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Natural Excipients: A Review

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Abstract

The use of natural excipients to deliver the bioactive agents has been hampered by the synthetic materials. However advantages offered by these natural excipients are their being non-toxic, less expensive and freely available. The performance of the excipients partly determines the quality of the medicines. 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. Earlier used natural excipients are carrageenan, thaumatin, lard, shilajit, aerosil, myrobalan, storax. Excipients are any component other than the active substances intentionally added to formulation of a dosage form. Novel drug delivery systems are developed to address the challenges of drug development such as bioavailability, permeability, and poor solubility. Global excipient markets are expected to grow rapidly with the emerging trends in the pharmaceutical industry. The pharmaceutical industry is marketing refinement in the physical structure of active pharmaceutical ingredients (APIs). This article gives an overview of natural excipients which are used in conventional dosage forms as well as novel drug delivery systems.

Keywords: Natural excipients, aerosol, storax, guar gum, alginates

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Introduction

Excipients were defined as 'the substance used as a medium for giving a medicament', that is to say with simply the functions of an inert support of the active principle or principles. [1] The specific application of natural poly-saccharide polymers in pharmaceutical formulations include to aid in the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use. [2] Today we have several pharmaceutical excipients of plant origin, like starch, agar, alginates, carrageenan, guar gum, xanthan gum, gelatin, pectin, acacia, tragacanth, and cellulose. These natural excipients find applications in the pharmaceutical industry as binding agents, disintegrates, sustaining agents, protective's, colloids, thickening agents, gelling agents, bases in suppositories, stabilizers, and coating materials. The advantages of natural plant-based excipients include that they are of low cost, natural origin, fairly free from side effects, biocompatible, and bio-acceptable, with a renewable source, environmental friendly processing, local availability, better patient tolerance, as well as public acceptance. [3] Excipients are also derived from natural sources, synthesized chemically, or prepared semi-synthetically starting from natural sourced materials. They range from simple, usually well-characterized, organic or inorganic molecules to highly complex materials that are difficult to fully characterize. Classification of excipients is based on their role in the pharmaceutical formulation,

their interactions influencing drug delivery, or their chemical and physico-chemical properties. [4] Excipients are also sometimes used to bulk up formulations that contain very potent active ingredients, to allow for convenient and accurate dosage. Depending on the route of administration, and form of medication, different excipients may be used. To stabilize the active ingredient, excipients are added, ensuring that the active ingredient stays "active", and, just as importantly, stable for a sufficiently long period of time that the shelf-life of the product makes it competitive with other products. Excipients also can serve to mask an unpleasant taste or texture and help ensure that the right amount of the API makes it to the right spot in the body at the right time. [5] **(Table 1)** [a]

Polysaccharides in pharmaceuticals

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 amylase are a few polysaccharides commonly used in controlled release dosage forms. Non-starch, linear polysaccharides remain intact in the physiological environment of the stomach and the small intestine, but are degraded by the bacterial inhabit-ants of the human colon which make them potentially useful in targeted delivery systems to the colon. [6]

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. [7] **(Table2)** [b], **(Table3)** [c] **and (Table4)** [d]

Pectin:

Pectins are non-starch, linear polysaccharides extracted from the plant cell walls. [34] In the food industry, folic acid incorporated microcapsules were prepared using alginate and combinations of alginate and pectin polymers so as to improve stability of folic acid. 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. [35] **(Table5)** [e] **and (Table 6)** [f]

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. Alginates offer various applications in drug de-livery, such as 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**.** [37]

Uses of alginates

- Alginates have proven to be effective for the symptoms of malignant wounds. [38]
- 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. [39]
- Alginates are thin, self-adhesive and conform well to contours. This increases the freedom to carry out normal daily activities. [40]

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. [41]

Modified starch was tested for general applicability of a new pregelatinized starch product in directly compressible controlled-release matrix systems. [42]

Use of starch

The two major components of starch are amylose and amylopectin. Amylose consists of long linear chains of α-1,4 linked glucose residues with relatively few α-1,6 linked branches whereas amylopectin is a highly branched molecule of shorter α-1,4 linked glucose molecules and more frequent α-1,6 branches. [43]

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. [44]

Chitosan

Chitosan is a natural positively charged (cationic) biopolymer derived from the hydrolysis of the polysaccharide chitin. [45] 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. [46]

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-Dglycopyranose units. [47]

- **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. [48]
- **Biological Properties: -** During the last two decades, chitosan has been used as a safe excepient in drug formulations.
    - 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. [49] **(Table7)** [g]

Volatile Oil

Baratta *et al*., 1998 Volatile oils are very complex mixtures of compounds. The constituents of the oils are mainly monoterpenes and sesquiterpines which are hydrocarbons with the general formula (C5H8)n. [51]

Menthol

Menthol was tested for improving the bioavailability of poorly water-soluble ibuprofen in the rectum with poloxamer. The effects of menthol and poloxamer 188 on the aqueous solubility of ibuprofen were investigated. [52]

Terpenes such as menthol, cineole and propylene glycol (PG) were tested as chemical enhancers to improve the skin penetration of propranolol. [53]

Caraway

Caraway seeds technically are half-fruits, the whole fruit being a schizocarp which comprises two distinct halves (‘mericarps’) which each contain one seed. We will use ‘seed’ where we refer to the agricultural product (half fruit) and ‘fruit’ when we refer to the entire schizocarp (containing two seeds).

