Chapter 2
Functionalization of Tamarind Gum for Drug Delivery

Amit Kumar Nayak and Dilipkumar Pal

Abstract Tamarind gum is a plant polysaccharide extracted from seed endosperm of the plant, *Tamarindus indica* Linn. (Family: Fabaceae). It is a neutral, nonionic, and branched polysaccharide having water solubility, hydrophilic, gel-forming, and mucoadhesive properties. In addition, tamarind gum is biodegradable, biocompatible, noncarcinogenic, and nonirritant. Tamarind gum is employed as a potential biopolymer in the fields of pharmaceutical, cosmetic, and food applications. In the recent years, it is widely tested and employed in various drug delivery applications as effective pharmaceutical excipients. Tamarind gum is being exploited in the formulation of oral, colon, ocular, buccal, and nasal drug delivery systems. Though tamarind gum is extensively used in various drug delivery formulations, it has some potential drawbacks such as unpleasant odor, dull color, poor solubility in water, tendency of fast degradability in aqueous environment. To overcome these restrictions, tamarind gum has been functionally derivatized through chemical treatment with a variety of functional groups such as carboxymethyl, acetal, hydroxyl alkyl, thiol, polymer grafting, etc. Recently, various functionally derivatized tamarind gums hold a great promise as potential pharmaceutical excipients in different kinds of improved drug delivery systems mainly because of its improved stability (lower degradability). These functionally derivatized tamarind gums hold enhanced mechanical behavior as well as competence in prolonged period-controlling drug releases. The present chapter contends with a broad review of different kinds of functionalizations of tamarind gum for their use in the development of various improved drug delivery systems. The first part includes sources, compositions, properties and uses of tamarind gum. Then, the latter part contains a comprehensive review of different functionalizations of tamarind gum in drug delivery.

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1 Introduction

Day by day, the medicinal and biomedical uses of various plant-derived materials are gaining significance over synthetic materials because of large availability in nature, eco-friendly renewable, and sustainable extraction facility with lower cost (Nayak et al. 2010, 2012; Pal and Mitra 2010; Pal et al. 2012). Among these materials, plant-derived natural gums have recently established their worth as biopolymers due to their biosafety, biodegradability, and inexpensive sustainable productions from the natural resources (Hasnain et al. 2010; Avachat et al. 2011; Nayak et al. 2015; Nayak and Pal 2012). Plant-derived gums are those natural polysaccharides, which contain manifold sugar units interconnected to compose macromolecular structures with a broad range of physiological characteristics (Nayak and Pal 2012, 2016). Gums are actually pathological byproducts of plants. Gums contain some salts (sodium, potassium, calcium, magnesium, etc.) of complex materials (Nayak and Pal 2016). Almost all natural gums are able to form gels (i.e., three-dimensional molecular networks). Gel strength of gums depends on several issues of the gum characteristics like molecular structure, concentration, ionic strength, pH, temperature, etc. (Jani et al. 2009; Rana et al. 2011). The natural gums exhibit swelling capacity as a result of the trap of larger water volume in-between the branches as well as chains (Nayak and Pal 2016). The majority of natural gums is metabolized by intestinal microflora and finally, is able to degrade the simpler sugar components (Rana et al. 2011; Prajapati et al. 2013). Moreover, intestinal enzymes are able to cleave these gums at the specific sites (Rana et al. 2011).

Recently, various plant-derived natural gums are being investigated and employed in the different kinds of drug delivery systems on account of their diverse characteristics (Jani et al. 2009; Prajapati et al. 2013). Most of these gums are biodegradable, biocompatible, and also safe enough for oral consumption (Prajapati et al. 2013). Unfortunately, there are several potential drawbacks with the use of plant-derived native gums in biomedical as well as pharmaceutical applications. These drawbacks include pH responsive solubility, uncontrolled hydration rate, viscosity decrease after longer storage, chances of microbial contaminations, etc. (Rana et al. 2011). To overcome these above-said drawbacks of plant-derived native gums, various kinds of functionalizations of different plant-derived native gums through chemical modifications like carboxymethylation (Pal et al. 2011; Das et al. 2014), carbamoylethylation (Sharma et al. 2004), cyanoethylation (Goyal et al. 2008), thiolation (Sharma and Ahuja 2011), graft modification (Mishra et al. 2006; Pandey et al. 2014), etc., are being researched by various groups. These functionalized natural gums not only limit various weaknesses of native gums but also make possible the utilization prospects as improved drug delivery excipients.

Amongst a variety of plant-derived polysaccharides, tamarind gum is promising biopolymer (Pal and Nayak 2015; Nayak 2016). It is extracted from tamarind seed endosperm and often, it is also called as tamarind kernel gum. Food and Drug Administration (FDA) has recognized this plant polysaccharide as a generally regarded safe (GRAS) substance in their GRAS Notice (2014). Therefore, it should be considered as safe for oral consumption. It is widely utilized as polymer in various applications such as pharmaceutical, cosmetic, food, chemical engineering, paper, textile, etc. (Pal and Nayak 2015; Nayak 2016). In the recent years, tamarind gum is being researched and exploited as valuable excipients in a variety of dosage systems for improved drug deliveries (Manchanda et al. 2014; Pal and Nayak 2015; Nayak 2016). Currently, the properties of tamarind gum have been improved through functionally modifications by chemical derivatization with different functional groups such as carboxymethyl, acetal, hydroxyl alkyl, thiol, etc. (Goyal et al. 2007, 2008; Kaur et al. 2012a, b). Additionally, grafting modifications of tamarind gum are also helpful to improve various potential polymer properties of tamarind gum (Manchanda et al. 2014). On the basis of the above discussion, the present chapter contends with a broad review of different kinds of functionalizations of tamarind gum for their use in the development of various improved drug delivery systems. The first part includes sources, compositions, properties, and uses of tamarind gum. Then, the latter part contains a comprehensive review of different functionalizations of tamarind gum in drug delivery.

2 Tamarind Gum: Sources, Composition, Properties, and Uses

2.1 Sources

Tamarind gum is a plant polysaccharide extracted from seed endosperm of the plant, *Tamarindus indica* Linn. (commonly known as 'Indian date'; '*Imli*', in Hindi; Family: Fabaceae) seeds (Pal and Nayak 2012). The extraction procedure of tamarind gum was first reported by Rao et al. (1946) and they extracted it from tamarind seed kernel powder. Rao and Srivastava (1973) and then Nandi (1975) further modified this extraction procedure to extract tamarind gum on the laboratory scales. In general, chemical and enzymatic procedures of tamarind gum extraction are employed. In chemical extraction procedure, tamarind seed kernel powder is generally soaked in the boiled water and then filtered to separate the extracted mucilage. The collected filtered mucilage material is put into the equal volume of ethanol or acetone to obtain precipitate gum. The extracted precipitate is then dried as tamarind gum (Nayak and Pal 2011). The enzymatic extraction procedure includes mixing up of tamarind seed kernel powder with ethanol and following reaction with the protease (an enzyme). Subsequent to the enzymatic treatment by protease, it is centrifuged. The supernatant is collected and treated with ethanol to

obtain precipitation of tamarind gum. The extracted precipitate is then dried as tamarind gum (Tattiyakul et al. 2010).

2.2 Composition

Tamarind gum is a neutral, non-charged and branch-structured polysaccharide (Nayak 2016). It is composed of (1 → 4)-β-D-glucan backbone-substituted with side chains of α-D-xylopyranose and β-D-galactopyranosyl (1 → 2)-α-D-xylopyranose linked (1 → 6) to glucose residues, where 55.4% of glucose, 28.4% of xylose and 16.2% of galactose units are present corresponding to a molar ratio of 2.8:2.25:1.0 (i.e., glucose:xylose:galactose) (Nayak and Pal 2011; Pal and Nayak 2015). Therefore, it is regarded as galactoxyloglucan (Nayak 2016). In the tamarind gum structure, glucose residues (80%) are substituted by xylose residues (1–6 linked) along with partly substituted by p-1–2 galactose residues (Lang et al. 1992; Manchanda et al. 2014). The molecular structure of tamarind gum is presented in Fig. 1. It is already reported that the molecular weight of tamarind gum is 2.5–6.5 × 10^5 (Zhang et al. 2008; Pal and Nayak 2015).

