Chapter 4
Plant Derived Polymers, Properties, Modification & Applications

Abstract Current polymeric research has explored various applications in drug delivery and its related biomedical applications. Natural polymers especially those are derived from plant sources has evidenced for growing interest and attention in biomedical and pharmaceuticals sectors. Owing to their relative abundance, low cost, and biodegradable and eco-friendly profiles, plant derived polysaccharides are more preferred over the synthetic polymers. Present work demonstrates the drug delivery applications of plant based polysaccharides especially in nanotechnology sector. Outstanding features of these polysaccharides attributed to its unique physico-chemical properties. These plants polymer based nanomaterials used or investigated as release retardant in sustained or controlled release drug delivery systems. Nanomaterials of these plant based polysaccharide exhibit high water content, functionality, biocompatibility, tunable size from submicrons to tens of nanometers, large surface area for multivalent bioconjugation, and interior network for the incorporation of therapeutics. These unique properties present great potential for the utilization of polysaccharide-based microgels/nanogels in tissue biomedical implants, engineering, bionanotechnology, and particularly, drug delivery.

Keywords Plant • Nanomaterials • Polysaccharides • Drug delivery • Biomedical • Natural polymer • Nanotechnology • Nanoparticles

4.1 Introduction

Owing to their relative toxicity and stability issues under physiological environment drugs are rarely administered as such since most of them are always formulated into a desirable dosage form with the support of active excipients. Active excipients are those excipients that may mask the toxic or undesirable effect of drug without affecting its significant biological activity. Additionally most of the recent formulations tend to enhance biological activity by increasing its stability profile especially under in vivo environment. According to International Pharmaceutical Excipients Council excipients are those substances, other than the active drug substances of finished dosage form, though some excipients also exert similar or different biological activity then active drug and sometime impart synergistic or cumulative effect

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to the active drug. Objectives of each and every excipients is to either aid the processing of the drug delivery system through its manufacture, protect, bioavailability, support or enhance stability, assist in product identification, or patient acceptability, or enhance any other features of the general safety and efficiency of the drug delivery system throughout storage or use [1]. Therefore excipients plays a major role in deciding the final fate of drug under both in vitro and in vivo environmental conditions. Currently a variety of excipients have been explored as binding, flavoring, suspending, lubricating, gelling, sweetening and bulking agent among others [2]. They also play an important role in preserving the efficiency, safety, and stability of active drug and guarantying that they deliver their assured benefits to the patients. One of the major advantages of excipients is that their utilization at optimal concentration offers enhanced functionality, pharmaceutical manufacturers with cost-savings in drug development and help in drug formulations innovation. Since excipients are the largest components of any pharmaceutical formulation, therefore its essential to determine their stability and toxicological parameters from pre formulation studies. They can be obtained from natural or synthetic origin and in contrast with natural excipients, synthetic excipients are more utilized in pharmaceutical dosage forms [3]. Owing to the exclusive properties and advantages over naturally derived compounds, including a low sensitivity to various ingredients or moisture, resulting in more efficient and effective pharmaceutical products, synthetic and semi-synthetic products are preferred more [3]. Synthetic and semi-synthetics excipients differentiated on the basis of their origin such as pure synthetic organic chemical called as synthetic compound and substance that is naturally derived but has been chemically modified is called as semi-synthetic.

Polymeric materials obtained from lipids, carbohydrates and protein covers a broad class of excipients. Most of them are derived from natural polysaccharides and their derivatives. Polysaccharides of plant origin endow a group of polymers that are widely used in pharmaceutical formulations and play a significant role in evaluating the underlying mechanism and rate of drug release from the dosage form. Currently variety of plant based polysaccharides have been explored as excipients in the formulation of solid, liquid and semisolid dosage forms in which they play distinct functions as film formers, matrix formers or release modifiers, disintegrates, binders, stabilizers, emulsifiers, suspending agents, thickeners or viscosity enhancers and muco adhesives [4, 5]. Additionally plant based natural polymers can also be used in the implants, micro particles, films, nanoparticles, beads, formulation and manufacture of solid monolithic matrix systems, inhalable and injectable systems as well as viscous liquid formulations [5–7]. These plant based polymers are not only considered over synthetic polymers because of its significant features such as biodegradability, biocompatibility, non toxic and low cost and relative abundance compared to their and synthetic counter parts [8, 9], however also as natural resources are renewable and provide constant supply of raw material if cultivated or harvested in a sustainable manner [10]. The most popular plant based natural polymers that are used in pharmacy and other fields are chitosan, ispaghula, acacia, agar, guar gum, carrageenan, gelatin, shellac and gum karaya. These natural polymers are extensively used in pharmaceutical industry as adjuvant, emulsifying agent and adhesive in packaging; and also suitable for cosmetic and pharmaceutical

product development. Moreover various wide ranges of applications in drug delivery have been explored since as polymers, they endow exclusive properties which so far have not been exhibited by any other materials [11]. Natural polymers can be conjugated with small molecular weight proteins, polypeptides, lipids, surfactants, drugs, peptides, metals, nucleic acid, antibody, etc. They can be modified in such a way so that large chains and functional groups can be conjugated with other low and high molecular-weight materials to attain new materials with a variety of physicochemical properties. To overcome their demerits, natural polymers are tailored by chemical modification. Various physico-chemical modification reports are also available on natural gums, mucilages and other polysaccharides suggesting their potential role in pharmaceutical industry especially in drug delivery [12, 13]. Owing to the rising concern towards natural polymeric materials as pharmaceutical excipients, it's very difficult to document all the polymers at one platform, though we tried to cover most of the plant based polymers with its physic-chemical modifications and current applications in pharmaceutical industry.

4.2 Sources of Plant Polymers

Diversity of natural polymers in nature confers variation in their structural and gelling properties. As a matter of fact native polymers show variability and versatility, associated with their complex structures, not found in other classes of polymers. Plant and algal derived polysaccharides are the precursors for the diverse polymers which are widely used in drug delivery industry as advanced therapeutics. From a view of commercial utilization plant derived polymers are at most priority, however more researches are currently enduring on algal polysaccharides because of its complex structure related gelling properties. Moreover mammalian and microbial polysaccharide is another foundation for the polymeric industries because of their unique properties or because they provide a cheaper and superior alternative to other materials derived from plant, animal, or synthetic sources. Throughout the whole literature we found that usage of polysaccharides falls into three distinct areas: food applications, nonfood applications and biological purpose, whereas their growth and evaluation requires considerable investment in time, money, and technology. Many of these native polysaccharides for which potential industrial applications have been claimed have not proved to be of commercial value. Thus latest tools are required for their better study. Further discoveries in polymeric sciences furnish the continuous supply of novel polysaccharide from novel origin which makes a trouble in covering all the polymers under one platform. Combining together, here our attempt addresses the nature's broad class of polysaccharide from diverse origin with their current advancements and contribution in the field of pharmaceutics. Exploration of extensive class of plant based polysaccharides suitable for nanodelivery, chiefly from natural sources with techniques to increase its development in pharmaceutics. Here in this chapter we have covered the following set of objectives to explore the diverse polysaccharides in pharmaceutical sciences.

- To cover the utmost diversity of natural polysaccharides with aim to distinguish their commercial and medicinal utilization according to their structure related gelling properties.
- Broad view of nano applications of these polymers
- Latest equipments and knowledge used in the structural interpretation and gelling properties evaluation of diverse polysaccharides from different foundation.

Natural polysaccharides based polymers guarantee a new class of compounds for the development of a variety of drug delivery systems. They are now distinguished as valuable polymers for their significant pharmaceutical properties. These renewable compounds are extremely advantageous as compared to synthetic polymers in properties like non-toxic, biocompatible and show a number of peculiar physico-chemical properties [14]. Polysaccharides have some common uniqueness which are significant from a view of its applications; they have the ability to form multiple hydrogen bonds implying the local stiffness of the molecules, generally giving them the property of being water-soluble, but they also can be water-insoluble when they form intermolecular hydrogen bonds with each other to give crystals or large, high molecular weight, insoluble crystalline aggregates, granules, or fibers; from this rigidity, they get a high thickener character [15]. Knowledge of solution properties is needed to understand the polysaccharides' behavior in different applications. The main factors affecting the solution properties of polysaccharides are the molecular structures of the polysaccharides themselves, for example, the content of side galactose units and degree of substitution, molar mass, and temperature, pH, and ionic strength circumstances [16].

Polysaccharides are present in all kind of organisms, mammals, plants and microorganisms (Table 4.1). Because of its abundance it's very difficult to furnish absolute classification of polysaccharides. Polysaccharide derived from plants polymers are nowadays of greatest interest. This interest is generated by the features of these natural sources, such as being able to produce biodegradable and biocompatible new products and as value-added materials [16]. Whereas algal galactans like agar, alginate and carrageenan are the major hydrocolloids used as texturing agents for food and non-food applications. Their extraordinary gelling and thickening properties make them more complex then plant polysaccharides [17, 18]. In this context mammalian and microbial polysaccharides also play a great contribution in pharmaceutical field [18–24]. More focusing event in studding the polysaccharides is to establish a relationship between its structural and gelation properties. Various chemical, physical and biochemical tools are now available for their precise chemical and structural characterization.

Recently advance techniques and equipments have provided a more precise view of the interaction between the structural and the gelling characteristics of these complex polysaccharides. The quantitative estimation of all the constituent sugars, moe specifically the acid labile 3,6-anhydrogalactose can be done by methanolysis and reductive acid hydrolysis procedures coupled to different chromatographic separations techniques. This advancement also presents the means of determining sugar linkages, substitutions and sequences using chemical, enzymatic and spectroscopic

Table 4.1 Classification of polysaccharides

Plant polysaccharides	Cellulose and its derivatives, starch (cyclodextrins and amylose) and its derivatives, rosin, inulin, pectin, psyllium and arabinogalactans (larch) Other polysaccharides from different sources like aloe, cereal, psyllium, quince seed and oat brans also play some important role. **Gums and mucilages** Xanthan gum, gellan gum, konjac glucomannan, Xyloglucan, Guar gum (guar beans), Karaya gum (Sterculia gum), Gum tragacanth (Astragalus shrubs), Chicle gum (From Chicle tree), Konjac glucomannan (From Konjac plant), Gum Arabic (Acacia tree), Gum ghatti (sap of Anogeissus tree), Locust bean gum (carub tree), Cashew gum Mastic gum (mastic tree), Tamarind kernel gum, Hakeagibbosa gum, Irvingiagabonensis, Moringaoleifer gum, Kyaha gum, Okra, Grewia, mucilage gum, Mimosa scabrella, Mimosa pudica, Albizia gum, Hupu gum, Lepidium sativum, Gum Copal, Gum Damar, Bhara Gum, Moi gum, Cactus mucilage, Cordia gum, Hakea, Karaya gum, Mucuna gum, Satavari mucilage, Ocimum seed, Mucilage, Leucaena seed gum, Cassia tora, Cashew gum, Asario mucilage, Bavchi mucilage, Abelmoschus mucilage, galactomannans (locust bean, guar, fenugreek and tara gum, hexofuranosides) Gum kondagogu, gum olibanum, Sida acuta gum (SAG), Cashew-nut tree exudate gum, gum from Meryta sinclairii, peach tree gum, angico gum, Laguncularia racemosa, Durian seed gums, Lepidium perfoliatum, Flaxseed gum, Albizia lebbeck gum, seeds of Gleditsia sinensis Lam gum, Mesquite gum (Prosopis spp.), Albizia procera gum, Yanang (Tiliacora triandra) leaves, Mesona Blumes gum, tamarind seed gum, Salvia macrosiphon) seed gum, hsian-tsao leaf gum, flamboyant (Delonix regia) seed gum, Boswellia and Commiphora gum, Angum gum, Gum karaya (Sterculia urens L.), Bael gum
Algal polysaccharides	**Brown algae**: mannitol, Alginates and fucose/fucans/fucoidans, sargassan, Laminaran, Polyuronan, alginic acid **Green algae**: Ulvan Oligo-Ulvans **Red algae**: Agar/Agarose (agarans), carrageenans, hypneans, porphyran, furcellaran, funoran, dulsan, and iridophycan, mannans, crystalline mannas and xylomannans, rhamnanns **Mirco alga**: Spirulan, sacran However certain green algae polysaccharides also play some important role. Cyanobacteria (cyanobacterial polysaccharide) of the genera Aphanocapsa, Cyanothece, Gloeothece, Synechocystis, Phormidium, Anabaena and Nostoc are able to produce sulfated polysaccharides containing uronic acids
Microbial polysaccharides	**Bacterial polysaccharide**: Bacterial cellulose, dextran, bacterial hyaluronic acid, xanthan, emulsan, β-d glucans, curdlan, alignate, gellan and pullulan, Scleroglucan and Schizophyllan. Bacterial Hyaluronic Acid, kefiran, exopolysacharide (EPS). xanthan gum, dextran, welan gum, gellan gum, diutan gum and pullulan. **Fungal polysaccharides** (Chitin, Scleroglucan, Lentinan, Schizophyllan Krestin, galactofurinase) **Yeast polysaccharide**: Zymosan, glucans, glycogen, mannan
Mammalian polysaccharides	Glycosaminoglycans (Hyaluronic acid or hyaluronan, Chondroitin sulphate), gelatin and heparin sulfate. Chitin and chitosan
Others	β 1,3-Glucans derived from a variety of natural sources (such as yeasts, grain, mushroom or seaweed), poly-gamma-glutamate (Aminoacid polymer)

methods. Developments in multi- and low-angle laser-light diffusion detectors coupled to high performance size exclusion chromatography now render the determination of molecular weight and molecular weight distribution of these galactans more accessible. Moreover techniques like NMR, rheology, dissolution techniques, bioadhesion testing methods, DSC, desulfation methods, various carbohydrate determination methods, SEC, freeze-drying, scanning electron microscopy, colorimetry, turbidimetry, X-ray diffraction method, plane polarized microscopy¸ fingerprinting approaches, Chromatographic separations of the fragments by HPLC, HPAEC and/or capillary electrophoresis and mass-spectrometric identification methods using the recently developed ESI-MS-MS and/or MALDITOF-MS technologies. (high performance size exclusion chromatography) coupled to multiple or low angle laser light scattering detectors, various other hydrolysis and chemical modification methods, establish a more clear link between structure and gelation of polysaccharides. From the view of their applications and structural complexicity now a day's polymers from algal sources are getting more magnitude of concern then from plants, mammalian and microbial resources. However here we have targeted certain gelling polysaccharides of natural origin with a objective to study its broad pharmaceutical applications, to testify their effectiveness in curing various human disorders and how current research is employing different tools in studying and improving their native properties [18–32].

