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REVIEW ARTICLE

From Nature to Medicine: Investigating the Role of Natural Compounds as Excipients in Pharmaceuticals

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ABSTRACT
Excipients are pivotal in oral solid dosage forms, serving binding, disintegration, lubrication, and controlled release functions. Natural excipients, sourced from polysaccharides, proteins, lipids, plants, and sweeteners, gain traction for their safety and green chemistry alignment. Polysaccharides like starches, cellulose derivatives, and gums bind and disintegrate tablets. Proteins like gelatin and collagen provide adhesion and controlled release. Lipids such as fatty acids and natural oils sustain drug release, while plant-based excipients like Gum Arabic and Guar gum stabilize formulations. Natural sweeteners like sucrose, mannitol, and sorbitol mask taste and enhance sweetness. Functions span binder and adhesive properties, disintegrating, lubricating, coloring, flavoring, and controlled release. Formulation factors include API compatibility, stability, regulation, and manufacturing impact. Future trends entail biotechnological, nanotechnological, and 3D printing advances, emphasizing green chemistry and recyclable packaging. Appreciating natural excipient roles is pivotal for patient-friendly oral solid dosage form development in pharmaceuticals.
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INTRODUCTION

Excipients are inactive substances in pharmaceuticals, enhancing stability and delivery. Natural excipients, derived from plants, ensure biocompatibility and safety in drug formulations. Examples include microcrystalline cellulose as a binder, starches for various functions, and guar gum as a thickener. They align with the demand for natural and sustainable ingredients in pharmaceuticals. Natural excipients play a crucial role in the pharmaceutical industry, serving as essential components in drug formulations. These substances, derived from natural sources, are integral to the development of stable, effective, and safe pharmaceutical products. Excipients are inactive substances added to medicinal formulations to improve various characteristics such as solubility, stability, and bioavailability, as well as to facilitate the manufacturing process. Natural excipients, often plant-based, are gaining prominence due to their biocompatibility, safety, and reduced risk of adverse effects compared to synthetic counterparts. [1] One common category of natural excipients includes cellulose derivatives like microcrystalline cellulose. Microcrystalline cellulose acts as a binder and filler in pharmaceutical tablets, enhancing their mechanical strength and aiding in the formation of a cohesive tablet structure. Derived from wood pulp or cotton, it is biodegradable and widely accepted for its inert nature, making it suitable for a variety of formulations. Starches are another significant group of natural excipients. Extracted from sources such as corn, wheat, or potatoes, starches serve multiple functions, including binding, disintegrating, and acting as fillers. They contribute to the mechanical strength of tablets and assist in their disintegration upon ingestion. Starches are valued for their versatility and compatibility with a range of active pharmaceutical ingredients. Gums, such as guar gum, are also commonly used natural excipients. Guar gum, derived from guar beans, is employed as a thickening agent, stabilizer, and binder in pharmaceutical formulations. Its ability to modify the rheological properties of liquids makes it valuable in creating consistent and uniform drug suspensions. Guar gum is known for its safety profile and its ability to enhance the viscosity of liquid

formulations. These natural excipients contribute not only to the physical attributes of pharmaceutical products but also to their overall performance. They aid in the controlled release of active ingredients, ensuring optimal therapeutic effects. Furthermore, natural excipients often exhibit biodegradability, aligning with the growing emphasis on sustainability in the pharmaceutical industry. [2] The use of natural excipients is driven by a desire to meet consumer demand for products with fewer synthetic additives. Patients are increasingly conscious of the substances they ingest and are more inclined toward natural and sustainable options. Natural excipients address this preference, providing a way for pharmaceutical companies to meet consumer expectations and differentiate their products in the market. Despite their advantages, challenges exist in the sourcing and standardization of natural excipients. The variability in composition and quality of natural materials can impact the consistency of formulations. Rigorous quality control measures are necessary to ensure the reliability and reproducibility of natural excipients in pharmaceutical manufacturing. [3]

