Asian Journal of Chemistry; Vol. 32, No. 6 (2020), 1259-1265

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22607

REVIEW

Chemical Modifications of Guar Gum for Drug Delivery Applications: A Review

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Received: 24 December 2019; *Accepted*: 14 February 2020; *Published online*: 30 May 2020; AJC-19867

Guar gum is a natural excipient extracted from the plant seed of *Cyamopsis tetragonolobus*, belonging to the Leguminosae family. In the pharmaceutical industries, it contributes an important role due to its non-toxicity, ease of availability, biodegradability and eco-friendly nature. The major constituents of guar gum is galactomannan which is composed of D-galactose anhydride and mannose anhydride. Hydroxyl groups present in galactomannan can be modified by carboxymethylation, grafting or cross-linking with other excipients for developing modified polymers having desirable properties. Guar gum is commonly used as a suspending, emulsifying, stabilizing, gelling and thickening agent in various dosage forms. The guar gum derivatives are also useful in controlling the drug release from the pharmaceutical dosage forms. In this review, different aspects of synthesis of guar gum derivatives and its applications in various drug delivery systems is described.

Keywords: Guar gum, Chemical modification, Drug delivery.

INTRODUCTION

Gums are naturally occurring substances which consist of polysaccharides having heterogeneous composition of carbohydrate and sugar units (glucose, xylose, mannose, rhamnose, galactose and uronic acid). They have interconnected molecular network in three dimensional pattern known as 'gels' and entrap water to form viscous colloidal solutions. The factors affecting the gel strength include the structure of the gel, concentration of gel, temperature, pH and ionic strength. They are the most abundantly used raw materials in industries as they show low toxicity and good biodegradability. From the early times, gums have been utilized in domestic items as well as for medicinal purposes. Natural gums possess gelling, thickening, stabilizing and binding properties [1,2]. Guar gum, also known as Guaran is obtained from the seed of *Cyamopsis Tetragonolobus* belonging to the Leguminosae family [3]. Guar seed consists of germ (43-47%), endosperm 35-42% and hull (14 -17%). The guar seed undergo different stages of industrial processes. Milling operation is used for separating the endosperm from the seed and then crushed it to the particular mesh size. Heat treatment is given to inactivate the enzymes present in certain parts of the seed germ. Guar gum is different from other plant gums and mucilage due to the lack of uronic acid. The major constituent of guar gum is Galactomannan which is composed of mannose anhydride (63.1%) and D-galactose anhydride (36.6%) [4]. There exists β→(1,4) glycoside linkage between D-mannose units which are present in a straight chain and β→(1,4) glycosidic linkage between the mannose and galactose units which are linked at the alternate position [5]. Structure of guar gum containing different subunit is shown in Fig. 1. The other constituents include protein, water, ash and fatty materials and their percentage is listed in Table-1 [6].

TABLE-1
CHEMICAL CONSTITUENTS PRESENT IN GUAR GUM [Ref. 6]

Constituents	Present (%)
Galactomannan	80
Water	12
Protein	5
Acid insoluble ash	2.0
Fat	0.7

Investigation of the chemical nature of galactomannan is carried out with the help of physical tests (X-ray analysis, optical

