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A Review of Natural Binders as Pharmaceutical Excipient in The Novel Drug Delivery System



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ABSTRACT

The oral route is the most popular route of administration for varied drugs because it is considered the safest, most popular, and less economical. Binders are agents used to impart the cohesiveness of the granules. This ensures that the tablet remains intact after compression. The researchers try to the new excipients for potential use as a binding agent in tablet formulations continue to the interest. This is because the different binding agents can help achieve the various mechanical strength of tablet and drug release properties for different pharmaceutical purposes. Natural binders like different starch, gums, mucilage's, dried fruits possess binding capacity as well as some other properties like filler, disintegrant & natural polymers are safe & economical than polymers like PVP. Gums became vital excipients in several pharmaceutical preparations due to their abundance, biodegradability, non-toxicity, and comparatively low cost. Gum has notable applications in pharmaceutical preparation as binders, disintegrants, suspending agents, emulsifiers. They are polymeric polysaccharides that are obtained from woody and nonwoody plant components such as bark, seeds, sap, roots, rhizomes, fruit, leaves, and plant gums are widely utilized in the formulation of pharmaceutical dosage forms. This article is mainly concentrated on reviewing some vital features of natural gums, their economic importance uses, and their pharmaceutical application.

INTRODUCTION

The oral route has been commonly adopted and the most convenient route for drug delivery. A tablet is the popular dosage form and 70% of the total medicines are dispensed.^[1]

For the formulation of solid dosage forms, several excipients are used. They include dyes, flavors, binders, emollients, fillers, lubricants, preservatives, and many more classifications. The traditional use of excipients in drug formulations was to act as inert vehicles to provide necessary weight, consistency, and volume for the correct administration of the active ingredient, but in modern pharmaceutical dosage forms, they often fulfill multifunctional roles such as modifying release, improving the stability and bioavailability of the active ingredient, enhancement of patient acceptability and ensure ease of manufacture. New and improved excipients continue to be developed to meet the needs of advanced drug delivery systems.^[2]

Both synthetic and natural polymers have been investigated extensively. Synthetic polymers have certain disadvantages such as high cost, toxicity, environmental pollution during synthesis, non-renewable sources, side effects, and poor patient compliance. However, the use of natural polymers for pharmaceutical applications are attractive because they are economical, readily available, low cost, nontoxic and capable of chemical modifications, potentially biodegradable, and with few exceptions, and also biocompatible.^[3]

Gums generally polysaccharides which are polymeric in nature of natural substance obtained from woody and nonwoody plant parts such as bark, seeds, sap, roots, rhizomes, fruit, leaves, and plant gums are widely used in the formulation of pharmaceutical dosage forms. They are translucent and amorphous substances and are soluble or partly soluble in water. They are insoluble in alcohol and most of the organic solvent. They form viscous adhesive solutions with water either by swelling or due to absorption. Pharmaceutically, important gums are gum acacia, tragacanth, gum karaya, gum ghatti, guar gum. Gums are characteristics of certain natural orders like *Leguminosae*, *Rosaceae*, *Combretaceae*, and *Sterculiaceae*. Gums in general, are used primarily as adhesives or thickening agents in printing, textiles, paper, paint, candy, food, and pharmaceutical industries^[4]. They are used as tablet binding agents, suspending agents, emulsifiers, stabilizers, and thickening agents. The major application of gum is as a binding agent in a tablet.

PHARMACEUTICAL EXCIPIENTS

Pharmaceutical excipients can be defined as nonactive ingredients that are mixed with therapeutically active compounds 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.

