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Review Article

Natural Gums and Mucilages: A Review on Multifaceted Excipients in Pharmaceutical Science and Research

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ABSTRACT
The application of natural polysaccharides in novel drug delivery systems to deliver the bioactive agents has been hampered by the synthetic polymers. The main benefits of the natural polysaccharides are their being biodegradable, biocompatible, non-toxic, richly available and less expensive. Because of the advances in drug delivery technology, natural polysaccharides are included in novel drug delivery to fulfill multitask functions and in some cases directly or indirectly control the extent and/or rate of drug release. Substantial research efforts have been directed towards developing safe and efficient natural based polysaccharide particulate drug delivery systems. The present review outlines the natural based polysaccharides, natural gums and mucilages and their isolation, purification, standardization and characterization characteristics along with their applications are covered. Also this review covers fabrication techniques for natural polysaccharide based particulate drug delivery systems, specifically micro and nanoparticle drug delivery systems with their characterization techniques and applications are discussed.

Keywords: Natural Polysaccharides; Natural gums and mucilages; Standardization; Applications; Modification.

INTRODUCTION

In this developing world, there is an immense demand for novel drug delivery systems, and there is a noteworthy increase in the approvals of similar systems. Natural excipients and their application in the pharmaceutical industry are super imposed by the presence of synthetic excipients. Natural excipients are preferred over the synthetic as they are inert, safe, non-toxic, biocompatible, biodegradable, low cost, eco-friendly and abundantly available in nature.[1-3] Conventionally, excipients were incorporated in dosage forms as inert vehicles but in modern pharmaceutical dosage forms they often accomplish multitask roles such as improvement of solubility of poorly soluble drugs enhance bioavailability, desired drug release, target specific in the form of microparticles, and nanoparticles.[4] Most of natural polysaccharides used in the food industry are regarded as safe for human consumption.

Natural polysaccharides are often included in the design of controlled drug delivery such as those target delivery of the drug to a specific site in the gastro intestinal tract (GIT), this can be achieved by various mechanisms including coating granules, pellets, tablets with polysaccharides having pH dependent solubility, or incorporating non-digestible polysaccharides that are degraded by bacterial enzymes present in the colon, this property makes these polysaccharides potentially useful in the formulation of colon-targeted drug delivery systems. The polysaccharides can also be modified in different ways to obtain tailor-made materials for drug delivery systems and thus can compete with the available synthetic excipients. With the increasing interest in excipients of natural origin, the pharmaceutical world has compliance to use most of them in their formulations. Moreover, the tremendous orientation of pharma world towards these naturally derived polysaccharides has become a subject of increasing interest to discover, extract and purify such compounds from the reported origin. The focus should be directed towards the development of the newer excipients, so that they can enter the pharmaceutical industry and newer formulations could be developed and formulation problems could be solved.[5, 6]

Natural Polysaccharides: Polysaccharides are composed of many monosaccharide residues that are joined one to the other by *O*-glycosidic linkages. Polysaccharides are commonly known as Cinderella of biopolymers, with wide range of applications.[7]

Their structures are often linear, but may contain various degrees of branching. In nature, polysaccharides have various resources from algal origin, plant origin, microbial origin and animal origin .Polysaccharides have a general formula of $C_x(H_2O)_y$ where x is usually a large number between 200 and 2500. Considering that the repeating units in the polymer backbone are often six-carbon monosaccharides, the general formula can also be represented as $(C_6H_{10}O_5)_n$ where $40 \leq n \leq 3000$.[8-10]

Classification of Natural Polysaccharides: Polysaccharides are extracted and isolated from plant seeds. (locust bean gum, guar gum, tara gum, and tamarind gum). They also play a major role in the structural integrity and mechanical strength of plant tissues by forming a hydrated cross-linked

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Table 1: Preliminary confirmative test for dried mucilage

Test	Observation	Inferences
Molisch's test: 100 mg dried mucilage powder + Molisch's reagent + conc. H_2SO_4 on the side of a test tube.	Violet green color observed at the junction of the two layers	Carbohydrate present
Ruthenium test: Take a small quantity of dried mucilage powder, mount it on a slide with ruthenium red solution and observe it under microscope.	Pink color develops	Mucilage present
Iodine test: 100 mg dried mucilage powder + 1 ml 0.2 N iodine solution.	No color observed in solution	Polysaccharides present (starch is absent)
Enzyme test: Dissolve 100 mg dried mucilage powder in 20 ml distilled water; add 0.5 ml of benzidine in alcohol (90%). Shake and allow to stand for few minutes.	No blue color produced	Enzyme absent (Distinction between dried mucilage and acacia)

three dimensional network (pectin). On the other hand, cellulose an essential ingredient of the cell wall in higher plants is most abundantly available biopolymer present in the nature.

Another most important classification of polysaccharide are tree exudates with an history of 5,000 years which are known for their properties like thickening, emulsifying, stabilizing, binding agents and matrix formers in both food and pharmaceutical industry (gum acacia, gum tragacanth and gum karaya). Gums are present in huge quantities in varieties of plants, animals, marine and microbial sources. Plant gums are very common with different structural and metabolic functions commonly found in family Leguminosae, Sterculiaceae, Bixaceae, Compositae, Combretaceae, Gigarginaceae.

The different available polysaccharides can be classified as follows.[8-11]

Based on the ionic charge: Gums have been classified into anionic, cationic and non-ionic. a) Anionic charged gums: tragacanth, arabic, karaya, gellan, agar, pectin, algin, carrgeenans. b) Cationic charged gums: chitosan. c) Non-ionic charged gums: guar gum, locust bean gum, tamarind gum, arabinans, xanthan gum, amylase, cellulose.

Based on the origin: a) Marine (sea weeds gum): alginates, agar, Carrageenans. b) Animal origin: chitin and chitosan, Chondroitin sulfate, hyaluronic acid. c) Plant origin: i) Seed gums–locust bean, guar, starch, cellulose, amylase. ii) Tree exudates-gum arabia, tragacanth, ghatti, karaya. iii) Tubers-Potato starch. iv) Extracts-pectin. d) Microbial origin (fungi and bacteria): glycan, pullulan, dextran, xanthan, gellan.

Based on the shape: a) Linear: amylase, pectin, cellulose. b) Branched: i) Short branched-guar gum, locust bean gum; ii) Long branched-amylopectin, karaya gum, gum tragacanth, gum arabic.

