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NATURAL POLYMERS USED IN MODIFIED DRUG DELIVERY AND ITS INCOMPATIBILITY: A REVIEW

P.R.Patil[*1],
R.U.Thorat[1], P.K.Puranik[1], R.V.Zinjan[1], V.K.Salve[1]

[1]Department of Pharmaceutics, Government College of Pharmacy, Aurangabad Opposite Govt. Polytechnic, Osmanpura, Aurangabad 431 005 (M.S.), INDIA

ABSTRACT

Nature has provided a huge variety of natural polymers with growing interest in recent era. This attributes to a number of factors which include their relative abundance, low cost, non-toxic, stable, biodegradable and eco-friendly profiles. Gum exudates are amongst the oldest natural polymers. They are already being used as thickening and stabilizing agents from last several years. Pharmaceutical dosage forms contain many additives besides the active ingredients to assist manufacturing and to obtain the desired effect. The advances in drug delivery have simultaneously urged the discovery of novel polymers which are safe and fulfill specific functions and directly or indirectly influence the rate and extent of release. The plant derived polymers comply with many requirements of pharmaceutical excipients.

This review focuses on safety issues and compatibility concerns of natural polymers with several categories of drug substances. The usage of these polymers in pharmaceutical formulations which contain synthetic drugs and contaminants like heavy metals, pesticides residues, microbial contaminants etc may result in secondary health complications. In this review, we describe the several natural polymers used in conventional dosage forms as well as novel drug delivery systems including sustained release matrix tablet formulations.

KEYWORDS : *Natural polymers, gum exudates, incompatibility, modified release, pharmaceutical application etc.*

Correspondence to Author

P.R.Patil

Department of Pharmaceutics, Government College of Pharmacy, Aurangabad Opposite Govt. Polytechnic, Osmanpura, Aurangabad 431 005 (M.S.), INDIA

Email: prpatilgcop@gmail.com

INTRODUCTION

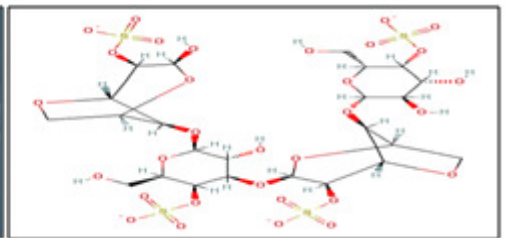
Natural and synthetic polymers have been successfully employed in the formulation of solid dosage forms and are specifically useful in the design of modified drug delivery systems. Most commonly used natural polymers are guar gum, xanthan gum, gum karaya, pectin, sodium alginate, tragacanth etc. Besides this invention is moving

towards other polymers like tamarind gum, okra gum etc. Recent trend shown that use of natural polymer is increased due to their non toxic nature, easy availability, biocompatible, cheap as compared to synthetic ones. Natural polymers also utilized in development of targeted drug delivery system e.g. Guar gum is used for colon targeted system sodium alginate is used to develop gastro retentive system. Various drugs along with natural polymer have been earlier studied shows better desired results. Most of the polymers are used with various categories of drugs in modified drug delivery system. [1-5]

COMMONLY USED NATURAL POLYMERS:

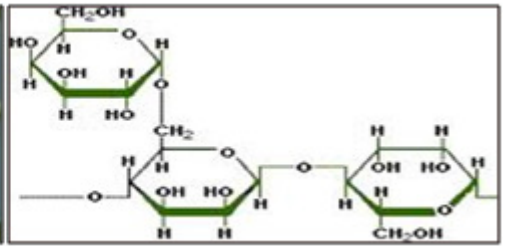
Natural polymers are widely used in modified drug delivery system and some of them are mentioned below. [6-12]

Carrageenan:



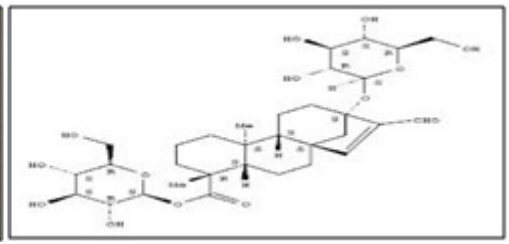
Carrageenans are high molecular weight polysaccharides obtained from certain species of red seaweeds *Chondrus cryspus* belonging to the family Rhodophyceae. There are three basic types of carrageenans i.e. kappa (κ), iota (ι) and lambda (λ). Incorporation of it into tablet matrices with various drugs and other excipients to alter release profiles has been studied, illustrating that it have good tablet-binding properties. Matrix tablets based on carrageenans with dual controlled release of Doxazosin mesylate has been studied.

