

Original Research Article

Functional pH-responsive Poly(Styrene-Co-2-[(diethylamino)methyl]-4-formyl-6-methoxy-phenyl acrylate) Copolymers for Grafting Tryptophan

Abstract

Vanillin or 4-hydroxy-3-methoxy benzaldehyde has been used for preparing tertiary amine cationic monomer. The monomer has been used as pH-responsive and the functional aldehyde group was used for the formation of Schiff base. The new monomer was abbreviated by DEAMVA and investigated using chemical analysis e.g. ^1H NMR, ^{13}C NMR and FT IR all data were in logic case. The copolymerization of Styrene with 10 and 25 mol % of DEAMVA has been implemented by free radical polymerization. The copolymers have been chemically and physically evaluated e.g. ^1H NMR, FTIR, GPC, and DSC. Post polymerization modification of copolymer with 25mol% (III b) was fabricated via immobilization with Tryptophan, and has also been investigated by the same instrument used lately. Moreover, the responsive property of the posted polymer to pH has also been tested by UV-vis. Spectroscopy.

Keywords: Functional polymer; pH-responsive; Styrene; Vanillin; Amino acid; Post Polymerization modifications

1. Introduction

Smart pH-responsive polymers are kind of polyelectrolytes that have acidic or basic groups in their main chain and either can donate or withdraw protons in response to changes in pH of media [1, 2]. The charge along the polymer chain is responsible for the electrostatic repulsion that increases in the hydrodynamic volume of the polymer molecules [3, 4]. Such kind of transition between tightly coiled and swollen state is affected by any condition that modify

the electrostatic repulsion, e.g. pH, ionic strength, and type of counter ions. The transition state from collapsed into expanded was explained by changes in the osmotic pressure exerted by mobile counter ions and has been neutralized the network charges [2]. Many applications for pH-responsive polymers with the greatest interest in biomedicine e.g. Drug delivery systems and Gene carriers [5-11].

In the last few decades many scientists were looking for green alternatives of styrene monomer due to its disadvantages like, hazardous air pollutants and emitting during metering mixing process and curing; moreover, the unreacted styrene continues to be released from composites during life cycle [12]. They focused their research in the renewable resources e.g. cellulose, starch, natural oil...etc. they have been performed as alternative to produce bio-based monomers [13]. The lignin produced from Vanillin becoming relatively easily accessible; still there are only a handful of reports on attempts to utilize vanillin as monomers for bio-based polymer synthesis [14, 15]. The chemical modifications on vanillin have implemented attributed to the presence of both aldehyde and hydroxyl active groups [2, 16]. It exposed to dimerization and polymerization process via electrochemical reductive with horseradish peroxidase [17].

Schiff's base was used in the coordination chemistry and was found to be stable under redox conditions [18]. Recently, vanillin was used to form Schiff bases [19]. Their biological activities have been widely reported in many publications [20-24]; the most useful articles by Yuan et al., they used Schiff base as a stimuli-responsive linker in the polymer chain [25]. The imine linkage is pH-responsive [26, 27]. Moreover; the complexes formation of the imine have also been used to achieve the pH-responsiveness of the linker [28-33]. Several articles have reported "click reaction" as linkers for many bio-based molecules [34-36]. In this work, we fabricated new pH-responsive polystyrene copolymers from vanillin as renewable resource. The aldehyde group was used for posting biomolecule by Schiff base.

2. Experimental

2.1. Material

(AIBN Acrōs) 2,2'-azobis(isobutyronitrile) was recrystallized from methanol, acryloyl chloride (98% Merck), vanillin (99% Acrōs), styrene (99% Acrōs), triethylamine (Merck), tryptophan (97 % Acrōs). Toluene, dichloromethane, tetrahydrofuran, and diethylether were distilled. Other chemicals were used as purchased.

2.2. Instruments

Bruker AV 500 spectrometer was used to record ^1H and ^{13}C NMR spectra in CDCl_3 or DMSO-d^6 at 500 MHz and 125 MHz. FT IR Vertex 70 Fourier transform infrared instrument for recording IR spectra. The Molecular weights (M) and dispersity (D) were analysed by size exclusion chromatography (SEC). Chloroform was used as eluent (containing of 0.1 vol% triethylamine). UV/vis spectroscopy (Perkin Elmer Lambda 45) was used to estimate the concentration of amino acid in post-polymer. The pH of polymer solution was in THF and measured by pH-meter model VWR pH100. Perkin Elmer Differential Scanning Calorimeter (DSC) Pyris 1 was used for the glass temperature T_g of solid polymers at heating and cooling rate of $5\text{ }^\circ\text{C}/\text{min}$.