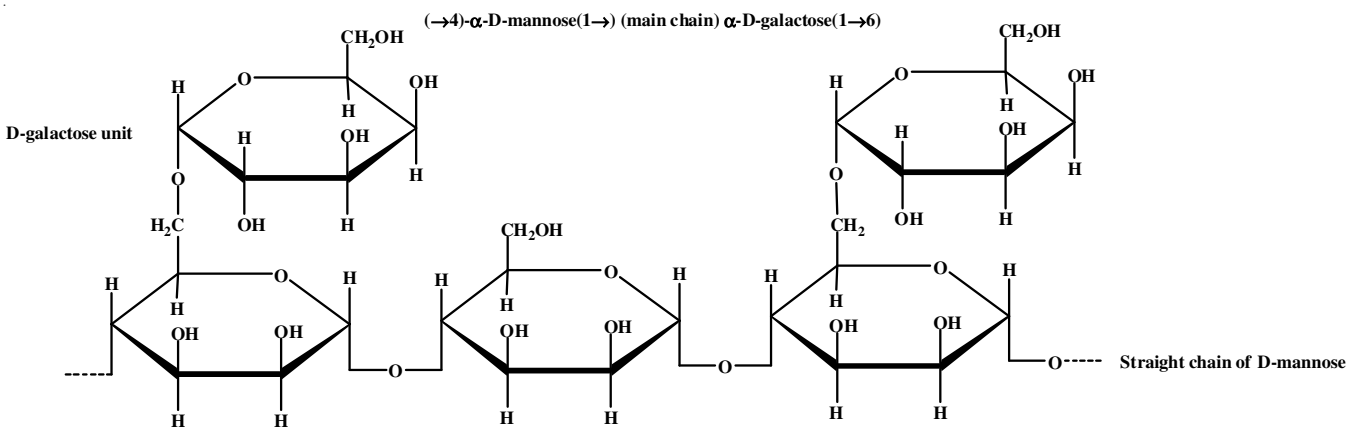

Fig. 1. Chemical structure of guar gum

rotation study, stress-strain measurement), chemical tests (acid hydrolysis, methylation, paper chromatography) and biological tests (enzyme hydrolysis) [4].

Gelling mechanism of guar gum: Guar gum has an ability to develop colloidal viscous solutions when dispersed in water. This occurs due to the entanglement of galactoside chains with the water molecules. This entanglement enhances the viscosity which is further responsible for thickening and gelling properties. Although guar gum is hydrophilic in nature, it doesn't absorb the moisture present in the atmosphere [7]. The viscosity of guar gum is related to shear rate and temperature. With an increase in the shear rate, a reduction in the viscosity of gum occurs. Similarly, increasing temperature disturbs the conformation of water molecules, thereby decreasing viscosity [8,9].

Chemical modifications of guar gum: The high hydrophilic nature of guar gum results in excessive swelling which increases the release rate of the incorporated drugs. Moreover, it is highly susceptible to microbial degradation. Therefore, modification of guar gum proved to be beneficial in overcoming the limitations associated with native guar gum [1]. Various methods for modifying guar gum include carboxymethylation, polyacrylamide grafting, succinate, benzoate and propionate linkage.

Carboxymethylation of guar gum: Guar gum can be modified to carboxymethyl guar gum as shown in Fig. 2. Purified guar gum was mixed with isopropanol and water in a round bottom flask placed on the magnetic stirrer. Then NaOH was added with 1 h continuous stirring at 50 ºC. After 0.5 h, mono-chloroacetic acid was added and stirring was continued for 4 h at 50 ºC. Ethanol was added to extract out the product which was separated with the help of centrifugation. The pH after third extraction was then adjusted to pH 7 using glacial acetic acid. The precipitate was then washed with ethanol and dried under vacuum and characterized [10]. Manna *et al.* [10] grafted carboxymethyl guar gum with gelatin and incorporated curcumin in the formulation. The results showed slow release of curcumin at the site of infection as well as prevention of microbial growth, thereby leading to improvement in wound healing process. Giri *et al.* [11] developed hybrid hydrogels by chemically modifying carbon nanotubes with carboxymethyl guar gum. The drug, diclofenac sodium was released from the formulation in a sustained manner *via* transdermal route [11]. Carboxymethyl guar gum has been successfully implemented for developing different drug delivery systems as shown in Table-2.