Natural Gums and Mucilages: Gums are considered to be pathological products formed following injury to the plant or owing to unfavorable conditions, such as drought, by a breakdown of cell walls (extra cellular formation; gummosis) while, mucilages are generally normal products of metabolism, formed within the cell (intracellular formation) and/or are produced without injury to the plant. Gums readily dissolve in water, whereas, mucilage form slimy masses. Gums are pathological products, whereas mucilages are physiological products. Acacia, tragacanth, and guar gum are examples of gums while mucilages are often found in different parts of plants. For example, in the epidermal cells of leaves (senna), in seed coats (linseed, psyllium), roots (marshmallow), barks (slippery elm) and middle lamella (aloe). Gums and mucilages have certain similarities- both are plant hydrocolloids. They are also translucent amorphous substances and polymers of a monosaccharide or mixed monosaccharides and many of them are combined with uronic acids. Gums and mucilages have similar constituents and on hydrolysis yield a mixture of sugars and uronic acids. Gums and mucilages contain hydrophilic molecules, which can combine with water to form viscous solutions or gels. The nature of the compounds involved influences the properties of different gums. Linear polysaccharides occupy more space and are more viscous than highly branched compounds of the same molecular weight. The branched compounds form gels more easily and are more stable because extensive interaction along the chains is not possible.[12]

Advantages of Natural Gums and Mucilages in Pharmaceutical Sciences: The following are a number of the advantages of natural plant–based materials.[13, 14]

- Biodegradable- Naturally available biodegradable polymers are produced by all living organisms. They represent truly renewable source and they have no adverse impact on humans or environmental health.
- Biocompatible and non-toxic- Chemically, nearly all of these plant materials are carbohydrates composed of repeating sugar (monosaccharides) units. Hence, they are nontoxic.
- Low cost- It is always cheaper to use natural sources. The production cost is also much lower compared with that for synthetic material. India and many developing countries are dependent on agriculture.
- Environmental-friendly processing- Gums and mucilages from different sources are easily collected in different seasons in large quantities due to the simple production processes involved.

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Table 2: Pharmacopoeial Specifications for Natural Gums and Mucilages

Excipient	Test	Pharmacopeia
Acacia	Microbial limit, ash values	USP, JP, PhEur
Alginic acid	Microbial limit, pH, loss on drying	USP, PhEur
Carrageenan	Solubility, viscosity, loss on drying, ash value	USP
Dextrin	Loss on drying, residue on ignition, reducing sugars	USP, BP, JP
Gelatin	Isoelectric point, microbial limit, residue on ignition, loss on drying, total ash, jelly strength	USP, JP, PhEur
Guar gum	pH, microbial contamination, apparent viscosity, loss on drying, ash, galactomannans, organic volatile impurities	USP, PhEur
Lecithin	Water, arsenic, lead, acid value, heavy metals	USP
Sodium alginate	Microbial limit, appearance of solution, loss on drying, ash, heavy metals	USP, PhEur
Tragacanth	Microbial limits, flow time, lead, acacia and other soluble gums, heavy metals	USP, JP, PhEur
Xanthan gum	pH, viscosity, microbial limits, loss on drying, ash, heavy metals, organic volatile impurities	USP, PhEur
Gellan gum	pH, microbial limit, loss on drying, moisture content, specific gravity, solubility, bulk density	USP

- Local availability (especially in developing countries)- In developing countries, governments promote the production of plant like guar gum and tragacanth
- because of the wide applications in a variety of industries.
- Better patient tolerance as well as public acceptance- There is less chance of side and adverse effects with natural materials compared with synthetic one. For example, PMMA, povidone.
- Edible sources- Most gums and mucilages are obtained from edible sources.

Disadvantages of Natural Gums and Mucilages: The following are a number of the disadvantages of natural plant–based materials.[13, 14]

- Microbial contamination- The equilibrium moisture content present in the gums and mucilages is normally 10% or more and, structurally, they are carbohydrates and, during production, they are exposed to the external environment and, so there is a chance of microbial contamination. However, this can be prevented by proper handling and the use of preservatives.
- Reduced viscosity on storage- Normally, when gums and mucilages come into contact with water there is an increase in the viscosity of the formulations. Due to the complex nature of gums and mucilages (monosaccharides to polysaccharides and their derivatives), it has been found that after storage there is reduced in viscosity.

Isolation and Purification of Natural Gums and Mucilages: Plant material is dried in sunlight (preferably) or in an oven at 105˚C to retain its properties unchanged. Generally, chlorophyll or pigments are present in the plant which should be removed before isolating the mucilage. Plant material must be treated with petroleum ether and chloroform (to remove pigments and chlorophyll) and then with distilled water. Care should be taken when drying the final isolated/extracted mucilage. It must be dried at a very low temperature (not more than 50˚C) or in a vacuum. The dried material is stored carefully in desiccators to prevent further moisture uptake or degradation.

Baveja et al., and Wahi et al., reported the following method for the isolation of mucilage. The fresh plant materials were collected washed with water to remove dirt and debris, and dried. Then, the powdered material was soaked in water for 5-6 h, boiled for 30 min, and allows standing 1 h so that all the mucilage was released into the water. The material was then squeezed from an eight muslin bag to remove the marc from the solution. Following this, three volumes of acetone was added to the filtrate to precipitate the mucilage. The mucilage was separated, dried in an oven at a temperature less than 50˚C, and the dried powder was passed through a No. 80 sieve and stored in a desiccator until required. The isolated mucilage from the plant was subjected to some preliminary confirmative testing.

Table No. 1 shows the preliminary confirmative test for dried mucilage.[15, 16]

Extraction is one of the most crucial procedures to achieve complete recovery of target compounds from plants. Recently, microwave energy has started to be used for the extraction of phytoconstituents from plants. It is a simple, fast, clean, eco-friendly and efficient method and saves energy, fuel and electricity.[17]

Microwave extraction follows the same principle as maceration or percolation, but the speed of breaking up of the plant cells and tissues is much higher. Microwave assisted extraction methods require a shorter time and less solvent, and provide a higher extraction rate and better products at a lower cost. Plant material is powdered in a mechanical blender for 5 min and then soaked in distilled water for 24 hrs in a 1000 ml beaker. It is kept in a microwave oven along with a glass tube to prevent bumping when subjected to microwave irradiation. The beaker is removed from the oven and allowed to stand for 2 hrs to allow the mucilage to be released into the water. It is then processed in a similar way to the conventional procedure, weighed and stored.[17]

Characterization and Standardization of Natural Gums and Mucilages: A suitable strategy is required to save money and time. Over-characterization is not desirable, because excessive use of time and resources could actually delay

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Table 3: Pharmaceutical Applications of Natural Gums and Mucilages

Common Name	Botanical Name	Family	Pharmaceutical Applications	Reference
Albizia gum	*Albizia Zygia*	*Leguminoseae*	Tablet binder	34-36
Asario Mucilage	*Lepidum Sativum*	*Cruciferae*	Suspending agent, emulsifying agent,	37, 38
Bavchi Mucilage	*Ocimum Canum*	*Labiatae*	Suspending agent, emulsifying agent	39
Cashew gum	*Anacardium occidentale*	*Anacardiaceae*	Suspending agent	40-43
Guar gum	*Cyamompsis tetraganolobus*	*Leguminoseae*	Binder, emulsifier, disintegrant	44-49
Gum acacia	*Acacia Arabica*	*Leguminoseae*	Suspending agent, emulsifying agent, binder in tablets, demulcent and emollient	50
Gum ghatti	*Anogeissus Latifolia*	*Combretaceae*	Binder, emulsifier, suspending agent	51
Gum Tragacanth	*Astragalus Gummifer*	*Leguminoseae*	Suspending agent, emulsifying agent, demulcent, emollient	52
Karaya gum	*Sterculiaurens*	*Sterculiaceae*	Suspending agent, emulsifying agent, dental adhesive, sustaining agent	53-61
Khaya gum	*Khaya grandifolia*	*Meliaceae*	Binding agent	62
Sodium alginate	*Macrocytis pyrifera*	*Lessoniaceae*	Suspending and sustained release agent	63-71
Xanthan gum	*Xanthomonas lempestris*	-	Suspending agent, emulsifier, stabilizer	72-74
Gellan gum	*Pseudomonas elodea*	-	Disintegrating agent	75

the launch of innovative excipients.