2.3. Synthesis of Monomer

2.3.1. Synthesis of 2-[(diethylamino)methyl]-4-formyl-6-methoxy-phenyl acrylate (DEMAVA) [20].

Step1: Synthesis of 3-[(diethylamino) methyl]-4-hydroxy-5-methoxybenzaldehyde [20]

10g (0.065 mol) of vanillin, (4-hydroxy-3-methoxy benzaldehyde), 10g (0.33 mol) of formaldehyde and 10g of diethylamine (0.136 mol) were dissolved in 150 mL ethanol in 250 mL round bottomed flask fitted with reflux condenser. They were refluxed in oil bath at $90\text{--}100\text{ }^\circ\text{C}$ for 3h. The mixture allowed cooling to room temperature. The solvent was removed under reduced pressure to collect the product. Yield %: 97%, Physical state: Yellowish white solid.

^1H NMR (500 MHz, CDCl_3): $\delta(\text{ppm}) = 1.18(\text{t}, 6\text{H}, 12\text{-CH}_3)$, $1.26(\text{br.}, \text{s}, 1\text{H}, 8\text{-OH})$, $2.73(\text{q}, 4\text{H}, 11\text{-CH}_2)$, $3.92(\text{s}, 2\text{H}, 9\text{-CH}_2)$, $3.94(\text{s}, 3\text{H}, 7\text{-CH}_3)$, $7.25, 7.34(\text{dd}, 2\text{H}, {}^4J = 1.6, 3,3\text{-Ar-CH}, 10\text{-NH}^+)$, $9.77(\text{s}, 1\text{H}, 1\text{-CHO})$.

^{13}C -NMR (125 MHz, CDCl_3): $\delta(\text{ppm}) = 10.82(2\text{C}, 12\text{-CH}_3)$, $46.35(2\text{C}, 11\text{-CH}_2)$, $55.85(1\text{C}, 10\text{-CH}_2)$, $56.01(1\text{C}, 8\text{-CH}_3)$, $109.68(1\text{C}, 4\text{-Ar-CH})$, $120.84(1\text{C}, 4\text{-Ar-CH})$, $125.75(1\text{C}, 5\text{-Ar-C})$, $127.99(1\text{C}, 3\text{-Ar-CH})$, $148.65(1\text{C}, 6\text{-Ar-CH})$, $154.87(1\text{C}, 7\text{-Ar-C})$, $191.65(1\text{C}, 2\text{-C=O})$.

IR (KBr): $\nu(\text{cm}^{-1})$: 2987 (s) (CH_2, CH_3), 1650 (s) (2-C=O), 1706 (s) (7-C=O), 820- 868 (m) (Ar-CH).

Step2: Synthesis of 2-[(diethylamino) methyl]-4-formyl-6-methoxyphenyl acrylate [20]

13.9g (0.058 mol) of 3-[(diethylamino) methyl]-4-hydroxy-5-methoxybenzaldehyde (**I**) was dissolved in 200 mL dry CH_2Cl_2 in two neck flask fitted with argon balloon. During stirring 12.3g (0.12 mol) of TEA was added. The reaction mixture allowed cooling in ice bath to 0-

5°C. After cooling, 5.4g (0.059 mol)acryloyl chloride was added drop wise. The yellowishsuspension was stirred at 5°C for 1h, and then allowed to stir at RT for 6 h. The precipitate was filtered and solvent was evaporated under reduced pressure. The product was extracted by CH₂Cl₂ and wash three times with 100ml distilled water then one time with 0.1M Na₂CO₃, and again with 100 mldistilled water, then product dried with MgSO₄ overnight. Yield %: 80%, Physical state: Orange solid.

¹H NMR (500 MHz, CDCl₃):δ(ppm) = 1.10(t, 6H,14-CH₃), 2.48 (q, 4H, 13-CH₂), 3.51 (s, 2H, 11-CH₂), 3.88 (s, 3H, 7-CH₃), 6.06 (dd, ²J = 1.3 Hz, ³J = 10.40 Hz,1H, 10a-CH), 6.37(dd, ³J = 10.40 Hz, ³J = 17.30 Hz, 1 H, 9-CH), 6.63 (dd, ²J = 1.3 Hz, ³J = 17.30 Hz, 10b-CH),7.25, 7.34 (dd, 3H, ⁴J = 1.6, ⁴J = 1.9, 3,3'- Ar-CH), 9.77 (s,1H, 1-CHO).

¹³C-NMR (125 MHz, CDCl₃):δ(ppm) =10.82 (2C, 12-CH₃), 46.35 (2C, 11-CH₂), 55.85 (1C, 10-CH₂), 56.01 (1C, 8-CH₃),109.68 (1C, 4'-Ar-CH), 120.84 (1C, 4-Ar-CH), 125.75 (1C, 5-Ar-C), 127.99 (1C, 3-Ar-CH), 148.65 (1C, 6-Ar-CH), 154.87 (1C,7-Ar-C), 191.65 (1C, 2-C=O).