Synthesis of polyacrylamide-grafted-guar gum: The procedure for the synthesis of polyacrylamide-grafted-guar gum is presented in Fig. 3. A solution of guar gum (2%) was prepared in water. To this solution, acrylamide was added with continuous stirring for 24 h. Nitrogen was purgated at 70 ºC through this mixture for 2 h and then ceric ammonium nitrate solution was added with continuous stirring for 5 h. After the mixture was cooled, quinhydrone was added. For obtaining the precipitate, acetone was finally added. The precipitates were then filtered out, washed with methanol, dried and stored

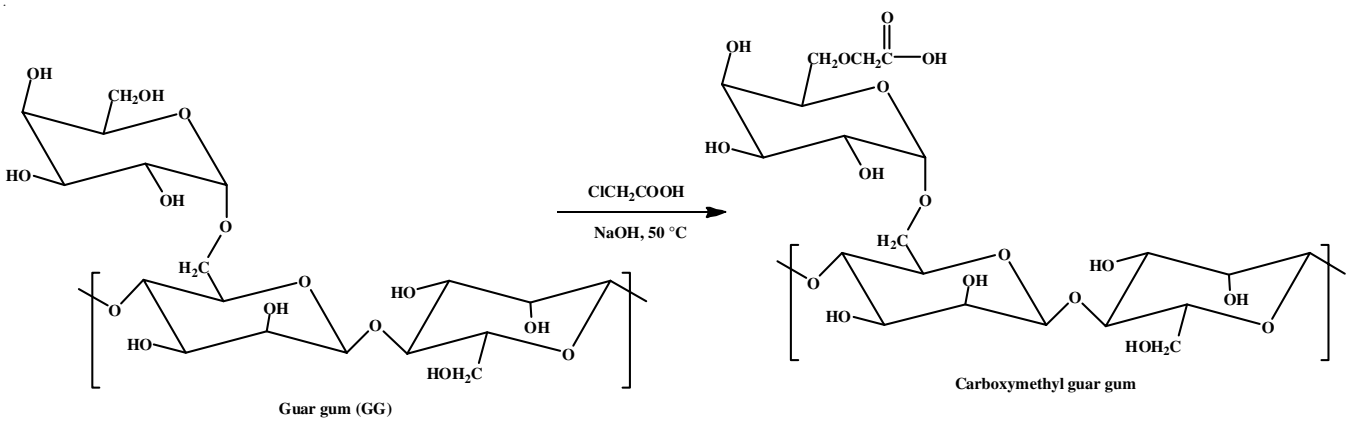

Fig. 2. Synthetic route of carboxymethyl guar gum

TABLE-2
DRUG DELIVERY APPLICATIONS OF SUBSTITUTED GUAR GUM

Drug	Formulation	Remarks	Ref.
		Carboxymethyl guar gum	
Curcumin	Gelatin film	Carboxymethyl guar gum grafted gelatin film loaded with curcumin was used for wound healing and antibacterial activity.	[10]
Diclofenac sodium	Polymer hydrogel	Carboxymethyl guar gum modified carbon nanotube hydrogels were loaded with diclofenac sodium, which showed sustained transdermal drug release.	[11]
Fluticasone	Tablet	Chitosan and carboxymethylated guar gum cross-linked complex was used for preparing tablets incorporating fluticasone. The formulation was useful in colonic drug delivery.	[12]
Metronidazole	Tablet	Crosslinking of calcium ions with partially carboxymethylated guar gum altered the swelling of the gel layer as well as drug release rate.	[13]
Tamoxifen	Tablet	Tamoxifen tablets were formulated with the help of carboxymethyl guar gum-chitosan complex and were useful in successfully delivering the drug to colon.	[14]
Bovine serum albumin	Microbeads	Carboxymethylated guar gum was cross-linked with various metal ions to develop microbeads, which showed gastric resistance when administered orally.	[15]
Abacavir sulfate	Microspheres	Abacavir sulfate loaded carboxymethylated guar gum microspheres were prepared using emulsion method. The release rate of the short lived drug was extended upto a time period of 28 h.	[16]
Bovine serum albumin	Beads	Beads were prepared by crosslinking carboxymethyl guar gum with barium chloride. The cross linked beads were resistant to the acidic environment and delivered the protein completely in the intestine.	[17]
Not available	Films	Films were developed by crosslinking calcium ion with waterborne polyurethane and carboxymethylated guar gum. The blend films showed improved miscibility as well as thermal stability.	[18]
Not available	Hydrogel	Super absorbent hydrogel was developed from carboxymethylated guar gum by partially hydrolyzing it with methacrylic acid.	[19]
Not available	Nanoparticles	Nanoparticles of carboxymethylated guar gum were prepared by sonication method and characterized.	[20]
