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NATURAL POLYMERS: AS PHARMACEUTICAL EXCIPIENTS AND THEIR APPLICATIONS IN DIFFERENT PHARMACEUTICAL FORMULATIONS - A REVIEW

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ABSTRACT

Advances in polymer science have led to the development of novel drug delivery systems which include: microspheres, nanoparticles, tablets, gels, transdermal patches, dermal patches, implants, noisome, and liposomes. Few polymers are obtained from natural resources, while the remaining are chemically synthesized and used. Therefore a large number of natural and synthetic polymers are presently available as a pharmaceutical excipients. But today, the extensive research in natural polymeric materials have gained focused and a growing attention; due to the interest in their eminent contribution to a number of pharmaceutically important factors like: relative abundance, economic, nontoxic, bio-degradable and eco-friendly nature; which makes it suitable for pharmaceutical industries to use them in variety of formulation and to develop a cost effective and economic dosage forms. Also their applicability in sustain and control release dosage forms have proved them to be a boon in the pharmaceutical and research sectors; to develop sustain and control release dosage forms. Owing to this potential applications of natural polymer in the field of pharmaceutical science, cosmetics, research, and other allied sciences, it becomes essential to emphasized on natural polymers as a pharmaceutical excipients. Thus in the present paper, natural polymers obtained from plants sources are evidently emphasized.

KEYWORD: Natural Polymer, Pharmaceutical Excipient, Natural Gums and Mucilage.

INTRODUCTION

A polymer is a large molecule (macromolecules) composed of repeating structural units. These Subunits are typically connected by covalent chemical bonds.[1] Pharmaceutical excipients or Polymers are becoming increasingly important in the field of drug delivery. Pharmaceutical excipients may be defined as the additives used to convert pharmacologically active substances into pharmaceutical dosage form which is suitable for administration to the patients.[2] The pharmaceutical applications of polymers, range from their use as binders in tablets to viscosity and flow controlling agents in: liquids, suspensions and emulsions. Polymers can be used as film coatings to disguise the unpleasant taste of a drug, to enhance drug stability and to modify drug release characteristics. Thus polymers may be Pharmaceutical excipient or additives used to convert pharmacologically active substances into pharmaceutical dosage form suitable for administration to the patients. Both synthetic and natural polymers are available but the use of natural polymers for pharmaceutical applications is always attractive because they are economical, readily available and non-toxic.[3] Various natural gums and mucilage have been examined as polymers for control and sustained drug release, in the last few decades. Natural polymers remain attractive, primarily because; they are commercial, readily available, capable of multitude of chemical modifications and potentially degradable and compatible due to their origin. Biodegradable polymers have been used widely as drug delivery systems because of their biocompatibility and biodegradability. Biodegradable polymer particles (e.g. Microspheres, Microcapsules, and Nanoparticles) are highly useful because they can be administered to a variety of locations *in-vivo* through a syringe needle.[4] Gum and mucilage are natural polymers widely used as conventional and novel dosage forms. Natural polymers are generally safe for pharmaceutical formulation. They are high molecular weight; water soluble polymers, made up of a monosaccharide unit and joined by a glucosidal bond.[5] Gummy excaudate of natural polymers such as protein, enzyme, muscle, fiber, polysaccharides have been used to formulate various pharmaceutical products.[5][6] The well-known natural polymers are gelatin, aloe mucilage, guar gum, gum karaya, bhara gum, sodium alginate, locust bean gum, okra mucilage, gum acacia, linseed mucilage, etc. These natural polymers are applicable in different pharmaceutical dosage forms like matrix controlled systems, microspheres, nanoparticles, buccal films and semi-solid formulations.[7][8] Gums are freely soluble in water while mucilage forms a slimy mass in the presence of water. Gum and mucilage are translucent, amorphous substances which are produced by plants as a protection during injury.[9]

Need of Herbal Polymers[10]

1. Economic - They are economic and their production cost is less than synthetic material.
2. Easy availability – In many countries, they are produced due to their application in many industries.
3. Non-toxic and Biocompatible – Chemically, nearly all of these plant materials are carbohydrates in nature and composed of repeating monosaccharide units. Hence they are non-toxic.
4. Biodegradable – Naturally occurring polymers produced by all living organisms show no adverse effects on the environment or human being.
5. Safe and devoid of side effects – They are from a natural source and hence, safe and without side effects.

