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Research Article

Chemistry for New drug discovery

Synthesis, Characterization and *Invivo* Evaluation of Poly Sulfoxy Amine Grafted Xanthan Gum

Rahul Laxman Jadhav[1*], Manisha Vyankatrao Patil[2] and Shaikh Siraj N[3]

[1]*Professor and Head Department of Pharmaceutical Chemistry, Gourishankar Institute of Pharmaceutical Education and Research, Limb, Satara, Maharashtra-415001, India*

[2]*Asst.Professor Department of Pharmaceutics, Adersh College of Pharmacy, Vita; Dist:* Sangli, *Maharashtra-416416, India.*

[3]*Associate Professor and Head Department of Pharmaceutics, Ali-Allana College of Pharmacy Akkalkuwa, Nandurbar, Maharashtra-425415, India*

Abstract: Natural polymers are hydrophilic in nature, economic, chemically inert, easily available, biodegradable, and non-toxic. Following problems associated with the use of gums include uncontrolled rates of hydration, pH dependent solubility, thickening, drop in viscosity on storage, and the possibility of microbial contamination. Chemical modification of gums not only minimizes these drawbacks but also alter their physicochemical properties. Recently, researchers have been modifying properties of natural gums to explore its more applicability. Aim of the current study was to explore Xanthan gum's applicability in mucoadhesive and other property by doing its Chemical modification. Sulfoxy amine modification of xanthan gum was carried out by reacting xanthan gum with thionyl chloride and further treated with ammonia. FTIR, elemental DSC, XRD and SEM were studied for confirmation of the modification. The modified xanthan gum showed improvement in the mucoadhesion, water uptake capacity, gelling property as well as viscosity as compared to unmodified xanthan gum. The results of X-ray diffraction study confirms the finding of DSC study. X-ray diffractogram confirmed XG is typical of amorphous substance while that of MXG is typical of crystalline substance with the characteristic peak appearing at 14.79, 25.66, 29.63 and 31.82 2θ. The 0.6% w/v of modified xanthan gum showed gelling property. The 0.6% w/v of modified Xanthan Gum showed gelling property where as Xanthan Gum required more than 1% w/v , it indicate that gelling property of Xanthan Gum has improved due to its modification. Mucoadhesive strength of modified xanthan gum was found to be 4±0.56 gm which is more than xanthan gum i.e. 1.5±0.94 gm. The ionic interactions may be taken place in between negatively charged mucus with cationic modified polymer and superior mucoadhesion can be achieved. Rapid and constant swelling behavior was observed by modified Xanthan gum. The SEM image of MXG showed that the grafting of Polysulfoxyamine onto XG brings about the change in the shape and size of the XG particles. The enhanced viscosity and gelling capacity of modified xanthan gum were also observed as compared to xanthan gum. In *vivo* acute toxicity study of Poly sulfoxy amine grafted xanthan gum was performed. The toxicological effects were observed in terms of mortality and expressed as LD_{50}. Results of Acute toxicity study shows LD_{50} value was more than 2 gm/kg indicating the low toxicity. These findings proved that modified xanthan gum may be used as promising excipient in various drug delivery systems.

Keywords: Xanthan gum, Mucoadhesion, viscosity enhancer, gelling agent, swelling agent, Acute Toxicity Study.

***Corresponding Author**

Rahul Laxman Jadhav , Professor and Head Department of Pharmaceutical Chemistry, Gourishankar Institute of Pharmaceutical Education and Research, Limb, Satara, Maharashtra-415001, India

