

Delivery of drugs using tamarind gum and modified tamarind gum: A review

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Review Article

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ABSTRACT

Tamarind seed polysaccharide is an emerging excipient, which is being used and investigated for the preparation of various dosage forms. Functionalization of tamarind gum (TG) enhances the properties of native tamarind polysaccharide like degradability, hydration, viscosity and swelling. Due to these excellent properties, researchers investigated the application of modified TG in various drug delivery systems. TG and modified TG are found to be appropriate for the designing of oral, nasal, ophthalmic, colonic and topical drug delivery systems. Moreover, they are used in the preparation of hydrogel-based drug delivery systems and novel drug delivery systems such as nanoparticles. Considering the above facts, additional research work is required to confirm the pharmaceutical uses of TG and modified TG in drug delivery. The current review deals with a comprehensive and valuable discussion on pharmaceutical applications of TG and modified TG.

Received: 10 July 2018, **Accepted:** 28 December 2018

Key Words: Carboxymethyltamarind gum, modified tamarind gum, tamarind gum.

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Bulletin of Faculty of Pharmacy, Cairo University, ISSN: 1110-0931, Vol. 57, No. 1

1. INTRODUCTION

The attention towards polysaccharides of natural origin is constantly rising since past decade. The natural polysaccharides are widely used in the field of food technology, cosmetics, pharmaceuticals and biomedical sciences. Exploitation of new sources of polysaccharides of different origin is well documented in the literature^[1]. They exhibit good mechanical properties and are widely used as fibers, films, adhesives, rheology modifiers, hydrogels, emulsifiers and drug delivery agents. Sodium alginate

(SA)^[2], xanthan gum (XG)^[3], guar gum, scleroglucan, and locust bean gums are some of the natural polysaccharides which are fueling the interest of the researchers dealing with the development of drug delivery systems^[4]. The functional groups of polysaccharides have been explored for chemical modification to change their properties like solubility, swelling, viscosity, and degradation^[5]. Some of the chemically modified derivatives of natural polysaccharides which are extensively used in drug delivery systems are given in (Table 1).

Table 1: Chemically modified natural polysaccharide

Natural polysaccharide	Chemical modification	Name of derivative	Pharmaceutical application
Sodium alginate	Alkylation	Alkyl-alginate	Release retardant ^[6]
	Thiolation	Thiolated alginate	Mucoadhesive delivery ^[7]
Guar gum	Carboxymethylation	Carboxymethyl guar gum	Transdermal delivery ^[8]
	Grafting	Polyacrylamide-guar gum	GRDF ^[9] Hydrogel ^[10] Matrix former ^[11]
Chitosan	Carboxymethylation sulfation	Carboxymethyl chitosan	Implant ^[12]
	Thiolation	Thiolated chitosan	Micro and Nanoparticles ^[13]
Pectin	Thiolation	Thiolated pectin	Mucoadhesive delivery ^[14]
	Acetylation	Phenyl acetyl pectin	Release retardant ^[15]
Xanthan gum	Carboxymethylation	Carboxymethyl xanthan	microparticles ^[16]
	Grafting	Acrylamide	Controlled release ^[17]

2. TAMARIND GUM - A VERSATILE NATURAL POLYSACCHARIDE

Tamarind (*Tamarindus indica*), usually known as Imli, is a member of the dicotyledonous family, Leguminosae. India produces about 0.3 million tons of tamarind yearly, of which the seed constitutes about 30-34% of the whole fruit. The potential for exporting tamarind from India in the past few years shows a good market for tamarind^[18]. The seed comprises of the seed coat or testa (20-30%) and the kernel or endosperm (70-80%). It contains 67.1 g/Kg crude fiber with a higher percentage of carbohydrate in the form of sugars^[19]. Tamarind seed is the raw material used in the manufacture of tamarind seed kernel powder (TKP), polysaccharide, adhesive and tannin. The seeds

are also used for other purposes and are presently gaining importance as an alternative source of protein, rich in some essential amino acids^[18].

2.1 Chemistry and properties of Tamarind Gum

Tamarind gum (TG) is obtained from the kernel of the seeds powder. Seeds contain 60-65% of a polysaccharide^[20]. It is chemically galactoxyloglucan. TG is a polymer with the average molecular weight of 52350 Daltons. It consists of glucose, xylose and galactose in a molar ratio of 3:2:1^[20,21]. The observed chain length of TG varies from 300-3000 glucose units^[22]. The structure of TG polysaccharide is given in (Figure 1).

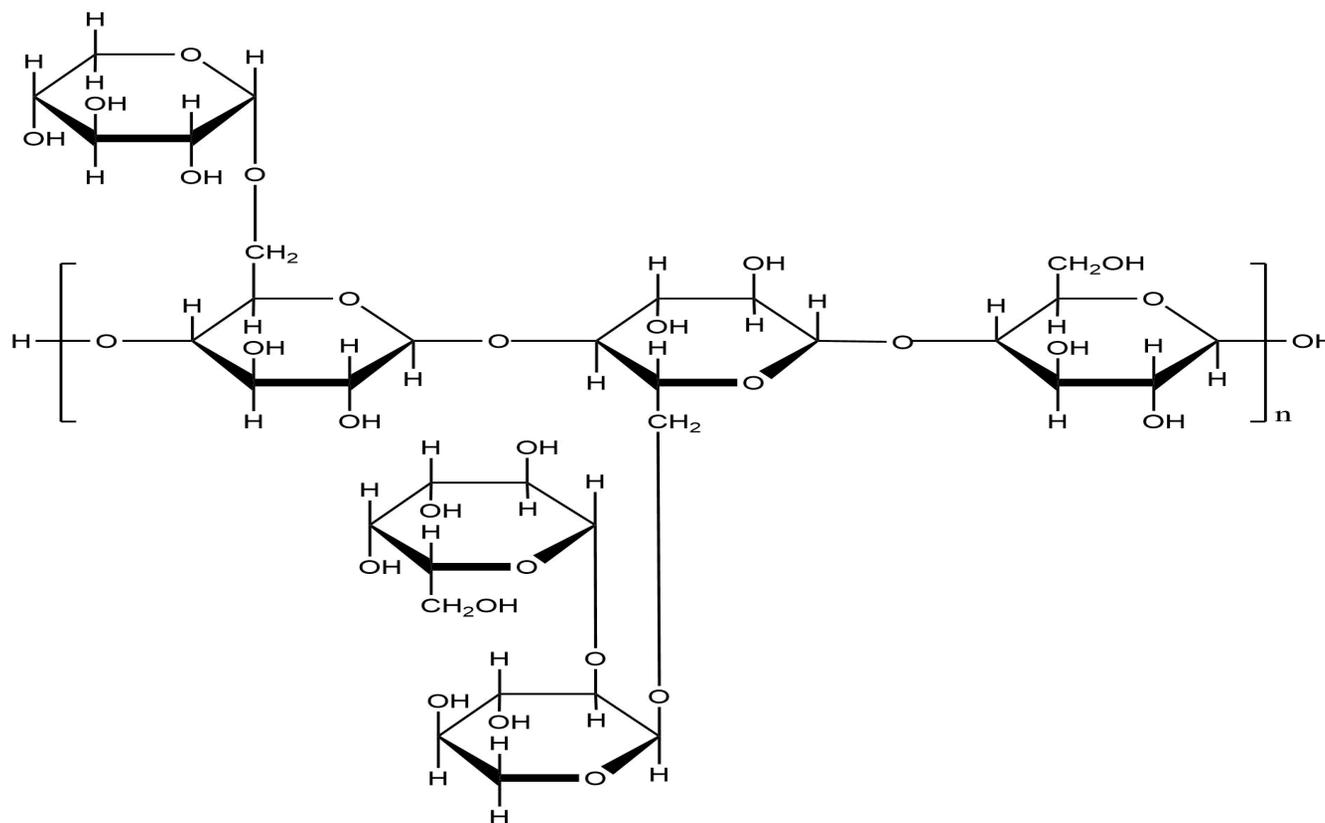


Fig. 1: Structure of TG^[23]

TG is a neutral, nonionic and branched polysaccharide. It is insoluble in organic solvents^[24] and dispersible in hot water to form a highly viscous gel. TG possesses properties like high viscosity, broad pH tolerance, and adhesion^[25]. It is non-carcinogenic^[26], non-toxic^[27,28], mucoadhesive^[29,30], biodegradable^[31] and biocompatible^[32,33] with high drug holding capacity^[25] and high thermal stability^[34]. TG contains cellulose-like backbone that carries xylose and galactoxylose substituents, and chemical residues similar to mucin (MUC-1) and episialin^[35]. TG is able to bind cell surface and intensify the contact between drugs and the adsorbing biological membrane due to similar nature to mucin^[36]. It swells in water and forms a mucilaginous solution after heating, exhibiting a typical non-Newtonian rheological behavior and pseudoplastic properties^[37]. TG

has the capability to form gels in the presence of sugar^[38] or alcohol^[39] and can be used to form pectin like gels in jams, jellies and other preserves. Also, it has the capacity to form ion gel with bio-based ionic liquids^[40]. It produces films with high tensile strength and flexibility^[34] which makes it a good excipient for ocular preparations. This film is transparent, nonhygroscopic, non-sticky and retains its form even on rough handling. Its Ferning pattern is similar to natural tear film^[21]. TG is comparatively cheap, non-irritant, eco-friendly and non-polluting than other semisynthetic or synthetic polymers. Due to its distinct advantageous properties, TG is used as the polymer in the fields of cosmetic and food industry^[4,19,21,41]. Recent studies showed that TG forms an excellent hydrogel by physical crosslinking, which makes it suitable for topical drug delivery^[42,43].

2.3 Isolation and purification of TG

Various methods have been reported in the literature to separate gum from the tamarind seeds^[4,21,44]. Initially, tamarind seeds are washed with water and heated to make outer coat brittle and friable. The seed coat is separated from the endosperm by crushing. The decorticated seed is powdered to obtain TKP. Thereafter, TKP is boiled with about 30-40 times its weight of 2 % w/v citric acid for about 30-40 min with continuous stirring and kept for 12 h in order to precipitate and settle out the proteins and fibers. The supernatant is separated by decantation and concentrated to about half of its volume. The resulting concentrate is mixed with ethanol in the ratio of 1:1 to precipitate seed polysaccharide. Further purification of TG can be done by washing with ethanol and acetone. The tamarind gum so obtained is dried at 50°C for 24 h, powdered and stored in container^[22,45].