IR (KBr): ν (cm⁻¹): 2987 (s) (CH₂, CH₃), 1650 (s) (2-C=O), 1706 (s) (8-C=O), 820- 868. (m) (Ar-CH).

2.4.Synthesis of Polymer

2.4.1. Synthesis of poly(Styrene-co-DEAMVA) with 10and 25 mol% of DEAMVA (2a)

A mixture of 10 and 25mol%, 1.088 g, and 2.176 g respectively of 2-[(diethylamino) methyl]-4-formyl-6-methoxyphenyl acrylate,4g (0.038mol) styreneand 10⁻³ mol% AIBN of the total mole% of monomers was dissolved in 70 mltoluene and then added to 100 ml round bottom flask. They were purged with argon for 15 min., and then heated in an oil bath at 70-80°C with continuous stirring for 6h. After cooling at room temperature followed in refrigerator,and was precipitated by solvent evaporation using rotatory evaporator.Polymer was purified by dissolved in THF, and re-precipitated in diethylether to remove the unreacted monomers and impurities. Yield %: 91%, and 82 for 10, and 25mol% respectively, Physical state: Yellowish white solid.

¹H NMR (500 MHz, CDCl₃):δ(ppm) = 0.50-2.71 (m, 9H, CH, CH₂-styrene repeating unit, 2CH₃ DEAMVA), 3.25-3.93 (m, 9H, 2CH₂, NCH₂, OCH₃ DEAMVA), 4.60-5.13 (m, 3H, CH, CH₂-DEAMVA repeating unit), 6.30-7.52(m, 6H, H-Ar), 9.75-9.97 (br., 1H, -CHO).

IR (KBr): ν (cm⁻¹): 2990(s) (CH-Aliphatic), 1720-1743 (s) (-C=O), 1134 (s) (-OCH₃).

2.4.2. Synthesis of 25mol% (2a-25) Poly(Styrene-co-DEAMVA)-post-tryptophan (2b) as a function of pH-responsive

In 50 ml round bottom flasks 1.0 g of 25mol% poly(Styrene-Co-DEAMVA) and 1.0 g of tryptophan has been dissolved in 30 ml THF. The reaction was implemented in different pH solutions pH4, pH7, pH9, pH10, pH12 by addition of NaOH and HCl. The mixtures were stirred gently for 2 h at room temperature. Solvent was removed under reduced pressure. After that the precipitate was dissolved in THF and re-precipitate in diethylether at -40 °C to remove impurities and unreacted molecules. Physical state: Brownish solid.

¹H NMR and IR of poly (Styrene-co-DEAMVA)-post-Tryptophan at pH12(IV)

¹H NMR (500 MHz, DMSO): δ (ppm) = 0.70-1.22 (m, 6H, 2CH₃, DEAMVA), 1.30-1.65 (m, 1H, CH repeating Styrene), 1.82-2.35 (m, 2H, CH₂ repeating styrene), 2.80-2.90 (m, 2H, 2NCH₂, DEAMVA), 3.30-3.40 (m, 2H, CH₂, DEAMVA), 6.10-6.34 (m, 1H, C=CH, Tryptophan), 6.80-7.85 (m, 9H, H-Ar), 8.5-8.6 (br. (s), 1H, CH=N), 9.30-9.942 (s) 1H, NH, Tryptophan).

IR (KBr): ν (cm⁻¹): 2995 (m) (CH-Aliphatic), 1663-1650 (s) (7-C=O), 1570-1560 (s) (4-CH=N), 1026-1107 (s) (8-OCH₃).

3. Results and Discussion

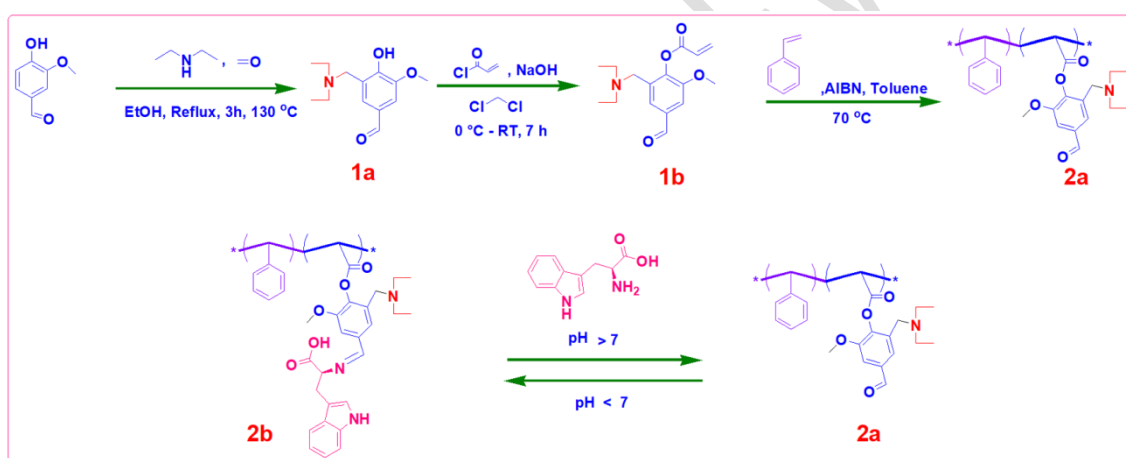
3.1. Synthesis of Monomer, copolymers and grafted copolymers

