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Advances in Natural Polymers as Pharmaceutical Excipients

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Abstract

Research in natural polymeric materials has witnessed growing interest and attention. This is attributable to a number of factors which include their relative abundance, low cost, and biodegrable and eco-firendly profiles. This article reviews the current applications of natural polymeric materials in pharmaceutical formulations. The pharmaceutical applications of some of the traditional and commercially available natural polymers were discussed. Emerging potential pharmaceutical excipients of natural origins were also discussed. The increasing research interests in this group of materials are indications of their increasing importance. It is believed that as technology and testing techniques advance, more understanding of their physicochemical nature would be gained that can enable them to be tailored for wider Pharmaceutical applications than their synthetic counterparts.

Keywords: Natural Polymeric materials; Pharmaceutical excipients; Biodegradable; Eco-friendly

Introduction

Drugs are hardly administered as such but are almost always formulated into a suitable dosage form with the aid of excipients, which serve various functions such as binding, lubricating, gelling, suspending, flavoring, sweetening and bulking agent among others [1]. The International Pharmaceutical Excipients Council defines excipients as substances, other than the active drug substances of finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture; protect, support orenhance stability, bioavailability, or patient acceptability; assist in product identification; or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use [2]. Excipients play a critical role in the creation of medicines, helping to preserve the efficacy, safety, and stability of active pharmaceutical ingredients (APIs) and ensuring that they deliver their promised benefits to the patients. Optimal use of excipients can provide pharmaceutical manufacturers with cost-savings in drug development, enhanced functionality and help in drug formulations innovation.

Excipients are the largest components of any pharmaceutical formulation. They can be of natural or synthetic origin and synthetic excipients have become commonplace in today's pharmaceutical dosage forms [3]. It is common knowledge that both synthetic and semi-synthetic products have enjoyed a long history of use, frequently offering unique properties and advantages over naturally derived compounds, including a low sensitivity to various ingredients or moisture, resulting in more efficient and effective pharmaceutical products [3]. But despite the many potential benefits of synthetic excipients, manufacturers must still address a number of challenges before their current universe of implementation can be expanded. The terms 'synthetic' and 'semi-synthetics are both broadly used to distinguish this family of excipients from those extracted from natural sources. Semi-synthetic typically refers to a substance that is naturally derived but has been chemically modified. Most excipients in use today fall into this category and there must be the 'natural' to obtain the 'semi-synthetic' excipients. In contrast, 'synthetic' 'is usually defined as a pure synthetic organic chemical that is derived from oil or rock [3].

Lipids, carbohydrates and proteins are natural polymeric materials. Natural polysaccharides, as well as their derivatives, represent a group of polymers that are widely used in pharmaceutical formulations and in several cases their presence plays a fundamental role in determining the mechanism and rate of drug release from the dosage form. These naturally occurring polymers have been employed as excipients in the pharmaceutical industry in the formulation of solid, liquid and semi-solid dosage forms in which they play different roles as disintegrates, binders, film formers, matrix formers or release modifiers, thickeners or viscosity enhancers, stabilizers, emulsifiers, suspending agents and muco adhesives [4,5]. Specifically, they have been used in the formulation and manufacture of solid monolithic matrix systems, implants, films, beads, micro particles, nanoparticles, inhalable and injectable systems as well as viscous liquid formulations [5-7].

Their growing role and application in the pharmaceutical industry may be attributable not only to the fact that they are biodegradable and toxicologically harmless raw materials of low cost and relative abundance compared to their and synthetic counter parts [8,9], but also because natural resources are renewable and if cultivated or harvested in a sustainable manner, they can provide a constant supply of raw material [10]. Furthermore, their extensive applications in drug delivery have been realized because as polymers, they offer unique properties which so far have not been attained by any other materials [11]. They can be tailored for many applications based on the very large chains and functional groups which can be blended with other low- and high–molecular-weight materials to achieve new materials with various physicochemical properties. Consequently, many of the widely used excipients today are chemical modifications of the natural excipients to overcome some of their disadvantages.

A couple of review articles on natural gums are available in literatures [12,13]. Some of the reviews covered the chemical structure,

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occurrence and production of exudate gums, their size and relative importance of the various players on the world market and focused on their application in food and other areas [13]. Due to the growing interest in the use of natural polymeric materials as pharmaceutical excipients, as demonstrated by the number of published scientific papers, it is difficult to cover all that might be available in a single article. It is intended in this review to discuss the uses of natural polymers as excipients in pharmaceutical formulations. Specific mention is made of some of the natural products already in use as pharmaceutical excipients and those being researched for this purpose.

Natural Polymeric Materials

Natural polymers are obtained from different sources and this review will attempt to briefly discuss them according to their sources. Mention is made of those that are relevant to the current topic.

Polysaccharides of the plant cell wall

Natural polymers which have their origin from the plant cell wall mainly include cellulose, hemicelluloses and pectin.

Cellulose: In higher plants, cellulose is an essential structural component and represents the most abundant organic polymer [5]. Cellulose is a linear unbranched polysaccharide consisting of β-1, 4-linked D-glucose units and many parallel cellulose molecules which form crystalline micro fibrils. The crystalline micro fibrils are mechanically strong and highly resistant to enzymatic attack and are aligned with each other to provide structure to the cell wall [14]. Cellulose is insoluble in water and indigestible by the human body. It is however digested by herbivores and termites. Cellulose obtained from fibrous materials such as wood and cotton can be mechanically disintegrated to produce powdered cellulose which has been used in the pharmaceutical industry as filler in tablets. High quality powdered cellulose when treated with hydrochloric acid produces microcrystalline cellulose which is preferred over powdered cellulose because it is more free-flowing containing non-fibrous particles. It is consequently employed as diluents or filler/binder in tablets for both granulation and direct compression processes [15]. The molecular structure of cellulose is shown in figure 1.

The formation of derivatives of cellulose is made possible by the hydroxyl moieties on the D-glucopyranose units of the cellulose polymer to give a variety of derivatives. Cellulose derivatives can be made by etherification, esterification, cross-linking or graft copolymerization [16]. Etherification yields derivatives such as hydroxyl-propyl-methyl-cellulose and carboxyl-methyl-cellulose, while esterification results in derivatives which include cellulose nitrate, cellulose acetate and cellulose acetate phthalate. These derivatives have found application in membrane controlled release systems such as enteric coating and the use of semi-permeable membranes in osmotic pump delivery systems. They have also enjoyed wide use and application in monolithic matrix systems. Extensive studies conducted on these derivatives have proven their ability to sustain the release of medicaments and most of these derivatives have been employed for this purpose [17,18].

Hemicellulose: Bound to the surface of cellulose microfibrils are complex polysaccharides which themselves do not form micro fibrils. These bound polysaccharides are called hemicelluloses and include xyloglycans, xylans, mannans and glucomannans, and β-(1→3, 1→4)-glucans [19]. They can be extracted from the plant cell wall with the aid of strong alkali.

Hemicelluloses have β-(1→4)-linked backbones with an equatorial

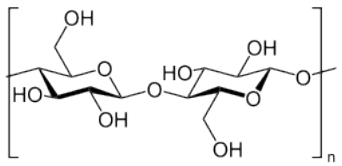

Figure 1: Molecular structure of powdered cellulose (n ≈ 500) or microcrystalline cellulose (n ≈ 220).

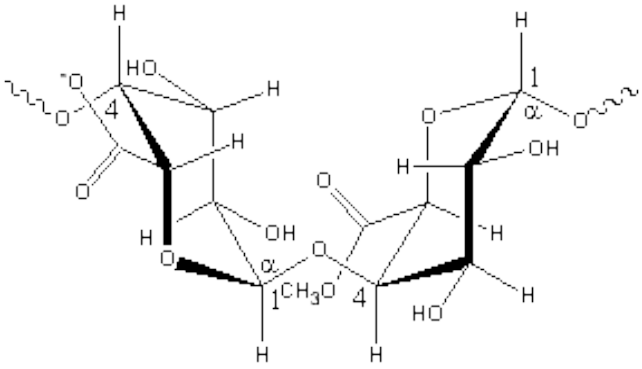

Figure 2: Molecular structure of pectin.

configuration. In contrast to cellulose which is crystalline and unbranched, hemicellulose is amorphous and branched. Although the xyloglycans have similar 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 [20].

