



# Synthesis and characterization of PEPO grafted carboxymethyl guar and carboxymethyl tamarind as new thermo-associating polymers

Nivika R. Gupta<sup>a</sup>, Arun Torris A. T<sup>a</sup>, Prakash P. Wadgaonkar<sup>a</sup>, P.R. Rajamohanam<sup>a</sup>,  
Guylaine Ducouret<sup>b</sup>, Dominique Hourdet<sup>b</sup>, Costantino Creton<sup>b</sup>, Manohar V. Badiger<sup>a,\*</sup>

<sup>a</sup> Polymer Science and Engineering Division, CSIR–National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

<sup>b</sup> ESPCI ParisTech/Sorbonne Universités, UPMC Univ Paris 06/CNRS UMR 7615, SIMM, 10 rue Vauquelin, F-75005 Paris, France

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## ABSTRACT

New thermo associating polymers were designed and synthesized by grafting amino terminated poly(ethylene oxide-co-propylene oxide) (PEPO) onto carboxymethyl guar (CMG) and carboxymethyl tamarind (CMT). The grafting was performed by coupling reaction between  $\text{—NH}_2$  groups of PEPO and  $\text{—COOH}$  groups of CMG and CMT using water-soluble EDC/NHS as coupling agents. The grafting efficiency and the temperature of thermo-association,  $T_{\text{assoc}}$  in the copolymer were studied by NMR spectroscopy. The graft copolymers, CMG-g-PEPO and CMT-g-PEPO exhibited interesting thermo-associating behavior which was evidenced by the detailed rheological and fluorescence measurements. The visco-elastic properties (storage modulus,  $G'$ ; loss modulus,  $G''$ ) of the copolymer solutions were investigated using oscillatory shear experiments. The influence of salt and surfactant on the  $T_{\text{assoc}}$  was also studied by rheology, where the phenomenon of “Salting out” and “Salting in” was observed for salt and surfactant, respectively, which can give an easy access to tunable properties of these copolymers. These thermo-associating polymers with biodegradable nature of CMG and CMT can have potential applications as smart injectables in controlled release technology and as thickeners in cosmetics and pharmaceutical formulations.

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## 1. Introduction

Over the past decade, thermo-associating polymers have gained considerable attention and are being widely investigated due to their interesting properties in response to temperature as a stimulus (Liu & Urban, 2010; Meng & Hu, 2010). Contrary to the conventional water-soluble polymers, thermo-associating polymers in aqueous solution exhibit an opposite temperature dependence to the rheological properties in which the inter-chain interactions increase and gel with increase in temperature. In most cases, the thermo-associating behavior is characterized by the presence of a polymer exhibiting an interesting thermodynamic property of lower critical solution temperature (LCST) (Bokias, Mylonas, Staikos, Bumbu, & Vasile, 2001). Therefore, if a polyelectrolyte chain is grafted with small chains of polymer having an LCST, the grafts start to become incompatible/hydrophobic with water upon increasing the temperature and the resulting hydrophobic character induces an association, which manifests into transient

network formation leading to increase in viscosity. The precipitation of the polymer however, is prevented by the high hydrophilic nature of the backbone polymer. Various combinations of synthetic water-soluble polymers and polymers with characteristic LCSTs have been shown to exhibit thermo-associating behavior. For example, poly(*N*-isopropylacrylamide) [PNIPAm], poly(acrylic acid)-g-poly(ethylene oxide) [PAA-g-PEO] or poly(acrylic acid)-g-poly(*N*-isopropylacrylamide) [PAA-g-PNIPAm] have been shown to display thermo-associating behavior (Durand & Hourdet, 1999; Kjoniksen, Iversen, Nystrom, Nakken, & Palmgren, 1998). The thermo-associating behavior of these polymers can be easily controlled by external parameters such as polymer concentration, nature and amount of added salt, pH and temperature. Nevertheless, the nature of both components (backbone and the polymer chains with LCST) is expected to play an important role in the macroscopic properties. Hourdet et al. (Durand & Hourdet, 1999) have developed a whole family of thermo-associating polymers by grafting side chains like PEO, PNIPAm, PEPO onto a hydrophilic polymer namely, sodium poly(acrylate) [PAA-Na]. An excellent review on thermo-responsive copolymers with the fundamental aspects and applications has been reported by Liu, Fraylich, and Saunders (2009).