Carbohydrate-containing structures are amongst the most complex, heterogeneous, and abundant biomolecules on earth. Diversity of polysaccharides has given germination to modern knowledge to understand its structure related gelling properties. It is essential to classify these compounds to distinguish their role and quality in the drug delivery systems. Throughout our literature survey we comes to conclusion that plant derived polysaccharides has wide applications in pharmaceutics however algal or sulphated polysaccharides gives more advancement to the area of polymeric sciences [5, 33]. Whereas mammalian polysaccharides are considered as non toxic biomolecules having excellent mucoadhesive capacity and many important applications in formulation of bioadhesive drug delivery systems. Besides its mucoadhesive properties, it was found that this biopolymer may enhance the absorption of drugs and proteins via mucosal tissues. Furthermore microbial polysaccharides are more economic and exclusive polymers provide an alternate source to the current polymers exploiting industries.

4.3 Methods of Extractions

4.3.1 Cold Extraction

5 g of dried algal material was dissolved in 250 mL of distilled water and kept in orbital shaking incubator for 12 h at 20–25 °C degree. To obtain polysaccharide fraction the insoluble fraction was removed by centrifugation (15,000 rpm at 4 °C).

The supernatant was separated and treated with ethanol (1:3 v/v). Ethanol precipitated fraction was again dissolved in distilled water and dialyzed. The obtained dialyzed sample was lyophilized weighed (0.38 g) and coded as EC [34].

4.3.2 Hot Extraction [Mild Acidic (EHA), Alkaline (EHB) and Radical Hydrolysis (EHR)]

5 g of dried algal material was extracted with HCl (0.1 M) and maintained at 80 °C with constant mechanical stirring for different periods of time. The acid solublized fraction was separated by centrifugation (15,000 rpm at 4 °C) for 15 min. Similar procedure was again repeated for alkaline hydrolysis using $NaBH_4$ (0.1 M). Both fractions were lyophilized and their yield was denoted as EHA and EHB. For all the procedures the reaction time between sample and hydrolyzing agent was limited to 2 h.

$$\%\,\text{yield of POR} = \frac{\text{Dry weight of Porphyran}\,(\text{g})}{\text{Dry weight of Seaweed}\,(\text{g})} \times 100$$

4.3.3 Radical Hydrolysis (EHR)

Radical hydrolysis was conducted by using ascorbate (0.1 M) and H_2O_2 (0.1 M) at 25 °C for 5 g of dried algal sample and the lyophilized product was denoted as HER [35–37]. The percentage yield was calculated on the basis of following equation:

$$\%\,\text{yield of POR} = \frac{\text{Dry weight of Porphyran}\,(\text{g})}{\text{Dry weight of Seaweed}\,(\text{g})} \times 100$$

4.3.4 Microwave Assisted Extraction (EM)

Domestic Microwave oven (CATA 2R, 140–700 W, Catalyst System, Pune, India) equipped with closed vessel (100 mL), power sensor, temperature sensor and temperature controller was used at conditions specified in the Table 4.1. 5 g of distilled water dissolved algal sample was introduced in to the closed vessel followed by opening of the vessel and cooling in an ice bath shortly to relieve the pressure. Subsequent procedures were similar to those for hot extraction of polysaccharides [29].

4.3.5 Ultrasonic Extraction (EU)

5 g of algal sample was dissolved in distilled water and placed in a 250 mL beaker. The beaker and its contents were placed in to 42 kHz bath (Branson Ultrasonic cleaning bath unit, model 1510 DTH) and extracted under specified conditions (Table 4.1). After this, the beaker was taken out of the sonication bath and subsequent steps were followed as mentioned in Hot extraction for polysaccharides [38].

4.3.6 Enzymatic Hydrolysis (EE)

5 g of algal sample was treated with different percent of weighed amount of *cellulase* in conditions as specified in Table 4.1. After the addition of distilled water pH was adjusted (4.5). Rest procedure was followed in a similar manner as followed in hot extraction method [39].

4.4 Chemical Composition Analysis

Chemical composition of polysaccharides can be determined by these methods. Total sugar content, galactose and 3, 6 anhydrogalactose (AGR) contents were estimated by phenol sulfate [40, 41] resorcinol methods. Furthermore sulfur and protein content were determined by toluidine [42, 43] methods [40–43]. The organic functional groups of the polysaccharides preparations can be identified by using an FTIR spectrophotometer via the KBr 141 pressed-disc method.

4.5 Physical Properties

4.5.1 Determination of Gelling Strength (GS)

5 % polysaccharide solution can be prepared in an autoclave at 100 °C. Gel formation took place in dark place at 25 °C after which the gel was kept at 10 °C overnight in a refrigerator [44]. Strength of the gel was measured at 20 °C using a Model TA-XT2 Texture analyser (Stable Micro System, Surrey, UK).

4.5.2 Determination of Gelling Temperature (GT) and Melting Temperature (MT)

The gelling and melting temperatures were measured according the method described by Craigie and Leigh [45]. For measurement of gelling temperature, 10 mL solution of agar was allowed to cool gradually and a thermometer was

emerged in the sol. The temperature at which the thermometer was fixed to the gel was noted. For melting temperature the gel was heated on a water bath and one iron ball (ca. 1 g of weight) was placed on the surface of the gel. The temperature at which the ball touched the bottom of the tube was noted.

4.5.3 Viscosity Measurement (VS)

Apparent Viscosity of polysaccharide can be measured by Brookfield Viscometer (Synchrolectric Viscometer, Stoughton, MASS 02072). Spindle No. 1 at 60 rpm was used for measuring apparent viscosities of agar samples (5 % in deionized water) at 60 °C.

4.5.4 Molecular Mass Determination (MM)

Owing to structural similarity with many polysaccharides, Agarose of known MW was taken as standard. 5 % polysaccharide solution of all fractions (test samples) and agarose (standard) was prepared in double distilled water. Flow time of the all solutions (test and standard) and solvent (double distilled water) was determined by using Cannon-Ubbeholde viscometer which gives the intrinsic viscosities [η] values of all preparation. Viscosity average MWs were calculated from the intrinsic viscosity using the Mark–Houwink equation for agarose, $[\eta] = 0.07\ M\ 0.72$ where [η] is mL/g [46, 47].

4.6 Physical-Chemical Modification of Plant Based Natural Polymers (PBNPS)

In contrast with synthetic polymers plant based natural polymers have their dominant features that can be physically or chemically modified for improvement in their respective utilization and applications. Owing to the diverse class of natural polymers it's very difficult to cover each and every polymer therefore here in this section we are more emphasizing on starch and cellulose based modification as an ideal tool to endow the strategic platform for other PBNPs. PBNPs can also be modified by grafting or conjugation on either linear or branched backbone or on its active functional groups. This type of tailoring can be achieved by surface modification, polymer-peptide conjugation, polymer-DNA conjugation, polymer-siRNA conjugation, conjugation of polymer-surfactant, polymer-antibody, polymer-gene and polymer-drug. These conjugates can be formulated in to nano or micro forms for their delivery at suitable site.

4.6.1 Chemical Modifications of Plant Based Natural Polymers (PBNPS)

Chemical modification of plant based natural polymer involves the polymer molecules in its native form. Modification is generally achieved through derivatization such as esterification, etherification and oxidation, crosslinking, cationization and grafting. Nevertheless, there has been shortage of new methodologies in chemical modifications since this type of modification endows issues concerning consumers and the environment. Currently polymeric science is adopting combinational treatment using various types of chemical treatments to create new kinds of modifications. In a similar way, chemical methods have been combined with physical modifications such as microwave, radiation and extrusion to produce modified polymer with specific functional properties. Overall merits of these modifications were to reduce the time of modification and encourage production. Owing to the presence of large amount of hydroxyl groups at the surface of PBNPs different chemical modifications have been attempted, including etherification, esterification, oxidation, silylation, polymer grafting, etc. noncovalent Surface modification by adsorbing surfactants and polymer coating has also been reported. Chemical modifications of plant based natural polymers (PBNPs) have been mainly conducted to alter their surface energy characteristics which can further improve compatibility, particularly when employed in conjunction with hydrophobic or nonpolar matrices in nanocomposites. Additionally chemical modifications establish stable negative or positive electrostatic charges on the surface of PBNPs. This introduction of charge provides better dispersion. Conducting this chemical modification or functionalization in a safe mode i.e. only alter the surface characteristics of PBNPs by maintaining the unique morphology. This step may avoid any polymorphic conversion and to preserve the integrity of the crystal. Various polymers especially polysaccharides have been chemically modified such as Kaur et al. [48] reported various surface modifications of starch e.g. microwave radiation with lipase as catalyst [49, 50], hydrophobic reaction of starch and alkenyl ketene dimer [51], esterification of starch nanoparticles with lipase as a catalyst [52], dual modified crosslink-phosphorylated [53], crosslinking coupled with osmotic pressure [54], starch-based hydrogels prepared by UV photopolymerization [55], starch esterified with ferulic acid [56], microwave-assisted synthesis of starch maleate and starch succinates [57, 58], microwave and ultrasound irradiation [59], hydroxypropylation and enzymatic hydrolysis [60], Ozone-oxidised starch [61–63].

4.6.1.1 Noncovalent Surface Chemical Modifications of Plant Based Natural Polymers (PBNPS)

Noncovalent surface chemical modifications of plant based natural polymers (PBNPs) are usually achieved by surface adsorption of surfactants. This was initially studied by Heux et al. [64, 65] who employed surfactant consisting of the

mono- and di-esters of phosphoric acid bearing alkylphenol tails and the obtained surfactant-coated CNs dispersed very well in nonpolar solvents [64]. it was further observed that surfactant molecules formed a thin layer of about 15 Å at the surface of the CNs [66]. Later on various surface modifier (ionic and non-ionic) were used to accelerate the characteristics of whole CNs based formulation [67]. Recently saccharide-based amphiphilic block copolymers were used to induce the surface modification on CNs, which resulted in to the excellent dispersion abilities in nonpolar solvents [68].

4.6.1.2 Tempo-Mediated Oxidation

At present, the more frequently used pre-treatment is TEMPOmediated oxidation. Certainly, the TEMPO-oxidized cellulose nanofibers, confers a complete class of nanocellulose valuable of consideration, in addition to PBNPs and MPBPs. This oxidation based method is the most reliable method for altering the surface modification of natural/raw cellulose, in which functional groups such as carboxylate and aldehyde can be incorporated into solid native cellulose under suitable conditions [69–74]. Additionally in contrast with energy consumption of repeated cycles of a high pressure homogenizer (700–1400 MJ/kg), this oxidation based pre-treatment considerably decline the consumption to values less than 7 MJ/kg [58, 60].

For chemical modification of plant based natural polymers (PBNPs) (2,2,6,6-Tetramethylpiperidine-1-oxyl)-mediated (or TEMPO-mediated) oxidation employed to convert the hydroxylmethyl groups present on their surface to their carboxylic form. Advantage of this reaction is that the oxidation reaction is highly selective for primary hydroxyl groups, thus the whole reaction is "green" and easy to execute. This reaction encompass the application of stable nitroxyl radical, the 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in the presence of NaBr and NaOCl. This TEMPO-Mediated Oxidation was initially explored by De Nooy et al. In his study he observed that only the hydroxymethyl groups of polysaccharides were oxidized, whereas the secondary hydroxyls remained unaffected. The whole method is based on of pre-treatment consisting cellulose fibers oxidation via the addition of NaClO to aqueous cellulose suspensions in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and NaBr (at pH 10–11 at room temperature). During this chemical reaction primary hydroxyl groups (C6) selectively transformed to carboxylate groups by means of the C6 aldehyde groups. Additionally only the NaOH and NaClO are consumed [73]. Owing to the presence of the repulsive forces among the ionized carboxylates (which overpower the hydrogen bonds by holding them together) nanofibrils within the fibers separate from each other [75]. Amount of NaClO supplemented in reaction determines number of carboxylate groups formed on the surface of the MPBPs i.e. more carboxylate groups when more amount of NaClO is added. Similarly this supplementation of NaClO allows the oxidation for extended time [76]. It was reported that enhancing the addition concentration of NaClO (3.8–5.0 mmol/g) increases the carboxylate content from 0.2 to 0.3 mmol/g. Additionally this reaction extends the oxidation time period from

Table 4.2 Effectiveness of TEMPO based oxidation reaction in terms of oxidation efficiency of their pre-treatment

Reaction	Raw material	Oxidation efficiency	Reference
TEMPO based oxidation reaction using NaClO at high concentration	Sulfite pulp	70–95 %	[77]
	Cotton linters	62 %	
	Ramie	85 %	
	Spruce holocellulose	96 %	

40–45 min to 115–130 min. TEMPO based oxidation reaction is applied over various sources such as cotton linters, tunicate, wood pulp, ramie, bacterial cellulose and even spruce holocellulose [74, 77]. These researchers have described the effectiveness of this reaction on the basis of their oxidation efficiency of their pre-treatment [77] (Table 4.2).