Glucomannan is mainly a straight-chain hydrocolloidal polysaccharide of the mannan family 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 which may differ depending on the source [21]. The component sugars may contain acetyl side branches on some of the backbone units which contribute to the solubility and swelling capacity of the glucomannans. The acetyl groups consequently enhance the solubility of the glucomannans as natural polysaccharides possessing the highest viscosity and water-holding capacity. Konjakglucomannan is the most commonly used type of glucomannan obtained by extraction from the tubers of *Amorphophalluskonjac K. Koch* (Fam. Ulmaceae). Konjacglucomannan has been investigated as an effective excipient in controlled release drug delivery devices in combination with other polymers or by modifying its chemical structure. Combination of konjacglucomannan and xanthan gum in matrix tablets has been shown to effectively retard drug release by stabilisation of the gel phase of the tablets by a network of intermolecular hydrogen bonds between the two polymers [22].

Pectins: Pectins are non-starch, linear polysaccharides extracted from the plant cell walls. They are predominantly linear polymers of mainly (1–4)-linked D-galacturonic acid residues interrupted by 1,2-linked L-rhamnose residues with a few hundred to about one thousand building blocks per molecule (molecular structure is shown in figure 2), corresponding to an average molecular weight of about 50, 000 to about 180,000 [23]. Being soluble in water, pectin is not able to shield its drug load effectively during its passage through the stomach and small intestine. It was found that a coat of considerable thickness was required to protect the drug core in simulated *in vivo* conditions

[23]. Hence the focus was shifted to the development of less soluble derivatives of pectin which get degraded by the colonic micro flora. Calcium salts of pectin reduced their solubility by forming an egg-box configuration. To overcome the drawback of high solubility of pectin, mixed films of pectin with ethyl-cellulose were investigated as a coating material for colon-specific drug delivery. These films combined the colon specific degradation properties of pectin with the protective properties of the water insoluble ethyl cellulose [23].

Polymeric hydrogels are widely used as controlled-release matrix tablets. Some researchers [24] investigated the high-methoxy-pectin for its potential value in controlled-release matrix formulations. The effects of compression force, ratio of drug to pectin, and type of pectin on drug release from matrix tablets were also investigated. The results of the *in vitro* release studies showed that the drug release from compressed matrix tablets prepared from pectin can be modified by changing the amount and type of pectin in the matrix tablets. A very low solubility pectin-derivative (pectinic acid, degree of methoxylation 4%) was found to be well suited as an excipient for pelletisation by extrusion/spheronisation. The capacity as an extrusion aid was found to be high. Formulations containing only 20% pectinic acid resulted in nearly spherical pellets. All pectinic acid pellets were mechanically stable. They possessed an aspect ratio of approximately 1.15–1.20 and released 30–60% of a low solubility model drug within 15 min in simulated gastric fluid (0.1M HCl) and intestinal fluid (phosphate buffer pH 6.8) [25].

Micro particulate polymeric delivery systems have been reported as a possible approach to improve the low bioavailability characteristics observed in standard ophthalmic vehicles (collyria) [26]. In this context pectin microspheres of piroxicam were prepared by the spray drying technique. *In vivo* tests in rabbits with dispersions of piroxicam-loaded microspheres also indicated a significant improvement of piroxicam bioavailability in the aqueous humour (2.5–fold) when compared with commercial piroxicameye drops.

Investigation on the suitability of amidated pectin as a matrix patch for transdermal chloroquine delivery has been reported [27]. This was in an effort to mask the bitter taste of chloroquine when orally administered. The results suggested that the pectin-chloroquine patch matrix preparation has potential applications for the transdermal delivery of chloroquine and perhaps in the management of malaria. Calcium pectinate nanoparticles to deliver insulin were prepared as a potential colonic delivery system by ionotropic gelation [28].

In relation to cosmetics, using citronellal as a model compound, pectin gel formulations were evaluated for controlled fragrance release by kinetic and static methods. These formulations showed a prolonged duration of fragrance release and limitation of fragrance adsorption to the receptor skin layers. The increase in pectin concentrations suppressed the fragrance release by a diffusion mechanism, thereby proving that pectin/calcium micro particles are promising materials for controlled fragrance release [29]. Drug delivery systems utilizing pectin is discussed by various researchers [30-35].

Gums and mucilages

Gums are natural plant hydrocolloids that may be classified as anionic or nonionic polysaccharides or salts of polysaccharides [36]. They are translucent, amorphous substances usually produced by plants as a protective after injury. Gums, mucilage, pectins and celluloses are classified as substances that are condensations of pentoses and or hexoses. When gum is hydrolyzed, it yields large proportion of sugars and complex organic acid nucleus. It is by means of these organic acids that they do form salts with calcium or magnesium. According to Claus and Tyler [36] it is difficult to distinguish between gums and mucilage. In their opinion, one attempt is to refer to gums as water soluble and mucilage as water insoluble and the other approach is to refer to mucilage as pathological product and gums as physiological products.

Gums and mucilage are produced in various ways by the plant. These substances can be formed from middle lamella as in the algae; cell wall as in the seed epidermis, seed endodermis, cells in the bark; special secretory cells as in the squill; in the schizogenous sacs as in the young stem of *Rhamnuspurshiana*, or by lysiogenous metamorphosis of the cell walls as in tragacanth and acacia [36].

Gums have found pharmaceutical application since the early 1800 having gums like tragacanth, acacia, sterculia appearing in the United States Pharmacopoeia of 1820 and sodium alginate and agar in the 1947 National Formulary. The gums have been used as suspending agents for insoluble solids in mixtures, as emulsifying agents for oils and resins and as adhesive in pill and troche masses. Some gums are used as demulcent and emollient in hand lotion while others are used as protective colloid and as binding and disintegrating agents in tablet formulations [36].

Google scholar entries on gums hit 7,500 in 2010 and were 8,260 a year later, showing the continuous interest in the use of these materials. There were 453 articles in the Wolter Kluwer's database while in Pubmed the number was 7,979 scholarly articles on gums and mucilage, showing the importance of gums in pharmacy. It seems that gums and mucilage are the most highly investigated in the recent time as potential pharmaceutical excipients.

Gums are naturally occurring components in plants, which are essentially cheap and plentiful. They have diverse applications as thickeners, emulsifiers, viscosifiers, sweeteners etc. in confectionary, and as binders and drug release modifiers in pharmaceutical dosage forms. However, most of the gums in their putative form are required in very high concentrations to successfully function as drug release modifiers in dosage forms due to their high swellability/solubility at acidic pH. Hence, gums need to be modified to alter their physicochemical properties. For example, the modification of gums through derivatisation of functional groups, grafting with polymers, cross-linking with ions and other approaches as well as the factors influencing these processes in the pursuit of making them suitable for modifying the drug release properties of pharmaceutical dosage forms and for other purposes have been discussed with respect to optimization of their performance [37].

Oral sustained release matrix tablets of water-insoluble drug, flurbiprofen was designed with natural gums and evaluated for the drug release characteristics using response surface methodology [38]. The central composite design for two factors at five levels each was employed to systematically optimize drug release profile. In their work matrix tablets were prepared by direct compression technique. Xanthan and acacia gums were taken as the independent variables. Fourier transform infrared spectroscopy was employed to study the stability of drug used and the interactions between polymers and drug. Percent drug release in 2 and 8 hours were taken as response variables (Y_1 and Y_2, respectively). These workers found that the gums have significant effect on the drug release. Polynomial mathematical models, generated for the response variables using multiple linear regression analysis, were found to be statistically significant ($P < 0.05$).