The chemical procedure has been described in **Scheme 1**. Monomer (**1b**) or 2-[(diethylamino)methyl]-4-formyl-6-methoxyphenyl acrylate (DEAMVA); it was prepared in two steps. The first is the preparation of (3-[(diethylamino)methyl]-4-hydroxy-5-methoxy-benzaldehyde) and has been occurred by the reaction of vanillin with diethylamine and formaldehyde according to Mannich reaction mechanism [1, 20]. The second is the preparation of 2-[(diethylamino)methyl]-4-formyl-6-methoxyphenyl acrylate (DEMAVA). It has been performed by the reaction of compound (**1a**) with acryloyl chloride and TEA to form (**1b**). They have been chemically investigated by ¹H NMR and ¹³C and FT IR. **Figure 1-3** proved all data and in logic state and has also been proved the presence of aldehyde group at 9.97 ppm and 196 ppm.

To optimize the general properties of styrene by free radical copolymerization with 10 and 25 mol% of DEAMVA were used in AIBA as initiator as **scheme 1**. The chemical structure was estimated by ¹H NMR and FT IR as shown in **Figure 4**. The ¹H NMR of copolymers **1a**,

2ademonstrated specific broad multiples peaks at $\delta = 0.73-1.35$ ppm of $2\text{CH}_3\text{DEAMVA}$, at $\delta = 7.08-7.62$ ppm of Ar-H of each styrene and DEAMVA, and at $\delta = 9.94$ of H-CHO of DEAMVA monomer. FTIR illustrated the presence of (C=O stretch) ester at 1745 cm^{-1} . The actually content of each monomer in the polymer main chain was detected from ^1H NMR spectra via the determination of the ratio of the intensity of the signals at 6.66 ppm (for H, Ar-H styrene) with signal at 9.94 ppm (for CHO of DEAMVA) as written in **Table 1**.

The aldehyde functional group in the polymer main chain was used for posting with any primary amino compound producing Schiff's base as in **Scheme 1**. The post-polymerization process was fabricated at room temperature in THF at different pH (pH4, pH7, pH9, pH10, pH12). Post-copolymer was investigated by ^1H NMR and FT IR. The ^1H NMR demonstrated the disappearance of aldehyde signal at 9.74 ppm and formation of new imino (HC=N) signal at about 8.5 ppm as in **Figure 3**. **Figure 4** showed FT IR spectra that proved the presence of imine (C=N stretch) at about 1563 cm^{-1} .



Scheme 1: Synthesis of new monomer, copolymers and post-polymer with Tryptophan.

Table 1: Yield, composition, conversion, number average molecular weight, polydispersity, and glass temperature of, Poly (S-co-DEAMVA) 10, 25 mole ratio of DEAMVA and Poly (S-co-DEAMVA)-post-try.

Polymer	Yield (%)	^1H NMR DEAMVA (mol %)	Conversion (%)	M_n^a (g/mol) 10^4	Đ^b	T_g^c (°C)
2a-10	91	6.35	-	44600	1.88	114
2a-25	82	17.67	-	17760	2.04	134
2b	76	-	84	15458	2.38	139