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1. INTRODUCTION

Natural polymers are hydrophilic in nature, economic, chemically inert, easily available, biodegradable, and non-toxic. Naturally occurring polysaccharides can be easily modified chemically and biochemically to impart desirable properties suitable for designing drug delivery systems[1]. A large number of plant based pharmaceutical excipients are available today. Gums and mucilages are the most commonly available plant ingredients with a wide range of applications in pharmaceutical and cosmetic industries. For biodegradability, easy availability and non toxicity, various natural polymers are preferred over synthetic polymer. Water soluble natural polymers are becoming increasingly important compound useful in a broad range of applications. Their importance lies, in their ability to function in environmentally protective ways. The most abundant natural polymers, for example, the polysaccharides cellulose and chitin, are linear polymers with poor water solubility[2]. The plant based polymers have been studied for their application in different pharmaceutical dosage forms like matrix controlled system, film coating agents, buccal films, microspheres, nanoparticles, viscous liquid formulations like ophthalmic solutions, suspensions, implants. Many natural polymeric materials have been successfully used in sustained-release tablets. These materials include: guar gum, isapghula husk. These have also been utilized as viscosity enhancers, stabilizers, disintegrates, solubilizers, emulsifiers, suspending agents, gelling agents and bioadhesives, binders. Problems associated with natural polymers like, Microbial growth, solubility, gelling strength,viscocity,can be improved by the chemical modification of these[2]. One of the natural polymers that have drawn a great interest of pharmaceutical researchers is xanthan gum (XG) because of its use as tablet excipient, viscosity modifier, *in situ* insert, stabilizer, hardener, suspending agent and emulsifier[3]. The output of XG is now the largest of the natural exoploysaccride because of its wide application in the petroleum oil, textile[4], food[5], cosmetic and pharmaceutical Industries[6]. Xanthan gum is a high molecular weight extracellular polysaccharide secreted by the xanthomonas campestris. It is commercially manufactured by the fermentation process. It is soluble in cold water to form a viscous solution[7]. The viscosity of xanthan gum has excellent stability over a wide pH range and the solution exhibits high pseudoplastic flow. Xanthan gum is linearly (1-4) linked β-D- Glucose backbone with trisaccharide side chain on even other glucose at C-3, containing a glucuronic acid residue linked (1-4) to a terminal mannose unit and (1-2) to a second mannose that connects to the backbone.[8] It exhibits unit of five monosaccharide formed by two d- glucose, two d- mannose and one d-glucuronic acid[9]. Various modification of XG has been made like grafting reaction with acrylamide for better control of their hydration property[10], grafting with ethyl acrylate for improvement in the stability, solubility as well as their absorbing capacity[11], grafting of poly acrylamide results in the faster release of drug[11]. Chemical modification with formaldehyde and carboxymethylation[12] has been found to increase dissolution rate of drugs. Chemical modification with sulfhydryl group mediated by carbodiimide was performed for increasing buccal mucoadhesive and stability[13]. Thiol derivatization of XG improved its mucoadhesion and made sustained released polymer for various drug delivery[14]. Modified xanthan gum mini matrices were prepared for monitoring oral discharge of highly soluble Soluplus-glibenclamide into gastric – luminal fluid [15]. Aim of the current study was to explore Xanthan gum's applicability in mucoadhesive & other property by performing its Chemical modification. The present study describes the modification of xanthan gum (MXG) for enhancing its positive attributes. The synthesized MXG was characterized by FTIR, elemental, DSC XRD and SEM analysis. Various properties like mucoadhesion, water uptake capacity, viscosity and gelling property were studied.

2. MATERIALS AND METHODS

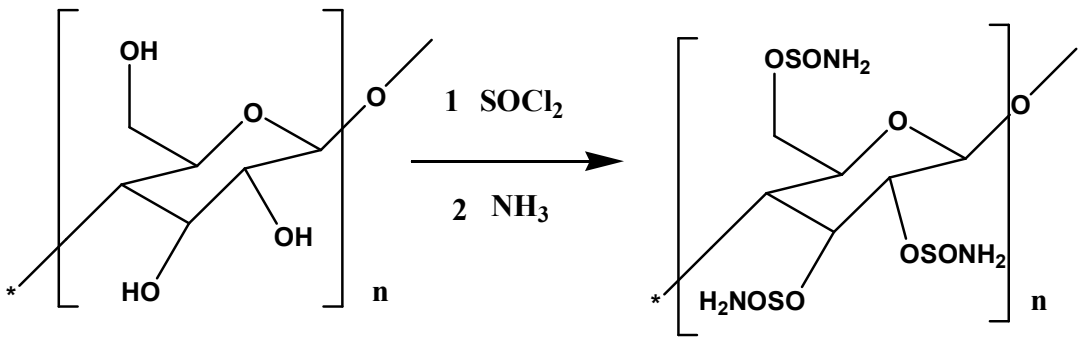
All synthetic chemicals were procured from local distributors and were of Loba Chemical Pvt. Ltd, Mumbai, India. Melting points were uncorrected. The microwave was used for synthesis of modification of xanthan gum.