The characterization of gums and mucilages is initially achieved by only a multiple technique approach.

For excipient analysis, analytical techniques can be classified according to the type of information generated.[18-20]

- Structure- Gums and mucilages are polysaccharides and contain sugars. So, confirmation of the different sugars is carried out by chromatography and structure elucidation can be carried out by NMR and mass spectroscopy.
- Purity- To determine the purity of the selected gum and mucilage, tests for alkaloids, glycosides, carbohydrates, flavanoids, steroids, amino acids, terpenes, saponins, oils and fats, and tannins and phenols are carried out.
- Impurity profile- Testing for impurities must be carried out using suitable analytical techniques.
- Physico-chemical properties- Color, odor, shape, taste, touch, texture, solubility, pH, swelling index, loss on drying, hygroscopic nature, angle of repose, bulk and true densities, porosity and surface tension. Different ash values are also estimated. The microbial load and presence of specific pathogens are also determined. *In vitro* cytotoxicity is also determined. Gums and mucilages are highly viscous in nature. So, the rheological properties of excipients are important criteria for deciding their commercial use. The flow behavior of the samples is determined.
- Toxicity- The acute toxicity of gums and mucilages are determined by the followings fixed-dose method as per OECD guideline No. 425. A sub-acute toxicity study, determination of the LD50 etc., is carried out in rats and guinea pigs of both sexes. Once analysis is complete, determination of the structure, composition and impurity profile enables a scientific dossier to be prepared describing the excipient. This information is of value for the regulatory dossier of the final pharmaceutical product that would contain the given excipient. Finally, gums and mucialges are added to pharmaceutical formulations. So a compatibility study is important. The compatibility studies of gum/ mucilage/ drugs are performed using spectrophotometry/ FTIR/ DSC.[21-29]

Pharmacopoeial Standard Specifications of Natural Gums and Mucilages: Different pharmacopoeias, like USP, PhEur, and JP give pharmacopoeial standards for specific gums. The Pharmacopoeial standard for different gums is shown in Table No. 2.[30, 31]

Applications of Natural Gums and Mucilages: Gums and mucilages of different sources and their derivatives represent a group of polymers widely used in pharmaceutical dosage forms. Various kinds of gums are used in the food industry and are regarded as safe for human consumption. However, there is growing concern about the safety of pharmaceutical excipients derived from natural sources. Plant gums and exudates are now screened for their use as pharmaceutical adjuvants. Mucilages of different origins are also used in conventional dosage forms of various drugs for their binding, thickening, stabilizing and humidifying properties in medicine. A

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Table 4: Applications of Natural Gums and Mucilages in Novel Drug Delivery Systems

Common Name	Botanical Name	Family	Pharmaceutical Applications	Reference
Acacia	*Acacia Senegal*	*Leguminosae*	Osmotic drug delivery	76
Bhara gum	*Terminalia bellericaroxb*	*Combretaceae*	Microencapsulation	77
Chitosan	-	-	Colon specific drug delivery, microspheres, nanoparticles	78
Cordia gum	*Cordia oblique willed*	*Boraginaecae*	Oral sustained release matrix tablets	79
Guar gum	*Cyamompsis Tetraganolobus*	*Leguminoseae*	Colon targeted drug delivery, microspheres	80-82
Gellan gum	*Pseudomonas elodea*	-	Ophthalmic drug delivery, sustaining agent,beads, hydrogels,	83-85
Karaya gum	*Sterculiaurens*	*Sterculiaceae*	Mucoadhesive and Buccoadhesive	86-89
Locust bean gum	*Cerataniasiliqua*	*Leguminoseae*	Controlled delivery	90
Mucuna gum	*Mucunaflagillepes*	*Papillionaceae*	Microspheres	91
Okra gum	*Hibiscus esculentus*	*Malvaceae*	Hydrophilic matrix for controlled release drug delivery	92
Sodium alginate	*Macrocytis pyrifera*	*Lessoniaceae*	Bioadhvesive microspheres, nanoparticles	93-96
Xanthan gum	*Xanthomonas lempestris*	-	Pellets, controlled drug delivery system	97, 98

newer use of different gums and mucilages in cosmetics and textiles has increased the demand and screening of gums has become an important pharmaceutical area. However, different gums and mucilages used as pharmaceutical adjuvants have stringent specifications, which few natural agents can fulfill.[32, 33]

Gums and mucilages have the following applications.[34-98]

- Applications in the food industry- Gums and mucilages have a variety of applications in the food industry. Different gums have different uses like water retention and stabilization (guar and locust bean gum), stabilizers for ice-cream, meat products and instant pudding (carrageenanas), dairy, confectionary and meat products (agar), confectionary, beverages, backed product, and sauces (gum arabic, tragacanth, pectins, alginates and xanthan gum).
- Pharmaceutical applications- Gums and mucilages have a variety of applications in pharmacy. They are used in medicine for their demulcent properties for cough suppression. They are ingredients of dental and other adhesives and can be used as bulk laxatives. These hydrophilic polymers are useful as tablet binders, disintegrants, emulsifiers, suspending agents, gelling agents, stabilizing agents, thickening agents, film forming agents in transdermal and periodontal films, buccal tablets as well as sustaining agents in matrix tablets and coating agents in microcapsules including those used for protein delivery.

Various gums and mucilages with their common names, biological sources, family and applications are listed in Table 3. Table 4 lists the different applications of gums and mucilages in novel drug delivery systems.[34-98]

- Industrial applications- Gums used in cosmetics (acacia, tragacanth and karaya gum), textiles (starch, dextrin, cellulose, pectins, and tamarind gum), adhesives (acacia gum, and tragacanth), lithography (gum arabic, tragacanth, and locust bean gum), paints (pectins, hemicellulose, and resins) and paper manufacturer (tamarind, and cellulose).

Modification/Grafting of Natural Polysaccharides, Gums and Mucilages: There are various methods for modifying the structures of polysaccharides. The introduction of hydrophobic, acidic, basic, or other functionality into polysaccharide structures can alter the properties of materials based on these substances.

There are two methods for modification or grafting of natural polysaccharides: Physical methods and chemical Methods.[99]

Physical Modification of Polysaccharides

- Physical Cross linking

In physical crosslinking, polysaccharides forms crosslinked network with counterion at the surface. High counterion concentration would require longer exposure times to achieve complete crosslinking of the polysaccharides. For physical crosslinking different methods have been investigated such as:

- Cross linking by ionic interaction
- Cross linking by Crystallization
- Hydrophobised polysaccharides

Microwave modification**:** Microwaves generate electromagnetic radiation in the frequency range of 300

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MHz to 300 GHz. On exposure to microwaves, the polar or charge particles tend to align themselves with electric field component of the microwaves which reverses its direction e.g. at the rate of 2.4 × 109/s at 2.45 GHz microwave frequency. As the charged or polar particles in a reaction medium fail to align themselves as fast as the direction of the electric field of microwaves changes, friction is created, which heated the medium.