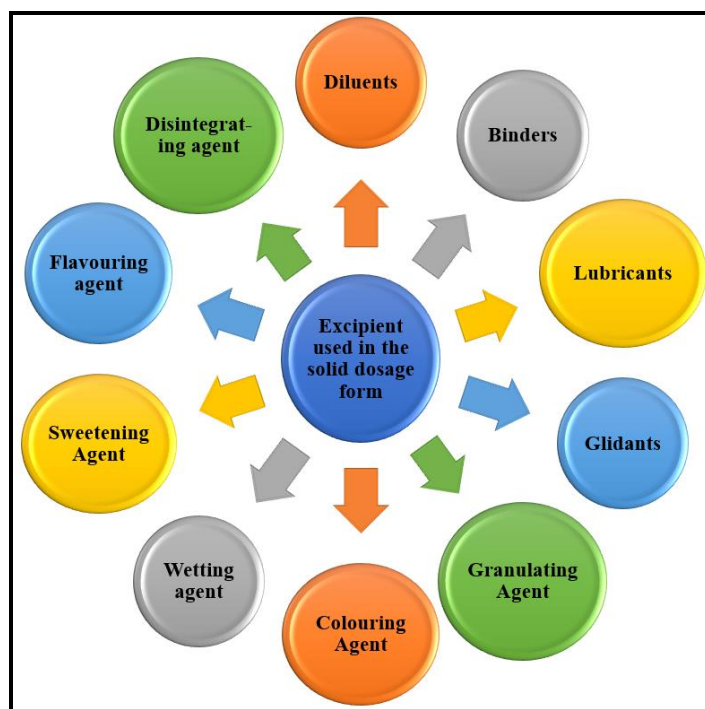


Figure No. 1: Excipients used in the solid dosage form

BINDING AGENT/BINDER^[5]

Binding agents or binders are useful in achieving various tablet mechanical strength and drug release properties for different pharmaceutical purposes. Binders are agents employed to impart cohesiveness to the granules. This ensures the tablet remains intact after compression as well as improving the flow qualities by the formulation of granules of derived hardness and size. The choice of a suitable binder for a tablet formulation requires extensive knowledge of the relative importance of binder properties for enhancing the strength of the tablet and also of the interactions between the various materials constituting a tablet. To hold various powders together to form a tablet is a binder, fillers usually do not have the good binding capacity, the binder is either added in a dry mix or mix in granulation or mix in granulating liquid, binder form matrix with fillers and drug embedded in it, on drying solid binder forms glue which holds the particles together, the wet binder is the most important

binders are hydrophilic & most times soluble in water. The mechanical properties of binder film are important as well and a good tablet binder should be able to offer flexibility and plasticity and yield without rupturing to absorb the effect of elastic recovery.

a. Ideal properties of tablet binder

- Physiologically inert.
- Acceptable to regulatory agencies.
- Physiologically and chemically stable.
- Commercially available in a stable form.
- Meet the standards of regulatory requirements.
- Should not interfere with the bioavailability of the drug.
- Able to cohesive compacts for directly compressed tablets.

b. Binder functionality

The selection of appropriate binder and levels for certain applications are usually empirical, involving some type of optimization and based upon previous company results functional characteristics, performance, cost, and bioavailability. The ability of a binder to produce strong, non-friable granules depends on the binder itself and the binder's distribution in the granulation. However, the use of too much binder or too strong and cohesive binder will produce harder tablets that will not disintegrate easily, hence, impairing drug release and can even cause excessive wear on the punches and dies. On the other hand, using a too low quantity of binder will produce friable granules that can generate a large number of fines, and produce tablets with lower crushing strength as a result.

Binders can be added either as dry powders in the blend or prepared beforehand as solutions and added during mixing. Generally, a large quantity of granulating liquid will yield a narrower particle size range along with coarser, harder granules due to the formation of solid bridges as with excipients such as lactose. Using a low viscosity binder to achieve certain granule hardness. This is likely since the polymer is already fully hydrated and dissolved within the blend. In general, it has been shown that the use of a dry binder added within the powder blend results in smaller granule sizes and a high level of larger lumps. [6]

When applying the binder solution during mixing, it is best to provide a uniform liquid spray with as small a droplet size as possible as this will have the largest surface area. This spray will have the greatest coverage throughout the powder bed and will prevent localized over wetting of granules which can result in oversized particles. The rate of binder addition is important as well since a consistent, steady rate is designed to obtain a narrower and consistent particle size distribution.

Typically, finer granules with lower bulk densities can be obtained when a smaller volume of liquid is added during mixing. Moreover, these granules of smaller particle sizes yield tablets with faster dissolution rates and lower hardness values. The mechanical properties of binder film are important as well and a good tablet binder should be able to offer flexibility and plasticity and yield without rupturing to absorb the effects of elastic recovery.^[7]

c. Effect of Binder in different properties of Tablet

- **Effect of binders on the mechanical strength of directly compressed tablets:**

The addition of a binder to a compound has been suggested to change the surface properties of the coarse compound particles as they are covered by the small binder particles. It was proposed that this surface coverage increased the surface area available for inter particulate bonding, thus increasing the number of bonds and also possibly creating stronger bonds, with a subsequently increased mechanical strength (Nystrom et al., Dub erg and Nystrom, 1985; Nystrom and Glazer, 1985).