2.1 Ethical Clearance

The animal experiment was carried as per the Protocol/ instructions approved by the Institutional Animal Ethical Committee, GIPER, Limb, Satara (CPCSEA Reg. No: 1988/Po/Re/S/17/CPCSEA Dated Oct.27, 2017).In this acute oral toxicity study Female Swiss Albino Mice having weight in the range of 20 to 25 gm was used as an animal model.

2.2 Synthesis of poly Sulfoxy amine grafted Xanthan gum

Sulfoxy amine xanthan gum was synthesized by mixing the 100 ml of pyridine with 10 gm of xanthan gum. To this, 8 ml thionyl chloride was added slowly with stirring. The reaction mixture was irradiated in the microwave for 1 min(four cycles of irradiations) and kept as it is for overnight. The solid product was filtered, washed with rectified spirit and then dispersed in 50 ml rectified spirit containing 10 ml ammonia. The contents of the flask was stirred for 2 hrs and then filtered and washed with 50. In rectified spirit solid wad collected and dried[16,17].



Xanthan gum Modified Xanthan gum

2.3 Characterization of poly sulfonyl amine grafted xanthan gum[18,19]

1. Fourier transforms infra-red spectroscopy: FT-IR spectral analysis of XG and MXG were recorded on a BRUKER FT-IR alpha ATR spectrometer.
2. Elemental analysis: CHNO was determined by Thermo finnigan, FLASH EA 1112 series.
3. Differential Scanning Calorimetry (DSC): Differential Scanning Calorimetrythermogram of XG and MXG were recorded in the temperature range of 40^{0}C – 300^{0}C at a heating rate 10 ^{0}C/min.
4. X-ray diffraction: X-ray diffraction of XG and MXG were recorded by employing X-ray diffractometer (Bruker AXS D8 Advance) using copper Kα-radiation generated at 40 Kv and 35 mA in the differential angle range of 3-60 (2θ) using XRD.
5. Zeta potential: To determine the charge of the modified molecule, Zeta potential was determined by Horeba SZ 100 instrument.
6. Scanning Electron Microscopy: The shape and surface morphology of XG & MXG were examined using scanning electron microscopes model Jeol 6390LA/ OXFORD XMX N. The samples were coated with gold & mounted on aluminum stub containing double adhesive carbon tape. The electron micrographs were taken at an accelerated voltage of 10 kv.

2.4 Physicochemical evaluation of poly sulfonyl amine grafted xanthan gum [20,21,22]

2.4.1 Mucoadhesion property

Mucoadhesive property was evaluated by the previously reported method [18,19]. The modified balance method was used for determining mucoadhesion strength. This detachment force gives the mucoadhesion strength.

2.4.2 Swelling Studies

The water-absorbing capacity of investigated xanthan gum was determined gravimetrically [20,21]. After fixing 30 mg disc (compressed by a single punch hydraulic press, 5.0-mm diameter) on a needle and dipping them into a beaker filled with simulated saliva solution (pH 6.75 at 37±0.5°C), the disc were weighed at predetermined time points. Before measuring, the swollen discs were drained of excess water. Water-uptake capacity was calculated using following equation:

Water uptake (mg) = {Wt-Wo}

Where,

Wt=Disc Wt. at a given time.
Wo=Initial Wt.

2.4.3 Gelling property and Gelling capacity

Gelling property was determined as per described method of Rupenthal *et al* [22]. The solution of Sulfoxy amine xanthan gum and xanthan gum (0.2–1%, w/v) in water were prepared in a test tube and left overnight. The test tubes were observed for their consistency by tilting them at 90° and classified as solutions, viscous solution or gels on the basis of their visual appearance.

The gelling capacity of XG and MXG were determined [23] by placing a drop of the solution in a vial containing 2 ml freshly prepared simulated tear fluid and visually observed the time taken for its gelling.

2.4.4 Viscosity

Viscosity of xanthan gum and modified xanthan gum were determined as previously reported method[24,25] by Brookfield viscometer (Brookfield DV-E Vis-cometer) at various speeds using spindle L1.

2.4.5 In Vivo Acute Toxicity Study of Poly Sulfoxy Amine Grafted Xanthan Gum

OECD guideline - 423 were used for performing oral acute toxicity[25]. The toxicological effects were observed in terms of mortality and expressed as LD_{50}. The MXG was administered in a single dose.The starting dose level was 300 mg/kg. Before dose administration, the body weights of each animal were determined, and the dose was calculated according to the body weight. Animals were observed individually after dosing during the first 30 min and periodically during the first 24 hrs and daily thereafter, for a total of 14 days.