2.3 Properties and Uses

Tamarind gum is an aqueous soluble and hydrophilic polysaccharide (Nayak 2016). It swells in aqueous solutions to produce mucilaginous gels, which usually confirms characteristic rheological behavior of non-Newtonian and pseudoplastic nature

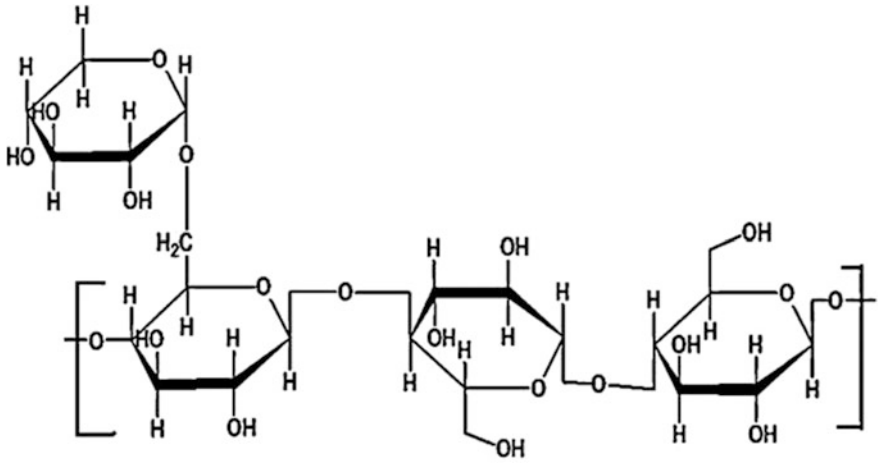

Fig. 1 Chemical structure of tamarind gum

(Joseph et al. 2012; Pal and Nayak 2015). The high degree substitution of glucan chains in the tamarind gum structure generates stiff as well as extended conformation with the aqueous volume occupancy in larger amounts in aqueous solutions. The native form of tamarind gum also demonstrates a tendency of self-aggregation in the aqueous solutions (Pal and Nayak 2015). The tamarind gum self-aggregates comprise lateral assemblies of single polysaccharidic strands, which can be explicated by the so-called Kuhn's model (Gupta et al. 2010; Nayak 2016). Tamarind gum is not soluble in the cold water, in general, and easily soluble in the warm water to produce highly viscous mucilaginous gels with broad pH tolerance along with adhesivity (Rao and Srivastava 1973). Like other natural gums, it is not soluble in methanol, ethanol, acetone, and ether (Joseph et al. 2012). It is stable in acidic pH. Tamarind gum can also forms gels in acidic as well as neutral pH. It possesses the ability to produce highly viscous gels with sugars (Gupta et al. 2010). Tamarind gum has been found as a biodegradable, biocompatible, noncarcinogenic, non-irritant polymer (Khanna et al. 1987; Avachat et al. 2011). It has also been illustrated as bioadhesive as well as mucomimetic biopolymer. Tamarind gum has also revealed anti-inflammatory, hepatoprotective, and antidiabetic nature (Samal and Dangi 2014). It also possesses film forming property with high flexibility and good tensile strength, high drug holding capacity, and high thermal stability (Pal and Nayak 2015). Like other xyloglucans, tamarind gum is not digested by the influence of human digestive enzymes. It may be considered as part of the dietary fiber fraction of the diet. However, it is fermented by means of intestinal microbiota (Hartemink et al. 1996). Even after degradation of the carbohydrate polymeric backbone of tamarind gum, several polysaccharide strains representing numerous species are capable to ferment into oligosaccharides (Nayak 2016).

Tamarind gum has already found its potential applications in the fields of food, pharmaceutical and cosmetic science (Pal and Nayak 2015; Nayak 2016). Recent years, tamarind gum is widely studied and also employed as one of the emerging plant-derived natural polysaccharides as pharmaceutical excipients (such as, thickener, suspending agent, emulsifier, gelling agent, binder, release modifier, etc.) in various drug delivery applications (Deveswaran et al. 2009; Gupta et al. 2010; Pal and Nayak 2015; Nayak 2016). Tamarind gum is employed as useful excipient in the formula of matrix tablets for numerous drugs (Chanda et al. 2008; Chandramouli et al. 2012). It is also exploited in the development of oral (Pal and Nayak 2012; Nayak et al. 2014a; Nayak 2016), buccal (Bangle et al. 2011; Avachat et al. 2013), colon (Mishra and Khandare 2011), nasal (Datta and Bandyopadhyay 2006), and ocular (Mehra et al. 2010) drug deliveries. Furthermore, tamarind gum finds its utilization as mucoadhesive biopolymers in the formulation of different bio-mucoadhesive drug delivery systems (Datta and Bandyopadhyay 2006; Bangle et al. 2011; Avachat et al. 2013; Pal and Nayak 2015; Nayak 2016). Tamarind gum has been exploited for the preparation of various multiple-unit sustained drug releasing carriers, such as spheroids, beads, microparticles, etc., for oral administration (Kulkarni et al. 2005; Nayak and Pal 2011, 2013; Nayak et al. 2013, 2014a, b; Pal and Nayak 2012; Jana et al. 2013; Bera et al. 2015).

3 Rationality of Tamarind Gum Functionalization

Though tamarind gum is extensively used in various biomedical applications including its wide application ranges in pharmaceutical formulations as excipients, it has some potential drawbacks (Manchanda et al. 2014; Pal and Nayak 2015; Nayak 2016). Native tamarind gum possesses unpleasant odor and dull color, (Kaur et al. 2012a; Meenakshi and Ahuja 2015). It also exhibits its poor solubility in water (Kaur et al. 2012a). Additionally, tamarind gum usually displays the presence of water insoluble components and possesses tendency of fast degradability in aqueous environment (Meenakshi and Ahuja 2015). To overcome these restrictions, tamarind gum has been functionalized by chemical modifications through incorporating a variety of functional groups (i.e., modifications of various functional groups of polymer structure) like carboxymethyl, acetal, hydroxyl alkyl, thiol, etc. (Goyal et al. 2008; Kaur et al. 2012a, b). Besides these, tamarind gum is also modified through polymer grafting (Manchanda et al. 2014). The functional derivatization of tamarind gum with functional groups interrupts the native tamarind gum structure organization, and thus, revealing the hydration of carbohydrate networks (Lang et al. 1992; Kaur et al. 2012b). These properties help to achieve high viscosity and low degradability. These functional derivatizations of tamarind gum also improve the self-life of it (Rana et al. 2011). In recent times, various functionally derivatized tamarind gum holds a great promise as potential pharmaceutical excipients in different kinds of improved drug delivery systems mainly because of its improved stability (lower degradability) (Rana et al. 2011; Kaur et al. 2012a; Meenakshi and Ahuja 2015).

4 Carboxymethylated Tamarind Gum in Drug Delivery

4.1 Carboxymethylation

Carboxymethylated gums are those modified gums, which are synthesized from the native gum through functional modification by the chemical means of attaching pendant carboxylic acid groups (–COOH) to the native gum structures (Togru and Arsian 2003; Olusola et al. 2014; Rana et al. 2011). Recently, in the polymer research, carboxymethyl modifications (i.e., carboxymethylation) of gums are an extensively studied conversion because of its technical simplicity low cost of chemical reagents and wide applications (Parvathy et al. 2005). Carboxymethylation of gums leads to add a variety of promising characteristics (Togru and Arsian 2003; Olusola et al. 2014). Generally, carboxymethylated gums exhibit to enhance hydrophilicity in addition to clarity of solutions as compared to that of the native gums (Rana et al. 2011). These potential characteristics improvement of the native gum makes them more soluble in aqueous medium. In general, native gums are made carboxymethylated through the conventional method by Williamson's etherification

reaction using monochloroacetic acid and sodium hydroxide in the aqueous milieu at higher temperature (Khalil et al. 1990). The Williamson's etherification reaction may direct to the nonspecific degradation via β elimination and/or peeling reaction initiated at decreasing sugar units because of highly alkaline pH environment, which sequentially decreases the molecular weight of the derivatized gum (Parvathy et al. 2005). Various natural gums are already carboxymethylated through this method (Maity and Sa 2014a, b).

Carboxymethyl tamarind gum is the carboxylic derivative of tamarind gum. The introduction of carboxymethyl group into the tamarind gum enables an anionic nature to it (Goyal et al. 2007). Carboxymethylation of tamarind gum makes it comparatively microbial as well as enzymatic resistant than the native gum (Manchanda et al. 2015). Carboxymethyl tamarind gum possesses higher viscosity and lower degradability in aqueous environments (Goyal et al. 2007). It also has the capacity to produce higher swelling in aqueous environments (Manchanda et al. 2015; Meenakshi and Ahuja 2015).

4.2 *Carboxymethylated Tamarind Gum Matrix Tablets for Sustained Drug Delivery*

In an investigation, Manchanda et al. (2015) reported the matrix-forming potential of carboxymethyl tamarind gum to develop and optimize sustained drug releasing matrix tablets. They have chosen glipizide (an effective oral antidiabetic; BCS class-II drug; short biological half-life of about 3.5 h) to assess the sustained drug releasing matrix-forming potential of carboxymethyl tamarind gum. In this study, Manchanda et al. (2015) synthesized carboxymethyl tamarind gum via carboxymethylation technique, where conventional carboxymethylation method using strong sodium hydroxide and monochloroacetic under heterogeneous reaction conditions was followed.

The synthesized product of carboxymethyl tamarind gum was found brownish-white in color. The melting point of it was found as 252–256 °C. The synthesized carboxymethyl tamarind gum was found soluble in water. The pH and viscosity of synthesized carboxymethyl tamarind gum solution (1% w/v) were 6.9 and 1225–1715 cps (at various shear rates), respectively. The carboxymethyl tamarind gum was characterized for its micromeritic characteristics, viz., bulk density, tapped density, angle of repose, Hausner's ratio, and Carr's index. In micromeritic evaluation of the synthesized carboxymethyl tamarind gum, bulk density of 0.60 g/cm^3, tapped density of 0.80 g/cm^3, angle of repose of 18.6°, Hausner's ratio of 1.15, and Carr's index of 32.0°. 17% of loss on drying were measured.

