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A preliminary study on the synthesis and characterisation of dopamine-grafted block copolymers

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ABSTRACT

Biodegradable and biocompatible polymers are increasingly gaining importance in biomedical applications. Herein, we report the development of a thermoresponsive and tissue-adhesive platform based on a block copolymer of poly(N-isopropyl acrylamide) (P(NIPAM)) and polydopamine, synthesized via RAFT polymerization. Following the synthesis of P(NIPAM) homopolymer, P(NIPAM) was used as a macro-RAFT agent to incorporate the aldehyde block of the copolymer. The presence of aldehyde groups in the block copolymer was exploited to attach dopamine via imine chemistry. Spectroscopic and chromatographic techniques confirm the structures of intermediate compounds and polymers. The dopamine release profile of the copolymer was monitored for 72 hours at pH 7.4, and the total amount of dopamine released was found to be 53%. The synthesis of a dopamine-grafted block copolymer, which combines PNIPAM's thermoresponsive properties with dopamine's surface adhesion capabilities, suggests this platform could be a promising material for various future applications, such as implant interfaces and antimicrobial applications.

Keywords: polydopamine, RAFT polymerization, biocompatible materials

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INTRODUCTION

Dopamine (DA, 3,4-dihydroxyphenylethylamine) is an important neuromodulator molecule produced by animals and plants. Dopamine plays a part in many body functions, and changes in dopamine levels in the body are linked to many diseases[1].

In recent years, polydopamine (PDA), synthesized either by polymerizing dopamine-based monomers or by grafting dopamine into the functional group of a polymer backbone, has vital use owing to its significant properties, including its photothermal properties, redox capabilities, coating, and natural antibacterial and surface adhesion characteristics[2-6]. All these properties are related to the chemical structure of dopamine, specifically the catechol and primary amino groups[7]. The synthesis of dopamine-based polymers requires further investigation due to their potential as promising biocompatible and antimicrobial materials in material science and biotechnology[8,9].

Controlled "living" radical polymerization (CLRP) techniques promote controlled chain growth, maintain active chain ends, and enable chain re-growth as needed[10]. The molecular weight, distribution, and functionality of polymers can be controlled through CLRP techniques. The primary CLRP techniques are atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer (RAFT), and nitroxide-mediated polymerization (NMP)[11]. CLRP is also widely used to obtain complex macromolecular structures such as blocks, stars, and grafts. CLRP's architectural control and functionalization capacity have an impact on the usage of these methods in biomedical applications, surface coatings, and nanotechnology[12]. RAFT polymerization is one of the most preferred CLRP techniques because it enables the synthesis of polymers with a predefined, narrow molecular weight range and polydispersity, possessing the desired structural properties[13,14]. Moreover, RAFT polymerization is crucial for tailoring the design of polymer-based advanced biomaterials.

In recent years, biodegradable and biocompatible polymers have gained significant attention in both biomedical applications and materials science[15]. Biodegradable polymers interact with biological molecules and are used in various applications, including drug delivery and tissue engineering[16]. These polymers degrade in the body over time, producing harmless byproducts. These features make them preferred in treatment methods that require controlled drug release[17].

Using RAFT polymerization, different polydopamine (PDA) polymers can be synthesized either by directly polymerizing dopamine monomers or by the conjugation of dopamine molecules into the polymer's main chain through its functional groups (post-modification)[18-21]. The applications of PDAs can be enlarged by combining polymers with different properties (hydrophobic, hydrophilic, thermoresponsive, etc.) using different architectures such as block, star, and graft copolymers[7].

A temperature-sensitive polymer, poly(*N*-isopropyl acrylamide) (P(NIPAM) or PNIPAAm), is an important smart polymer that can change the conformation of its polymer chains by changing temperature. So, this property makes P(NIPAM) an excellent choice for the synthesis of temperature-sensitive systems in biomedical applications[22,23].

In a study by Mocan et al., a series of polystyrene-*b*-poly(*N*-isopropyl acrylamide) (PS-*b*-PNIPAM) block copolymers were synthesized via RAFT polymerization. Subsequently, innovative nanoporous membranes with fully temperature-controllable permeability were produced using the self-assembly and non-solvent induced phase separation (SNIPS) methods for these copolymers. As a result, it was determined that the permeability increased by almost 400% when the temperature rose from room temperature to 50°C, and this thermo-responsive characteristic was fully reversible[24]. In another study, micelles prepared from the amphiphilic block copolymer poly(*N*-isopropylacrylamide-*co*-acrylamide)-*b*-poly(*n*-butyl methacrylate), containing the poorly water-soluble anticancer drug methotrexate, were shown to achieve drug release and exhibit efficacy against cancer cells when combined with localized hyperthermia[25,26]. Furthermore, PNIPAM-protein-based conjugates were utilized for thermally controlled on-off switchable protein release owing to PNIPAM's lower critical solution temperature (LCST) behavior[27].