^aNumber average molecular weight,

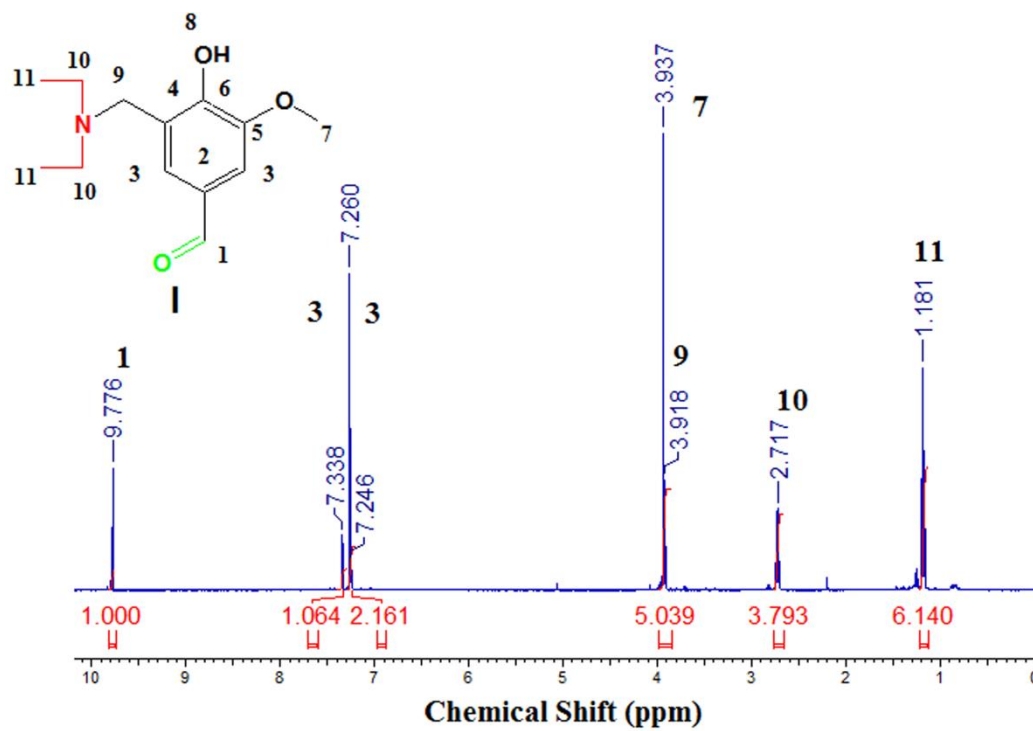
^bPolydispersity,^cGlass transition temperature,^dLower critical solution temperature.

Figure 1: ¹H NMR (CDCl₃) of 2-[(diethylamino)methyl]-4-formyl-6-methoxyphenyl acrylate.