The addition of a binder that increases elasticity can decrease tablet strength because of the breakage of bonds as the compaction pressure is released (Nystrom C et al.,1982).

- **Effect of amount of binder and compaction pressure on tablet porosity:**

Increasing the amount of binder added to a compound resulted in a gradual decrease in tablet porosity as more of the inter particulate voids were filled with the binder. For example, the addition of the binders most prone to undergo plastic deformation gave the most pronounced effect of the amount of binder of tablet porosity.

An increase in compaction pressure during tableting resulted in a gradual decrease in porosity as more of the inter particulate voids were filled with a binder. For example, the addition of the binders most prone to undergo plastic deformation gave the most pronounced effect of the amount of binder on tablet porosity.

An increase in compaction pressure during tableting resulted in a gradual decrease in porosity as the particles were brought into closer proximity to each other. It appeared that the effect of the binder on tablet porosity was generally more pronounced when the compaction pressure was low.

- **Effect of binder on tablet strength:**

The addition of a binder to a compound generally increases the tablet strength. The increase in tablet strength was influenced by properties associated with both the binder and the compound and these will be dealt with in the followings section. The strength of tablets composed of some mixture was higher than that of tablets made often individual materials, referred to a synergistic effect.

- **Effect of binder deformability and particle size on tablet strength:**

The addition of a binder with a high propensity for plastic deformation resulted in a pronounced increase in tablet strength compared to that of the pure compound. This result is associated with poor compatibility and moderate deformability that had only a small effect on both tablet strength and porosity.

- **Effect of amount of binder and compaction pressure on tablet strength:**

Earlier studies regarding the amount of binder have suggested that the amount corresponding to a surface area ratio of unity, i.e., the amount required to cover the compound particles with the binder, resulted in the highest tablet strength [Nystrom et al.,1982]. The addition of a binder above this amount had less effect on tablet strength. The amount corresponding to a surface area ratio of unity was assumed to be necessary to increase and change the nature of the surface area available for inter particulate bonding and thereby increase tablet strength.

TYPES OF BINDERS

a) Classification based on their resource:^[8]

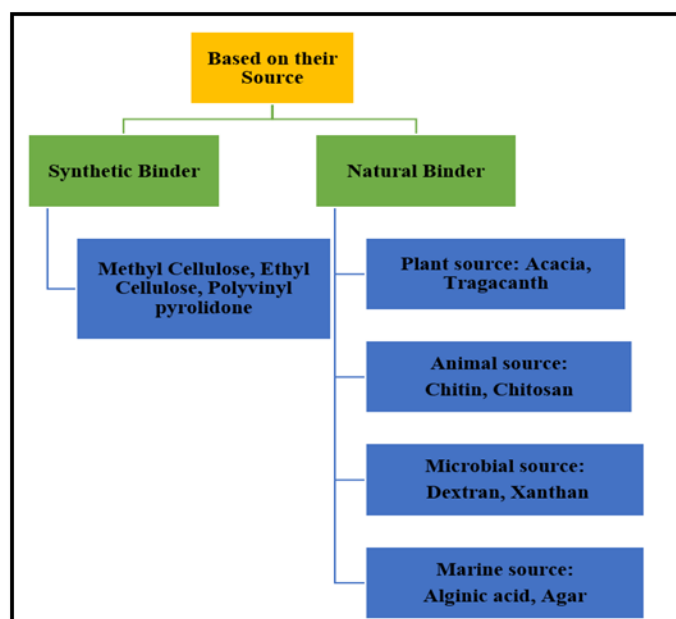


Figure No. 2: Classification of binders based on resource

Advantages Natural Binder:

- Natural polysaccharides are widely used in the pharmaceutical and food industry as excipients and additives due to their low toxicity, biodegradable, availability, and low cost.
- They can also be used to modify the release of the drug, thereby, influencing the absorption and subsequent bioavailability of the incorporated drug.^[9]

Disadvantages of Polymer binders:

- Polymer binders can lead to processing difficulties such as rapid over granulation. Over time they occasionally lead to tablet hardening and a decrease in dissolution performance.
- When polymer binders are chosen, the addition of strong disintegrants such as super disintegrants is typically required but these are considerably expensive and harm product stability as well as film coating appearance of the finished product.^[10]

Disadvantages of synthetic polymer

- High in cost, produces side effects, and poor patient compliance.

