

REVIEW ARTICLE

Natural Excipients- A Review

S. Dharmendra ^{*1}, J.K. Surendra², M.Sujata³, S. Shweta¹

¹Charak Institute of Pharmacy, Mandleshwar., M.P., India.,

²Sagar Institute of Research and Technology, Bhopal, M.P., India

³Khallikote College, Berhampur, Orissa, India

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ABSTRACT

With the increasing interest in polymers of natural origin, the pharmaceutical world has compliance to use most of them in their formulations. Pharmaceutical formulation development involves various components in addition to the active pharmaceutical ingredients. The plant derived gums and mucilages comply with many requirements of pharmaceutical excipients as they are non-toxic, stable, easily available, associated with less regulatory issues as compared to their synthetic counterpart and inexpensive; also these can be easily modified to meet the specific need. Most of these plant derived gums and mucilages are hydrophilic and gel- forming in nature. The traditional concept of the excipients as any component other than the active substance has undergone a substantial evolution from an inert and cheap vehicle to an essential constituent of the formulation. This article gives an overview of natural excipients which are used in controlled drug delivery systems. Therefore, we conclude that the natural excipient proposed can be used as binder, diluent and disintegrant in oral disintegrating tablets and immediate release dosage forms. Mainly the natural excipient used is biocompatible, cost effective and provides as nutrition supplements.

Key words: *Natural excipient, mucilages, Diluent, Disintegrant, Binder, Pharmaceutical application Pharmaceutical excipient.*

INTRODUCTION

In recent years, plant derived polymers have evoked tremendous interest due to their diverse pharmaceutical applications such as diluent, binder, disintegrant in tablets, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels and bases in suppository ^[1]; they are also used in cosmetics, textiles, paints and paper-making ^[2]. These polymers such as natural gums and mucilage are biocompatible, cheap and easily available and are preferred to semi synthetic and synthetic excipients because of their lack of toxicity, low cost, availability, soothing action and non irritant nature ^[3-6]. A large number of plant-based pharmaceutical excipients are available today. Ability to produce a wide range of material based on their properties and molecular weight, natural polymers became a thrust area in majority of investigations in drug ^[7,8]. This review gives an insight of plant based novel drug release-retarding materials which have been recently studied as carriers not only in the conventional sustained release dosage forms but also in buccal drug

delivery systems, gastroretentive systems and microcapsules. Present day consumers look for natural ingredients in food, drugs, and cosmetics as they believe that anything natural will be more safe and devoid of side effects. As natural excipients are non toxic and compatible ^[10-15] and the RDTs are also called as orodispersible, mouth dissolving, oral disintegrating, fast melting, quick dissolving and freeze dried wafers ^[11]. These are not only useful in administration of drugs in pediatric and geriatric patients but in patients suffering from dysphagia, leading to improved patient compliance ^[16,17]. Often times people experience inconvenience in swallowing conventional tablets and capsules ^[18,19]. In ODTs formulations, the commonly used mixture of excipients comprising at least one disintegrant (1-15%), a diluent (10-85%), a binder (1-10%), a lubricant, and optionally, a swelling agent, a permeabilizing agents, sweeteners, and flavoring agents to achieve the effectiveness of the formulation ^[19,20].

WHAT IS A PHARMACEUTICAL EXCIPIENT?

Pharmaceutical excipients can be defined as nonactive ingredients that are mixed with therapeutically active compound(s) to form medicines. The ingredient which is not an active compound is regarded as an excipient.

- Excipients affect the behavior and effectiveness of the drug product more and more functionality and significantly.

- The variability of active compounds, excipients and process are obvious components for the product variability

WHAT IS NATURAL EXCIPIENTS?

Natural excipients and derivatives occur ubiquitously throughout the plant and animal kingdoms. Examples of polymers or derivatives that have been used or investigated as vaccine adjuvants are:-

- ❖ Individual saponins derived from the South American tree *Quillaja saponaria*.
- ❖ Keyhole limpet hemocyanin (KLH), a nonheme copper containing protein found in anthropods.
- ❖ MPL, a monophosphoryl derivative of the Lipid A molecule found in gram-negative bacteria.
- ❖ Leishmania elongation initiation factor (LeIF), a protein produced by the parasite leishmania.
- ❖ Ricin, a potent immunotoxin obtained from the seeds of castorbean plants.