Guar gum:



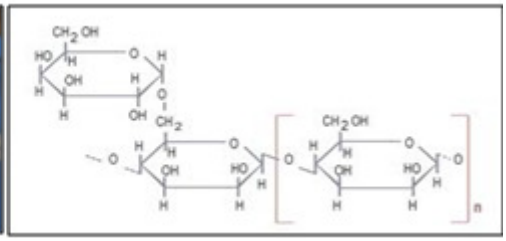
Guar gum is obtained from endospermic seeds of *Cyamopsis tetragonolobus* belonging to family Leguminosae. Guar gum occurs as nearly odorless, white to yellowish-white powder with a bland taste. Chemically guar gum is polysaccharides composed of galactose and mannose. It is made up of a linear chain of β-D-mannopyranose joined by β-(1–4) linkage with α-D-galactopyranosyl units attached by 1, 6- links. Synthetic derivatives of guar gum such as guar acetate, guar phthalate, guar acetate phthalate, oxidized guar gum and sodium carboxymethyl guar have also been investigated for their pharmaceutical applications. Oral administered guar gum-based colon-targeted 5 - Fluorouracil tablets are successfully prepared which shows the better results.

Karaya gum:



It is dried gummy exudates of *Sterculia urens* belonging to family Sterculiaceae. It is branched heteropolysaccharides consist of D-galactouronic acid and D-glucoronic acid. It is used as thickening agent in pharmaceutical preparations. Sustain release matrix tablet of Tramodol and Diltiazem hydrochloride has been prepared and studied successfully with combinations.

Locust bean gum:

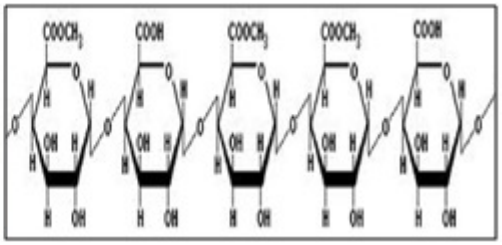


Locust bean gum is derived from the seeds of the leguminous plant *Ceratania siliqua* belonging to family Leguminosae. Locust bean gum consists mainly of a neutral galactomannan polymer made up of 1, 4-linked D-mannopyranosyl units and every fourth or fifth chain unit is substituted on C6 with a D-galactopyranosyl unit. The ratio of D-galactose to D-manose differs and this is believed to be due to the varying origins of the gum materials and growth conditions of the plant during production. Sustained release of Diclofenac sodium has been already studied for matrix systems made from locust bean gum.

Okra gum:

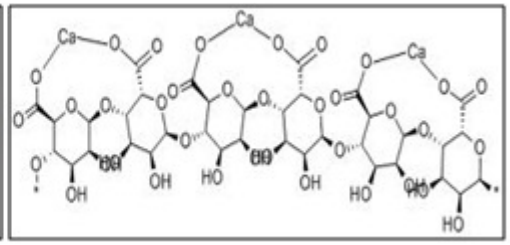
Okra gum, obtained from the fruits of Hibiscus esculentus, is a polysaccharide consisting of D-galactose, L-rhamnose and L-galacturonic acid. It was evaluated as a controlled release agent in modified release matrices, in comparison with sodium carboxymethyl cellulose (NaCMC) and hydroxypropylmethyl cellulose (HPMC), using Paracetamol as a model drug. The results indicate that its matrices could be useful in the formulation of sustained release tablets.