Chemical Modification of Polysaccharides

- Chemical crosslinking

Chemical crosslinking of polysaccharide is a versatile method with good mechanical stability.

During crosslinking counterions diffused into the polymeric and crosslinking agent reacts with polysaccharides forming either intermolecular or intramolecular linkages.

- Crosslinking by radical polymerization
- Crosslinking by addition reaction
- Crosslinking by condensation reaction

Graft copolymerization of polysaccharides: Graft copolymers by definition, consists of a long sequence of one polymer with one or more branches of another polymer. With the help of preformed polymer (polysaccharide in case of grafted polysaccharides) the synthesis of graft copolymer process will start. The free radical sites will create on this preformed polymer with the help of external agent. The agent should be effective enough to create the required free radical sites, at the same time should not be too drastic to rupture the structural integrity of the preformed polymer chain. Once the free radical sites are formed on the polymer backbone, the monomer can get added up through the chain propagation step, leading to the formation of grafted chains.[100]

- Vinyl/acryl graft copolymerization
- Chemical initiating system
- Radically initiating system

Other methods

- Ester and ether formation using saccharide oxygen nucleophiles, including enzymatic reactions and aspects of regioselectivity
- The introduction of heteroatomic nucleophiles into polysaccharide chains
- The oxidation of polysaccharides, including oxidative glycol cleavage, chemical oxidation of primary alcohols to carboxylic acids, and enzymatic oxidation of primary alcohols to aldehydes
- Reactions of uronic-acid-based polysaccharides, nucleophilic reactions of the amines of chitosan and the formation of unsaturated polysaccharide derivatives.[101]

Many studies have been carried out in fields including food technology and pharmaceuticals using polysaccharides. The Literature reviles that the extensive effort have been made in pharmaceutical research laboratory for the development of excipient from natural polysaccharides. The Literature survey also reviles the use of various physical and chemical methods for modification of polysaccharides for improving its activity.

Some of them are:[121]

Basavaraj et al (2011) designed and characterized sustained release Aceclofenac matrix tablets containing tamarind seed polysaccharide. They extracted tamarind seed polysaccharide (TSP) from tamarind kernel powder and utilized it in the formulation of matrix tablets containing Aceclofenac by wet granulation technique and evaluated for its drug release characteristics. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations), *in vitro* drug release and stability studies. All the formulations showed compliance with pharmacopieal standards. The *in vitro* release study of matrix tablets were carried out in phosphate buffer pH 7.4 for 12 hr. Among the formulations, they observed that F5 shows 98.062% better controlled release at the end of 12 hr. The results indicated that a decrease in release kinetics of the drug was observed by increasing the polymer concentration. The drug release of optimized formulations F-5 follows zero order kinetics and the mechanism was found to be diffusion coupled with erosion (non-Fickian diffusion/anomalous). The stability studies were carried out according to ICH guideline which indicates that the selected formulations were stable.

Tushar Deshmukh et al (2011) evaluated the gum obtained from of *Butea monosperma* as a tablet binder employing ibuprofen as a model drug. The gum was isolated from bark of *Butea monosperma* Lam. Physicochemical characteristics of gum were studied. Different formulations of tablets using *Butea monosperma* gum were prepared by wet granulation method. The binder concentrations in the present tablet were 2, 4, 6, 8, 10 and 12% w/v. Tablets were prepared and subjected for evaluation of hardness, friability, drug content uniformity. Preliminary evaluation of granules showed that, 1.75 to 2.06 granule % friability, 30.11 to 33.82º angles of repose and 4.146 to 6.512 compressibility index %. Tablet hardness was found to be in the range of 2.52 to 4.86 kg/cm2, 155 to 267 sec disintegration time and more than 90.00% dissolution in 105 min. From their study, it can be concluded that *B. monosperma* gum at 8% w/v exhibited good binding properties comparable to that of 10% starch. Gum can be used as a binding agent for the preparation of tablets.

Sandhya P et al (2010) in their work, evaluated mucilages obtained from *Malva sylvestris* and Pedalium murex as Suspending Agent. The purpose of their study was to search for a cheap and effective natural excipient that can be used as an effective alternative for the formulation of pharmaceutical suspensions. The suspending properties of *Malva sylvestris* and *Pedalium murex* mucilage were evaluated comparatively with *Acacia* at concentrations of 0.5, 1, 1.5, and 2% w/v in calcium carbonate suspension. Characterization tests were carried out on purified *Malva sylvestris* and *Pedalium murex* mucilage. From the parameters of sedimentation volume, flow rate, redispersibility abilities, it was observed that suspension prepared using *Pedalium murex* mucilage showed better suspendability of all the materials investigated followed by the suspension prepared using *Malva sylvestris*. They

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Table 5: Examples of Modified Gums and Applications

Gums and Mucilage	Modification Technique	Application	Reference
Karaya gum	Heat Treatment at various temperatures in a hot air oven	Disintegrating agent	102
Agar and Guar gum	Heat Treatment at various temperatures in a hot air oven along with co-grinding of both materials	Disintegrating agent	103
Acacia gum	Chemical modification of acacia gum using epichlorhydrine	Disintegrating agent	104-106
Starch	Physico-chemical treatment of to starch for modification	Disintegrating and binding agent	107-112
Sesbania gum	Chemical modification of *Sesbania*gum with tartaric acid for a sustained release formulation and chemical modification of gum with acetone: chloroform mixture for gelling agent	Sustained release formulation, gelling agent	113
Guar gum	Chemical modification of guar gum with glutaraldehyde for colonic delivery, chemical modification using isopropanol as a filmcoating material	Colonic delivery, film coating, disintegrating agent, hydrogel	114-116
Tamarind Powder	Chemical modification of tamarind powder using epichlorohydrin and partial degradation of β-galactosidase	Sustained release formulation, rectal drug delivery	117
Okra gum	Chemical modification with acrylamide synthesis	Controlled drug delivery	118-120

concluded that the extracted mucilage from fruits of *Pedalium murex* and *Malva sylvestris* has the potential of a suspending agent even at low concentration and can be used as a pharmaceutical adjuvant.

Olubunmi Olayemi et al (2011) evaluated *Brachystegia eurycoma* seed mucilage for use as a tablet binder in metronidazole formulations in comparison with gelatin. The granules were formulated by the wet granulation method using the extracted mucilage and gelatin as binder at 1, 2, 4, 6%w/w concentrations. The granules were found to possess good flow property as indicated by the angle of repose, Hausner's ratio and Carr's index. The formulated tablets were evaluated for uniformity of weight, thickness, tablet hardness, friability, disintegration times, drug assay and dissolution profile. Generally, the tablets formulated from *Brachystegia eurycoma* seed mucilage were softer than those of gelatin, had good uniformity of weight and disintegrated within the official specified times for uncoated tablets. They indicate the efficacy of *Brachystegia eurycoma* seed mucilage as a binder where fast release of a drug is desired.

A. S. Mann et al (2007) evaluated the suspending properties of *Cassia tora* (family Leguminosae) comparatively with those of compound tragacanth, *Acacia* and gelatin at concentration range of 0.5 – 4.0% w/v in sulphadimidine suspension. Characterization tests were carried out on purified *Cassia tora* mucilage. Sedimentation volume (%), rheology and particle size analysis were employed as evaluation parameters. The values obtained were used as basis for comparison of the suspending agents studied. They found that *Cassia* mucilage is safe for use as a suspending agent in human and pet foods based on the levels of use, which are comparable to the use levels of other suspending agents.