Contour plots were drawn to depict the relationship between response variables and independent variables. These workers concluded that the formulated matrix tablets followed zero-order kinetics with negligible drug release in 0.1N HCl at pH 1.2. Their objective of a formulation that would avoid the gastric effects of flurbiprofen was achieved. The mechanical and disintegration properties of paracetamol tablets formulated with *Delonixregia* seed gum (DRSG) as a binder have been studied [39]. Tragacanth (TRG) and acacia (ACG) were used for comparison. Results showed that an increase in concentration of the binder increased the tensile strength while the brittle fracture index (BFI) was reduced. The crushing strength - friability/disintegration time ratio was ranked in the order: DRSG > ACG > TRG at 1%, w/w binder concentration. The ranking of high binder concentrations was ACG > TRG > DRSG. The results suggested that *Delonixregia* seed gum may be useful as a binder at low concentration and as sustained release matrix at high concentration. Another natural gum, damar was investigated as a novel micro encapsulating material for sustained drug delivery [40]. Micro particles were prepared by oil-in-water emulsion solvent evaporation method employing ibuprofen and diltiazem hydrochloride as model drugs. Micro particles were evaluated for particle size, encapsulation efficiency and *in vitro* drug release kinetics. The effect of different gum: drug ratios and solubility of drug on micro particle properties was principally investigated. Gum damar produced discrete and spherical micro particles with both drugs. With a freely water soluble drug (diltiazem hydrochloride), gum damar produced bigger (45-50 μm) and rapid drug releasing micro particles with low encapsulation efficiencies (44-57%). Conversely, with a slightly water-soluble drug (ibuprofen), small (24-33 μm) micro particles with good encapsulation (85-91%) and sustained drug delivery were achieved. An increase in gum: drug ratio resulted in an increase in particle size and encapsulation efficiency but decreased the drug release rate in all cases. Drug release profiles of all micro particles followed zero order kinetics.

Seaweed polysaccharides

Seaweed gums are typified by the carrageenans, agar and the alginates.

Alginates: Alginates are natural polysaccharide polymers isolated from the brown sea weed (Phaeophyceae). Alginic acid can be converted into its salts, of which sodium alginate is the major form currently used. They are linear polymers consisting of D-mannuronic acid and L-guluronic acid residues arranged in blocks in the polymer chain. These homogeneous blocks (composed of either acid residue alone) are separated by blocks made of random or alternating units of mannuronic and guluronic acids. Alginates offer various applications in drug delivery, such as in matrix type alginate gel beads, in liposomes, in modulating gastrointestinal transit time, for local applications and to deliver the bio molecules in tissue engineering applications [41].

Bio-adhesive sodium alginate microspheres of metoprolol tartarate for intranasal systemic delivery were prepared to avoid the first-pass effect, as an alternative therapy to injection, and to obtain improved therapeutic efficacy in the treatment of hypertension and angina pectoris. The microspheres were prepared using emulsification-cross linking method. *In vivo* studies indicated significantly improved therapeutic efficacy of metoprolol from microspheres. There was sustained and controlled inhibition of isoprenaline-induced tachycardia as compared with oral and nasal administration of drug solution [42].

A new insert, basically consisting of alginates with different hydroxyl-ethyl-cellulose content was developed to maintain a constant drug level over a certain period in the eye that was not possible with conventional eye drop application. This study showed good tolerance of the new calcium-alginate-insert applied to the ocular surface for controlled drug release [43]. In order to achieve a 24h release profile of water soluble drugs, sodium alginate formulation matrices containing xanthan gum or zinc acetate or both were investigated. The release of the drug from the sodium alginate formulation containing only xanthan gum was completed within 12h in the simulated intestinal fluid, while the drug release from the sodium alginate formulation containing only zinc acetate was completed within 2h in the same medium. Only the sodium alginate formulation, containing both xanthan gum and zinc acetate achieved a 24h release profile, either in the simulated intestinal fluid or in the pH change medium (pH 1.2). The helical structure and high viscosity of xanthan gum possibly prevented zinc ions from diffusing out of the ranitidine hydrochloride sodium alginate-xanthan gum-zinc acetate matrix so that zinc ions react with sodium alginate to form zinc alginate precipitate with a cross-linking structure. The cross-linking structure might control a highly water-soluble drug release for 24h [44].

In a comparative study, alginate formulation appeared to be better than the poly-lactide-co-glycoside (PLG) formulation in improving the bioavailability of two clinically important antifungal drugs clotrimazole and econazole. The nanoparticles were prepared by the emulsion-solvent-evaporation technique in case of PLG and by the cation-induced controlled gelling in case of alginate [44].

Carageenans: The carrageenans are sulphated marine hydrocolloids obtained by extraction from seaweeds of the class Rhodophyceae, represented by *Chondruscrispus, Euchemaspinosum, Gigartinaskottsbergi, Gigartinastellata, Iradaealaminariodes*. These are red seaweeds growing abundantly along the Atlantic coasts of North America, Europe and the western Pacific coast of Korea and Japan [45-47]. Carrageenan is not assimilated by the human body. It provides only bulk but no nutrition. Carrageenan has been categorized into 3: kappa (κ), iota (ι) and lambda (λ). Lambda (λ-type) carrageenan produces viscous solutions but does not form gels. While the Kappa (κ-type) carrageenan forms a brittle gel, the iota (ι-type) carrageenan produces elastic gels [48]. Studies have shown that the carrageenans are suitable in the formulation of controlled release tablets [49-51].

Gum agar: Gum agar is extracted from the red-purple marine algae of the Rhodophyceae class. The species include *Gelidiumcartilagineum* and *Gracilariaconfervoides* which grow abundantly in the waters along the coast of Japan, New Zealand, South Africa, Southern California, Mexico, Chile, Morocco, and Portugal [46, 52, 53].

Microbial polysaccharides

Natural polysaccharide gums have also been obtained as carbohydrate fermentation products including Xanthan gum, produced in pure culture fermentation by the bacteria *Xanthomonascampestris*. It was originally obtained from the rutabaga plant [53]. Gellan gum is a microbial polysaccharide obtained by fermentation by *Pseudomonas elodea* [53,54]. Pullulan is an extracellular homo-polysaccharide of glucose produced by many species of the fungus *Aureobasidium*, specifically *A. pullulans.*

Xanthan gum: Xanthan gum, a complex microbial exo-polysaccharide produced from glucose fermentation by Xanthomonas campestrispv. Campestris, a plant bacterium. It has a molecular weight of about 2 million [55]. The gum consists of D-glucosyl, D-mannosyl, and D-glucuronyl acid residues in a molar ratio of 2:2:1. It also contains

O-acetyl and pyruvyl residues in variable proportions [56]. Xanthan gum is an acidic polysaccharide gum of penta-saccharide subunits. The penta-saccharide subunits form a cellulose backbone with tri-saccharide side-chains.

The applications of xanthan gum have been widely researched. It is non-toxic and has been approved by the Food and Drug Administration (FDA) for use as food additive without quantity limitations [57]. Xanthan gum has been used in a wide range of industries including food, oil recovery, cosmetics and pharmaceutical industries. This wide application is due to its superior rheological properties. It is used as stabilizer for emulsions and suspensions. The gum forms highly viscous solutions which exhibit pseudoplasmic flow behavior [58]. The literatures are littered with uses of xanthan as a pharmaceutical material [59-61].

Gellan gum: DeacylatedGellan gum (Gellan) is an anionic microbial polysaccharide, secreted from *Sphingomonas elodea*, consisting of repeating tetrasaccharide units of glucose, glucuronic acid and rhamnose residues in a 2:1:1 ratio: [→3)–β–D–glucose–(1→4)–β–D–glucuronic acid–(1→4)– β–D–glucose–(1→4)–α–L–rhamnose–(1→]. In the native polymer two acyl substituents, L-glyceryl at O(2) and acetyl at O(6), are present on the 3-linked glucose. On average, there is one glyceryl per repeating unit and one acetyl for every two repeating units. DeacylatedGellan gum is obtained by alkali treatment of the native polysaccharide. Both native and deacylatedGellan gum are capable of physical gelation [62]. To induce Gellan gelation it is necessary to warm up preliminarily a concentrated water solution of the polysaccharide: when the temperature is decreased, the chains undergo a conformational transition from random coilsto double helices (Coil-Helix Transition). Then a rearrangement of the double helices occurs leading to the formation of ordered junction zones (Sol-Gel Transition) [63] thus giving a thermo-reversible hydrogel [64]. Much stronger physical thermo-reversible hydrogels are also obtained by addition of mono and divalent ions to Gellan solutions [65], or in acidic conditions [66].

The physical gelation properties make this polysaccharide suitable as a structuring and gelling agent in food industries. Gellan is also exploited in the field of modified release of bioactive molecules. Aqueous solutions of Gellan are used as *in situ* gelling systems, mainly for ophthalmic preparation and for oral drug delivery [67]. Physical Gellan hydrogels, prepared with mono or divalent cations, are used also for the preparation of tablets, beads [68] or microspheres. Interpenetrating polymer networks [69] or co-cross linked polymer networks [70] based on Gellan and other polysaccharide systems have also been developed as drug delivery matrices.