Not available	Graft Copolymer	Graft copolymerization of polybutyl methacrylate and partially carboxymethylated guar gum (sodium salt) was performed using ammonium nitrate as redox initiator.	[21]
Not available	Graft copolymer	Copolymer was synthesized using partially carboxymethylated guar gum grafted with 4-vinyl pyridine.	[22]
		Polyacrylamide-grafted-guar gum	
Verapamil HCl, Nifedipine	Microgels	Hydrogel microspheres were developed by grafting polyacrylamide on guar gum with the help of emulsification technique.	[24]
5-Amino salicylic acid	Tablet	Grafting of guar gum with polyacrylamide was performed in microwave radiation.	[25]
Diclofenac sodium	Hydrogel nanocomposites	Polyacrylate grafted carboxymethyl guar gum was used for preparing hydrogel nanocomposites, which transdermally delivered diclofenac sodium at a controlled rate.	[26]
Diltiazem hydrochloride	Matrix tablets	Matrix tablets were prepared from modified guar gum (polyacrylamide grafted) for colonic release of diltiazem hydrochoride.	[27]
Not available	Hydrogel	Hydrogel was developed as a copolymer using guar gum grafted with acrylamide for hexavalent chromium ion sorption.	[28]
Not available	Graft Copolymer	Carboxymethylated guar gum was grafted with *N*-(hydroxymethyl)acrylamide using potassium peroxymonosulfate and thiourea as the redox initiator.	[29]
Not available	Flocculation agent	Cationic guar gum grafted with polyacrylamide was synthesized at low temperature with the help of polymerization method.	[30]
Isoniazid	Hydrogel	Polyacrylate grafted guar gum was blended with polyvinyl alcohol for the development of pH-sensitive hydrogels incorporating antitubercular drug isoniazid.	[31]
Not available	Injectables	Carboxymethyl guar gum was grafted with poly (ethylene oxide-*co*-propylene oxide) for the synthesis of thermo-associating polymers, which had the ability of controlling the drug release from various formulations.	[32]
Ciprofloxacin	Hydrogel microspheres	A blend of acrylamide grafted guar gum and chitosan was utilized in developing ciprofloxacin encapsulated hydrogel microspheres.	[33]
		Guar gum succinate	
Ibuprofen	Beads	pH-sensitive carrier system was developed in the form of guar gum succinate-sodium alginate beads for colonic delivery of the drug.	[35]
Doxorubicin	Nanoparticles	Doxorubicin loaded gold nanoparticles were coated with folic acid-guar gum succinate conjugate for the treatment of cancer.	[36]
Not available	Polymer electrolyte membrane	Polymer electrolyte membrane was developed using guar gum succinate to improve the aqueous solubility and ionic conductivity of native guar gum.	[37]
Not available	Superabsorbent hydrogels	Superabsorbent hydrogels were synthesized by reacting guar gum with succinic anhydride using esterification method. The formulation showed high biodegradability as well as water absorbency.	[38]