3. CHEMICAL MODIFICATION OF TG

Despite being well suited for pharmaceutical application, TG exhibits some potential drawbacks. TG has a dull color and unpleasant odor. Its insolubility in water

and degradation in an aqueous environment has forced the scientists to chemically modify its functional groups^[46]. Various modifications which have been executed till date include carboxymethylation^[47], acetylation^[48], hydroxyl-alkylation^[49] and thiolisation^[50,51]. Such modifications have caused alteration in the solubility, viscosity, swelling and stability of TG.

3.1 Carboxymethylation of TG

Carboxymethyl tamarind gum (CMTG) is the derivative of TG containing carboxymethyl ($\text{CH}_2\text{-COOH}$) groups. It is anionic in nature and used as a sodium salt. Chemically, its structure is similar to TG with addition of carboxymethyl group at C6 position which gives anionic nature to the polymer. Structure of CMTG is given in (Figure 2). Molecular weight of CMTG is approximately $\sim 9.14 \times 10^5$ g/mol with intrinsic viscosity 9.0 dL/g, which is higher than TG^[52]. Molecular weight and viscosity of CMTG may vary with the degree of substitution of carboxymethyl group. Addition of carboxymethyl group increases the hydrophilicity of TG and resists its biodegradation^[47]. CMTG is soluble in cold water^[53].

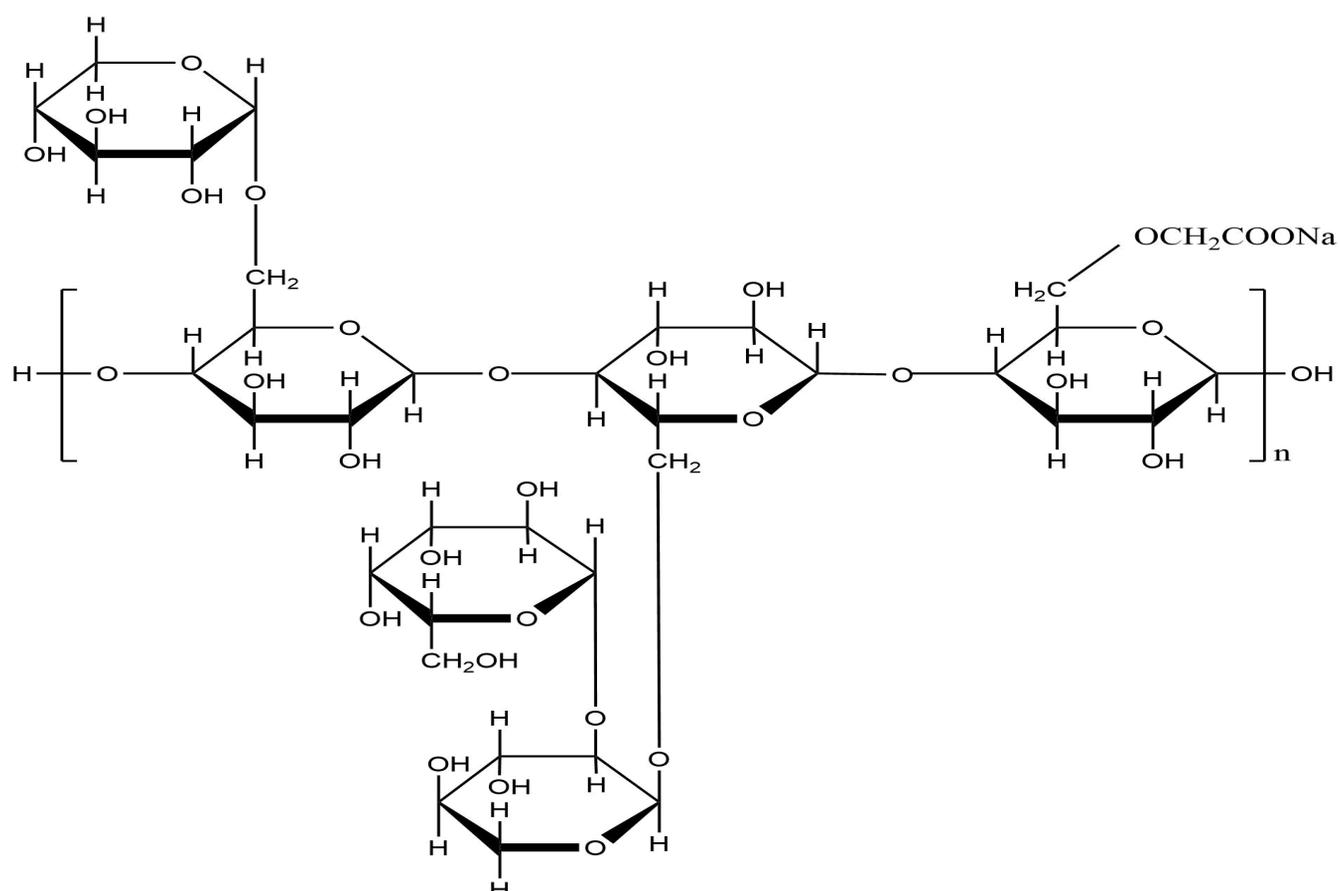
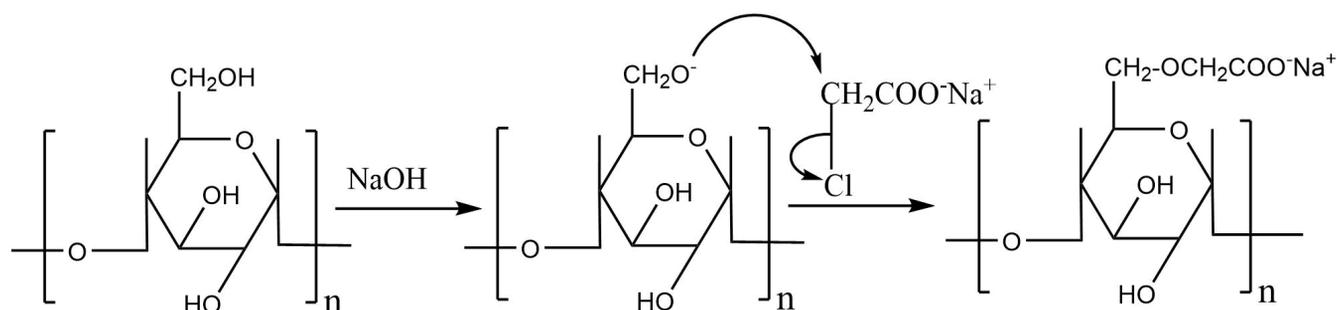


Fig. 2: Structure of carboxymethyl TG^[54].

Carboxymethylation of TG can be done with monochloroacetic acid in the presence of sodium hydroxide as a catalyst. Scheme of carboxymethylation of TG is given in (Figure 3). Carboxymethylation of TG

improves properties of native TG like unpleasant odor, dull color, water solubility, swelling, viscosity, bioadhesion, and biodegradability, thus making it appropriate for pharmaceutical applications^[53].

Fig. 3: Carboxymethylation of TG^[52]

The swelling property of CMTG matrix tablets was studied by using gravimetric method in purified water. CMTG showed greater swelling than TG. The results indicate that an increase in degree of substitution (DS) of CMTG also increases its swellability. The enhancement in the swelling profiles may be due to carboxymethylation. The carboxymethylation of polymer increases the hydrophilicity which improves polymer wetting as well as swelling^[55]. CMTG shows pH dependent swelling. In acidic environment, it has limited swelling while in basic environment it shows high swelling. Being an anionic polysaccharide, the carboxylic acid group of CMTG undergoes protonation at acidic pH which minimizes the repulsive forces between negatively charged carboxylate ions. As a result, the swellability of CMTG is reduced. This property of CMTG is desirable to avoid the release of acid labile drugs in gastric environment^[52]. On the contrary, the basic environment causes deprotonation of carboxylic acid which causes electrostatic repulsion in between the negatively charged carboxylate ions. As a result, the network structure of the polymer may expand and absorb large amount of medium due to increase in its swellability. Such pH dependent swelling of CMTG could be beneficial for oral site specific drug delivery systems.

CMTG shows higher bioadhesion than TG which can be attributed to the highly hydrophilic nature of the polymer. CMTG contains hydroxyl and carboxyl groups

which can form non-covalent bonds with biological tissue, resulting in bioadhesion^[50].