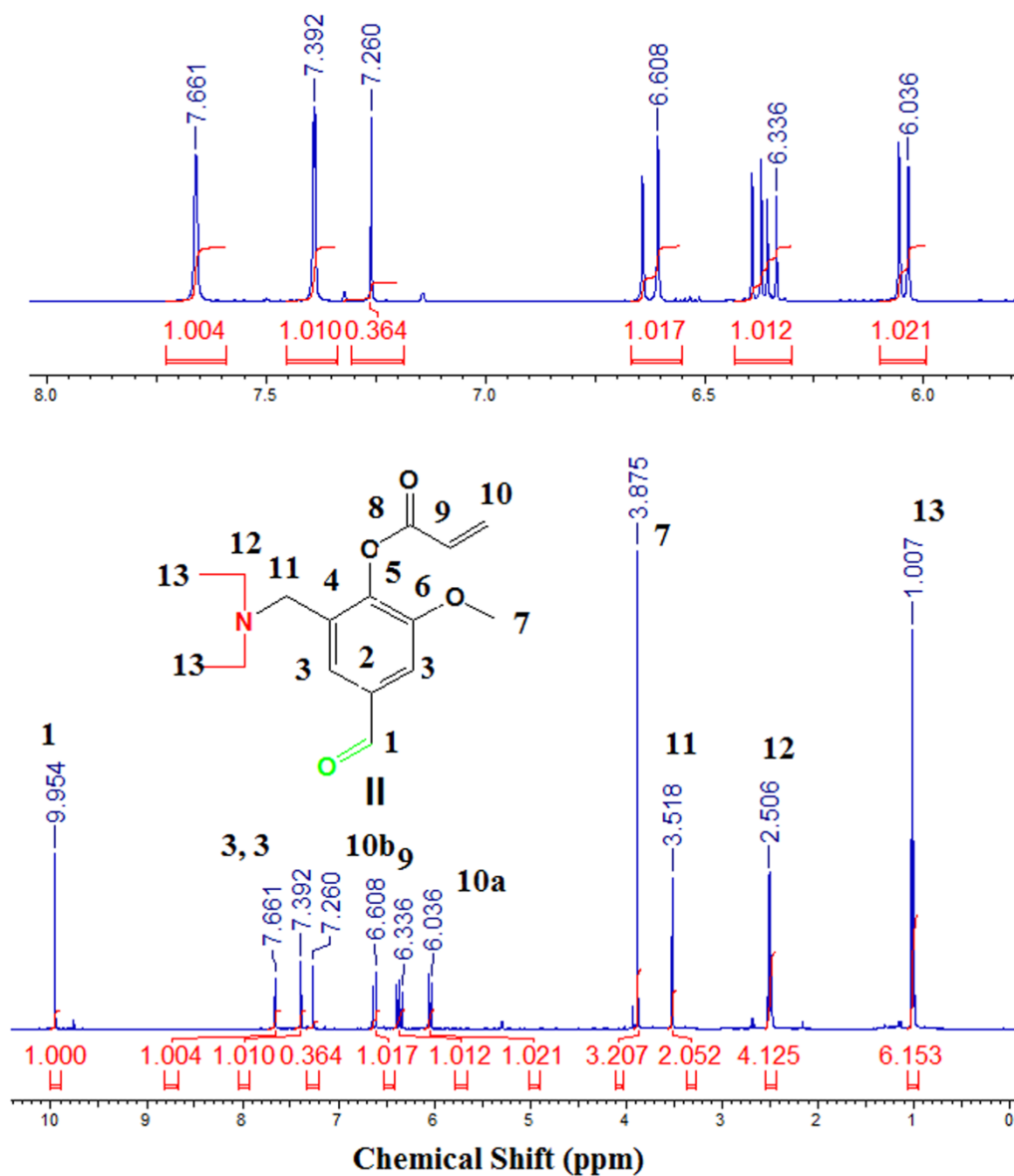


Figure 2: ^1H NMR (CDCl_3) of 2-[(diethylamino)methyl]-4-formyl-6-methoxyphenyl acrylate (DEMAVA).

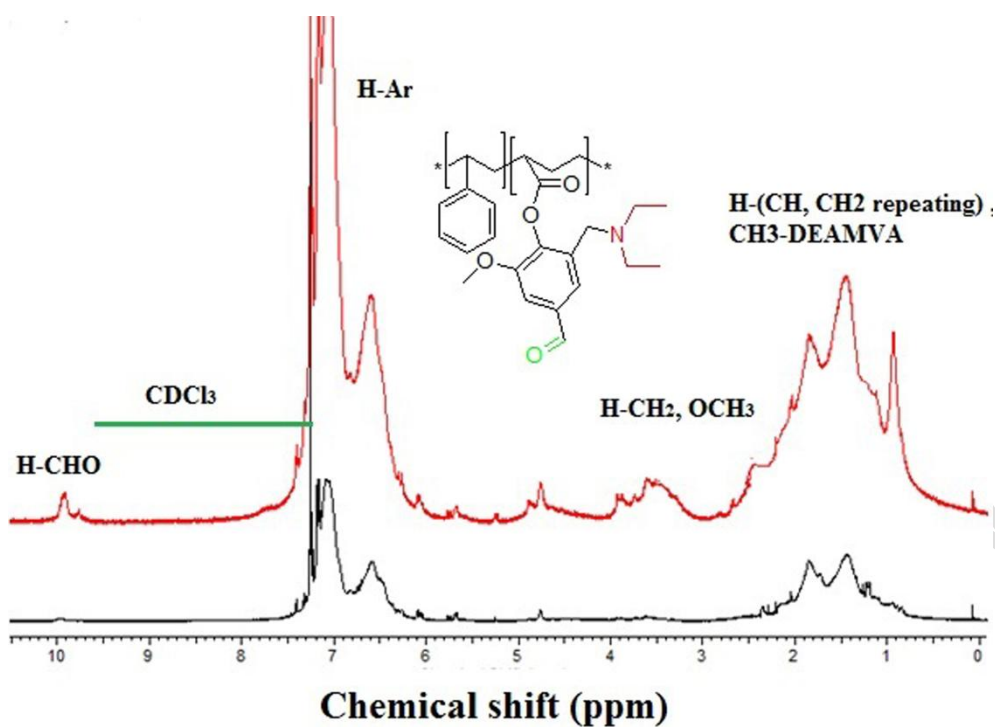


Figure 3: ^1H NMR spectra (CDCl_3) of $\text{P}(\text{S-co-DEAMVA})$ 10, 25 mole ratio of DEAMVA

