Review Article

Natural Excipients used for Formulation of Pharmaceutical Beads

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ABSTRACT

The Herbal or natural excipients have a great advantage over their synthetic analogues as these are non-toxic, less expensive and freely available. The increasing awareness about these herbal excipients, which are manly polymers of natural origin, the pharmaceutical industries is getting more inclined towards their use in formulation development. The plant derived gums, polymers from natural sources like carrageenan, thaumatin, lard, storax, agar, gum acacia, tragacanth and many more to name comply with many requirements of pharmaceutical excipients. These can be preferred for formulation development as being stable and involving less regulatory issues as compared to their synthetic counter parts. They can also be easily modified to meet the specific needs, thereby being a potent and economic vehicle for delivering active pharmaceutical ingredient in formulation. Due to advances in drug delivery technology, excipients are included in novel dosage forms to fulfill specific functions and also in some cases to increase the bioavailability of the drug. Recent trends towards the use of natural products demand the replacement of synthetic additives. Natural excipients have been studied for their application in different pharmaceutical dosage form such as tablets, beads etc. Natural excipients that are mainly used are natural polymers, gums and waxes.

Keywords: Natural excipients, Beads, polymers, waxes, Gums.

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INTRODUCTION

Excipients are the substances or compound other than the active pharmaceutical ingredient and packaging materials that affect finished product quality. Excipients are the pillar of pharmaceutical formulations that determine dosage form as well as pharmacokinetics and pharmacodynamics of drug.[1] Nowadays majority of excipients used are synthetic excipients that causes various side effects in pharmaceutics , so industries are impending natural resources as they are safe, non-toxic, biocompatible, less expensive and widely available. Excipients partly decide the status of the medicines.[2] The long- established conception of the excipients as any component other than the active substance has gone through a considerable development from an inert and affordable vehicle to an necessary set up of the formulation. Natural excipients are studied for their uses in different formulations such as tablets, nanoparticles, microspheres, beads etc. This review mainly focuses on natural excipients that are used in formulation of solid dosage form i.e., Beads. Natural excipients mainly used in formulation of beads are natural polymers, gums, waxes etc.[3]

1. NATURAL POLYMERS:

These polymers are naturally discovered in plants and animals e.g., cellulose, starch, resins, proteins etc. Natural polymers play important role in pharmaceutical formulations, they are used in preparation of microspheres, beads, films, nanoparticles, implants, injectables as well as liquid formulations. In this dosage form polymeric materials have many roles such as binders, viscosity enhancers, thickeners, disintegrants, emulsifiers, suspending agent, bio adhesive, gelling agent.[2]

Importance of herbal polymers over synthetic polymers:

1) Easily available: Natural polymers are low-priced than synthetic ones and grow in the form of herbs in many countries and have no side effects. They are produced in large amount hence their availability can be guaranteed than synthetic polymers.

2) Economic: Natural polymers are low-priced than synthetic polymers, hence its production cost is also less.

3) Biodegradable: Natural polymers are obtained from living organisms hence there is no side effects on human being and environment on the other hand, synthetic polymers have adverse effects as they are prepared with the help of chemicals.

4) Bio-compatible and non-toxic: As all the plant materials are carbohydrates in nature, they are non-toxic as compared to synthetic polymers.

5) No side effects: Natural polymers are found in plants and animals hence they have no side effects.[4]

2. POLYMERS FROM PLANT ORIGIN:

Cellulose:

Sources: Biological source of pure cellulose is cotton fiber this is generally used in pharmaceutical, or chemical engineering but not used as food grade cellulose. Other sources of cellulose are corn, jute ,rice, wheat straw, hemp.[2]

Composition: The plant cell wall is made up of cellulose, hemicellulose and pectin. It is an organic polysaccharide made up of long chains of anhydro-D-glucopyranose units (AGU) with every cellulose molecule consist of three hydroxyl groups per AGU, with the exception of the terminal ends.

Applications:

- It is used as diluent/binder in tablets.
- It is used in dressings
- It is used in various drug formulations, as coating agent, ointment base, etc.[5]

Agar:

Sources: Agar is made up of dried gelatinous substance acquire from Gelidium amansi (Gelidaceae). It is also acquired from red algae like gracilaria (Gracilariaceae) and Pterocladia (Gelidaceae). Mainly raw material that is procure from natural sea weeds are used to make agar, alginates etc.[2]

Composition: Agar is made up of mixture of agarose and agaropectin. Agarose is a polymer made by duplicating monomeric unit of agarobiose whereas, agarobiose is a disaccharide composed of D- galactose and 3,6-anhydro-l-galactopyranose. Agaropectin is a heterogeneous mixture of smaller acidic molecules. Gelling property of agar is caused by the aggregation of hexagonal fibers with six double helices.