		Guar gum alkylamine	
Not available	Water resistant films	Guar gum alkyl amine was modified into guar gum benzamide for developing water-resistant biopolymer cast films, which inhibit the growth of microorganisms.	[39]
Ciprofloxacin	Nanocomposite microbeads	Nanocomposites of ciprofloxacin and guar gum alkyl amine impregnated with silver nanoparticles were prepared for controlled release of the anti-microbial agents.	[40]
Silver nanoparticles	Nanocomposites	Guar gum alkyl amine stabilized silver nanoparticles were developed for wound healing applications.	[41]
Not available	Nano-biocomposite films	Nano-biocomposite films showing effective results against microbes were synthesized by immobilizing silver nanoparticles on cationic guar gum alkyl amine.	[42]
		Guar gum benzoate	
Not available	Nano composite film	Bio-based castable nanocomposite film was developed by using guar gum benzoate nanoparticles and gelatin for enhancing mechanical and antimicrobial properties as well as thermal insulation.	[43]
		Guar gum propionate	
Not available	Nanoparticles	Guar gum propionate nanoparticles possessing antimicrobial applications were synthesized with the help of solvent shifting technique.	[44]
Not available	Not available	Guar gum propionate was prepared by microwave technique for enhancing the physico-chemical properties of guar gum.	[45]

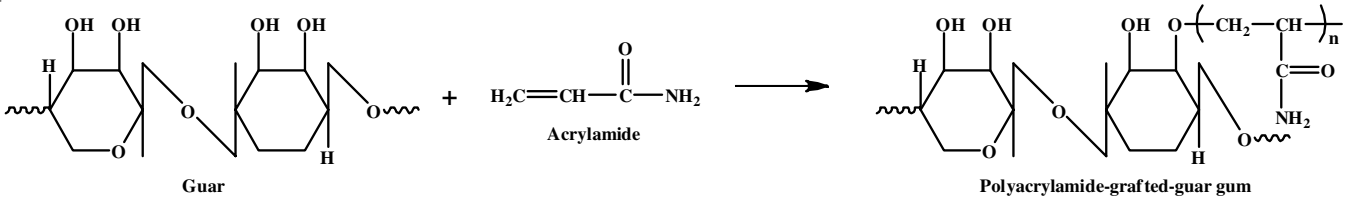

Fig. 3. Synthetic route of polyacrylamide-grafted-guar gum

in a desiccator and then characterized [23]. Soppimath *et al.* [24] utilized emulsification method for the preparation of polyacrylamide grafted guar gum hydrogel. The factors affecting the release of verapamil hydrochloride and nifedipine from hydrogen included the solubility of drug and the pH of surrounding medium. The results concluded an enhancement in the swelling of hydrogel when the pH of surrounding medium was alkaline [24]. Sen *et al.* [25] used microwave-assisted method for the synthesis of polyacrylamide grafted guar gum. The release rate of 5-aminosalicylic acid from the formulation was low in stomach (acidic environment) but high in intestine (alkaline environment). Furthermore, percentage grafting also affected the release rate. As the percentage grafting increased, the drug release decreased [25]. Drug delivery applications of polyacrylamide-grafted-guar gum are shown in Table-2.

Synthesis of guar gum succinate: The initial step of its preparation involved the reaction of succinic anhydride with aqueous solution of guar gum in the presence of 4-dimethyl-aminopyridine with constant stirring for 24 h at room temperature (Fig. 4). The neutralization of product was done by addition of NaOH solution and followed by the addition of ethanol for precipitating the desirable material. Dialysis was performed for removing out the undesirable materials, followed by vacuum drying of the required product. Guar gum succinate was evaluated for FTIR, drug release, cytotoxicity and swelling studies [34]. Seeli *et al.* [35] performed the crosslinking of guar gum succinate-sodium alginate beads with barium ions to prepare a carrier system which delivered ibuprofen directly into the colon. The presence of carboxylic acid group in the polymer network led to the maximum swelling of beads in alkaline medium and not in acidic medium, thereby increasing the release rate of the drug in colon. Rajkumar and Prabharan [36] utilized conjugates of guar gum succinate and folic acid for encapsulating multi-functional gold nanoparticles loaded with doxorubicin. The nanoparticles disintegrated in acidic medium, thereby releasing 90% of doxorubicin at a controlled rate. Drug delivery applications of guar gum succinate are shown in Table-2.

