

LOCUST BEAN GUM AND ITS APPLICATION IN PHARMACY AND BIOTECHNOLOGY: AN OVERVIEW

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ABSTRACT

Locust bean gum is a versatile biopolymer which finds its application in various fields. The conventional use of Locust bean gum as an excipient in drug products generally depends on the thickening, gel forming and stabilizing properties. A need for prolonged and better control of drug administration has increased the demand for tailor made polymers. Various significant works have been carried out in combination with the other polymers to make the formulation sustained and targeted. Recently a new work has been carried out by its chemical modification specifically its carboxymethylation derivative to improve its physico-chemical characteristics in terms of increased aqueous solubility. This derivatized gum can be used for the preparation of sustained release micro beads. Even locust bean gum has also finds its application in the field of biotechnology specifically in tissue engineering for the manufacturing of tissue scaffolds. Thus the gum has wide application in the both pharmaceutical and biotechnological field.

Keywords: Biodegradable Polymers, Galactomannans, Locust Bean Gum, Drug Delivery.

INTRODUCTION

Polymers are high molecular weight compounds consisting of monomers which are repeating small units offers as a backbone to the macromolecular structure. They are arranged either in linear or branched or cross-linked fashion. Nowadays, much emphasis has been given on the use of various natural polymers as drug delivery carriers in the pharmaceutical field. The outstanding property of the natural polymers are their degradation and erosion behavior and so they are called as natural biodegradable polymers.^{2,3}The natural biodegradable polymers can be degraded or eroded by enzymes introduced *in vitro* or generated by surrounding living cells. Thus the biocompatibility and biodegradability of many naturally occurring polysaccharides make them useful as drug carriers.⁴⁻⁷They have also got advantage that they pose less toxicity problems of their own. But sometimes biopolymers also differ in their molecular weight and their physical and chemical properties to varying extents depending on their sources and method of isolation and purification. Traditionally, excipients were included in drug formulations as inert vehicles that provided the necessary weight, consistency and volume for the correct administration of the active ingredient, but in modern pharmaceutical dosage forms they often fulfill multi-functional roles such as improvement of the stability, release and bioavailability of the active ingredient, enhancement of patient acceptability and performance of technological functions that ensure ease of manufacture.^{8, 9} Thus it is now identified that excipients can potentially influence the rate and extent of absorption of drug. 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.¹⁰⁻¹⁴Polymeric materials have fulfilled different roles in the preparation of various dosage form such as binders, matrix formers or drug release modifiers, film coating formers, thickeners or viscosity enhancers, stabilisers, disintegrants, solubilisers, emulsifiers, suspending agents, gelling agents and bioadhesives.¹⁵⁻¹⁹ Polymers are often utilized in the design of novel drug delivery systems such as those that target delivery of the drug to a specific region in the gastrointestinal tract or in response to external stimuli to release the drug. This can be done via different mechanisms including coating of tablets with polymers having pH dependent solubilities or incorporating non-digestible polymers that are degraded by bacterial enzymes in the colon. Non-starch, linear polysaccharides are resistant to the digestive action of the gastrointestinal enzymes and retain their integrity in the upper gastrointestinal tract. Matrices manufactured

from these polysaccharides therefore remain intact in the stomach and the small intestine, but once they reach the colon they are degraded by the bacterial polysaccharidases. Kumar *et al.* studied this property which makes these polysaccharides exceptionally suitable for the formulation of colon-targeted drug delivery systems.^{5, 10} The drug release from the biodegradable natural polymeric system is generally controlled by three competing mechanisms like diffusion, swelling and erosion. Sodium alginate,²⁰⁻²⁴ xanthan gum,²⁵⁻²⁷ guar gum,²⁸⁻³⁰ gum arabic,³¹⁻³² tragacanth,³³ gellan gum³⁴⁻³⁶ are some of the natural polymers that have already been explored in the pharmaceutical field for their role in drug delivery systems as carriers.

The source of natural polymers is the carbohydrate molecules. These polysaccharides have been extracted or isolated from plant seed sources such as locust bean gum, guar gum, tara gum and tamarind. The polysaccharides or gums are derived from the endosperm of various plants (mainly from Leguminosae) seeds, where they function as reserve materials utilized during germination. Most of these polysaccharides share basic structural similarities known as galactomannans. Thus galactomannans are polysaccharides consisting mainly of the monosaccharide mannose and galactose units. The mannose elements form a linear chain linked with galactopyranosyl residues as side chain at varying distances depending on the plant origin.³⁷ Like other galactomannans, locust bean gum is also derived from the endosperm of the seeds of *Ceretonia siliqua* Linn belonging to the family Fabaceae.