Application:

- Agar is used for preparation of jellies, tissue culture and microbiology studies
- Agar is used as clarifying agent in brewing
- Agar is used as fruit preservative
- Agar is used as suspending agent, emulsifying agent, suppositories, tablet disintegrants, laxative etc.[6]

Starches:

Sources: The majority of plants naturally contain starch, a carbohydrate, starch grains which are found primarily in seeds and underground organs. Maize, rice, wheat, and potato starches are acceptable for use in pharmaceuticals. Pharmaceutical-grade starches can be found in grains, cereals, or underground plants' tubers, rhizomes, or roots. The availability, simplicity of extraction, and yield are the primary determinants of the starch source to be used.[7]

Composition: The two different alpha-glucans that make up starch are amylose, a non-branching helical polymer made of 1,4-linked D-glucose monomers, and amylopectin, a highly branched polymer composed of both 1,4- and 1,6-linked D-glucose monomers.[2]

Applications:

- Thermoplastic starch has a variety of uses, including as an adhesive, sizing agent for textiles, and in packaging, containers, and films.
- Starch is used as diluent, disintegrant, binder, absorbents, glidant etc.
- Starch is used as an excipient in novel drug delivery systems for nasal, oral, periodontal, and other site-specific delivery systems.
- Starch is used in topical preparations; for example, it is used in dusting powders for its absorbency.
- In ointment compositions applied to the skin, it serves as a protective covering.
- Starch mucilage is used as an emollient.[8]

Inulin:

Sources: A naturally occurring polysaccharide, inulin can be found in sources such as Dehlia bulbs, dandelion roots, Inula Helenium (Compositae), *Saussuria lappa* or chicoral roots, and *Cinchonium intybus*.[2]

Composition: The natural polymers known as fructans—which make up inulin—have terminal glucose and are made up of fructose units. A (2-1) glycosidic link connects the fructose units in inulin. The fructose units' range in size from 2 to 60. The plant species and harvesting time can be used to determine how polydispersity and chain length vary.

Applications:

It is used to stabilize substances, transport drugs, and treat conditions like diabetes and constipation.

Combining inulin and Eudragit ® RS, biodegradable colon-specific films that can withstand breakdown by gastric and intestinal fluids are created.[9]

Guar Gum:

Sources: Galactomannan polysaccharide, or guar gum, is a substance that is obtained from guar beans. It is also called as guar Calcutta lucern, Gum Cyamopsis, Cyamopsis gum. Guar gum is obtained from endosperm of the seeds of Cyamopsis tetragonolobus Linn. (Leguminosae).

Composition: Guar gum is made up primarily of high molecular weight galactomannans, a linear polysaccharide with some of its (14)-diequatorially linked -D-mannose monomers coupled to single sugar side chains of -D-galactose attached. Guar gum's backbone is made up of 1,4 connected D-mannopyranoses, to which each alternating mannose and D-galactose is joined 16.22 on average.[10]

Applications:

- Guar gum is mainly useful for colon delivery as it can be degraded by specific enzymes in this region of GIT.
- Gum protects drug in stomach and small intestine and delivers drug to specific sites.
- It is polymer mainly used as sustain releasing agent
- Guar gum is employed as a carrier in medicine delivery systems since it is a polymer that is mostly used as a sustain-releasing agent.
- Carboxymethyl guar film is employed as a stabilizing and thickening ingredient in the development of transdermal treatment systems.[1]

Chitin:

Sources: Chitin is a naturally found biopolymer and polysaccharide derivative bearing amino and acetyl groups and organic constituent in skeletal material of invertebrates. It contains 2-acetamido-2-deoxy-(1-4)-b D-glucopyranose residues (N-acetyl-D-glucosamine units) and mucopolysaccharides and dispersed in shell of crustaceans, in cell wall of fungi and microorganisms, in cuticle of insects.