Mahmud H. S. et al (2008) investigated the Gum exudates from *Khaya senegalensis* (Family Meliaceae) plants for its physicochemical properties such as pH, water sorption, swelling capacity and viscosities at different temperatures using standard methods. The gum is slightly soluble in water and practically insoluble in ethanol, acetone and chloroform. It swells to about 10 times its original weight in water. Water sorption studies revealed that it absorbs water readily and is easily dehydrated in the presence of desiccants. A 5 %w/v mucilage concentration gave a viscosity value which was unaffected at temperature ranges (28 – 40 °C). They found that the swelling ability of *Khaya senegalensis* gum provides potentials for its use as a disintegrant in tablet formulation, as a hydro gel in modified release dosage forms.

R. Deveswaran et al (2009) studied disintegrant property of mucilage and seed powder of Isapghula by formulating dispersible tablets of famotidine. Hardness of the tablets was found to be in the range of 4.0 kg/cm2 for all formulations. The wetting time decreased with the increase in concentration of seed and mucilage powder. The tablets showed 96.1-99.3% of the labeled amount of drug, indicating uniformity in drug content. The mucilage powder was found to have better disintegrating property compared to the seed powder. All the formulations were found to be within the acceptable limits of official weight variation test and they exhibited good friability.

Ravi Kumar et al (2009) investigated the Polysaccharide mucilage, derived from the seeds of fenugreek, *Trigonella foenum-graceum* L (family Leguminosae), as disintegrant for use in mouth dissolving tablet formulations containing metformin hydrochloride. Mucilage extracted from fenugreek seeds were subjected to toxicity studies, it showed that extracted mucilage was devoid of toxicity. Fast disintegrating tablet (FDT) of metformin HCl was

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formulated using different concentration (2, 4, 6 8 and 10% w/w) of natural disintegrant viz; isolated mucilage of fenugreek seed and synthetic superdisintegrants like croscarmellose sodium and were compared. Disintegration time and drug release were taken as the basis to optimize the rapidly disintegrating tablet. Prepared tablets were evaluated for thickness, hardness, friability, uniformity of weight, disintegration time, wetting time and dissolution study. The formulated tablets had good appearance and better drug release properties as compared to the marketed conventional tablets. Fenugreek mucilage in the concentration of 4% gives shorter disintegration in 15 sec. and shows 100% drug release within 18 min. is selected as the optimized formulation (F2). They revealed that fenugreek mucilage showed better disintegrating property than the most widely used synthetic superdisintegrants like Acdi-sol in the formulations of FDTs. Studies indicated that the extracted mucilage is a good pharmaceutical adjuvant, specifically a disintegrating agent.

Phani Kumar G. K. et al (2011) developed sustained release matrix tablets of Lornoxicam for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. Tamarind Seed Polysaccharide (TSP) as a natural binder and it is source obtained from *Tamarindus indica* .The tablets were formulated by wet granulation method by using 10%, 20%, 30%, and 40% Tamarind Seed Polysaccharide (TSP) as a natural binding agent and its optimized batch was compared with maximum ratio of various binders (HPMC K4M, Sodium CMC, Guar Gum). Tablets with highest binder concentration showed maximum hardness (8.0 kg/cm2) and minimum friability (0.25%). After 24 hours tablets with 20% TSP binder showed maximum drug release (99.45%) and tablets with 40% TSP binder showed minimum drug release (62.55%). With increasing the percentage of natural polymer (TSP), release rate decreased, though drug release pattern was mainly dependent on the type of polymer. Among all the formulations, formulation LT - 2 which contain 20% TSP binder release the drug which follows Zero order kinetics via, swelling, diffusion and erosion. The FTIR study revealed that there was no chemical interaction between drug and excipients.

Anuradha Mishra and Sunita Pal (2007) carried out the synthesis and characterization of polysaccharide-based material Okra mucilage. A water-soluble food grade polysaccharide was grafted with polyacrylonitrile (PAN) using ceric ammonium nitrate/nitric acid redox initiator for modifying their properties for potential industrial applications. Ceric ion initiated solution polymerization under N2 atmosphere was found to be an efficient method for the formation of graft copolymers. The effect of variables such as the monomer concentration, initiator concentration, reaction time and temperature on the grafting efficiency (%GE) and percent grafting (PG) was discussed. Evidence of grafting was provided by the characterization of Okra mucilage and its graft copolymers by Fourier transform infrared spectroscopy (FTIR), scanning electron microscope (SEM), differential scanning calorimetry (DSC) and X-ray diffraction (XRD) patterns. Grafting of polyacrylonitrile onto Okra mucilage, a polysaccharide of vegetable origin, offers a new polymeric material with properties that can be exploited industrially. They concluded that grafting only improves the properties of mucilage by introducing more reactive sites and without making any change in the molecular mobility of chelating groups of polysaccharide.

Sutar P. B. et al (2008) crosslinked polyacrylamide grafted pectin with varying amount of glutaraldehyde and they observed that the cross-linked product showed better film forming property and gelling property than pectin. The pH dependent release of salicylic acid was observed due to pH dependent swelling of the crosslinked hydrogel.

Gurpreet Kaur et al (2009) evaluated the possible use of inter polymer complexed (IPC) films of chitosan (CH) and carboxymethyl tamarind kernel powder (CMTKP) for colon release of budesonide. They found that the results strongly indicate versatility of CH-CMTKP IPC films to deliver budesonide in the colon.

CONCLUSION

Natural materials have advantages over synthetic ones since they are chemically inert, non-toxic, less expensive, biodegradable and widely available. Polysaccharides show variability and versatility, due to their complex structure. Thus polysaccharides and their derivatives are emerging in the last years as one of the most used biomaterials in the field of novel drug delivery system, especially being chosen by a lot of researchers as carriers to be used in the preparation of particulate drug delivery systems. Recently, much attention has been paid to the modification of natural polysaccharides in order to obtain novel hybrid materials. These modified polysaccharides could be applied in the design of various stimuli-responsive controlled release systems. This contribution is intended to develop other natural sources as well as with modifying existing natural materials for the formulation of novel drug delivery systems, biotechnological applications and other delivery systems. Majority of investigations on natural polymers in novel drug delivery systems plays around polysaccharides. Natural gums can also be modified to have tailor-made products for drug delivery systems to compete with the synthetic excipients available in the market. Though the use of traditional gums has continued, newer gums have been used and some of them with exceptional qualities. There is huge scope for research on newer natural gums and mucilages obtained from plants and could be further exploited in future as a novel natural polymer for development of different drug delivery systems in pharma industry.

REFERENCES

1. Guo J, Skinner GW and Harcum WW: Pharmaceutical application of naturally occurring water soluble polymers. Pharmaceutical Science and Technology Today 1998; 1: 254-261.
2. The joint IPEC-PQG good manufacturing practice guide for pharmaceutical excipients, Europe, 2006.