Synthesis of guar gum alkyl amine: Synthetic route of guar gum alkyl amine is shown in Fig. 5. Guar gum was taken in a three-necked round bottom flask and isopropyl alcohol

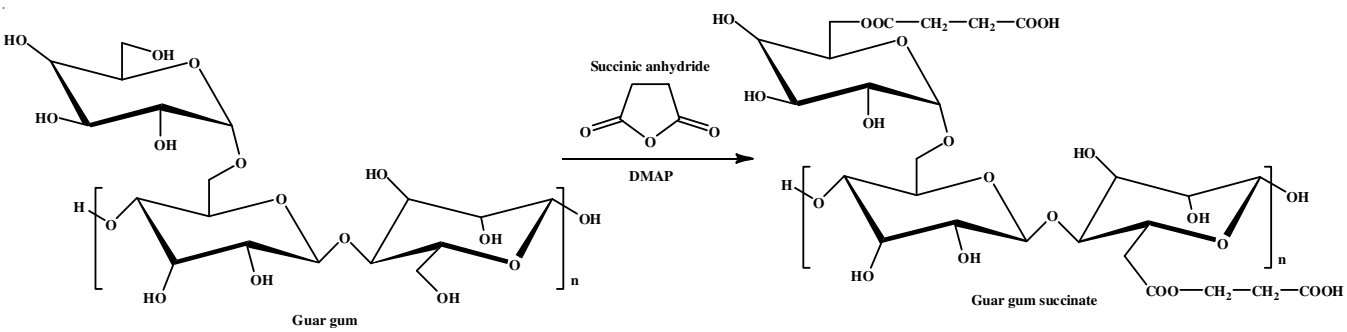

Fig. 4. Synthetic route of guar gum succinate

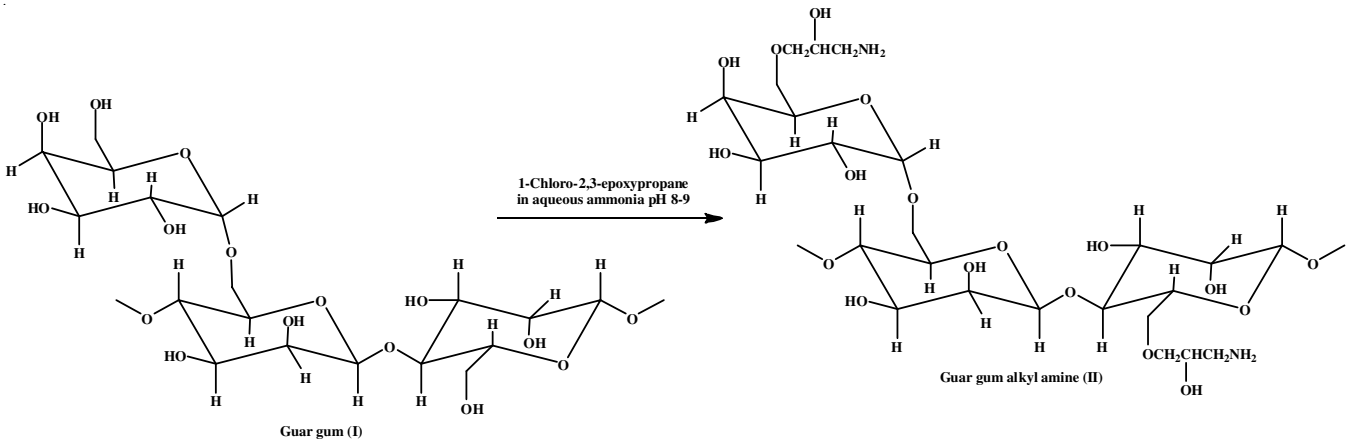

Fig. 5. Synthetic route of guar gum alkyl amine

was added with continuous stirring at 100 rpm. Nitrogen purging was carried out for an hour followed by addition of ammonium hydroxide and 1-chloro-2,3-epoxypropane. The light yellow coloured product was filtered, washed again with a mixture of ethanol and distilled water, vacuum dried and ultimately stored in desiccator and then characterized. Islan *et al*. [40] co-encapsulated guar gum alkylamine stabilized silver nanoparticles and an antibiotic *e.g.*, ciprofloxacin to synthesize biopolymeric beads. The resulting beads showed synergistic effect of both the antimicrobial agents against *Psedomonas aeruginosa*, *Staphylococcus aureus* and *Bacillus cereus*. The synthesized guar gum also prevented the destruction of silver nanoparticles by the acidic environment of stomach which was further useful in treating intestinal infections [40]. Auddy *et al*. [41] synthesized a nanobiomaterial consisting of guar gum alkylamine and silver nanoparticles. It instigated the keratocyte migration towards the site of injury, stimulated wound closure and therefore reduced the healing time [41]. Drug delivery applications of guar gum alkylamine are shown in Table-2.