3.2 Cynoethylation of TG

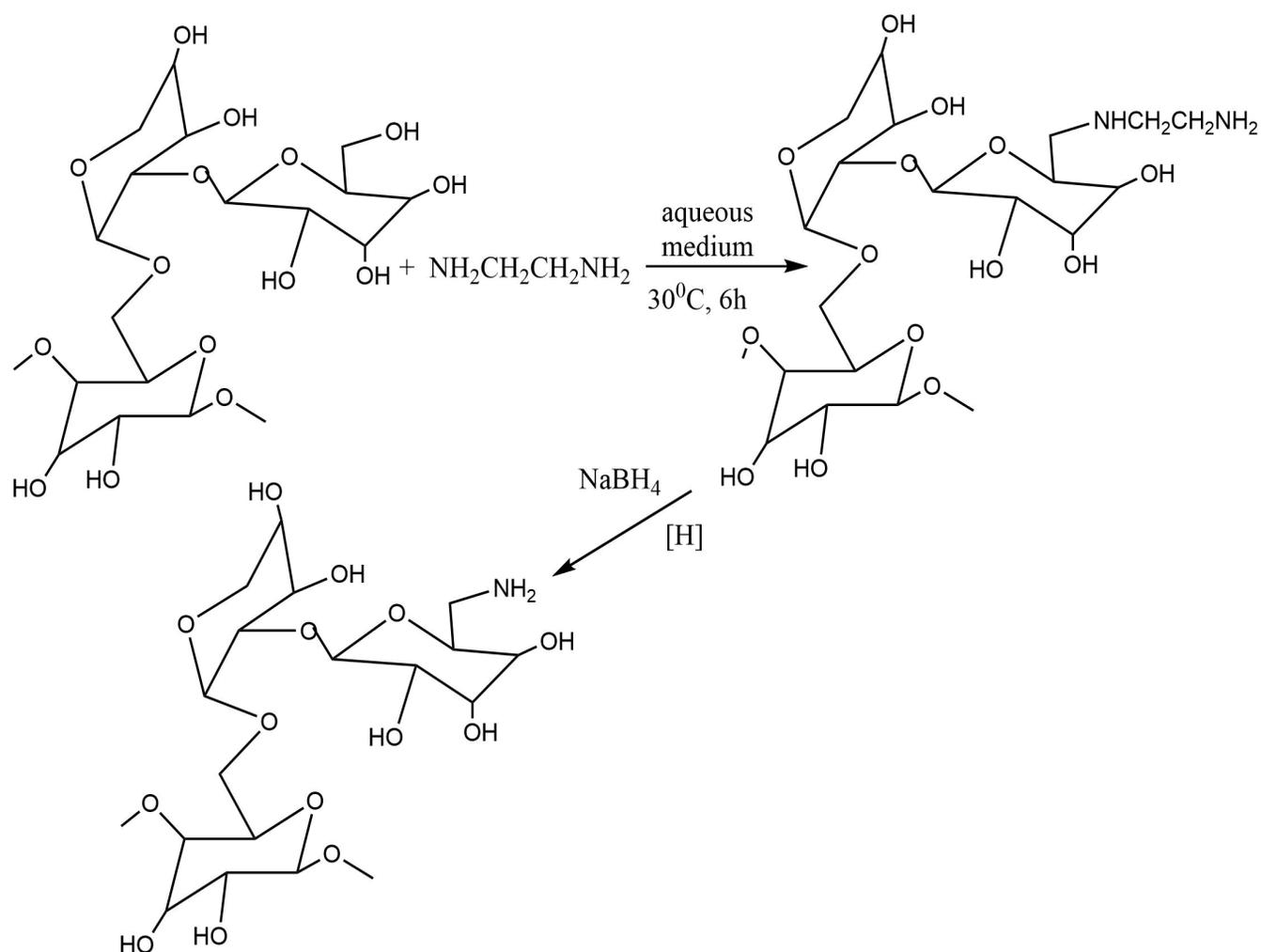
Cynoethylation of TG is performed with acrylonitrile in presence of sodium hydroxide. Cynoethylation improves the properties like cold water solubility, viscosity, and biodegradation of TG. It is used in non-food applications^[56].

3.3 Acetylation of TG

Acetylation of TG can be done with glacial acetic acid and anhydrous sodium acetate. The acetyl derivative of TG is hydrophobic in nature^[48].

3.4 Amination of TG

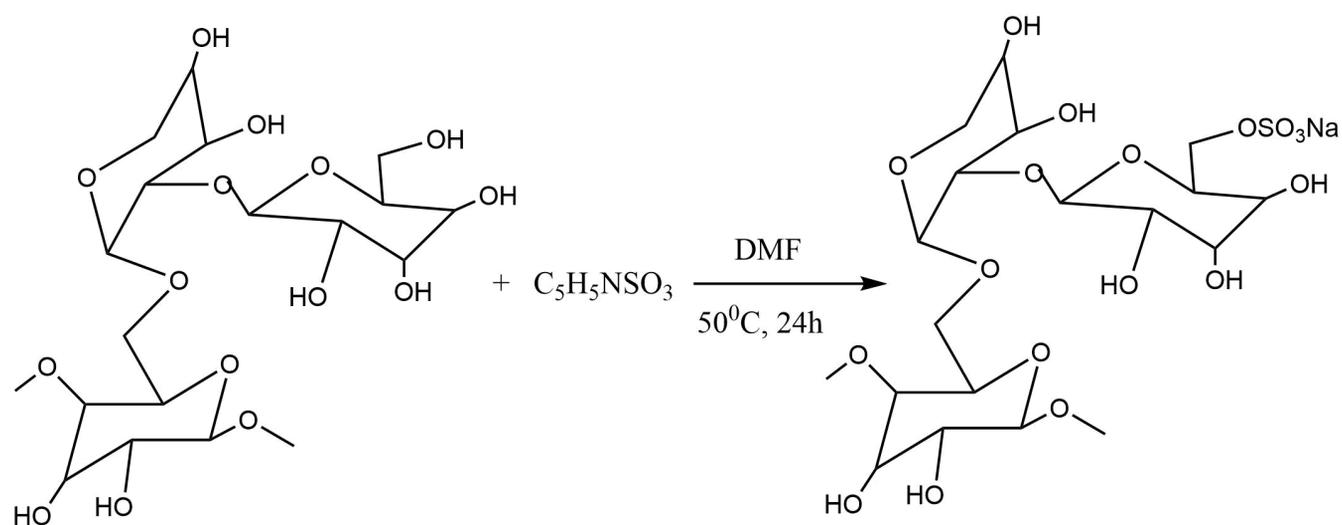
An amine derivative of TG is prepared using ethylene diamine in presence of sodium borohydride as a reducing agent (see Figure 4). It is cationic in nature^[57]. Amination of TG improves properties like hydrophilicity, swelling, and mucoadhesion of TG. Aminated TG forms strong gel in water which can be attributed to the complexation reaction between NH_2 groups and water molecules to form $\text{NH}_3^+\text{-OH}^-$. This interaction aids in the retention of the water molecules inside the matrix of aminated xyloglucan. Also, aminated TG exhibits antimicrobial activity^[58]. Aminated TG shows higher bioadhesion than the sulfated and carboxymethylated TG^[50]. It has been used in the development of buccoadhesive patch of pentazocine^[59].

Fig. 4: Synthesis of aminated TG^[50]

3.5 Sulfonation of TG

A sulfated derivative of TG is prepared using sulfur

trioxide-pyridine complex in presence of DMF and sodium hydrogen carbonate (Figure 5). Sulfated TG may be used as release retardant in bioadhesive drug delivery^[50,51].

Fig. 5: Synthesis of sulfated TG^[50]

3.6 Thiolation of TG

The thiolated TG is synthesized by using thioglycolic acid in presence of hydrochloric acid (Figure 6). The

thiolated derivative is white in color and water soluble with higher mucoadhesion than native TG. It was used in mucoadhesive topical delivery of metronidazole^[60], and oral delivery of acyclovir^[61] and lopinavir^[62].

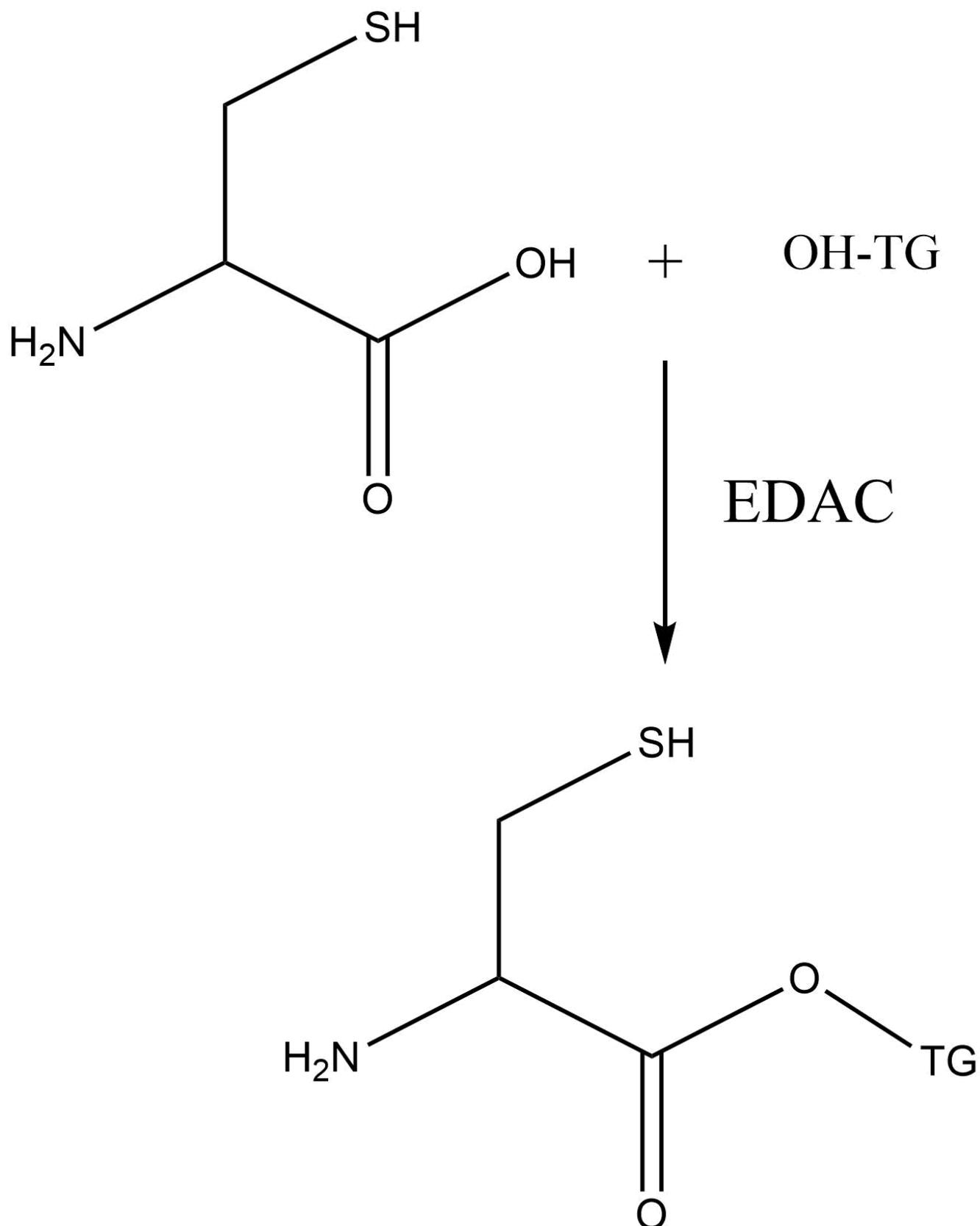


Fig. 6: Scheme for thioated TG^[63]

3.7 Crosslinking of TG

Crosslinked TG can be used as a release retardant or matrix former in sustained or controlled drug delivery. Epichlorohydrin is used for the crosslinking of TG. It is used as a release retardant and matrix former for oral delivery of drugs^[45]. Crosslinked TG has been used to develop matrix tablets of diclofenac^[64] and ketoprofen^[64], and mucoadhesive buccal patch of metronidazole^[65].