In a 2017 study by Zhang et al., a thermoresponsive surface was developed for culturing and harvesting human mesenchymal stem cells (hMSCs) by depositing PNIPAAm onto polydopamine (PDA) coated cell culture substrates. hMSCs were cultured on the prepared PNIPAAm-*g*-PDA coated surface and harvested by switching from physiological to ambient temperature. The results showed that hMSCs could detach from the PNIPAAm-*g*-polydopamine surface after the temperature was lowered. Furthermore, the detached hMSCs were able to proliferate on the PNIPAAm-*g*-PDA coated surface for further growth and harvest. The study presented the synthesis of a biocompatible and thermo-responsive surface for hMSCs that can be harvested[28].

Combining materials like polydopamine (PDA) and poly(*N*-isopropyl acrylamide) (PNIPAM) enables the development of specific applications, such as antimicrobial coatings, targeted drug delivery, and biosensor systems. Despite this progress, further research is still needed to develop these systems. Although few examples of PNIPAM-*b*-PDA block copolymer synthesis via RAFT polymerization exist, our study employs a different strategy[18-21]. Instead of conventional dopamine-based monomers, dopamine was grafted to the polymer using pH-sensitive imine bonds. This approach not only facilitates tunable control over the amount of conjugated dopamine but also the amount of dopamine conjugated to the polymer can be adjusted in a controlled manner.

For this purpose, herein we employed RAFT polymerization to synthesize p-(2-methacryloxyethyl)benzaldehyde) (MAEBA) and *N*-isopropylacrylamide block copolymers. Grafting of dopamine was then achieved via pH-sensitive imine bonding between the free aldehyde groups in the MAEBA block and the amine groups in the dopamine molecule. The chemical structure of the resulting dopamine-grafted copolymer was thoroughly characterized using spectroscopic and chromatographic methods. Finally, the dopamine release of this block copolymer at the physiological pH of 7.4 over a 72-hour period was investigated.

METHODOLOGY

Chemicals

Dopamine hydrochloride (≥98% (TLC)), 4-hydroxybenzaldehyde (98%), 2-bromoethanol (95%), methacryloyl chloride (97%, contains monomethyl ether hydroquinone as a stabilizer), triethylamine (≥99.5%, Et_3N), *N*-isopropylacrylamide (NIPAM, ≥99%), chloroform-*d* ($CDCl_3$), dimethyl sulfoxide-d_6, phosphate buffered solution (PBS), potassium carbonate (for analysis EMSURE® ACS, ISO, Reag. Ph Eur.), toluen (ACS reagent, ≥99.5%), tetrahydrofuran (≥99.9%, anhydrous, contains 250 ppm BHT as inhibitor, THF), acetonitrile (EMPLURA®, CH_3CN), and dimethylsulfoxide (ACS reagent, ≥99.9%, DMSO) were purchased from Sigma-Aldrich; dichloromethane (Ph. Eur., NF, DCM), hexane (extra pure), and diethyl ether (BP, Ph. Eur) were purchased from ISOLAB and all chemicals were used as received. Azobisisobutyronitrile (AIBN) and *N*-isopropylacrylamide were purified by crystallizing in ethanol, and then they were dried overnight at 25°C in a vacuum oven to remove the inhibitor separately.

Butyl 2-cyanopropan-2-yl-carbonotrichioate (CBPA) and aldehyde functional monomer (MAEBA, p-(2-methacryloxyethoxy)benzaldehyde) were synthesized according to a published procedure[29,30].