Utilizing the synthesized carboxymethyl tamarind gum, matrix tablets of glipizide (an oral antidiabetic drug) were formulated via direct compression technique. For the formulation optimization of these matrix tablets of glipizide, a 3^2 full

factorial optimization design with two independent variables and three dependent variables was employed to optimize drug release profile using response surface methodology. Concentration of carboxymethyl tamarind gum and type of diluent (here lactose, starch and microcrystalline cellulose) were analyzed as independent variables in the 3^2 full factorial design. The dependent variables (responses) selected were percent of glipizide release at 4, 8 h and swelling index. From the results, the response surface plots related with independent variables and dependent variables were developed to select the optimum formulation. To prepare matrix tablets of glipizide using the synthesized carboxymethylated tamarind gum, granules were prepared. The granules were characterized for their micromeritic properties and the angle of repose was found as 23°–31°, which indicates satisfactory flow behavior of these prepared granules. The drug contents, average weights, weight variations, friabilities, and harnesses of all these glipizide matrix tablets were assessed. The uniform drug content in these matrix tablets was observed as it was within 95 ± 2%. The average weight and weight variation were within the pharmacopoeial limit. The range hardnesses and friabilities were 6.5–7.1 kg/cm^2 and 0.24–0.65%, respectively. The results of hardness and friability indicated suitable mechanical strength, which are helpful for good handling of these prepared matrix tablets.

The Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) analyses confirmed the absence of drug (glipizide)-polymer (carboxymethylated tamarind gum) interaction within these matrix tablets. Scanning electron microscopy (SEM) analyses revealed comparatively rougher surface of carboxymethylated tamarind gum than native tamarind gum.

The swelling behavior of these carboxymethylated tamarind gum matrix tablets of glipizide was evaluated in phosphate buffer medium, pH 7.4. Swelling indices were found to be increased with the concentrations of carboxymethylated tamarind gum using microcrystalline cellulose as diluent. These matrix tablets were also assessed for in vitro glipizide-releasing pattern in phosphate buffer medium, pH 7.4. In vitro glipizide-releasing pattern was observed inversely proportional to the carboxymethylated tamarind gum concentrations and depends on type of diluents. The in vitro glipizide-releasing from all these tablets suggested sustained drug releasing pattern over 20 h. The drug release also followed the kinetic model of zero-order and mechanism of non-Fickian drug release (anomalous release).

4.3 Carboxymethylated Tamarind Gum Nanoparticles for Ocular Drug Delivery

Biopolymeric nanoparticles made of carboxymethylated tamarind gum for ocular drug delivery were formulated by Kaur et al. (2012a). They have utilized commercial carboxymethylated tamarind gum to prepare ocular nanoparticles of tropicamide (an anti-muscarinic drug). In this study, interactions between anionic carboxymethylated tamarind gum and divalent Ca^{2+}-ions were employed to prepare

ionotropically gelled nanoparticulate carriers made of carboxymethylated tamarind gum. On the basis of this mechanism, tropicamide loaded carboxymethylated tamarind gum nanoparticles were formulated via ionotropic gelation using Ca^{2+}-ions as ionic cross-linker ion as well as dioctyl sulfosuccinate as stabilizing agent. The formulation of these nanoparticles of tropicamide was optimized through employing three levels and two factors based central composite design. Carboxymethylated tamarind gum concentrations and calcium chloride (as cross-linker) concentrations were chosen as independent factors. Encapsulation efficiency and particle size were analyzed as responses (dependable factors). The preliminary trial study containing 13 experimental run suggested that the concentrations of carboxymethylated tamarind gum and Ca^{2+}-ions influenced the particle sizes of the carboxymethylated tamarind gum nanoparticles loaded with tropicamide. This occurrence can be infer that the anionic carboxymethylated tamarind gum concentration possessed more pronounced effect than the ionotropic cross-linker (calcium chloride) concentration on the particle size of these ionotropically gelled carboxymethylated tamarind gum nanoparticles containing tropicamide. An increment in carboxymethylated tamarind gum concentration was found to increase the particle sizes of these nanoparticles. This occurrence can be explained by insufficient interaction of cross-linker with polymer used. This occurrence can also be explained by the fact that the increased polymer concentrations enhanced the viscosity of the solution. It was also found that the increase in drug encapsulation of these nanoparticles with the declining polymer concentrations and raising concentration of cross-linker can be due to the high cross-linking at the raising concentration of cross-linker. The increasing polymer (here carboxymethylated tamarind gum) concentration resulted in declining of drug encapsulation in these nanoparticles, which was more pronounced at the higher cross-linking concentration of calcium chloride during nanoparticles preparation.

The optimal calculated values of these two investigated factors were estimated as 0.10% w/v of carboxymethylated tamarind gum concentration and 0.11% w/v calcium chloride to formulate optimized carboxymethylated tamarind gum nanoparticles containing tropicamide. The optimized formulation of tropicamide loaded carboxymethylated tamarind gum nanoparticles showed particle size of 339 nm and drug encapsulation efficiency of 15.57%.

The ionotropic interaction between anionic carboxymethylated tamarind gum and divalent Ca^{2+}-ions was demonstrated by FTIR spectroscopy. Optimized tropicamide loaded nanoparticles were characterized via transmission electron microscopy (TEM) analysis. The TEM microphotograph of the optimized nanoparticles revealed the ovoid morphological shape (Fig. 2) and particle sizes were found within the range of 2–40 nm.

Ex vivo corneal permeation of the optimized tropicamide loaded nanoparticles was evaluated using isolated goat cornea by the modified Franz diffusion cell. The result of the corneal permeation of the optimized nanoparticles was compared with the result of corneal permeation of conventional tropicamide aqueous solution. No significant difference between the percentages of corneal tropicamide permeation from these two ocular formulations (optimized tropicamide loaded nanoparticles

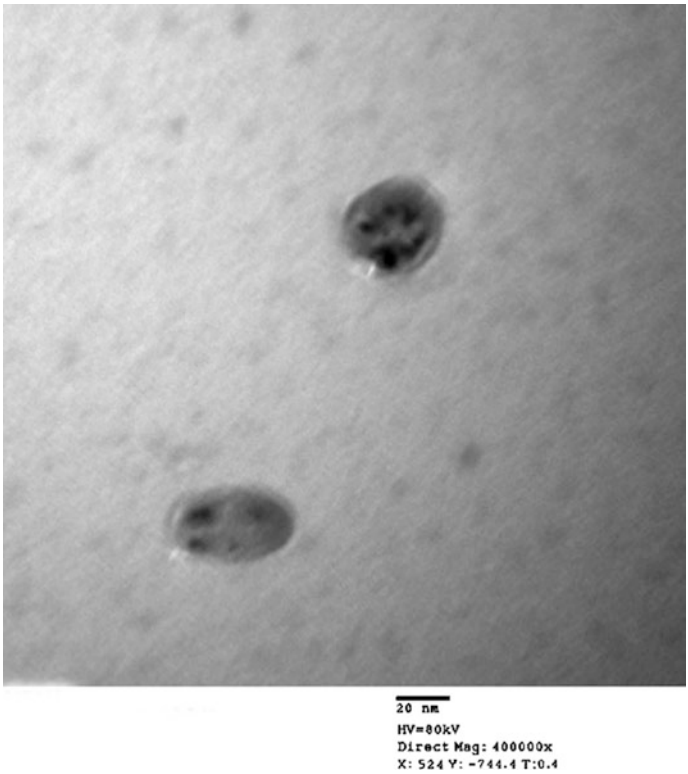

Fig. 2 TEM microphotograph of tropicamide loaded carboxymethylated tamarind gum nanoparticles (Kaur et al. 2012a, b). Copyright ©2011 with permission from Elsevier B.V.

and conventional tropicamide aqueous solution) was observed. Ex vivo mucoadhesivity of these carboxymethylated tamarind gum nanoparticles was judged through measuring the adsorbed mucin amounts by the tested nanoparticles within 24 h. 87.67% of absorbed mucin was estimated by the mucin glycoprotein assay of nanosuspension containing optimized tropicamide loaded carboxymethylated tamarind gum nanoparticles. Being an anionic polymer, carboxymethylated tamarind gum contains –COOH groups, which could form hydrogen bonds with the oligosaccharide chains of mucin. Mucin adsorption by tropicamide loaded optimized carboxymethylated tamarind gum clearly indicated excellent mucoadhesivity of these nanoparticulate carriers for ocular delivery of tropicamide.

Ex vivo ocular tolerance of these optimized carboxymethylated tamarind gum nanoparticles containing tropicamide was assessed using hen's egg test on the chorioallantoic membrane (CAM) of chicken eggs. The results of this ex vivo ocular tolerance study indicated that these optimized tropicamide loaded nanoparticles were nonirritant and excellent ocular tolerability. The results of ex vivo corneal tropicamide permeations, ex vivo mucoadhesion as well as ex vivo ocular

tolerance studies clearly demonstrated the suitability of these optimized tropicamide loaded carboxymethylated tamarind gum nanoparticles as an effective ocular drug delivery carrier.

4.4 Carboxymethylated Tamarind Gum Spheroids for Controlled Drug Delivery

In a research, Gowda et al. (2014) designed controlled drug releasing spheroids composed of carboxymethylated tamarind gum. They utilized commercial carboxymethylated tamarind gum to formulate these controlled drug releasing spheroids. The commercial carboxymethylated tamarind gum was characterized for pH and viscosity. The pH of 1% w/v solution of carboxymethylated tamarind gum was found as 4.50 ± 0.29. This value was considered as advantageous to be used to develop drug releasing carriers as this would not cause any chances of gastrointestinal irritation when consumed orally. 38 cps viscosity in distilled water, 40 cps viscosity in pH 1.2 buffer, and 45 cps viscosity in pH 7.2 buffer were measured for 1% w/v solution of carboxymethylated tamarind gum.