Chemical hydrogels of Gellan are usually prepared via chemical cross linking of preformed physical networks, in order to enhance their mechanical properties, and to obtain slower drug release profiles. The aim of the present work was the development of a novel Gellan chemical hydrogel, with tunable physicochemical properties, obtained by cross linking the polymer chains with L-lysine ethyl ester moieties. As a first step, amidation of Gellan carboxyl groups in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and *N*-hydroxy-succinimide (NHS) was carried out it is well known that EDC and NHS have the ability to mediate the amide bond formation between amino and carboxyl groups. Ethyl ester of L-lysine (Lys) was used in order to protect the carboxyl group, thus avoiding the intermolecular reaction among the L-lysine molecules. Chemical hydrogels with different cross linking degrees were prepared, and their physico-chemical and rheological properties were studied and compared with the corresponding physical gels. The new networks, that were also investigated as matrices for modified oral release, using model molecules with different steric hindrance, can be proposed as carriers for the delivery of high molecular weight drugs such as proteins. Furthermore, the observed peculiar mechanical and rheological properties can be properly modulated in order to give matrices suitable for the depot systems [71,72].

Pullulan: Insulin (Ins) spontaneously and easily complexed with the hydrogel nanoparticle of hydrophobized cholesterol-bearing pullulan (CHP) in water. The complexed nanoparticles (diameter 20–30 nm) thus obtained formed a very stable colloid. The thermal denaturation and subsequent aggregation of Ins were effectively suppressed upon complexation. The complexed Insulin was significantly protected from enzymatic degradation. Spontaneous dissociation of Insulin from the complex was barely observed, except in the presence of bovine serum albumin. The original physiological activity of complexed Insulin was preserved in vivo after i.v. injection [73]. Figure 3 shows the microscopic view of pullulan in the solid and in the presence of water.

Animal polysaccharides

Natural gums have also been obtained from animal sources. Examples include chitin and chitosan. Chitin is a structural polysaccharide which takes the place of cellulose in any species of lower plants and animals. It therefore occurs in fungi, yeast, green, brown and red algae and form the main component of the exoskeleton of insects and shells of crustaceans [46]. Chitin is insoluble in water but when treated with strong alkali, it forms the water-soluble polysaccharide

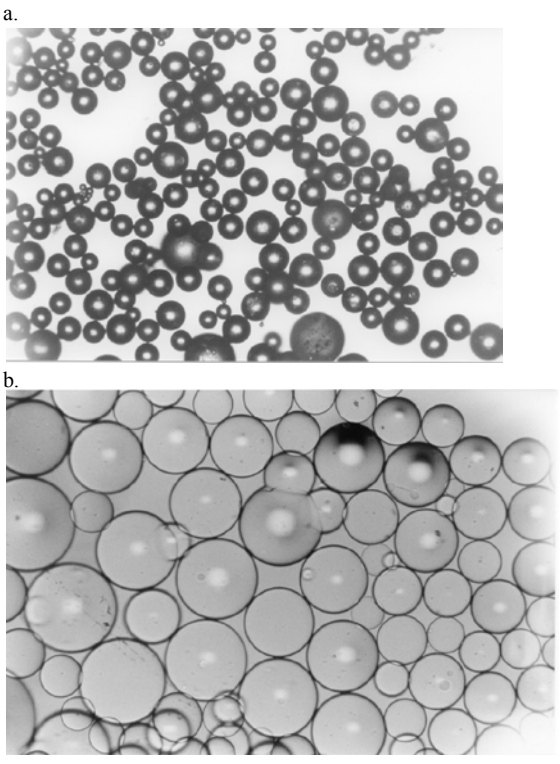

Figure 3: Crosslinkedpullulanmicroparticles (a) in dry state (b) in aqueous fluid.

chitosan which is the only polysaccharide carrying a positive charge [46].

Exudates gums

Plants, which form the sources of exudate gums, when cut give a viscous, sticky fluid which exudes from the incision and tends to cover and seal the opening. Gum exudates are therefore believed to be produced by plants in order to seal-off infected sections of the plant and prevent loss of moisture due to physical injury or fungal attack [46]. The fluid eventually dries to a brittle, translucent, glassy, hard mass. These gum exudates are secreted by various organs of the plant. They include tragacanth gum and acacia gum or gum Arabic.

Acacia gum: Acacia gum or gum Arabic is the dried gummy exudate from the stems and branches of *Acacia Senegal* (Fam. Leguminosae) and other related African species of acacia [74,75]. Gum arabic is a branched molecule of 1, 3-linked β-Dgalactopyranosyl units. It consists of monosaccharide sugarss such as arabinose, glucuronic acid and rhamnose. Studies recorded success with gum Arabic as a matrix microencapsulating agent for the enzyme, endoglucanase [74]. In this study gum Arabic was shown to give slow release endogucanase from the formulation. In another study gum arabic was used as an osmotic suspending and expanding agent to prepare monolithic osmotic tablet systems [76]. There was zero order release of the active for up to 12 hours at a pH of 6.8. Heterogeneity of *Acacia senegal* gum by sodium sulfate –induced precipitation has been studied [77].

Tragacanth gum: Gum tragacanth is a branched, heterogeneous, and anionic carbohydrate which consists of two major fractions: tragacanthin (water-soluble) and bassorin (water-swellable) [78]. It is not understood yet if the two polysaccharides are in a physical mixture or chemically bonded to each other, although easy separation procedures favor the former hypothesis. Bassorin and tragacanthin composition differ particularly in terms of their uronic acid and methoxyl content [79]; it has been suggested that bassorin is a complex structure of polymethoxylated acids and on demethoxylation, probably yields tragacanthin [80]. Gum tragacanth has been known and used for thousands of years. It is defined by the Food Chemical Codex as the dried gummy exudation obtained from different species of Astragalus (fam. Leguminosae) [81]. It has been classified as generally recognized as safe at the 0.2–1.3% level in food stuffs in the USA since 1961[79] and has the number E413 in the list of additives approved by the Scientific Committee for Food of the European Community. The capacity of gum tragacanth to extensively modify the rheology of aqueous media even at fairly low concentration is the most important factor in evaluating tragacanth and is regarded as a measure of its quality and also a guide to its behavior as a suspending agent, stabilizer, and emulsifier [81]. A few studies have been devoted to functional properties of gum tragacanth, and most of the works on structural and functional properties of the gum as well as its application in various fields have been done. Recently the flow behavior of six species of Iranian gum tragacanth dispersions was investigated at different temperatures and ionic strengths, within a concentration range (0.05–1.5% w/w) using a controlled shear rate rheometer. The steady shear measurements showed that all of the gum dispersions had shear-thinning natures. The power law model was used to describe the rheological properties of dispersions and Arrhenius model was used to evaluate the temperature effect. The workers carried out composition analysis; surface tension measurement, particle size analysis, and color measurement of all the species were also carried out. Their results indicated that the six species of gum tragacanth studied exhibited significantly different physicochemical properties [82].

Mucilage gums: Many seeds contain polysaccharide food reserves which produce intracellular seed gums usually obtained by extraction from the seeds. Guar gum is obtained from the ground endosperms or seeds of the plant *Cyamopsistetragonolobus* (Fam. Leguminosae). Locust bean gum is obtained from the endosperms of the hard seeds of the locust bean tree (Carob tree), *Ceratoniasiliqua* (Fam. Caesalpiniaceae) [53].