\* Corresponding author. Tel.: +91 2025902187; fax: +91 2025902612.  
E-mail address: [mv.badiger@ncl.res.in](mailto:mv.badiger@ncl.res.in) (M.V. Badiger).

Besides totally synthetic polymers, polysaccharide based thermo-responsive polymers are attracting increasing attention recently in biomedical applications. Polysaccharides are available in a variety of structure with different properties. Since they contain reactive functional groups, they can be easily modified chemically. Furthermore, their high stability, non-toxicity and biodegradability with gel forming property lead their applications in food and pharmaceuticals. In the recent past, many studies have been devoted to hydrophobically modified polysaccharides. For example, hydrophobically modified chitosan polymers (Bokias et al., 2001; Kjoniksen et al., 1998; Thatte, 2004), thermo-responsive graft copolymers of carboxymethyl cellulose (CMC) have been reported in the literature. An interpenetrating networks (IPNs) based on guar gum and poly(*N*-isopropylacrylamide) PNIPAm, with a major focus on swelling kinetics has been reported (Li, Wu, & Liu, 2008). Recently, Zhang et al. (2009) have reported on the synthesis and characterization of thermo-sensitive graft copolymer of poly(*N*-isopropylacrylamide) and carboxymethyl chitosan. Similarly, Shi and Zhang (2007) and Zhang et al. (2009) studied the grafting of poly(*N*-isopropylacrylamide) onto carboxymethylhydroxypropyl guar (CMHPG). However, it was intriguing to note from their study that, they did not observe the formation of hydrogel in their system but obtained thermo-sensitive polymer solutions. The polymer solutions did not exhibit thermo-thickening behavior but resulted in macroscopic phase separation. Huh, Hashi, Ooya, and Yui (2000) reported on the synthesis and characterization of carboxymethyl dextran and poly(*N*-isopropylacrylamide-*co*-*N*,*N*-dimethylacrylamide). Very recently, Pasale, Cerroni, Ghugare, and Paradossi (2014) have reported on the design and synthesis of multi-responsive hydrogels based on azide-derivative of hyaluronate and propargyl end functionalized telechelic PNIPAm using “click chemistry” approach.

Most of the thermo-associating polymers based on synthetic and natural polymers, exhibit either phase separation or decrease in viscosity upon heating. The true thermo-thickening (viscosity increase with temperature without undergoing macrophase separation) behavior is observed in a few cases which strongly depends on the balance of hydrophilic/hydrophobic components, concentrations and molecular weight of LCST side chains, pH and presence of salts in aqueous solutions.

Some of the polysaccharides used in the design and synthesis of thermo-associating polymers include Chitosan (Chung, Bae, Park, Lee, & Park, 2005; Kim, Cho, Lee, & Kim, 2000; Seetapan, Mai-ngam, Pluckaveesak, & Sirivat, 2006; Zhang et al., 2009), Hyaluronic acid (Yang, Kataoka, & Winnik, 2005b), carboxymethyl cellulose, alginates (Karakasyan, Lack, Brunel, Maingault, & Hourdet, 2008; Karakasyan et al., 2010), Pullulan (Belbekhouche, Ali, Dulong, Picton, & Le Cerf, 2011; Deguchi, Akiyoshi, & Sunamoto, 2003; Dulong, Mocanu, Picton, & Le Cerf, 2012; Mocanu, Mihai, Dulong, Picton, & Lecerf, 2011) and dextran (Huh et al., 2000; Karakasyan et al., 2008; Kurisawa & Yui, 1998). Bokias et al. (2001), have reported on the synthesis and aqueous solution properties of thermo-associating graft copolymers based on carboxymethyl cellulose [CMC] bearing PNIPAm side chains, CMC-*g*-PNIPAm. Tizzotti et al. (2010) have reported on thermo-associative guar-based grafted copolymers by “grafting onto” method through the CuAAC coupling showing reversible physical gelation. However, polysaccharides namely, guar gum (GG) and tamarind kernel powder (TKP) are not fully explored in synthesizing thermo-associating polymers based on them. Guar gum is a water-soluble nonionic polysaccharide extracted from the seeds of *Cyanopsis tetragonoloba*, constituted by a  $\beta$ -1, 4- mannose backbone with randomly distributed  $\alpha$ -1,6-galactose side chains. The mannose/galactose ratio is generally 2:1 (Staros & Swingle, 1986). Tamarind kernel powder (TKP) is derived from the seeds of the tree *Tamarindus indica*. TKP is composed of (1 $\rightarrow$ 4)- $\beta$ -D-glucan backbone substituted with side