Gowda et al. (2014) employed extrusion/spheronization technique for the preparation of these carboxymethylated tamarind gum spheroids to investigate the influence of compression of prepared spheroids into the matrix tablets for controlled drug release. In this work, lornoxicam (a NSAID) was used as model drug. Owing to undersized biological half-life of lornoxicam (approximately 3–5 h) and to restrict the chances of the gastrointestinal disturbances, it should be beneficial to be used through controlled releasing carriers for oral use. In these formulations of carboxymethylated tamarind gum, spheroids containing lornoxicam and microcrystalline cellulose were utilized as spheronization enhancer. For the different formulations, lornoxicam loaded spheroids were prepared through maintaining different ratios of microcrystalline cellulose:carboxymethylated tamarind gum: lornoxicam (drug), such as, 72.5:2.5:2.5% w/w (BD-1), 70:5:25% w/w (BD-2), 67.5:7.5:25% w/w (BD-3), 65:10:25% w/w (BD-4), 62.5:12.5:25% w/w (BD-5), and 60:10:25% w/w (BD-6). From the optimization study, Gowda et al. (2014) identified the optimal formula of process variable settings for optimized spheroids, which were prepared at 6000 rpm for 5–15 min of time durations.

The narrow range of spheroids size distribution was seen, when spheroids were formed using carboxymethylated tamarind gum of 2.5–15.0% w/w concentrations. In case of spheroids made of above 15% w/w of carboxymethylated tamarind gum, the extrusion mass cohesiveness was found to be augmented and this might have resulted due to the fact of greater resistance to stream through the extruder die utilized. An extrusion of the wetted mass through wetted die was noticed with the water level rising. This resulted tacky extrudates for the further processing were attained when carboxymethylated tamarind gum concentration in the preparation of spheroids was less than 15% w/w. From the preliminary trial studies, it was noticed

that the resistance of extrudate amounts at higher concentration of carboxymethylated tamarind gum (more than 15% w/w) to round up by the spheronizer device was found to be comparatively greater. The level of carboxymethylated tamarind gum concentrations was selected less than 15% w/w in the carboxymethylated tamarind gum spheroids containing lornoxicam prepared. From the results of the preliminary trial experimentation, it was observed that spheroids production was sufficient with the maximum percentage yield and acceptable level of sphericity, when spheronization time of 15 min and spheronization speed of 1600 rpm were employed.

Various micromeritic characteristics such as mean particle sizes, angles of repose, trapped densities, granule densities, Carr's indices, and friability values of different batches of lornoxicam loaded carboxymethylated tamarind gum spheroids were measured. The results indicated any significant differences among various batches of carboxymethylated tamarind gum spheroids. Mean particle sizes of these lornoxicam loaded carboxymethylated tamarind gum spheroids were measured as 1125 ± 0.56 to 1345 ± 0.23 μm. The friability values of these spheroids were measured within the range of 0.43 ± 0.08 to $0.53 \pm 0.07\%$, which indicated that the friability values of all the batches were within the compendia limits. The angles of repose of these spheroids were measured within the range of 23.45°–26.30°, suggesting good quality of flow properties of these lornoxicam loaded carboxymethylated tamarind gum spheroids.

The SEM analyses of these lornoxicam loaded carboxymethylated tamarind gum spheroids demonstrated spherical shaped morphology with smooth surface. The smooth surface morphology of these spheroids might have influenced the results of the friability and angle of response. These spheroids were also subjected to the DSC analyses and the DSC results indicated that the decomposition temperature of the encapsulated drug, lornoxicam (i.e., 218.74 °C) was almost same, even when it was processed with the carboxymethylated tamarind gum and other excipients to prepare these spheroids. This phenomenon may be explained by the fact that there was absence of interactions between lornoxicam and excipients used in the preparation of lornoxicam loaded carboxymethylated tamarind gum spheroids. These results indicated that lornoxicam was in stable form within these formulated carboxymethylated tamarind gum spheroids.

Drug loadings (%) among all these of lornoxicam loaded carboxymethylated tamarind gum spheroids were within the range of 19.59 ± 1.12–$22.30 \pm 0.39\%$. The highest drug loading was observed for the spheroids of formulation BD-1 ($22.30 \pm 0.39\%$). Drug entrapment efficiencies were measured within the range in-between 91.42 ± 1.12 and $96.04 \pm 0.20\%$. The highest entrapment efficiency was found for the spheroids formulation BD-3 among all the spheroids prepared.

The optimized formulation of lornoxicam loaded carboxymethylated tamarind gum spheroids was compressed with mixing 20% Avicel® PH 200 as filler and 10% w/w anhydrous lactose. Actually, prior to the compression, slugs were prepared using prepared spheroids, Avicel® PH 200 and anhydrous lactose. Then, slugs of prepared spheroids, Avicel® PH 200, and anhydrous lactose were passed through the Multimilli screen (0.5″). The granules were sieved through sieve #40. The

ultimate granules were processed through blending with 1% of magnesium stearate and then compressed for 1 min with various fixed loads of 5–12.5 tons by using a hydraulic press (containing 12.7 mm die with flat faced punches). The weight variations, hardness, and friability of these prepared compressed matrices were assessed. Hardness and friability of these compressed matrixes were found within pharmacopoeial limits. Therefore, it was seen that hardness and friability were found to be increased with the increasing of compression forces.

For the in vitro dissolution study, lornoxicam loaded spheroids made of carboxymethylated tamarind gum were capsulated within hard gelatin capsules. The in vitro dissolution was performed using freshly prepared dissolution media of phosphate buffer, pH 7.2 at the temperature of 37 ± 1 °C, and paddle-speed of 50 rpm. In in vitro dissolution, it was observed that the increasing carboxymethylated tamarind gum concentration level from 2.5 to 15% directed a significant decrease in drug releases from these lornoxicam loaded carboxymethylated tamarind gum spheroids. It was also observed that lornoxicam loaded spheroids BD-1, BD-2, and BD-3 made of carboxymethylated tamarind gum in concentration of 2.5, 5 and 7.5% w/w released 97.20 ± 1.50, 79.35 ± 1.70, and 66.89 ± 1.40%, respectively, at the end of 7 h of in vitro dissolution study, demonstrating polymer (here carboxymethylated tamarind gum) concentration was insufficient to sustain the drug release. In contrast, lornoxicam release from BD-4 spheroids made of 10% carboxymethylated tamarind gum was found significantly sufficient in comparison with other formulation batches of spheroids. The formulation BD-4 was found to release drug of 98.13 ± 0.90% at 12 h. The sustained drug release could be because of high concentration of carboxymethylated tamarind gum. This occurrence could be a characteristic sign of slower penetration of dissolution media into the matrix. The formulation BD-5 and BD-6 containing 12.50% w/w and 15% w/w carboxymethylated tamarind gum exhibited insufficient release of drug due to high carboxymethylated tamarind gum concentration. The sustained drug releases from these spheroids were following in order of BD-6 > BD-5 > BD-4 > BD-3 > BD-2 > BD-1. Among all these formulations, spheroids BD-4 composed of 10% w/w carboxymethylated tamarind gum were identified as optimized formulation on the basis of its physicochemical as well as release characteristics. The drug release from spheroids BD-4 showed zero-order kinetic model, which is an indicative of controlled release. In the stability study, it was found that these spheroids were found to be stable enough over 60 days.

4.5 Carboxymethylated Tamarind Gum-Chitosan Interpolymeric Complexation-Based Film Coating for Colon Drug Delivery

Kaur et al. (2010) developed chitosan (deacetylated chitin, cationic natural polymer)-carboxymethylated tamarind gum interpolymer complexation film for the

better delivery of budesonide (a second generation glucocorticoids) in the colon. In designing of such an improved colon drug delivery system, they have planned to coat uncoated budesonide tablets of 25 mg average weight, which contained 3 mg of budesonide. These tablets were formulated through weight granulation procedure using Eudrajit L100-55 or chitosan-carboxymethylated tamarind gum inter polymeric complex as binder.

Average weight of uncoated core tablets was calculated as 24.67 ± 1.10 mg and this result was within the USP tolerance limit. Axial as well as radial diameters of uncoated core tablets were within 1.75–1.80 and 3.98–4.02 mm, respectively. Hardness of these uncoated tablets was measured 4.50 ± 0.50 kg/cm^2 and friability was measured within the range, 0.36–0.46% w/w. The uncoated budesonide tablets formulated with 10% w/w Eudrajit L100-55 or chitosan-carboxymethylated tamarind gum inter polymeric complex as binders demonstrated to show cracking of the tablet matrix in-between 30 min, when exposed to 0.1 M HCl. 27.20 ± 1.25 mg was measured as average weight of the coated matrix tablets and it was within the official limit. 2.02–2.08 and 4.01–4.15 mm were measured as the axial and radial diameter of these coated tablets. Though, these coated tablets displayed swelling as these showed any cracking following the contact of these matrix tablets to 0.1 M HCl for a period of 2 h.

The formation of interpolymeric complex between cationic chitosan and anionic carboxymethylated tamarind gum was confirmed by FTIR spectroscopy. Actually, carboxymethylated tamarind gum possesses negative ionic charge because of the presence of –COOH groups through the carboxymethylation; while owing to the presence of NH_3^+ groups, chitosan possesses positive charge. The processing of both the polymers of opposite charges (negative charged carboxymethylated tamarind gum and positive charged chitosan) undergone a spontaneous, which results in a solid mass due to interpolymeric complexation. Kaur et al. (2010) studied viscosity of chitosan-carboxymethylated tamarind gum mixture solution to investigate the stoichiometric complexation between the two oppositely charged polymers. They found to decrease as the proportion of chitosan in the chitosan-carboxymethylated tamarind gum mixture decreased. The minimum viscosity of the supernatant of the chitosan-carboxymethylated tamarind gum was obtained through reacting cationic chitosan with anionic carboxymethylated tamarind gum in the ratio of 2:3, which indicated minimum reaction.