3.8 Partially degraded TG

Partially degraded TG is obtained by removing galactose residue from TG using beta-galactosidase enzyme. It shows thermoreversible gelation similar to Poloxamer 407 which makes it a suitable excipient in development of

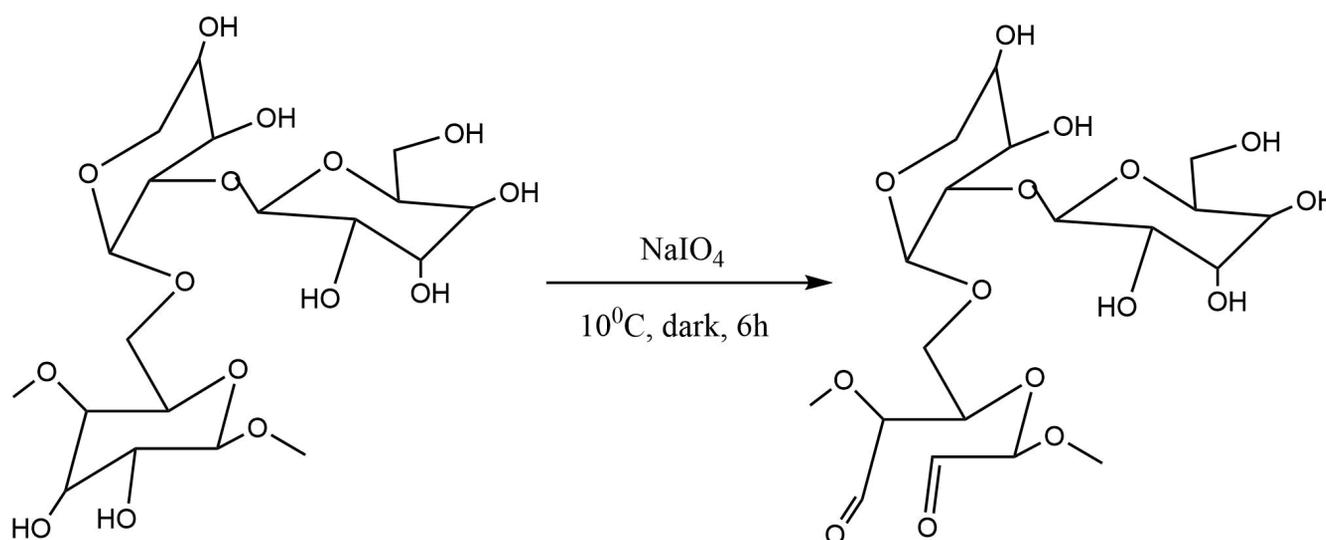


Fig. 7: Synthesis of oxidized TG^[73]

3.10 Graft-modified TG

Grafting of TG with polyacrylamide and poly (N-vinyl-2-pyrrolidone) improves properties like matrix forming ability and mucoadhesion respectively^[74,75]. Ahuja and Verma, (2014) attempted microwave-assisted synthesis of graft copolymer of carboxymethyl tamarind seed polysaccharide and polyacrylonitrile^[76]. The results of swelling study revealed higher swelling of the graft copolymer in acidic and alkaline pH whereas lesser swelling at pH approaching to neutral. It indicates usefulness of graft co-polymer of TG in designing the pH-responsive applications.

4. PHARMACEUTICAL APPLICATIONS OF TG AND MODIFIED TG

4.1 Liquid orals

TG acts as a suspending agent by reducing the settling of particles and promoting the redispersion of settled particles. Paracetamol suspension has been prepared successfully using TG as a suspending agent. It also forms

thermoreversible formulations for ophthalmic, oral, nasal and rectal delivery of drugs^[66]. It has been used to prepare sustained release vehicle for delivery of ibuprofen and ketoprofen^[67], oral sustained delivery of paracetamol^[68] and cimetidine^[69], nasal delivery of ondansetron^[70], rectal delivery of indomethacin and diltiazem^[71], and ocular delivery of pilocarpine^[72].

3.9 Oxidized TG

Oxidation of tamarind gum is carried out in aqueous solution by using periodate as oxidizing agent (see Figure 7). It is used in combination with chitosan to form hydrogels which has application in food and cosmetics^[73].

a stable emulsion at very low concentration^[19,33].

Partially degraded TG has been evaluated as sustained release vehicle for oral administration of indomethacin and diltiazem. The drug loaded aqueous solution was converted into gel in stomach after oral administration and showed Higuchi release kinetics. A threefold increment in the bioavailability of indomethacin was observed as compared to the suspension. The results of this study suggest the potential of the enzyme-degraded TG gels as vehicles for oral sustained delivery of drugs^[77]. Similarly, cimetidine formulations were prepared with partially degraded TG. After oral administration of cimetidine to rabbits, the results of bioavailability were found to be close to the commercial formulation^[69]. In another study, theophylline was investigated for oral sustained delivery in rabbits. The partially degraded TG helped to improve the bioavailability of theophylline by 1.7-2.5 folds as compared to the commercial oral sustained-release liquid dosage forms^[78]. Investigated liquid orals dosage form is listed in (Table 2).

Table 2: Investigated liquid orals based on TG and modified TG

Therapeutic agent	Formulation Type	Technique used	Excipients used	Role of Polymer	Animals used
Paracetamol ^[79]	Suspension	Trituration	TG	Suspending agent	NA
Nimesulide ^[80]	Suspension	Trituration	TG	Suspending agent	NA
NS ^[28]	Emulsion	Wet gum method	TG-ca st or oil	Emulsifying agent	NA
Indomethacin, Diltiazem ^[77]	Liquid-In situ gel	Homogenization	Partially degraded TG	Vehicle for sustained release	Rats
Cimetidine ^[69]	Liquid-In situ gel	Homogenization	Partially degraded TG	Vehicle for sustained release	Rabbits
Theophylline ^[78]	Liquid-In situ gel	Homogenization	Partially degraded TG	Vehicle for sustained release	Rabbits

TG-tamarind gum; NS- Not specified; NA- Not applicable

4.2 Oral drug delivery

4.2.1 Binder and matrix former in tablets

The applicability of TG and modified TG in tablet dosage forms is summarized in (Table 3). TG and modified TG are used as dry binder as well as wet binder (aqueous and non aqueous) to prepare tablets. TG and CMTG have been used as dry binder for development of diclofenac^[81]. TG has been used as a binder for wet granulation and suitable polymer for sustained release of terbutaline sulphate^[82] and diclofenac sodium^[83]. TG and epichlorohydrin crosslinked TG has been investigated for the preparation of sustain release salicylic acid tablets. Crosslinked TG showed propensity to control the release of salicylic acid for extended period of time^[84]. The ability of CMTG to improve the hardness of the tablet is reported by Huanbutta *et al.*, 2016. They found that disintegration time of diclofenac sodium tablets containing CMTG was more than TG^[85]. Matrix tablets of aceclofenac prepared by non aqueous wet granulation, using PVP as binder and TG as release retardant, showed sustained release for period of 12 h with anomalous release mechanism^[86]. Due to the unique properties of TG like hydrophilicity, viscosity and high swelling, it has been used for formation of matrix tablets to achieve controlled release of drugs. TG forms hydrophilic matrix from which drug gets released in sustained or controlled manner for 8 to 24 h. The retardation of drug release from the matrix depends on the physicochemical properties of the drug. It has been used in the development of gastroretentive drug delivery due to its mucoadhesive property. It has also been combined with other polymers like hydropropylmethylcellulose (HPMC) for preparation of matrix tablets^[25]. TG has played an important role in the development of novel formulations like spheroids, microbeads, mucoadhesive microparticles, interpenetrating polymer networks (IPNs), microparticles and floating beads^[19,21].

TG has been explored as matrix former for preparation of sustained release tablet of verapamil HCl. Tablets prepared with TG showed high drug holding capacity. The in vitro release pattern of TG matrix was compared with the matrix of other polymers such as ethyl cellulose (EC), hydroxyethylcellulose (HEC) and HPMC, as well as commercial sustain release tablet. The results indicated a good correlation between in vitro and in vivo studies^[25]. TG has been studied for controlled release behavior of water soluble and water insoluble drugs. Water soluble

drugs showed anomalous release while water insoluble drugs showed near case II or zero order release behavior. It indicates that the release was controlled, by diffusion and erosion mechanism. The diluents like lactose and microcrystalline cellulose (MCC) prominently affected the release kinetics of water soluble and water insoluble drugs^[45]. The drug loading has negative effect on drug release from TG tablets. Compaction pressure and amount of lubricant up to 2% has no significant effect on the rate of drug release from TG tablets^[87].

TG has been used in combination with HPMC, PVP, cellulose acetate phthalate (CAP) and ethyl cellulose (EC) for development of matrix tablets of naproxen^[88] and metformin^[89]. The addition of HPMC in formulation increased the swelling while CAP and EC decreased swelling of the tablets. The prepared tablet showed ability to retard naproxen release over a period of 8h^[88]. The floating tablet of metformin was optimized by Rajab *et al* (2014), using different polymer ratios of PVP, TG, and HPMC. They concluded that the difference in the in vitro performance of tablets is due to the differences in the hydrophilic properties of the polymers and the ability of PVP to interact with HPMC or TG^[89]. This indicates that TG exhibits good release retardant property when used alone or in combination with other hydrophilic polymers.

TKP, acrylic acid, and polyamidoamine were used for the synthesis of pH-responsive polymer, intended for oral controlled release of 5-aminosalicylic acid. The swelling study indicated pH-responsive nature of the synthesized polymer. The in vitro release profiles of drug showed sustained release behavior over a period of time, indicating that the polymeric material could find potential applications for controlled oral delivery of various therapeutic agents^[90].