Disadvantage Of Herbal Polymers[10][11]

1. Slow Process – As the production rate depends upon the environment and many other factors which can't be changed to any desirable extents, therefore natural polymers have a slow rate of production.
2. Heavy metal contamination – There are probabilities of having Heavy metal contamination, which is often associated with herbal excipients.
3. Microbial contamination – There are chances of microbial contamination during production of natural polymers as they are exposed to various external environments.
4. Batch to batch variation – Synthetic manufacturing is controlled procedure with fixed quantities of ingredients while production of natural polymers is completely dependent on environment and various physical factors which are not under any controlled procedures.
5. The uncontrolled rate of hydration—Due to differences in the collection of natural materials at different times, as well as differences in region, species, and climatic conditions; the percentage of chemical constituents present in a given material may vary.

Table 1: Sources Of Natural Polymers[12]

From animals	From vegetables	From minerals
Beeswax,	Kokum butter,	Bentonite,
Cochineal,	Pectin,	Kieselghur,
Gelatin,	Starch,	Kaolin,
Honey,	Peppermint,	Paraffin's,
Lactose,	Cardamom,	Talc,
Spermaceti,	Vanilla,	Calamine,
Lanolin,	Turmeric,	Fuller's earth,
Musk,	Saffron	Asbestos

Pharmaceutical Application: Natural polymers are most commonly used as adjuvant in pharmaceutical preparations such as: thickener, binder, emulsifier, stabilizer, disintegrant, and gelling agents. These natural polymers obtained from various sources can be used in development of sustained release and controlled release formulations.[13]

Binding Agent: Different natural polymers have been used as binding agents in various pharmaceutical formulations. Several studies on natural polymers or mucilage's, suggest them to be useful as a binding agents in formulations and through these studies it was found that natural polymers have good binding properties than that of synthetic polymers, therefore making them appropriate and suitable for using them as pharmaceutical excipients. Mucilage obtained from *Cassia sophera* and *Asparagus racemous* were evaluated for their binding properties compared to starches, and was found that mucilage exhibit good binding properties as compared to starches.[14]

Evaluating *Trigonella foenum gracecum* & *plantago ovate* mucilage as a binder in tablet formulation showed good binding properties as well as shown a comparable release data as that of starches.[15] A study indicating that gum mucilage obtained from *Cissus populnea* & *Acacia senegal*; found to be good binding agent in Paracetamol tablets after its evaluation.[16] Evaluating *Chlorophytum borivilianum* mucilage as pharmaceutical excipient showed a good suspending properties as that of Tragacanth and thus can be used as suspending agent and also as an effective binder.[13] Seeds of *Vinga mungo* (L) was evaluated as binder in tablet formulation and the studies have shown it to be exhibiting good binding properties.[17]

Gelling Agent

Gels are a relatively newer class of dosage form which are formed by entrapment of large amounts of aqueous or hydro-alcoholic liquid in a network of colloidal solid particles which may consist of inorganic substances, such as aluminum salts or organic polymers of natural or synthetic origin. Depending upon the nature of colloidal substances and the liquid in the formulation, such as Carbomers, that impart an aesthetically pleasing, clear, sparkling appearance to the product; which can be easily washed off from the skin with water.[18]

Natural Gel Forming Agents

Polymers are used to give the structural network which is essential for the preparation of gels.

Natural Gel Forming Agents Are Classified As

a) **Protein:** Collagen, Gelatin

b) **Polysaccharides:** Agar, Alginic Acid, Sodium Carrageenam, Tragacanth, Pectin, Guar gum, Cassia tora, Xanthum gum, Gellum gum.[19]

Studies show that *Trigonella foenum gracecum L.* polymer has been used to prepare intra nasal gel using diazepam as model drug.[20] Mucilage obtained from leaf of *Cocculus Hisutus* has been used to prepare gel of flurbiprofen. Study showed that leaf mucilage can be used as base for gel preparation too.[21]

Suspending Agent

Suspending agent are excipients that help active pharmaceutical ingredients stay suspended in the formulation and prevent caking at the bottom of the container. One of the properties of a well-formulated suspension is that it can be easily re-suspended with a moderate agitation or shaking.[22]

When preparing any pharmaceutical formulation, choosing the right excipient is crucial in maintaining the integrity and stability of the medicament. Of these excipients, is the addition of suspending agents and or stabilizers to ensure the homogenous distribution of the active ingredient, and ultimately achieving the chemical and physical stability of the formulation.[23] A number of excipients have been used over the years as suspending agents either for oral or topical applications.

