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2-Hydroxyl Methacrylate based Triblock Copolymers by Atom Transfer Radical Polymerization

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ABSTRACT

One of the simplest and powerful Controlled Radical Polymerization (CRP) techniques is atom transfer radical polymerization. It has been widely studied and utilized since new polymeric materials synthesis using novel structures can be achieved by polymerizing many monomers under simple conditions. Polymers with low polydispersity and controlled molecular weight can be obtained using the ATRP technique since it has synthetic flexibility and simplicity. Polymerizations were performed to prepare two ABA triblock copolymers with three monomers in two different batches where A=2-diethylamino ethyl methacrylate (DEA) B=2-Hydroxyethyl Methacrylate (HEMA) in the first batch. In contrast, A (i.e., DEA) was replaced by methyl methacrylate (MMA) in the second batch. Therefore, the resulting two-triblock copolymers were DEAHEMA- DEA and MMA-HEMA-MMA. This process was carried out using transition metal catalyst Cu (I) Br, 2, 2'-bipyridine (bpy) as a ligand and diethyl meso-2, 5-dibromoadipate as a bifunctional ATRP initiator in Methanol at room temperature. The resulting block copolymers were analyzed for polymer conversion using a 500MHz Bruker Avance 1H NMR spectrophotometer in deuterated Methanol (CD3OD) and micelle formation, which was analyzed by changing solvents (D2O and CDCl3).

Key words: *Atom transfer radical polymerization, Atom transfer radical addition, Controlled radical polymerization, 2-diethylamino ethyl methacrylate, Degenerative chain transfer, Gel permeation chromatography*

INTRODUCTION

Developing new polymeric materials with well-defined composition, architectures with controlled functionalities and topologies are important in polymer science. It is based on the availability of the methods [1, 2]. The polymers have great commercial significance. The pharmaceutical applications of polymers range from coating agents to mask the unpleasant taste of drugs to binding agents in tablets and flow and viscosity controlling agents in solutions, suspensions, emulsions. Polymers are used to formulate a controlled drug delivery system and targeted drug delivery [3]. They form contact lenses, artificial tissue engineering, and protein transport [4]. Living polymerization, a technique of polymer synthesis, allows well-defined polymers to be prepared.

Michael Szwarc first discovered it in 1956. Living polymerization is a chain-growth polymerization in which the chain transfer reactions are absent, and the capability of the growing polymer chain to end has been

eliminated [5]. The chain initiation rate is greater than its propagation. It is a popular choice for the synthesis of block polymers. The first living polymerization technique discovered was an ionic process [6]. But this technique was limited concerning its marked sensitivity towards moisture, carbon dioxide, and the several acids and basic compounds. In addition, copolymerization is often difficult because of the monomers' reactivity ratios. To overcome this drawback, the new polymerization technique, i.e., free radical polymerization was developed and is now extensively used by industries. Living polymerization is a radical process that has remained a long-standing purpose in polymer science and is a suitable technique for many monomers with carbon-carbon double bonds and is tolerant of various solvents, impurities, and functional groups frequently met in the industry. Living polymerization is also called controlled polymerization, where polymerization takes place in a controlled manner without chain termination. The advantages of this technique are the use of predetermined molecular weight monomers and control over end groups. A primary choice for the preparation of block copolymers is living polymerization because it allows polymer synthesis in stages and the addition of different monomers at each stage. The most common Controlled Radical Polymerization (CRP) are Atom Transfer Radical Polymerization (ATRP), Nitroxide Mediated Polymerization (NMP), Degenerative chain Transfer (DT), and Reversible Addition Fragmentation chain Transfer polymerization (RAFT) [7, 8]. ATRP is one of the successful, powerful, and economical polymer synthesis techniques. Hence, in the present study, ATRP is employed as a method of interest.