Caraway essential oil has been used as a flavouring for liquors and toothpaste, while the seeds have been used as a spice and flavouring. [54]

Application of excipients

1. **Application of starch in rubber**
    - In 1970s, replacement of coom by starch was studied in the researching centers of northern areas in the USA. Reinforcing action of rubber caused by cross-linked starch xanthate was similar to that of moderate coom.
    - **Carvalho *et al*** from France mixed natural latex with starch to establish natural starch-rubber compound material. [55]

2. **Domestic application**
    - **Ma *et al*** added starch into lotion to establish NBR/argilla nanometer compound to obtain stripping-structural compound materials. The results demonstrated that argilla content was in 5-20 portions, and with the more and more usage of starch, hardness, extending intensity, and tensile strength were increased. [56]
    - **Zhao *et al*** used elasticizer-modifying starch to replace some coom or gum acacia in tyre processing. The results suggested that modified starch might improve entirety of tyre. Due to a good biodegradation, starch used as a filler of rubber can be used to produce environmental-friendly materials and products which have extensive application prospects. [57]

Applications of chitosan in Pharmaceuticals

- It is good diluents in direct compression of tablets, use binder for wet granulation, slow release of drugs from tablets and granules, film controlling drug release. [58]
- It increases viscosity in solutions preparing hydrogels, improves the dissolution of poorly soluble drugs, absorption enhancer for nasal and oral drugs, biodegradable polymer for implants and carrier to vaccine delivery and gene therapy. [59]

Conclusion

Today the stress is on patient compliance and to achieve this objective there is a spurt in the development of NDDS. As the herbal excipients are promising biodegradable materials, these can be chemically compatible with the excipients in drug delivery systems. In addition herbal excipients are non-toxic, freely available, and less expensive compared to their synthetic counterparts. They have a major role to play in pharmaceutical industry. Therefore, in the years to come, there is going to be continued interest in the natural excipients to have better materials for drug delivery systems.

Table 1.Classification: - Source on origin .[a]

from animal	from Vegetable	from Minerals
Beeswax,	Kokum butter,	Bentonite,
Cochineal,	Pectin,	Kieselghur,
Gelatin,	Starch,	Kaolin,
Honey,	Peppermint,	Paraffins,
Lactose,	Cardamon,	Talc,
Spermaciti,	Vanilla,	Calamine,
Lanolin,	Tumeric,	Fuller's earth,
Musk,	Saffron,	Asbestos etc.
Suet etc.	Guargum etc	

Table 2.The different available gums and mucilage's can be classified as follows .[b] **[8-13]**

Charge	Source	Semi-synthetic	Shape	Chemical structure
Non-ionic seed gums: Guar, locust bean, tamarind,xanthan, amylose,arabinans, cellulose,galactomannans.	**Marine origin/algal (seaweed) gums:** Agar,carrageenans,alginic acid, laminarin.	**Starch derivatives**: Hetastarch, starch acetate, starch phosphates.	**Linear**: Algins, amylose, cellulose, pectins.	**Homoglycans**: Amylose, arabinanas, cellulose.
Anionic gums: Arabic, karaya, tragacant, gellan, agar, algin, carrageenans, pectic acid.	**Plant origin**: a) Shrubs/tree exudates-gum arabica, gum ghatti,gum karaya,gum tragacanth, khaya and albizia gums. b) Seed gums-guar gum, locust bean gum, starch, amylase. c) Extracts-pectin, larch gum. d) Tuber and roots-potato starch.	**Cellulose derivatives**: Carboxy methyl cellulose (CMC), Hydroxy ethylcellulose, hydroxy propyl methylcellulose(HPMC), Methylcellulose(MC), Microcrystallincellulose (MCC).	**Branched**: (a) Short branches-Xanthan, xylan, galactomanan. (b) Branch-on-branch-Amylopectin, gum arabic, tragacanth.	**Diheteroglycans**: Algins,carragennans,galactomannans. **Tri-heteroglycans**: Arabinoxylans, gellan, xanthan. **Tetra-heteroglycans**: Gum arabic, psyllium seed gum. **Penta-heteroglycans**: Ghatti gum, tragacanth.
	Animal origin: Chitin and chitosan,chondroitin sulfate, hyaluronic acid.			