Locust bean gum: It is also called carob gum, as it is derived from the seeds of the leguminous plant carob, *Ceratoniasiliqua* Linn (Fam. Caesalpiniaceae). Locust bean gum has an irregularly shaped molecule with branched β-1, 4-D-galactomannan units (See figure 4 for molecular structure). This neutral polymer is only slightly soluble in cold water; it requires heat to achieve full hydration and maximum

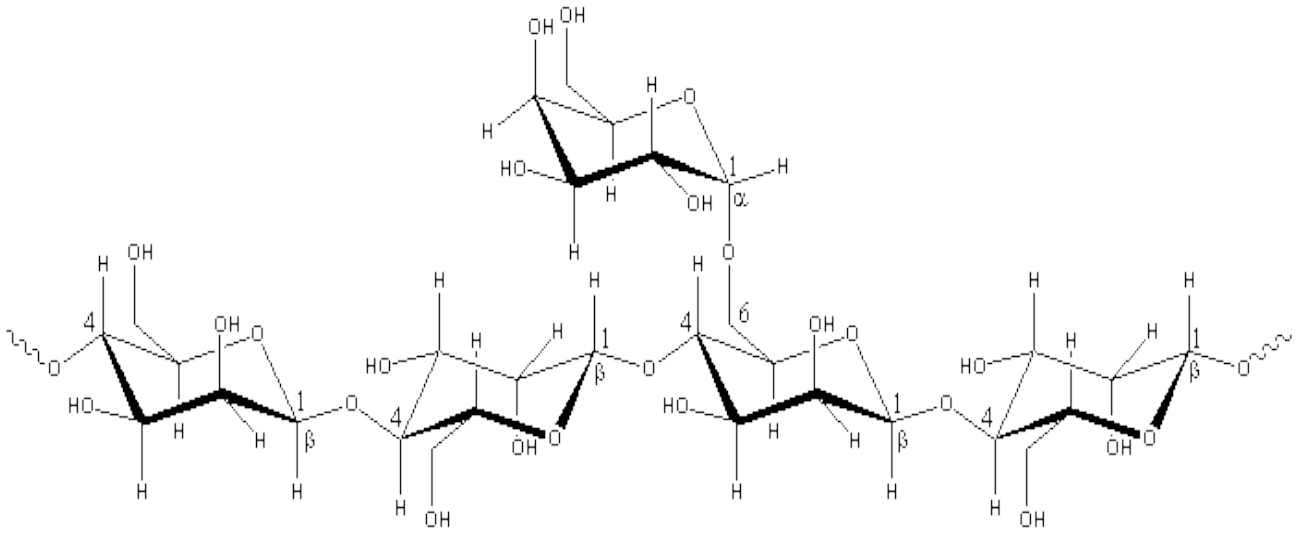

Figure 4: Molecular structure of Locust bean gum.

viscosity. Cross-linked galactomannan however led to water-insoluble film forming product-showing degradation in colonic microflora The colon-specific drug delivery systems based on polysaccharides, locust bean gum and chitosan in the ratio of 2:3, 3:2 and 4:1, were evaluated using *in vitro* and *in vivo* methods Core tablets containing mesalazine with average weight of 80mg were prepared by compressing the materials using 6-mm round, flat, and plain punches on a single station tablet machine. The formulated core tablets were compression coated with different quantities of locust bean gum and chitosan. The *in vitro* studies in pH 6.8 phosphate buffer containing 2%w/v rat caecal contents showed that the cumulative percentage release of mesalazine after 26 hr was 31.25 ± 0.56, 46.25 ± 0.96, and 97.5 ± 0.26, respectively. The *in vivo* studies conducted in nine healthy male human volunteers for the various formulations showed that the drug release was initiated only after 5hr, which is the transit time of small intestine. *In vitro* drug release studies and *in vivo* studies revealed that the locust bean gum and chitosan as a coating material applied over the core tablet was capable of protecting the drug from being released in the physiological environment of stomach and small intestine and was susceptible to colonic bacterial enzymatic actions with resultant drug release in the colon (Figure 4).

Guar gum: Guar gum, obtained from the ground endosperms of Cyamposistetragonolobus, consists of chiefly high molecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycosidic linkages and shows degradation in the large intestine due the presence of microbial enzymes. The structure of guar gum is a linear chain of β-D-mannopyranosyl units linked (1→4) with single member α-D-galacto-pyranosyl units occurring as side branches. It contains about 80% galactomannan, 12% water, 5% protein, 2% acid soluble ash, and 0.7% fat. Guar gum has a molecular weight of approximately 1 million, giving it a high viscosity in solution. This galactomannan is soluble in cold water, hydrating quickly to produce viscous pseudo plastic solutions that although shear-thinning generally have greater low-shear viscosity than other hydrocolloids. This gelling property retards release of the drug from the dosage form, and it is susceptible to degradation in the colonic environment.

Guar gum is a non-ionic polysaccharide that is found abundantly in nature and has many properties desirable for drug delivery applications. However, due to its high swelling characteristics in aqueous solution, the use of guar gum as delivery carriers is limited. Guar gum can be modified by derivatization, grafting and network formation to improve its property profile for a wide spectrum of biomedical applications. Guar gum and its derivatives in various forms such as coatings, matrix tablets, hydrogels and nano/micro particles can be exploited as potential carriers for targeted drug delivery [83]. An oral controlled drug delivery systems for highly water-soluble metroprolol using guar gum (30 (M1), 40 (M2) or 50% (M3) as a carrier in the form of a three-layer matrix tablet was formulated by wet granulation technique using starch paste as a binder. Three-layer matrix tablets of metoprolol tartrate were prepared by compressing on both sides of guar gum matrix tablet granules of metoprolol tartrate M1, M2 or M3 with either 50 (TL1M1, TL1M2 or TL1M3) or 75 mg (TL2M1, TL2M2 or TL2M3) of guar gum granules as release retardant layers. Both the matrix and three-layer matrix tablets were evaluated for hardness, thickness, drug content uniformity, and subjected to in vitro drug release studies. The amount of metoprolol tartrate released from the matrix and three-layer matrix tablets at different time intervals was estimated by using a HPLC method. Matrix tablets of metoprolol tartrate were unable to provide the required drug release rate. However, the three-layer guar gum matrix tablets (TL2M3) provided the required release rate on par with the theoretical release rate for metoprolol tartrate formulations meant for twice daily administration. The three-layer guar gum matrix tablet (TL2M3) showed no change either in physical appearance, drug content or in dissolution pattern after storage at 40°C/75% RH for 6 months. The FT-IR study did not show any possibility of metoprolol tartrate/guar gum interaction with the formulation excipients used in the study. The results indicated that guar gum, in the form of three-layer matrix tablets, is a potential carrier in the design of oral controlled drug delivery systems for highly water-soluble drugs such as metoprolol tartrate [84]. Similar results was obtained with guar gum at 65,75, and 85% in a three layer tablet of tri-metazidinedihydrochloride controlled release formulation [85].

A novel tablet formulation for oral administration using guar gum as the carrier and indo-methacin as a model drug has been investigated for colon-specific drug delivery using in vitro methods. Drug release studies under conditions mimicking mouth to colon transit have shown that guar gum protects the drug from being released completely in the physiological environment of stomach and small intestine. Studies in pH 6.8 phosphate buffered saline (PBS) containing rat caecal contents have demonstrated the susceptibility of guar gum to the colonic bacterial enzyme action with consequent drug release. The pre-treatment of rats orally with 1 ml of 2% w/v aqueous dispersion of guar gum for 3 days induced enzymes specifically acting on guar gum thereby increasing drug release. A further increase in drug release was observed with rat caecal contents obtained after 7 days of pre-treatment. The presence of 4% w/v of caecal contents obtained after 3 days and 7 days of enzyme induction showed biphasic drug release curves. The results illustrated the usefulness of guar gum as a potential carrier for colon-specific drug delivery. The scientists concluded on the study that the use of 4% w/v of rat caecal contents in PBS, obtained after 7 days of enzyme induction provided the best conditions for in vitro evaluation of guar gum [86]. Poly-acryl-amide-*grafted*-guar gum (pAAm-*g*-GG) was prepared by taking three different ratios of guar gum to acrylamide (1:2, 1:3.5 and 1:5). Amide groups of these grafted copolymers were converted into carboxylic functional groups. Fourier transform infrared (FTIR) spectroscopy and differential scanning calorimetry were used to characterize copolymers. Tablets were prepared by incorporating an antihypertensive drug viz., diltiazem hydrochloride. In-vitro drug release was carried out in simulated gastric and intestinal conditions. Effect of drug loading on release kinetics was evaluated. Release continued up to 8 and 12 h, respectively, for pAAm-*g*-GG and hydrolyzed pAAm-*g*-GG copolymers. Nature of drug transport through the polymer matrices was studied by comparing with Higuchi, Hixson-Crowell and Kopcha equations. The researchers found out that the drug release dissolution-controlled in case of unhydrolyzed copolymer while in the hydrolyzed copolymers, drug release was swelling-controlled initially (i.e., in 0.1N HCl), but at later stage, it became dissolution-controlled in pH 7.4. These observations led to the conclusion that Hydrolyzed pAAm-*g*-GG matrices are pH sensitive , which positioned them as potential materials for intestinal drug delivery [87].