Atom transfer radical polymerization (ATRP)

ATRP has changed to a powerful synthetic technique in polymer chemistry. Its use has resulted in the controlled synthesis of combinations and homopolymers of block copolymers. Professor Mitsuo sawamato, prof. Krzysztof Matyjaszewski and Dr. Jin-shan Wang discovered this technique in 1995 [9]. Timothy E. Patten and Krzysztof Matyjaszewski explained the polymer synthesis by ATRP in their work. By using ATRP, many monomers including styrenes methacrylates and acrylonitrile can be polymerized and copolymerized with predetermined molecular weight and molecular weight distribution (polydispersity) final polymer. The name of ATRP is originated from the atom transfer step, which is the crucial elementary reaction in charge of controlling the growth of polymer chains.

The roots of ATRP can be found in Atom Transfer Radical Addition (ATRA), triggers the formation of alkenes and adducts of alkyl halides into 1:1ratio and catalyzes by transition metal complexes [10]. ATRA is a modification of the Kharasch addition reaction, which requires either the existence of radical initiators or light. The mechanism has been carried out in Initiation and Propagation, but ATRA usually involves only one-step, i.e., addition. More than one additional step is feasible if the condition can be modified and ATRA becomes ATRP [11]. In simple terms, ATRP is a sequence of repeated ATRA reactions. However, in ATRP, termination reactions are diminished; therefore, controlled polymerization is termed. In the ATRA process, transition metal species 'Mt n' abstract halogen atom 'X' from the organic halide 'R-X' to form oxidized species 'Mt n+1X'and the radical R* with the central carbon atom. In the following step, this radical reacts with alkene 'Y' to from intermediate radical species 'RY*.' The reaction occurs between oxidized species Mtn+1X' and intermediate radical species 'RY*'which leads to a target product 'RYX.' It recreates the decreased transition metal species 'Mt n' to promote a new redox procedure. Thus, the active species or radicals can be developed by a reversible redox procedure catalyzed by a transition metal complex. ATRP is on the basis of a reversible transition of the halogen atoms (X) between dormant species (R-X) and transition metal catalyst (Mt n /Ligand) by redox process to form an active chain end (R*) and a transfer metal deactivator in a higher oxidation state (Mt n /Ligand), where the rate constant of activation is 'kact' and deactivation is 'kdeact.' The growth of the polymer chain takes place by adding radicals to monomers, where the constant rate of termination and propagation are 'kt,' and 'kp', respectively [1, 2, 7, 12, 13].

In some cases, a few percent of the termination reactions can be seen in ATRP. It may be due to radical coupling. ATRP was generated using a suitable catalyst and an initiator with a suitable adjusting and structure reaction conditions. The rate of increasing molecular weights is proportional to the conversion and polydispersities [6, 14]. In mechanism of ATRP is embodied more simply with copper as a catalyst, where 'keq' (keq= kact / kdeact) is the atom transfer equilibrium constant for the dormant species [15]. The kinetic studies obtained are useful for determining the polymerization rate concerning monomer, initiator, and metal-ligand. The magnitude of atom transfer equilibrium constant 'keq 'determines the polymerization rate. A small equilibrium constant leads to slow the polymerization rate. Even too large an equilibrium constant can cause large-scale termination due to high radical concentration. The ratio of Ligand to copper may affect the rate of

polymerization. The kinetically optimum ratio of Ligand to copper for the polymerization of methyl acrylates and styrenes was found to be 2:1. The polymerization rate will be slower if the ratio is below 2:1, which will not be affected above this ratio.

Components of ATRP

Monomers

Different classes of various monomers can be successfully polymerized or copolymerized using the ATRP technique. The monomers including acrylates (e.g., methacrylates), acrylamides (methacrylamides), styrenes, and acrylonitriles help to stabilize the propagating radicals [15]. Each monomer has its atom transfer equilibrium constant for its dormant and active species under the same conditions with the same catalyst. To control the polymerization rate, the rate of radical deactivation and the concentration of propagating radicals have to be adjusted for a specific monomer. The monomers used in this work are Methyl Methacrylate (MMA), 2-Hydroxyethyl Methacrylate (HEMA), and 2 (diethylamino) methacrylate (DEA).