Types of Natural Excipients

1. Plant Based Excipients

- **Albizia gum:** Cuttings from the Albizia julibrissin tree (Fabaceae) yield Albizia julibrissin gum, comprising β-1-3 linked D-galactose units and some β-1-6-D-galactose units. Explored as a natural emulsifier for food and medicine, it shows promise as a substitute for gum arabic. In pharmaceutical applications, Albizia julibrissin gum-coated tablets, when subjected to gut microbiota digestion, facilitate drug release. This highlights its potential in controlled drug delivery systems, offering a natural and effective alternative for coating tablets and ensuring targeted release in the gastrointestinal tract.
- **Almond gum:** Almond gum comes from the apricot tree of the Rosaceae family. It is a water-soluble gum that oozes from the wounds of the almond tree. Almond gum contains sugars such as aldonic acid, L-arabinose, L-galactose and D-mannose. The various components that make up almond gum have the ability to emulsify, thicken, lengthen, bond, polish and stabilize. Almond gum has been studied for its ability to bind to tablet formulations. When the concentration of almond gum was compared to synthetic gum, drug release increased and non-Fickian diffusion was determined as the release. Almond gum has been found to be useful in the preparation of uncoated tablets.[4]
- **Cashew gum:** The liquid that comes out of the root bark of the cashew tree (Anacardium occidentale, family: Anacardiaceae) is called cashew gum. Although hydrolysis of gum produces L-arabinose, L-rhamnose, D-galactose, and glucuronic acid, the gum itself contains galactose, arabinose, rhamnose, glucose, and other sugar residues. Cashew gum has been studied for its gelling ability. The gel made with 5.0% mucilage was found to be excellent and comparable to the commercial preparation. There are no skin problems during gel preparation. It was observed that the viscosity, drug content and physical properties of the gel remained constant at all temperatures for three months. The binding capacity of cashew gum was also investigated. This study compared the adhesive properties of gum arabic and cashew gum. What is important is that the amount of gum increases and the disintegration time of the tablet increases with release control. Studies have shown that increasing the polymer ratio slows down drug release.[5]
- **Gellan gum:** Pseudomonas elodea secretes a repeating tetrasaccharide unit consisting of one α-L-rhamnose, one β-D-glucuronic acid, and two β-D-arabinoses. It is an anionic deacetylated exopolysaccharide. A rhamnose and a glucuronic acid residue and the chemical structure of the polysaccharide have been identified. Changes in the glucuronic acid neutralization level of different salts will cause slight changes in the molecular formula of gellan gum. Aqueous solutions of gellan gum used in medicine are used in microspheres, oral delivery, and ophthalmic formulations. Hydrogels, controlled particles, agents, gelling agents, and nondispersive products are some of the applications of gellan gum in ophthalmic drug delivery.[6]
- **Guar gum:** Guar gum is obtained from carob seeds and its main product is galactomannan, of which 34.5% is galactose anhydride and 63.4% is mannose anhydride. It is widely used in the pharmaceutical industry as an oral sustained-release drug carrier and requires the use of cross-linked microspheres and controlled-release matrices for intestinal drugs. Guar gum has many uses in addition to medicine, including as a laxative, appetite suppressant, emulsifier, binder, and separating agent. Galactomannan triacetate derivative forms a stable, transparent film. Refined guar shells need to be removed from the stems, and hydrolysis by high alkali concentrations affects viscosity. This study demonstrates that guar gum tablets are a potential commercial alternative to diltiazem extended-release tablets for drug delivery control.[7]