Below are few examples that are commonly used in practice[23]

a) Methylcellulose

b) Guar gum

c) Xanthan gum

d) Carboxy methyl cellulose sodium

e) Gelatin

In a study, carried out by Kumar. R. *et al*, mucilage obtained from *Abelmoschus esuclentus,* showed good suspending property when evaluated in paracetamol suspension.[24] In another study carried out by Suma Padmaja B *et al.* on *Abelmoschus esculentus* fruit mucilage, suggests that it can be used as a matrix forming material for controlled release matrix tablets[25]

Various Natural Polymers And Their Pharmaceutical Uses:

There are various natural polymers which have been used as pharmaceutical excipients such as-

Tamarind Seed Polysaccharide

a) Tamarind fruit and seeds.

b)Tamarind seeds.

Figure 1: Tamarind Seed.

Tamarindus indica, a member of evergreen family. Tamarind xyloglucan is obtained from endosperm of the seed of the tamarind tree, Tamarind gum, also known as Tamarind Kernel Powder (TKP) is extracted from the seeds. The seeds are processed into gum by choosing healthy seeds, removal of seed coat, separation, hammer milling, grinding and sieving. Tamarind gum is non Newtonian and yield very higher viscosities than most starches at equivalent concentration. This has led to its application as stabilizer, thickener, gelling agent and binder in food and pharmaceutical industries.[26]

Tamarind Seeds Consist of

The white kernel obtained from tamarind seeds which is utilized for producing tamarind kernel powder. Tamarind kernel is rich in protein, carbohydrates, fibers and oils. Polysaccharide (35 - 55%), Proteins (18-20%). [26]

Extraction of *Tamarindus Indica* Seed Polysaccharide

Tamarind seed polysaccharide is extracted using reflux in a condensation system using water as solvent. Temperature of extraction media was maintained at 70^{o}C & duration of extraction adjusted about to 6hours. The extraction thimble was a Whattman cellulose thimble with 33 mm internal diameter and 80 mm external length.[27]

Table 2: FTIR Spectroscopy result of *Tamarindus indica.*[27]

Frequency(cm^{-1})	Assignment
3645.87	O-H Stretch
3508.70	O-H Stretch
2925.81	C-H Stretch
1505.80	N-O asymmetric stretch
1384.79	C-H rock
1332.72	C-H bend

Table 3: Micrometric studies of Tamarind seed polysaccharide[27]

Parameters	Results for Tamarind seed polysaccharide
Bulk density gm/ml	0.63 ± 0.03
Tapped density(gm/ml)	0.83 ± 0.04
Bulkiness(ml/gm)	1.58 ± 0.072
Carr's index	24.17 ± 1.20
Hausner's ratio	1.03 ± 0.07
Ash Value (%)	0.56
Water-soluble Ash	0.42
Acid-soluble Ash	0.30
pH	6.1
Angle of repose (o)	29.45
Swelling index (%)	90

From the study of Verma Shubham, *et al* it was found that isolated mucilage showed good flow property. Therefore Tamarind seed polysaccharide as a pharmaceutical excipient can be used in formulating different dosage forms.[27]

FENUGREEK MUCILAGE

Trigonella Foenum-graceum, commonly known as Fenugreek, is an herbaceous plant of the leguminous family.[28] The seeds of *Trigonella foenum graecum L.* are also known as fenugreek seed or Methi, Methi Dana, in Hindi. It is an herbaceous plant of *leguminaceae* family. The seeds of *Trigonella foenum graecum L.* are also used as vegetables and also functions as a preservative and are added to pickles. The ripe fenugreek seeds have few medicinal values such as in treatment of: dysentery, dyspepsia, enlargement of liver, diabetes and chronic cough.[29] Fenugreek seeds possesses high percentage of mucilage which does not dissolve in water but it forms a viscous tacky mass when exposed to other fluids.[28]

a) Fenugreek leaves

b) Fenugreek seeds

Figure 2: Fenugreek Images

Nutrition profile[30]

Fenugreek leaves contain these nutrients per 100 g of edible portion.