- The synthetic polymers are non-recyclable, creates environmental pollution during synthesis.
- Processing difficulties can be created by the Polymer binder such as rapid over granulation, increase in tablet hardness, and decrease in dissolution performance.
- Additions of the strong disintegrating agent are needed with polymer binder which is very expensive and has a negative outcome on product stability.^[11]

b) Classification based on their function:

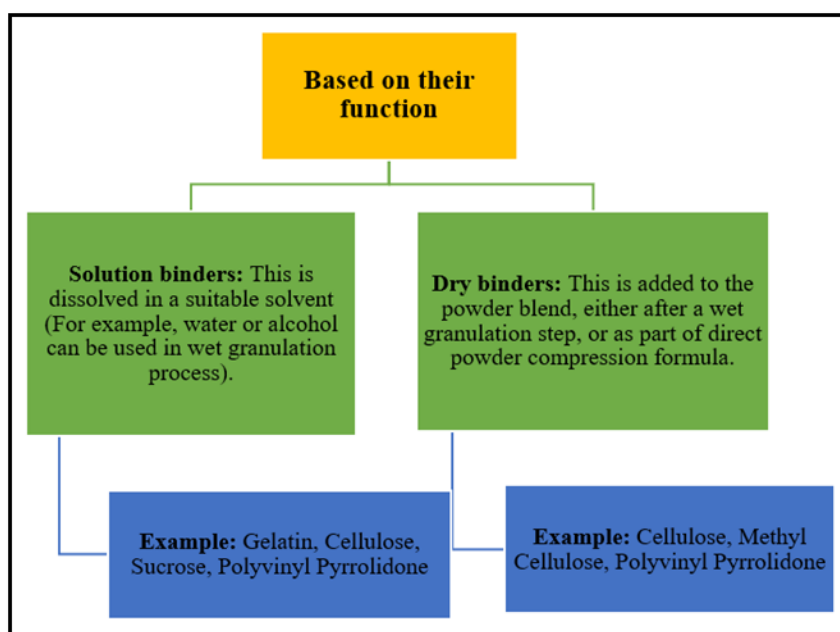


Figure No. 3: Classification of binders based on function^[12]

LIST OF TABLET BINDER USED IN PHARMACEUTICAL PREPARATION^[13,14,15]

Table No. 1: Different Binder used in the Pharmaceutical Preparation

SR. NO.	NAME OF TABLET BINDER	CONCENTRATION (%)
1	Acacia	1-5
2	Copovidone	2.0 - 5.0 (in direct compression & wet granulation)
3	Carbomer	0.75 - 3
4	Ceratonia	0.15 - 0.75
5	Liquid Glucose	5 - 10
6	Methyl Cellulose	1 - 5
7	Magnesium Aluminium Silicate	2 - 10
8	Sodium Alginate	1 - 3
9	Polyethylene oxide	5 - 85
10	Povidone	0.5 - 5
11	Gelatin	1 - 3 wet mix
12	Carboxy methyl cellulose Sodium	1-6
13	Polymethacrylate	10 - 35 dry mix
14	Sorbitol	2 - 10 wet mix
15	Zein	30 wet granulations

GUMS AS BINDERS

Gums are usually pathological products and are produced when the plant is growing under unfavorable conditions or is injured. Thus, they are the abnormal products of plant metabolism. The process is known as “gummosis”. The term gum was probably applied to natural plant exudates that had oozed from tree barks. Gums are translucent and amorphous substances, produced by plants. Gums are soluble or partly soluble in water. They are insoluble in alcohol and most of the organic solvent. They form viscous adhesive solutions with water either by swelling or due to absorption. An aqueous solution of gum is usually laevorotary, they are plant hydrocolloids and may be anionic or non-ionic polysaccharides.^[16]

Gums are grouped into three major categories namely natural gums, modified gums, and synthetic gums.