- **Gum acacia:** Acacia gum, also known as gum arabic, is obtained from the dried stems and branches of Acacia arabica or Acacia Senegal. Arab acid consists of potassium, calcium and magnesium and forms a branched molecule with a galactopyranosyl backbone. It is used as a stabilizer in emulsions, integrated osmotic tablets, tablet binders and as an osmotic suspending agent and foaming agent in cosmetics. Its soothing properties make it useful in cough, diarrhea and throat preparation. It is widely used in the food, beverage and pharmaceutical industries as a matrix microencapsulation agent to provide gradual release and enhance the stability of enzymes and endoglucanases in drug preparation.[8]
- **Gum karaya:** Tragacanth or karaya gum, derived from the Sterculia urens family, comprises uronic acid and glycoheteropolysaccharides, lacking a methoxy group. Its diverse medicinal applications include thickening, stabilizing, emulsifying, and serving as dental adhesives. Gum karaya is extensively employed in crafting sustained-release tablets in the food, paper, and textile industries, and functions as a matrix in laxatives, showcasing its multifaceted role in pharmaceutical and industrial settings.
- **Gum ghatti:** Gum ghatti, also known as gum gum, is derived from the large-leafed maywort (Crimsonaceae) plant and contains calcium salts of high-molecular-weight complex polysaccharides, including sugars and uronic acids. The main components of capping acid (a polysaccharic acid) are arabinose, galactose and mannose. Provides stable oil-in-water emulsions for use in the production of fat-soluble vitamin preparations. It is used in medicine as a stabilizer, binder, thickener, emulsifier and suspending agent. Chewing gum is edible. It is used as a health supplement for Indian women after childbirth.
- **Gum tragacanth:** It is a dry gelatinous substance obtained from the stems and branches of the legume plant Astragalus. Water-soluble tragacanth and water-swellable basal in are two components of tragacanth, a branched heterogeneous anionic carbohydrate. Tablets contain 10-25% tragacanth mucilage as a binding agent. Tragacanth is obtained from the juice of the Astragalus plant and is often used as an additive in tablet formulations. As a natural gum, it has many beneficial properties that make it suitable for medical use. Gum tragacanth acts as a binder to help bind the components of the tablet together. Its adhesive properties cause tablet particles to bind during compression, helping to form a strong tablet. Additionally, tragacanth can act as a thickener and stabilizer, adding viscosity to tablet formulations and improving their overall texture. This product improves the quality and performance of the final product, making it a versatile excipient in tablet production.
- **Locust bean gum:** The medicinal quality of the seeds of the carob tree, Ceratonia siliqua (Family: Fabaceae), is used to make carob gum (LBG), commonly known as carob gum. To achieve full hydration, separation and maximum viscosity, polymers require heat. It is neutral and slightly soluble in cold water. Chewing gum is made of protein, cellulose, D-galactomannan and pentane. The super disintegrant power of this gum was studied using dispersible tablets containing carob seed gum in comparison with the super disintegrant croscarmellose sodium. This gum has been researched for its compression abilities as well as control abilities. Since it protects the tablet when applied to the main tablet, it works as a convenient vehicle for the delivery of the drug to the intestine, making it possible to use the drug into the intestine.[9]
- **Mango gum:** Mango gum, sourced from the bark of Mangifera indica in the Anacardiaceae family, is a dried, gummy exudate polysaccharide. Extensive studies have focused on its binding and sustained release properties. Tablet formulations containing mango gum exhibited improved drug release. Research also explored its disintegrating qualities, revealing a weak correlation between disintegrating efficiency and the swelling index. Notably, mango gum proved effective in the creation of mouth-dispersing tablets, showcasing its potential as a versatile pharmaceutical excipient for enhancing drug delivery and formulating tablets with desirable characteristics for oral administration.[10]
- **Tamarind gum:** Tamarind gum, or tamarind seed powder (TKP), is derived from Tamarindus vulgaris seeds. It features a unique polysaccharide structure with α-D-xylan replacing the glucopyranose residue in the side chain at the O-6 position and (1-4)-β-D-glucan in the backbone. Some xylose residues at position 2 undergo gamma-D-galactosylation. Resembling the plant cell wall component xyloglucan, tamarind gum's polymer composition, glucosylxylosyl: galactosyl in a 3:1:2:1 ratio, suits various applications. Beyond its use in chewing gum, it finds pharmaceutical applications in hydrogels, spheres, ocular mucoadhesive drug delivery, and nasal sprays, showcasing its versatility in medical formulations.[11]
- **Tara gum:** Tara gum is obtained from the seeds of Caesus aeruginosa (Fabaceae or Leguminosae) and is rich in galactomannans with a mannose/galactose ratio of 3:1. High viscosity solutions can be

produced with only 1% concentration. In medicine, tara gum is used for control release of means in gastroretentive tablets, which causes swelling of the gum, thereby delaying the floating and release of the drug. It combines with tara gum to improve digestion and increase floating time on paper. Tara gum can also be used in emulsion formulations, demonstrating its versatility in drug formulations and can be used in controlled release strategies and improved drug delivery.[12]

- **Xantham gum**: Xanthan gum, a microbial exopolysaccharide produced by Xanthomonas campestris during glucose fermentation, is known as passionflower gum, keltrol, rhodigel, polysaccharide B-1459, and vanzan NF. Its main structure comprises repeating pentasaccharide units with two D-glucopyranosyl, two D-mannopyranosyl, and one D-glucopyranosyl uronic acid. Similar to cellulose, the polymer's backbone features (1_4)-linked β-D-glucopyranosyl units. Xanthan gum finds diverse applications, including controlled drug delivery and sustained release formulations in pharmaceuticals. Additionally, it serves as a stabilizer for suspensions and emulsions and functions as an emulsifier, stabilizer, and suspending agent in toothpaste and creams.[13]