One more TEMPO-mediated oxidation based methodology reported by Isogai et al., Isogai et al., and Saito et al. [78–80] based on the same principle apart from pH 7, NaClO instead and NaBr, and replacement of the primary oxidant NaClO with $NaClO_2$. In one review Isogai et al. [78, 79] already discussed the dissimilarity among these two processes. During first process oxidation of C_6-primary hydroxyls of wood cellulose achieved by TEMPO/NaBr/NaClO system at pH 10 and at room temperature, however very little amount of aldehyde groups (<0.08 mmol/g) are present in the oxidized cellulose [78, 79]. On contrary no aldehyde groups is obtained by the TEMPO/NaClO/$NaClO_2$ system at pH 5–7, from oxidized wood cellulose with a higher molecular weight. Moreover concentration of carboxylate was found to be 0.8 mmol/g, and the optimum reaction time and temperature required are higher [78, 79]. Recently TEMPO electro-mediated reaction discovered by Isogai et al. [78, 79] was explored as an alternative method to oxidize the C6-primary hydroxyls of cellulose. Electro-mediated oxidation with TEMPO at pH 10, and 4-acetamido-TEMPO at pH 6.8 in a buffer solution were recently applied to softwood bleached kraft pulp explored as new sustainable method to yield MPBPs. Such MPBPs must be having carboxylate and aldehyde groups on its surface so that and it could well replace the first two systems, however longer oxidation times are required, resulting in to high yield more than 80 % and preserves the main characteristics of TEMPO-oxidized MFC produced from bleached softwood kraft pulp [78, 79]. This procedure of pre-treatment with TEMPO oxidation is followed by mechanical treatment, which can be achieved using a cooking blender or an ultra turax system. To remove the partial fibrillated MPBPs, generally centrifugation is employed separation on a laboratory scale. However now day's sonication is employed inspite of blending in order to separate the TEMPO oxidized pulp and it was observed that the sonication time influences the yield of nanofibrils [75, 81]. TEM characterization confirmed the transformation of 97.5 % of the fiber suspension into MPBPs with a width of 3–5 nm. On contrary Li and Renneckar [82], measured an average thickness value of 1.38 nm and a length of

580 nm with the help of AFM after 30 min of sonication. Various researchers established apparent relationship between sonication time and its significant impact on the nanofibril dimensions. It has been reported that with longer sonication time thickness decreased to 0.74 nm and the length to 260 nm.

It was observed that when this TEMPO-mediated oxidation was employed for oxidation of CNs only half of the accessible hydroxymethyl groups are available to react, whereas the other half is buried within the crystalline particle. Araki et al. [83] demonstrated CNs maintained their initial morphological integrity and formed a homogeneous suspension when dispersed in water after the TEMPOmediated oxidation. This is due to the presence of the newly installed carboxyl groups that imparted negative charges at the CN surface and thus induced electrostatic stabilization. Later on similar observations were reported by Montanari et al. [71]. In his study he has observed that excessive TEMPO-mediated oxidation decreases crystal size which results in to the partial delamination of cellulose chains. Similarly various authors have investigated the degrees of oxidation that can be examined by using specific amounts of the primary oxidizing agent (NaOCl). Such an investigation was based on supramolecular structure, morphology, and crystallographic parameters of the CNs. It was observed that many TEMPO-oxidized or carboxylated natural polymers such as CN suspensions when dispersed in water give display birefringence patterns and do not show flocculation or sedimentation. This occurs due to the polyanionic character carried by the negative charges on the CNs surfaces.

4.6.1.3 Cationization of Plant Based Natural Polymers

During this process positive charges are introduced on the surface of plant based natural polymers (PBNPs) e.g. weak or strong ammonium containing groups, such as epoxypropyltrimethylammonium chloride can be grafted onto the plant based natural polymers (PBNPs) surfaces [84]. This can be achieved by the nucleophilic addition of the alkali-activated cellulose hydroxyl groups to the epoxy moiety of epoxypropyltrimethylammonium chloride. Ultimately aforementioned step resulted in stable aqueous suspensions of PBNPs such as CNs with unexpected thixotropic gelling properties. Shear birefringence was reported in some reports while no liquid crystalline chiral nematic phase separation was observed which may lead to high viscosity of the suspension.

4.6.1.4 Esterification, Silylation and Other Surface Chemical Modifications of Plant Based Natural Polymers

Sassi and Chanzy have reported homogeneous and heterogeneous acetylation of plant based natural polymers such as CNs. In this study they have induced homogeneous and heterogeneous acetylation by using acetic anhydride in acetic acid [85]. After TEM and X-ray diffraction analysis of acetylated samples, only a limited reduction in CN length was observed. This was happened because of limited

reduction in CN length was observed, which was further explained by nonswelling mechanism which only affects the cellulose chains localized at the crystal surface. The partially acetylated molecules instantaneously partition into the acetylating medium as they adequately solublize during homogeneous acetylation whereas the cellulose acetate stay insoluble due to the presence of unreacted cellulose chains in surrounded the crystalline core. In some cases of natural plant based polymers concurrent occurrence of hydrolysis and acetylation has been also reported e.g. as found in the case of cellulose. Application of some prominent simultaneous esterification/hydrolysis based reactions were also explored in the case Fischer esterification of amorphous cellulose chains as a viable one-pot reaction methodology that allows isolation of acetylated CNs in a single-step process [86, 87]. Yuan et al. [88] has recently explored the environmentally friendly CN surface acetylation which involves low reagent consumption and simple-to-apply procedure. Another reaction which is recently employed on cellulose matrix was based on alkenyl succinic anhydride (ASA), development of ASA-CA emulsion, to yield acylated CNs with high hydrophobic features. Highly substituted CN esters were recently developed by Berlioz et al. via highly efficient method (fatty acid chains based on dried CNs via a gas-phase process) for an almost complete surface esterification of CNs proceeded from the surface of the substrate to the crystal core. This method yielded fully reacted (esterified) CN without change in its native morphological features. Reaction of natural plant based polymers with organic fatty acid chlorides [having different lengths of the aliphatic chain (C12 to C18)], was also reported which resulted in high density of C18 fatty acid, advantageous enough for further grafting on such lengthy aliphatic chain (C12 to C18) [89]. Silylated based PBNPs modification was observed in case of cellulose whiskers. This has been resulted from acid hydrolysis of tunicate which have been partially silylated by a series of alkyldimethylchlorosilanes. This reaction yielded a product with the carbon backbone of the alkyl moieties ranging from a short carbon length to longer lengths [90]. Degree of silylation (DOS) plays an important role in deciding solubility of cellulose and its dispersion in solvent e.g. DOS between 0.6 and 1, encourages dispersion in solvents of low polarity leading to stable suspensions with preserved morphological integrity whereas at time when DOS >1 leads to deeper silylation (chains in the core of the crystals became silylated) which can further resulted in to disintegration of the crystals and ultimately the loss of original morphology characteristics. However some highly silylated CN was investigated by Roman and Winter as nanocomposites [91]. Lastly, it has been observed that *N*-octadecyl isocyanate based modification assist in improving the stiffness and ductility of the resultant nanocomposites [92].

4.6.1.5 Carboxymethylation and Acetylation

Carboxymethylation is another chemical pre-treatment which increases the anionic charges in the formation of carboxyl groups on the surface of the MPBPs. In previous work carboxymethylated MPBPs was compared its dimensions with

non-pretreated MPBPs [93] and it was observed that carboxymethylation treatment makes the fibrils highly charged and easier to liberate. Moreover it was observed that net specific energy consumption required after carboxymethylation was 2.2 MWh/t per pass through a microfluidizer, whereas 5.5 MWh/t per pass was required to obtain MPBPs without pre-treatment [94]. Zimmermann's research group developed acetylation process in which grafting of acetyl moieties intend to reduce the hydrophilicity of MPBPs and increase the chemical affinity between MPBPs and a nonpolar solvent. For improving compatibility with the PLA matrix Tingaut et al. [95] developed PLA/MFC biocomposites with acetylated MPBPs. Further they observed that concentration of an acetyl content above 4.5 % encourages significant alteration in the crystalline structure of MPBPs. In this study acetylation was done in the inner crystalline regions of the MPBPs and prevents hornification upon drying. Modification with acetyl groups reduces the chances of hydrogen bonding between MPBPs and therefore facilitates improved dispersibility in an apolar polymeric matrix. It was later discovered that MPBPs especially MFC can be stored in a dry form which allow its possible industrial-scale production.

4.6.1.6 Polymer Grafting of Plant Based Natural Polymers

Two main approaches, specifically, the "grafting-onto" and "grafting-from" has been carried on the surface of plant based natural polymers during polymer grafting. First strategy involve the grafting on to the open ends hydroxyl groups at the PBNPs surface of presynthesized polymer chains by using a coupling agent. In second strategy "grafting-from" *in situ* surface-initiated polymerization (from immobilized initiators on the substrate) has been carried out to form the polymeric chains. First approach was initially utilized by Ljungberg et al. [96]. In his work he has grafted maleated polypropylene onto the surface of tunicate-extracted CNs, which was resulted in to nanocrystals with good compatibility and high adhesion when dispersed in atactic polypropylene. Grafting of amine terminated polymers on the surface of TEMPO-mediated oxidized was investigated by Araki et al. [83] and Vignon et al. [97] Similarly grafting of DNA oligomers on the surface of CNs was studied by Mangalam et al. [98] All of these researchers reported high grafting density that was enough for grafted chains to crystallize at the surface of CNs. Cocrystallization phenomenon was first reported by Cao et al. [99] to yield grafted CNs polymer. This research has further promoted cocrystallizations of the free chains of the respective polymer matrices during CN-based nanocomposite processing. Additionally this phenomenon of cocrystallization significantly enhances the interfacial adhesion by inducing the formation of a co-continuous phase between the matrix and filler, resulted in to the highly improved mechanical strength of the resulting nanocomposites. Second approach known as "grafting from" was first reported by Habibi et al. [100], who has utilized stannous octoate (Sn(Oct)2) as a grafting and polymerization agent to graft polycaprolactone onto the surface of CNs via ring-opening polymerization. Pranger et al. [101] studied *in situ* polymerization of furfuryl alcohol from the surface of cellulose whiskers.

Later on various researchers produced thermoresponsive substrates by the polymerization of vinyl monomers from the surface of CNs [102].

4.6.2 *Procedure for the Development of Microfibrillated Plant Based Polymers (MPBPS) by Physical Modification*

MPBPs is currently fabricated from a number of different natural sources e.g. wood, bleached kraft pulp (starting material for MPBPs production) [73, 76, 94, 103–105], and bleached sulfite pulp [106, 107] (Figs. 4.1 and 4.2). Still various sources are needed to explore to fulfill the demand for such raw materials offering environmental benefits owing to their renewable nature and their low energy consumption in production [108]. Considering cellulose, Eucalyptus sulfite wood pulp, Bleached Luffa cylindrica fibers, Bleached sulfite pulp, Bleached sisal pulp, Sisal fibers (Agave sisalana), Elemental chlorine free bleached hardwood kraft pulp from Birch, Mixture of pine and spruce pulps (*Betula pendula*), Bleached and unbleached kraft hardwood pulps, Softwood sulfite pulp of spruce (*Picea abies*) and white fir (*Abies alba*), Wheat straw (*Triticum sp.*) Refined fibrous wheat straw (Vitacel, Rettenmaier & Sohne GmbH & Co.KG), Refined beech wood (Fagus sylvatica) (Mikro-Technik GmbH & Co. KG), Refined fibrous beech wood pulp (Arbocel, Rettenmaier & Sohne GmbH & Co. KG), Bleached sulfite softwood (Domsjo ECO Bright), Elemental chlorine free bleached hardwood kraft pulp from Birch (*Betula pendula*), Domsjo dissolving plus (Sweden), Softwood dissolving pulp (Domsjo), Wood pulp, Softwood dissolving pulp (Domsjo), Softwood dissolving pulp (Domsjo), Bleached kraft bamboo (*P. pubescens*), Domsjo dissolving plus (Sweden), Bleached sulfite pulp, Sisal fibers (*Agave sisalana*), are the main sources as reported by Lavoine et al. [109].