Initiators

The common initiator used in ATRP is a metal halide (RX). Defining the number of growing polymer chains is the key role of the initiator in ATRP. In case the initiation is fast, the number of growing chains is constant and equal to the initiator's initial condensation, providing a negligible sum of transfer and termination reactions. Suppose the initiation is not complete at the beginning of the reaction. In that case, it may lead to polymer production with higher molecular weights and higher polydispersities than the desired ones. In ATRP, the polymerization rate is first order concerning initiator concentration, while the degree of polymerization is reciprocal to the initial concentration of the initiator. Rapid and selective migration of halide group 'X' between the transition metal complex and the growing polymer chain is necessary to obtain well-defined polymers with slight variation in polydispersities. The common halides used are bromine and chlorine, which give the best molecular weight control, while iodine is used in acrylate polymerizations in copper-mediated ATRP66 [14]. Fluorine is not utilized since the C-F bond is too strong to be cleaved [11, 14, 16]. Initiation must be fast and quantitative. Alkyl halides containing active substituents on the carbon of aryl, allyl, or carbonyl groups are mainly used as ATRP initiators. The compounds having weak R-X bonds may also be utilized as ATRP initiators, e.g., S-X, N-X, and O-X. Macro initiators are formed by initiating moiety to the macromolecular species and can produce block copolymers [2]. The cleavage of the R-X bond is dependant mostly on the structure of the initiator and the choice of transition metal catalyst [2].

Catalyst

One of the highly significant elements of ATRP is the catalyst. It is a transition metal complex Such as one or more ligands. Several transition metals have been extensively used in ATRP as a catalyst. Out of these, copper is the most superior catalyst due to its versatility, availability, and relatively low cost. In contrast, other metals like iron, nickel, ruthenium, palladium, rhenium, and rhodium were effective for various monomers [12, 14]. The catalyst has a major effect in determining the position of the atom transfer equilibrium. It also has an important role in solubilising the transition metal in the solvent and regulating the redox potential of the center for proper reactivity and dynamics of exchange between the active and dormant species [17]. There are a few requirements to be an efficient ATRP catalyst [15]. The metal centre must have a couple of readily accessible oxidation states separated by an electron to promote atom transfer. A metal centre must have an affinity for halogen. The Ligand should form a strong complex with the metal.

Solvents

The ATRP can be performed in bulk, solutions or suspensions, and emulsions. The solvent becomes necessary when the resulting polymer is insoluble in its monomer. Various factors determine the selection of solvents. Solvents sometimes can cause initiation of chain transfer reaction, catalyst poisoning, solvent aided side reactions; therefore, the interactions of solvent with the catalytic system should be taken into consideration.26. Various solvents like Methanol, benzene, toluene, diphenyl ether, anisole, acetone, water, and carbon dioxide have been used for different monomers in ATRP [12].

Temperature

Increasing temperature prompts raising the rate constant of radical propagation and atom transfer equilibrium constant, thus accelerating the polymerization rate. However, elevated temperatures can induce different side reactions and chain transfer [16]. It can be concluded that the solubility of catalysts enhances at a higher temperature, while at the same time, catalyst decomposition can occur at higher temperatures [14]. Therefore, the optimum temperature conditions depend on the type of monomer, catalyst, and the desired molecular weight. This work has been performed at room temperature.

Applications of HEMA- based copolymer

- It can be used in the production of coatings to protect cells and delicate drugs such as proteins, peptides, DNA, etc. [11, 18].
- It is used in various drug delivery systems to increase drug bioavailability.
- HEMA is a popular choice of a monomer in the formulation of optical drug delivery systems such as contact lenses [19-21].
- It is widely used in the manufacturing of targeted drug delivery systems and controlled release formulations e.g.hydrogel, enteric-coated tablets
- It has great importance in nanoscience and tissue engineering. The HEMA-based polymer as a biocompatible material has been well recognized [5, 21, 22]. The molecular structures of the initiators, monomers and the Ligand used for this work.