3. RESULTS AND DISCUSSION

The evidence from melting point (MXG: 195-200^{0}C, XG: 210-215^{0}C), and percentage yield (MXG:12gm), revealed that compound was synthesized. FTIR spectra were recorded in the range of 4000-400 cm^{-1} and are presented in Figure 1. Xanthan gum shows a broad absorption band at 3332 cm^{-1} due to OH. Aliphatic CH stretching peak appearing at 2918 cm^{-1}, while the peak appearing at 1602 cm^{-1} is due to carboxyl group. The bending absorption band at 1406 cm^{-1} and 1020 cm^{-1} can be attributed to –CH of methyl and C-O-C of cyclic ether respectively. The spectrum of MXG shows the characteristic absorption band of NH_2 group 3392 cm^{-1}. The broad shape of OH group of xanthan gum convert into sharp spikes indicates the substitution occurred on the hydroxyl group of xanthan gum. The peak appearing at 2916 cm^{-1} and 1406 cm^{-1} can be ascribed to CH stretching and bending of alkanes. The cyclic ether stretching was observed at 1016 cm^{-1}. The intensity of signal of hydroxyl groups has decreased which support the fact that the concentration of hydroxyl functions in the XG has declined.

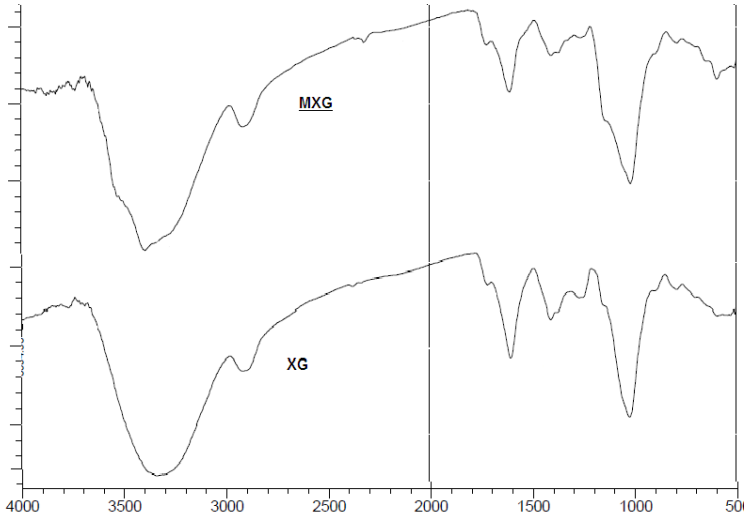
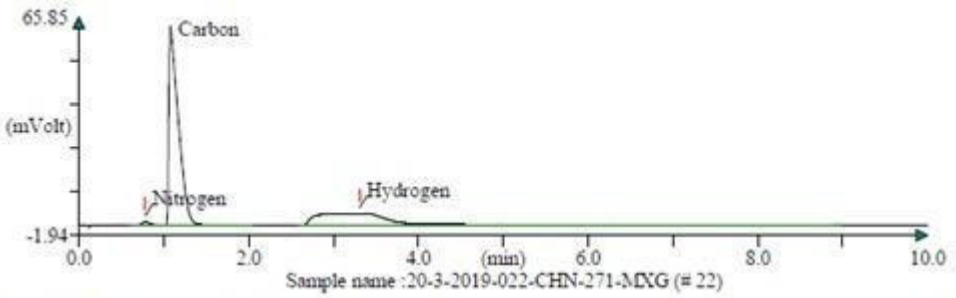


Fig 1. FTIR Spectra of MXG And XG



eak Number (#)	Retention Time (min)	Area (.1*uV*sec)	Element %	Componer
	0.783	72897	0.640	Nitroger
	1.083	4809051	35.512	Carbon
	3.308	2357206	5.614	Hydroger
		7239154	41.766	

Fig 2. Elemental Analysis CHNO of MXG

The percentage of C H N and O elements of MXG is presented in fig. 2 were found to be C: 35.51, H: 5.61, N: 0.64 and O:37.75. The presence of nitrogen element peak in the spectrum indicates the substitution of amino group taking place on the XG.