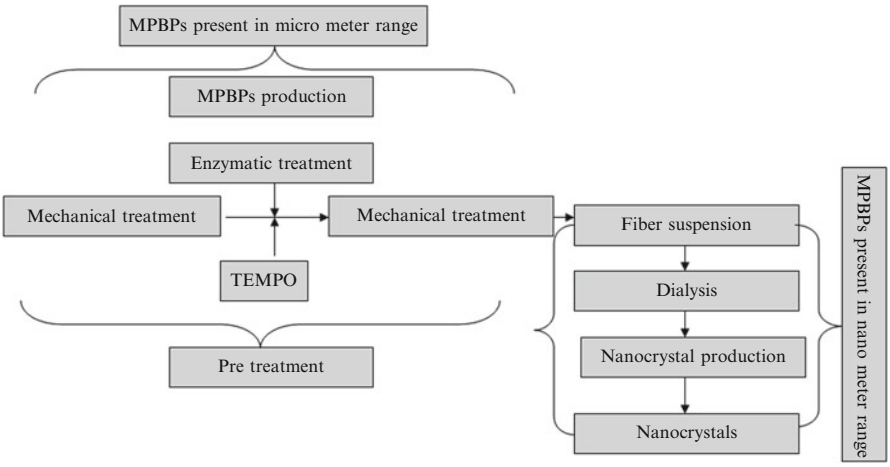

Fig. 4.1 Schematic representation of production of microfibrillated natural polymers

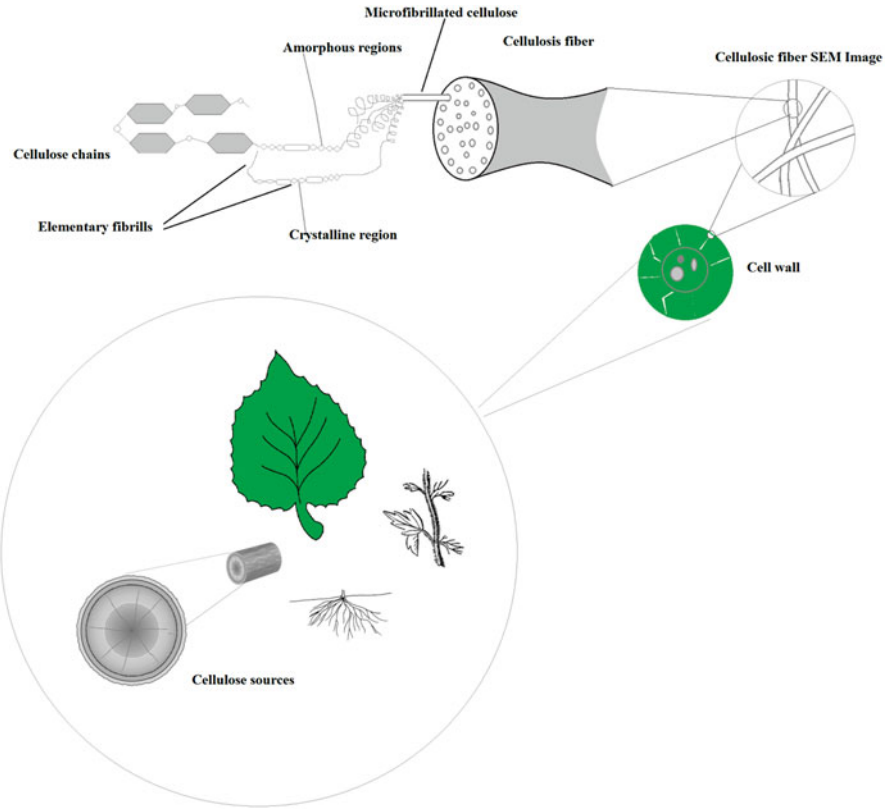

Fig. 4.2 Illustration demonstrating microfibrillated plant based polymers and their arrangement in plants

Irrespective of the source, natural polymers are manufactured from a pulp suspension mainly using a mechanical treatment. There are several types of equipments available to defibrillate the pulp and obtain nanopolymer. Various physical methods have been applied to transform the raw cellulose in micrometer size in to suspension or nano crystal form in nanometer size. Various physical methods that can be applied for this purpose are mentioned below.

4.6.2.1 Mechanical Treatments

Homogenizer and Microfluidizer

With the help of Gaulin homogenizer, Turbak et al. [110], for the first time applied mechanical treatment produce to manufacture all kinds of microfibrillated cellulose [93, 103, 111–115]. During this type of modification slurry of selected natural polymer is forced at elevated pressure and fed via a spring-loaded valve assembly. Fibers

are subjected to a huge pressure dive under elevated shearing forces. This was carried out by allowing the valve to open and close in quick progression. Combined force aggravates high degree of fibrillation of the cellulose fibers [115]. Equipment, Gaulin homogenizer most frequently used the microfluidizer since it makes it possible to obtain more uniformly sized fibers [111]. This equipment function when the masses of wood pulp passes through thin z-shaped chambers under high pressure [116] which results in the formation of very thin cellulose nanofibers. During this mechanical process chambers of different sizes are employed to increase the degree of fibrillation. This equipment used various time supplementation of raw material passage from chamber which consequently increases the number of passes. This factor limits the likely scaling-up of production and consequently creates negative environmental force with high energy consumption.

Grinding Process

Transformation of raw micro natural polymer in to fibrillated polymer can also be achieved by grinding process. There are various equipments used for grinding raw plant based polymer. Using equipment known as grinder, Masukoc was the first researcher to build and sell apparatus. Grinder generates shearing forces that help in breakdown of the cell wall structure. During this process raw material in form of pulp is passed through a static grind stone and a rotating grind stone revolving at about 1500 rpm. Grinder promotes separation of microfibrill by breakdown the cell wall which contains nanofibers in a multilayer structure. This step encourages individualized nanofibers from the pulp when material passes from the grinder after multiple attempts. It has been observed that multiple passes of raw fibers from *Pinus radiate* influence MPBPs morphology. After sequential one to three passes, maximum raw material turned into sub-micron-size and nano-sized fibers, whereas after five passes, most of the fibers became nanosized fibers. No significant changes were observed in the fiber morphology after passing raw material from grinder at higher number thus it was concluded after that five passes through the grinder the fibrillation of pulp fibers was roughly complete. In contrast with homogenization process, this grinding require only few passes to obtain plant based fibrillated natural polymer in micro or nano range. No. of passing usually determine the size or dimension of cellulose fiber. Nevertheless pulp degradation caused by grinding process in terms of reduction in length might affect the strengthening and physical properties of PNMPs [117]. As discussed above its very difficult to determine the length and suitable analysis of related characteristics therefore they cannot be monitored in comprehensive manner. Several authors have attempted to evaluate the chain length which was based on the results obtained from the intrinsic viscosity in cupriethylene diamine. Pohler et al. [118] proven that microfluidizer reduces the chain length more than the grinder. Couple of years before Uetani and Yano [115] used blender (with an ABS-BU motor, Vita Mix, and a CAC90B X-TREME 2 L bottle, WARING) with a well equipped tamper to produce microfibrillated cellulose. This equipment has efficiency to defibrillated different wood fiber suspensions

(0.1–1.5 wt%) at different stirring speeds, from 5000 to 37,000 rpm. However it's difficult to deduce best mechanical treatment since product obtain from this blender is not very homogeneous, even it doesn't acquire the capacity to transform whole plant based raw fibers in to micro fibrils. It was reported that it induces less damage then grinder treatment but still it's difficult to conclude which treatment can known to be the best treatment.

Cryocrushing

One rarely used and the most expensive method which cannot be scale up called as cryocrushing as suggested by Dufresne et al. [119]. He has crushed frozen pulp with liquid nitrogen [120, 121]. Owing supercritical nature of nitrogen, liquid nitrogen enter inside the cell, this penetration cause the crystallization of cell (Ice crystals within the cells are then formed), and eventually mechanical crushing is employed to breakdown the cellular wall and release wall fragments. So far this method is applied over many pulps and other plant material (sugar beet pulp, wheat straw and soy hulls, flax, hemp, and rutabaga fibers and soybean stock) to yield microfibrill polymer with varying nano dimensions [120–122].

Electrospinning

In contrast to all these methods electrospinning methods can be employed to obtain fibrillated PNMPs process of cellulose regeneration. However this process require more fundamental studies are currently dedicated to this method [123–126].

Energy Consumption and New Processes

Above mentioned methods require mechanical treatments with high energy utilization. Energy consumption (70,000 kWh/t) in case of homogenizer estimated was initially estimated by Eriksen et al., whereas energy consumption in case of microfluidizer estimated by Zimmermann et al., reaches up to 8.5 kWh [127, 128]. As discussed above in case of microfluidizer fibrillation depends on the number of times raw material passes through the assembly therefore for 10 L of PBNPs pulp it takes about 15 min to pass through a microfluidizer once and let there are overall four passes during this process then consumed energy can be calculated accordingly (8.5 kW, and its value increased to 14,875 kW with only three passes more). Since the most difficult thing that need further research is variation in mass during each pass (i.e. mass doesn't remain ideal) so for estimating single pass energy each time mass should be calculated. Process become more difficult when pulp solution obtained is less homogenous. Later on various authors' studied the factors (e.g. number of passes, the pressure, and the speed) that influence the rate of formation of microfibrills and films, mainly the nature of material (bleached and unbleached

kraft hardwood pulps) on consumption of energy [129, 130]. These authors' have done the comparative study of the energy consumption and physical properties of MFC produced by different processing methods, namely a homogenizer, a microfluidizer, and a grinder. From this study it was deduced that, in spite of its high energy consumption, homogenizer resulted in MFC with the highest specific surface area and films with the lowest water vapor transmission rate. Furthermore films produced during both process (microfluidizer and a grinder) offered better optical, physical, and water interaction properties. This unique features obtained from these processes suggested that these materials could be created with additional cost-effective approach for packaging purposes. Alternatively exploration of other less energy-consuming disintegration methods also turn into precedence in protecting the industrialization of MPBPs production. Presently combinations of various pre-treatments and mechanical methods have been employed to yield suitable microfibrill. Additionally in order to obtain MFC with low energy consumption or via a faster process, every year new equipment is being studied or developed. Heiskanen, Harlin, Backfolk, and Laitinen [131] has modified the process and tested with extrusion. Later on SUNPAP (2009), Papiertechnische Stiftung (PTS) in Germany, developed commercial process, Cavitron®. Recently novel fractionation devices have been developed to classify different MPBPs qualities [132].

4.6.3 Pre-treatment

Various approaches have been employed in order to obtain fibers that are less stiff and cohesive. These approached help in reducing the energy required for fibrillation. Among these approaches three approaches (avoiding the hydrogen bonds, adding a repulsive charge, reducing the DP or the amorphous link between individual PNMPs) are more preferred during pre-treatment. Protocols that are more favorable according to these considerations are:

4.6.3.1 Enzymatic Pre-treatment

Enzymatic modification has mainly used hydrolyzing enzymes in its modification and one of its products is syrup be it glucose syrup or high fructose corn syrup. With research, there are more enzymes being identified for use in modification of polymer. Combinational treatment is employed by combining enzymatic hydrolysis with mechanical shearing and high pressure homogenization (105 and 170 MPa) to obtain PNMPs in desirable nano range. Paakko et al. [133] conducted the whole process by introducing the enzymatic treatment with endoglucanase between two refining steps. Step is achieved by before passing the pulp slurry through the microfluidizer. Main positive point of enzymatic hydrolysis than acid hydrolysis it is less aggressive and allows selective hydrolysis of the non-crystalline cellulose, which facilitates the mechanical disintegration [133, 134]. Enzyme supplementation

promotes cell wall degradation and prevents the blockage in Z-shaped chamber of microfluidizer [135]. It has been observed that in some cases more specific enzymatic treatment is required e.g. pre-treatment with C-type endoglucanase enzyme studied by Henriksson et al. [135], to treat some disorder in the structure in order to attack the cellulose and attain its conformation that encourage its desirable properties.

After the mechanical treatment with Gaulin homogenizer, these researchers examined non-pretreated PNMPs in contrast with enzyme-pretreated MFC, as well as enzyme-pretreated PNMPs. This pre-treatment with endoglucanase allows the disintegration of cellulosic wood fiber pulp by enhancing its swelling in water, additionally this eco-friendly pretreatment present more favorable structure on the MFC, since it decreases the fiber length and enhances the amount of fine material, in contrast to end product obtained from acid hydrolysis pre-treatment. It was also studied that pretreatment with endoglucanase appeared to be a very promising method for industrial applications and important for first pilot production of PNMPs [134].

4.6.4 Post-treatments

In addition to the pretreatment, post-treatments in combination with pretreatment are progressively carried out in order to increase the features of microfibrillated natural polymer. In contrast with various pre-treatment approaches utilization of post-treatment still remains small. Goal of these two protocols are very distinctive since the primary objective of pre-treatment is to decrease the energy consumption of PNMPs production, while the post-treatment mainly aims to improve the PNMPs or to incorporate new features, from the viewpoint of new probable applications. In order to develop PNMPs films with good barrier properties, Rodionova et al. [136] carried out the acetylation of MFC from kraft pulp. Based on results [136], it was observed that hydroxyl groups replacement by acetyl groups occurs at surface of the PNMPs as well as amorphous regions for long reaction times. Later on it was studied that acetylation is an essential tool for bacterial cellulose to improve the optical properties of nanocomposite films [137]. Nogi et al. [138] studied that acetylation was also used to improve the thermal properties. In order to obtain hydrophobic MFC, Andresen et al. [139] modified the surface of MFC by means of silylation with chlorodimethyl isopropylsilane. It has been seen among some natural polymers that when the silylation conditions were too strong, PNMPs lost its microfibrillar structure and consequently it was concluded that with a degree of surface silylation (between 0.6 and 1), some natural polymer e.g. MFC could be dispersed into an organic solvent without losing its characteristics or properties. Some post-treatments among PNMPs e.g. MFC, encourage nanocomposite applications after their grafting with suitable coupling agents. Most of the post-treatments (Table 4.3) provide MFC with a hydrophobic character in order to improve its compatibility with non-polar polymers and thus play a major role in the elaboration of nanocomposites. However some post-treatments emerge to endow

Table 4.3 Post-treatments among MFC

Coupling agents	Purpose & applications	References
MFC+ titanate	To enhance the adhesion between MFC and epoxy resin matrix	[140]
Titanate + MFC	MFC with enhanced hydrophobic surface property	[106]
MFC oxidation with cerium IV	MFC with a hydrophobic surface layer, nanoscale electronic and optoelectronic devices	[106]
Grafting of hexamethylene diisocyanate.	MFC with more hydrophobic surface layer, nanoscale electronic and optoelectronic devices	[106]
Succinic and maleic acids coupled to the MFC	MFC with a hydrophobic surface layer, nanoscale electronic and optoelectronic devices	[106]
N-octadecyl isocyanate onto MFC	To improve the MFC's compatibility with polycaprolactone, using an in situ solvent exchange	[92]
N-octadecyl isocyanate onto MFC	To improve the MFC's compatibility with polycaprolactone	[141, 142]
Grafting cellulose with octadecyldimethyl (3-trimethoxysilylpropyl) ammonium chloride (ODDMAC)	MFC films with antibacterial property	[143]

microfibrillated cellulose with some new functionality. Owing to the unique features MFC that are attractive in different fields. Primary aim of this work is to reduce the energy consumption of MFC production so as to fulfill with a political agenda and gain market interest and second goal is to improve MFC properties in order to endorse a novel biomaterial with unique characteristics that can compete against the current non-biopolymers.