chains of  $\alpha$ ,D-xylopyranose and  $\beta$ -D- galactopyranosyl. It is a non-ionic, neutral, branched polysaccharide in which glucose, xylose and galactose units are present in the ratio of  $\sim$ 3:2:1 (Staros, Wright & Swingle, 1986) because of which it is widely known as Xyloglucan.

Since, GG and TKP are non-ionic in nature their solubility in water is poor and hence the commercial grades of carboxymethyl derivatives (carboxymethyl guar, CMG and carboxymethyl tamarind, CMT) (see Fig. 1) of these polysaccharides are more useful and improve the aqueous solubility significantly.

In this paper, we report on the synthesis and thermo-associating properties of two graft copolymers namely (i) carboxymethyl guar-*g*-PEPO [PEPO = poly(ethylene oxide-*co*-propylene oxide)], CMG-*g*-PEPO and (ii) carboxymethyl tamarind-*g*-PEPO, CMT-*g*-PEPO. The grafting was performed by coupling reaction between amino terminated thermo-responsive PEPO with CMG and CMT using water-soluble EDC as a coupling agent. The aim of the work was to examine a structure-property relationship in terms of thermo-associating and rheological behavior and to investigate the influence of external parameters on the process of association. The structural characteristics of all the graft copolymers were performed using FT-IR and NMR spectroscopy. The thermo-associating behavior of graft copolymers was studied using fluorescence spectroscopy and rheometry. Since these polymers are non-toxic, bio-compatible and thermo-thickening at tunable temperature close to physiological conditions, they show promising applications as smart injectables in controlled drug delivery.

## 2. Experimental

### 2.1. Materials

Carboxymethyl guar (CMG) and carboxymethyl tamarind (CMT) were commercial products and were kindly provided by Dabur India Ltd., India; Jeffamine M-2005 (Plurionics), an amino terminated poly(ethylene oxide-*co*-propylene oxide) (PEPO) with 84 mol% of propylene oxide, was purchased from Huntsman, Belgium. The coupling agent, 1-(3-(dimethylamino) propyl)-3-ethyl carbodiimide hydrochloride (EDC) was obtained from Fluka, USA; *N*-hydroxysuccinimide (NHS) was purchased from Aldrich Chemical Company, USA; Other solvents used were of analytical grade and obtained from S.D Fine Chemicals, India. Except CMG and CMT, all the other chemicals were used as received. Water used for the experiments was purified using a Millipore laboratory unit (Q-Millipore, 18.2 M $\Omega$ ).

### 2.2. Purification of polysaccharides (CMG and CMT)

The commercial CMG and CMT samples were purified using the following procedure:

Ten gram of CMG/CMT was taken in a 1 L conical flask and 500 mL acetone was added to remove any organic soluble moieties. The entire mass was stirred with a magnetic needle on a magnetic stirrer for 12 h at room temperature (25 °C). Then it was filtered and dried. The dried CMG/CMT was dissolved in 1 L deionized water and centrifuged at 8000 rpm for 40 min. The supernatant liquid was dialyzed against water using a dialysis membrane with MWCO of 12 kDa. The dialysis was carried out for 24 h by frequently changing the external water. The dialyzed solution was then freeze-dried to obtain white cotton like material. The purified CMG/CMT were used for all the experiments.

### 2.3. Characterization of CMG, CMT and PEPO

The average molecular weight and polydispersity of CMG and CMT were measured by size exclusion chromatography (SEC) using OHpak SB-804HQ and Pullulan Standards from Shodex. The solvent,

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