) through simple chemical reactions. Gloria et al. investigated the synthesis of amphiphilic hyaluronan (HA) and poly (3-hydroxyalkanoate) (PHAs) grafting copolymers by the use of CDI [86]. Starch-PEI as a reducing agent and a stabilizer, Dhanya et al. grafted on PEI to starch by CDI to form an effective drug delivery platform [67]. Among these researches, CDI acted as coupling agent connecting two kinds of different compounds to form various novel functional materials.

Comparing with these results, CDI was often used to connect starch or other polysaccharide with PEI, acid, or other compounds, which could make starch or other polysaccharide function and changed its own characteristic. Then, CDI could also be used as activating agent, Betaine-coupled cationic pullulan as an operational gene carrier was studied by M.R. Rekha et al [68]. Pullulan-PEI conjugate through collagen synthesis became an effective gene carrier, and similarly CDI activated pullulate [66]. In the study of the efficacy of vinyl imidazole grafting of cationic pullulan and dextran as gene delivery carriers, CDI also acted as an activator [70]. Among these studies, CDI activated pullulan and then bound PEI to prepare a low toxic delivery vector.

Epoxy halogen replaces alkyl take ECH as an example

ECH was often used to prepare starch microspheres as cross-linking agent. At the same time there were many applications in which ECH was used as the coupling agent. For example, epoxy-active intermediates with double bonds were established by the reaction of acrylic acid with ECH, and then a ring cleavage-addition reaction was achieved using the epoxy group in ECH and the hydroxyl group in the starch molecule. The attachment of fluorescein to the native cassava starch chain has developed a new type of Nano fluorescent starch to make starch show strong fluorescence by ECH connection. By modifying cellulose surface used ECH, Pan Hong et al. yielded a bisexual surfactant with structural novelty and significant surfactant [87]. Starch has received much attention as a basic substrate for designing different adsorbents. ECH was not difficult to connect starch with amine, which could effectively adsorb anionic organic pollutants in water. Another method was that grafting tertiary-butyl aromatics to starch by ECH connecting could also prepare adsorbent. Xiao fei et al coupled chitosan to N, N-dimethyl hexadadanine to form tetraterylated chitosan, which had therapeutic effects on non-alcoholic fatty liver disease. ECH was widely used as a coupling agent. From these applications, their coarse features were that the polysaccharides were grafted with other compounds by ECH in order to make the polysaccharides various functions. ECH was typically used as crosslinking-agent to prepare starch microsphere. Those microspheres were mainly prepared into adsorbents, fluorescent agents, and medical therapeutic substances [98-100].

Conclusion

As a kind of coupling agents, the applications of PEI, IPDI, CDI and ECH were summarized in the field of starch functionalization. PEI was suitable for coupling agent due to its active amine group, while IPDI was widely used due to its two isocyanate groups. CDI was often used as an activating agent in the meantime it was also used as the coupling agent. Recently, ECH was typically used as crosslinking-agent to prepare starch microspheres as well as coupling agent to graft functional group on starch.

In terms of reaction conditions, PEI coupled starch were mild than ones of IPDI, and the former was more easy to achieve. In general, the reaction-conditions of both IPDI and CDI required inert gas protection, and even the catalysts were used, sometimes, the higher temperature and longer reaction time were necessary too. Therefore, we concluded that PEI was more apposite as coupling agent for starch grafting reaction.

In respects of coupling costs, the prices of several coupling agents were similar, due to the differences in the reaction conditions, the costs of grafted starches were different. When IPDI and CDI were as coupling agents, the reaction conditions were harsher, so, the costs of grafted starches were relatively higher.

In the future, starch can be combined with more multifunctional compounds by direct way to develop innovative starches with more functions, such as emulsification, adsorption, and thickness. However, a current problem is that PEI, IPDI, and ECH are toxic, their toxicities are inconclusive after these coupling agents are grafted on polysaccharides, simultaneously, these remanent compounds of coupling reactions are uncertain yet, all of these is a barrier in food plant, therefore, more deep studies are necessary in the future. Certainly, in addition to the food industry, the coupled functionalized starches are widely used in paper making, textile, and decoration, hence, continuous researches on coupling starches are of great and far-reaching significance.

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