Due to the upper hand of CMTG over TG, it is widely accepted by the researchers for the preparation of various controlled release systems. CMTG shows low swelling at acidic pH and is highly desirable for its application as drug delivery matrix in the harsh environment of the stomach. The matrix of CMTG remained intact for 24h and showed ability to release the drug at higher pH. From the CMTG matrix, drug is released by non-Fickian release mechanism^[52]. To control burst release from CMTG matrix, CMTG is used in combination with HPMC for delivery of tramadol. The combination of CMTG and HPMC showed good matrix integrity and showed regulated and complete release of tramadol at the end of 10h with anomalous release

mechanism. The results revealed that the HPMC can prevent the initial burst release of drug while CMTG can sustain the drug release at later stage of release profile. The study indicated that appropriate balance between concentration of polymers could give better results^[91]. The mucoadhesive gastroretentive tablet of metformin has been prepared using CMTG. The results indicated that replacement of fraction of CMTG with HPMC in formulation can help to adjust swelling and metformin release while adhesion of swollen tablets remained unchanged^[92]. Hence, CMTG can be used as a matrix former, release retardant and mucoadhesive

agent in the development of oral sustained or controlled drug delivery system.

Further, thiolated CMTG has been used for the gastroretentive delivery of simvastatin, due to its high mucoadhesive nature. Initially, TG is chemically modified to CMTG and converted to thiomers by conjugation with cysteine. The tablets prepared using CMTG thiomers showed linear drug release retardation with increasing amount of thiomers over a period of 8h. Tablets containing highest thiomers concentration showed more drug permeation and highest mucoadhesive strength^[93].

Table 3: Investigated TG and modified TG as binder and release retardant

Therapeutic agent	Formulation type	Technique used	Excipients used	Role of Polymer	Animals used
Diclofenac sodium ^[81]	Tablet	Direct compression	TG, CMTG	Binder	NA
Diclofenac sodium ^[85]	Tablet	Dry granulation	TG, CMTG	Binder	NA
Terbutaline sulphate ^[82]	Tablet	Wet granulation	TG	Binder, release retardant	NA
Diclofenac sodium ^[83]	Tablet	Wet granulation	TG	Release retardant	NA
Salicylic acid ^[84]	Tablet	Direct compression	TG-epichlorohydrin	Release retardant	NA
Aceclofenac ^[86]	Tablet	Wet granulation	TG	Release retardant	NA
Verapamil HCl ^[25]	Tablet	Direct compression	TG	Release retardant	Rabbits
Tramadol ^[94]	Multilayer Tablet	Wet granulation followed by compression	TG	Release retardant, matrix former	NA
Salicylic acid, indomethacin, theophylline ^[45]	Tablet	Direct compression	TG, TG-epichlorohydrin	Release retardant	NA
Caffeine ^[87]	Tablet	Direct compression	TG	Release retardant	NA
Naproxen ^[88]	Tablet	Wet granulation	TG-HPMC, TG-CAP, TG-EC	Matrix former	NA
Metformin ^[89]	Tablet	Wet granulation	TG-PVP-HPMC	Mucoadhesion	NA
5-aminosalicylic acid ^[90]	Film	Crosslinking followed by freeze drying	TG-acrylic acid-polyamidoamine	pH dependent release	NA
Tramadol ^[91]	Tablet	Wet granulation	CMTG-HPMC	Release retardant	NA
Simvastatin ^[93]	Tablet	Direct compression	Thiolated CMTG	Mucoadhesive	NA
Famotidine ^[95]	Tablet	Wet granulation followed by compression	TG-Xanthan Gum	Matrix former	NA
Verapamil HCl ^[96]	Tablet	Non aqueous wet granulation	HPMC-CMTG	Bioadhesive	NA

TG-tamarind gum; CMTG- carboxymethyl tamarind gum; HPMC- hydropropylmethyl cellulose; XG- xanthan gum; NA- not applicable

4.2.2 Interpenetrating networks

Interpenetrating networks (IPNs) is the novel approach used for oral delivery of drugs. The delivery of drug from the TG based matrices can also be controlled by generating IPN structures between TG and suitable polymer within the matrix (see Table 4). Aceclofenac loaded IPN microparticles of chitosan and TG blend has been prepared using glutaraldehyde as a crosslinking agent. IPNs showed sustained release of aceclofenac over a period of 8 h. The *in vivo* studies in carrageenan induced rat-paw oedema model indicated sustained action of aceclofenac loaded IPNs^[97]. The matrix tablets of aceclofenac loaded IPNs showed sustained release over 8h with anomalous diffusion release mechanism. These matrix tablets might be helpful to minimize dosing frequency and reduction of various side effects of aceclofenac during prolong period

of treatment^[98]. TG- sodium alginate (SA) IPNs have been prepared by wet granulation/covalent cross-linking method and ionotropic gelation, for controlled release of propranolol^[99] and diltiazem^[100] respectively. The IPN matrices showed drug release up to 24h with non-Fickian release mechanism. The oral IPN beads of diltiazem exhibited comparatively higher AUC values than the pure drug in rats. It can be inferred that IPNs of TG-SA would be useful matrices for water-soluble drugs.

CMTG has also attracted the scientists dealing with the IPNs based drug delivery. IPNs containing acyclovir has been prepared using CMTG and SA by ionotropic gelation method. The IPNs are spherical in shape with rough surface texture. The CMTG and SA in weight ratio of 3:1 showed maximum drug entrapment. The *in vitro* release data revealed that less than 23% of acyclovir was released

in acidic medium (pH 1.2) followed by faster release of drug in phosphate buffer (pH 6.8). The drug release was controlled by diffusion and swelling kinetics of IPNs with non-Fickian drug release behavior^[101]. The aceclofenac loaded glutaraldehyde crosslinked IPNs has been prepared by using gelatin and CMTG as a polymer. The addition of CMTG in formulation improved the drug entrapment efficiency of the IPNs. The prepared IPNs retarded drug

release in HCl and extended it in phosphate buffer, pH 6.8. The release of aceclofenac from IPNs was dependent upon the extent of crosslinking and concentration of CMTG. The in vitro drug release was controlled by polymer chain relaxation/swelling and simple diffusion. Aceclofenac loaded IPNs showed anti-inflammatory activity for 7 h in albino rats. The results suggest potential application of IPNs of gelatin-CMTG in oral controlled drug delivery^[102].

Table 4: Investigated TG and modified TG based IPNs

Therapeutic agent	Formulation type	Technique used	Excipients used	Role of Polymer	Animals used
Aceclofenac ^[97,98]	IPNs, (Tablet)	covalent cross linking followed by direct compression	TG-CH (GA)	Release controlling agent	Rat
Propranolol ^[99]	IPNs, (Tablet)	Wet granulation/covalent cross linking	TG-SA (GA)	Release retardant	NA
Diltiazem ^[100]	IPNs (beads)	Ionotropic gelation and covalent cross linking	TG-SA (CaCl ₂ and GA)	Release retardant	Rats
Aceclofenac ^[102]	IPNs	covalent cross linking followed by freeze-drying	CMTG-Gelatin (GA)	Release retardant	Rats
Acyclovir ^[101]	IPNs	Ionotropic gelation	CMTG-SA (CaCl ₂)	Release controlling agent	NA
Aceclofenac ^[103]	IPNs	covalent cross linking	CMTG-CH	Release retardant	NA

TG-tamarind gum; SA-sodium alginate; CH-chitosan; GA-glutaraldehyde; CMTG-carboxymethyl tamarind gum; NA- not applicable

4.2.3 Hydrogels

Hydrogels are three dimensional crosslinked polymeric network structures which are highly porous and have tendency to absorb aqueous medium without getting dissolved in it. Due to the unique properties of hydrogels, they are widely used in drug delivery^[104]. TG and modified TG have been used, alone or in combination with other polymers, by various researchers for the preparation of hydrogel-based drug delivery systems (see Table 5). Moxifloxacin loaded TG based hydrogels has been prepared by physical gelation method. TG was used in the concentration range of 10 to 25 % w/w. Drug loaded TG solutions were heated on water bath at 70 °C for 5 minutes and stored at 5 °C for 2h. TG hydrogels were thermostable in nature and formed spreadable hydrogels. The prepared hydrogels have capacity to retard drug release for longer time in its active form and showed good antimicrobial activity^[42]. Further, TG has been used

in combination with carboxymethylcellulose (CMC) for synthesis of citric acid crosslinked hydrogel dressings. The prepared hydrogel dressing showed pH dependent swelling and high vancomycin loading with non-Fickian release. Hydrogel dressings were hemocompatible and exhibited marked wound healing activity in mice^[105].

The phase-separated hydrogels containing ciprofloxacin has been prepared by using gelatin and CMTG. The hydrogels were prepared by using glutaraldehyde as a crosslinking agent. Microstructural analysis suggested the formation of phase-separated hydrogels. The prepared hydrogel exhibited good mucoadhesivity, biocompatibility and pH-dependent swelling behavior. The drug loaded hydrogels showed good antimicrobial activity and the drug release from the hydrogel was pH dependent and diffusion controlled. The release study indicated that the gelatin-CMTG based phase separated hydrogels can be effectively used as vehicle for the enteric drug delivery^[106].

