CARBOXYMETHYL ETHERS OF LOCUST BEAN GUM- A REVIEW

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ABSTRACT
Locust bean gum is a popular natural polymer which is mostly used in food industry as well as in pharmaceutical industry. This natural polymer is conventionally used as an excipient in manufacturing different formulations which mainly depends on its thickening and gelling property. Locust bean gum can easily be modified to its carboxymethyl derivative which in turn can be used as sustained release delivery carrier as rate controlling polymer. The modified gum shows improved physical properties like good aqueous solubility, acceptable solution viscosity and clarity compared to the native one. The main reaction is carried out in presence of mono-chloroacetic acid under catalytic conditions like sodium hydroxide in aqueous environment and sodium bicarbonate in non-aqueous environment. But the degree of substitution of carboxymethyl group in the structure of locust bean gum is an important criterion. Various scientists have put forward various sophisticated methods to determine the degree of substitution. The most classical method is done by titrimetric method. Various other modern instruments are coming up for this purpose like Fourier Transform Infrared Spectroscopy method, Nuclear Magnetic Resonance method and Raman Spectroscopy method. This review describes the different methods for the preparation of carboxymethyl locust bean gum and the analysis of the degree of substitution of carboxymethyl group by using different analytical techniques.

Keywords: Locust Bean Gum, Carboxymethylation, Degree of Substitution, Analytical methods

INTRODUCTION
Polymers are macromolecules comprised of repeating units of small molecules, the monomer. The monomers can be linked together to form linear polymer or branched polymer or cross linked polymers. Linear polymer and branched polymer are referred to as thermoplastic materials as they flow on heating. They also show solubility in certain solvents. Locust bean gum is a branched polymer. Biopolymers or natural polymers are an attractive class of biodegradable polymers since they are derived from natural sources, easily available, relatively cheap and can be modified by suitable reagent. The specific application of plant-derived polymers in pharmaceutical formulations include their use in the manufacture of solid monolithic matrix systems, implants, films, beads, micro particles, nano particles, inhalable and injectable systems as well as viscous liquid formulations1-3. The successful formulation of a stable and effective dosage form therefore depends on the careful selection of excipients. The present trend focuses on an increasing interest in the use of natural ingredients in food, drugs and cosmetics 4-6.

Locust bean gum, a non starch polysaccharide consisting of galactose and mannose in the ratio 1:4 and hence they are known as galactomannan7. The mannose elements form a linear chain linked with galactopyranosyl residues as side chain at varying distances depending on the plant origin8. Being a galactomannan locust bean gum has a wide application in pharmaceutical field. It is also known as Carob bean gum and is derived from the seeds of the leguminous plant Ceratonia siliqua Linn belonging to the family Fabaceae. This gum is widely cultivated in the Mediterranean region and to a smaller extent also in California. The brown pods or beans of the locust bean tree are processed by milling the endosperms to form locust bean gum. It 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 9. The ratio of D-galactose to D-mannose differs and this is believed to be due to the varying origins of the gum materials and growth conditions of the plant during production. The physico-chemical properties of galactomannan are strongly influenced by the galactose content10 and the distribution of the galactose units along the main chain11. Longer galactose side chains produce stronger synergistic interactions with other polymers11 and greater functionality12. Since it is a neutral polymer and its viscosity and solubility are therefore little affected by pH changes within the range of 3-11 13-17.

Fig. 1: Structure of locust bean gum16

Various properties are there which make locust bean gum a good choice in drug delivery.

- They are biocompatible, biosorbable and biodegradable in nature.
- It is non-teratogenic and non-mutagenic according to Joint FAO/WHO Expert Committee on Food Additives held in Geneva, April75.
- Acceptable shelf-life.
- Degradation products are excreted readily.

Nowadays a trend has come to modify non-starch polymer in order to modify their physico-chemical properties. Thus the modified natural polymers can be defined as the natural polymers altered to improve their biodegradation profile and also physico-chemical characteristics. Generally labile polar functionalities are added to the polymer to enhance the degradability of the polymer. The extent and nature of polymer modification is vital as excess modification can hamper the biodegradation and the added functional group may be converted to toxic degradation products18-21. This modification of natural polymers is achieved by chemical modification or enzymatic alteration. The chemical modification involves harsh conditions in comparison to the enzymatic method.

Locust bean gum, non-starch polysaccharides can be chemically modified to alter their physico-chemical properties to improve...
Carboxymethylated Locust bean gum can be synthesized by either of the two methods given by different scientists:

1. By following non-aqueous method.  
2. By following aqueous method.

**Synthesis by non-aqueous method**

Finely powdered Locust bean gum and sodium bicarbonate are mixed well manually in a pestle mortar. To this 1% v/v of ethanol and solid monochloro-acetic acid is added. The reaction was carried out at ambient or elevated temperature (60, 80, 98°C) for 2 hours with intermittent manual mixing with a glass rod, by addition of dilute acetic acid to phenolphthalein end point. Salts formed were removed by repeated washings with 70% aqueous ethanol for 15 minutes followed by 100% ethanol and solvent exchange drying. 