Instruments

Nuclear magnetic resonance (NMR) spectra were acquired with a Bruker BioSpin AG Avance 500 MHz spectrometer (^{1}H: 500 MHz, ^{13}C: 125 MHz) in $CDCl_3$ and DMSO-d_6 solvents. All chemical shifts are expressed in ppm (δ) relative to $Si(CH_3)_4$ (δ=0 ppm) as an internal standard. The average molecular weight (*M*n) and the molecular weight distribution index (PDI) (M_w/M_n) of the polymers were determined using a Viscotek GPCmax Gel Permeation Chromatography (GPC) instrument. A mobile phase of HPLC-grade tetrahydrofuran (THF) containing 0.05% butylated hydroxytoluene (BHT) was pumped at a rate of 1 mL/min and maintained at 35 °C. Polymer solutions, prepared in THF at a concentration of 4-5 mg/mL, were injected in 50 µL aliquots. Narrow-polydispersity polystyrene (PS) standards from Polymer Laboratories were used for calibration. The Bruker Alpha model was used for the FT-IR analyses. UV spectra were obtained using a Hitachi U-2900 UV-Vis spectrophotometer.

Synthesis of poly(N-Isopropylacrylamide) homopolymer (P(NIPAM))

Butyl 2-cyanopropan-2-yl-carbonotrithioate (CBPA) as the RAFT agent (17 mg, 0.058 mmol), NIPAM (0.5 g, 4.0 mmol), and azobis(isobutyronitrile) (AIBN, 1.2 mg, 0,007 mmol) were added to a septum-sealed flask and dissolved in 4.4 mL toluene[31]. The ratio of polymerization was determined as [M]$_0$/[RAFT-agent]/[AIBN]=75:1:0.125. The flask was placed in an ice bath, and nitrogen gas was passed through the reaction mixture for 45 minutes. Then, the reaction was placed in the oil bath pre-set to 70 °C and stirred at 400 rpm for 17 hours. After 17 hours, the seal of the flask was opened to the air environment. The polymerization solution was concentrated by partially evaporating the toluene, and the polymer in the flask was precipitated in a beaker with 10 times more hexane to remove the unreacted monomer and the RAFT agent. The purified polymer was then dried under vacuum overnight.

Block copolymer synthesis, poly(N-Isopropylacrylamide)-block-poly(p-(2-methacryloxyethoxy)benzaldehyde) (P(NIPAM-b-MAEBA))

The molecular weight of the P(NIPAM) homopolymer was determined as 4.36 kDa by using ^{1}H NMR analysis. 96 mg of homopolymer, 0.25 g (1.1 mmol) of p-(2-methacryloxyethoxy)benzaldehyde (MEABA) monomer, and 0.55 mg (3.3 mmol) of AIBN were weighed. They were added into a septum-sealed flask and dissolved in 1.65 mL toluene. The molar ratio of polymerization $[M]_o$/[MacroRAFT-agent]/[AIBN] was set to 50:1:0.150. The flask was placed in an ice bath, and nitrogen gas was passed through the reaction mixture for 45

minutes. The reaction was then placed in an oil bath pre-set to 70°C and stirred at 400 rpm for 18 hours. After 18 hours, the seal of the flask was opened to the air environment. The polymerization solution was concentrated by partially evaporating the toluene, and the block copolymer in the flask was precipitated in a beaker with 10 times more diethyl ether to remove the unreacted monomer and the precursor homopolymer and centrifuged. This process was done twice in total. The obtained polymer was dried overnight in a vacuum oven. The average molecular weight (M_n) of the copolymer was determined by gel permeation chromatography (GPC), and the $M_{n,NMR}$ value was determined by ^{1}H NMR analysis.

Grafting of dopamine to block copolymer

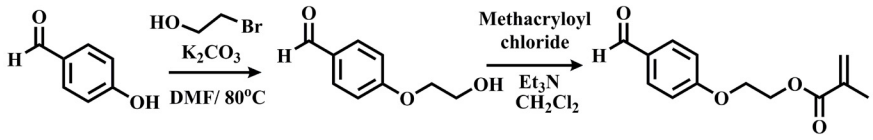
40 mg (0.0033 mmol) of block copolymer was dissolved in a DMSO/water (4/1, v/v) solution mixture. 20 mg of dopamine.HCl (0.13 mmol) was weighted to be 1.2 times the amount needed for the repeating aldehyde units in the copolymer, and 46 μL of triethylamine (0.27 mmol) was added to the mixture, which was stirred for 20 hours at room temperature to increase the amount of dopamine. Then, the mixture was transferred to the dialysis membrane (MWCO=3500) and dialyzed against deionized water, changing the water every 6 hours. The dispersion in the membrane was then lyophilized and stored at +4°C for future use.