Drug delivery system

The polymer has large applications in the pharmaceutical industry. It is used to formulate various drug delivery systems ranging from targeted to controlled drug delivery systems. It can be used as a binding agent in tablets and viscosity controlling agents in solutions, suspensions, and emulsions. The polymer can also be used as film coatings on implants or catheters, on pills or capsules, or to mask the bitter taste of the drug. It can enhance drug stability and alter drug release characteristics [18]. HEMA-based hydrogels are potentially biocompatible hydrogels because of their hydrophilic nature. Hydrogels made up of synthetic polymers have great significance in tissue engineering, as they have been found useful for cell encapsulation. Block copolymers are linear copolymers made up of blocks containing identical monomer units covalently bound to the sequence of blocks of other identical monomer units. There are different types of block copolymers:

- AB di-block
- ABA tri-block
- ABC tri-block
- ABCD tetra-block

ABA tri-block copolymer consists of two segments, mainly hydrophilic and hydrophobic. These segments can self-assemble into micelles or the other aggregates with a hydrophilic corona/shell and hydrophobic core in optimum conditions [23]. The core allows the incorporation of drugs of similar nature. It means the hydrophobic core allows incorporating hydrophobic drugs and the hydrophilic outer shell in nature stabilizes the aggregation structure [24]. The characteristics of these polymers can be altered by the kinds of chemical structures and chain length of each block.

Aims and objective

This project aimed to prepare HEMA-based linear block copolymers and characterize their micelle formation by changing solvent. In this work, HEMA based ABA triblock copolymers are supposed to be prepared in two batches using poly (HEMA) as a hydrophilic sequence and poly (DEA) as a hydrophobic sequence in the first batch while poly (DEA) to be replaced by poly (MMA) another hydrophobic sequence in the second batch with their predetermined molecular weights. In addition, to analyze the micelle formation of these resulted copolymers using different solvents by 1H NMR technique.

MATERIALS AND METHODS

Materials

The monomers HEMA (97%, Sigma Aldrich, London, UK), DEA (99% Sigma Aldrich, London, UK), MMA (99% Sigma Aldrich, London, UK) were purified by passing through an activated neutral aluminium oxide

filled in a column to remove inhibitor or oxidant and kept in the fridge The Cu (I) Br as a catalyst,2,2'-bipyridine(bpy) and bifunctional ATRP macro initiator diethyl meso 2,5-dibromoadipate (98% Sigma Aldrich, London, UK) and used in the same form. Silica used to remove copper catalyst from final product was column chromatography grade silica gel 60 (0.063-0.200mm) bought from fluka, Methanol.

Apparatus

Vacuum pump system for filtration, Rota vapour (Buchi R-205), Vacuum desiccators, Inert gas (Nitrogen) assembly: to avoid copper oxidation, this may result due to reaction with atmospheric oxygen. Proton nuclear magnetic resonance (1H NMR) spectrometer: To determine the conversion of monomers into block copolymer. 1H NMR spectroscopy is one of the powerful analytical techniques due to its simplicity, rapidity, and sensitivity [25, 26]. Therefore, copolymer composition was determined using 1H NMR spectroscopic data. 1H NMR spectra were obtained from Bruker Avance 500NMR at 500.13 MHz. 1H NMR chemical shifts in CDCl3, CD3OD, and D2O were recorded from the down field from 0.00ppm.