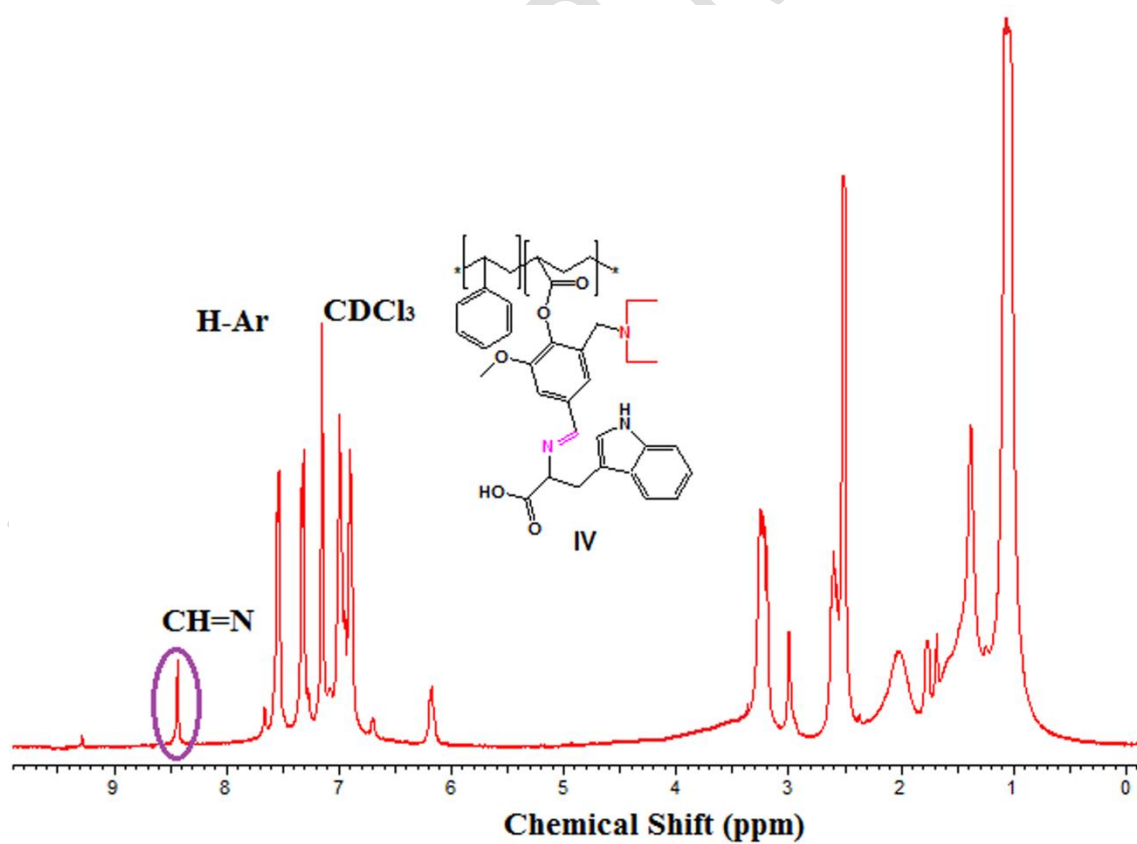


Figure 4: ^1H NMR spectra (DMSO) of $\text{P}(\text{styrene-co-DEAMVA})\text{-g-Tryptophan}$

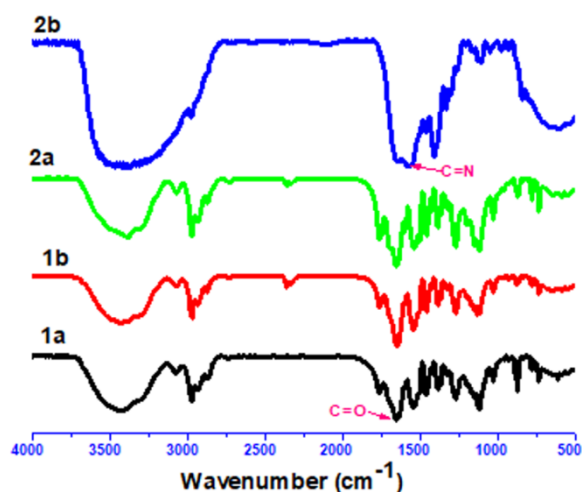


Figure 5: IR spectra KBr for DEAMV (I), DEAMVA (II), Poly (Styrene-*co*-DEAMVA) (III b) and grafted copolymers IV.

3.2. Polymer characterization

3.2.1. Molecular weight

Size exclusion chromatography was used for determination of number average molecular weight (M_n) and dispersity (D) of polymers using Polystyrene (PS) as standard in $CHCl_3$. **Table 1** summarized all recorded data for all copolymers. **Figure 6** shows the relation between molecular weight and $\log M$ as recorded by GPC and demonstrated one peak, that demonstrated the disappearance of low molecular weight like monomers or impurities.

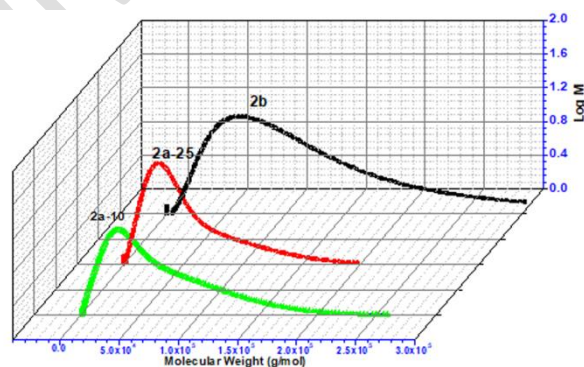


Figure 6: GPC molecular weight of copolymers

3.2.2. Conversion of poly (Styrene-Co-DEAMVA) to poly(Styrene-Co-DEAMVA)-g-tryptophan

The conversion of poly (Styrene-Co-DEAMVA) to poly (Styrene-Co-DEAMVA)-post-tryptophan by the chemical reaction, absorption was measured as function with pH at constant time (2h) for each test. The polymer solution was diluted to 10^{-3} W/V for each run. **Figure 7** illustrates the UV-vis. Spectroscopy of post reaction between poly(Styrene-Co-DEAMVA) with tryptophan. We noticed the disappearance of C=O aldehyde group at 250-270 nm and formation of new bond at 340-380 nm of C=N imine linkage. The formation of imino linkage has increased with increasing the pH value starting with pH5 which showed about zero absorbance and has been increased gradually till the highest value of absorbance pH12. **Figure 8** shows the relation between pH and absorbance intensity at constant time.