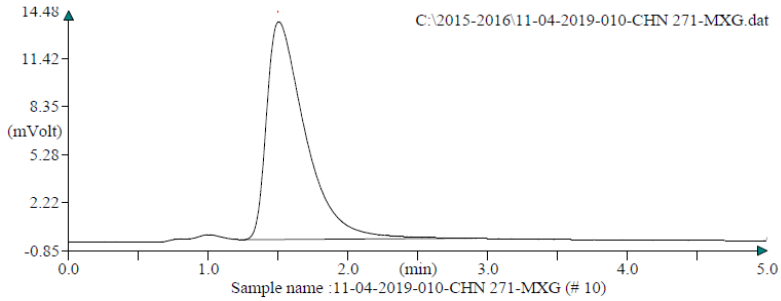


Fig 3. Oxygen Elemental Spectra of MXG

As per Figure 3 Thermogram of XG shows a broad endotherm at 88.5 ^{0}C whereas MXG shows endothermic peak at 59.4 ^{0}C. DSC curve of XG is presented in fig 4is like that of amorphous material. In the DSC curve of MXG, one more endothermic peak observed at 245 ^{0}C which may be due to the modification.

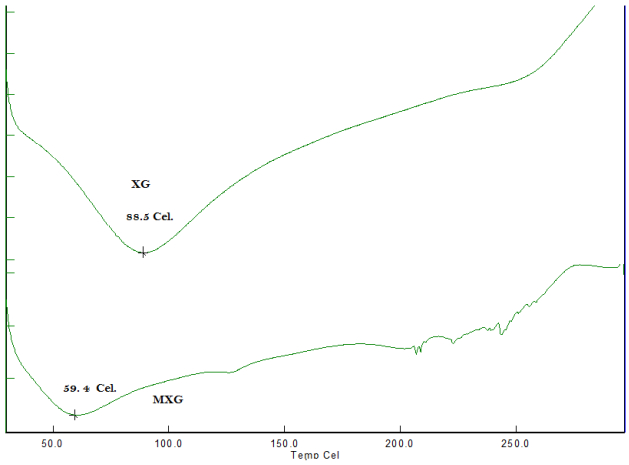


Fig 4. DSC Spectrum of XG and MXG

The XRD Spectrum of XG & MXG is presented in fig 5. The results of X-ray diffraction study conform the finding of DSC study. X-ray diffractogram of XG is typical of amorphous substance while that of MXG is typical of crystalline substance with the characteristic peak appearing at 14.79, 25.66, 29.63 & 31.82 2θ.

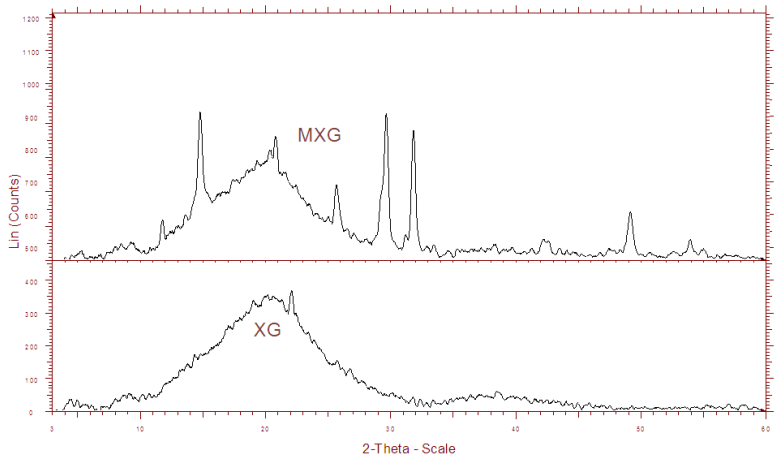


Fig 5.The XRD spectrum of MXG and XG

Presence of charge on polymer is unique properties of polymer which can be utilized in designing of dosage form. Zeta potential of the Modified molecule, MXG was determined by Horeba SZ 100 instrument.