Chitosan-carboxymethylated tamarind gum inter polymeric complex films were evaluated for swelling in acidic buffer (pH 1.2) for 2 h and in alkaline buffer (pH 7.4) for 22 h. Kaur et al. (2010) found considerably low swelling of interpolymeric complex films in the alkaline pH. The swelling of interpolymeric complex films exhibited a decreasing of limiting value, when carboxymethylated tamarind gum concentration was found decreasing in the chitosan-carboxymethylated tamarind gum interpolymeric complex to 60% w/w. In addition, with the increasing concentration of carboxymethylated tamarind gum, swelling index was found to be increased. The interpolymeric complex films composed of 30:70 ratio of chitosan-carboxymethylated tamarind gum exhibited an enhanced swelling pattern

in comparison with those, which were composed with chitosan-carboxymethylated tamarind gum in a ratio of 40:60.

The in vitro releasing of drug from formulated tablets was assessed in different pH 1.2 for 2 h, pH 7.4 for 3 h, and pH 6.8 for 19 h. The uncoated budesonide tablets containing Eudrgit L100-55 as binding agent exhibited the release of 24% drug (budesonide) in the acidic pH (1.2) within 2 h. The residual amount of budesonide was found to be released speedily from these uncoated tablets in alkaline pH (7.4) within 4 h. The tablets coated with chitosan:carboxymethylated tamarind gum ratio of 60:40 released budesonide of 6% in the acidic pH (1.2) and furthermore, release of 21% budesonide was detected in the alkaline pH (7.4). The uncoated budesonide matrix tablets containing 40:60 or 50:50 ratio of chitosan-carboxymethylated tamarind gum as binder were found to have released 50 and 52% of budesonide, respectively on the acidic pH. Furthermore, these tablets were found to be released 72 and 75% of budesonide, respectively, in the pH 7.4. These results suggested that the chitosan-carboxymethylated tamarind gum, when employed alone as a binding agent, was unable to sustain the release of budesonide in acidic pH (stomach pH). In addition, the matrix tablets containing 50:50 ratio of chitosan:carboxymethylated tamarind gum employing as binding agent and when these matrix tablets were coated using the same solution, it was found to release 9% of budesonide in the alkaline pH of 7.4 (intestinal pH). These chitosan-carboxymethylated tamarind gum interpolymeric complex based matrix tablets were found to release 28% of budesonide in the alkaline pH of 6.8 within 24 h. The total releases of budesonide in pH 6.8 after 24 h, which was found to be released in pH 6.8 after 24 h, were 16%.

In vitro release of budesonide from tablets containing chitosan-carboxymethylated tamarind gum interpolymeric complex or Eudragit L100-55 was used as binding agent on the chronological exposure to the dissolution media containing rat cecal content or chitosanase enzyme of a variety of pH-range (1.2, 7.4 and 6.8),. The budesonide release was significantly ($p < 0.05$) amplified in the rat cecal content containing dissolution media in comparison with that of the dissolution media lacking rat cecal content. The releases of budesonide in rat cecal contents after 24 h from these chitosan-carboxymethylated tamarind gum matrix tablets containing Eudragit L100-55 as binding agent were improved to 99, 70 and 59%, from 84, 36 and 25%, respectively, when these uncoated tablets were coated with chitosan-carboxymethylated tamarind gum using 40:60, 50:50 and 60:40 ratio. The ultimate contact of these budesonide matrix tablets containing chitosan:carboxymethylated tamarind gum of 50:50 as binding agent, which were also coated using the same solution released budesonide of 74% to the release medium containing rat cecal contents. However, in the release medium absenting rat cecal content, it was found to release budesonide of 30%. Increment in the in vitro release of budesonide in the release medium containing rat cecal contents revealed the susceptibility of interpolymeric complex (composed of chitosan and carboxymethylated tamarind gum) to the polysaccharides present in the colon. The absolute budesonide release was not evidenced even after a period of 24 h from the

coated matrix tablets coated with chitosan:carboxymethylated tamarind gum in a ratio of 40:60 or 50:50. The presence of enzyme, chitosanase improved the budesonide release amount from these coated interpolymeric complex matrix tablets. It was also observed that the ultimate contact of these matrix tablets coated using chitosan and carboxymethylated tamarind gum ratio of 40:60 or 50:50 in the dissolution medium containing chitosanase for a period of 19 h augmented the in vitro budesonide release amount from these coated matrix tablets containing Eudragit L100-55 as binding agent to 92.43 and 83.25%, respectively, in the release medium containing rat cecal contents. However, in the release medium absenting rat cecal content, it was found to release budesonide of 70.50 and 59.80%, respectively. Release kinetic of budesonide was found to be following zero-order kinetic model as well as transport mechanism of super case-II in each release media studied including release media containing chitosanase and rat cecal content. These results suggested resistance of the interpolymeric complex between chitosan and carboxymethylated tamarind gum in the release media of different pH studied. As per the results, the in vitro budesonide release occurred because of slower erosion of the polymeric matrix. The budesonide matrix tablets coated with 40:60 and 50:50 ratio of chitosan:carboxymethylated tamarind gum containing Eudragit L100-55 or chitosan:carboxymethylated tamarind gum as binder were observed to show physical as well as chemical stability on storage at relative humidity of 75% and temperature of 40 °C. Any kinds of color changes as well as weight of these tablets were not observed.

In the pharmacokinetic study in the Sprague-Dawley rats, the uncoated budesonide matrix tablets containing Eudragit L100-55 were found incapable to retard the release of budesonide, in vivo. The in vivo plasma concentration of budesonide was observed to augment rapidly after oral administration of uncoated matrix tablets. 1091.99 ng/ml of t_{max} was attained within 2 h. The period to attain C_{max} after oral administration of uncoated matrix tablets was observed to delay to 8 h for the coated tablets. The in vivo results clearly suggested the incapability of the interpolymeric complex films to resist the budesonide release in the gastric pH. Nevertheless, the in vivo plasma concentration in rats orally administered with the coated matrix tablets of 50:50 and 40:60 ratio of chitosan:carboxymethylated tamarind gum augmented progressively after a time period of 4 h and after 8 h, it was found turned down. These results suggested the proneness of the polymers employed (chitosan and carboxymethylated tamarind gum) to degrade the matrix by the polysaccharidases present in the colon. Histopathology of rat colon after oral administration of the chitosan-carboxymethylated tamarind gum interpolymeric complex film coated tablets exhibited a significant decrease ($p < 0.05$) in the TNBS-induced ulcerative colitis in comparison to that after the oral administration of the uncoated matrix tablets. From this study, it was found that the matrix tablets coated with chitosan and carboxymethylated tamarind gum in a ratio of 40:60 can be envisioned to recommend a great deal of guarantee in colonic delivery of drugs.

4.6 Carboxymethylated Tamarind Gum-Poly Vinyl Alcohol Cryogels for Sustained Drug Release

In a research, Meenakshi and Ahuja (2015) prepared and characterized composite cryogels of carboxymethylated tamarind gum-poly vinyl alcohol employing freeze–thaw treatment. Metronidazole (an imidazole derivative and antibacterial agent) widely used in bacterial vaginosis and periodontotis was investigated as model drug in this study. Metronidazole-loaded carboxymethylated tamarind gum-poly vinyl alcohol cryogels were optimized using three factors and three levels central composite design employing the concentration of carboxymethylated tamarind gum, concentration of poly vinyl alcohol and freeze–thaw cycle numbers as the factors (independable variables); whereas in vitro drug release rate was estimated as the response (dependable variable). The optimization analysis by response surface methodology showed the combined influence of concentrations of carboxymethylated tamarind gum as well as poly vinyl alcohol on the in vitro release of metronidazole from these cryogels. At the lower levels of carboxymethylated tamarind gum on increase of poly vinyl alcohol concentration, the percentage metronidazole release was found decreased, which can be explained by the fact of cryogel formation with higher cross-linking density. With the increasing concentration of carboxymethylated tamarind gum, the release of metronidazole was found to be increased. However, the effect of carboxymethylated tamarind gum concentration was found to be comparatively more prominent at the higher levels of poly vinyl alcohol. At the medium as well as lower levels of poly vinyl alcohol, increased concentration of carboxymethylated tamarind gum resulted increment followed by fall in the in vitro drug release rate. The enhancement in carboxymethylated tamarind gum concentration resulted in higher percentage in drug release. In contrast, this increased the contact of these newly synthesized cryogels to freeze–thaw cycles from medium to lower levels, which decreased the drug releasing rate. The optimized calculated parameters were poly vinyl alcohol concentration of 8.45%, carboxymethylated tamarind gum concentration of 6.00 w/v and freeze–thaw cycles of 4 and this showed percent drug release of 75.77% (optimization predicted value was 79.77%; percent prediction error of 4.93%).

In vitro swelling behavior of optimized carboxymethylated tamarind gum-poly vinyl alcohol composite cryogel was carried out in phosphate buffer solution (pH 6.8) for 24 h. Swelling patterns of different prepared cryogels demonstrate deviations of swelling rates. Nevertheless, any significant model explaining link in-between the swelling behaviors, freeze–thaw cycling as well as concentration of polymers employed to prepare cryogels might not be found. The swelling patterns of optimized carboxymethylated tamarind gum-poly vinyl alcohol cryogels also indicated an early rapid drug release rate and slower rate towards an equilibrium swelling.