CLASSIFICATION OF EXCIPIENTS

Excipients are commonly classified according to their application and function in the drug products:

- ✓ Binders, Diluents
- ✓ Lubricants, Glidants, Disintegrants
- ✓ Poolishing Film formers and coatings agents
- ✓ Plasticizers, Colorings
- ✓ Suspending agents Preservatives, antioxidants
- ✓ Flavorings, Sweeteners, Taste improving agents
- ✓ Printing inks, Dispersing agents

Gums and mucilage:

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). Mucilage's 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. Mucilage's are physiological products ^[23].

Tamarind Gum:

Tamarind xyloglucan is obtained from the endosperm of the seed of the tamarind tree, *Tamarindus indica*, a member of the 21 evergreen families. Tamarind Gum, also known as Tamarind Kernel Powder (TKP) is extracted from the seeds. Microspheres formed were in the size range of 230 - 460 μm . In another study Diclofenac sodium matrix tablets containing TSP was investigated. The tablets prepared by wet granulation technique were evaluated for its drug release Characteristics ^[39,40].

Hibiscus rosasinensis:

Hibiscus rosa-sinensis Linn of the Malvaceae family is also known as the shoe-flower plant, China rose, and Chinese 32,33 hibiscus ^[41].

Guar gum:

Guar gum comes from the endosperm of the seed of the legume plant *Cyamopsis tetragonolobus*. Refined guar splits are obtained when the fine layer of fibrous material, which forms the husk, is removed and separated from the endosperm halves by polishing. Strong acids cause hydrolysis and loss of viscosity, and alkalis in strong concentration also tend to reduce viscosity. It is insoluble in most hydrocarbon solvents ^[42].

Locust bean gum:

Locust Bean Gum (LBG) (also known as Carob Gum) is obtained from the refined endosperm of seeds from the carob tree *Ceretonia siliqua* L. It is an evergreen tree of the legume family. Carob bean gum is obtained by removing and processing the endosperm from seeds of the carob tree ^[43].

Honey locust gum:

It is known botanically as *Gleditsia triacanthos*, and belongs to the order Leguminosea (suborder Mimoseae). The gum is obtained from the seeds ^[44,45].

Khaya gum:

Khaya gum is a polysaccharide obtained from the incised trunk of the tree *Khaya grandifoliola* (family Meliaceae). The fact that the gum is naturally available, inexpensive and non-toxic has also fostered the interest in developing the gum for pharmaceutical use. Further work has also shown its potential as a directly compressible matrix system in the formulation of 61 controlled release tablets ^[46].

Aloe Mucilage:

Aloe mucilage is obtained from the leaves of *Aloe barbadensis* Miller. The aloe parenchyma tissue or

pulp has been shown to contain proteins, lipids, amino acids, vitamins, enzymes, inorganic compounds and small organic compounds in addition to the different carbohydrates. Many investigators have identified partially acetylated mannan (or acemannan) as the primary polysaccharide of the gel, while others found pectic substance as the primary polysaccharide [74].

Hakea Gum:

Hakea gum a dried exudate from the plant *Hakea gibbosa* family Proteaceae. Gums that are acidic arabinogalactans (type A). Molar proportions (%) of sugar constituents Glucuronic acid, Galactose, Arabinose, Mannose, Xylose is 12:43:32:5:8. [48]

Konjac glucomannan:

Konjac glucomannan, which is extracted from the tubers of *Amorphophallus konjac* is a very promising polysaccharide for incorporation into drug delivery systems. Highly hydrophilic galactomannan is obtained from the seeds of *Mimosa scabrella* (a brazilian leguminous tree called bracinga) of the Mimosaceae family. Its seeds provided 20–30% of galactomannan (G) with a mannose: galactose ratio of 1.1:1. [49].