KINDERFARMS Ex. 1026
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

3. Tommasina C and Matricardi P: Polysaccharide hydrogels for modified release formulations. Journal of Controlled Release 2007; 119: 5-24.
4. Hamman JH and Tarirai C: Functional excipients. Chem Today 2006; 24: 57-62.
5. Shirwaikar A and Prabhu SL: Herbal excipients in novel drug delivery systems. Indian Journal of Pharmaceutical Science 2008; 70: 415-422.
6. Beneke CE, Viljoen AM and Hamman JH: Polymeric plant derived excipients in drug delivery. Molecules 2009; 14: 2602-2620.
7. Stephen AM and Churms SC: Food polysaccharides and their applications. Taylor and Francies, CRC Press, New York, Edited by Stephen AM, Phillips GO and Williams PA, 2006: 1-24.
8. Koleng JJ, McGinity JW and Wiber WR: Handbook of pharmaceutical excipients. Pharmaceutical Press, Edition 6, Edited by Raymond C Rowe, Paul J Sheskey and Marian E Quinn, 2009: 1-3.
9. Kokate CK, Purohit AP and Gokhale SB: A Textbook of Pharmacognosy. Nirali Prakashan, Pune, Edition 22, 2003: 136-139.
10. Kottke KM: Modern Pharmaceutics. Marcel Dekker, New York, 2002: 287-333.
11. Richardson PH, Willmer J and Foster TJ: Dilute solution properties of guar and locust bean gum in sucrose solutions. Food Hydrocolloid 1998; 12: 339-348.
12. Evans WC, Trease and Evans: Pharmacognosy. Harcourt Brace & Co., Asia Pvt. Ltd, Singapore, Edition 14, 1996: 196-208, 213-215.
13. Edward MR: Modern Pharmaceutics. Marcel Dekker, New York, 2002: 287-298.
14. Aslam A and Parrott E: Effect of aging on some physical properties of hydrochlorthiazide tablets. Journal of Pharmaceutical Science 1971; 60: 263-266.
15. Kokate CK, Purohit AP and Gokhale SB: A Textbook of Pharmacognosy. Nirali Prakashan, Pune, Edition 21, 2003: 147-154, 157.
16. Rangari VD: Pharmacognosy and Phytochemistry. Career Publication, Nashik, India, 2006: 400-444.
17. Kulkarni GT: Microwave assisted fast extraction of mucilages and pectins. Indian Journal of Pharmaceutical Education and Research 2009; 43: 260-265.
18. Mohammed A: Text Book of Pharmacognosy. CBS Publishers and Distributors, New Delhi, India, Edition 3, 2005: 23-30.
19. Ansari SH: Essential of Pharmacognosy. Birla Publications Pvt. Ltd., New Delhi, India, 2006: 63-90.
20. Venkata RE: Chemical and biological aspects of selected polysaccharides. Indian Journal of Pharmaceutical Science 1992; 54: 90-97.
21. Stephen AM and Churms SC: Food Polysaccharides and Their Application. Taylor and Francies, CRC Press, New York, Edited by Stephen AM, Phillips GO and Williams PA, 2006: 1-24.
22. Baveja SK, Ranga Rao KV and Arora J: Examination of natural gums and mucilages as sustaining materials in tablet dosage forms. Indian Journal of Pharmaceutical Science 1988; 50: 89-92.
23. Wahi SP, Sharma VD and Jain VK: Studies on suspending property of mucilage of *Hygrophila spinosa* and *Hibiscus esculents Linn*. Indian Drug 1985; 22: 500-502.
24. Geetha B and Shivalinge Gowda KP: Microwave assisted fast extraction of mucilages and pectins. Indian Journal of Pharmaceutical Education and Research 2009; 43: 260-265.
25. www.dowcorning.com
26. Raymond CR, Paul JS and Marian EQ: Handbook of pharmaceutical excipients. Pharmaceutical Press, Edition 6, 2009: 298.
27. Marini A, Berbenni V and Pegoretti M: Drug excipient compatibility studies by physicochemical techniques: The case of Atenolol. Journal of Thermal Analysis and Calorimetry 2003; 73: 547-561.
28. Allen LV and Luner PE: Handbook of pharmaceutical excipients. Pharmaceutical Press, Edited by Raymond CR, Paul JS and Marian EQ, Edition 6, 2009: 685.
29. Collet J and Moreton C: Pharmaceutics: The Science of Dosage Form Design. Churchill Livingstone, U. K., 2002: 289-305.
30. Vatanasuchart N, Naivikul O, and Charoenrein S: Molecular properties of cassava starch modified with different UV irradiatons to enhance baking expansion. Carbohydrate Polymers 2005; 61: 80-87.
31. Khan MA, Bhattacharia SK and Kader MA: Preparation and characterization of ultra violet (UV) radiaton cured bio-degradable films of sago starch/PVA blend. Carbohydrate Polymers 2006; 63: 500-506.
32. Desai KG and Park HJ: Study of gammairradiation: effects on chitosan micropartcles. Drug Delivery 2006; 13: 39-50.
33. Micard V, Belamri R, Morel M and Guilbert S: Properties of chemically and physically treated heat gluten films. Journal of Agricultural Food Chemistry 2000; 48: 2948-2953.
34. Ofoefule SI and Chukwu A: Application of Abelmoschus esculents gum as a mini-matrix for furosemide and diclofenac sodium tablets. Indian Journal of Pharmaceutical Science 2001; 63: 532-535.
35. John GL, Declan MD and James EK: The use of Agar as a novel filler for monolithic matrices produced using hot melt extrusion. European Journal of Pharmaceutics and Biopharmaceutics 2006; 64: 75-81.
36. Oluwatoyin AO: Assessment of Albiziazygia gum as a binding agent in tablet formulations. Acta Pharmaceutica 2005; 55: 263–276
37. Jani GK, Shah DP and Jain VC: Evaluating mucilage from Aloe barbadensis Miller as a pharmaceutical excipient for sustained-release matrix tablets. Pharmaceutical Technology 2007; 31: 90-98.
38. Avachat MK and Dhamne AG: Oral controlled release drug delivery system with husk powder from Lepidium sativum seeds. Patent No. WO02100438.