In vitro dopamine release assay

The release of dopamine was measured using the dialysis method. The experiment was conducted in triplicates. 50 mg of dopamine-conjugated copolymer dissolved in 3 mL of distilled water and then transferred into the dialysis bag and incubated at 37°C in 50 mL of phosphate-buffered saline solution (PBS, pH 7.4). A 1 mL sample was taken at specific intervals (0.5, 2, 4, 8, 10, 24, 48, 56, and 72 h) over 72 hours, and the same amount of fresh medium was added at each interval. The amount of dopamine released from the samples was determined using a previously prepared calibration curve of dopamine, and the maximum absorbance value was measured at 280 nm with a UV-Vis spectrophotometer. Dopamine cumulative release percentages were calculated using the obtained data. Then, the cumulative percentages of dopamine release were plotted against time.

RESULTS and DISCUSSION

For synthesizing block copolymer, an aldehyde functional monomer (p-(2-methacryloxyethoxy)benzaldehyde, MAEBA) were first prepared according to previously described in the literature[29] (Scheme 1).



Scheme 1. Synthetic pathway for (p-(2-methacryloxyethoxy)benzaldehyde (MAEBA)

In the first step p-(2-hydroxyethoxy)benzaldehyde (PEHBA) compound was synthesized. The existence of the characteristic functional groups of PEHBA was confirmed by ^{1}H NMR, with signals at 2.67 ppm for the hydroxyl group, at 4.01 and 4.16 ppm for the methylene protons, at 7.84 and 7.03 ppm for the phenyl group, and at 9.87 ppm for the aldehyde proton (Figure 1).

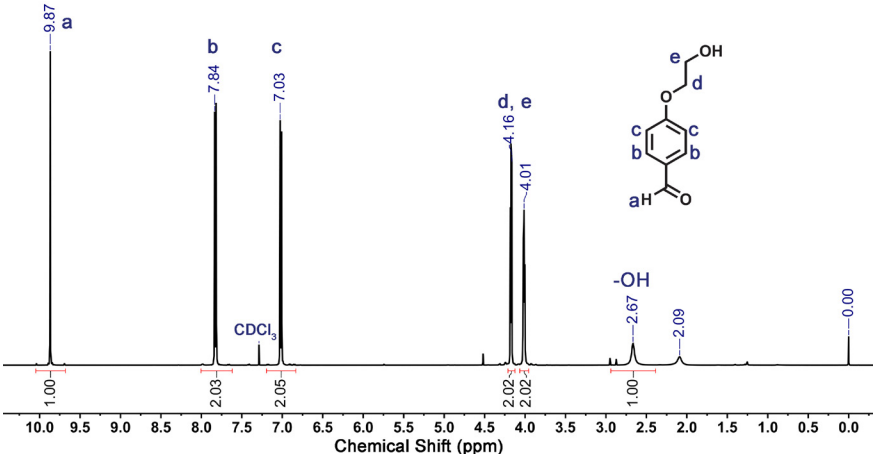


Figure 1. ^{1}H NMR spectrum of p-(2-hydroxyethoxy)benzaldehyde in $CDCl_3$

Secondly, p-(2-methacryloxyethoxy)benzaldehyde (MAEBA) was synthesized by using a precursor molecule (PEHBA). The existence of the characteristic functional groups of MEABA was confirmed by ^{1}H NMR with the signal at 1.96 ppm for methyl group, at 4.33 and 5.53 ppm for methylene protons, at 5.61 and 6.15 ppm for double bond, at 7.05 and 7.85 ppm for the aromatic group, and the signal at 9.91 ppm denotes the aldehyde proton (Figure 2).