**Synthesis by aqueous method**

Locust bean gum was derivatized to sodium carboxymethyl Locust bean gum by mixing it with 4ml water heated to 80°C for 15 minutes and cooled. Then 56% w/v of ice-cold sodium hydroxide solution was added drop wise over a period of 45 minutes. Monochloroacetic acid solution was added slowly for a period of 1 hour to the above mixture and maintained at 15°C. The temperature of the mixture was raised slowly to 65°C and stirred for another 1 hour. The wetted mass was washed with methanol for 15 minutes. The pH of the suspension was adjusted to neutrality with glacial acetic acid. Then it is dried at 50-60°C.

**Analytical tools for the structure characterization of carboxymethylated locust bean gum**

The total degree of substitution can be defined as the average number of functional groups introduced in the polymer. This mainly determines the properties of polysaccharides derivatives including carboxymethylated products. The functionalization even affect the properties of that particular polymer. In most cases it is found that partially substituted polysaccharide is much more potent compared to fully substituted ones. Since fully substituted polysaccharides may undergo undesirable reactions like oxidation or depolymerization. The exact determination of degree of substitution and functionalization pattern is important for the optimization of reaction conditions in order to understand the structure property relationship. The degree of substitution should be monitored to optimize the properties of the modified polysaccharides for specific manufacturing process. Carboxymethylation to low extent may lead to an uneven distribution of carboxymethyl moieties. Various methods are there to analyze the total degree of substitution. A brief account of this is furnished in this review article.

**Determination of degree of substitution by wet method**

The classical methods to determine the degree of substitution is by simple acid-base titration. This method is very useful because no expensive equipments are required and at the same time degree of substitution value is also very reproducible provided the procedure is carried out very carefully. Here the conversion of the salt form to free acid form and vice versa was carried out. This can be done by taking the acid form of the carboxymethylated polysaccharide, which can be obtained by a treatment of the sodium salt form of the polymer dispersed in ethanol with concentrated hydrogen chloride, can be titrated with a sodium hydroxide solution of known molarity. Mostly applied is the back titration method, which was proposed as standard procedure of CMS and CMC. The sodium salt of the polymer is converted to the free acid form. Subsequently, aqueous sodium hydroxide is added to a known amount of the free acid form leading to the sodium carboxylate. The excess of sodium hydroxide is back titrated permitting to degree of substitution. According to Mukhopadhyay et al. degree of substitution is calculated by:

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DS = \frac{0.162 A}{1-0.058 A}
\]

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DS = \text{Degree of substitution}
\]

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A = \text{M} \text{equivalents of NaOH required per gram of sample}
\]

**Determination of degree of substitution by fourier transform infrared spectroscopy method**

The degree of substitution of carboxymethylation was quantitatively determined by Fourier Transform Infrared Spectroscopy by calculating the ratio between the intensity of hydrogen bond to that of intensity of carboxyl stretching of ether. Both the native and modified gum samples were blended with solid potassium bromide and the pellet was prepared. The spectra were scanned from 400 to 4000 cm⁻¹ under dry air at room temperature. Infrared measurement was carried out in the transmission mode in which the infrared beam directly passes through the sample and spectral data were then converted from transmittance into absorbance unit. Fourier Transform Infrared Spectra were plotted as relative intensity against wave number cm⁻¹ Band area changes with increase in degree of substitution. Fourier Transform Infrared Spectra indicated the introduction of carboxymethyl moiety whose intensity increased with increase in degree of substitution.
Determination of degree of substitution by nuclear magnetic resonance method

At present, the most important and sophisticated instrument used for measurement of degree of substitution is 13C CP/MAS NMR spectroscopy. From the 13C CP/MAS NMR spectrum the average degree of substitution can be calculated from the ratio of area of the carboxyl signals. Compared with 13C CP/MAS NMR spectra of dissolved samples are significantly increased which enables spectra recorded in this way to be evaluated for the purpose of determining the total degree of substitution.

Properties

One of the most important goals of carboxymethylation of locust bean gum is to obtain water soluble derivatives. This modified gum can be used typically in pharmaceutical purposes as rate controlling polymer. They behave as a typical polyelectrolyte.

The interaction of carboxylic groups with multivalent metal cations can be used to form so called ionotropic gels which are characterized by the formation of gels through ion pairing and can be used to form so called ionotropic gels which are used to control release of drugs in pharmaceutical delivery systems. The interaction of carboxylic groups with multivalent metal cations can be used typically as rate controlling carriers for a variety of therapeutic agents. The interaction of carboxylic groups with multivalent metal cations can be used to obtain water soluble derivatives. This modified gum finds use in the preparation of micro particles and developed by these methods show the following characteristics.

CONCLUSION

Thus a non-starch polysaccharides locust bean gum which is a galactomannan can easily be carboxymethylated in order to modify their physical characteristics like solubility, solution viscosity and clarity. It can be modified by both aqueous and non-aqueous method too. In both the cases, carboxymethylation is simple, cost effective and eco-friendly. Thus the carboxymethylated locust bean gum developed by these methods show good degree of substitution. This modified gum finds use in the preparation of microparticle and other sustained release preparation. Their degree of substitution has been determined by traditional wet chemistry method and also by applying modern analytical techniques like FTIR, Raman Spectroscopy and NMR Study. When compared to the traditional wet chemistry methods, the spectroscopic methods developed in this study are relatively simple, fast without the use of toxic chemicals requiring smaller sample size. Thus these techniques are superior or as they give both qualitative and quantitative measurement.

REFERENCES