Table 1: Pharmaceutical application of natural gums

S. No.	Common name	Botanical name	Family	Pharmaceutical application
1	Albizia gum	*Albizia gummifera*	Leguminoseae	Tablet binder
2	Cashew gum	*Anacardium occidentale*	Anacardiaceae	Suspending agent
3	Cordia gum	*Cordia oblique willed*	Boraginaecae	Oral sustained release matrix tablets
4	Gellan gum	*Pseudomonas elode*	-	Disintegrating agent
5	Guar gum	*Cyamompsis tetraganolobus*	Leguminoseae	Binder, emulsifier, disintegrant
6	Gum acacia	*Acacia arabica*	Leguminoseae	Suspending agent, emulsifying agent, binder in tablets, demulcent and emollient
7	Gum ghatti	*Anogeissusla tifolia*	Combretaceae	Binder, emulsifier, suspending agent
8	Gum Tragacanth	*Astragalus gummifer*	Leguminoseae	Suspending agent, emulsifying agent, demulcent, emollient
9	Karaya gum	*Sterculia uren*	Sterculiaceae	Suspending agent, emulsifying agent, dental adhesive, sustaining agent
10	Locust bean gum	*Ceratania siliqua*	Leguminosae	Binders, matrix formers, drug release modifiers, coatings, thickeners, viscosity enhancers, suspending agents, or gelling agents
11	Tamarind gum	*Garcinia gummi-gutta*	Fabaceae	Thickening and stabilizing agent
12	Xanthan gum	*Xanthomonas lempestris*	-	Suspending agent, emulsifier, stabilizer

2. Polysaccharides:

- **Starch:**

Source: The primary carbohydrate reserve element in green plants is starch, which is mostly found in seeds and subterranean organs. Granules, or starch grains, are the form in which starch is found. Several starches are approved for use in medicine, and these include potato (Solanum tuberosum), wheat (Triticum aestivum), rice (Oryza sativa), and maize (Zea mays). [14]

Composition: A carbohydrate known as starch, or amylum, is made up of many glucose units bonded together by glycosidic linkages. It is made up of two polymers: amylopectin, which is highly branched and contains both α-1,4 and α-1,6 connected D-glucose monomers, and amylose, which is a non-branching helical polymer made up of α-1,4 linked D-glucose monomers. [15,16]

- **Cellulose derivatives:**

Source: Cellulose derivatives are processed chemically for use in a variety of commercial applications, such as food, medicine, textiles, and cosmetics. They are primarily derived from wood pulp, cotton, and crops like bamboo.
Composition: It is an organic polysaccharide with the formula $(C_6H_{10}O_5)_n$, made up of a linear chain of several hundred to more than ten thousand β(1→4) connected glucose units. The primary components of plant cell walls are pectin, hemicelluloses, and cellulose. [17]
Applications:
1. The pharmaceutical industry primarily uses microcrystalline cellulose as a diluent/binder in tablets for the granulation and direct compression.
2. Drug formulations use carboxylated methyl cellulose as a binder, film-coating agent, ointment base, and other purposes.
3. Wound dressings are made from fibers made of cellulose acetate. [18]