- **Natural Gums:** They are obtained in a natural state such as the tree exudates, extracted from seeds of some legumes or seaweed hydrocolloids. eg.: gum arabica, guar gum, tragacanth.

- **Modified Gums:** They are chemically modified natural gums or derivatives of naturally occurring materials such as cellulose or starch. eg.: Carboxymethylcellulose.
- **Synthetic Gums:** They are completely synthesized chemical products. eg.: polyvinyl pyrrolidone, polyethylene oxide.

Classification of Natural Gum

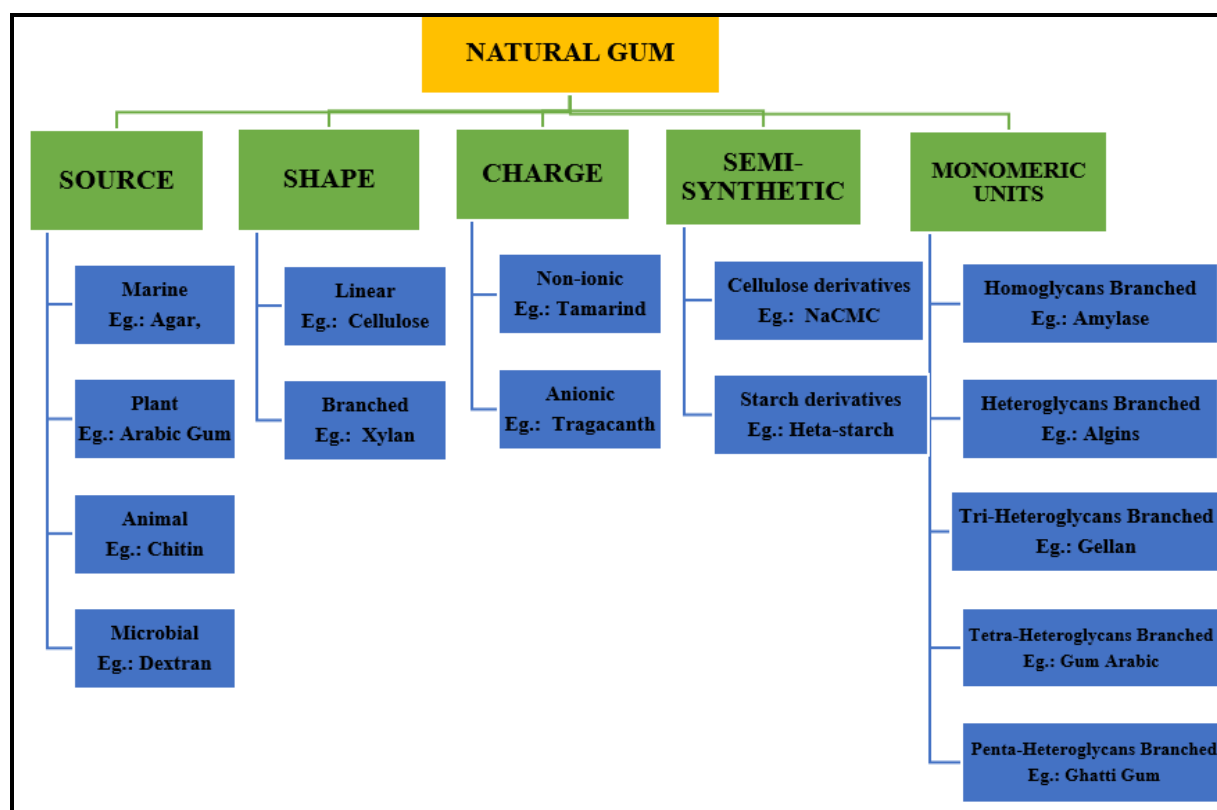


Figure No. 4: Classification of natural gum^[17]

Advantages of natural gum

- They are biodegradable polymers as they are produced by living organisms.
- The production is eco-friendly.
- They are biocompatible and non-toxic.
- Relatively cheap as the production cost is very low.
- Readily available as a local source or through cultivation.
- Many of the gums are obtained from an edible source, hence they are easily acceptable.^[18]