KINDERFARMS Ex. 1026
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

39. Patel MM, Chauhan GM and Patel LD: Mucilage of lepidiumsativum, Linn (Asario) and ocimumcanum, sims. (Bavchi) as emulgents. Indian Journal of Hospital Pharmacy 1987; 24: 200-202.
40. Ahmed BJ and Al-Ghazawi M: Sustained release characteristics of tablets prepared with mixed matrix of sodium carragennan and chitosan: Effect of polymer weight ratio, dissolution media and drug type. Drug Development and Industrial Pharmacy 2005; 31: 241-247.
41. Bonferoni MC, Rossi S, and Tamayo M: Employment of λ-carrageenan in a matrix system. Journal of Controlled Release 1994; 30: 175-182.
42. Pontes UR: Determination of HLB of Anacardium gum. Rev Farm Bioquim 1971; 2: 83-91.
43. Zakaria MB and Zainiah AR: Rhelological properties of cashew gum. Carbohydrate Polymers 1996; 29: 25-27.
44. Pawar H and D'mello PM: Isolation of seed gum from *Cassia tora* and preliminary studies of its applications as a binder for tablets. Indian Drugs 2004; 41: 465-468.
45. Gowthamrajan K, Kulkarni GT and Muthukumar: Evaluation of Fenugreek mucilage as gelling agent. International Journal of Pharmaceutical Excipient 2002; 3: 16-19.
46. Kulkarni GT, Gowthamarajan K and Rao BG: Evaluation of binding property of *Plantago ovata* & *Trigonella foenum gracecum* mucilage. Indian Drugs 2002; 39: 422-425.
47. Kale VV, Kasliwal R and Parida SK: Formulation and release characteristics of guar gum matrix tablet containing metformin HCl. International Journal of Pharmaceutical Excipient 2004; 2: 75-80.
48. Khullar P, Khar RK and Agrawal SR: Evaluation of guar gum in the preparation of sustained release matrix tablets. Drug Development and Industrial Pharmacy 1998; 24: 1095-1099.
49. Heda A and Shivhare U: Study of some natural hydrophilic polymers as matrix forming materials for sustained release tablet formulation. International Journal of Pharmaceutical Excipient 2004; 2: 69-74.
50. Shefter E: Handbook of pharmaceutical excipients. Pharmaceutical Press, Edited by Raymond CR, Paul JS and Marian EQ, Edition 6, 2009: 703.
51. Jain NK and Dixit VK: Studies on gums and their derivatives as binding agent. Indian Journal of Pharmaceutical Science 1988; 50: 113-114.
52. Owen SC: Handbook of pharmaceutical excipients. Pharmaceutical Press, Edited by Raymond CR, Paul JS and Marian EQ, Edition 6, 2009: 782.
53. Sharma VD: Studies on emulsifying property of mucilages of *Hibiscus esculentus*. Indian Journal of Natural Products 1985; 1: 3-6.
54. Wahi SP and Jain VK: Studies on suspending property of mucilages of *Hygrophila spinosa* and *Hibiscus esculentus Linn*. Indian Drugs 1985; 22: 500- 502.
55. Edwin J, Edwin S, and Dosi S: Application of Hibiscus leaves mucilage as suspending agent. Indian Journal of Pharmaceutical Education and Research 2007; 41: 373-375.
56. Jani GK and Shah DP: Evaluation of mucilage of *Hibiscus rosasinensis Linn* as rate controlling matrix for sustained release of diclofenac. Drug Development and Industrial Pharmacy 2008; 34: 807-816.
57. Prajapati ST, Prajapati VD and Acharya SR: Characterization of disintegration properties of *Plantago ovata* mucilage in the formulation of dispersible tablets. Indian Journal of Pharmaceutical Education and Research 2006; 40: 208-211.
58. Mithal BM and Kasid JL: Evaluation of the emulsifying properties of *Plantago ovata* (Ispaghula) seed husk. Indian Journal of Pharmaceutical Science 1964; 26: 316-319.
59. Mithal BM and Kasid JL: Evaluation of the suspending properties of *Plantago ovate* (Ispaghula) seed husk. Indian Journal of Pharmaceutical Science 1965; 27: 331-335.
60. Sreenivasa Rao B, Prasanna RY and Mary S: Design and studies of gum karaya matrix tablet. International Journal of Pharmaceutical Excipients 2000; 2: 239-242.
61. Munday DL and Philip JC: Compressed Xanthan and karaya gum matrices: hydration, erosion and drug release mechanisms. International Journal of Pharmaceutics 2000; 203: 179-192.
62. Odeku OA and Itiola OA: Evaluation of the effects of khaya gum on the mechanical and release properties of paracetamol tablets. Drug Development and Industrial Pharmacy 2003; 29: 311-320.
63. Razdan B: Evaluation of gum as suspending agent in sulphadimidine suspensions. Indian Journal of Pharmaceutical Science 2003; 65: 665-668.
64. Verma PRP: Evaluation of *Leucaenal eucocephala* seed gum in tabletting. STP Pharma Sciences 2002; 12: 109-112.
65. Verma PRP and Razdan B: Studies on *Leucaenal eucocephala* seed gum: evaluation of suspending properties. STP Pharma Sciences 2001; 11: 289-293.
66. Anroop B, Bhatnagar SP and Ghosh B: Studies on *Ocimum gratissimum* seed mucilage: evaluation of suspending properties. Indian Journal of Pharmaceutical Science 2005; 67:206-209.
67. www.cpkelco.com/pectin/applications.html
68. http://www.ippa.info/applications_for_pectin.html
69. Kulkarni GT, Gowthamrajan K and Bramaji Rao G: Evaluation of binding properties of selected natural mucilages. Journal of Science and Industrial Research 2002; 61: 529-532.
70. Howard JR and Timmins P: Controlled release formulations. U.S. Patent No. 4792452.
71. Seiyaku F: Sustained-release dilazep hydrochloride tablets containing sodium alginate. Japan Patent No. 01025721.
72. Thierry N, George C and John F: Alginate and gellan gum as tablet coating. U.S. Patent No. 6326028 B1.
73. Kulkarni D, Dwivedi AK and Sarin JPS: Tamarind seed polyose: A potential polysaccharides for sustained release of verapamil hydrochloride as a