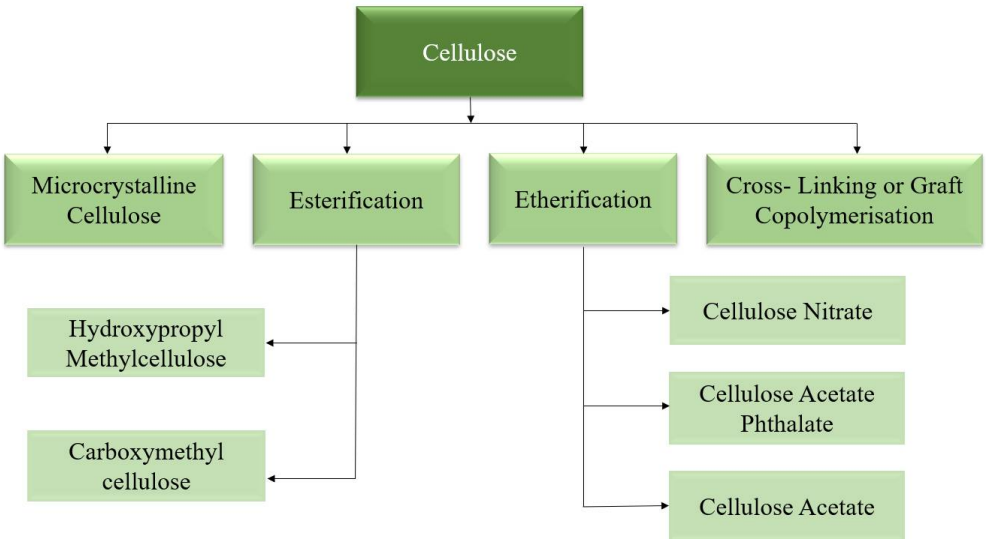

Fig. 1: Cellulose derivatives

- **Agar:**

Source: Agar, commonly known as agar-agar, is made of dried gelatinous material derived from *Gelidium amansii* (Gelidaceae), though it can also be made from some other red algae species, including *Pterocladia* (Gelidaceae) and Gracilaria (Gracilariaceae). [19]
Composition: Agarose and agaropectin are combined to form agar. The repeating monomeric unit of agarobiose makes up the linear polymer known as agarose. In contrast, Agarobiose is a disaccharide consisting of 3,6-anhydro-L-galactopyranose and D-galactose. Agaropectin is a poorly gelling heterogeneous collection of smaller acidic molecules.
Applications:
1. Agar is utilized as a suppository gelling agent, emulsifying agent, surgical lubricant, tablet disintegrant, and medium for Laxative and bacterial culture.
2. In addition, it's utilized in tissue culture research, confections, jellies, and microbiological studies. [20]

- **Alginates:**

Source: Brown seaweed yields alginate, a linear polymer that is soluble in water.
Composition: It is made up of 1-4 linked residues of -L-glucuronic and -Dmannuronic acid.
Applications:
1. Tablets containing alginate are utilized for the intestinal medication delivery mechanism.
2. Alginate is also used as an encapsulating substance to deliver drugs to mucosal tissue under control.
3. Additionally, mucoadhesive drug delivery devices are made with it. [21]

3. Proteins

- **Gelatin:**

Collagen can be denaturated or undergo physical-chemical degradation to yield gelatin, a high molecular weight polypeptide. 19 amino acids make up gelatin, which is a protein also. It can dissolve in water. Other proteins derived from animals include fibrin, albumin, and elastin.
Applications: Emulsifiers, foaming agents, colloid stabilizers, biodegradable film-forming substances, and microencapsulating agents are a few examples of these. [22]

- **Collagen:**

Source: The main protein found in animal connective tissues is collagen. Pork and cattle bones, as well as the skin of pigs and cows, are the most abundant sources of collagen.

Composition:

There are 27 different forms of collagen, and they are all made up of various polypeptides, the majority of which are glycine, proline, hydroxyproline, and lysine. The adaptability of the only the glycine content affects the collagen chain.

Applications:

1. In ophthalmology, collagen films are employed as drug delivery devices to allow for the gradual release of integrated medications.
2. Moreover, tissue engineering applications included the creation of artificial blood arteries and valves, skin replacement, and bone substitutes. [23]

4. Lipids:

- **Fatty acids:**

Source: Animal and plant sources both include fatty acids. Vegetable oils (including olive, coconut, and sunflower oil), nuts, seeds, and avocados are examples of plant-based supplies. Sources derived from animals comprise meat, fish, dairy, and eggs.

Composition: Long hydrocarbon chains with a carboxylic acid group at one end make up fatty acids. They fall into three categories: monounsaturated fatty acids, which have one double bond; polyunsaturated fatty acids, which have several double bonds; and saturated fatty acids, which have none.

Applications:

Fatty acids are used in many different ways. Because they are a key part of cell membranes and a concentrated source of energy, they are vital to human nutrition. They are also utilized as raw materials in the chemical and pharmaceutical sectors, as well as in the manufacturing of soaps, detergents, and cosmetics. [24]

- **Waxes:**

Source: Numerous plant and animal sources include waxes. Commonly present on the surface of leaves, fruits, and stems, plant waxes offer defense against pests and water loss. Both the beeswax that honeybees create and the wool wax (lanolin) that sheep produce contain animal waxes.