4.6.5 Dual Modifications

Recommendation for physical modification is sometime preferred over chemical since it can be safely used as a modification process in food products as it does not involve any chemical presence which some causes harm to biological tissue. Various physical methods have been employed for different plant based natural polymer using a combination of chemical and physical or chemical and enzymatical methods (Table 4.4).

Owing to the diverse class of PBNPs, here in this section we have only discussed the starch based physical or chemical modifications. Deetae et al. [53] combined methodology (physical as well as chemical) using crosslinking with sodium trimeta-

Table 4.4 Physical methods reported for starch modifications

Treatments	References
Corona electrical discharges	[144]
Deep freezing	[145, 146]
Instantaneous controlled pressure drop (DIC) process	[147, 148]
Iterated syneresis	[149]
Mechanical activation-with stirring ball mill	[150]
Micronization in vacuum ball mill	[151]
Multiple deep freezing and thawing	[146]
Osmotic-pressure treatment	[152]
Pulsed electric fields treatment	[153]
Superheated starch	[154]
Thermally inhibited treatment (dry heating)	[151, 155, 156]

phosphate and phosphorylation on rice starch, provided modified rice starch with good freeze-thaw stability. Whole procedure was conducted in the presence of osmotic-pressure enhancing salts [53]. These salts caused an increase final viscosity with a sharp decline in breakdown. It has been observed that trigger in osmotic pressure enhances the activity of the crosslinking agent [157]. UV induced polymerization is used to prepare starch-based hydrogels. During this procedure polymerization performed by treatment acryloylated starch with zwitterionic monomer 3-dimethyl (methacryloyloxyethyl) ammonium propane sulfonate (DMAPS). It was observed that this type of polymerization induces a unique salt-tolerant swelling behavior in modified starch [55]. Ou et al. [56] developed modified starch via esterification with ferulic acid which yielded in to starch ferulate. In contrast to native, starch ferulated starch exhibited higher water holding capacity, lower viscosity and much less retrogradation during low storage temperature [56]. Similarly Xing et al. [57] developed efficient method in esterifying starch, microwave-assisted esterification, to produce starch maleate using the dry method had a reaction efficiency of up to 98 %. Jyothi et al. [58] developed efficient method of producing succinylated cassava starch with microwave assistance to decrease the use of chemicals and enhance production. Later on it was observed that microwave and ultrasound irradiation can be employed for the esterification of carboxymethyl cold-water-soluble potato starch with octenylsuccinic anhydride which consequently shorten the esterification time from a few hours to a few minutes. Derivates produced during this process present outstanding emulsifying and surfactant performance properties [59]. For achieving more successful dual modification process, Karim et al. [60] utilized native starch in form of corn and mung bean starch. Native starch was modified by partial enzymatic treatment followed by hydroxypropylation with propylene oxide. Modified starch proved to have significant functional properties in contrast with hydroxypropyl starch prepared with untreated native starch [60].

4.6.6 Ozonation

In addition to above mentioned methods various other methods such as ozonation have been developed with more development in polymeric sciences and its allied fields. This process carries extra oxygen atom therefore act as powerful oxidant and can be applied for process of ozonation. According to previous reports this process enhances the carboxyl and carbonyl contents and concentration keep on increasing with time of exposure to ozone. In contrast hypochlorite oxidation process where large amount of salts are produced this powerful oxidant (ozone) is a clean and leaves no residues behind unlike [61].

Chan et al. [62] observed that there was a difference in the rate of starch oxidation among starches from various sources. An and King [63] found that starch those are produced in the presence of amino acids were more suitable alternatives in contrast to highly chemically oxidized starch and found useful as thickening agents.

As mentioned above physical modifications are safer for processing of food products since it does not involve any chemical presence. Owing to the diversity of plant based polymers, here in this section we have only discuss starch based modification. Some new strategies developed in physical modification for PBNPs are highlighted in Table 4.4. Pukkahuta et al. [152] utilized "Osmotic-pressure treatment" (OPT) in the presence of high salt solutions to obtain a uniform starch suspension and heat distribution. After treatment with the gelatinization temperatures potato-starch treated changed from a B to a A type. A uniform heat distribution is an advantage of this method in contrast to heat-moisture treatment which helps in production of modified starch at large scale. Similarly Szymonska et al. [145] reported the deep freezing and thawing of moistened starch to increase the crystallinity of the granules, however Szymonska et al. [146] also reported that multiple deep freezing and thawing caused an irreversible disruption of the crystalline order. Process of deep freezing and thawing was repeated until the moisture content in the solid phase was less than 20 %. It was observed that most of the starch showed conversion towards B-type X-ray diffraction pattern suggesting a disruption of the crystalline property [149]. Since there is no involvement of any type of chemicals therefore there is no concern for the effect on the environment and safety issues to be addressed. Process called as iterated syneresis was similar to multiple deep freezing and thawing. Other physical modification including instantaneous controlled pressure drop and DIC lead to increase in gelatinization transition temperatures and enzymatic hydrolysis while gelatinization enthalpy decreased after treatment. During this procedure saturated steam at a fixed pressure and predetermined time was injected before it drops towards vacuum to pursue the short pressurization. Other mechanical actions such as collision, friction, impingement, shear, etc can also be employed to modify the crystalline structures and properties of the starch granule. This process is called as mechanical activation or micronization. During this process large particle breakdown to form smaller particles however the tiny particles agglomerate and form large particles, resulting in to the decrease in gelatinization temperature and viscosity of the treated sample [150,

151]. Han et al. [153] reported the pulsed electric field (PEF) technology (non-thermal food preservation method) to study the effect of the treatment on starch. They have observed that starch molecules rearranged and destructed resulting in to the constant decrease in gelatinization properties, viscosity and crystallinity. Nemtanu and Minea [144] also reported that with increase of exposure time to corona electrical discharges, solubility, gel consistency and clarity of starches decreased. Dehydration of starch is done to achieve thermal inhibition which is carried out (a) by dehydrating starch until it becomes anhydrous, (b) treating it to a temperature of hundred degree Celsius for a period of time. The effect of heating can also be increased by an alkaline condition. Chiu et al. [155] suggested that pastes obtained from theses starches had increased resistance to viscosity breakdown and a non-cohesive texture. Ionic gums such as sodium alginate, CMC and xanthan act as crosslinking agents to form graft copolymers through ester formation. Such type of gums induced thermal inhibition [156]. Production of spreadable particle gels with spherulite morphology and creamlike texture upon cooling can be obtained by heating a starch solution to a temperature between 180 and 220° to form superheated starches. It was observed that in contrast with native starch dry superheated starches when mix with cold water gives immediate gel-like texture [154]. Two processes fluidized bed heating and extrusion heating were applied over on amaranth starch-rich fraction. Treatment with fluidized bed heating lead to some loss in crystallinity but granule integrity was preserved whereas extrusion heating caused a high degree of granule disruption and almost complete loss of crystallinity [158].

4.7 Genetic/Biotechnology Modification

Development in genetic engineering allows genetic modification of various natural plant based polymers probably by targeting the enzymes of the biosynthetic pathways of the respective NPBPs. Owing to the diverse classification of PBNPs, here in this section we have only discussed starch which can present the better ideology/platform for the modification of others. Current development in genetic engineering science allows transgene technology to produce genetically modified starches which can prevent the environmentally harmful post-harvest chemical or enzymatic modification [159]. It was observed that activity of these enzymes plays an important role in affecting the functionality, reactivity and applicability in non food and food applications of these modified starches. Traditional plant-breeding techniques or modern biotechnology can be applied to accomplish genetic modification in a more successful way [160]. Some of the key modifications of starches that have been done genetically are mentioned below. For alteration of specific structural motifs in potato starch, repression of starch phosphorylating enzyme R1 was used in the of potato starch [161]. Similarly modification for potato cell lines was achieved by treatment with an *Escherichia coli* glg B encoding a glycogen branching enzyme [162]. Starch obtained after this treatment contains higher amount of short amylopectin chains

with lower content of phosphate which can be used to give hard and adhesive gels. Alike to potato cell line total cassava root biomass can be treated with ADP-glucose pyrophosphorylase for enhancing the total cassava root biomass by 2.6 fold [163]. Modification of starch was also investigated when a full length cDNAs encoding a second starch branching enzyme isoform was isolated and an antisense starch branching enzyme A RNA was produced on transgenic potato plants. During this study complete reduction in starch branching enzyme A was observed. The average chain length of amylopectin was greater in modified starch and it was observed that the composition and structure of the potato starch was completely altered. Additionally higher levels of phosphorous were also reported [164]. Similarly Safford et al. [165] reported the same study by the modification of starch obtained from potato (showed altered amylopectin branch patterns). Verhoeven et al. [166] explored the tree mutagenised grains of the diploid oat (Avena strigosa): mutants lam-1, lam-2 and sga-1. It was investigated that two mutagens (lam-1 and lam-2) lacked in GBSS activity and amylose component thus endow mutations of the waxy type [166].

4.8 Applications of Plant Based Polysaccharides

Plant based polysaccharides are having various established applications in biomedical, tissue engineering, pharmaceutical sciences and other areas. Our current concern is to cover plant based natural polymers and their nanotechnological applications in different field. Table 4.5 covered various modifications of natural polymers and its nanotechnological application in different drug delivery systems.

4.8.1 Cellulose

In 1838 French chemist Anselme Payen discovered cellulose by isolating it from plant matter and determined its chemical formula. Cellulose is a linear unbranched organic polysaccharide with the molecular formula $(C_6H_{10}O_5)n$, consisting of $\beta(1 \rightarrow 4)$ linked D-glucose units from several hundred to over ten thousand (Fig. 4.3). Among all plant cell wall polysaccharides e.g. hemicelluloses, pectin, cellulose forms a vital structural component in higher plants and corresponds to the most abundant organic polymer [359, 360]. Linearly arranged various parallel cellulose molecules form crystalline microfibrils which are mechanically strong and highly resistant to enzymatic attack and are aligned with each other to provide structure to the cell wall. This organic polysaccharide is insoluble in water and indigestible by the human body [361, 362], however digested by herbivores and termites. Fibrous materials (such as wood and cotton) derived cellulose such as wood and cotton, can be mechanically treated (disintegrated) to produce powdered cellulose. This powdered form has been used in the pharmaceutical industry as filler in tablets. Treatment of high quality powdered cellulose with hydrochloric acid produces

Table 4.5 Various modification of plant based natural polysaccharides and its nano applications

Polymer	Modification	Nano applications	Drug delivery applications	References
Cellulose	(a) Sulfonation (b) Oxidation by TEMPO (c) Ester linkages via acid chlorides (d) Cationization via epoxides (e) Ester linkages via acid anhydrides (f) Urethane linkages via isocyanates (g) Silylation (h) SURFUNCELL (Surface functionalisation of cellulose with noble metals NPs through a selective nucleation)	(a) Nanocrystalline cellulose (NCC) (b) Nano-fibrils (c) Nano fibrillar cellulose matrices (d) Au, Ag, Pt, Fe_2O_3, Cds, PbO NPs (e) CA/TiO_2 hybrid membranes (f) Micrometer-long hybrid nanofibers (CdS NPs/bacterial cellulose hybrid nanofibers) (g) Hybrid Fe_3O_4@Amino cellulose NPs (h) Ag–Pd alloy nanoparticles (i) Cellulose whiskers (j) Magnetic NPs (k) pH-sensitive core–shell NPs (l) Cellulose-chitosan NPs (m) Fluorescent CMC NPs (n) Cellulose based semiconductors NCs	(a) Multi-particulate drug delivery of Aphidicolin nanosuspension (b) Transversal drug delivery of primaquine cellulose based niosomes (c) Various cellulose based formulations: PQ/- Eudragit® RL 100-, ethyl cellulose polymers with various penetration enhancers, PQ/ethyl cellulose polymer mixed with Mygliol® 840 plus the antioxidant alpha-tocopherol)	[167–187]
Xyloglucan	(a) Degalatosylation (b) β-galactosidase degradation (c) Synthesizing thiolated xyloglucan (TXG)	(a) pH dependent xylogucan nano aggregates (b) Self-assembled polystyrene/xyloglucan nanospheres	Xyloglucan mucoadhesive polymer is suitable for anti-protozoal and antimicrobial drug delivery	[188–195]
Galactomannan	Enzymic oxidation on the C-6 of the galactose side units (a) Oxidation (TEMPO or TEMPO-NaBr-NaClO system) (a) Etherification, (b) Esterification, (c) hydroxypropylation, (d) carboxymethylation	(a) Galactomannan and chitosan Nps (b) Gold Nps (c) Guar gum Nps (Cationic, carboxymethyl, hydroxylpropyl, and carboxymethylhydroxypropyl galactomannans)	Lichen galactomannan and its vanadyl (IV) complex on peritoneal macrophages and leishmanicidal activity.	[196–204]

(continued)

Table 4.5 (continued)