Disadvantages of natural gum

- Microbial contamination due to high moisture content and possible degradation.
- Environmental and seasonal factors will influence the quality variation of gums.
- Natural gums are found to show a decrease in viscosity on storage.
- The difference in the collection and climatic conditions also leads to a quality variation of gums.
- Potential antigenicity- The nanospheres made up of heat-denatured natural polymers can cause anaphylactic shock.^[19]

NATURAL GUMS AND THEIR USES^[20,21,22,23,24]

Table No. 2: Examples of Natural gums and their uses

SR. NO.	GUM	BOTANICAL NAME	FAMILY	APPLICATION IN PHARMACY
1	Almond gum	<i>Prunus communis</i>	<i>Rosaceae</i>	Suspending agent, Thickening agent, Stabilizer
2	Aegle gum	<i>Aegle marmelos</i>	<i>Rutaceae</i>	Binder, Thickening agent
3	Gum moringa	<i>Moringa olifera</i>	<i>Moringaceae</i>	Disintegrating agent
4	Gum acacia	<i>Acacia catechu</i>	<i>Leguminosae</i>	Suspending agent, Antioxidant, Astringent
5	Prunus gum	<i>Prunus domestica</i>	<i>Rosaceae</i>	Binder, Tonic
6	Tamarind gum	<i>Tamarindus indica</i>	<i>Fabaceae</i>	Gelling agent, Stabilizer, Binder
7	Gum ferrule	<i>Ferula gummosa</i>	<i>Apiaceae</i>	Binder
8	Ayoyo gum	<i>Corchorus olitorius</i>	<i>Tiliaceae</i>	Emulsifying agent, Thickening agent, Binder
9	Cordia gum	<i>Cordia obliqua</i>	<i>Boraginaceae</i>	Binder, Stabilizer
10	Guar gum	<i>Cyamopsis tetraganobus</i>	<i>Leguminosae</i>	Binding agent
11	Okra gum	<i>Hibiscus esculentus</i>	Malvaceae	Binder and hydrophilic matrix for CDDS
12	Albizia gum	<i>Albizia zygi</i>	Leguminoseae	Tablet binder
13	Badam gum	<i>Prunus amygdalus</i>	Rosaceae	Binding, sustaining, and transdermal film-forming agent
14	Khaya gum	<i>Khaya grandifolia</i>	Meliaceae	Binding agent
15	Neem gum	<i>Azadirachta indica</i> <i>A. Juss.</i>	Meliaceae	Suspending agent, binder, and transdermal film-forming agent

PHARMACEUTICAL APPLICATION OF NATURAL GUM

- **Gums in Tablets Formulation:** Natural gums have a wide range of pharmaceutical applications that include their use as a binder, disintegrator in tablets, and used as sustaining agents in the tablet. Natural polymer, gums modify the drug release from formulations. Natural gum has good binding property in wet granulation for the manufacturing of tablets. [25]
- **Gums as Sustaining Materials in Dosage Form:** Natural gums are widely used in pharmaceutical dosage forms as biodegradable polymeric materials. The use of several natural gums such as Guar gums, xanthan gums, and karaya gum has been explored for the development of sustained-release dosage forms.
- **Gums as Emulsifying and Suspending Agent:** Gums are widely used in pharmacies as thickeners, suspending agents, and emulsifying agents. Natural gums are hydrophilic colloids that form dispersion with water and increase the viscosity of the continuous phase so that the solid particle suspended is sufficient for a long time to measure the uniform dose. [26]
- **Gums in Microencapsulation:** Microencapsulation is defined as a process to entrap one substance with another substance. The gums because of their ability as a coating and matrix-forming agent can be utilized for microencapsulation of drug particles for sustaining the drug release. Several gums such as Xanthan, gum guar has been utilized in microencapsulation. [27]
- **Gums as Film Formers:** Film-forming systems are novel approaches to conventional, topical, and transdermal systems. They became a promising method for drug reservoirs in transdermal, buccal drug delivery systems. Various film modifiers like Xanthan gum, carrageenan gum, and locust bean gum were provided with proper texture to film and reduce the recrystallization of a drug.
- **Gums as Gelling Agent:** Some thickening agents are gelling agents (gallants), which form a gel that dissolves in the liquid phase a colloid mixture that forms a weakly cohesive internal structure. Galactomannan interacts synergistically with xanthan gums and carrageenan to form an elastic gel.
- **Gums as Coating Agent:** Plant-based materials can be modified and have been widely used for and non-functional as well as functional purposes, to coat tablets, capsules, granules,

powders, and pellets. Grewia Gum as a film coating agent in theophylline tablet formulation. [28]