Methodology

Synthesis of DEA-HEMA-DEA triblock copolymer by ATRP

A typical synthesis of DEA-HEMA-DEA triblock copolymer was performed as follows: a usually accessible bifunctional ATRP macro initiator **(Figures 2 and 3)** Diethyl meso-2, 5-dibromoadipate was dissolved in 10ml Methanol with moderate stirring. The Cu (I) Br catalyst and 2, 2'- bipyridine (bpy) Ligand were added under dry nitrogen to avoid oxidation due to the copper catalyst. The reaction mixture quickly turned dark brown. After 10 minutes, the HEMA monomer was added to the reaction mixture under nitrogen. An increase in viscosity was observed. After 1hour of duration, DEA was added to the dark brown reaction solution. The reaction mixture was kept under a dry nitrogen purge for the next 48 hours till the polymerization was completed. After 48 hours, on exposure to air, the reaction solution turned blue, indicating the oxidation of copper. The unpurified reaction solution was purified by passing the solution through a silica gel60 column to eliminate the catalyst. The blue catalyst adsorbs onto the silica, and brown Ligand is adsorbed by silica, leaving purified light yellow Copolymer–solvent solution behind. The solvent was evaporated using rota vapour, which gives highly viscous colourless Copolymer, which was then sent for 1H NMR analysis, and rest of the product was stored in the fridge.

Synthesis of MMA-HEMA-MMA triblock copolymer by ATRP

A typical synthesis of MMA-HEMA-MMA triblock copolymer was performed by the same method as mentioned above with the same experimental conditions. But in this process of synthesis monomer, DEA was replaced by MMA monomer. Highly viscous colourless Copolymer was produced, and then sent for 1H NMR analysis, and the rest of the product was stored in the fridge.

RESULTS AND DISCUSSION

A 1H NMR spectrum of HEMA in deuterated Methanol and a 1H NMR spectrum of DEA in deuterated Methanol is indicated in 1. In contrast, the 1H NMR spectrum of MMA in deuterated Methanol is shown in **Figure 1**. Peaks 'a' (at δ =1.95, 1.93 and 1.92 ppm for HEMA, DEA, and MMA respectively) are characteristic of backbone hydrogen. Peaks 'b' (at δ=5.6, 6.1 ppm) confirms the presence of hydrogen in ethylene groups of HEMA and DEA and MMA; peaks 'c' (at δ=4.28ppm) in HEMA and DEA while peak 'c' in MMA (at δ=4.8ppm); are characteristics of α-hydrogens in ester groups present peaks 'd' (at δ=3.86ppm for HEMA, δ=2.8ppm for DEA and δ=3.73 for MMA) are characteristics for ethyl hydrogen in HEMA and DEA and MMA. Peak 'e' (at δ=4.62ppm) and peak 'f' (at δ=1.06ppm) are characteristics of hydrogen in the ethyl groups of tertiary amines of DEA.

Through controlled radical polymerization, the synthesis of ABA triblock copolymer becomes effective when a bifunctional initiator is used along with two steps monomer addition [4]. A diethyl meso -2, 5-dibromoadipate, a commercially available bifunctional ATRP initiator, was used for polymerization. It contains two bromine atoms; these initiate the process of polymerization and donate bromine to form oxidized species with ligand species and leaves radical. The reaction between oxidized species and radicals leads to polymer formation. It also contains two ester groups that resemble the structure of the monomers. The polymers were analyzed with 1H NMR. The different chain lengths of the polymers were achieved with a variation of molar ratios of

monomers, initiator, catalyst, and Ligand. The various designs of polymers have great significance in the formulation of drug delivery systems. Therefore, hydrophilicity and hydrophobicity are considered as these factors influence the efficacy of drug load into the micelle. The Tables given below summarise the synthesis parameters and explain the 1H NMR analysis results for the polymer conversion **(Table 1)**.

A representative 1 H NMR spectrum of DEA-HEMA-DEA polymer in deuterated Methanol (CD3OD) is shown in **(Figure 4)**. Peak 'a' (δ=4.04ppm) represents the hydrogen in ester groups of both HEMA and DEA, respectively; peak 'b' (δ=2.8ppm) and peak 'c'(δ=3.76ppm) are characteristics of hydrogen in ethylene groups of HEMA and DEA respectively. Peak'd' (δ=2.65ppm), peak 'e' (δ=1.17ppm) are characteristic of hydrogen in the ethyl group of tertiary amines of DEA and peak 'f' (δ=2.02ppm) and peak 'g' (δ=0.94 to 1.21) are backbone hydrogens. Peaks representing double bonds in **(Figure 1)** have been disappeared and the presence of peaks at around 1ppm indicates the polymer conversion that can be observed in **(Figure 4)**. A representative 1 H NMR spectrum of MMA-HEMA-MMA in deuterated Methanol is shown in **(Figure 5)**. Peak 'a' (δ=4.05ppm) represents the hydrogen in ester groups HEMA and MMA. Peak 'b' (δ=3.76ppm) is a characteristic of hydrogen in the ethylene group of MMA. Peak 'c' (δ=1.95ppm) and peak 'f' (δ=0.94 to 1.10ppm) are backbone hydrogens. Peak'd' (δ=1.17ppm) is a characteristic of hydrogen in the ethyl groups of tertiary amines of MMA. There are no peaks for the double bond, and the appearance of peaks at 1.0ppm indicates the polymer conversion, as shown in **(Figure 5)**.