Polymer	Modification	Nano applications	Drug delivery applications	References
konjac glucomannan KGM	(e) Phosphorylated (f) glucomannan (g) By alkali and sodium (h) carboxymethylcellulose (enzymatic, alkali and acid hydrolysis) (i) Hydrogen bonds formation (j) Number of junction zones Length of connecting chains (k) Deacetylation process	(a) Mannose receptors targeted GM Nps (b) Galactomannan and chitosan (protein particular carrier) (KGM, KGM-KOH, KGM-CMC and KGM-CMC-KOH) (c) Conjugate with kappa carrageenan, acetan (xylinan), gellan gum, alginate and chitosan		[205–208]
Rosin	Polymerized rosin (PR)	Rosin NPs(hydrocortisone)	Rosin transparent wax preparation	[209–212]
Cyclodextrin	(a) Aqueous organometallic catalysis in aqueous media (hydrogenation, hydroformylation, oxidation, reduction and carbon-carbon coupling reactions) (b) α-cyclodextrin-dodeca (2, 3) benzoate (c) hexakis (6-amino-6-deoxy)-α-cyclodextrin hexahydrochloride (d) hexakis (6-amino-6-deoxy)-dodeca (2, 3)-*O*-methyl-α-cyclodextrin hexahydrochloride (e) hexa (6)-*O*-methyl-α-cyclodextrin (f) heptakis (6-azido-6-deoxy)-β-CD-tetradeca (2, 3)acetate	(a) Meglumine antimoniate-beta-cyclodextrin conjugates (b) Paclitaxel loaded Nonsurfactant Cyclodextrin Nanoparticles (c) Enhanced antiviral activity of Acyclovir loaded into β- cyclodextrin -poly(4-acryloylmorpholine) conjugate nanoparticles (d) aminated β-cyclodextrin silver nanoparticles (e) cyclodextrin–poly(anhydride) nanoparticles (f) β-cyclodextrin-modified TiO2 nanoparticles (f) Tamoxifen citrate loaded amphiphilic β-cyclodextrin nanoparticles (g) Camptothecin loaded amphiphilic β-cyclodextrin nanoparticles (h) Cyclodextrin-covered gold nanoparticles	(a) Oral delivery of meglumine antimoniate-beta-cyclodextrin complex (b) Beta-cyclodextrin as an absorption enhancer of the water-soluble drug meglumine antimoniate (c) Meglumine antimoniate-beta-cyclodextrin conjugates	[213–233]

Starch	Microwave radiation with lipase as catalyst a) Hydrophobic reaction of starch and alkenyl ketene dimer b) Esterification of starch nanoparticles with lipase as a catalyst c) Dual modified crosslink-phosphorylated d) Crosslinking coupled with osmotic pressure e) Starch-based hydrogels prepared by UV photopolymerization f) Starch esterified with ferulic acid g) Microwave-assisted synthesis of starch maleate and starch succinates h) Microwave and ultrasound irradiation i) Hydroxypropylation and enzymatic hydrolysis j) Ozone-oxidised starch	(a) Starch-Stabilized Silver Nanoparticles (b) Hydroxyl propyl starch NPs (c) starch-coated iron oxide nanoparticles (d) Nasal starch insulin NPs starch capped water soluble copper (e) idarubicin propylated starch NPs (f) supramagnetic carboxymethyl starch NPs (g) amylomaize coenzyme Q10 NPs	Primaquine-Conjugated Gum Arabic Microspheres oxidized starch imine derivatives	[52, 234–240]
Xanthan gum	α-Galactosidase enzyme treatment Modified with formaldehyde to improve the dissolution rate.	Starch–xanthan gum Chitosan/xanthan Gum/montmorillonite nanocomposites Konjac glucomannan/xanthan gum	Amphotericin B-Gum Arabic Conjugates To improve the bioavailability of Berbrine, antiprotozoal drug Colon targeted metanidazole by xanthan gum	[241–249]
Guar gum	Silanization of guar gum (trimethylsilyl chloride) derivatization, grafting and network formation Carboxymethylation	Polyacrylamide/guar gum graft copolymer silver nanoparticles Tamoxifen loaded Guar gum Acrylic acid grafted guargum–nanosilica	Guar gun for Acyclovir delivery Colon targeted metanidazole by guar gum	[201, 241, 250–261]

(continued)

Table 4.5 (continued)

Polymer	Modification	Nano applications	Drug delivery applications	References
Arabinogalactan	With 5-amino salicyclic acid with isonicotinic acid hydrazide	gold nanocomposites (Au, Ag, Pd, and Pt protected by natural polymer arabinogalactan) Core-shell colloidal structure of nanobiocomposites of gold nanoparticles	Efficacious treatment of experimental leishmaniasis with amphotericin B-arabinogalactan water-soluble derivatives. Deaxtran and arabinogalactan conjugates	[241, 262–294]
Inulin	Tosylated and azidated inulins O-(aminoethyl)inulin β-hydroxyalkyl ethers of inulin inulin with amidoxime groups and coordination with copper(II) ions poly(acrylic acid) grafted inulin carboxy methylation of inulin Modified inulin 2 6 using tetramethylsilane (TMS)	Hydroxyapatite Nps (carboxymethyl inulin derivative) Inulin multi-methacrylate (IMMA) Nps Inulin PEG-ylated Nps		[295–309]
Locust beam	β-mannanase, β-mannosidase and α-galactosidase cleavage carboxyl, hydroxyl, and phosphate derivatives of these polymers	Locust bean based polymer-lipid NPs		[310–314]
Gum tragacanth	Using epichlorhydrine. Effect of gamma irradiation Lactose addition Mechanical degradation (microfluidization)	Fabricated silver nanoparticles	Binding agent in antiprotozaol drug delivery	[272–277, 279, 280]

Gum Arabic	Methylation β-D-mannanase degradation acetylation Addition of monovalent metal	Nanoparticles with affinity ligands specific for antibodies Magnetic nanoparticles with oleylamine Maltose and gum arabic hybrid gold nanoparticles Silver nanoparticles in gum arabic based semi-IPN hydrogen	Amphotericin B-gum arabic conjugates Self-gelling primaquine-gum arabic conjugate for primaquine	[241, 281, 282, 284–289, 291, 294, 315, 316]
Gum khatti	Methylation Acylation deionized water treatment Microwave assisted synthesis of polyacrylamide grafted gum ghatt	Size-controlled silver nanoparticles Insulin nanoparticles using chitosan and Arabic gum Noble metal nanoparticles Beta-lactoglobulin-polysaccharide nanoparticles	Trichostatin as an antiprotozoal agent	[317–322]
Pectin	Pectins except glycine Methyl ester (glycylglycinemodified pectin) Deesterified by base, plant or fungal pectin esterase or esterified inacid methanol Arabinase, pectin esterase and pectin acetyl esterase degradation UV irradiation Heat inactivated pectin methylesterase and NaCl Endo-arabinanase and α-L-arabinofuranosidase Modification in their degrees of methylation and acetylationCalcium binding efficacy modification Citrus pecin (potassium pectate), were modified with a low amount of UV-absorbing substituents Protease, arabinanase/galactanase mixture, polygalacturonase structural modifications	Thiolated pectin nanoparticles pectin-based nanoparticles for poorly soluble drugs β-lactoglobulin–pectin nps pectin–iron oxide magnetic nanocomposite Formation of nano-hydroxyapatite crystal in situ in chitosan–pectin polyelectrolyte complex network	Metronidazole loaded pectin microspheres Nystatin, clotrimazole, amphotericin B, miconazole, ketoconazole or griseofulvin oral pectin based delivery Zn/pectin beads with a eudragit coating	[323–341]

(continued)

Table 4.5 (continued)

Polymer	Modification	Nano applications	Drug delivery applications	References
Gellan (ion activated gelling polymer)	Methacrylated Gellan Gum esterified Gellan Gum Gellan gum grafted cinnamate photo crosslinkable polymer Fermentation mediated esterification Ionotropic gelation of gellan with trivalent Al+3 ions and covalent cross-linking with glutaraldehyde (GA) for Al+3/gellanbeads Peptide- modification of gellan gum Gellan gum films with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide cross-linker Gellan gum and egg albumin preparation Microwave assisted synthesis of acrylamide grafted gellan Monovalent cation salts addition for Commercial gellan preparation TEMPO oxidation Deacylation of gellan Gellan forms coupled networks with konjac glucomannan and tamarind xyloglucan, Phase-separated networks with kappa carrageenan and calcium alginate Interpenetrating networks with agarose and gelling maltodextrin Complex coacervates with gelatin under acidic conditions	Gellan gel beads containing magnetic nanoparticle Gellan gum blended PEI nanocomposites	Swellable gellan gum for acyclovir deliver Gellan gum for antiprotozaol drug delivery Chitosan and gelln gum based delivery of clindamycin In situ gellan gum gel for secnidazole delivery	[342–358]

(2,2,6,6-Tetramethylpiperidine-1-oxyl)-mediated (orTEMPO-mediated)

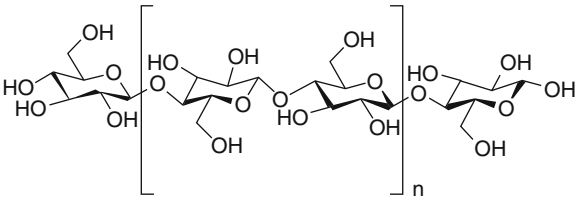

Fig. 4.3 Chemical structure of a powdered cellulose (n ≈ 500) or microcrystalline cellulose (n ≈ 220)

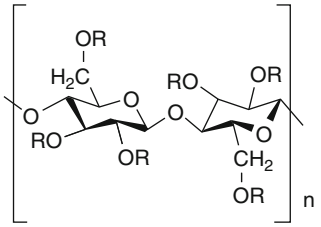

Fig. 4.4 Chemical structure of hydroxypropylmethylcellulose

Where R is H, CH_3 or $[CH_3CH(OH)CH_2]$.

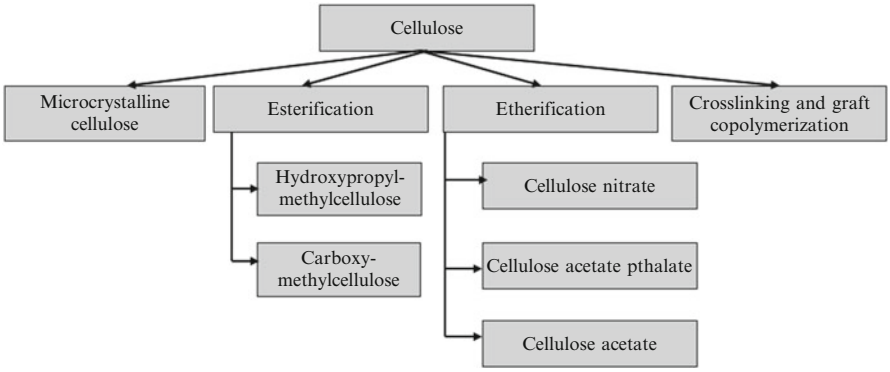

Fig. 4.5 Derivatization and modification of cellulose

microcrystalline cellulose. Microcrystalline cellulose is preferred over powdered cellulose because it is more free-flowing containing non-fibrous particles and therefore used in the pharmaceutical industry as a diluent/binder in tablets for both the granulation and direct compression processes [363]. Derivatization of cellulose can be achieved by replacing/modifying open hydroxyl moieties on the D-glucopyranose units of the cellulose polymer to give a variety of derivatives (Fig. 4.5). This process involves various physical/chemical modification which are fixed according to post and pre treatment procedures during which chief chemical reactions such as etherification, esterification, cross-linking or graft copolymerization are conducted. Esterification results in derivatives which include cellulose nitrate, cellulose acetate and cellulose acetate phthalate whereas etherification yields derivatives such as

hydroxyl-propyl-methylcellulose and carboxyl-methyl-cellulose. These all chemical products have outstanding application in membrane controlled release systems or monolithic matrix systems such as film or enteric coating and the use of semi-permeable membranes in osmotic pump delivery systems. Partly O-methylated and O-(2-hydroxypropylated) cellulose ether derivative known as hydroxypropylmethylcellulose has been extensively studied as an excipient in controlled release drug delivery systems due to its gel forming ability. These derivatives are having wide use and applications in monolithic matrix systems. Various reports and investigations have proven their potential to sustain the release of medicaments and most of these derivatives have been employed for this purpose [364].

4.8.2 Hemicellulose

A hemicellulose is a heteropolymer (matrix polysaccharides), such as arabinoxylans, consisting xyloglycans, xylans, mannans and glucomannans, and β-(1 → 3, 1 → 4)-glucans (Fig. 4.4) [365].

4.8.2.1 Arabinoxylans

These polysaccharides are bound to the surface of cellulose microfibrils which themselves do not form micro fibrils can be extracted from the plant cell wall with the aid of strong alkali. In contrast with cellulose (crystalline, unbranched strong, and resistant to hydrolysis), hemicellulose has a random, amorphous structure with little strength. Unlike cellulose, hemicelluloses have β-(1 → 4)-linked backbones with an equatorial configuration, consists of shorter chains—500–3000 sugar units. In addition, hemicellulose is a branched polymer, while cellulose is unbranched. Though the xyloglycans have alike backbone as cellulose, they contain xylose branches on 3 out of every 4 glucose monomers, while the β-1,4-linked D-xylan backbone of arabinoxylan contains arabinose branches [366].

4.8.2.2 Glucomannans

Glucomannan is mainly a straight-chain hydrocolloidal polysaccharide of the mannan family, consisting of β-1,4 linked D-mannose and D-glucose monomers (with acetyl side branches on some of the backbone units), with about 8 % branching through β-(1 → 6)-glucosyl linkages. The component sugars are β-(1 → 4)-linked D-mannose and D-glucose in a ratio of 1.6:1, but the mannose:glucose ratio may differ depending on the source [367]. The acetyl groups contribute to its solubility and swelling capacity of the glucomannans and enhance the solubility of the glucomannans by supporting glucomannans in making a soluble natural polysaccharide with the highest viscosity and water-holding capacity. It is diversely

present very in nature and specifically derived from tubers, softwoods, roots and plant bulbs. Glucomannan is called as konjac Glucomannan as it is the most commonly used type of Glucomannan which is extracted from the tubers of *Amorphophallus konjac* (Ulmaceae) and act as a potential excipient in controlled release drug delivery devices in combination with other polymers or by modifying its chemical structure. As mentioned, it is a very promising polysaccharide for incorporation into drug delivery systems. According to previous investigation konjacglucomannan and xanthan in combination efficiently slow down drug release by stabilization of the gel phase of the tablets. Stabilization is achieved by a network of intermolecular hydrogen bonds between the two polymers [368].