The gum is finally achieved by milling the endosperms. *Cerqueria et al.* have also extracted the gum from seeds with the help of water followed by precipitation with ethanol.³⁷ Locust Bean gum has a wide potential in drug formulation due to their extensive application as food additives and their recognized lack of toxicity. It can be tailored made to suit the demands of applicants in both the pharmaceutical and biomedical areas. This group of polymers possesses a number of characteristics that makes it useful as a formulation aid, both as a conventional excipient and more specifically as a tool in polymeric- controlled drug delivery.³⁸ It consists mainly of a neutral galactomanan 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.^{39, 40} The ratio of D-galactose to D-mannose and this is believed to be due to the varying origins of the gum materials and growth conditions of the plant during production. (Fig. 1)

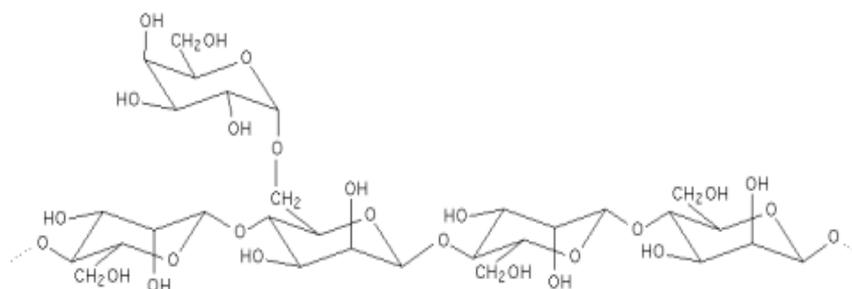


Fig. 1: Structure of Locust Bean Gum consisting of Mannose and Galactose

The physico chemical properties of galactomanan are strongly influenced by the galactose content⁴¹ and the distribution of the galactose units along the main chain.⁴² Longer galactose side chains produce stronger synergistic interactions with other polymers^[41] and greater functionality.⁴⁰ Since it is a neutral polymer and its viscosity and solubility are therefore little affected by pH changes within the range of 3-11.

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, April'75.
- Acceptable shelf-life.
- Degradation products are excreted readily.

The objective of the review article is to focus on the present use and the diversified application of Locust Bean Gum in both the pharmaceutical and biotechnological fields.

Pharmaceutical Application

There are various reports that Locust bean gum can be used in pharmaceutical and biotechnological purpose.

Various novel drug delivery systems

Oral controlled release system continued to be the most popular ones among all the delivery systems and Locust bean gum shows a wide application in the development and preparation of various novel drug delivery systems.

Locust bean gum has found a wide place in the preparation of mucoadhesive buccal tablets in combination with Chitosan in different combinations where the locust bean gum to chitosan ratios are 2:3, 3:2, 4:1. Vijayraghavan *et al.* prepared mucoadhesive buccal tablets of Propranolol HCl containing various weight ratios of Locust bean gum and Chitosan and coated it with 5% w/v Ethyl Cellulose.⁴⁴ The mucoadhesive property of the formulation containing 2:3 was highest compared with other ones. Even its drug release profile was 98% in 60 mins. Further bioavailability study was carried out taking sixteen healthy human volunteers. The bioavailability was highest for the formulation containing 2:3 of Locust bean gum to Chitosan. Therefore the study indicated that the locust bean gum along with Chitosan show a mucoadhesive property for buccal tablets.⁴⁴

It has also been used in the design and preparation of oral controlled release anhydrous bioadhesive tablets of theophylline.⁴⁵⁻⁵⁰ Tablets of anhydrous theophylline were prepared by direct compression method and were subjected to *in vitro* drug dissolution for 12 hours using the USP dissolution apparatus basket type at a speed 100rpm and temperature 37±5°C using gastric fluid pH 1.2. The bioadhesive strength of the tablets were measured as the force of detachment against the porcine gastric mucosa. The *in vitro* release study as well as the retention time of the bioadhesive tablets on the mucous membrane were investigated to develop a bioadhesive polymer

based controlled release delivery system and to evaluate the performance of such a delivery device. The formulation containing locust bean gum showed a good bioadhesive property. It was also found that an increase in the gum combination increases the drug release profile beyond 12 hours whereas there is no significant effect of gum concentration on the bioadhesive strength of the tablets.