Pectin:



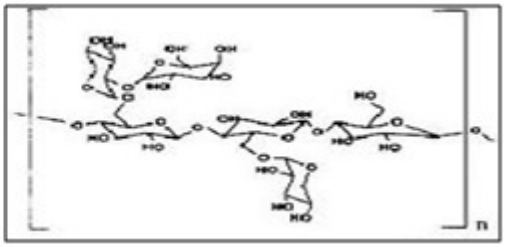
Pectin is non-starch, linear polysaccharides extracted from the plant *Citrus aurantium*. Belonging to family Rutaceae .Pectin is a high-molecular-weight, carbohydrate-like plant constituent consisting primarily of chains of galacturonic acid units linked as 1,4-a-glucosides, with a molecular weight of 30 000–100 000. Experimentally, pectin has been used for the oral sustained delivery of Nicorandil. Similarly sigmoidal release of Indomethacin has been studied from pectin matrices.

Sodium alginate:



Sodium alginate consists chiefly of the sodium salt of alginic acid. Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown coloured powder. These polymers consist of two different monomers in varying proportions, namely β-D-mannuronic acid and α-L-guluronic acid linked in α- or β-1, 4 glycosidic bonds as blocks of only β-D-mannuronic acid or α-L-guluronic acid in homopolymers or alternating the two in heteropolymeric blocks. In tablet formulations, sodium alginate may be used as both a binder and disintegrant. Extended release tablets of Alfuzosin hydrochloride which shown the drug release effect for 24 hrs has been studied. Also evaluation of alginate based Mesalazine tablets for intestinal drug delivery has been successfully studied.

Tamarind Gum:

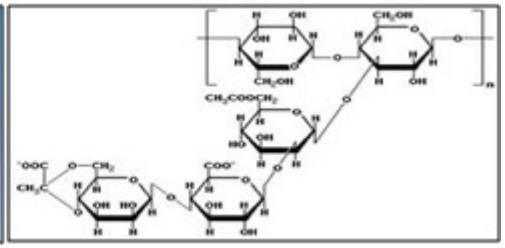


Tamarind is obtained from the endosperm of the seed of the tamarind tree i.e.*Tamarindus indica*. Tamarind gum is a polysaccharide composed of glucosyl: xylosyl: galactosyl in the ratio of 3:2:1. Xyloglucan is a major structural polysaccharide in the primary cell walls of higher plants. It shows advantages as non-carcinogenicity, mucoadhesivity, biocompatibility, high drug holding capacity and high thermal stability. It was also examined for its sustained release property using Acetaminophen, Caffeine, Theophylline and Indomethacin.

Tragacanth:

Tragacanth is a naturally occurring dried gum obtained from *Astragalus gummifer* belonging to family Leguminosae. The gum consists of a mixture of water-insoluble and water soluble polysaccharides. Water-insoluble portion called as Bassorin, which constitutes 60–70% of the gum, while the remainder of the gum consists of the water-soluble material called tragacanthin. On hydrolysis, tragacanthin yields L-arabinose, L-fructose, D-xylose, D-galactose, and D-galacturonic acid. Sustain release tablet of Phenytoin using tragacanth has been successfully studied.

Xanthan gum:



Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium *Xanthomonas compestris*. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β-D-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronicacid-α-D-mannose

attached with alternate glucose residues of the main chain. Xanthan gum showed a higher ability to retard the drug release. It is also used as a thickening agent. Controlled-release tablets of Diltiazem hydrochloride was prepared by using xanthan gum have been reported to sustain the drug release in a predictable manner and the drug release profiles of these tablets were not affected by pH and agitation rate.