4.8.3 Starches

Starch or amylum (Fig. 4.6) is a storage and structural polysaccharide consisting of a large number of glucose units joined together by glycosidic bonds, chiefly present in plants as energy source. Various sources of starches have been used for pharmaceutical purpose such as maize (*Zea mays*), rice (*Oryza sativa)*, wheat (*Triticum aestivum*), and potato (S*olanum tuberosum*) [369]. Generally starch present in two forms modified and native starch. Starch whether in the native or modified form has been used as one of the key pharmaceutical excipients in pharmaceutical tablet and capsule formulations. Modified Starch is evaluated as pregelatinized starch product in directly compressible controlled-release matrix systems which can be prepared by enzymatic degradation of potato starch followed by precipitation (retrogradation), filtration and washing with ethanol whereas native starch may not be suitable in controlled release drug delivery systems due to substantial swelling and rapid enzymatic degradation resulting in too fast release of

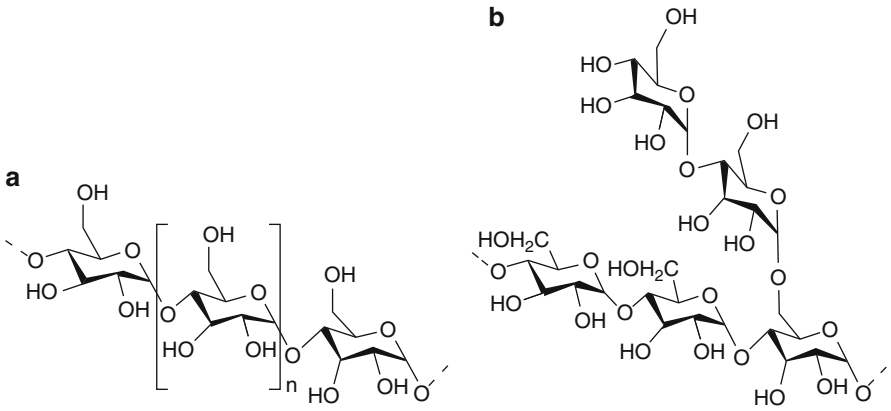

Fig. 4.6 Chemical structure of starch, with (**a**) amylose and (**b**) amylopectin

many drugs. Owing to this derivatives of native starch that are more resistant to enzymatic degradation as well as crosslinking and formation of co-polymers. Moreover most of them serve various functions such as binder, aiding drug delivery, bulking or disintegrant. Currently starch based micro-capsulated delivery systems can be used to deliver proteins or peptidic drugs orally [369]. Recently starch was modified using interfacial cross-linking agent, terephthaloyl chloride, to form starch/bovine serum albumin mixed walled microcapsules. During this procedure native or amino-protected aprotinin was loaded in microcapsules by supplementing protease inhibitors in the aqueous phase. This procedure was performed with the help of cross linking agent. Modified starch in form of microcapsules showed protective effect for bovine serum albumin. It was observed that acetylation of starch significantly reduces its swelling and enzymatic degradation [370]. According to previous findings, acetylation of potato starch considerably delay drug release compared to that of natural potato starch film. During the investigation on Amylose-rich maize starch (Hylon VII™) for tablet film coating it was observed that the temperature of the coating pan did not influence the roughness of the coated tablet at low spray rates, whereas at high spray rates increases the temperatures, resulted in to the smooth films. This was resulted in to the rapid dissolution rate Hylon VII™ coated tablets in an acid medium (releasing 75 % of the drug). Various other reports on the amylose and native starches as film forming agent were explored [371–375]. In another work ethyl-cellulose was employed with amylase in combination to generate aqueous and non-aqueous based coatings for colon drug delivery has been reported [376].

4.8.4 Pectin

Pectin (Fig. 4.7) is the purified non-starch, linear polysaccharides extracted from the plant cell walls especially by acid hydrolysis from the inner portion of the rind of citrus peels i.e. *Citrus Simon* or *Citrus Aurantium*, (Rutaceae). This water soluble linear galacturonic acid polysaccharide mainly composed of α-1,4-linked Dgalacturonic acid residues interrupted by 1,2-linked L-rhamnose residues with a few hundred to about one thousand building blocks per molecule, equivalent to an average molecular weight of about 50,000 to about 1,80,000 [377]. since galacturonic acid polysaccharides contains different neutral sugars such as arabinose, rhamnose, xylose, glucose, and galactose, therefore composition of pectin varies according to the botanical source, e.g. pectin from citrus contains lower amount of neutral sugars and has a lesser molecular size in comparison to the pectin obtained from apples [378, 379]. Owing to its water solubility, this polysaccharide is not able to protect its drug load efficiently for the period of its passage from the stomach and small intestine [377]. Against this pH variable *in vivo* environment, drug core should be protected with significant thickness or layers of polymer, thus the whole center of attention was inclined to the progress of low water soluble pectin derivatives which get degraded by the colonic micro flora. Derivatization or modification of pectin reduces their solubility e.g. calcium derivatives of pectin were found to reduce the

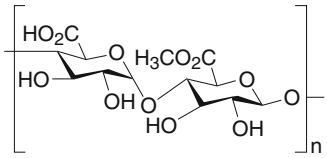

Fig. 4.7 Chemical structure of pectin

solubility by forming an eggbox configuration. Ethyl-cellulose was also examined as a coating material for colon-specific drug delivery. This combination was developed to overcome the drawback of high solubility of pectin and provide colon specific degradation properties of pectin with the protective properties of the water insoluble ethyl cellulose [380]. Pectin based hydrogels widely investigated used as controlled-release matrix tablets. Pectin in form of high-methoxy-pectin showed their potential in controlled-release matrix formulations and the drug release from compressed pectin based matrix tablets can be modified by altering the concentration and nature of pectin in the matrix tablets. It was observed pectinic acid (degree of methoxylation 4 %) with retarded solubility was suitable as an excipient for pelletisation by extrusion/spheronisation. According to previous work presence of 20 % pectinic acid in formulations is suitable for the formation of approximately all spherical beads which were mechanically stable and showed drug release at physiological pH 6.8 [381]. Pectin based micro particulate polymeric delivery systems have been investigated as a possible approach to improve the low bioavailability characteristics [382]. Spray dried pectin microspheres of piroxicam showed a considerable improvement of piroxicam bioavailability when compared with marketed piroxicameye drops. Modification of pectin such as amidated pectin was investigated to mask the bitter taste of chloroquine when orally administered [383]. Study showed potential applications of pectin-chloroquine patch matrix for the transdermal delivery of chloroquine. Similarly calcium pectinate nanoparticles were prepared to deliver insulin in colon [384]. Additionally pectin gel formulations has wide application in cosmetics for the prolonged release of cosmetic compounds such as citronellal responsible for the fragrance and proved as promising materials for controlled fragrance release [385].

4.8.5 Inulin

Inulin (Fig. 4.8) is a naturally occurring storage polysaccharide obtained from Dehlia, *Inula Helenium* (Compositae), *Saussurea lappa* (Compositae) or chicory roots, Dendelion, *Taraxacum officinale* (Compositae). Burdock root, *Cichonium intybus* (Compositae) [386]. This polysaccharide contains mixture of oligomers and belongs to the group of gluco-fructans, widely present in plants such as artichoke, garlic, onion, and chicory. As far as structural features are concerned inulin molecules contain from two to more than 60 fructose molecules linked by β-2,1-bonds. According to previous investigation inulin is not digested properly in the upper gastrointestinal tract, however this polysaccharide hydrolyzed by colonic

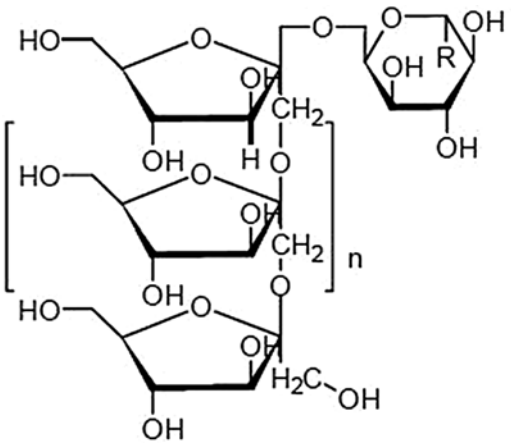

Fig. 4.8 Chemical structure of inulin

microflora [387, 388]. For delivering drug or any other therapeutic substance in gastric and intestinal fluids, inulin with a high degree of polymerization was used in combination with Eudragit® RS (that could withstand break down by the gastric and intestinal fluids) to prepare biodegradable colon-specific films [387]. In an alike study it was reported that using the combination of two different grades of Eudragit® RS and Eudragit® RL when mixed with inulin showed better swelling and permeation properties in colonic medium rather than other gastrointestinal media [389]. Earlier investigation on inulin based hydrogels for colon-specific drug delivery systems proven that methylated inulin hydrogels exhibit comparatively high rate of water uptake and anomalous dynamic swelling behavior pH sensitive hydrogel by UV irradiation were investigated by derivatization of inulin with methacrylic anhydride and succinic anhydride [388]. This pH sensitive hydrogel system exhibit exhibited a reduced swelling and low chemical degradation in acidic medium. However it shows good swelling and degradation properties in simulated intestinal fluid especially in the presence of its specific enzyme called inulinase [295].

4.8.6 Rosin

Rosin (Fig. 4.9) also called colophony or Greek pitch (*Pix græca*), is a low molecular weight (400 Da) natural polymer obtained from the oleoresin of various *Pinus sp.* by heating fresh liquid resin to vaporize the volatile liquid terpene components. It contains abietic and pimaric acids and exhibit excellent film-forming properties. According to recent report, Rosin and its derivatives investigated as potential biopolymer for various pharmaceutical applications such as film-forming and coating properties, matrix materials in the tablets for sustained and controlled release and microencapsulation [390]. Recent report explored its improved drug release properties matrix tablets and pellets [391] when its synthesized by a reaction with polyethylene glycol 200 and maleic anhydride. This work lead to the

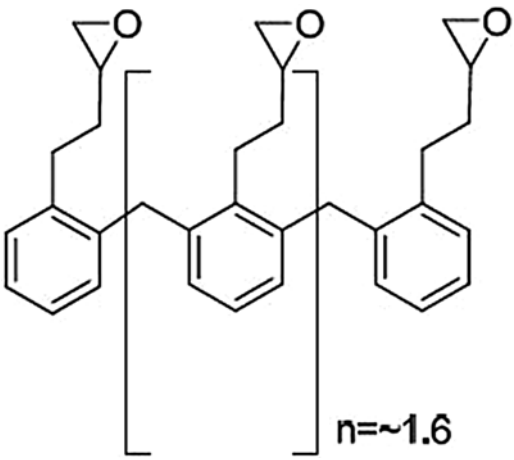

Fig. 4.9 Structure of Rosin

development of potential derivatives which can be suitable for sustain release of the tablets. Similarly high polymerization of rosin films showed excellent potential as coating materials for the development of sustained release dosage forms [392]. Various investigations on rosin derivatives (glycerol ester of maleic rosin) and their film forming and coating properties established their potential as potential coating materials for pharmaceutical products as well as in sustained release drug delivery systems. It was observed that rosin concentration has profound effect on the release of the hydrocortisone from rosin based nanoparticles which has demonstrated its potential as effective nanoparticulate drug delivery systems [209].

4.8.7 Plant Based Gums

Plant has its own established mechanism to secrete viscous, sticky fluid exudate gums in order to seal-off infected sections of the plant and prevent loss of moisture due to physical injury or fungal attack [393]. These exudates have their own unique property to convert in to brittle, translucent, glassy, hard mass. This property recently explored as a potential tool in retaining various drugs and other therapeutic candidates for their sustained, controlled or specified release from the desired dosage forms. There are various types of gums (mentioned below) secreted by plants currently investigated for their pharmaceutical applications.

4.8.7.1 Gum Arabic

Acacia gum or gum Arabic is the dried gummy exudation obtained from the *Acacia arabica* (Leguminosae) and other related African species of acacia [241, 394]. The gum has been recognized as a branched molecule of 1, 3-linked β-D-galactopyranosyl

units. It is an acidic polysaccharide containing D-galactose, L-arabinose, L-rhamnose, and D-glucuronic acid and is mainly used in oral and topical pharmaceutical formulations as a suspending and emulsifying agent. Previous study has explored gum Arabic as a matrix microencapsulating agent for the enzyme, endoglucanase [394], shown the slow release endoglucanase from the formulation. Gum Arabic was used as an osmotic suspending and expanding agent to prepare a monolithic osmotic tablet system. The optimum system delivered the water-insoluble drug, naproxen, at a rate of approximately zero order for up to 12 h at a pH of 6.8.58 Sustained release of ferrous sulphate was achieved for 7 h by preparing gum Arabic pellets. An increase in the amount of gum Arabic in the pellets decreased the rate of release.

4.8.7.2 Tragacanth Gum

This gum is obtained from the branches of *Astragalus gummifer* (Leguminosae). 22 and anionic carbohydrate which consists of two major fractions: tragacanthin (water-soluble) and bassorin (water-swellable) [395]. Tragacanthic acid is composed of D-galacturonic acid, D-xylose, L-fructose, D-galactose, and other sugars. It's very difficult to understand the clear physical or chemical relationship between tragacanthin and bassorin since both fractions can be easily separated. As far as the chemical nature and composition are concerned bassorin and tragacanthin differ mainly in terms of their uronic acid and methoxyl content [396]. It has been demonstrated that bassorin is a complex structure of polymethoxylated acids and on demethoxylation, perhaps yields tragacanthin [397]. Tragacanth when employed as the carrier in the formulation of 1- and 3-layer matrices produced suitable release prolongation either alone or in combination with other polymers. It has been suggested that supplementation of tragacanth in aqueous media results in the improvement of rheological behavior at very low concentration, thus considered as potential as a suspending agent, stabilizer, and emulsifier [398]. Only few reports have been explored on the functional properties of gum tragacanth and its application in various fields. Recent investigation has demonstrated the flow behavior of Iranian gum tragacanth at different concentration dispersions, showed that all of the gum dispersions had shear-thinning natures and exhibit significant physicochemical properties [399].