Locust bean Gum has got synergistic effect with Xanthan Gum when used in matrix tablets. Venkataraju *et al.* did a comparative study of Xanthan Gum, Locust bean Gum and combination of Xanthan Gum and Locust bean Gum in different proportions to prepare matrix tablets.⁴⁰ Xanthan Gum is a hydrophilic, anionic heteropolysaccharide whereas Locust bean Gum is a non-ionic polysaccharide and its hydration process is independent of pH. The drug release was slower from the matrices which were composed of both xanthan gum and locust bean gum compared with the tablets whose composition was only locust bean gum and xanthan gum. The burst release of drug from xanthan gum matrix tablet in acidic pH was observed. Again increase of Locust bean Gum matrix tablets a rapid erosion of the hydrated layer was found. But this burst release in acidic pH was absent especially increase of combined xanthan-locust bean gum matrix tablets.^{51,52} It exhibited a well controlled effect by the use of synergistic interaction between two biopolymers to produce a strong and elastic gel around the core of the matrices in the presence of a ternary component by controlling the drug release from the matrices containing the xanthan-locust bean gum formulation.⁵³⁻⁵⁷ A commercially available tablet system (TIMER) developed by Pen West Pharmaceutical Company consisting of Locust Bean Gum and xanthan gum showed *in vitro* and *in vivo* controlled release potential.⁵⁶

Locust bean Gum is also used for the preparation of Colon targeted drug delivery system along with Chitosan. If Locust bean gum and Chitosan is taken in the ratio of 2:3, then a good colonic activity is obtained. From *in vitro* and *in vivo* studies revealed that locust bean gum and chitosan was capable of protecting the drug from being release in the stomach and small intestine and was susceptible to colonic bacterial enzymatic action with resultant drug release in colon.¹⁰

Carragenan- Locust bean Gum mixture was taken in multiphase emulsification technique for sustained drug release of gentamicin. In the preparation of w/o/w emulsion various proportions of iota-Carragenan and Locust bean Gum were investigated.⁵⁷

Maiti *et al.* derivatized locust bean gum to sodium carboxy methyl locust bean gum under controlled conditions to prepare hydrogel beads. It also possesses gelation property in presence of aluminum chloride. The study revealed that carboxymethyl derivatization of locust bean gum led to the formation of gelled beads through ionotropic gelation method with Al⁺³ ions. Discrete, spherical high yielded beads with smooth surface morphology could be obtained. Glipizide loaded beads were in size range of 1250-1262 μm and as high as 97.68% drug entrapment efficiency was achieved. The drug release was comparatively slower in acidic dissolution media than in alkaline media due to different degree of swelling in different dissolution media. It was found that with the increase in concentration of gelling ion in the gelation medium led to more

dense beads and resulted in slower drug release profile. It can be concluded that carboxymethyl locust bean gum could be a useful carrier for oral drug delivery.⁵⁸

Solubility enhancement of poorly water soluble drugs

Locust Bean gum has a property to increase the solubility of some lipophilic drugs. This has been proved by the fact that when Lovastatin, poorly water soluble drug was taken to prepare solid dispersion by using modified Locust Bean Gum as carrier. Locust bean gum was modified by heating where there is irreversible decrease in viscosity keeping its swelling property unchanged. It was found with increase in concentration of modified Locust Bean Gum, there is an increase of solubility of Lovastatin. Dissolution study revealed that solvent evaporation is the most convenient and effective method for solubility of enhancement of poorly soluble drug, Lovastatin. *In vivo* study showed significant decrease in HMG Co-A reductase activity incase of solid dispersion of Lovastatin compared to that of plain Lovastatin. Thus modified Locust Bean Gum can be used as a potential carrier in enhancing the dissolution rate and bioavailability of Lovastatin.⁵⁹

Therapeutic purpose

Locust Bean Gum is incorporated in ophthalmic preparation of cholinergic agents like Echothiophate iodide to enhance drug's therapeutic activity therapy allowing a reduction in dosage. Locust Bean Gum potentiates the action of the drug therapy reducing the side effects of the drug. Generally the concentration of Locust Bean Gum is from about 0.02% to about 1%w/v.