Composition: Esters of long-chain fatty acids and long-chain alcohols are what waxes are. They usually comprise a blend of these substances, creating a barrier that is both hydrophobic and protective.

Applications:

Axes are used in many different industries, such as the food industry (such as coatings for fruits, candies, and cheeses), pharmaceuticals (such as ointments and creams), cosmetics and personal care products (such as lip balms and moisturizers), and industrial processes (such as lubricants, polishes, and in the production of candles and coatings). [25]

- **Natural oils:**

Source: Plant seeds, nuts, and fruits are the main sources of natural oils, along with animal adipose tissue. Fish and cod liver oil are examples of animal-based oils, whereas common plant-based oils are olive, soybean, palm, and coconut oils.

Composition: Triglycerides, which comprise three fatty acid molecules esterified to a glycerol backbone, are what make up natural oils. Depending on the source, natural oils have different compositions with differing degrees of saturation and fatty acid chain length.

Applications:

There are several uses for natural oils. They are frequently used as salad dressings, cooking oils, and flavor enhancers in food preparation and cooking. Additionally, because of their emollient and moisturizing qualities, they are utilized in skincare and cosmetics products. In industrial operations, natural oils are also used as lubricants, in the synthesis of different chemicals and minerals, and in the creation of biofuels. [26]

5. Natural Sweeteners:

- **Sucrose:**

Source: The two main sources of sucrose, or table sugar, are sugarcane and sugar beets. Though in smaller amounts, it can also be found in a variety of fruits and vegetables that grow organically.

Composition: One glucose molecule and one fructose molecule joined by a glycosidic bond to form sucrose, a disaccharide. It is a highly delicious solid that crystallizes.

Applications:

Due to its tasty and adaptable nature, sucrose is frequently utilized as a sweetener in the food and beverage sectors. As a generic sweetener in a variety of processed goods, it is used in baking, confectionery, desserts, and beverages. [27]

- **Mannitol:**

Source: Seaweed, celery, mushrooms, and other fruits and vegetables naturally contain mannitol, a sugar alcohol. Moreover, it can be manufactured industrially by reducing mannose or hydrogenating fructose.
Composition: A polyol, or sugar alcohol, mannitol shares a molecular structure with glucose. It is a crystalline powder that is white in color and tastes sweet, though not as sweet as sucrose.
Applications:
There are numerous uses for mannitol in the food and medicine sectors. It is a sweetening ingredient in reduced- and sugar-free goods including candies, chewing gum, and meals suitable for diabetics. Due to its capacity to improve palatability and conceal off-putting flavors, mannitol is frequently utilized as an excipient in pharmaceutical formulations, especially in the form of tablets and capsules.[28]

- **Sorbitol:**

Source: Another naturally occurring sugar alcohol is sorbitol, which can be found in a variety of fruits such berries, pears, apples, and peaches. Moreover, glucose can be hydrogenated to generate it.
Composition: A polyol with a structure like glucose is sorbitol. It tastes sweet and is a white, crystalline powder that is about half as sweet as sucrose.
Applications:
In the food business, sorbitol is frequently used as a bulking, humectant, and sweetening agent. It is frequently found in reduced- and sugar-free goods, such as beverages, chewing gum, baked goods, and candies. Because of its non-cariogenic qualities, sorbitol is also utilized as a sweetener in medicinal formulations and as a component in mouthwash and toothpaste. Sorbitol is also utilized in the personal care and cosmetics sectors. [29]

Functions of Natural Excipients

- **Tablet Granulation**

The process of granulating particles to increase their size is known as granulation. Among the most crucial steps in the manufacturing of solid dosage forms like tablets and capsules is this procedure. Natural excipients that can function as binders in granulation include starches, gelatin, and gums (such as guar gum and acacia). They enhance the granules' flow characteristics by aiding in the binding of the particles to create granules of the appropriate size and strength.[30]

- **Enhancing Dissolution Rate**

Certain naturally occurring excipients function as surfactants, including lecithin, polysorbates (like the Tween series), and sorbitan esters (like the Span series). Drug particles can be soaked and dispersed more quickly when surfactants lower the interfacial tension between the solid particles and the dissolving media. This raises the surface area that may dissolve and speeds up the dissolving process.[31]
By making the dissolving media more viscous, naturally hydrophilic polymers like alginate, gums (like guar gum and xanthan gum), and cellulose derivatives (like hydroxypropyl cellulose and hydroxypropyl methylcellulose) can increase the rate of dissolution. Faster dissolving may result from this viscosity enhancement's ability to increase medication diffusion and inhibit drug precipitation.[32]