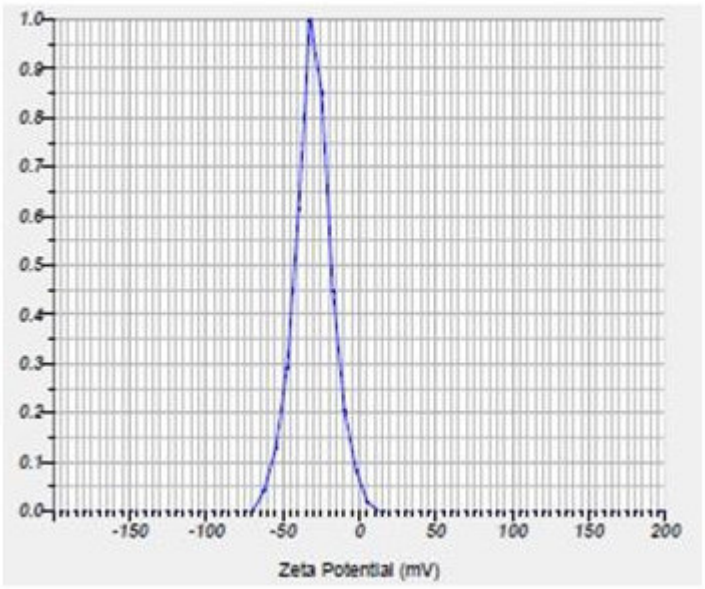


Fig 6. Zeta potential of Modified Xanthan Gum

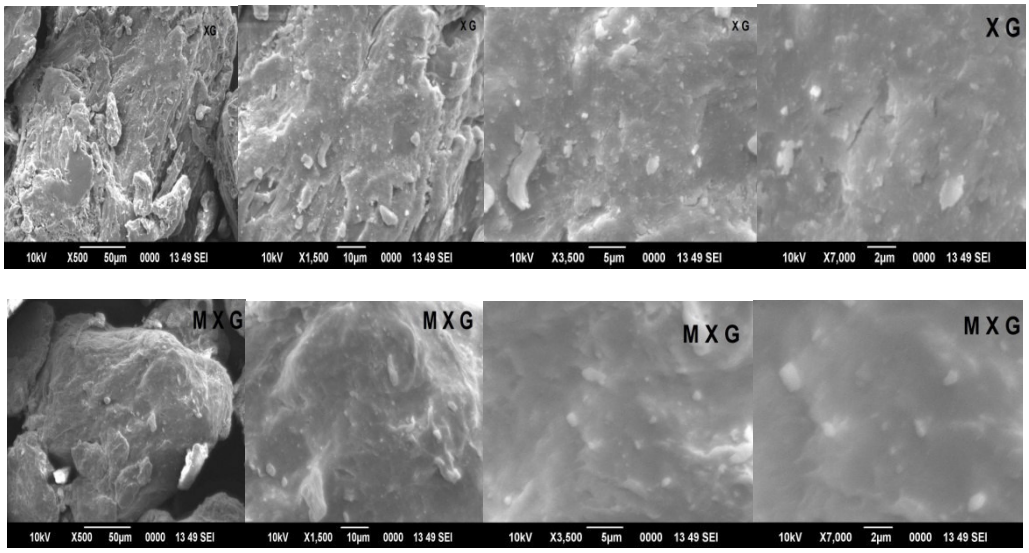


Fig 7. Exhibits the surface morphology of XG& MXG

The Zeta Potential and SEM photographs of MXG showed in Figure 6 & 7 polyhedral structure with smooth surface while XG shows rough surface. The SEM image of MXG shows that the grafting of polysulfone onto XG brings about the change in the shape and size of the XG particles. Mucoadhesion may be defined as the adhesion between a polymer and mucus. Mucoadhesion of chitosan and other polymer were first studied by Lehr et al (1992) [18]. He observed the adhesion properties of chitosan persisted well during repeated contacts with chitosan and the substrate, with the chitosan in a swollen state. It was suggested that not only adhesion by hydration involved but also additional mechanisms such as hydrogen bonding and ionic interaction were also Involved Ionic interactions take place between negatively charged mucus with cationic polymer and mucoadhesion can be achieved. In the present study, the mucoadhesive strength of modified xanthan gum is presented in Figure .8 which was found to be 4±0.56 gm and is more than xanthan gum i.e. 1.5±0.94 gm. The higher bioadhesion may be due to the formation of ionic interaction of cationic primary amine group of modified xanthan gum with negatively charged mucin[26].