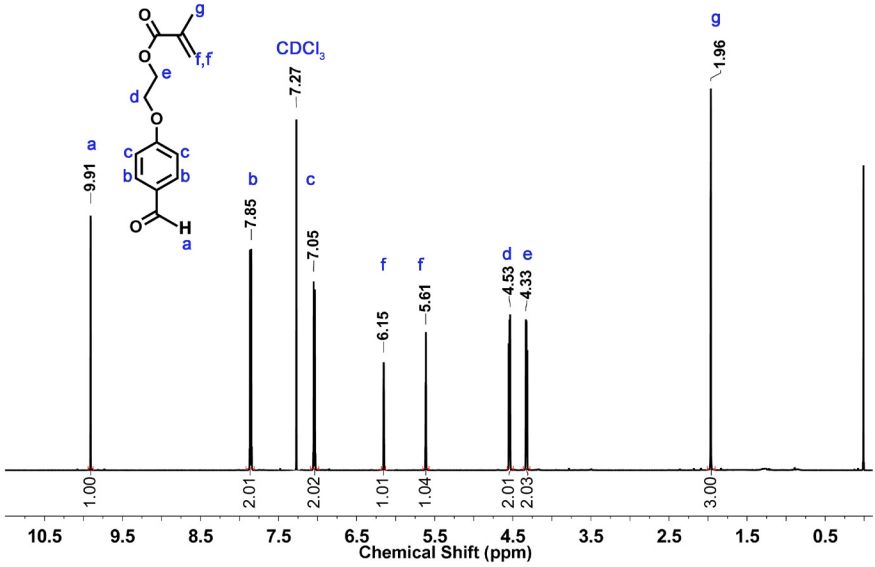
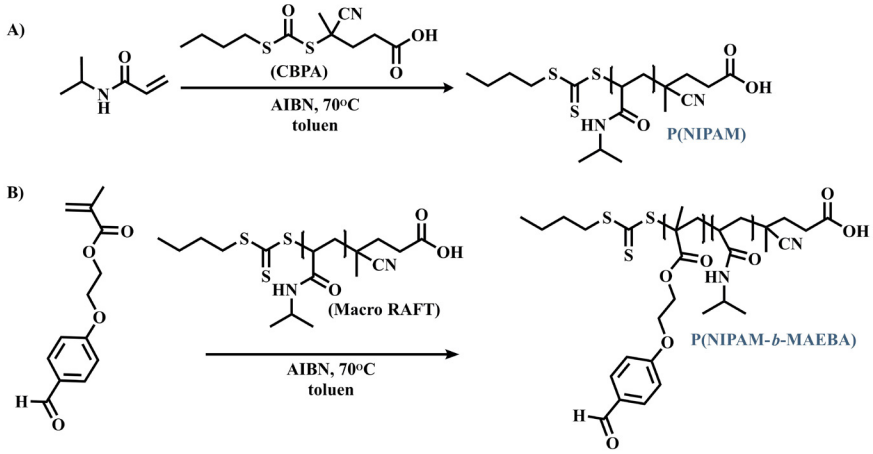


Figure 2. ^{1}H NMR spectrum of p-(2-methacryloxyethoxy)benzaldehyde in $CDCl_3$

A two-step sequential RAFT polymerization procedure was then employed to obtain an aldehyde-functional block copolymer. Briefly, CBPA chain transfer agent (RAFT Agent) was used to obtain a Poly(*N*-isopropyl acrylamide) homopolymer, which was then used as a Macro-RAFT agent to polymerize the monomer of MAEBA. The P(*N*-isopropylacrylamide) (P(NIPAM)) homopolymer was synthesized at a molar ratio of $[M]_0$/[RAFT agent]/[AIBN]=75:1:0.125. Polymerization was performed at 70°C for 17 hours (Scheme 2A). After the polymerization was completed, the homopolymer was purified by dissolving it in tetrahydrofuran and then dropping it into cold hexane to remove any leftover monomers and RAFT agents.



Scheme 2. Synthetic pathway for block copolymer by RAFT polymerization

The chemical structure of homopolymer and monomer conversion was determined by ^{1}H NMR spectrum shown in Figure 3A. The degrees of polymerization (DPs) of the P(NIPAM) was found to be 36 by comparing the integration of the signal of methylene protons in -CH_2-S-C=S at 3.36 ppm from the RAFT agent and the amide proton at 6.43 ppm in the polymer backbone (Figure 3A).