The optimized carboxymethylated tamarind gum-poly vinyl alcohol cryogels was characterized by means of SEM, FTIR, DSC, and XRD analyses. The SEM photographs revealed that the carboxymethylated tamarind gum particles were of

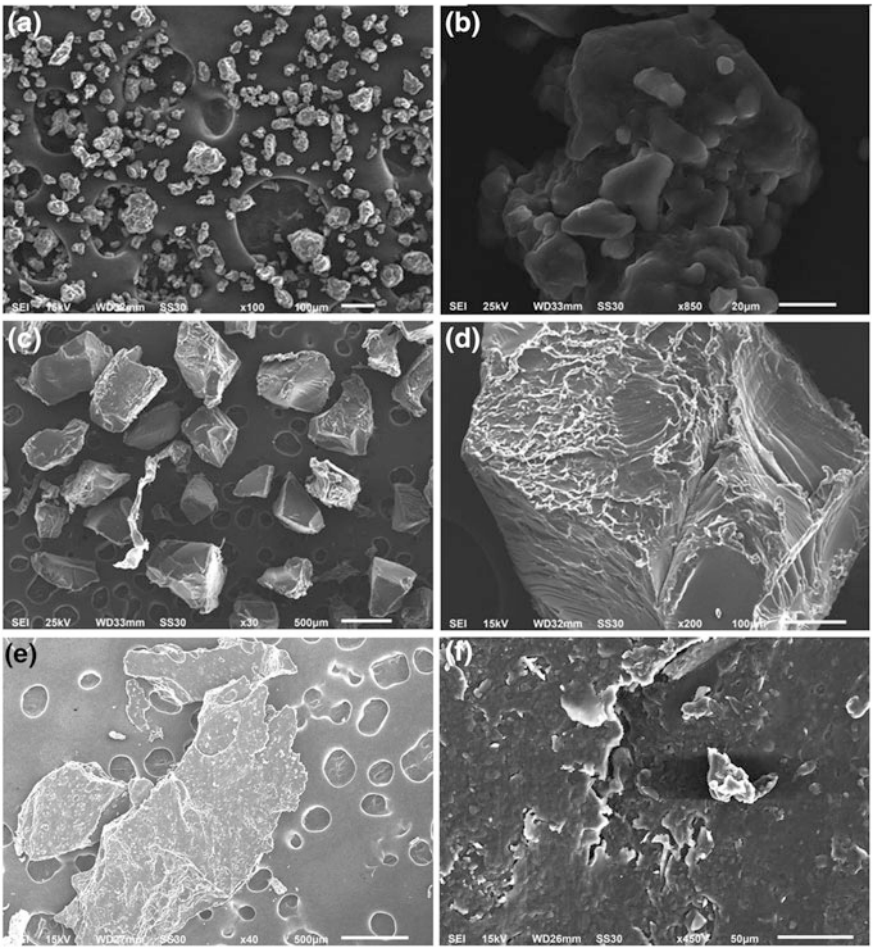

Fig. 3 SEM photograph showing **a** shape and **b** surface of carboxymethylated tamarind gum, **c** shape and **d** surface of poly vinyl alcohol, **e** shape and **f** surface of carboxymethylated tamarind gum-poly vinyl alcohol composite cryogel (Meenakshi and Ahuja 2015). Copyright ©2014 with permission from Elsevier B.V.

polyhedral shaped with straiated surface. The newly synthesized composite cryogel particles made of carboxymethylated tamarind gum-poly vinyl alcohol appeared as amorphous flakes with a granular as well as porous surface (Fig. 3). FTIR, XRD, and DSC analyses indicated the chemical interactions between carboxymethylated tamarind gum and poly vinyl alcohol in the synthesized cryogel structure. In addition, DSC analysis revealed higher thermal stability of these carboxymethylated tamarind gum-poly vinyl alcohol cryogels.

5 Thiolated Tamarind Gum in Drug Delivery

5.1 Thiolation

Mucoadhesion of naturally derived polysaccharide through derivatization with thiol functional group containing reagents has been employed to enhance the bio-mucoadhesive as well as cohesive characteristics of various polymers (Sharma and Ahuja 2011). Thiolated polymers (commonly called as thiomers) are considered as latest generation of biomucoadhesive polymers, which mimic the natural mechanism of secreted mucus glycoprotein through covalently fixing on the mucus layer by means of disulfide bonds (Bernkop-Schnürch et al. 2003; Bahulkar et al. 2015). Thiol (–SH) side chains of different polymers can interact with the sulfur-rich subdomains of mucus glycoprotein bonding through disulfide bonds in-between the mucus layer and mucoadhesive polymers (Sharma and Ahuja 2011). These thiolated polysaccharides structure stronger covalent bonds (S–S disulfide bonds) via appearing in contact with mucus glycoproteins (Bernkop-Schnürch et al. 2003). This improved mucoadhesion facilitates localization of dosage systems at the drug targeting site (Sharma and Ahuja 2011; Bahulkar et al. 2015). In addition, the disulfide bonds enhance the stability of matrices through delaying disintegration and erosion by increasing swelling behaviors (Bahulkar et al. 2015). Apart from the mucoadhesivity addition, thiolation of polysaccharides imparts enhancement of oral mpermeation of proteins and peptides (Bernkop-Schnürch et al. 2003), inhibition of efflux proteins, enzymes (Bernkop-Schnürch et al. 2001), and exhibits in situ gelling properties (Krauand et al. 2003). Thiolation or thiol modification of numerous natural polymers such as karaya gum (Bahulkar et al. 2015), alginate (Martinez et al. 2011), pectin (Sharma and Ahuja 2011), xyloglucan (Mahajan et al. 2013; Sonawane et al. 2014), gellan gum, etc., has been profitably researched.

5.2 Thiolated Tamarind Gum in Mucoadhesive Drug Delivery

Kaur et al. (2012a, b) synthesized and characterized thiolated tamarind gum. The thiol functionalized tamarind gum was synthesized through esterification by using thioglycolic acid with hydrochloric acid, where esterification of hydroxyl (–OH) groups of galacoxylan moiety of tamarind gum with the carboxylic (–COOH) groups of thioglycolic acid occur. Through the repeated washings using methanol, the unreacted acid was removed. The determination of thiol (–SH) group substitution on the synthesized thiolated tamarind gum was done through thiol groups quantifications by means of the Ellman's method. Thiolated tamarind gum was estimated 104.50 mM of thiol groups/gram through the Ellman's method.

The thiol functionalized tamarind gum was found as off white colored and also found soluble in water. Thiolated tamarind gum was characterized via infrared (IR) and DSC analyses. Both the instrumental analyses (IR and DSC) confirmed the thiol functionalization on the tamarind gum. The IR spectra of thiolated gum displayed the characteristic peak of thiol (–SH) groups (2586.54 cm^{-1}) and hydroxyl (–OH) groups (3367.71 cm^{-1}). The DSC thermal curve showed a broad endotherm at 81.87 °C (heat of infusion, 22.85 J/g) followed by a fairly sharp endotherm at 145.38 °C (heat of fusion, 75.88 J/g). Thiolated tamarind gum was also characterized by XRD and the X-ray diffractogram of thiolated tamarind gum showed a typical pattern of diffraction, which was similar to the native tamarind gum with the absence of sharp peaks with greater intensity demonstrating a higher crystallinity degree due to thiolation. SEM analyses of thiolated tamarind gum displayed a polyhedral morphology. The surface morphology of thiolated tamarind gum revealed a rougher surface of thiolated tamarind gum compared to native tamarind gum (Fig. 4).

Compacts (13 mm diameter) of thiolated tamarind gum (200 mg) and native tamarind gum (200 mg) were prepared via direct compression technique. Compacts were assessed for the mucoadhesive potential and compared. The maximum forces of the detachment of thiolated tamarind gum compacts and native tamarind gum compacts from mucin-coated model membrane were measured as 4062.50 ± 845.15 and 592.90 ± 161.48 mN, respectively. These results indicated improved mucoadhesion of thiolated tamarind gum as compared to the native tamarind gum (6.85 fold greater).

On the basis of the mucoadhesive results, mucoadhesive gels of metronidazole (as a model drug) composed native and thiolated tamarind gum. These 1% w/v metronidazole mucoadhesive gels were prepared by employing Carbopol 974 P as a gelling agent. The viscosities of these gels were determined by Brookfield viscometer. Viscosities of these gels were in order of: native tamarind gum > Metrogyl® > thiolated tamarind gum (Fig. 5). Biomucoadhesive strengths of these prepared and marketed gels were also compared to marketed gel of metronidazole (Metrogyl®). Mucoadhesive strengths of these gels were estimated by modified physical balance using fresh chicken intestinal membrane from the gel surface and maximum mucoadhesivity was measured for the mucoadhesive gels of metronidazole-containing thiolated tamarind gum as mucoadhesive agent. The mucoadhesive strengths of these mucoadhesive gels were in order of: thiolated tamarind gum > native tamarind gum > Metrogyl®. The adhesiveness and hardness of these gels were measured in the order of: native tamarind gum > Metrogyl® > thiolated tamarind gum. The cohesiveness of these mucoadhesive gels was found in the order of: thiolated tamarind gum > tamarind gum > Metrogyl®. Among these, mucoadhesive gels of thiolated tamarind gum exerted highest cohesiveness, least values of hardness and adhesiveness.