Table 3.Pharmaceuticals application or uses of natural gums and mucilage .[c]

Common name	Botanical name	Family	Pharmaceutical applications
Agar	*Gelidium amansii*	Gelidaceae	Suspending agent, emulsifying agent, gelling agent in suppositories, surgical lubricant, tablet disintegrates, medium for bacterial culture, laxative. [14]
Albizia gum	*Albizia zygia*	Leguminoseae	Tablet binder. [15]
Aloe mucilage	*Aloe species*	Liliaceae	Gelling agent, sustained release agent. [16]

Bavchi mucilage	*Ocimum canum*	Gigarginaceae	Suspending agent, emulsifying agent. [17]
Cassia tora	*Cassia tora Linn*	Leguminoseae	Binding agent. [18]
Gum acacia	*Acacia arabica*	Combretaceae	Suspending agent, emulsifying agent, binder in tablets, demulcent and emollient in cosmetics. [19]
Gum ghatti	*Anogeissus latifolia*	Leguminoseae	Binder, emulsifier, suspending agent. [20]
Gum tragacanth	*Astragalus gummifer*	Malvaceae	Suspending agent, emulsifying agent, demulcent, emollient in cosmetics and sustained release agent. [21]
Khaya gum	*Khaya grandifolia*	Labiatae	Binding agent. [22]
Satavari mucilage	*Asparagus racemosus*	Aapocynaceae	Binding agent and sustaining agent in tablet. [23]
Tamarind seed polysaccharide	*Tamarindus indica*	Leguminoseae	Binding agent, emulsifier, suspending agent, sustaining agent. [24]
Gellan gum	*Pseudomonas elodea*	---	Disintegrating agent. [25]

Table 4.Applications of gums and mucilage's in NDDS .[d]

Common name	Botanical name	Family	Pharmaceutical applications
Bhara gum	*Terminalia bellerica roxb*	Combretaceae	Microencapsulation. [26]
Cordia gum	*Cordia obliqua willed*	Boraginaecae	Novel oral sustainedrelease matrix forming agent in tablets. [27]
Cactus mucilage	*Opuntia ficus-indica*	—	Gelling agent in sustained drug delivery. [28]
Karaya gum	*Sterculia urens*	Sterculiaceae	Mucoadhesive and buccoadhesive. [29]
Locust bean gum	*Ceratania siliqua*	Leguminoseae	Controlledrelease agent. [30]
Mucuna gum	*Mucuna flagillepes*	Papillionaceae	Microspheres. [31]
Okra	*Hibiscus esculentus*	Malvaceae	Hydrophilic matrix for controlled release drug delivery. [32]
Sodium alginate	*Macrocytis pyrifera*	Lessoniaceae	Bioadhvesive microspheres, nanoparticles, microencapsulation.[33]

Table 5.Controlled release formulation using pectin .[e] [36]

Dosage form	Type of pectin	Application
Tablets	Pure and standardized pectin	Binding agents and delayed drug release
Gel beads	LM-pectin	Pectin beads prepared by ionotropic gelatin
Gel beads	LM-pectin(amidated)	Sustained release drug delivery using calcium pectinate gel beads
Pellets	LM-pectin	Calcium petinate or calcium alginate-pectinate prepared by ionotropic gelation.
Particulates	LM-pectin	Alginate-pectin-polylysine system
Microspheres	LM-pectin	Pectin-based microspheres prepared by emulsification technique
Coated pellets	LM-pectin (amidated and non-amidated)	Insoluble calcium pectinate gel coating for sustained release delivery prepared by interfacial complexation

HM-pectin = high methoxy pectin; LM-pectin = low methoxy pectin

Table 6.Colon-specific drug delivery using pectin .[f]

Dosage form	Type of pectin	Application
Tablets	Calcium pectinate	Compression of calcium pectinate (matrix system)
Tablets	HM-pectin and LM-pectin	Matrix system
Tablets	Amidated LM- pectin and calcium salt of pectin	Direct compression of amidated or calcium of pectin alone or incorporated with ethylcellolose
Gel beads	LM-pectin (amidated)	Calcium pectinate gel beads for protein delivery
Film coated tablets	HM-pectin or LM-pectin	Coating with HM-pectin or LM-pectin combined with commercially aqueous polymer dispersion
Capsule with plug	LM-pectin	Direct compression of pectin/ pectinase-plug

HM-pectin = high methoxy pectin; LM-pectin = low methoxy pectin; HPMC = hydroxypropyl methylcellculose.

Table 7.List of chitosan based formulations prepared by different methods.[g] [50]

Types of system	Method of preparation	Drug
Tablets	Matrix Coating	5-ASA ,DiclofenacSodium, Theophylline , Mesalamine, Glipizide and Propranolol HCl
Capsules	Capsule shell	Insulin
Microspheres/ Microparticles	Emulsion cross-linking	Gentamicin Sulphate, Hemoglobin, Diclofenac, Clarithromicin
	Coacervation/precipitation	
	Spray-drying	Propranolol-HCl
	Ionic gelation	Cimetidine, Famotidine, Bovine serum albumin.
	Sieving method	Bovine serum albumin (BSA)
		Clozapine
Nanoparticles	Emulsion-droplet coalescence	Gadopentetic acid
	Coacervation/ precipitation	
	Ionic gelation	
	Reverse micellar method	Bovine serum albumin, Ovalbumin
		Ascorbic acid, Cyclosporin A
		Doxorubicin
Beads	Coacervation/ precipitation	Bovine serum albumin, Insulin
Films	Solution casting	Ofloxacin, Paclitaxel
Gel	Cross-linking 5	Fluorouracil

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