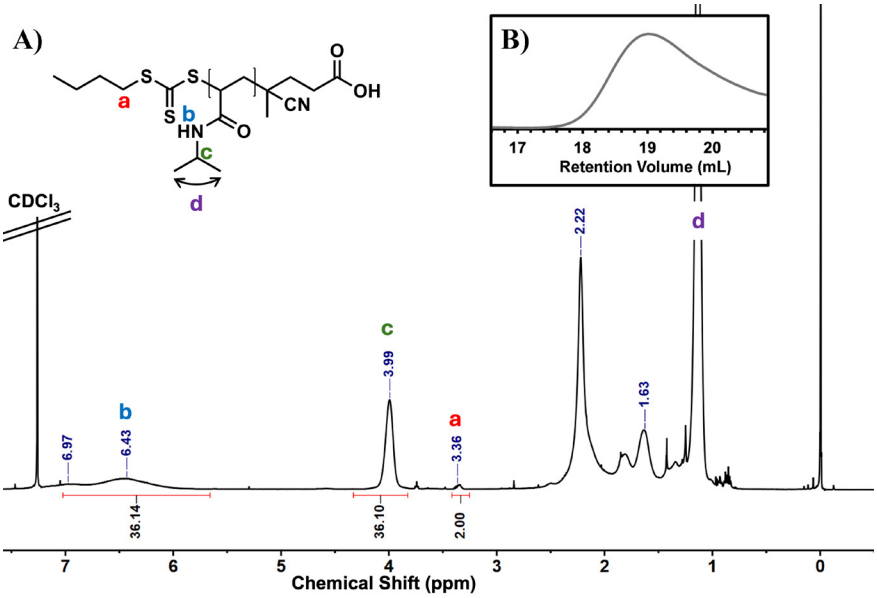


Figure 3. A) ^{1}H NMR spectrum of P(NIPAM) in $CDCl_3$, B) GPC chromatogram of P(NIPAM)

The $M_{n,\ NMR}$ was calculated to be 4.36 kDa, whereas the number average molecular weight ($M_{n,\ GPC}$) was found to be 1.32 kDa, with an M_w/M_n ratio of 1.25 (Figure 3B, Table 1).

Subsequently, the homopolymer was used as a Macro-RAFT agent to extend the MAEBA block of the copolymer in the presence of AIBN and MAEBA monomer in toluene for 18 h (Scheme 2B) with a ratio $[M]_0$:[RAFT agent]:[AIBN]=50:1:0.15. Comparison of ^{1}H NMR spectra of homopolymer P(NIPAM) and P(NIPAM-*b*-MAEBA) demonstrated the successful synthesis of P(NIPAM-*b*-MAEBA). Figure 4A shows new signals at 9.80, 7.74, and 6.92 ppm assigned to aldehyde and aromatic moieties of the MAEBA units. The DPs of P(NIPAM-*b*-MAEBA) was determined from ^{1}H NMR end group analysis by comparing the integrals of peaks at 6.39 (-N*H*C=O of P(NIPAM)) and with 9.80 ppm (aldehyde protons of P(MAEBA)), which were calculated as 33. The $M_{n,\ NMR}$ was calculated to be 12.09 kDa, whereas the number average molecular weight ($M_{n,\ GPC}$) was found to be 29.45 kDa, with an M_w/M_n ratio of 1.50 (Figure 4B, Table 1).

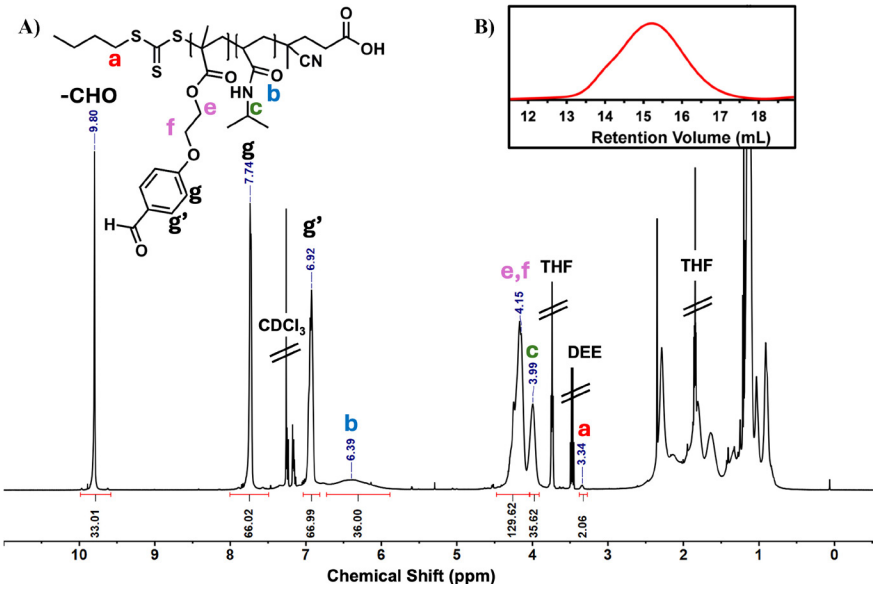
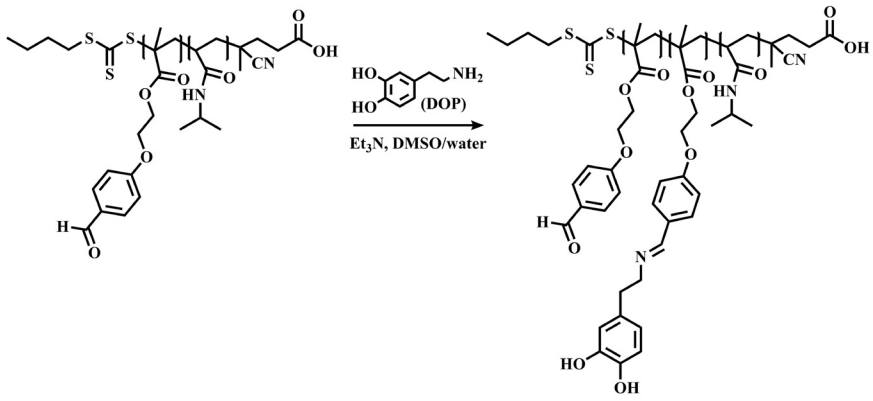