Grewia gum: Grewia genus is today placed by most authors in the Family Malvaceae, in the expanded sense as proposed in the Angiosperm Phylogeny Group (APG). Formerly it was placed in either the linden Family (Tiliaceae) or the Spermamanniaceae. However, these were both not monophylectic with respect to other Malvales. Grewia and similar genera have been merged into the Malvaceae. Together with the bulk of the former spermanniaceae, Grewia is in the

Family Grewiodeae and therein the tribe Grewieae, of which it is the type genus [88].

The genus was named by the father of modern taxonomy, Carolus Linnaeus (1707-1778), in honor of the Nehemiah Grew (1641-1712). Grew, from England, was one of the leading plant anatomists and microscope researchers of his time, and his study of pollen laid the groundwork for modern-day palynology [89]. Briefly, Carl Linnaeus (Latinized as Carolus Linnaeus, also known after his ennoblement as Carl von Linne [90] who lived from 23 May 1707 – 10 January 1778) was a Swedish botanist, physician, and zoologist, who laid the foundations for the modern scheme of binomial nomenclature. He is known as the father of modern taxonomy, and is also considered one of the fathers of modern ecology [90]. About 150 species of Grewia have been confined and most of them were said to be in Africa -[91].

There were ten (10) citations in International Pharmaceutical Abstracts (IPA) database on grewia Family a year ago, in EBSCO there are thirty-six (36) while in PubMed there were thirty-eight (38) citations in 2010 on Grewia.

Increased interest on *Grewia mollis*as a potential pharmaceutical excipient has been on since the last decade and has been investigated for its phytochemical, toxicological and histopathological properties [92]. In their work they used soxhlet extraction to obtain the crude materials from the stem bark of the plants along with those of *Boswelliadalziellii, Jatrophacurcas* and *Pterocarpuserinaceus* claimed to be of medicinal values in Nigeria. The study showed that tannins, saponins, flavonoids, glycosides, balsam, phenols, terpenes, steroids were present while alkaloids were absent. The study further demonstrated that the plant is safe for human consumption with LD 50 of 1500 mg/kg body weight. The extracts showed no structural effects on the liver and heart.

The actual investigation on the pharmaceutical uses of *Grewia mollis* was documented in the early 2000's [93-98]. The scientists investigated some physicochemical and rheological characteristics as well as water vapor permeability of the aqueous-based films. The gum was investigated for its binding properties in sodium salicylate tablets [96] and the effect of granulating fluid on the release profile of drug containing the gum [98]. Other workers [99] also found that method of incorporating the gum into tablet formulation had effect on tablet properties, where they discovered that incorporation by activation with water produced better tablet properties than when incorporate by wet granulation or direct compression. Scientists [100] evaluated the gum by acid treatment, heating and some modification showed reduced viscosity and improved drug release from tablets. More recently other researchers [101] investigated the binding property of the gum in comparison with both untreated gum and gelatin in paracetamol tablet formulations. Compression properties of the formulations were analyzed using density measurements and assessed by compression equation of Heckel. The mechanical properties of the formulations were assessed using crushing strength and friability as well as crushing strength friability ratio. The drug release properties of the tablets formed were assessed using disintegration and dissolution times. Tablet formulations containing treated grewia gum exhibited low onset of plastic deformation, while that of untreated gum and gelatin were relatively high onset of deformation. The friability of paracetamol tablet formulation increased with increase in acid concentration and treatment time. The crushing strength, disintegration and dissolution times decreased with increase in acid concentration and treatment time. Tablets containing untreated gum possessed high crushing strength, disintegration and dissolution times and low friability compared to those containing gelatin and the treated gum. Depending on the desired onset of action of medicament acid treated grewia gum can be used in formulation of conventional tablets especially if the formulation does not require sustained release [102]. Advancement in technology and analytical tools will continue to aid the understanding of natural polymers and better position them for use as pharmaceutical excipients. Grewia gum was extracted from the inner stem bark of *Grewia mollis* and characterized by several techniques such as gas chromatography (GC), gel permeation chromatography (GPC), scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and thermo gravimetric analysis of the extracted sample. Spectroscopic techniques such as x-ray photoelectron spectroscopy (XPS), Fourier-transformed infrared (FT-IR), solid-state nuclear magnetic resonance (NMR), and 1H and 13C NMR and NIR techniques were also used to characterize the gum [103,104]. The gum is a typically amorphous polysaccharide gum containing glucose, rhamnose, galactose, arabinose and xylose as neutral sugars. It has an average molecular weight of 5925 kDa expressed as the pullulan equivalent. The gum slowly hydrated in water, dispersing and swelling to form a highly viscous dispersion exhibiting pseudo plastic flow behavior. Fractions of the gum obtained by centrifugation successively at 4500 rpm for 30 minutes with average molecular weights between 230 and 235 kDa showed improved aqueous solubility that was useful in delivering more solids to the substrate when used as a film coating agent [104].

Okra gum: Okra is a tall erect annual plant botanically known as *Abelmoschusesculentus* (Fam. Malvaceae). It is widely cultivated and grown in most tropical part of Nigeria. Okra has been used as food and soup in Africa [105] and Asia [106] and has been a subject of research in agriculture and food [105,107-119]. Okra is known for its viscous mucilaginous solution which results when it is crushed and extracted in water [120]. The potential of okra gum as a pharmaceutical excipient has received attention in literatures as a binder [121,122], control release [123], film coating [124], bio-adhesive [125] and suspending [126-128] agent. Okra gum has been evaluated as a controlled-release agent in modified release matrices, in comparison with sodium carboxy-methyl-cellulose (NaCMC) and hydroxyl-propyl-methyl-cellulose (HPMC), using Paracetamol as a model drug. Tablets were produced by direct compression and the in-vitro drug release was assessed in conditions mimicking the gastro intestinal system, for 6 h. Okra gum matrices provided a controlled-release of Paracetamol for more than 6 h and the release rates followed time-independent kinetics. The release rates were dependent on the concentration of the drug present in the matrix. The addition of tablet excipients, lactose and Avicel, altered the dissolution profile and the release kinetics. Okra gum compared favorably with NaCMC, and a combination of Okra gum and NaCMC or on further addition of HPMC resulted in near zero order release of paracetamol from the matrix tablet. The results indicated that Okra gum matrices was useful in the formulation of sustained-release tablets for up to 6h [129].

Kyaha gum: Khaya gum is obtained by extraction from Khaya*senegalensis* and *Khayagrandifoliola* (Fam. Meliaceae). The comparative binding effects of khaya gum obtained from *Khayasenegalensis* and *Khayagrandifoliola* in paracetamol tablet formulation were evaluated [130]. The mechanical properties of the tablets were assessed using the tensile strength (T), brittle fracture index (BFI) and friability (F) of the tablets while the drug release properties were assessed using disintegration and dissolution times. The tensile strength, disintegration and the dissolution times of tablets increased with the increase in binder concentration while F and BFI decreased.

K. senegalensis gum produced strong tablets with long disintegration and dissolution times compared to *K. grandifoliola* gum. The results showed that *K. senegalensis* will be more appropriate as a binding agent than *K. grandifoliola* when high mechanical strength and slow release profiles of tablets are desired.

Moringaoleifer gum: A natural gum obtained from plant *Moringaoleifera* gum was extracted by using water as solvent and precipitated using acetone as non-solvent. Physical characteristics such as, solubility, swelling index, loss on drying, and pH were studied. Diclofenac sodium was used as model drug for the formulation of gels. Seven batches of drug loaded gels with concentration of mucilage ranging from 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, and 8.5 were formulated by using glycerin as plasticizer and methyl paraben as preservative. The pH, viscosity, and *in vitro* diffusion profiles were studied. The gels prepared with 8.0% of mucilage were found to be ideal and comparable with a commercial preparation [131].