1) Carbohydrates: 6.0 g
2) Protein: 4.4 g
3) Fat: 0.9 g
4) Calcium: 395 mg
5) Phosphorus: 51 mg
6) Iron: 1.93 mg
7) Total energy: 49 kcal

At present fenugreek gum is at great demand owing to its considerable amount of applications in the industries. Fenugreek, being an annual legume plant which is native to the Mediterranean region but is also grown in Central East Asia and Africa. India is a chief and an important exporter of Fenugreek seeds. Moreover, in India fenugreek seeds are used as spice and also in various natural medicines. In a study carried out by Saxena Ashwin *et al*, the mucilage derived from the seed of fenugreek, was investigated for use in matrix formulation containing propranolol hydrochloride.[31]

Application of fenugreek gum powder

The presence of galactomannan in high proportion as the major component, in fenugreek gum powder, it has the quality of controlling blood sugar and blood lipid therefore making it very valuable for obesity and diabetic patients. Fenugreek gum powder also helps in reducing cholesterol, hypertension and chance of heart attack and also possess distinctive properties which helps lower the blood sugar level. Owing to these many medicinal properties of fenugreek; fenugreek gum powder is used in many formulations of tablet and capsules producing synergistic effects. [26]

Extraction of *Trigonella foenum graecum L.* Seed Mucilage

Trigonella foenum graecum seeds Mucilage is extracted by hot water extraction method in which seeds are washed with water and dried at room temperature. The dried and clean seeds are further placed in water to boil for 12 hours at 45°C for release of mucilage into water. Further the material is squeezed through a muslin cloth to remove the marc from the filtrate and the filtrate is allowed to cool in a refrigerator and the mucilage is precipitated using ethanol.

Table 4: FTIR Spectroscopy Result of *Trigonella Foenum Graecum L.* Mucilage[27]

Frequency(cm^{-1})	Assignment
3654	O-H stretch
2914.16	C-H
2853.35	C-H
2621.98	C=C
1425.17	C-H Bend
1368.37	C-H Rock
1029.45	C-H Bend out of plane

Table 5: Micrometric studies *Trigonella Foenum Graecum L.* mucilage[27]

Parameters	Results for *Trigonella Foenum Graecum L.* mucilage
Bulk density(gm/ml)	0.66 ± 0.043
Tapped density(gm/ml)	0.94 ± 0.098
Bulkiness(ml/gm)	1.48 ± 0.099
Carr’s index	28.2 ± 3.11
Hausner’s ratio	1.39 ± 0.057
Ash Value (%)	1.02
Water-soluble Ash	0.68
Acid-soluble Ash	0.56
pH	7.9
Angle of repose (o)	29.20
Swelling index (%)	90

From the studies carried out by Verma Shubham *et al*, it is found that *Trigonella Foenum Graecum L* mucilage has a good flow property and it also possess several other good characteristics that are suitable from the pharmaceutical point of view and therefore it can be used as pharmaceutical excipient in the formulation and development of newer dosage forms.[27]

GREWIA GUM

Grewia polysaccharide gum is extracted from the inner core stem of the edible plant *Grewia mollis*, Juss, (Family-Tiliaceae). The polysaccharide gum consists of glucose and rhamnose as the main monosaccharide components and galacturonic acid as the main sugar acid. The Grewia gum possess binding and bio-adhesive properties as reported in the literature.[32][33][34][35]

Extraction and purification of grewia gum:

The dried, pulverized inner stem of *Grewia mollis*; is dispersed in 0.1% w/v sodium metabisulphite solution which is further allowed to hydrate for 48 hours stirring the mixture continuously for 2 hours and then passing it through a muslin bag to remove extraneous materials. Further the filtrate is treated with 0.1N NaOH and centrifuged at 3,000 rpm for 10 minutes. The supernatant is further treated with acidified ethanol, containing 0.1N HCl, and centrifuged as described previously. The precipitate is filtered through muslin bag to remove excess ethanol before air-drying the product at 50^{o}C in the oven for 24 hours. The dried product is then passed through a 1.0 mm sieve and stored in air-tight container for further usage.[11]

Table 6: Micrometric studies of Grewia Polysaccharide.[11]

Parameters	Results for Grewia Polysaccharide
Bulk density(gm/ml)	0.16±0.00
Tapped density(gm/ml)	0.2 ± 0.01
Hausner's ratio	1.3 ± 0.02
Ash Value (%)	6.1 ± 0.36
Water-soluble Ash	3.4±0.20
pH	5.7±0.03
Angle of repose (o)	30.4 ±0.47
Moisture content (%)	10.6 ±2.01

ROSIN


Figure 3: Rosin[17]

Rosin, also known as **Colophony** or **Greek pitch.** Rosin is a natural and a non-volatile resinous mass obtained from *Pinus palustris.* Owing to abundant availability and various other characteristics which suggests it to be used as a polymer for different drug delivery systems. Various controlled and targeted drug delivery systems can be developed and formulated using Rosin.[38] [39]

Properties of rosin

Dehydrobietic acid, a derivative of rosin is a good anti-tumor compound.[40] Rosin possess superior emulsifying properties and therefore rosin based creams possess good spreadability and are also homogeneous in nature.[41] Rosin can be extensively used in transdermal drug delivery systems owing to its significant property to help in skin permeability.[42]

Pharmaceutical Applications of Rosin

Pellets of diclofenac sodium coated with Rosin based polymer showed sustained release effect.[43]

Okra Mucilage

Okra (*Abelmoschus esculentus*) mucilage as pharmaceutical excipients.

Abelmoschus Gum, also known as okra gum is obtained from the fresh fruits of the plant *Abelmoschus esculentus* (family *Malvaceae*). Okra gum consist of galactose, galacturonic acid, and rhamnose, with some fractions of glucose, mannose, arabinose and xylose.[44]

Available literature suggests that in various studies, okra gum was utilized as a binder in Paracetamol tablet formulations; which showed a faster onset of action than that of gelatin. The crushing strength and disintegration times of these tablets, is directly proportional to the increase in binder concentration; higher the concentration of binder, higher is the crushing and disintegration time, while there is subsequent decrease in friability. Although gelatin produces tablets with higher crushing strength, okra gum produced tablets with extended disintegration times than those containing gelatin. Therefore it can be concluded that okra gum can be used as a matrix agent in sustain drug delivery systems.[12]

Figure 4: Okara.

Extraction Procedure[45]

Okra (*Abelmoschus esculentus*) pods are carefully washed and dried under shade for 24 hours & further dried at 30–40°C until it gave constant weight and size is reduced using a grinder. The resultant powder is then passed from sieve no. #22 to achieve fine powder which is further stored in air tight container for later usage.

Extraction of Mucilage

Step1: Powdered fruits soaked in 500ml of distilled water and further heated at 60°C with continuous stirring for about 4 hours. The concentrated solution; filtered through a muslin cloth & cooled at 4°C-6°C.

Step2: The mucilage was then further isolated using acetone from the cool filtrate, while filtering though the muslin cloth. The mucilage is obtained by drying it, till it gives constant weight at temperature 35–45°C in hot air oven. Hard mucilage cake are further grind and sieved through sieve # 22, & stored in desiccator for further usage.

Table 7: Micrometric study of Okra gum[45]

parameter	values
Angle of repose (^{o})	27.29
Carr's index (%)	76.42
True density (gm/ml)	3.05
Bulk density (gm/ml)	0.690
Bulkiness (ml/g)	1.46
Mean particle size (µ)	52.50

Hibiscus Rosasinensis Mucilage.

Hibiscus *rosa-sinensis* Linn, Family: *Malvaceae*. A.K.A shoe-flower, China rose, and chines hibiscus.

Figure 5: Hibiscus Rosasinensis.