- **Controlled Release Agents**

When a polymer-natural or synthetic-is carefully mixed with a pharmaceutical or other active agent so that the active agent is released from the material in a predetermined fashion, the result is controlled drug delivery. Matrix matrices containing the active pharmaceutical ingredient (API) can be formed using natural polymers. These matrices regulate the drug's release either by controlling its diffusion through the matrix or by gradually eroding the matrix itself. Certain natural excipients can increase the bioavailability of poorly soluble medications. Examples of these excipients are lipid-based excipients like phospholipids or triglycerides. Better medication solubility and absorption can be achieved by adding these excipients to controlled-release formulations, which will enhance therapeutic results. [33]

- **Colouring and Flavouring Agents**

Among them are caramel, which is produced of caramelised sugar and is used in both cola and cosmetic goods, and annatto, a reddish-orange pigment derived from the achiote seed. Paprika Elderberry juice, turmeric (curcuminoids), saffron (carotenoids), cochineal (red dye made from the cochineal insect, Dactylopius coccus), betanin extracted from beets, pandan (Pandanus amaryllifolius), blue food colouring, and green food colouring made from chlorella algae (chlorophyll).[34]

TRENDS IN EXCIPIENT SAFETY EVALUATION:

All pharmaceutical items and most food products contain excipients. Novel excipients may be one of the new technologies being tested to improve the quantity or pace of drug absorption. Improved drug delivery may be possible using novel physical strategies like lysosomes or drug-and-excipient nanoparticles, particularly for oral medications that are difficult to manufacture or absorb. Foods, medications, and nutritional supplements may have their flavour enhanced or concealed by new

excipients. Excipient evaluation is one of several worldwide and national guidelines, recommendations, and laws that have been proposed and approved for usage in response to the increased scrutiny that drug product impurities have recently received. This conference covered new ideas for development, rules, guidelines, and guidelines pertaining to contaminants in excipients, as well as novel drug delivery systems that use excipients. It also included suggestions for how to improve the guidelines in order to hasten the regulatory approval of these chemicals.

CURRENT AND FUTURE METHODS FOR THE SAFETY ASSESSMENT OF EXCIPIENTS:

Chemicals known as excipients are added to food or medicine goods when it is thought required for the product's production. Because they are intended to be pharmacologically inert, inactive, and therapeutically inert, these chemicals add little to no therapeutic value to the product. Because of their importance in creating pharmaceutical goods that would not be possible to make without them, they have historically been referred to as "pharmaceutical necessities."

There are several functional categories of excipients for use in drug products. The list is large but involves examples such as

- Antioxidants, that is, butylated hydroxyanisole (BHA), ascorbic acid (vitamin C), and butylated hydroxytoluene (BHT)
- Preservatives, that is, benzalkonium chloride, thimerosal, and benzyl alcohol,
- Colors, that is, Red 40 and FD&C Green,
- Flavorings, that is, cherry syrup, monosodium glutamate (MSG), and lactose,
- Solubilizing agents, that is, ethanol, dimethyl sulfoxide (DMSO), and water,
- Suspending agents, that is, acacia and carboxymethylcellulose, and
- Thickening agents, that is, waxes and petroleum jelly.

There are many uses for these and other excipients and they can be found in products such as tablets, capsules, solutions, suspensions, creams, ointments, suppositories, injectables, inhalants, and so on.

TOXICITY:

When excipients and their inert nature are discussed, a common question comes up. Can excipients be harmful? How could they be dangerous if they are inert? The 16th-century toxicology pioneer Paracelsus famously declared, "Poison is in everything and nothing is without poison." It can be either a poison or a cure depending on the dosage.3. But until about 1937, the possible toxicity of excipients received little consideration. An elixir of a comparatively insoluble and unpleasant-tasting sulfonamide antibacterial medication was sought for by a chemical business. One of its chemists discovered that by using a toxicologically untested diethylene glycol (DEG) as the excipient, he could create a solution of this antimicrobial that had a pleasing blue colour and a sweet flavour. Elixir of Sulfanilamide was the name of the product, which was later sold and recommended by doctors until a tragedy involving the children who consumed it happened. It was found that the consumption of DEG caused over 100 deaths and several hundred cases of kidney failure in youngsters. The US Food, Drug and Cosmetic Act (FD&C Act), also known as the Copeland-Lea Act of 1938, was eventually passed by Congress as a result of popular outcry. This law, among others, transferred the responsibility for the safety of pharmaceuticals from the federal government to the manufacturer. Congress passed the Food Additive Amendments in 1958, which also gave US food makers the responsibility for ensuring the safety of food additives. It is of great interest to learn that the word excipient or any specific concern for their potential toxicities are “not” mentioned in the FD&C Act, since it was an excipient that was responsible for the genesis of this powerful law.