DRUG NATURAL POLYMERS COMBINATION:

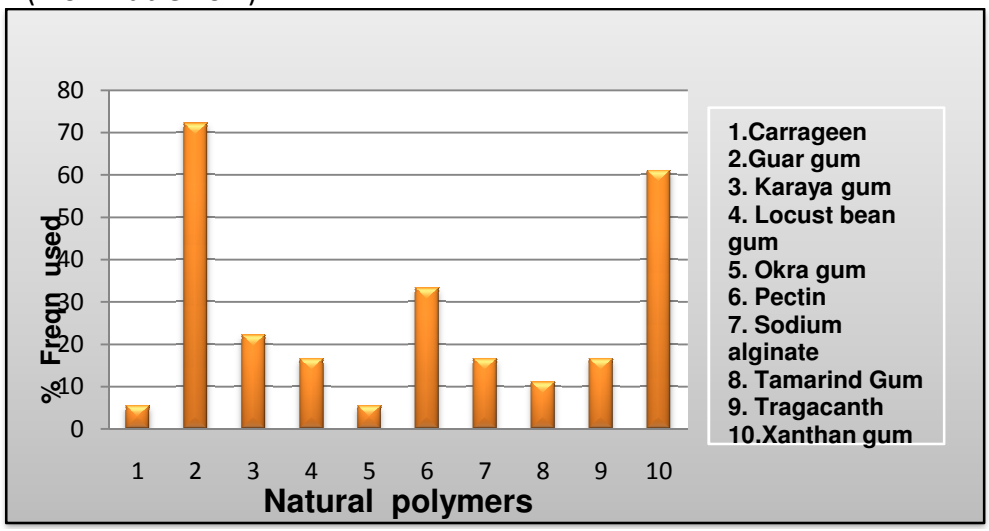
From the literature it has been revealed that various categories of drugs has been studied with natural polymers as shown in Table no.1

Table 1: Drug polymer combination[13-47]

No	Category	Drug	Polymer
1	Analgesic	Aceclofenac	Guar gum, Tragacanth
		Diclofenac	Tamarind gum, Gum acacia, Gum cordial
		Ibuprofen	Xanthan gum
		Indomethacin	Pectin
2	Anti-arrhythmic	Diltiazem HCL	Locust bean gum, karaya gum, Tamarind gum, Gellan gum,Chitosan, Ghatti gum, Damar Gum, okra gum, Rosin
3	Anti-amoebic	Metronidazole	Shellac
4	Anti-microbial	Ciprofloxacin Hydrochloride	Chitosan, Guar gum
5	Anti-androgen	Flutamide	Xanthan gum ,Guar gum
6	Anti-anginal	Nicorandil	Gaur gum, Xanthan gum ,Pectin, Alginate, Chitosan,
		Nifedipine	Sodium alginate
		Nimodipine	Locust bean gum, Olibanum gum
7	Anti-asthmatic	Salbutamol sulphate	Sodium alginate, Pectin
		Terbutaline sulfate	Guar gum, Xanthan gum
8	Anti-cancer	5-Fluorouracil	Guar gum
9	Anti-depressant	Venlafaxine	Guar gum , Xanthan gum ,Gum rosin
10	Anti-diabetic	Glipizide	Guar gum, xanthan gum, Karaya gum
		Repaglinide	Guar gum, Xanthan gum, Pectin
11	Anti-diuretic	Furosemide	Guar Gum, Pectin, Xanthan Gum
12	Anti-epileptic	Phenytoin	Guar gum, Xanthan gum, Tragacanth, Gum acacia
13	Anti-HIV	Zidovudine	Guar Gum
14	Anti-hypertensive	Atenolol	Guar gum, Xanthan gum,
		Doxazosin mesylate	Carrageenans
		Losartan	Guar gum, Xanthan gum, Karaya gum
		Metoprolol succinate/tartarate	Guar gum ,Karaya gum / Starch
		Propanolol	Xanthan gum, Locust bean gum,
		Valsartan	Guar gum, Pectin
15	Anti-ulcer	Cimetidine	Xanthan gum
		Famotidine	Xanthan gum, Chitosan
		Ranitidine hydrochloride	Guar gum, Sodium alginate, Gum acacia, Psyllum, Sesbania gum

16	Anti-viral	Acyclovir	Tamarind gum
17	Anti-psychotic	Quetiapine fumarate	Gum karaya , Xanthan gum
18	Skeletal muscle relaxant	Chlororxoxazone	Guar gum , Gum acacia, Tragacanth

The following graph shows various natural polymers and their % frequency used in sustained release matrix tablet formulation. (From Table no.1)