KINDERFARMS Ex. 1026
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

model drug. Indian Journal of Pharmaceutical Science 1997; 59: 1-7.
74. Dhopeshwarkar V and Zatz JL: Evaluation of xanthan gum in the preparation of sustained release matrix tablets. Drug Development and Industrial Pharmacy 1993; 19: 999-1017.
75. Antony PJ and Sanghavi NM: A new disintegrant for pharmaceutical dosage forms. Drug Development and Industrial Pharmacy 1997; 23: 413-415.
76. Beneke CE, Viljoen AM and Hamman JH: Polymeric plant-derived excipients in drug delivery. Molecules 2009; 14: 2602-2620.
77. Nayak BS and Patro KB: Design and evaluation of controlled release bhara gum microcapsules of famotidine for oral use. Research Journal of Pharmacy and Technology 2008; 1: 433-437.
78. Wang C, Xiong FU and Lian Sheng Y: Water soluble chitosan nanoparticles as a novel carrier system for protein delivery. Chinese Science Bulletin 2007; 52: 883-889.
79. Mukherjee B, Dinda SC and Barik BB: Gum Cordia: A novel matrix forming material for enteric resistant and sustained drug delivery- A Technical Note. AAPS PharmSciTech 2008; 9: 1-21.
80. Cárdenas A, Higuera-Ciapara I and Goycoolea FM: Rheology and aggregation of Cactus (*Opuntiaficus indica*) mucilage in solution. Journal of the Professional Association for Cactus Development 1997; 1: 152-159.
81. Krishnaiah YSR: Development of colon targeted oral Guar gum matrix tablets of Albendazole for the treatment of helminthiasis. Indian Journal of Pharmaceutical Science 2003; 65: 378-385.
82. Chourasia MK and Jain SK: Potential of guar gum microspheres for target specific drug release to colon. Journal of Drug Targeting 2004; 12: 435- 442.
83. Miyazaki S, Kawasaki N, Kubo W, Endo K and Attwood D: Comparison of in situ gelling formulations for the oral delivery of cimetidine. International Journal of Pharmaceutics 2001; 220: 161-168.
84. Coviello T, Dentini M, and Rambone G: A novel cocross linked polysaccharide: studies for a controlled delivery matrix. Journal of Controlled Release 1998; 55: 57-66.
85. Agnihotri SA, Jawalkar SS and Aminabhavi TM: Controlled release of cephalexin through gellan gum beads: Effect of formulation parameters on entrapment efficiency, size, and drug release. European Journal of Pharmaceutics and Biopharmaceutics 2006; 63: 249-261.
86. Alur HH, Pather SI and Mitra AK: Evaluation of the gum from *Hakea gibbosa* as a sustained-release and mucoadhesive component in buccal tablets. Pharmaceutical Development and Technology 1999; 4: 347-358.
87. Chourasia MK and Jain SK: Pharmaceutical approaches to colon targeted drug delivery systems. Journal of Pharmaceutical Science 2003; 6: 33-66.
88. Chavanpatil MD, Jain P and Chaudhari S: Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. International Journal of Pharmaceutics 2006; 316: 86-92.
89. Park CR and Munday DL: Evaluation of selected polysaccharide excipients in buccoadhesive tablets for sustained release of nicotine. Drug Development and Industrial Pharmacy 2004; 30: 609-617.
90. Xiaohong MG, Michae JT and John NS: Influence of physiological variables on the in-vitro drug-release behavior of a polysaccharide matrix controlled-release system. Drug Development and Industrial Pharmacy 2003; 29: 19-29.
91. Anthony AA and Nwabunze OJ: Mucuna gum microspheres for oral delivery of glibenclamide: In vitro evaluation. Acta Pharmaceutica 2007; 57: 161-171.
92. Kalu VD, Odeniyi MA and Jaiyeoba KT: Matrix properties of a new plant gum in controlled drug delivery. Archives in Pharmaceutical Research 2007; 30: 884-889.
93. Pornsak S, Srisagul S and Satit P: Use of pectin as a carrier for intragastric floating drug delivery: Carbonate salt contained beads. Carbohydrates and Polymers 2007; 67: 436-445.
94. Sungthongjeen S, Pitaksuteepong T and Somsiri A: Studies on pectins as potential hydrogel matrices for controlled release drug delivery. Drug Development and Industrial Pharmacy 1999; 12: 1271-1276.
95. Giunchedi P, Conte U and Chetoni P: Pectin microspheres as ophthalmic carriers for piroxicam: Evaluation in vitro and in vivo in albino rabbits. European Journal of Pharmaceutical Science 1999; 9: 1-7.
96. Ying DY, Parkar S and Luo XX: Microencapsulation of probiotics using kiwi fruit polysaccharide and alginate chitosan. International Society for Horticultural Science, Acta Horticulturae 2000; 753: 6-15.
97. Datta R and Bandyopadhyay AK: A new nasal drug delivery system for diazepam using natural mucoadhesive polysaccharide obtained from tamarind seeds. Saudi Pharmaceutical Journal 2006; 14: 115-119.
98. Vendruscolo CW, Andreazza IF and Ganter JL: Xanthan and galactomannan (from *M. scabrella*) matrix tablets for oral controlled delivery of theophylline. International Journal of Pharmaceutics 2005; 296: 1-11.
99. Patil S: Crosslinking of Polysaccharides: Methods and Applications. Latest Reviews 2008; 6: 1-18.
100. Ravi K, Anupama S and Mahadevan N: Grafting Modification of The Polysaccharide By The Use Of Microwave Irradiation- A Review, International Journal of Recent Advances in Pharmaceutical Research 2012; 2: 45-53.
101. Chand DK and Lee-Ruff E: Organic Chemistry, Private Practice, UK, 2013, 27.

KINDERFARMS Ex. 1026
KINDERFARMS LLC. v. GENEXA INC.
PGR2023-00051

102. Murali Mohan Babu GV, Himasankar K and Janaki Ram B: Studies on preparation and evaluation of modified form of gum karaya. Indian Journal of Pharmaceutical Science 2002; 64: 244-249.
103. Jani GK, Goswami JM and Prajapati VD: Studies on formulation and evaluation of new superdisintegrants for dispersible tablets. International Journal of Pharmaceutical Excipients 2005; 2: 37-43.
104. Rama Rao N and Rao UM: Hypochlorate modified potato starch: A new potato starch derivative as potential tablet disintegrant. International Journal of Pharmaceutical Excipients 2000; 3: 216-219.
105. Gohel MC, Patel SD and Shah NK: Evaluation of synthesized cross-linked tragacanth as a potential disintegrant. Indian Journal of Pharmaceutical Science 1997; 59: 113-118.
106. Trivedi BM, Patel PM and Patel LD: Crosslinked gum acacia as a disintegrant. Indian Journal of Pharmaceutical Science 1986; 48: 188-190.
107. Baveja JM and Misra AN: Modified guar gum as a tablet disintegrant. Pharmazie 1997; 52: 856-859.
108. Cartilier L, Mateescu MA and Dumoulin Y: Crosslinked amylose as a binder/disintegrant in tablets. U.S. Patent No. 5616343.
109. Cartilier L, Chebli C: Cross-linked cellulose as a tablet excipient. U.S. Patent No. 5989589.
110. Rong-Kun C, Mirwais S and Michael L: Evaluation of the disintegrant properties for an experimental, cross-linked polyalkylammonium polymer. International Journal of Pharmaceutics 1998; 173: 87-92.
111. Fenyvest E, Antal B, Zsadon B and Szejtli J: Cyclodextrin polymer, a new tablet disintegrating agent. Pharmazie 1984; 39: 473-475.
112. Okafor IS, Ofoefule SI and Udeala OK: A comparative study of modified starches in direct compression of a poorly water soluble drug (hydrochlorothiazide). Boll Chim Farm 2001; 140: 36-39.
113. Patel GC and Patel MM: Preliminary evaluation of sesbania seed gum mucilage as gelling agent. International Journal of Pharmaceutical Technology and Research 2009; 1: 840-843.
114. Chaurasia M and Jain NK: Crosslinked guar gum microspheres: A viable approach for improved delivery of anticancer drugs for the treatment of colorectal cancer. AAPS PharmSciTech 2006; 7: E143-E151.
115. Gliko-KabirI, Yagen B, Penhasi A and Rubinstein A: Phosphated crosslinked guar for colon specific drug delivery: Preparation and physicochemical characterization. Journal of Controlled Release 2000; 63: 121-127.
116. Sandolo C, Coviello T and Matricardi P: Characterization of polysaccharide hydrogels for modified drug delivery. European Biophysics Journal 2007; 36: 693-700.
117. Miyazaki S, Suisha F and Kawasaki N: Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. Journal of Controlled Release 1998; 56: 75-83.
118. Singh B, Chauhan GS and Kumar S: Synthesis characterization and swelling responses of pH sensitive psyllium and polyacrylamide based hydrogels. Carbohydrate Polymers 2006; 67: 190-200.
119. Gohel MC, Patel MM and Amin AF: Development of modified release Diltiazem HCl tablets using composite index to identify optimal formulation. Drug Development and Industrial Pharmacy 2003; 29: 565-574.
120. Mishra A, Clark JH and Pal S: Modification of Okra mucilage with acrylamide: synthesis, characterization and swelling behavior. Carbohydrate Polymers 2008; 72: 608-615.
121. Arsul VA and Lahoti SR: Natural Polysaccharides as Pharmaceutical Excipients. World Journal of Pharmaceutical Research 2014; 3: 3776-3790.

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