Extraction of Hibiscus mucilage

The collected fresh leaves of Hibiscus rosa-sinensis linn; are washed with distill water to remover dirt and are further dried and powdered. This powder; is later soaked for 5-6 hours and then boiled for 30 minutes and kept aside for an hour to release the mucilage completely into the water. The material is then squeezed through a eightfold bag of muslin cloth to separate the marc from the solution. The resultant is further precipitated in acetone to three times the volume of filtrate. The obtained mucilage is further dried in oven at a temperature < 50 °C.[12]

Tara Gum

Figure 6: Caesalpinia spinosa.

Caesalpinia spinosa, a small tree of family *Leguminosae*. Commonly known as Tara is a gum obtained from the endosperm of seed of *Caesalpinia spinosa*. Tara gum is a odorless, white powder; produced by separating and grinding the endosperm of the mature black colored seeds of Tara plant. The major component of the gum is a galactomannan polymer similar to the main components of guar and locust bean gums. In various pharmaceutical and food industries, Tara gum is used as a thickening agent and a stabilizer around the world. Further studies also gave an idea about its applications in various patents like; the use of tara gum as a controlled release formulations includes a gastro retentive controlled release tablets and emulsions for various drugs like: metformin hydrochloride, ciprofloxacin hydrochloride, clozapine can be seen.[7]

Table 8: Applications of natural polymers in drug delivery [12] [46]

Gum	Biological Source	Application
Xanthium	*Xanthomonas lempestris*	Pellets, controlled drug delivery
Tamarind	*Tamarinds indicia*	Hydrogels, ocular mucoadhesive drug delivery
Sodium alginate	*Macrocytis peripheral*	Bioadhesive microspheres, nanoparticles
Pectin	*Citrus aurantium*	Beads, floating beads, colon drug delivery, pelletization
Okra	*Hibiscus esculentus*	Hydrophilic matrix for controlled release
Locust bean	*Ceratania siliqua*	Controlled release agent
Kasaya	*Sterculi aurens*	Mucoadhesive and Buccoadhesive
Ispagol	*Plantago psyllium,Plantago ovate*	Colon drug delivery, gastro retentive
Galan	*Pseudomonas elodea*	Ophthalmic drug delivery, sustaining release agent, beads, Hydrogels
Guar gum	*Cyamompsis tetraganolobus*	Colon targeted drug delivery, cross-linked microspheres
Cordia	*Cordia oblique willed*	sustained release matrix former
Bhara gum	*Terminalia belleri caroxb*	Microencapsulation
Acacia	*Acacia senegal*	Osmotic drug delivery
Luciana seed gum	*Luciana*	Emulsifying agent, suspending agent, binder in tablets,
Khaya gum	*Khayagr andifolia*	Binding agent
Cashew gum	*Anacardium Occidental*	Suspending agent
Cassia tora	*Cassia tora Linn*	Binding agent
Agar	*Gelidium amansii*	Suspending agent, emulsifying agent, gelling agent in suppositories
Gum ghatti	*Anogeissus latifolia*	Binder, emulsifier, suspending agent
Acacia	*Acacia arabica*	Suspending agent, emulsifying agent, binder in tablets
Albizia	*Albizia zygia*	Tablet binder

CONCLUSION

Thus from the above review it can be concluded that polymers play an important role in pharmaceutical industries and also there is an extensive use of natural polymers in last few decades; which gives a clear idea that natural polymers have been utilizes in various formulations in which they are applicable as: suspending, binding, emulsifying, & gelling agents. Natural polymers like gums and mucilage's obtained from various biological sources find their way as biodegradable polymers in pharmaceuticals, cosmetology and also in many food industries. Several studies on Natural polymers suggest them to be advantageous, economic & less toxic as compared to synthetic polymers. Owing to these many advantages of natural polymers over synthetic polymers; many drug delivery systems like: microspheres, nanoparticles, implants, transdermal & ocular systems etc. are been prepared using natural polymers. Thus it becomes very important to explore newer natural polymers and study them massively for their future applications in pharmaceutical industries and subsequently develop newer dosage forms and drug delivery systems using these isolated natural polymer.

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