Table 5: Investigated TG and modified TG based hydrogels

Therapeutic agent	Formulation type	Technique used	Excipients used	Role of Polymer	Animals used
Moxifloxacin ^[42]	Hydrogel	Physical gelation	TG	Matrix former	NA
Vancomycin ^[105]	Hydrogel film	Chemical crosslinking	TG-CMC (CA)	Matrix former	mice
Moxifloxacin ^[107]	Hydrogel film	Chemical crosslinking	TG-CMC (CA)	Matrix former	NA
Ciprofloxacin ^[106]	Phase separated hydrogels	Solution casting, Covalent crosslinking	TG-gelatin CMTG-gelatin (GA)	Mucoadhesive, Vehicle for enteric drug delivery	NA
Metronidazole ^[108]	Cryogel	Physical crosslinking	CMTG-PVA	Release controlling agent	NA
Moxifloxacin ^[54]	Hydrogel film	Chemical crosslinking	CMTG	Matrix former	NA
Aspirin ^[74]	Hydrogel tablet	Microwave assisted grafting, Wet granulation	TKP-g-PAM	Matrix for pH dependent release	NA
NS ^[109]	Hydrogel	Grafting	CMTG-HEMA	Matrix for Bone tissue engineering	NA
NS ^[110]	Hydrogel	copolymerization	CMTG-g-Polyacrylonitrile	adsorbant	NA

TG-tamarind gum; CA- citric acid; CMTG-carboxymethyl tamarind gum; CMC- carboxymethylcellulose; GA-glutaraldehyde; PVA-polyvinyl alcohol; NA- not applicable; NS- not specified

The metronidazole loaded composite hydrogels of CMTG and polyvinyl alcohol has been prepared by freeze thaw-treatment. The higher concentration of CMTG increases drug release while higher levels of PVA in cryogels favors sustained release of drug. The optimized cryogel showed maximum swelling up to 600%, lesser degree of crystallinity and enhanced thermal stability than the individual polymers. The prepared cryogels released 75% of metronidazole over period of 6 h following the Higuchi release kinetics. The result suggests potential application of CMTG-PVA cryogels in drug delivery^[108]. Hydrogel has also been prepared by grafting hydroxyethyl methacrylate (HEMA) on CMTG. The prepared hydrogel material was suitable for effective adhesion, growth and further clustering of bone precursor cells. The hydrogel was compatible for growing cells. Hydrogel made of CMTG:HEMA at a ratio of 1:10 can be suitable for bone tissue engineering and thus may have clinical as well as commercial application in the future^[109].

4.2.4 Spheroids and pellets

Besides tablet dosage form, TG and CMTG have also been used for the preparation of drug loaded spheroids and pellets (see Table 6). The spheroids of diclofenac have

been prepared using TG as release modifier and MCC as filler. Extrusion spherization technique has been used for the preparation of spheroids. The in vitro release studies exhibited zero-order release kinetics. The bioavailability study indicated that the developed spheroids have ability to sustain the drug release over 8 h and could improve the extent of absorption and bioavailability of the drug^[111]. Sustained release tablet of lornoxicam has been prepared by extrusion/spherization using CMTG and MCC. The prepared spheroids showed good flow properties due to their spherical shape. The formulation with 10% w/w CMTG sustained the release of lornoxicam over a period of 12h. The results suggest the potential use of CMTG and MCC blends for the development of controlled drug delivery systems^[112]. Also, CMTG has been used for the development of lansoprazole^[113] and curcumin^[114] pellets using extrusion-spherization technique. MCC was used as filler in combination with CMTG for preparation of pellets. Solid dispersion pellet prepared with CMTG showed two fold increase in the oral bioavailability of curcumin in rats than the pellet of pure drug. These studies indicate the industrial suitability of CMTG in development of pharmaceutical formulations by extrusion-spherization technique.

Table 6: Investigated TG and modified TG based spheroids and pellets

Therapeutic agent	Formulation type	Technique used	Excipients used	Role of Polymer	Animals used
Diclofenac ^[111]	Spheroids	Extrusion spherization	TG-MCC	Release retardant	NA
Lornoxicam ^[112]	Pellets	Extrusion spherization	CMTG-MCC	Release retardant	NA
Lansoprazole ^[113]	Pellets	Extrusion spherization	CMTG-MCC	Release retardant	NA
Curcumin ^[114]	Pellets	Extrusion spherization	CMTG-MCC	Carrier	Rats
Ibuprofen ^[115]	Pellets	Extrusion spherization	CMTG-MCC	Carrier	NA

TG-tamarind gum; MCC-microcrystalline cellulose; NA- not applicable

4.2.5 Microbeads

Table 7 summarizes the application of TG and CMTG in microbead formulations. TG is used for the development of pH-sensitive microbeads in combination with SA^[116], gellan gum^[117] and pectin^[118]. pH-sensitive composite beads of TG and sodium alginate/ gellan gum for controlled release of diclofenac sodium^[119] and metformin^[116] have been prepared by ionotropic gelation method using calcium chloride as a crosslinking agent. TG-polymer beads showed high drug encapsulation and good mucoadhesivity. Microbeads showed pH dependent swelling with minimum swellability in 0.1N HCl and high swellability in phosphate buffer of pH 6.8 or 7.4. Microbeads showed tendency to control the drug release

for prolonged period. From microbeads, drug is released by swelling and relaxation of the matrix^[119]. The in vivo studies of Metformin loaded mucoadhesive microbeads showed prolonged (10 h) anti-diabetic effect in alloxan induced diabetic rats due to retention of microbeads in stomach^[116-118]. Further, TG is utilized in development of floating microbeads. Alginate gel-coated oil-entrapped calcium alginate-TG-magnesium stearate composite floating beads have been used for intragastric risperidone delivery. The beads exhibited superior buoyancy and sustained drug release property. The drug is released by the anomalous diffusion driven mechanism. The composite beads are suitable for intragastric delivery of risperidone over a prolonged period of time^[120].

Table 7: Investigated TG and modified TG based microbeads

Therapeutic agent	Formulation type	Technique used	Excipients used	Role of Polymer	Animals used
Metformin ^[116]	beads	Ionotropic gelation method	TG-SA (CaCl ₂)	Mucoadhesive,	Rats
Metformin ^[117]	beads	Ionotropic gelation method	TG-gellan (CaCl ₂)	Mucoadhesive,	Rats
Metformin ^[118]	beads	Ionotropic gelation method	TG-Pectin (CaCl ₂)	Mucoadhesive,	NA
Diaclofenac ^[119]	beads	Ionotropic gelation method	TG-SA (CaCl ₂)	Matrix former	NA
Risperidone ^[120]	Floating microbeads	Ionotropic emulsion gelation	TG-SA (CaCl ₂)	Matrix former	NA
Aceclofenac ^[121]	microbeads	Free radical polymerization, Ionic crosslinking	Polyacrylamide-g-CMTG (ferric ion)	pH responsive release	NA

TG-tamarind gum; SA-sodium alginate; CMTG-carboxymethyl tamarind gum; NA- not applicable

4.2.6 Microspheres

Very few reports are available on the applicability of TG and modified TG in the microparticle based drug delivery systems (see Table 8). TG has been used in combination with alginate for preparation of mucoadhesive microspheres for oral gliclazide delivery. Ionotropic gelation method was used for the preparation of microspheres. Calcium chloride was used as a crosslinker. The gliclazide loaded TG-alginate microspheres showed prolonged in vitro release over 12 hours at gastric and intestinal pH conditions. The release of gliclazide in gastric pH was comparatively slow and sustained than intestinal pH. TG-SA microspheres exhibited good mucoadhesivity. After an oral administration of TG-alginate microspheres to the alloxan-induced diabetic rats, a significant hypoglycemic effect was observed^[122].

Glipizide loaded sodium trimetaphosphate crosslinked

Table 8: Investigated TG and modified TG based microspheres

Therapeutic agent	Formulation type	Technique used	Excipients used	Role of Polymer	Animals used
Gliclazide ^[122]	Oral microparticles	Ionotropic gelation	TG-SA (CaCl ₂)	Mucoadhesive	Rats
Glipizide ^[123]	Oral microparticles	w/o emulsification	Thiolated TG (STMP)	Permeation enhancer	Rats
Lopinavir ^[62]	Oral microparticles	Ionotropic gelation method	Thiolated TG-SA (CaCl ₂)	Mucoadhesive	Rats

TG-tamarind gum; STMP-sodium trimetaphosphate; NA- not applicable

4.2.7 Nanoparticles

In last few years, TG and modified TG have been used for the preparation of nanoparticles (see Table 9). Mucoadhesive nanoparticles of TG-SA were prepared for the oral sustained delivery of anticancer drug, irinotecan. The drug-loaded nanoparticles were prepared by ion-gelation method using calcium chloride as crosslinking agent. The in vitro drug release profile showed initial burst release followed by controlled release pattern, showing up to 60% drug release in 12h. TG may be suitable for formulation of mucoadhesive nanoparticles for better efficacy and sustained delivery of irinotecan with reduced toxicity^[124].

The ciprofloxacin loaded CMTG nanoparticles were synthesized by ionotropic gelation method using magnesium chloride as a crosslinker. The prepared nanoparticles were ovoid in shape. The concentration of CMTG and crosslinker had a positive effect on encapsulation efficiency. The antibacterial assay results revealed greatest zone of inhibition by ciprofloxacin-

mucoadhesive microspheres were prepared using TG and thiolated TG by w/o emulsification method. Thiolated TG microspheres showed high entrapment efficiency and mucoadhesion than TG microspheres. Microspheres prepared with thiolated TG controlled drug release over a period of 8h and showed better control of blood sugar in alloxan induced diabetic rats. Hence, thiolated TG offers a better polymer for multiparticulate drug delivery systems^[123].

Mucoadhesive microspheres of lopinavir have been prepared using thiolated TG and SA by ionotropic gelation method. The in vitro release profile showed that the microspheres have ability to control release up to 6 h and follows case I type of release behavior. The study indicated improvement of lopinavir bioavailability in rats due to absorption enhancing effect of thiolated TG^[62].

loaded CMTG nanoparticles in *Micrococcus luteus*. The results of cytotoxicity study indicated minimum toxic nature of ciprofloxacin-loaded CMTG nanoparticles^[125].

Besides, silver nanoparticles (AgNP) have been prepared by in situ reduction and capping with CMTG. The prepared nanoparticles exhibited average particle size of ~20-40 nm and showed long time stability. These AgNPs inhibit the growth and biofilm formation of both Gram positive and Gram negative bacterial strains even at low concentration of antibiotics. CMTG-capped AgNPs have potential for bio-medical application against multi-drug-resistant microbes, with minimal cytotoxicity towards mammalian cells^[126].