Composition: Chitin is a macromolecule composed of the sub-unit N-acetyl glucosamine present in outer skeleton of crustaceans such as shrimp shell, crabs and insects. Chitin is a natural mucopolysaccharide consisting of 2-acetamido-2-deoxy-β-D-glucose through the connection of β (1-4).[9]

Applications:

- Chitin is used as excipient and drug carriers
- It is used in tissue engineering, cosmetics, wound dressing, stem cell technology etc.[10]

Xanthan Gum:

Sources: Xanthan gum, a naturally occurring polysaccharide kind of sugar, is made from the bacterium Xanthomonas campestris, which is found on cabbage plants.

Composition: It is made up of pentasaccharide repeat units with the molar ratios of 2:2:1 for glucose, mannose, and glucuronic acid. A D-glucose unit that is -(1,4)-linked and two mannose units are attached to the main chain's spaced glucose residues.[1]

Applications:

- Xanthan gum is utilized in a variety of products as a thickening and stabilizing agent.
- It is used in topical and oral formulations
- It is used to create sustain release matrix formulations for tablets, beads, pellets, and other forms of conventional drug administration that are less likely to cause side effects.
- Reduces side effects associated with conventional drug delivery.[11]

Collagen:

Sources: Collagen is naturally occurring protein present in fibrous tissue like bone, cartilage, tendons, blood vessels, skin, cornea, ligament disc and gut. Collagen is found in both inside and outside the body cells.

Composition: Collagen is mostly composed of glycine, proline, hydroxyproline, lysine, amino acid and these amino acids form three strands which shows triple-helix structure characteristics of collagen, which is generally composed of one supplementary chain and two homologous chains, these chains are coiled around one another in cable form.[12]

Applications:

- Due to its tiny size, vast surface area, high adsorptive capacity, and capability to disperse in water to form transparent colloidal solution, collagen is utilized to create nanoparticles and nanospheres.
- It has potential to be used as sustained release formulation.
- Collagen is also use to make collagen sponges that are useful in management of severe burns.
- In ophthalmology, collagen is employed as a slow-release medication delivery method.[13]

Gelatin:

Sources: Mammalian (mainly bovine and porcine) bone and other materials are used to make the majority of commercial gelatin. Collagen, the primary protein component of skin, bones, and connective tissue in all animals, including fish and insects, is hydrolyzed by enzymes to produce gelatin. Gelatin is also obtained by acid treatment i.e., type A, e.g., HCL, H_2SO_4, gelatin obtained by alkaline treatment is known as type B, after both the treatments solutions are filtered, deionized and concentrated by vacuum evaporation and membrane filtration method.

Composition: Gelatin is water soluble proteinaceous substance made by destruction of native collagens. It consists of large number of glycine, proline,4-hydroxy proline residues[14]

Applications:

- Gelatin is widely used in food, pharmaceuticals, cosmetic industries due to its water binding and gel forming ability.
- Gelatin is used in tablet coating to reduce dusting, to mask unpleasant taste etc.
- Microencapsulated oils are created using gelatin for a variety of nutritional and medicinal reasons.

- Solutions of modified gelatin (3.0-5.5) and salts are commonly used as plasma substitute during emergency surgery.[2]

Chitosan:

Sources: Chitosan is a naturally occurring polymer that can be created by deacetylating chitin.[17]

Composition: chitosan is a linear polysaccharide made up of different amounts of 2-amino-2-deoxy-(1-4)-b-D-glucopyranose residues (D glucosamine units) because of deacetylation of chitin, chitosan can be liquified in water by formation of salts with different acids on amino group of D- glucosamine units.[9]

Applications:

- Chitosan and their derivatives are used as safe and effective absorption enhancers to promote various drug delivery of peptide and proteinous drugs.
- Chitosan has been successfully applied in development of drug carriers for controlled drug delivery.[15]

Alginate:

Sources: Alginate is a naturally occurring, water soluble, anionic linear polysaccharide obtained from brown seaweed

Composition: It is composed of 1-4 linked-1-glucuronic and D-mannuronic acid residues.[2]

Applications:

- Alginate is used to prepare mucoadhesive drug delivery systems
- Alginate works best in the formulation of beads.
- It acts as encapsulation materials for controlled drug delivery to mucosal tissue
- It also helps in wound healing
- Alginate based tablets are used for intestinal drug delivery system.[16]

3. NATURAL GUMS:

Natural gums made from plants can be used as a binder, suspending agent, dissolving agent, gelling agent, or emulsifying agent in the administration of drugs. Additionally, they are used to create preparation for both an immediate and prolonged release. Gums are a possible contender for usage in a variety of pharmaceutical formulations for cutting-edge drug delivery systems.[3]

Definition: Gums are created naturally by plants when internal plant tissues fall apart through a process known as gummosis. This results in cavities, which then change into modified carbohydrates known as gums.