By changing solvents (D2O and CDCl3), the poly (DEA-HEMA-DEA) triblock reversibly exhibited three different states. These are dissolved states, a micelle with HEMA as core and a micelle with a DEA core. In the spectrum of triblock in d2o shows only peaks for HEMA where HEMA formed hydrophilic micelle corona and hydrophobic DEA formed the core of the micelle. In CDCl3, only peaks for DEA are obtained as DEA. Hydrophobic segment of DEA formed micelle corona and hydrophilic segment of HEMA formed micelle core. Another poly (MMA-HEMA-MMA) poly also exhibited similar micelle as a HEMA core and micelle as MMA corona in the solvents mentioned earlier. In the spectrum of triblock in D2O, only peaks for HEMA were obtained as HEMA where hydrophilic segment formed micelle corona, and hydrophobic MMA formed the core of the micelle. In CDCl3, only peaks for MMA are obtained as MMA, the hydrophobic segment of MMA formed micelle corona, and hydrophilic HEMA formed micelle core **(Figure 6)**.

Table 1. Summary of Synthesis Parameters for Triblock Copolymer Using DEA and MMA

No.	Target block copolymer composition	Initiator (gm)	HEMA (mol)	DEA (mol)	Cu(I)Br (mol)	bpy (mol)	Reaction time (Hrs)	Conversion (%)
1	DEA_{10}-$HEMA_{20}$-DEA_{10}	0.42	3.0	4.26	0.33	0.72	48	≈100
2	DEA_{10}-$HEMA_{40}$-DEA_{10}	0.21	3.0	2.13	0.17	0.36	48	≈100
3	DEA_{20}-$HEMA_{40}$-DEA_{20}	0.21	3.0	4.26	0.17	0.36	48	≈100
4	MMA_{10}-$HEMA_{20}$-MMA_{10}	0.42	3.0	2.3	0.33	0.72	48	≈100
5	MMA_{10}-$HEMA_{40}$-MMA_{10}	0.21	3.0	1.15	0.17	0.36	48	≈100
6	MMA_{20}-$HEMA_{40}$-MMA_{20}	0.21	3.0	2.3	0.17	0.36	48	≈100