Aminated TG forms self-assembled spherical nanoparticles of 60 nm size at a very low concentration (0.2%, w/v) in an aqueous medium and forms strong hydrogel. The TG-NH₂ shows better antimicrobial activity in comparison to chitosan. This modified TG has potential applications in the medical and bionics field because it possesses biocompatibility and strong hydrogel behavior

with very useful blue fluorescence^[58]. Acyclovir loaded thiolated TG nanoparticles have been prepared using sodium trimetaphosphate as a crosslinker. The prepared acyclovir nanoparticles have showed high drug entrapment and mucoadhesion. The *in vitro* drug release behavior

indicated sustained release of acyclovir from nanoparticles over a period of 8 h. The *in vivo* study in rats indicated improvement in bioavailability of acyclovir compared to the marketed formulation^[61].

Table 9: Investigated TG and modified TG based nanoparticles

Therapeutic agent	Formulation type	Technique used	Excipients used	Role of Polymer	Animals used
Irinotecan ^[124]	Oral nanoparticles	Ionotropic gelation method, homogenization followed by lyophilization	TG-SA (CaCl ₂)	Mucoadhesive	NA
Acyclovir ^[61]	Oral nanoparticles	Mechanical stirring followed by lyophilisation	Aminated TG (STMP)	Mucoadhesive	Rats
Silver ^[126]	nanoparticles	Situ reduction and capping	CMTG	Carrier	NA
Ciprofloxacin ^[125]	nanoparticles	Ionotropic gelation method followed by lyophilization	CMTG (MgCl ₂)	Carrier	NA

TG-tamarind gum; CMTG-carboxymethyl tamarind gum; STMP- sodium trimetaphosphate; NA- not applicable

4.2.8 Solid dispersion

TG has also been explored to enhance solubility of aceclofenac, atorvastatin and irbesartan by solid dispersion technique. Satle and Agrawal (2012) suggested that the proper use of TG can enhance solubility of poorly soluble drugs^[127]. Further, effect of method of preparation of solid dispersion on dissolution rate of celecoxib has been studied using TG. Solid dispersions have been prepared using co-grinding method, kneading method and solvent deposition. Dissolution rate of drug was increased as the TG concentration increased and optimum weight ratio was found to be 1:4 (drug:TG). Among all the methods, though the solvent deposition technique improved the dissolution rate to maximum, co-grinding technique was found to be suitable from practical point of view and commercialization^[128].

4.3 Buccal drug delivery

TG can be used in the formulation of buccal drug delivery systems like buccal tablets, buccal films, and buccal patches (see Table 10). TG shows buccoadhesive property and ability to control release over a period of 8h. TG has been used in buccal drug delivery of various drugs

like rizatriptan benzoate^[129], nifedipine^[130], nitrendipine^[131], benzydamine^[32], lidocaine^[23] and metronidazole^[19,21]. Simple compression method has been used to prepare mucoadhesive buccal patches of benzydamine and lidocaine. The patch is adhered for more than 8h to buccal mucosa and showed controlled drug release^[32]. The metronidazole loaded epichlorohydrin crosslinked mucoadhesive patches of TG have been prepared by solvent casting method for buccal delivery. Drug loaded patches showed adequate mucoadhesive strength. More than 70 % of drug got diffused across the semi-permeable membrane at low concentration of plasticizer and crosslinker. So, TG can be well utilized to develop buccal drug delivery system with optimum mucoadhesive strength^[65]. Buccal bioadhesive patches of pentazocine hydrochloride have been prepared by employing aminated and sulfated derivatives of TG. The *in vitro* release of the drug was found to be dependent on the swelling index of polymers. The sulfated TG patch released drug at a faster rate as compared to the aminated TG patches. The oral administration of aminated patches to rats was found to enhance the bioavailability of pentazocine hydrochloride 2.8 times as compared to the oral solution^[59].

Table 10: Investigated TG and modified TG based buccal drug delivery systems

Therapeutic agent	Formulation type	Technique used	Excipients used	Role of Polymer	Animals used
Rizatriptan benzoate ^[129]	Buccal Film	Solvent casting	TG-Carbopol 934	Bioadhesive	NA
Nifedipine ^[130]	Tablet	Direct compression	TG-Carbopol 934	Mucoadhesive, Matrix former	NA
Nitrendipine ^[131]	Tablet	Wet granulation	TG- Z. Mauritiana mucilage	Mucoadhesive, release retardant	NA
Benzzydamine, lidocaine ^[32]	Buccal patch	Direct compression	TG	Mucoadhesive	NA
Metronidazole ^[65]	Buccal patch	Solvent casting	TG-Epichlorohydrine	Mucoadhesive	NA
Pentazocine hydrochloride ^[59]	Buccal Film	Solvent casting	Aminated TG	Mucoadhesive	Rabbits

TG-tamarind gum; NA- not applicable

4.4 Ophthalmic drug delivery

The high viscosity and mucoadhesive nature of TG make it a suitable excipient in development of ocular formulations (see Table 11). These properties of TG improve residence time of drug in ocular cavity. TG is used in the formulation of mucoadhesive gels and nanoparticles. Pilocarpine, rufloxacin and ofloxacin have been successfully investigated for ocular drug delivery

using TG^[19,21,132]. TG has been used as a viscosity modifier and mucoadhesive agent in the preparation of ocular timolol formulations. In rabbit model, TG has improved duration of action of timolol and proved to be suitable for ocular administration in cases of elevated intraocular pressure^[133]. Further, gentamicin and ofloxacin ophthalmic solutions have been prepared using TG as a mucoadhesive agent and investigated for the bioavailability enhancement

in rabbit model. The viscous preparation of TG improved the drug absorption and decreased the drug elimination indicating its suitability for the ophthalmic delivery of antibiotics^[35]. TG prolongs the precorneal residence time of rifloxacin, improves drug residence in the cornea and acts as a vehicle for the ocular treatment of bacterial keratitis in rabbit model^[134]. TG is also found to be suitable for maintaining wetness in eyes. The study performed by Rolando and Valente (2007) in 30 patients, suggested that the 1% TG is suitable for frequent use in the therapy of dry eye syndrome^[135]. Further, study was designed to investigate the potential clinical benefit of a combination of hyaluronic acid and TG-polysaccharide in managing dry eye disease (DED). Total 49 subjects with DED were used in the study. Patients treated with hyaluronic acid and TG showed statistically significant improvement in the Ocular Surface Disease Index score compared to the baseline and control groups. The results of this clinical trial indicated the combination of hyaluronic acid and TG appears to be effective in improving the symptoms of dry eye^[136].

The in situ gelling system of dorzolamide hydrochloride has been formulated using CMTG, xanthan gum, SA and gellan gum in order to improve the precorneal retention and improve ocular bioavailability. All formulations were converted into gel when exposed to artificial tear fluid (pH 7.4) within one minute and are found to be pseudoplastic

and mucoadhesive in nature, which improves corneal retention of drug. The CMTG based gels showed sustained release of drug over a period of 8h. Optimized formulations showed good physical stability after sterilization and were found to be nonirritant with no ocular damage in ocular irritancy test on rabbits. Isotonicity studies revealed that formulations are isotonic with that of blood cells. The proposed in situ gel of drug has feasibility to form gel when in contact with the tear fluid and may be a viable alternative to the conventional eye solutions^[137].

Dilbaghi and co-workers (2013) have prepared tropicamide loaded nano-aggregates prepared for ophthalmic delivery. TG and Poloxamer 407 were used as polymers. Tropicamide loaded TG nano-aggregates showed high mucoadhesion and a high corneal permeation as compared to commercial formulation^[138]. Ophthalmic CMTG nanoparticles of tropicamide were prepared by ionotropic gelation method using calcium chloride as crosslinking agent. The concentration of CMTG and crosslinking agent showed positive effect on particle size and drug encapsulation efficiency. The result of ex vivo corneal permeation of tropicamide across isolated goat cornea from CMTG nanosuspension was comparable to the aqueous drug solution. Further, the ex vivo bioadhesion and ocular tolerance test revealed the mucoadhesive nature of the nanoparticles^[139].

Table 11: TG and modified TG based ophthalmic drug delivery systems

Therapeutic agent	Formulation type	Technique used	Excipients used	Role of Polymer	Animals used
Timolol ^[133]	Aqueous solution	Simple mixing	TG	Viscosity modifier, mucoadhesive	Rabbits
Timolol ^[140]	Film	Molding	TG	Film former, release modifier	Rabbits
Gentamicin Ofloxacin ^[35]	Aqueous solution	Simple mixing	TG	Viscosity modifier, mucoadhesive	Rabbits
Rufloxacin ^[134]	Aqueous solution	Simple mixing	TG	Viscosity modifier, mucoadhesive	Rabbits
Pilocarpine ^[132]	In-situ gel	Simple mixing	SA-TG	Improve gel consistency	Rabbits
Tropicamide ^[138]	Nano-aggregates	Magnetic stirring with lyophilization	TG-Poloxamer 407	Mucoadhesive	NA
Tropicamide ^[139]	Nanoparticles	IGM with lyophilization	CMTG-CaCl ₂	Mucoadhesive	NA
Dorzolamide hydrochloride ^[137]	In situ gel	Simple mixing	CMTG-XG, CMTG-GG	Gelling agent	Rabbits

IGM-Ionotropic gelation method; TG-tamarind gum; SA-sodium alginate; XG-xanthan gum; GG-gellan gum; CMTG- carboxymethyl tamarind gum; NA- not applicable

4.5 Nasal drug delivery

TG and CMTG have been used in the development of nasal gels and mucoadhesive thermoreversible gels (see Table 12). Drugs like diazepam, zolmitriptan, ketorolac tromethamine and venlafaxine have been investigated for nasal drug delivery^[19,141]. Nasal gel of diazepam has been prepared using natural mucoadhesive agent, TG. It has been observed that the mucoadhesive strength, viscosity and gelling property of TG was higher than HPMC and carbopo 1934. The results suggested that due to the presence of numerous carboxyl and hydroxyl groups, TG adopts more favorable macromolecular conformation favorable for mucoadhesion than HPMC and carbopol 934. HPMC

may form a weaker bond with mucus, which is due to less number of available hydrogen bonding sites or unfavorable condition for entanglement. The in vitro drug release from TG containing formulation was greater than the synthetic polymers^[142].