Injuries to the bark or stem can also cause gums to form. Additionally, fungus and bacteria can damage the plant and cause it to develop gums. Most gums are released from the stem, and very few are found in the roots, leaves, and other sections of the plant.[17]

4. CLASSIFICATION OF GUMS:

Table 1: Pharmaceutical applications of various natural gums, mucilages and their modified forms.[3]

SR.NO.	Basis	Class	Example
1.	Charge	Non-ionic gums Anionic gums	Guar gum, locust bean gum, tamarind gum, xanthan gum, gum Arabic, Karraya gum, Gellan gum, Carrageenans.
2.	Shape	Short branch Branch on branch	Xanthan gum, guar gum Gum Arabic, tragacanth gum
3.	Origin	Seed gums Plant exudates Microbial exudates See weed	Guar gum, karaya gum, ipomoea, fenugreek, locust bean gum, premcem gum, lesquerella fendleri gum Chicle gum, konjac, gum Arabic, gum ghatti, gum karaya, acacia gum, tragacanth Dextran, gellan gum, xanthan gum, tara gum, spruce gum Sodium alginate, alginic acid, carrageenan's, agar-agar
4.	Gelatin behavior	Cold set gels Heat set gels Re-entrant gels	Gellan gum, flaxseed gum, gelatin Konjac Xyloglucan
5.	Chemical structure	Galactomannans Glucomannans Uronic acid containing gums Tri-heteroglycans Tetra-heteroglycans Penta-heteroglycans	Fenugreek gum, guar gum, locust bean gum, tara gum, cassia gum, dhaincha gum. Konjac Xanthan gum Gellan gum Gum Arabic, Psyllium seed gum Gum ghatti, tragacanth

5. ADVANTAGES OF NATURAL GUMS:

1) Local bioavailability: Governments in developing nations encourage the production of plants with widespread applications in numerous industries, such as guar gum and tragacanth.

2) Biocompatible and non-toxic: All the plant materials are carbohydrates made up of repeating sugar, hence they are non-toxic and biocompatible.

3) Low cost: India and many developing countries are dependent on agriculture, so it is always cheaper to use natural sources. The production cost is also lower as compared to synthetic ones.

4) Environmentally friendly: Due to the straightforward production procedures used, gums from various sources are readily gathered in significant numbers.

5) Better patient tolerance and public acceptance: There are fewer side effects of natural materials as compared to synthetic ones. e.g., PMMA, povidone.[17]

6. APPLICATION OF GUMS AS GELLING AGENT:

- Gums have properties that can form gel alone, or in combination with others.
- Three-dimensional network, that is form by various inter and intra molecular association, results in gelling properties in gum, these networks are brought about by physical or chemical treatment.
- E.g., 1) In alginic acid, interaction occurs with calcium ions that results in gel formation

  2) Galactomannan interacts synergistically with xanthan gums and carrageenan to form elastic gel e.g., locust bean gum.[18]

7. APPLICATIONS OF GUMS AS SUSTAINING MATERIALS IN DOSAGE FORM:

Applications of gums as sustaining components in dosage forms include the use of gums in tablets, suspensions, and matrix systems to prolong drug release. Guar gums, xanthan gums, and karaya gums are examples of gums that when in contact with water become hydrated and gel. Because of this, when gums are employed in formulations, their gelling tendency is typically carefully regulated, resulting in sustained release over an extended period of time.[19]

8. APPLICATION OF GUMS IN NDDS: [3]

Table 2: Application of Gums in NDDS

Sr.No	Common name	Novel drug delivery system
1	Acacia	Osmotic drug delivery
2	Bhara gum	Microencapsulation
3	Cordia gum	Novel oral sustained release matrix forming agent in tablets, Suspension.
4	Guar gum	Colon targeted drug delivery, Cross-linked microspheres
5	Gellan gums	Ophthalmic drug delivery, beads, Floating in-situ gelling.
6	Karaya gums	Mucoadhesive and buccoadhesive.
7	Locust bean gum	Controlled release agent.
8	Sodium alginate	Bio-adhesive, Microspheres.
9	Tamarind gum	Mucoadhesive drug delivery, Sustained releases.
10	Xanthan gum	Pellets, Controlled drug delivery system