Mimosa pudica:

Mimosa pudica, commonly known as sensitive plant belongs to family Mimosaceae. Mucilage of *M. pudica* is obtained from seeds, which is composed of d-xylose and d-glucuronic acid. *Mimosa* seed mucilage hydrates and swells rapidly on coming in contact with water. Earlier the seed mucilage was 75 evaluated for binding and disintegrating agent [50,51].

Fenugreek:

Trigonella Foenum-graceum, commonly known as Fenugreek, is an herbaceous plant of the leguminous family. Fenugreek seeds contain a high percentage of mucilage. Although it does not dissolve in water, mucilage forms a viscous tacky mass when exposed to fluids. Like other mucilage- containing substances, fenugreek seeds swell up and become slick when they are exposed to fluids [50].

Mucilage in Plant Parts:

Mucilages found in rhizomes, roots and seed endosperms may act primarily as energy reserves whereas foliar mucilages appear not to serve as storage carbohydrates [7]. Generally, it has been assumed that foliar mucilages are merely secondary plant metabolites, but there are reports [8], the ionic balance of plant cells and as carbohydrate reserves. It has been suggested that

the ability of mucilage to hydrate may offer a mechanism for plants to resist drought [9].

Intra Cell Mucilage:

Source	Part
Orchids sp.	Corn
Musa paradisiacal	Pulp
Aloe	Succulent plant

Cell-Membrane Mucilage: Secondary Wall Mucilage:

Source	Part
<i>Althaea officinalis</i> . L.	Root
Cinnamomum sp.	Bark
Barosma betulina, Thunberg	Leaves

Metamorphosis of Cell-Wall

Pith and Medullary Ray Cells:

- *Astragalus* sp., yielding Tragacanth.

Parenchyma Cells of Wood and Bark:

- Cherry-gum, yielded by some of the Amygdalaceae.

Various Cells of the Bark:

- *Acacia senegal*, yielding Gum arabic. primary wall as an intercellular substance: making up the pith, medullary ray, parenchyma and other
- Thallus of *Chondrus crispus*, Stackhouse and of the origin of mucilage.

PHARMACEUTICAL APPLICATIONS OF GUMS IN DDS:

In the presence of counter ions, this polymer is capable of forming gels that are particularly strong when formed with divalent ions. Important parameters, like the gel strength, were studied to find a reliable indicator of the gel ocular bioavailability [26]. A recent study reports the preparation of microspheres obtained by the emulsion cross-linking method of gellan and poly (vinyl alcohol) in the presence of different amounts of glutaraldehyde as a cross-linking agent and of an antihypertensive drug [37]. The new microspheres were spherical, with smooth surfaces and with a narrow unimodal size distribution. By increasing the cross-link density, microspheres with smaller size were obtained due to the formation of a more rigid network [38].

PHARMACEUTICAL APPLICATION OF MUCILAGES:

Mucilages are most commonly used as adjuvant in pharmaceutical preparations, with wide range of applications such as thickening, binding, disintegrating, suspending, emulsifying, stabilizing and gelling agents. Mucilages may be used as sustained and controlled release formulations.

POLYSSACHARIDES:**Pectin:**

Pectins are non-starch, linear polysaccharides extracted from the plant cell walls. [24] The blended alginate and pectin polymer matrix increased the folic acid encapsulation efficiency and reduced leakage from the capsules as compared to those made with alginate alone, they showed higher folic acid retention after freeze drying and storage [25].

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. Various applications in drug delivery are 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 [25].

Uses of alginates

- Alginates have proven to be effective for the symptoms of malignant wounds [25].
- Bleeding in malignant wounds is caused by the absence of platelets and the abundance of friable capillaries. Because bleeding occurs easily, it is essential that dressings do not adhere or cause trauma. Alginates are ideal for bleeding wounds as they have haemostatic properties [26, 27].

Starch:

Starch that is a natural polysaccharide polymeric material widely exists in fruit, root, pedicle, and leaf of plants.

Starch is classified into:-

I. Raw starch, II. Physical-modified starch or chemical-modified starch [28].

Modified starch was tested for general applicability of a new pregelatinized starch product in directly compressible controlled-release matrix systems [29,30].