4.8.7.3 Mucilage Gums

Recently various mucilage gums have been explored from seed by different extraction procedures such as guar gum from the ground endosperms or seeds of the plant *Cyamopsistetragonolobus* (Fam. Leguminosae) and locust bean gum from the endosperms of the hard seeds of the locust bean tree (Carob tree), *Ceratoniasiliqua* (Fam. Caesalpiniaceae) [400]. These polysaccharides have been investigated for their potential role in drug delivery and other pharmaceutical applications.

4.8.7.4 Locust Bean Gum

Locust bean gum (Fig. 4.10) or carob gum, irregularly shaped molecule with branched β-1, 4-D-galactomannan units, derived from the seeds of the carob, *Ceratoniasiliqua* Linn (Fam. Caesalpiniaceae). For achieving full solubility with complete hydration and highest viscosity this neutral charged polymer requires heat. This feature encourages its coating strength and imparts protection to several drug candidates against several degradation factors *in vivo*. Colon-specific drug delivery systems based on polysaccharides using locust bean gum and chitosan was developed. It was observed that when these coating materials was applied over core tablet it endow better shielding affect by protecting the drug from being released in the physiological environment of stomach and small intestine. Additionally it also provides protection against colonic bacterial enzymatic actions with resultant drug release in the colon.

4.8.7.5 Guar Gum

Guar gum (Fig. 4.11), high molecular weight hydrocolloidal polysaccharide consist of linear chain of β-D-mannopyranosyl units linked (1 → 4) with single member α-D-galacto-pyranosyl units occurring as side branches. This Cyamposistetragonolobus endosperms derived polysaccharide contains glycosidic linked galactan and mannan

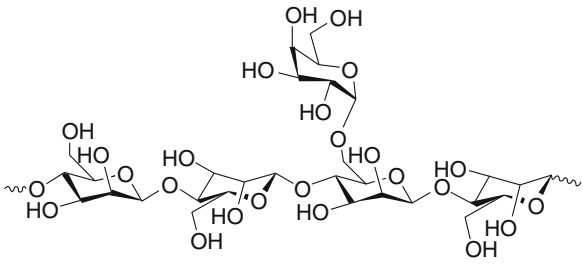

Fig. 4.10 Chemical structure of locust bean gum

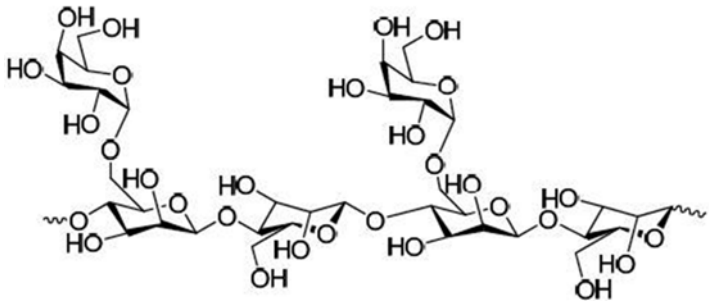

Fig. 4.11 Chemical structure of guar gum

units and shows degradation in the large intestine due the presence of microbial enzymes. Guar gum has high molecular weight with high apparent viscosity in solution and shows solubility in cold water with its complete swift hydration to yield viscous pseudo plastic solutions. However it was observed that its shear-thinning usually have better low-shear viscosity than other hydrocolloids. This high viscosity and molecular weight dependent gelling property delays the drug from its dosage form, and become more vulnerable against susceptible to degradation in the colonic environment. This galactomannan based non-ionic polysaccharide that abundantly present in nature and endow many significant properties desirable for drug delivery applications. Nevertheless owing to its elevated swelling features in water, the utilization of this galactomannan based polysaccharide is limited. Recently various physico-chemical methods have been employed to improve its property such as derivatiztion, grafting and network formation. Such modification allows its more utilization for biomedical applications. Additionally this plant based natural polymer can be exploited in various forms such as matrix tablets, hydrogels, nano/micro particles and coatings can be exploited as potential carriers for targeted drug delivery [401]. One report suggested the significant role of guar gum in oral controlled drug delivery systems for highly water-soluble metroprolol as a carrier in the form of a three-layer matrix tablet. During this study it was observed that three-layer guar gum matrix tablets provide the desirable release rate for metoprolol tartrate formulations with no change either in physical appearance, drug content or in dissolution pattern and did not show any possibility of metoprolol tartrate/guar gum interaction with the formulation excipients used in the study [402]. Same results were obtained in guar gum based three layer tablet of tri-metazidinedihydrochloride controlled release formulation [403]. In another report where guar gum potential was explored as a carrier for colon-specific drug delivery in form of a novel tablet formulation for oral administration using indo-methacin as a model drug. It was observed that this galactomannan based polysaccharide protects the drug from being released entirely in the physiological environment of stomach and small intestine. Based on these investigations it was concluded that 4% w/v of rat caecal contents in PBS offers the best conditions for in vitro assessment of guar gum [404]. In one more investigation guar gum was modified by using acrylamide grafting in which amide groups of these grafted copolymers were transformed into carboxylic functional groups and finally tablets were prepared by incorporating diltiazem hydrochloride. Based on in-vitro drug release data it was observed that that the drug release dissolution was controlled in case of unhydrolyzed copolymer in contrast with hydrolyzed copolymers, drug release was swelling-controlled at first, however at later stage, it became dissolution-controlled. This report suggested potential role of pH sensitive hydrolyzed pAAm-*g*-GG matrices for intestinal drug delivery [405].

4.8.7.6 Grewia Gum

Grewia genus which was formerly categorized under linden Family (Tiliaceae) or the Spermamanniaceae and has been now merged into the Malvaceae [406]. Its increasing citations in International Pharmaceutical Abstracts database, EBSCO

and in PubMed augment its interest on *Grewia mollis*as as a potential pharmaceutical excipient [407]. In concern with its polysaccharide based pharmaceutical evaluation, the first report was documented in the early 2000s [408–416], in which researchers have explored some physicochemical and rheological characteristics as well as water vapor permeability of the aqueous-based films. During this investigation effect of gum derived from *Grewia mollis*as, on the binding properties in sodium salicylate tablets [413] and its influence on the granulating fluid on the release profile of drug [414] were evaluated. Later on in a study researchers have observed that method of incorporating the gum into tablet formulation had significant effect on tablet properties. Additionally it was discovered that introduction by activation with water produced improved tablet properties than when incorporate by wet granulation or direct compression [415]. It was observed that acidic hydrolysis of the gum and some chemical modifications showed reduced viscosity and improved drug release from tablets [416–418]. In recent work some workers have explored the significant role of gum in binding in contrast with both untreated gum and gelatin in paracetamol tablet formulations [419]. It was observed that tablet formulations containing treated grewia gum exhibited low onset of plastic deformation, enhanced friability was found with increase in acid concentration and treatment time and decrease in crushing strength, disintegration and dissolution times with increase in acid concentration and treatment time was observed. Other researchers concluded that acid treated grewia gum, depending on the desired onset of action of medicament, can be used in formulation of conventional tablets especially if the formulation does not require sustained release [420]. With the advancement in analytical tools it's now possible to characterize the natural polymers in much better way then the conventional technologies. Technologies such as gel permeation chromatography, gas chromatography, differential scanning calorimetry, scanning electron microscopy, thermo gravimetric analysis, ^{1}H and ^{13}C-NMR, solid-state nuclear magnetic resonance, Fourier transformed infrared, x-ray photoelectron spectroscopy, and NIR techniques have been utilized to characterize the gum [421, 422]. Based on the analysis it was observed that polysaccharide gum is a normally amorphous polysaccharide gum containing rhamnose, glucose, arabinose, galactose, and xylose as neutral sugars with an average molecular weight of 5925 kDa expressed as the pullulan equivalent. As far as its physical properties are concerned gum gradually hydrated in water. This dispersion swells to form a highly viscous dispersion having pseudo plastic flow behavior. Technique like centrifugation gives better molecular weights range between 230 and 235 kDa of gum when centrifuged successively at 4500 rpm for 30 min. Such processes improve the aqueous solubility and useful in delivering more solids to the substrate when used as a film coating agent [422].

4.8.7.7 Okra Gum

Okra gum is obtained from plant which is widely cultivated and grown in most tropical part of Nigeria known as *Abelmoschusesculentus* (Fam. Malvaceae). This plant is widely consumed as food in Asia and Africa and therefore considered as

subject of research in agriculture [423, 424]. Okra is popular for its viscous mucilaginous solution which is formed when heated and extracted in water [425]. This high molecular weight polysaccharide gum is reported as pharmaceutical excipient in various reports as a suspending [425–427], control release [428], film coating [429], binder [430, 431], and bio-adhesive [432] agent. Okra gum is documented as controlled-release agent in modified release matrices, in contrast with sodium carboxymethyl- cellulose and hydroxyl-propyl-methyl-cellulose, using Paracetamol as a model drug. Results showed that an okra gum matrix was useful in the formulation of sustained-release tablets for up to 6 h [428].

4.8.7.8 Kyaha Gum

Recent report explored the relative binding effects of khaya gum obtained from *Khayasenegalensis* and *Khayagrandifoliola* (Fam. Meliaceae) in paracetamol tablet formulation were evaluated [433]. In one report mechanical properties of the tablets using khaya gum were assessed using the tensile strength, brittle fracture index and friability of the tablets while the drug release properties were evaluated by means of disintegration and dissolution times. It was observed that the brittle fracture index and friability decreased whereas tensile strength, disintegration and the dissolution times of tablets increased with the increase in binder concentration. It was also concluded that gum obtained from *K. senegalensis* produced strong tablets with extended disintegration and dissolution times in contrast with those obtained from *K. grandifoliola* gum. Based on reports it was finally suggested that gums obtained from *K. senegalensis* will be more suitable as a binding agent than *K. grandifoliola* when high mechanical strength and slow release profiles of tablets are required.

4.8.7.9 Moringaoleifer Gum

Moringaoleifera derived gum was investigated for its physical features such as loss on drying, swelling index, solubility, and pH in form of gel based formulations using Diclofenac sodium as model. It was studied that 8.0 % mucilage gels prepared were found to be ideal and equivalent with a marketed preparation [434].

4.8.7.10 Irvingiagabonensis

Seeds of *Irvingia gabonensis,* commonly known as ‘African mango’ or ‘bush mango’ contains large amount of lipids and polymeric constituents [423, 435–440] which are very important to pharmaceutical scientists as excipients. Mucilage isolated from the kernel is of great pharmaceutical significance and has been used as binding agent in tablet formulation [441], as emulsifying and suspending agent [442]. Moreover the lipid has been employed in sustained release ingredient

[443–445], as suppository base [446–448], tableting as lubricant, microencapsulation [449], and as a part of film coating process [446]. Polysaccharide extraction can be achieved by using aqueous dispersion in petroleum ether or diethyl ether [450], however simultaneous extraction processes for both lipis and polysaccharide content has not been reported yet [451]. Irvingiagabonensis mucilage was investigated for use as suspending and emulsifying agent and its rheological behavior was evaluated against tragacanth. It was observed that formulated suspensions of Irvingia mucilage at all concentrations gave higher final sedimentation height and sedimentation volume values. Furthermore it was also documented that 2.0 % w/v Irvingia mucilage (as an emulsifying agent) when compared against tragacanth and acacia gum showed stability throughout the 6 weeks of study. This observation led to conclusion that Irvingia mucilage presents superior properties than acacia and tragacanth. This performance was found to be much better, even at lower concentrations in the formulation of emulsions and suspensions. Iirvingia lipid based suppository base has also been investigated and it was observed that irvingia fat can be actively employed as suppository base. Furthermore the potential binding effects of mucilage on sustained release tablets, metronidazole tablets and as lubricating potential in tablet formulations have been investigated.

4.8.7.11 Hakeagibbosa Gum

This water-soluble gum is obtained from Hakeagibbosa (hakea), having considerable muco adhesive and sustained-release properties especially for the formulation of buccal tablets. Hakeagibbosa gum is recently investigated in flat-faced tablets using chlorpheniramine maleate as model drug [452]. It was observed that hakea coated tablet significantly extend the in vitro release up to several hours and characterization results suggested the absence of chemical interactions. Additionally force of detachment for directly compressed and wet granulated tablets was increased as the amount of hakea per tablet was increased. Researchers also reported that hakea, might not only be employed to prolong the chlorpheniramine maleate release from a buccal tablet, however it also displayed excellent mucoadhesive properties. The underlying mechanism behind this is the slow relaxation of the hydrated hakea which can cause chlorpheniramine maleate release in a sustained manner.

4.8.7.12 Psyllium Mucilage

Mucilage derived from Psyllium, has been investigated for its tablet binding properties [453]. This mucilage is derived from the seed coat of *Plantagoovata* (Fam. Plantaginaceae) [454]. Isolation is achieved by milling of the outer layer of the seeds yield smooth texture mucilage. Psyllium hydrogels were investigated by insulin as model drug and N, N'-methylene-bis-acryl-amide as cross-linker. Formulation showed controlled release of the active ingredient [455].

4.8.7.13 Miscellaneous Gums and Mucilage

Various gums have been explored for pharmaceutical significance such as *Colocassiaesculenta* [456], seeds of *Linumusitatissimum* [457], malva nut gum [458] and *Sterculiafoetida* gum for swelling and erosion modulator in controlled release matrix tablets of diltiazem hydrochloride.

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