9. NATURAL WAXES:

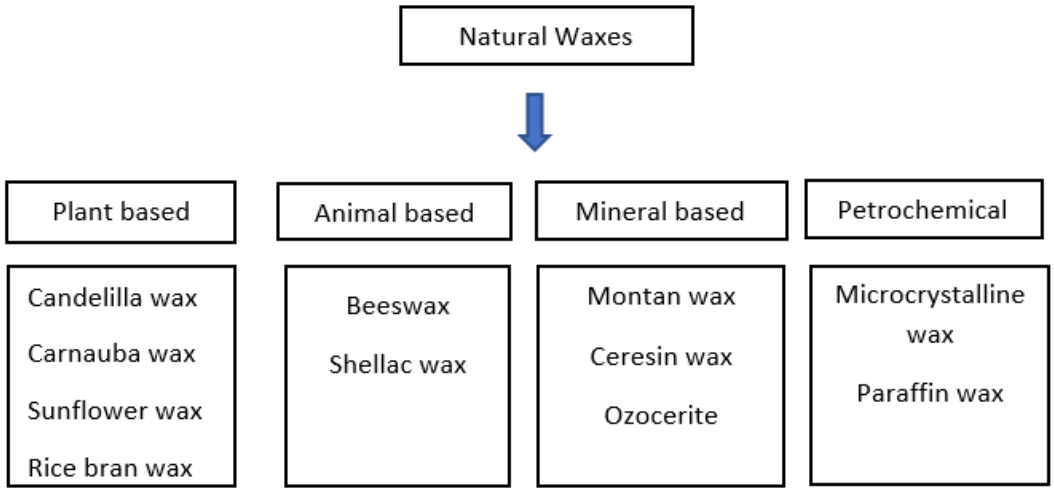
Waxes are the organic molecules that are characteristically consists of long aliphatic alkyl chain. Waxes have various properties such as low melting viscosity, occasionally buffable, strong temperature dependence of solubility and consistency, re-solidifying unchanged after melting at 40°C to 140°C approx.

Waxes are the substances that are generally used in making of cosmetic products, coating purposes, for molding preparation, used as polymer.[20]

10. CLASSIFICATION OF WAXES:

Waxes are divided into Natural and Synthetic waxes. Within the natural waxes, there are four different types of waxes: plant, animal, mineral and petrochemical waxes.

Table 3: Classification of Waxes



11. GENERAL PROPERTIES OF DIFFERENT TYPES OF WAXES:

Table 4: General properties of different type of Waxes

Sr.No	Name	General properties
1.	Candelilla wax	• Good at hardness but have less crystallinity • Some stickiness at higher temperature • Insoluble in water but highly soluble in organic solvents
2.	Carnauba wax	• High crystallinity and high contraction • Very hard and brittle • Good emulsification properties and excellent binding capacity • Good elasticity and less viscosity
3.	Beeswax	• Moderately hard and little bit sticky • With different polarities shows excellent retention of oils • Provide matt surfaces • Plastic at body temperature
4.	Sunflower wax	• Shows narrow melting curve with contents below 55°C • It forms hard and homogeneous thermally stable gels
5.	Berry wax	• Provide silky and soft feeling to the skin • Has no crystallinity

12. MOST COMMON APPLICATIONS OF NATURAL WAXES:

Table 5: Most common application of natural waxes

Sr.No	Name	Type of wax	Applications
1.	Candelilla wax	Plant wax	Acts as glazing agent and binder, used in the formulation of lipstick, pharmaceutical tablets, chewing gums.
2.	Sunflower wax	Plant Wax	Used in light colored lipsticks and lip balms
3.	Rice bran wax	Plant wax	Used in mascaras and skin care products, pharmaceutical, food, polymer, leather industries.
4.	Berry wax	Plant wax	Used as additive in lipstick, mascaras and lip gloss, cosmetics and eyebrow pencils
5.	Paraffin wax	Petroleum based	Used in candles, coating, packaging
6.	Montan wax	Mineral Wax	Used as coating agents in pharmaceutical industries, used as lubricants, mold releasing agent, anti-blocking agent.(20)

CONCLUSION

The advent of natural excipients is attractive because they are economical, abundant, non-toxic, and capable of chemical modification, potentially biodegradable and biocompatible. Natural excipients have been studied for their application in different pharmaceutical dosage form such as tablets, nanoparticles, microsphere, beads etc.

Natural excipients mainly used in the formulation of beads are natural polymers, gums and waxes, therefore in coming years, there is going to be continued interest in the natural excipients to have better materials for drug delivery system.

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