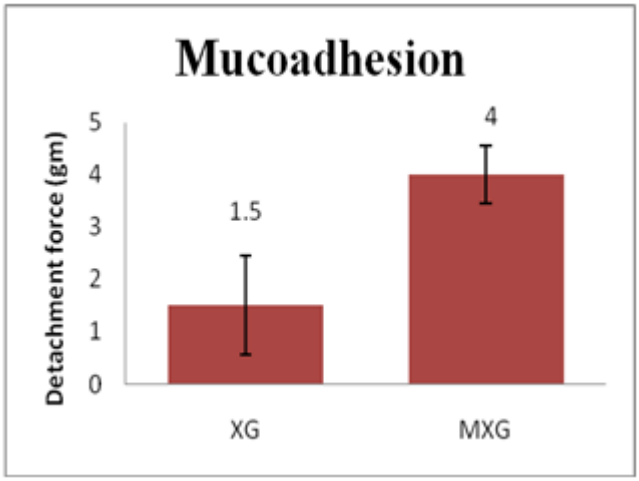


Fig 8. Force of Detachment in gm of XG and MXG

Being responsible for stability and mucoadhesive properties, swelling behavior is a relevant mechanism causing adhesion between the polymer and mucus layer due to swelling, absorbing and capillary process. The swelling behavior has a great impact on the stability, release of embedded drug, adhesive property and cohesiveness[26]. Therefore swelling behavior of XG and MXG were determined. Mucoadhesive polymer swells up by initiating water absorption from the underlying mucosa, which leads to considerable strong adhesion. The MXG showed constant swelling time due to greater cohesiveness. Rapid and constant swelling was observed by MXG. Due to these results, MXG may be allowed for a prolonged drug release and a reduced dosing frequency. Furthermore, the unmodified XG showed uneven water uptake result and over swelling with disintegration of disc after three hours.

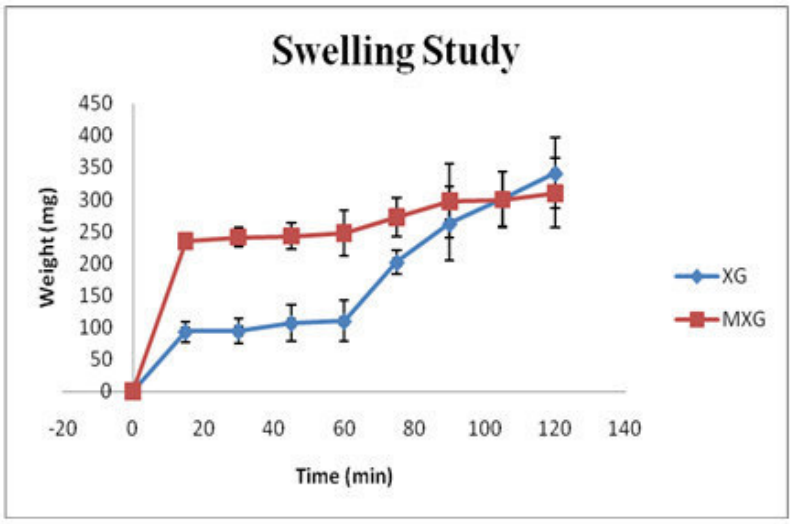


Fig 9. Time dependent water uptake behavior of MXG and XG disc in simulated saliva solution

Swelling behavior is presented in Figure 9 the time dependent water uptake behavior of MXG and XG disc in simulated saliva solution. The gelling property of MXG increased by 2X fold as compared to the unmodified XG. The gel of 1 % of XG was dispersed in the solution within 1 hour; however MXG remains for more than 12 hours.

Table 1. Gelling Property & Gelling Capacity Of Mxg And Xg

	Parameters		XG	MXG
1	Gelling Property (%w/w)	solution	0.2	0.2
		Viscous	0.8	0.4
		Gel	1.2	0.6
2	Gelling Capacity of Solution	L Less than 1 hr	1	0.4
		L Less than 8 hr	-	0.6
		More than 8 hr	-	0.8

As per Table 1 the aqueous solution of XG and MXG showed pseudoplastic flow behavior. However the result of MXG showed enhancement of viscosity. This might be impartment of cationic amine character to its backbone chain, which decreases coulombic repulsion and enhances the entanglement of backbone chain resulting in increasing the viscosity[27].