Synthesis of guar gum benzoate: Guar gum was soaked in aqueous isopropanol for 24 h and added to DMSO after decanting off the solvent. The homogenous solution was then poured into a three neck flask linked with a mechanical stirrer, purging nitrogen device and condenser. Addition of benzoyl chloride and purgation of nitrogen was carried out with continuous stirring for 3 h. To a solution, methanol was added which led to the formation of precipitates which were collected after filtration (Fig. 6). Then biopolymer was preserved in a vacuum desiccator [43]. Applications of guar gum benzoate are shown in Table-2.

Synthesis of guar gum propionate: Dried guar gum containing less than 2% (w/w) moisture content was added to formic acid present in a four necked flask equipped with a mechanical stirrer, condenser, nitrogen purging system and dropping funnel. The reaction was initiated by heating the mixture at 25 ± 2 ºC for 5 min. The mixture was then heated at 70 ± 5 ºC with dropwise addition of propionyl chloride. Continuous stirring of the mixture was done for 1 h followed by pouring of ethanol. After centrifugation final product of guar gum propionate was collected and preserved in desiccator [44]. Iqbal *et al*. [45] utilized microwave irradiation technique for synthesizing guar gum propionate *via* acid anhydrides (Fig. 7). The resulting product showed favourable industrial applications as an emulsifier and binder [45] (Table-2).

Patents filed on guar gum modifications: Various patents filed on the derivatives/modifications of guar gum are listed in Table-3. Carboxymethylation of guar gum was performed by three step process *viz*. alkalization, etherification and after treatment. Guar gum was treated with sodium hydroxide at 20-25 °C for 30 min followed by reaction with monochloro acetic acid to obtain etherification reaction liquid. The reaction mixture was cooled and pH was adjusted to 7.5. The obtained carboxymethylated guar gum was washed with ethanol. The final product exhibited high degree of substitution, high visco-