Zolmitriptan and Ketorolac tromethamine loaded thermoreversible in situ mucoadhesive intranasal gels were prepared for migraine therapy. Thermoreversible gel was prepared by cold method using Poloxamer 407 as a thermoreversible polymer and TG and SA as mucoadhesive polymers. TG containing formulations showed anomalous drug release and were found to be safe for nasal administration. Pharmacokinetic study in

rabbits showed improved nasal bioavailability of drug over oral route^[143]. Recently, it has been proved that mucoadhesive microparticles (10 μ m) of TG can achieve selective deposition and retention of drug in the olfactory mucosa^[144].

Thermoreversible gel formed by partially degraded TG has been used for nasal delivery of ondansetron. The partially enzyme degraded TG of 2.5% w/w formed gels at 25–30°C. The in vitro release of ondansetron hydrochloride

from the enzyme degraded TG gels followed Higuchi kinetics over a period of 5 h at 34°C by anomalous transport mechanism. Histological examination of nasal mucosa following a single administration of the gels showed no evidence of mucosal damage. Absolute bioavailability of ondansetron hydrochloride was significantly increased from 28.64% in case of the oral drug solution to 52.79% in case of the nasal in situ gel in rabbits. The results of this study suggest the potential of the enzyme-degraded xyloglucan gels as vehicles for nasal delivery of drugs^[70].

Table 12: Investigated nasal drug delivery systems based on TG and modified TG

Therapeutic agent	Formulation type	Technique used	Excipients used	Role of Polymer	Animals used
Diazepam ^[142]	Gel	Magnetic stirring	TG	Gelling agent, Mucoadhesive, viscosity modifier	NA
Zolmitriptan and tromethamine ^[143]	Thermoreversible gel	Cold method	TG-Poloxamer 407	Mucoadhesive	Rabbits
Ketorolac	Thermoreversible gel	Cold method	TG-Poloxamer 407	Mucoadhesive	NA
Venlafaxine hydrochloride ^[141]	Thermoreversible gel	Cold method	Partially degraded TG	Vehicle	Rabbits
Ondansetron ^[70]	Thermoreversible gel	Cold method	CMTG- Poloxamer 407	Mucoadhesive	NA
Granisetron HCl ^[145]	Thermoreversible gel	Cold method			

TG-tamarind gum; NA- not applicable

4.6 Colon targeted drug delivery

The ability of TG to degrade in colon makes it a suitable polymer for development of colon targeted drug delivery. Ibuprofen drug has been studied using TG for colon targeting. The results of in vitro drug release study indicate that the matrix tablets prepared by using TG are able to carry most of the drug to the colon and restrict the release in upper GIT^[146]. The tablet coated with chitosan-CMTG interpolymer complex has been prepared for colon drug delivery of budesonide. The complex was used as a binder in tableting and tablets were coated with complex. The interpolymer complexed (IPC) film showed swelling in acidic medium as well as in basic medium. High swelling in acidic environment was observed due to the protonation and repulsion in between free ammonium groups of chitosan. The tablets coated with interpolymer complex restricted the drug release at pH 1.2. From complex, drug was released by erosion of polymers and followed zero order kinetics. The results of in vivo study indicated that the tablets coated with IPC film has ability to inhibit the release of drug in gastric pH and rapid release is observed between 4 to 8h followed by decrease, possibly due to the degradation of polymers in rats colon. From the results, the tablet coated with chitosan-CMTG interpolymer complexed films were found to be efficient to deliver drug in distal part of gastrointestinal tract as expected in colon targeted drug delivery^[147].

4.7 Transdermal drug delivery

TG and CMTG exhibit excellent film-forming ability and can be used in transdermal delivery of drugs (see Table 13). Topical films of TG have been used in wound healing and skin tissue engineering. Iodine loaded tamarind films have been successfully developed to treat

wounds^[19,21]. The ciprofloxacin loaded phase separated films have been prepared by using gelatin and TG or CMTG for skin tissue engineering. Glutaraldehyde was used as crosslinker and polyethylene glycol as plasticizer. The polysaccharide containing films supported better proliferation of human keratinocytes as compared to the control. The stress relaxation study suggested better relaxation properties of CMTG film. Drug loaded films showed good antimicrobial activity. The results indicated that the prepared films may be useful as matrix for skin tissue engineering and controlled drug delivery application^[148].

Polyvinyl alcohol and CMTG composite film containing ciprofloxacin has been prepared using glutaraldehyde as crosslinking agent^[149]. FTIR spectroscopy suggested the occurrence of hydrogen bonding amongst the components of the films. All the films were viscoelastic in nature. Ciprofloxacin loaded films showed excellent antimicrobial property against *E. coli*, suggesting that the drug is released in its active form. Cell proliferation study using human keratinocytes revealed better cell proliferation in the CMTG containing films as compared to the control (PVA only) film. The study proposed potential application of the PVA-CMTG films in wound dressings and other skin diseases where topical application of the drug is required.

Enzyme degraded TG has been used as sustained release vehicle for the topical delivery of ibuprofen and ketoprofen. It acts as the thermoreversible polymer and forms gels at body temperature when used in the concentration range of 1 to 2% w/v, which is too low than the concentration of Poloxamer 407 (25% w/v). Partially enzyme degraded TG helps to enhance the bioavailability of studied drugs than Pluronic F127 gels^[67].

Table 13: Investigated transdermal drug delivery systems of TG and modified TG

Therapeutic agent	Formulation type	Technique used	Excipients used	Role of Polymer	Animals used
Iodine ^[150]	Film	Solution casting	TG-Epichlorohydrin	Film former	Rats
Alfuzocin ^[151]	Film	Solution casting	TG	Film former, release retardant	NA
Ciprofloxacin ^[148]	Phase separated film	Solution casting	TG-gelatin CMTG-gelatin (GA as crosslinker)	Matrix for skin tissue engineering	NA
Ciprofloxacin ^[149]	Films	Solution casting	CMTG-PVA (GA as crosslinker)	Matrix for skin tissue engineering	NA
Ibuprofen, Ketoprofen ^[67]	Thermoreversible gel	Homogenization	Enzyme degraded TG	Gelling agent, sustain release vehicle	NA
Itraconazole ^[152]	Microemulsion based gel	Mixing	TG	Gelling agent, Bioadhesive	NA

TG-tamarind gum; CMTG-carboxymethyl tamarind gum; GA- Glutaraldehyde; NA- not applicable

4.8 Rectal drug delivery

Partially degraded TG by galactosidase enzyme is used for the development of rectal drug delivery due to its thermoreversible nature. It has been investigated for the delivery of indomethacin and diltiazem. The thermoreversible gel exhibited gelation temperature in the range of 27 to 22 °C. The in vitro drug release from the thermoreversible gels followed Higuchi kinetics over a period of 5h. Formulated gels showed sustained drug release than the marketed formulation^[71].

4.9 Pulmonary drug delivery

Partially degraded TG has been used for the preparation of mucoadhesive microspheres of Montelukast for pulmonary delivery. Spray-drying technique was used to prepare microspheres employing lactose monohydrate as carrier for dry powder inhalation (DPI). In vitro characterization of optimized microsphere formulation demonstrates its suitability as dry powder inhalation. A promising in vitro aerosol performance was observed for the developed formulation of DPIs suggesting high deep lung deposition of drug. The data of in vivo studies showed drug residence up to 6h. It provided high and prolonged drug concentration within lungs after pulmonary administration in rats^[153].

4.10 Periodontal drug delivery

In situ gel of lidocaine has been formulated using poloxamer as a thermoreversible gelling agent and TG as a mucoadhesive polymer, by cold method. The in vitro study depicted the fast onset of drug action but sustained the release (90%) till 2h. It offers an alternative to painful injection therapy of anesthesia during dental surgery, with fast onset of anesthetic action lasting throughout the dental procedure^[23].

4.11 Parenteral drug delivery

Partially degraded TG has been used in the development of intraperitoneal mitomycin C injection. It was used as a sustained release vehicle. Intraperitoneal injection of gel resulted in a broad concentration–time profile for drug in both, the ascites and the plasma, compared with a narrow peak and rapid disappearance from both sites when this drug was given i.p. as a solution^[154].

Gupta *et al.*, (2015) synthesized thermo-associating polymer by grafting amino terminated poly(ethylene oxide-co-propylene oxide) (PEPO) onto CMTG. The grafting was performed by coupling reaction between NH₂ groups of PEPO and COOH groups of CMTG using water-soluble EDC/NHS as coupling agents. The graft copolymer, CMTG-g-PEPO exhibited interesting thermo-associating behavior. The results indicate that the thermo-associating polymer with biodegradable nature of CMTG can have potential applications as smart injectables in controlled release technology and as thickeners in cosmetics and pharmaceutical formulations^[155].

4.12 Miscellaneous applications

Singh and Kumar, (2011) have prepared CMTG initiated and catalyzed sol-gel polymerization of tetramethoxysilane nanohybrids for immobilizing α -amylase for starch hydrolysis. The immobilization improved the affinity and catalytic properties of amylase, besides the enzyme under immobilized state showed more thermal stability. The immobilization using nanohybrids doubled the enzyme activity along with improvement in the working conditions. The nanohybrid improved the overall stability, affinity and catalytic property of α -amylase^[156].

5. CONCLUSION

Tamarind seed is an underutilized raw material in India. The proper use of the tamarind seed may fetch better return to the pulp processing industries that in turn may help the people who gather or even cultivate the tree.

In order to overcome the short comings like processing cost, availability, toxicity and compatibility, there is need to search new excipients. Currently, TG has gained popularity for its utility in the preparation of various pharmaceutical dosage forms. Literature survey reveals that the TG and modified TG have great potential in the development of various drug delivery systems and further research can enlighten its industrial applicability as an excipient. The review demonstrates the possibilities of using TG as promising pharmaceutical excipient in various pharmaceutical formulations.

6. ACKNOWLEDGEMENT

We are immensely obliged and thankful to Principal,

Government College of Pharmacy, Karad. We also extend our gratitude to President, Yashoda Technical Campus, Satara for catering legitimate facilities for carrying out the work.

7. CONFLICT OF INTERESTS

There are no conflicts of interest.

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