In vitro drug releases from these mucoadhesive gels containing metronidazole (made of thiolated tamarind gum and native tamarind gum) were compared with marketed metronidazole gel (Metrogyl®). From the in vitro metronidazole releasing

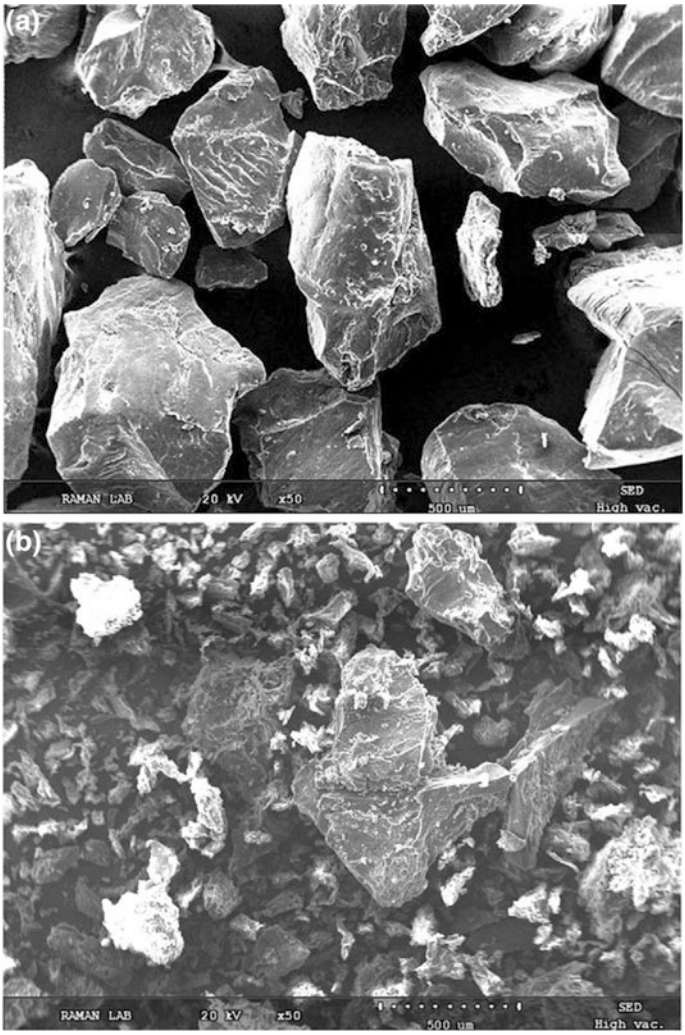

Fig. 4 SEM images of **a** native tamarind gum and **b** thiolated tamarind gum (Kaur et al. 2012a, b). Copyright ©2012 with permission from Elsevier Ltd.

pattern, it was seen that the marketed gel provided the slowest metronidazole release, followed by thiolated tamarind gum; whereas the fastest metronidazole release was measured from the metronidazole gel containing native tamarind gum as mucoadhesive agent (Fig. 6). These gels were found dependent upon the diffusion of metronidazole from the viscous gel matrix. Native tamarind gum and marketed gel formulations of metronidazole followed first-order kinetic model of drug releasing, while thiolated tamarind gum-based mucoadhesive gel formulation of metronidazole followed best fit Higuchi's square root kinetic model. The in vitro

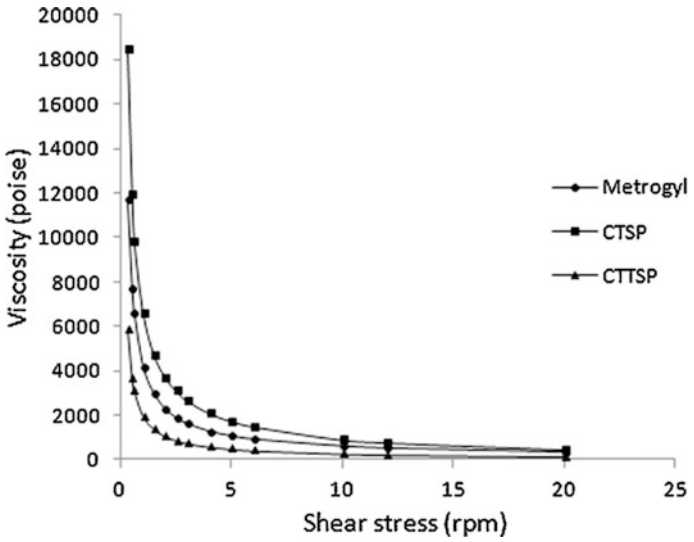

Fig. 5 Rheological profile of various mucoadhesive gels (Kaur et al. 2012a, b). Copyright ©2012 with permission from Elsevier Ltd.

metronidazole release from the thiolated tamarind gum-based mucoadhesive gels of metronidazole was found to follow diffusion-based drug release mechanism.

6 Graft-Modified Tamarind Gum in Drug Delivery

6.1 Graft Modification

Grafting of polymers is an effectual method for the modification of characteristics of various natural polymers as well as synthetic polymers (Singha et al. 2008; Thakur and Thakur 2015; Thakur et al. 2016). The modification of natural polymeric substances through graft copolymerization proffers opportunities to tailor their physical as well as chemical characteristics, to functionalize polymeric structures for imparting advantageous characteristics onto these and also uniting the benefits of both synthetic and natural polymers (Wang and Wang 2013; Thakur et al. 2012, 2013a, b, c, d, 2014a, b; Thakur and Singha 2011). Therefore, grafting copolymerization is currently considered as an effectual procedure for the enhancement of the compatibility in-between natural and synthetic polymers to synthesize new polymeric materials with improved hybrid properties (Bhattacharya and Mishra 2004; Bhattacharya and Ray 2009). Grafting of polymers entails the attachment of polymeric chains, typically a monomer, to the backbone polymeric structure (Thakur et al. 2014a; Thakur and Thakur 2015). Important methods

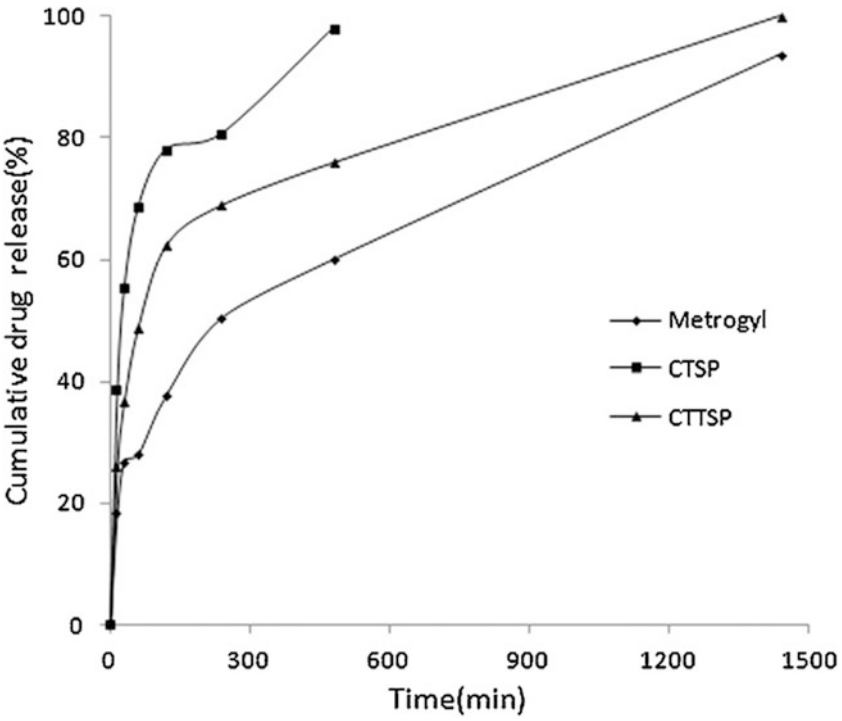

Fig. 6 In vitro release profile of metronidazole from various mucoadhesive gels (Kaur et al. 2012a, b). Copyright ©2012 with permission from Elsevier Ltd.

employed for the polymer grafting are conventional radical grafting, macromonomer radical grafting, high-energy initiation grafting, microwave-assisted grafting, radiation initiation grafting, electron beam initiated grafting, atom transfer radical grafting, etc. (Bhattacharya and Mishra 2004; Bhattacharya and Ray 2009; Wang and Wang 2013; Thakur and Thakur 2015). Recent years, using graft copolymerization methods, synthetic grafts have been introduced in numerous polysaccharides like cellulose (Thakur et al. 2013a), alginate (Sand et al. 2010), chitosan (Prashanth and Tharanathan 2003), xanthan gum (Pandey et al. 2001), guar gum (Pandey et al. 2014, 2015), amylopectin (Sarkar et al. 2013; Ahuja et al. 2014), gum tragacanth (Masoumi and Ghaemy 2014; Hemmati and Ghaemy 2016; Singh et al. 2016), tamarind gum (Ahuja et al. 2013; Ghosh and Pal 2013; Meenakshi et al. 2014), gum acacia (Tiwari and Singh 2008), gellan gum (Vijan et al. 2012; Nandi et al. 2015), okra gum (Mishra and Pal 2007; Mishra et al. 2008), cashew gum (Guilherme et al. 2005), gum ghatti (Rani et al. 2012; Mittal et al. 2014, 2015), psyllium polysaccharide (Singh et al. 2008), bael gum (Setia and Kumar 2014), etc.

6.2 *Tamarind Gum-g-Polyacrylamide as Matrix for Controlled Release of Drug*

Ghosh and Pal (2013) investigated pH dependent hydrogels of graft-modified tamarind gum as matrix-forming material for controlling of drug release. The graft-modified tamarind gum was chemically synthesized by means of grafting with polyacrylamide chains on the tamarind gum backbone in the microwave irradiation and presence of a reaction initiator (i.e., ceric ammonium nitrate). The graft copolymerization mechanism is based on the fact, where the microwave energy is being absorbed by the polysaccharidic structure and produces free radicals. Free radicals are usually recombined with each other via the steps of initiation, propagation, and termination to synthesize grafted copolymer of tamarind gum. Different graft copolymers of tamarind gum and polymethacrylamide were synthesized as a result of altering reaction constraints and optimized copolymerization with the respect of percent grafting (%), intrinsic viscosity, and radius of gyration.