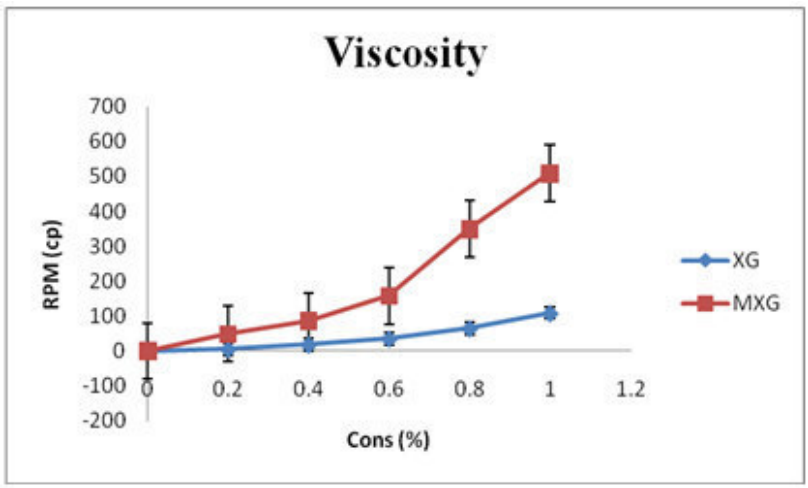


Fig 10. Viscosity of MXG and XG

When shear stress is increased, viscosity is progressively reduced but upon removal of shear, the initial viscosity is recovered as presented in Figure 10. This behavior results from the ability of the MXG molecule, in solution, to form intermolecular aggregates through hydrogen bonding and polymer entanglements. These aggregates are progressively disrupted under the influence of the applied shear, hence the highly pseudoplastic flow characteristics in solution. This property might be providing long term stability to the colloidal system.

3.1 In Vivo Acute Toxicity Study of Poly Sulfoxy Amine Grafted Xanthan Gum

Studies describe xanthan gum as a safe material, inducing low or minimal toxic effect; therefore it is generally recognized as

safe for food application. In the present study, acute oral toxicity of modified xanthan gum was determined according to the OECD guideline 423. The dose was selected from a fixed level 300 mg/kg weight of flow chart. No of moribund or death of animals were observed. At this dose level, from a group of 3 animals, no mortality was observed. Therefore further 2000 mg / kg dose level was studied. As per Table 2 there were no moribund at this level indicates the LD_{50} value of modified XG was more than 2000 mg/kg as depicted in Table .2 . Hence similar to the xanthan gum, modified xanthan gum is also having less acute toxicity.

Table 2: Acute Toxicity of MXG

Dose level (mg/ kg)	No. of mortality
300	Nil
2000	Nil

The Sulfoxy amine XG was successfully synthesized by reacting XG with thionyl chloride and further treated with ammonia. The characterization of modified xanthan gum was difficult to its structural complexibility with the help of FTIR, CHNO, DSC, XRD and SEM spectra showed the modification of XG taken place. Modified xanthan gum may provide cationic character for mucoadhesion, hence showing greater mucoadhesion than xanthan gum. The results of X-ray diffraction study confirms the finding of DSC study. X-ray diffractogram of XG is typical of amorphous substance while that of MXG is typical of crystalline substance with the characteristic peak appearing at 14.79, 25.66, 29.63 & 31.82 2θ. The 0.6% w/v of modified xanthan gum showed gelling property where as xanthan gum required more than 1 % w/v. mucoadhesive strength of modified xanthan gum was found to be 4±0.56 gm which is more than xanthan gum i.e. 1.5±0.94 gm.. Gelling property, gelling capacity and viscosity of MXG were found to be higher than the XG and these features might be utilized in ocular drug delivery. The LD_{50} value of modified xanthan gum was more than 2 g/kg indicated less acute toxicity.

Abbreviation

MXG: Modified Xanthan Gum
XG: Xanthan Gum
FTIR: Fourier Transform Infrared Spectroscopy
CHNO analysis: Carbon, Hydrogen, Nitrogen and Oxygen analysis
DSC: Differential Scanning Calorimetry
XRD :X-ray diffraction
SEM: Scanning Electron Microscopy

4. CONCLUSION

The synthesized Modified Xanthan Gum was characterized by FTIR, DSC, XRD, elemental analysis, SEM analysis and forMucoadhesion, water uptake capacity, viscosity and gelling properties were studied. All properties are in acceptable range. Finally we concluded that the enhanced Mucoadhesion strength and modified swelling features might make the MXG polymer a potential excipient for various Mucoadhesive drug deliveries.

5. FUNDING ACKNOWLEDGEMENTS

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6. ACKNOWLEDGEMENTS

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7. AUTHORS CONTRIBUTION STATEMENT

Dr.Rahul Jadhav did the literature search & performed the research work. Dr. Shaikh Siraj N conceived the presented idea, provided intellectual content, He Performed a part of research work. Manisha Patil performed some evaluation & evaluated the results, reviewed the manuscript. All authors have participated equally in the execution of laboratory study.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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