Figure 4. A) ^{1}H NMR spectrum of P(NIPAM-b-MAEBA) in $CDCl_3$, B) GPC chromatogram of P(NIPAM-*b*-MAEBA)

The aldehyde groups in the backbone of the block copolymer were used to attach amino compounds through a condensation (Schiff base) reaction, forming imine bonds. Dopamine molecules were grafted onto the aldehyde groups of the P(NIPAM-*b*-MAEBA) copolymer backbone in a basic medium (Scheme 3).



Scheme 3. Synthetic pathway for grafting of dopamine to block copolymer

^{1}H NMR analysis confirmed the successful grafting of eight dopamine molecules. This calculation was based on the signal integration ratios of the amide proton (6.39 ppm) from the P(NIPAM) block, the aldehyde (-CHO) proton (9.80 ppm) from the P(MAEBA) block, and the imine bond proton (11.65 ppm) (Figure 5). Additionally, the ^{1}H NMR calculation determined the molecular weight of the dopamine-loaded block copolymer to be 13.32 kDa.

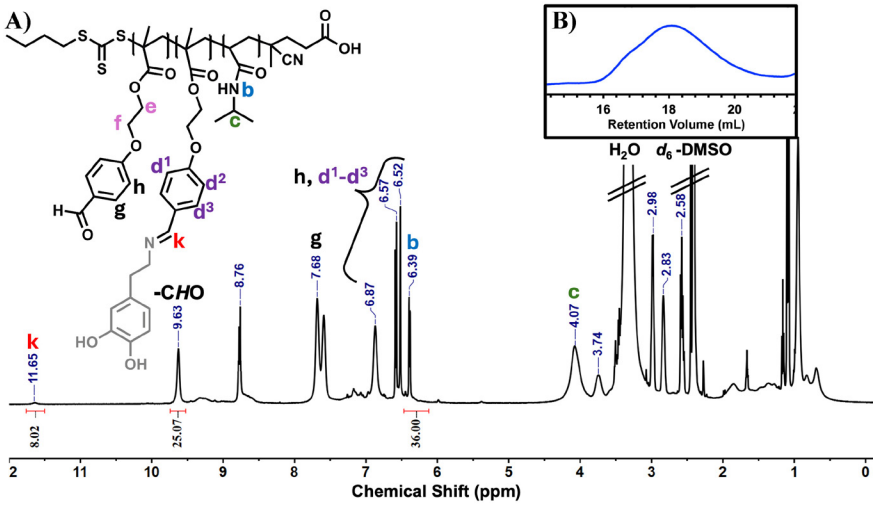


Figure 5. A) ^{1}H NMR spectrum of P(NIPAM-*b*-MAEBA/DOP) in DMSO-d_6, B) GPC chromatogram of P(NIPAM-b-MAEBA/DOP)

As detailed in Table 1, the molecular characterization of the synthesized polymers revealed a shift to higher molecular weights in the GPC distribution after the addition of each block, as illustrated in Figures 3B, 4B, and 5B. Since the GPC system was calibrated with linear polystyrene standards, the GPC

results for all polymers varied significantly from the ^{1}H NMR findings due to the differing chemical structures.

Table 1. Conversion, molecular weight, and polydispersity indexes (*Đ*) of polymers

Polymer	^{1}H NMR[a]		GPC[b]	
	$M_{n,NMR}$ (kDa)	Conversion (%)	$M_{n,GPC}$ (kDa)	Đ
P(NIPAM)	4.36	48	1.32	1.25
P(NIPAM-b-MAEBA)	12.09	66	29.45	1.50
P(NIPAM-b-MAEBA/DOP)	13.32	24	30.87	1.76

[a]Determined by ^{1}H NMR spectrum, [b]Determined by THF-GPC, polystyrene (PS) standards used for calibration.