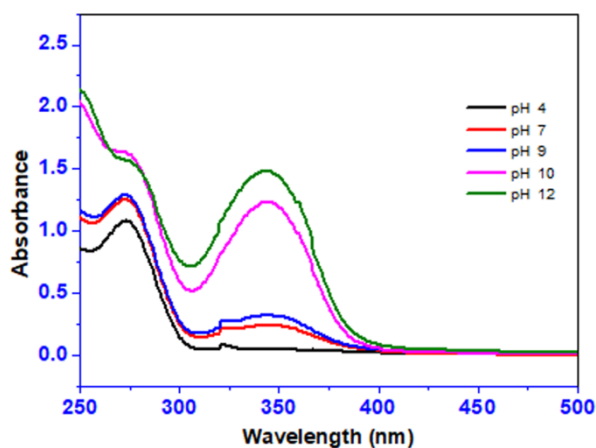


Figure 7: UV-vis. Spectroscopy for the formation of grafted poly (Styrene-Co-DEAMVA)-post-tryptophan as increasing in absorbance from pH5-pH12.

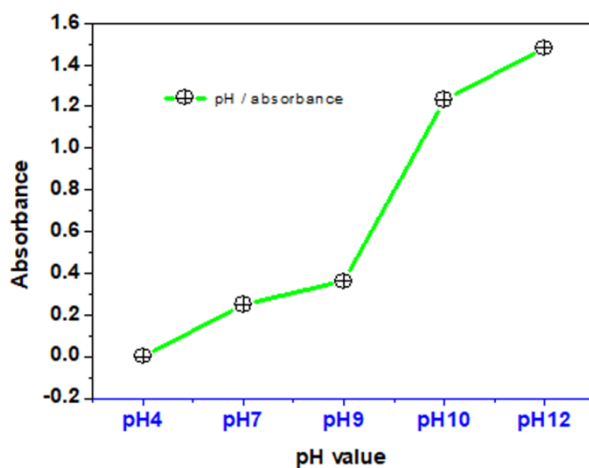


Figure 8: Relation between pH values and absorbance

3.2.3. Glass transition temperature

The glass transition temperature (T_g) was measured for all polymers. It was detected by Differential Scanning Calorimeter at heating rate 5 °C/min. It was recorded as the mid-point inflection in the thermogram. They have been tabulated in **Table 1** for copolymers and post-copolymer. a single T_g for each sample, which indicating the formation of random copolymers as shown in **Figure 9**[36]. The T_g of the homo-polystyrene(PS) showed at 100°C[37]. Copolymerization with DEAMVA change the hydrophobic and hydrophilic groups demonstrated in aromatic and tertiary amine respectively that increased T_g , which attributed to decrease in the spacing and therefore increasing in the interaction between polymer chains producing lesser flexibility and T_g of the polymer increased [36]. By introducing post molecule in copolymer (**2b**) main chain has directly influenced on raising the T_g due to the steric hindrance of aromatic molecule.

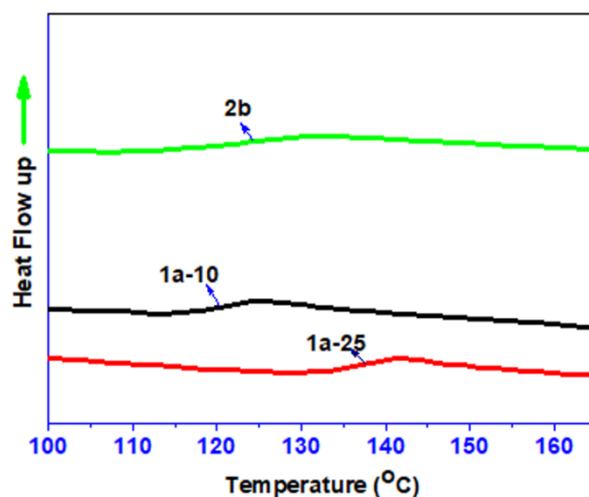


Figure 9: DSC shows the T_g of copolymers and grafted copolymer

4. Conclusion

We prepared functional polystyrene copolymers. The pH-responsive monomers have tertiary amine and aldehyde groups, and were prepared in two steps. We used free radical polymerization of styrene with two mole ratios of new monomer for fabricating copolymers. The post-polymerization was created by the reaction of aldehyde group with primary amine. Tryptophan was used post-polymerization. The uv.vis. Spectroscopy was used for detecting the post-polymer formation through the Schiff base absorption at different pH values. The highest absorption at pH12 and lowest at pH4 have been observed.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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