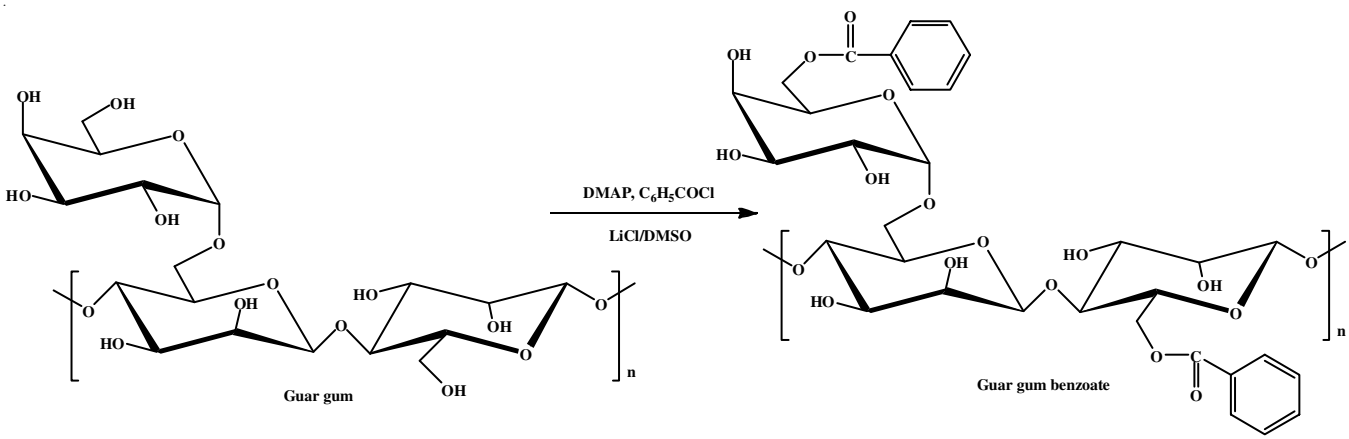

Fig. 6. Synthetic route of guar gum benzoate

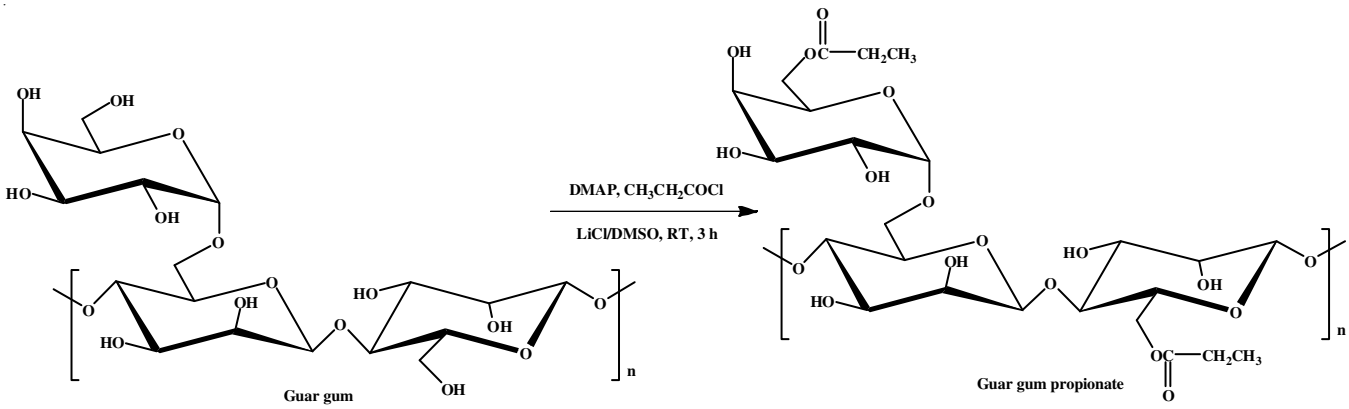

Fig. 7. Synthetic route of guar gum propionate

TABLE-3
PATENTS FILED ON GUAR GUM MODIFICATION

Patent No.	Year	Topic	Ref.
US5536825A (USA)	1996	Derivatized guar gum composition and process for making it	[46]
US20060110415A1 (USA)	2006	Topical delivery system for cosmetic and pharmaceutical agents	[47]
CN101979414A (China)	2010	Method for synthesizing carboxymethyl guar gum	[48]
CN10379264A (China)	2013	Preparation method of carboxymethyl guar gum	[49]
US20150044285A1 (USA)	2015	Pharmaceutical soft gelatin capsule dosage form with modified guar gum	[50]

sity, high solubility and low content of water insoluble substances [49].

Conclusion

Guar gum is easily available, biocompatible and cheap non-toxic gum employed for diverse pharmaceutical applications. Modifications of guar gum offer interesting opportunities to further explore its application with tunable properties. Modification of guar gum by different methods leads to an enhancement in its physical and chemical properties as well as customerized drug delivery applications. Advantages of modification of guar gum include enhanced mucoadhesive properties, matrix forming ability, mechanical and thermal properties and stability. Modified guar gum must be evaluated for toxicity profiling and regulatory issues must be addressed before exploring its commercial viability. In conclusion, various modifications of guar gum led to a feasible exploring in diverse drug delivery applications.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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