Carob Bean Gum or Carob pod fibre was also got the ability to control familial hypercholesterolemia. It has been assessed by carrying out experiments taking 18 familial hypercholesterolemia patients. They were fed with and without Locust Bean Gum to assess the hypolipidemic effect of Locust Bean Gum. Plasma cholesterol, low density lipoprotein cholesterol (LDL-C), high- density lipoprotein cholesterol, very low density lipoprotein cholesterol and triglycerides were measured at 2-week intervals and compared to control feeding periods. High- density lipoprotein/LDL ratios increased in both groups. The use of food products with Locust Bean Gum in children and adults is a unique approach to treating familial hypercholesterolemia. Locust Bean Gum food acceptance was good, and there were no significant side effects.⁶⁰

Viscosity development

The great advantage of galactomannan is their ability at relatively low concentration to form very viscous solutions that are only slightly affected by pH, added ions and heating process^{65, 66} Locust bean gum and there derivatives (anionic, cationic and non-ionic) develop very high viscosity in aqueous solution. In the pharmaceutical industry it can be used as viscosity enhancer in the liquid preparation. The gum controls the flow characteristics of the vehicle present in the formulation. Locust bean gum differs from other galactomannan due to difference in the mannose/galactose ratio.^{61, 62} Too much high concentration will produce a high viscous solutions resulting in entanglement of the polymeric chains.

The gelation of locust bean gum in concentrated sucrose solution has been studied as a function of temperature, LBG and sucrose concentration. A critical gelling concentration of approximately 1% w/w LBG in 60% w/w sucrose was measured. The gelation rate initially increased with decrease in temperature until a maximum in gelation rate was found close to -5°C. LBG exhibited incompatible behavior at high sucrose concentration as a rheological inversion was detected for sucrose concentration greater than 50% w/w sucrose (T 1.5% w/w LBG), where the polymer rheology changed to that resembling a concentrated LBG/Sucrose solution. From this study, Richardson *et al* thus determined the required concentration of LBG which can be added in syrup solution containing sucrose.⁶³⁻⁶⁸

Biotechnological Application

Tissue engineering

Tissue engineering provides combinations of cells, acellular biomaterials, drugs, genes or gene products that may be designed,

specified, fabricated and delivered simultaneously or sequentially as therapeutic agents.⁶⁹ One of the tissue applications of tissue engineering is tissue scaffolds. Tissue scaffolds are three dimensional interconnected matrix of high porosity which is used as scaffold for seeding cells for tissue reconstruction, repair or remodeling. Tissue scaffolds are either naturally derived or synthetic in nature. The scaffolds can be classified into two different categories based on their shelf life. The two categories are permanent and temporary implants. Permanent scaffolds those that retain their shape and strength through the process of regeneration/repair of the organ while the temporary scaffolds degrade over a period of time with the regeneration of the organ or tissue.⁷⁰

Various galactose based polysaccharides are used as natural scaffold. Locust Bean Gum is used for the preparation of Multidirectional scaffolds⁷¹ suspension of gum was inserted into a freeze capsule and freeze dried. The resulting cell culture process scaffold was 1-10mm thick and opaque when dry and greater than 2-20mm, thick and opaque when wet. Scaffolds of Locust Bean Gum can also be prepared by uni-directional freezing-axial, radial, log method also. Thus Locust Bean Gum scaffold can be prepared and cell culture can be inserted within it for its growth and bioactivity.

In future there is a great scope of research and development in this field taking Locust Bean Gum.

CONCLUSION

Although excipients have traditionally been included in formulation as inert substances to mainly make up volume and assist in the manufacturing process, they are increasingly included in dosage forms to fulfill specialized functions for improved drug delivery because many new drugs have unfavorable physicochemical and pharmacokinetic properties. Locust bean Gum has a wide application whether in the field of novel drug delivery system as rate controlling excipients or in tissue engineering as scaffold formation. The unique property to form gel with trivalent cation is also quite advantageous. Under neutral conditions Locust bean gum is generally quite stable at room temperature. The molecule can be tailor made for a number of applications. Polymer controlled drug delivery is still in the developmental stage. Thus the large variety of applications as well as the steadily increasing number of research workers engaged in the studies of Locust bean gum due to their unique properties have made significant contributions to many types of formulations and suggest that the potential of locust bean gum as novel and versatile. This galactomannan will be even more significant in future.

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