Both topical and systemic administration of excipients have been linked to a number of distinct toxicities. Dermal toxicities, such as hypersensitivity to lanolin, benzoic acid, para-aminobenzoic acid (PABA), and local anaesthetics; phototoxicity to cinnamon oil, bergamot oil (found in perfumes), and 8-methoxypsoralen with ultraviolet A light (PUVA) as a treatment for psoriatic lesions; and contact dermatitis to propylene glycol, polyethylene glycol, and oleic acid have been noted in relation to the topical application of certain excipients.

Some excipients have been linked to systemic administration, such as renal tubular necrosis from intravenous (IV) or subcutaneous (SC) administration of β-cyclodextran, respiratory toxicities in young children from inhaling benzyl alcohol solutions, digestive issues from lactose ingestion, allergic reactions from sulfites ingestion, and diarrhoea from mannitol-containing solution ingestion. It is crucial to keep in mind the toxicological maxim, "The dose makes the poison."

Little progress was made in the years that followed, from 1938 until the 1990s, in further regulating excipients and raising awareness of their unique toxicities. There was less instruction on how to design a plan for evaluating them, thus they were either examined separately or with their medicinal products for toxicity. Guidelines for the safety testing of excipients were released later in 1996 by the Safety Committee of the International Pharmaceutical Excipients Council ([IPEC]-Americas)5. This

recommendation outlined the various toxicological tests that have to be carried out in accordance with the therapeutic route of administration in order to identify excipient toxicities.

Regulatory Toxicology

How can a pharma sponsor lawfully include an excipient in a drug product when the FDA lacks a formal regulatory procedure to assess excipients independently? Recall that a new excipient may be qualified if it has been used in previously approved drug products, has been generally recognised as safe (GRAS) as a direct food additive, has a similar level of exposure or route of administration in an approved drug product, or has a similar duration of exposure linked with a prior approved use. Nonetheless, as stated in FDA/CDER's excipient advice, it might be required to update the excipient's safety database to current standards.

The FDA's guidance recommends the acquisition of toxicology data from the following types of studies

- Safety pharmacology with an emphasis on cardiovascular, respiratory, and central nervous systems,
- Pharmacokinetic/absorption, distribution, metabolism, and excretion (ADME) studies,
- ICH S2B genetic toxicology battery,
- Reproduction toxicology,
- Appropriate duration repeats dose studies in 2 species (rodent and nonrodent mammal), and
- Carcinogenicity studies, if warranted.

The expected clinical route of administration for the excipient must be used for testing. It is advised to discuss the appropriate testing with the relevant FDA/CDER review division before starting any investigations. The IPEC paper and the FDA/CDER Excipient Guidance7 both contain specific instructions about the modes of administration. [35]

CONCLUSION

In conclusion, natural excipients are indispensable in formulating oral solid dosage forms due to their diverse functionalities. Their appeal lies in their safety, alignment with green chemistry principles, and effectiveness across various roles in pharmaceutical formulations. From facilitating binding and disintegration to enabling controlled release and taste masking, natural excipients are integral for ensuring medication efficacy, stability, and patient acceptance. Ongoing advancements in biotechnological approaches, nanotechnology, and sustainability initiatives hold promise for further innovation in natural excipient research and development. Recognizing and harnessing the potential of natural excipients are crucial for enhancing the quality and accessibility of oral solid dosage forms in the pharmaceutical industry. As the field progresses, the intersection of biotechnology, nanotechnology, and sustainable practices is likely to drive continuous improvements, reinforcing the importance of natural excipients in pharmaceutical formulations. In summary, the multifaceted benefits of natural excipients position them as key players in the evolution and enhancement of oral solid dosage forms, shaping the future landscape of pharmaceutical development.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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