INCOMPATIBILITIES WITH NATURAL POLYMERS:

Natural polymers are widely used but before formulating any formulation its compatibility study plays major role. Some of the incompatibilities with natural polymers are shown in Table no.2

Table 2: Name of polymer along with its source and incompatibilities[47]

Common name	Botanical source	Family	Polymer Incompatibilities
Acacia	*Acacia arabica*	Leguminosae	Amidopyrine, Apo morphine, Cresol, Ethanol (95%), Ferric salts, Morphine, Phenol, Physostigmine, Tannins
Carrageenan	*Chondrus cryspus*	Rhodophyceae	Cationic materials
Gellan gum	*Pseudomonas elodea*	-	-
Guar gum	*Cyamopsis tetragonolobus*	Leguminosae	Acetone, Ethanol (95%),Tannins, Strong Acids and Alkalis
Gum tragacanth	*Astragalus gummifer*	Leguminosae	Benzalkonium chloride, Chlorobutanol, Methyl paraben
Karaya gum	*Sterculia urens*	Sterculiaceae	-
Locust bean gum	*Ceratania siliqua*	Leguminosae	-
Pectin	*Citrus aurantium*	Rutaceae	Not observed
Sodium alginate	*Macrocystis pyrifera*	Phaeophyceae	Acridine derivatives, Crystal violet, Calcium salts , Phenyl mercuric acetate
Xanthan gum	*Xanthomonas compestris*	-	Cationic surfactants, Polymers, Preservatives

PHARMACOPOEIAL SPECIFICATIONS OF NATURAL POLYMERS:

USP given the specifications such as loss on drying, heavy metal contents, total ash value and microbial limits for natural polymers as shown in Table no. 3

Table 3: Pharmacopoeial specification of polymer[48]

No	Polymer	LOD*	Heavy metal*	Total Ash*	Microbial limits for absence of
1	Carrageenan	12.5	0.004	35.0	Salmonella , E. coli
2	Gellan gum	15.0	-	4-14	Salmonella , E. coli
3	Guar gum	15.0	0.002	1.5	-
4	Pectin	10.0	-	-	Salmonella
5	Tapoica starch	16.0	0.002	-	E. coli
6	Tragacanth	-	0.002	-	Salmonella , E. coli
7	Xanthan gum	15.0	0.003	-	Salmonella , E. coli

LOD-Loss on drying, * indicates % value

CHARACTERIZATION OF NATURAL POLYMERS:

Natural polymers are characterized for following parameters are mentioned below. [49, 50]

a) Identification:

The identification of natural polymers can be done from various chemical tests like Molish test, Iodine test, Ruthenium test (mucilage).

b) Physico-chemical properties:

The physiochemical properties like color, odour, shape, texture can be evaluated by visual observation. Flow properties like bulk and tapped density are determined by using density apparatus. Solubility, pH, swelling index, loss on drying, ash values are also estimated. As these polymers are viscous in nature their rheological properties are also estimated.

c) Structural determination:

These polymers mainly composed of polysaccharides and contain sugar. Its structural elucidation can be done by NMR Spectroscopy.

d) Compatibility:

Gums are obtained from natural sources so its Compatibility study can be done by

Suitable analytical techniques like DSC etc

e) Microbial test:

As it is obtained from natural origin and it contains moisture so it is major source for microbial growth. So these are tested for the absence of different micro-organisms.

f) Pesticide residue:

Column and gas chromatography is recommended as principal method for determination of Pesticide residue.

g) Toxicity study:

Toxicity study can be done in animal like Rats and Guinea pig by determining LD50 value.

CONCLUSION:

Natural gums are promising biodegradable polymeric materials. It is clear that natural polymers have many advantages over synthetic ones and has been established in the field of pharmaceuticals. However, there is a need to identify, isolate and modify other natural polymers amongst the nature as well as its evaluation in relation to not only the quality and efficacy but with the compatibility of existing natural polymeric material for its safe use in pharmaceutical formulations. Therefore, in the years to come, there will be continued interest in natural polymers and their modifications.

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