Irvingiagabonensis: *Irvingiagabonensis* (AubryLecomte ex O'Rorke) Baill. Commonly known as 'African mango' or 'bush mango' is a tree of 15-40 m, with a bole slightly buttressed [132-135]. The plant is a wild forest tree [134,136] with dark green foliage and yellow fragrant flowers and occurs in the wild lowland forest; 2-3 trees occur together and in some areas, it is reported to be widespread. *I.gabonensis* is largely distributed in Africa [137-140]. The fruit is spherical with smooth yellow fibrous mesocarp and hard endocarp when ripe. The seed from the plant has been of interest in the food [136,141-143], beverages [144-146], medical [135,147-152] and pharmaceutical [153-162] as well as cosmetic circles [163]. The seed of the plant contains lipids and polymeric constituents [105,137,146,164-167]. Both the lipids (dika fat) and the polymeric (gum) components are of importance to the pharmaceutical scientists as excipients in Africa and the developing world. The mucilage from the kernel has been used as binding agent in tablet formulation [153], as emulsifying and suspending agent [105,168]. On the other hand, the lipid has been employed in tableting as lubricant [162,169], sustained release ingredient [154,155,170], microencapsulation [171], as suppository base [158,159,172] and as a component of film coating operation [158]. The lipids component of *I.gabonensis* seeds have been traditionally extracted using n-hexane [169] or other organic solvents [172]; and more recently an enzymatic approaches for extracting the lipid components have been investigated [173]. The polymeric component of the seed has been extracted from aqueous dispersion using petroleum ether [153] or diethyl ether [174]. None of the extraction processes described in the literature provided for simultaneous extraction of the lipid and polymer component until recently [175]. This was to overcome adverse environmental consequences of disposal of organic solvents used in its extraction and also address worker's safety concerns and cost of extraction. A lot have appeared in literature on the application of both the gum and the fat from this plant. The mucilage extracted from the kernels of Irvingiagabonensis was evaluated for use as suspending and emulsifying agent [168]. The rheological behavior of the mucilage was studied and compared to that of tragacanth. As a suspending agent, Irvingia mucilage was compared to tragacanth at various concentrations (0.5, 1.0, 1.5 and 2.0% w/v) in the formulation of sulphanilamide suspensions. At all concentrations the formulated suspensions with Irvingia mucilage gave higher Hu (final sedimentation height) and F (sedimentation volume) values. As an emulsifying agent, the properties of Irvingia mucilage was compared to tragacanth and acacia gum. The emulsions prepared with 0.6, 1.0, and 1.5% tragacanth and Irvingia 'cracked' within six days while that with 12.5% w/v acacia started showing signs of creaming at the tenth day. The emulsion prepared with 2.0% w/v Irvingia mucilage was however stable throughout the six weeks of study. The results indicate that Irvingia mucilage performed better than acacia and tragacanth even at lower concentrations in the formulation of emulsions and suspensions.

The potential of irvingia fat as a suppository base has been evaluated [158,172]. The binding effects on metronidazole tablets [153], sustained release profiles on some tablets [154,155] as well as lubricating potential in tablet formulations [162] incorporating irvingia gum have been studied.

Hakeagibbosa gum: The muco adhesive and sustained-release properties of the water-soluble gum obtained from Hakeagibbosa (hakea), for the formulation of buccal tablets. Flat-faced tablets containing hakea were formulated using chlorpheniramine maleate (CPM) as a model drug had been investigated [176]. In the study two types of tablets were prepared: uncoated tablets (type I) and tablets in which all but one face of the type I tablet was coated with hydrogenated castor oil (Cutina) using a compression coating technique (type II). FTIR, differential scanning calorimetry (DSC), UV spectroscopy, and acid–base titrations were used to evaluate the properties of the formulations. Mathematical modeling of the CPM release data was developed to elucidate the mechanism of drug release. The muco adhesive strength was evaluated by quantitating the force of detachment. Finally, the rates of water uptake and erosion were determined for the buccal tablets. The time required for 90% of the CPM to be released in vitro ($t_{90\%}$) was used as a basis for comparison. For formulations that did not contain hakea, the $t_{90\%}$ was 14min for both directly compressed and wet granulated tablets, whereas the $t_{90\%}$ for wet granulated tablets containing 2 or 32mg hakea/tablet was 36 and 165min, respectively. Directly compressed tablets containing 2, 12, 22, and 32mg hakea/tablet displayed $t_{90\%}$ values of 48, 120, 330, and 405min, respectively. DSC, FTIR, UV spectroscopy and acid–base titration experiments suggested the absence of chemical interactions. The force of detachment for directly compressed and wet granulated tablets increased from 0.70 ± 0.3 to 4.08 ± 0.52 N and from 0.65 ± 0.28 to 3.94 ± 0.31 N as the amount of hakea per tablet was increased from 0 to 32 mg, respectively, at a 5 N attachment compression force. The workers concluded that hakea, may not only be utilized to sustain the release of CPM from a unidirectional-release buccal tablet, but it also exhibited excellent mucoadhesive properties. The mechanism by which CPM release was sustained was more likely due to slow relaxation of the hydrated hakea.

Psyllium mucilage: Psyllium mucilage is obtained from the seed coat of *Plantagoovata* (Fam. Plantaginaceae) by milling the outer layer of the seeds [177]. Psyllium has been evaluated for its tablet binding properties [178]. Hydrogels of psyllium and methacrylamide prepared using *N*,*N*'-methylene-bis-acryl-amide as cross-linker and loaded with insulin showed controlled release of the active ingredient [179].

Other natural gums and mucilage: *Sterculiafoetida* gum has been investigated as a swelling and erosion modulator in controlled release matrix tablets of diltiazem hydrochloride [180]. The pharmaceutical uses of other gums have been explored. These include *Colocassiaesculenta* [181], seeds of *Linumusitatissimum* [182], malva nut gum [183].

Inulin

Inulin is a naturally occurring storage polysaccharide found in many plants such as onion, garlic, artichoke, and chicory. Chemically, it belongs to the gluco-fructans and consists of a mixture of oligomers

and polymers containing 2 to 60 (or more) β-2-1 linked D-fructose molecules. Most of these fructose chains have a glucose unit as the initial moiety. The inulin has been incorporated into Eudragit RS films for preparation of mixed films that resisted degradation in the upper GIT but digested in human fecal medium by the action of Bifidobacteria and Bacteroids [184]. Various inulin hydrogels have been developed that serve as potential carriers for the introduction of drugs into the colon [185]. Vinyl groups were introduced in inulin chains to form hydrogels by free radical polymerization. Inulin was reacted with glycidylmethacrylated in N,N-dimethylformamide in the presence of 4-dimethylaminopyridine as catalyst. 1H and 13C NMR spectroscopy were used for the characterization of the obtained reaction product and revealed the conversion of the incorporated vinyl groups into covalent crosslink's upon free radical polymerization of aqueous solutions of the derivatized inulin [185].

Starches

Starch whether in the native or modified form has been used as one of the key pharmaceutical excipients in pharmaceutical tablet and capsule formulations. It serves various functions such as bulking, binder, disintegrant or aiding drug delivery. Microcapsules containing a protein and a proteinase inhibitor were prepared to deliver proteins or peptidic drugs orally [186]. Starch/bovine serum albumin mixed-walled microcapsules were prepared using interfacial cross-linking with terephthaloyl chloride. The microcapsules were loaded with native or amino-protected aprotinin by incorporating protease inhibitors in the aqueous phase during the cross-linking process. The protective effect of microcapsules with aprotinin for bovine serum albumin was revealed *in vitro*.

Acetylation of starch considerably decreases its swelling and enzymatic degradation [187]. Starch-acetate (SA) based delivery systems for controlled drug delivery has been reported [187]. These workers reported that acetylated of potato starch substantially retard drug release compared to that of natural potato starch film.

Tablet film coating with amylose-rich maize starch has been investigated [188]. These workers carried out a study on the use of aqueous –based amylose-rich starch (Hylon VII™) film coating of the tablets. Using a side vented pan coating system, they investigated the influence of plasticizer concentration, temperature of coating pan and the spray rate of the coating solution. In their study they observed that at low spray rates, the temperature of the coating pan did not affect the roughness of the coated tablet but at high spray rates, high temperatures gave smooth films. The dissolution rate of all Hylon VII™ –coated tablets was rapid in an acid medium, releasing 75% of the drug. Other works on the use of amylose and native starches as film forming agent in pharmaceutical film coatings have been reported [189-192]. A combination of amylose and ethyl-cellulose aqueous and non-aqueous based coatings for colon drug delivery has been reported [189-191,193]. Some workers [194] sourced and obtained cellulose and microcrystalline cellulose from maize cobs and they compared the tablet properties of paracetamol tablets made by direct compression with microcrystalline cellulose (MCC) as sole excipients with a multi-excipient formula in wet granulation and found that the former possesses better tablet properties apart from the added advantages of direct compression and fewer ingredients. Scientists have evaluated the physicochemical and powder properties of alpha- and micro-crystalline cellulose derived from maize cobs and they found that it has comparable attributes to Avicel® as a pharmaceutical excipient [195]. Other work on MCC and cellulose derived from maize cobs have been reported [196,197].