The synthesized tamarind gum-g-polyacrylamide was evaluated for the matrix-forming materials for controlled release using aspirin (a NSAID, widely used in various pain relief man agent). To prepare tamarind gum-g-polyacrylamide matrix tablets of aspirin, guar gum was employed as binder in the ratios of 10:1:0.3. The prepared tablet matrix was characterized by FTIR and SEM analyses. FTIR results clearly indicated nonexistence of any kinds of chemical interaction(s) in-between aspirin and the tamarind gum-g-polyacrylamide matrix, recommending aspirin-tamarind gum-g-polyacrylamide matrix compatibility in the matrix tablets. SEM analyses revealed morphological changes, indicating physical (but, not chemical) interaction in-between aspirin and the tablet matrix (Fig. 7).

The swelling behavior of these tamarind gum-g-polyacrylamide matrix tablets of aspirin was measured at 37 °C in buffer solutions of different pH (1.2, 6.8 and 7.4) for 24 h. On contact with the buffer solutions, dry polymeric matrices of the tablets (tamarind gum-g-polyacrylamide) might be hydrated, swelled and then, formed a gel-like barrier layer, which delayed in vitro releasing of drug from the grafted matrices. It was also seen that the swelling pattern of tablet matrices was found

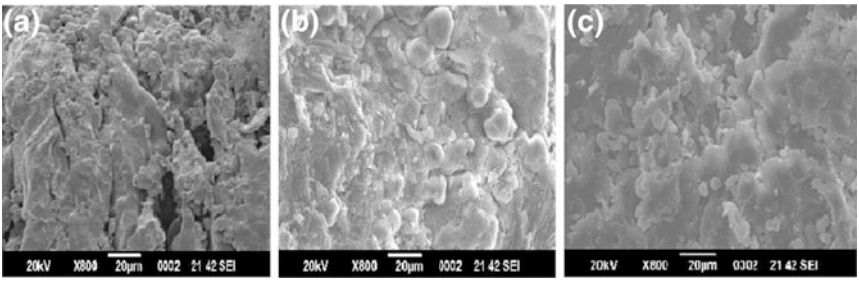

Fig. 7 SEM photographs of **a** tamarind gum-g-polyacrylamide 6, **b** aspirin, and **c** tablet (Ghosh and Pal 2013). Copyright ©2013 with permission from Elsevier B.V.

higher with the increment in percent grafting. The matrix erosion rate was found lower with the increment in percent grafting. This occurrence can be characterized by the fact that the larger hydrodynamic volume should be occupied by higher molecular weight polymeric chains due to hydration. Since the polymeric chains of the swelled matrices became more hydrated, it experienced simultaneous swelling of tablet matrices, drug dissolution and also, drug diffusion into the bulk swelling medium. After attaining the equilibrium swelling, ionic strengths of the polymeric matrices were amplified. This produces lesser rate of erosion of the polymeric matrices and this phenomenon maintains the delayed drug release or controlled drug release from the drug releasing matrices. In view of the fact that, with the enhancement in the equilibrium swelling of the tablet matrices, the ionic strengths of the matrices raise and this occurs in declining of the rate of erosion similar to the lesser drug releasing rate from the matrices.

In vitro drug release behavior of these synthesized tamarind gum-g-polyacrylamide matrix tablets of aspirin was evaluated using dissolution apparatus USP in 900 ml of the buffer solutions of different pH (1.2, 6.8 and 7.4) maintained at 37 °C and 100 rpm. The drug (here aspirin) was found to be released completely from these matrix tablets after 24 h. In this research, it was detected that the rate of in vitro aspirin release from the newly synthesized tamarind gum-g-polyacrylamide based matrix tablets was low in the acidic pH but found to be released in much higher rate in the neutral as well as alkaline pHs. This was also observed that higher percent grafting lowered the rate of aspirin releases (controlled). It was also seen that with the increasing of percent grafting, swelling of matrices was found to be increased; whereas the erosion of tablet matrices and the release rate of aspirin were found decreased. The aspirin release rate from these tamarind gum-g-polyacrylamide based matrix tablets containing aspirin followed zero-order kinetic model and non-Fickian diffusion mechanism (Fig. 8), recommending the controlled release of aspirin. These types of grated tamarind gum based hydrogel tablets can be useful for the lesser gastrointestinal tract targeted drug delivery through oral administration.

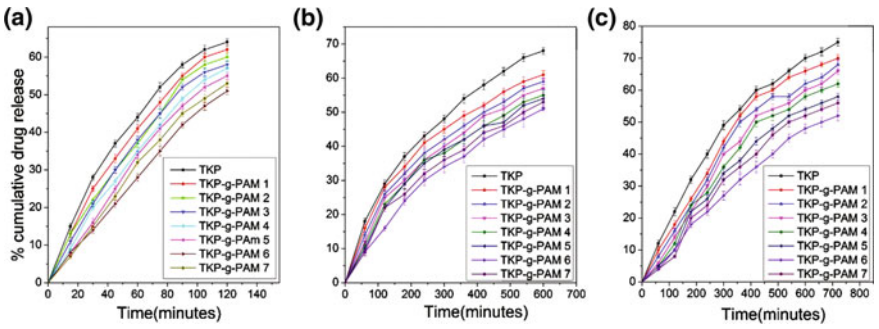

Fig. 8 Cumulative in vitro drug release profiles of tamarind gum-g-polyacrylamide based matrix tablets containing aspirin at **a** pH 1.2, **b** pH 6.8, and **c** pH 7.4. (Ghosh and Pal 2013). Copyright ©2013 with permission from Elsevier B.V.

6.3 *Tamarind Gum-g-Poly(*N*-Vinyl-2-Pyrrolidon) in Mucoadhesive Drug Delivery*

Ahuja et al. (2013) synthesized graft copolymers of tamarind gum with *N*-vinyl-2-pyrrolidone through microwave assisted graft copolymerization technique using ammonium persulfate as initiator and evaluated the synthesized graft copolymers of tamarind gum for the use as mucoadhesive polymers in the mucoadhesive drug delivery. In this research, the tamarind gum was isolated from tamarind kernel powder. Aqueous solutions containing 10% w/v native tamarind gum, 1% w/v *N*-vinyl-2-pyrrolidone and 10 mM/mL were irradiated using a microwoven at 20–60% microwave power for 60–150 s to prepare different batches of graft copolymers of tamarind gum. The process of graft copolymerization was statistically optimized by means of central composite design (2 factors and 3 levels), where microirradiation exposure time and microwave power were evaluated as independent factors and grafting efficiencies were analyzed as dependent responses. The statistical optimization-based response surface methodology indicated a mutual influence of microwave power and exposure time on percent grafting efficiency. It was also noticed that maximum grafting of *N*-vinyl-2-pyrrolidone on the tamarind gum took place at the lower microwave power for a longer time or at higher microwave power for a smaller period of exposing. At the elevated microwave power exposure for an exposure time of longer period resulted in lesser grafting efficiency, which appeared to be due to hydrolysis or degradation of the polymeric backbone. The optimal parameters were obtained 20% microwave power and 132 s microwave exposure time. The optimized batch of tamarind gum-g-poly (*N*-vinyl-2-pyrrolidon) has a maximum percent of grafting efficiency of 51.60% (where the predicted value was −56.86%).

These graft copolymers of tamarind gum and *N*-vinyl-2-pyrrolidone were also characterized using SEM, FTIR, XRD, and DSC analyses. These characterization analyses confirmed the formation of tamarind gum-g-poly(*N*-vinyl-2-pyrrolidon). The tamarind gum-g-poly(*N*-vinyl-2-pyrrolidon) was also assessed for biomucoadhesive application through the preparation of buccal patches containing metronidazole. Weight variation, thickness, assay, and friability of these metronidazole-containing buccal patches were assessed. The buccal patches were found of uniform weight (average) and uniform drug contents. The thickness of these patches was found within the range, 1.02–1.12 mm. The friability of the buccal patches was of less than 2%. The in vitro metronidazole release from these buccal patches composed of tamarind gum-g-poly(*N*-vinyl-2-pyrrolidon) was also tested. Almost similar drug releasing pattern was observed from these patches. These buccal patches exhibited drug release (less than 80%) and good ex vivo mucoadhesion time with chicken pouch membrane over a period of 9.3 h.

7 Conclusion

Though tamarind gum offers a great alternative to the other natural polysaccharides, it is imperative to understand the effect of introduction of suitable functional groups on its chemical structure for the better end applications in different areas. Tamarind gum is a plant-derived biocompatible polysaccharide, which is cheap and easily available in the nature. Various functionalized tamarind gum materials like carboxymethylated tamarind gum, thiolated tamarind gum, graft copolymerized tamarind gum, etc., have been explored as improved biomaterial for the formulation of effective drug delivery devices to achieve the desired drug releasing profiles because of their favorable physicochemical, biological, and mechanical properties. Several research works for the different types and patterns drug delivery applications employing various functionalized tamarind gum demonstrate the significant usefulness of the functional modifications of tamarind gum. The current chapter focuses on the different functionalized tamarind gum materials as prospective biopolymers in the formulation of effective drug delivery systems, which should be supportive for the drug delivery researchers.

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