Amphoteric Starch:

Amphoteric starches have been used as wet-end and size-press papermaking additives by aid in retention, drainage and strength properties. They can also be used as ceiling tile additives drilling fluid additives, viscosity modifiers and agents in ore recovery operations [31].

Chitosan:

Chitosan is a natural positively charged (cationic) biopolymer derived from the hydrolysis of the polysaccharide chitin [32]. Chitin is an amino polysaccharide (combination of sugar and protein) abundantly available natural biopolymer found in

the exoskeletons of crustacean like shrimp, crab, lobster and other shellfish [33].

Properties of Chitosan:

CS is a linear randomly distributed, hetero polysaccharide consisting of S (1-4) linked 2-acetamido-2-deoxy-S-D-glucopyranose and 2-amino-2-deoxy-S-D-glycopyranose units [34].

Physicochemical Properties:

Chitosan is highly basic polysaccharides due to presence of primary amino group in its structure. The main factors which may affect the CS properties are its molecular weight and degree of deacetylation (DD). These factors enable the researcher to formulate different grades of CS which differ primarily in molecular weight and degree of deacetylation [35].

Biological Properties:

- Due to its bioadhesive property, it can adhere to hard and soft tissues and has been used in dentistry, orthopedics and ophthalmology and in surgical procedures.
- It also has a fungistatic or bacteriostatic, anticancerogen and anticholestermic action [36].

APPLICATION OF POLYSACCHARIDES:-

- Natural polysaccharides are extensively used for the development of solid dosage forms.
- These polymers of monosaccharide's (sugars) are inexpensive and available in a variety of structures with a variety of properties.
- They are highly stable, safe, non-toxic, and hydrophilic and gel forming in nature.
- Pectin's, starch and amylose are a few polysaccharides commonly used in controlled release dosage forms.

HERBAL EXCIPIENTS USED IN NOVEL DRUG DELIVERY SYSTEM

Excipients of natural origin are of particular interest to us for reasons of reliability, sustainability and avoiding reliance upon materials derived from fossil fuels. Plant products are therefore attractive alternatives to synthetic products because of biocompatibility, low toxicity, environmental "friendliness", and low price compared to synthetic products.

A. Polysaccharides in pharmaceuticals: a) Pectins, b) Alginates, c) Starches, d) Chitosan:

B. Gums: a) Guar gums, b) Gum acacia, c) Karaya gum, d) Xanthan gums:

C. Volatile oils: Volatile oils are generally mixtures of hydrocarbons and oxygenated compounds derived from these hydrocarbons. Many oils are terpenoid in origin;

some of them are aromatic derivatives mixed with terpenes (e.g. cinnamon and carvacrol) although aromatic in structure, are terpenoid in origin^[53].

a) Methanol: Methanol is obtained by steam distillation of the flowering tops of *Mentha piperita* belonging to the family Labiatae. HPMC gel as a reservoir system containing menthol as penetration enhancer and 60% v/v ethanol-water as solvent system^[54]. Methanol was tested for improving the bioavailability of poorly water-soluble ibuprofen in the rectum with poloxamer^[55,56].

b) Caraway: Caraway fruit consists of the dried, ripe fruits of *Carum carvi* (Umbelliferae). The volatile oil consists of ketone carvone and the terpene limonene. In another attempt, a limonene-based transdermal therapeutic system (TTS) was prepared to study its ability to provide the desired steady-state plasma concentration of nicorandil in human volunteers^[57].

CONCLUSION:

In addition to conventional pharmaceutical excipients as bulking agents, substance used for masking taste/texture or as a substance used to aid during manufacturing process, Novel excipients offer broad range of additional properties suitable to preserve the integrity of active constituents of the formulation and enhance its self life. The synthetic polymers can be designed or modified as per requirement of the formulation; by altering polymer characteristics and on the other hand herbal pharmaceutical excipients are biocompatible, non toxic, environment friendly and economical. It seems conceivable that in the near future, kilogram quantities of fusion proteins, fibronectin, poly (lysine), or hemolysin could become available as off-the-shelf excipients or as designer excipient kits. Excipients that have never been used before must pass formidable regulatory requirements before being incorporated into approved dosage forms^[58].

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