Subsequently, a calibration curve (y=0.01465x+0.00176, R^2=0.99941) for dopamine was plotted by measuring the absorbance values at 280 nm using a UV-Vis spectrophotometer (Figure 6A). The amount of dopamine in the P(NIPAM-*b*-MAEBA/DOP) (1 mg/mL in DMSO) was found to be 78.11µg via calibration curve (Figure 6B).

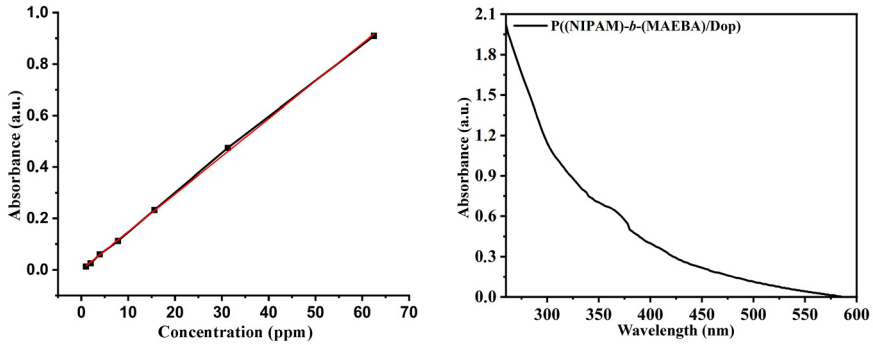


Figure 6. A) Dopamine calibration curve in DMSO and B) UV-Vis spectrum of the P(NIPAM-*b*-MAEBA/DOP) copolymer

An *in vitro* dopamine release assay was conducted using a dialysis method in phosphate-buffered saline (PBS, pH 7.4). A 1 mg/mL polymer solution in DMSO/water (1/3, v/v) was dispersed in PBS and incubated at 37°C for 72 hours. While dopamine release within the initial 10 hours was approximately 18%, a total of 53% of dopamine was released from the polymer over the 72 hours (Figure 7).

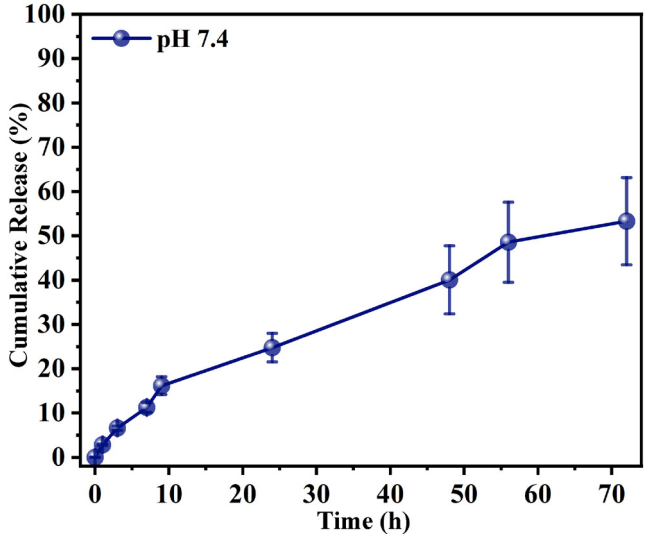


Figure 7. *In vitro* dopamine release profile of P(NIPAM-*b*-MAEBA/DOP) polymer in PBS at pH 7.4 at 37°C

In conclusion, this study developed a potential thermoresponsive and tissue-adhesive platform by synthesizing a block copolymer of P(NIPAM-*b*-MAEBA/DOP) through RAFT polymerization. The spectroscopic and chromatographic analyses confirmed the successful synthesis and structure of both intermediate compounds and the final polymer. This platform exhibited a sustained dopamine release of 53% over 72 hours at pH 7.4. The combination of P(NIPAM)'s well-known thermoresponsive behavior with dopamine's robust surface adhesion properties suggests this copolymer could be a promising material for various future applications. Its potential applications range from antimicrobial solutions to advanced uses in areas such as implant interfaces, with a significant impact in biomedical fields.

STATEMENT OF ETHICS

This study does not require any ethical permission.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Concept, design, supervision, and resources, PSOO; data collection and/or processing, IM, BA; analysis and/or interpretation, IM, BA, PSOO; literature search, IM, PSOO; writing, IM, PSOO; critical reviews and supervisions, PSOO.

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