Dextran

Dextran hydrogels have been shown to be the promising carrier for the delivery of drugs to colon [198-200].

Cyclo dextrins

Cyclo dextrins (CyDs) are cyclic oligosaccharides consisting of six to eight glucose units joined through α-1, 4glucosidic bonds. CyDs remain intact during their passage through stomach and small intestine. However, in the colon, they undergo fermentation from the presence of vast colonic micro flora into small saccharides and thus absorbed from these regions [201,202]. CyDs form inclusion complexes with drug molecules because the interior of the molecule is relatively lipophilic while the exterior is hydrophilic [202]. It has been investigated through a study in healthy human volunteers that β CyDs are degraded to a very small extent in the small intestine but are completely digested in large intestine. Most bacterial strains that are isolated from human beings are capable of degrading CyDs. This has been proved by their ability to grow on cyclo dextrins by utilizing them as the sole carbon source and by the stimulation of cyclo dextrinase activity as low as 2–4 hr of exposure to CyDs. This property of the drug may be exploited for the formation of colon targeted drug delivery systems. Several CyD conjugates have been prepared and the enantio selective hydrolysis has been described. Formulation of pro-drug of CyDs with drug molecules can provide a versatile means for construction of not only colon targeted delivery systems, but also delayed release systems. Biphenyl acetic acid (BPAA), an anti-inflammatory drug, was conjugated with α-, β- and γ -CyDs and *in vivo* release pattern was investigated in rat after oral administration. The CyD pro-drug maintained the physical integrity in stomach and small intestine which is reflected from the observations that the absorption of pro-drugs from upper GIT was negligible, and after 6 hr most of the pro-drug approached the caecum and colon. The α- and γ -CyD amide pro-drugs were hydrolyzed to the maltose conjugate in the colon while the α- and γ -CyD ester pro-drugs produced BPAA in the caecum and colon. The anti-inflammatory effect of the α- and γ -CyD ester pro-drugs was assessed and compared with those of BPAA alone and the drug CyD complex prepared by the kneading method in a molar ratio of 1:1. In the case of β-CyD complex, a rapid anti-inflammatory response was observed from the small intestine after a fast dissolution of the complex. In sharp contrast, the γ -CyD ester pro-drug required a fairly long lag time to exhibit the drug activity, because BPAA was produced after the pro-drug had reached the caecum and colon [203,204]. Some investigators [205] prepared two CyD conjugates: ester and amide conjugates. They showed that ester conjugate released the drug preferentially when incubated with the contents of caecum or colon, whereas no appreciable drug release was observed on incubation with the contents of either stomach or intestine in intestinal or liver homogenates or in rat blood. Systemic side effects of prednisolone were significantly reduced when conjugated with α-CyD [206]. The lower side effect of the conjugate was attributed to passage of the conjugate through the stomach and small intestine without significant degradation or absorption, followed by the degradation of the conjugate site-specifically in the large intestine.

Curdlan

Curdlan is a neutral, essentially linear (1"3)-β-glucan which may have a few intra- or inter-chain (1"6) linkages. Curdlan's unusual

rheological properties among natural and synthetic polymers underlie its use as a thickening and gelling agent in foods. Apart from being tasteless, colourless and odourless, the main advantages are that in contrast to cold-set gels and heat-set gels, the heating process alone produces different forms of curdlan gel with different textural qualities, physical stabilities and water-holding capacities [207]. Gels of variable strength are formed depending on the heating temperature, time of heat-treatment and curdlan concentration. The safety of curdlan has been assessed in animal studies and *in vitro* tests and it is approved in food use in Korea, Taiwan and Japan as an inert dietary fibre. It is registered in the USA as a food additive (Figure 5).

Scleroglucan

Among these macromolecules, scleroglucan (Sclg) also seems to be potentially useful for the formulation of modified release dosage forms and numerous studies have been devoted to this specific topic [208]. Scleroglucan (Sclg) is a branched homo polysaccharide consisting of a main chain of (1-3)-linked b-D glucopyranosyl units bearing, every third unit, a single b-D-glucopyranosyl unit linked (1-6). This polysaccharide is resistant to hydrolysis and its solutions show an interesting rheological behaviour: viscosity remains practically constant, even at high ionic strength, up to pH-12 and to 90°C.

Interest in this polysaccharide was first aroused in 1967 [209]. Sclg is a general term used to designate a class of glucans of similar structure produced by fungi, especially those of the genus Sclerotium. The commercial product is termed Scleroglucan, but it is also known with other names according to the company that produces the polysaccharide (e.g., Actigum, Clearogel, Polytetran, Polytran FS, Sclerogum). Because of its peculiar rheological properties and its resistance to hydrolysis, temperature and electrolytes, Sclg has various industrial applications, especially in the oil industry for thickening, drilling muds and for enhanced oil recovery and in food industry [209, 210]. In pharmaceutical products, Sclg may be used as a laxative in tablet coatings and in general to stabilize suspensions. Recently carboxymethyl derivative of scleroglucan (Scl-CM) with a 65±5% carboxylic group degree of derivatization (DD) was synthesized and characterized. Aqueous solutions of the polymer underwent to a sharp transition toward a gel like behavior in the presence of divalent ions such as Ca^{+2}. Physical hydrogels with different Scl-CM/Ca^{+2} ratios were prepared and characterized for their rheological behavior. Their potential as drug delivery systems were also evaluated. To this end three non-steroidal anti-inflammatory drugs (NSAIDs) were loaded into the hydrogels obtained with 2% w/v solution of Scl-CM and 0.05 and 0.1 M $CaCl_2$. The release rate of the drugs was critically related to the salt concentration. By an appropriate combination of the hydrogels prepared using different amounts of salt, it was possible to obtain a system able to release diclofenac with zero-order kinetics. Primary skin irritation tests showed a good biocompatibility of the new polymer, as well as of its hydrogels. These results suggested a potential of the new hydrogels for the development of modified delivery systems in oral and topical formulations [211,212].

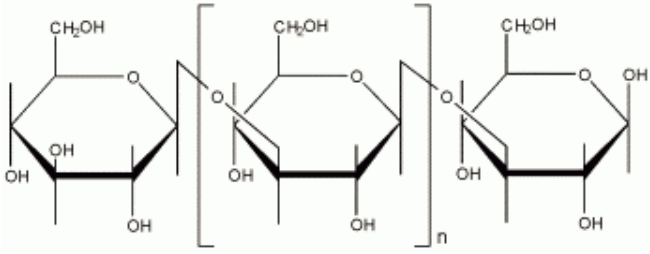

Figure 5: Structural formular of curdlan.

Rosin

Rosin is a low molecular weight (400 Da) natural polymer obtained from the oleoresin of *Pinussoxburghui, Pinuslongifolium* and *Pinustoeda.* It has as components abietic and pimaric acids. Rosin and its derivatives have enjoyed growing roles in Pharmacy. They have been investigated for microencapsulation, film-forming and coating properties, and as matrix materials in tablets for sustained and controlled release [213,214].

Studies on the film forming and coating properties of rosin and the glycerol ester of maleic rosin showed that rosin has excellent film forming properties with good to be used as coating materials for pharmaceutical products as well as in sustained-release drug delivery systems. The rosin films were biodegradable and biocompatible [214]. Derivatives of rosin have been synthesized by reaction with polyethylene glycol 200 and maleic anhydride. The derivative proofed suitable for sustaining drug release from matrix tablets and pellets [215]. Rosin nanoparticles loaded with hydrocortisone retarded the release of the active and demonstrated the potential of rosin production of effective nanoparticulate drug delivery systems [216].

Conclusion

The research into and use of excipients from natural sources was reviewed and were discussed according to their classes. Natural polymeric excipients and their modifications have continued to dominate the research efforts of scientists in finding cheap, less expensive, biodegradable, ecofriendly excipients. Some of these excipients have obvious advantages over their synthetic counterparts in some specific delivery systems due to their inherent characteristics. If the current vigorous investigations on the use of natural polymeric materials are sustained and maintained, it is probable that there would be a breakthrough that will overcome some of the disadvantages of this class of potential pharmaceutical excipients that would change the landscape of the preferred pharmaceutical excipients for drug delivery in the future.

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