PHARMACEUTICAL APPLICATION OF NATURAL POLYMER

- **Natural Polymers for Intelligent Drug Delivery:** Some natural polymers respond to certain environmental factors such as ions, pH, enzymes, temperature, and electromagnetic fields. Such polymers are known as intelligent, smart, stimuli, and environmental-responsive polymers.^[29] These polymers in response to certain environmental factors that trigger specific drug release to affected tissues or cells. Example: For colon-specific drug delivery systems, cross-linked Plantago psyllium gum (with meth acrylamide) was employed as its response to pH, and they produced hydrogels that respond to ions as well as pH^[30]. Pectin derived from plant cell walls depends on its degree of esterification response to ions, pH, and enzymes. While cellulose derivatives respond to ions, pH, and temperature and have been utilized for colon-specific drug delivery. [28]
- **Natural Polymers for BioMEMS:** BioMEMS refers to biomedical or biological microelectronic mechanical systems. The process of utilizing and customization of microfabrication technologies for biomedical applications. Microneedles are fabricated for transdermal delivery. Carboxymethyl cellulose (CMC) and amylopectin for fabrication of Microneedles using photolithography for the micro moulds. Plant polymers should be explored for the fabrication of microneedles and BioMEMS.^[31]
- **Natural Polymers for Nano Drug Carriers:** Natural gums have also been utilized for the development of nanoparticles. The development of nanoparticles using guar gum, kondagogu, gum ghatti has wide advantages and the development of polyelectrolyte nanoparticles using Moringa gum has shown complexation techniques for controlled and extended-release of the molecularly entrapped drug.^[32]
- **Natural Polymers for Theranostics:** A theranostic is a delivery system fabricated to deliver both medicine and imaging agent(s) in a single dose, bridging the gap between imaging and therapy, thereby facilitating real-time monitoring of therapeutic efficacy of the incorporated drug. Metallic nanoparticles have been used as theranostic as well as synthetic and natural polymeric nanoparticles^[33]. Natural polysaccharides due to their excellent biocompatibility, low toxicity, biodegradability, and functionalities that the body can identify, make them excellent materials for Theranostics. The nanoparticles were then characterized

for in-vitro cellular uptake, *ex-vivo* tissue distribution, *in-vivo* distribution, and tumor targeting. Other natural polymers such as alginate, dextran, and chitosan have been used. Plant polysaccharides should be explored in the fabrication of theranostic as they exhibit functionalities recognized by the body as compared to those of the polymers in biological systems. Polysaccharides are the materials for drug targeting and concentration at the site of action. Considering cancer therapy, some polysaccharides have exhibited anti-tumor activity. The incorporation of chemotherapeutic into a polysaccharide carrier may enhance cancer therapy.^[34]

CONCLUSION

Natural excipients development is gaining a lot of attention these days. Polymers play a significant role in drug delivery. So, the selection of polymer plays a very important role in drug manufacturing. Excipients that haven't been used before should formidably regulatory requirements before being incorporated into approved dosage forms. There are large numbers of natural polymers utilized in pharmaceutical preparations. Natural gums as pharmaceutical excipients are attractive because they are economical, abundant, non-toxic, and capable of chemical modifications, potentially biodegradable, and biocompatible.

The applicability of gums has been well established within the fields of pharmaceuticals. Gums may be used as the binding agent. They have been shown good potential as a binding agent as well as they possess some other properties like fillers, disintegrating agents, sustain releasing agents.

Natural polymers shown good binding property in wet granulation, granules are stable and fewer friable compared with other binders. Natural binders are non-polluting renewable resources for the sustainable provider of cheaper pharmaceutical excipient or product.

Many studies have been carried out in fields including food technology and pharmaceuticals using gums. Gums have several advantages over synthetic materials. Therefore, in the years to come, there'll be continued interest in natural gums and their modifications aimed at the development of better materials for drug delivery systems and the formulation of novel drug delivery systems, biotechnological applications, and other delivery systems.

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