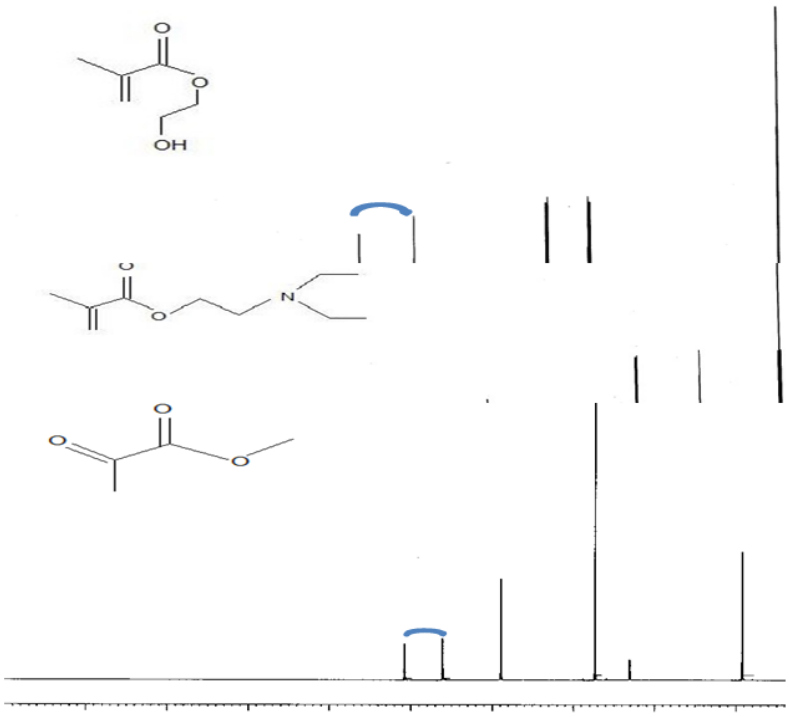


Figure 1. ^{1}H NMR

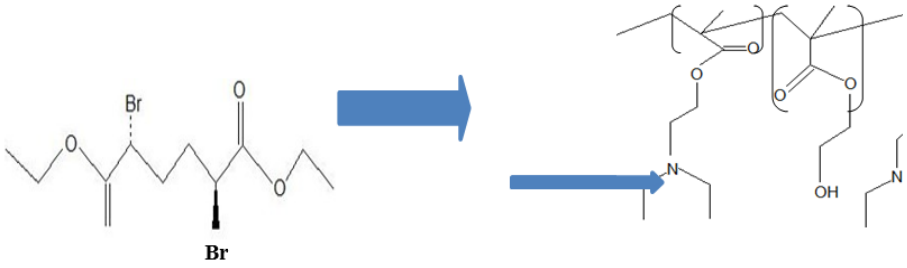


Figure 2. The Reaction Scheme for the Synthesis of DEA-HEMA-DEA Triblock via ATRP Using Commercially Available Bifunctional ATRP Macro initiator

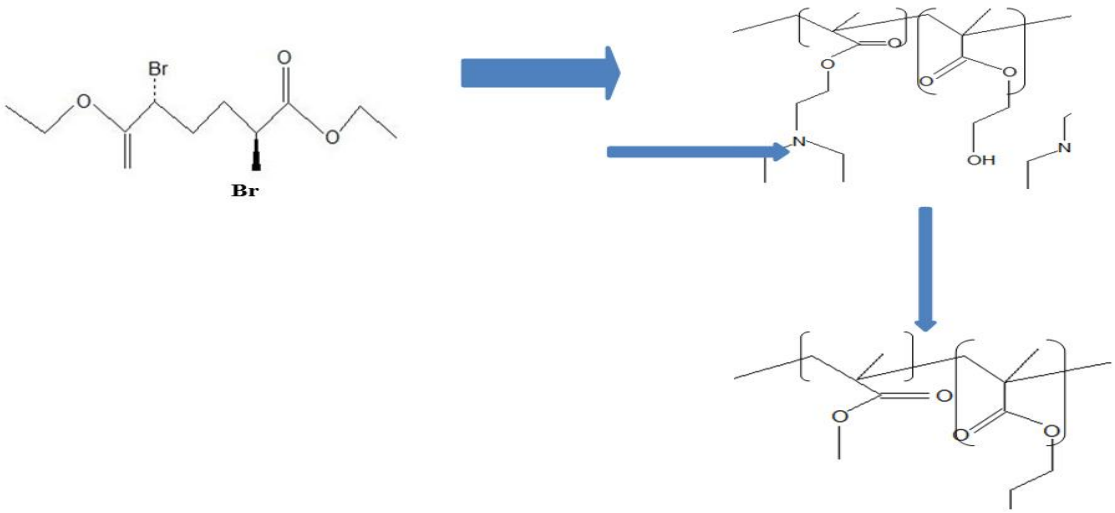


Figure 3. The Reaction Scheme for the Synthesis of MMA-HEMA-MMA Triblock via ATRP Using Commercially Available Bifunctional ATRP Macroinitiator

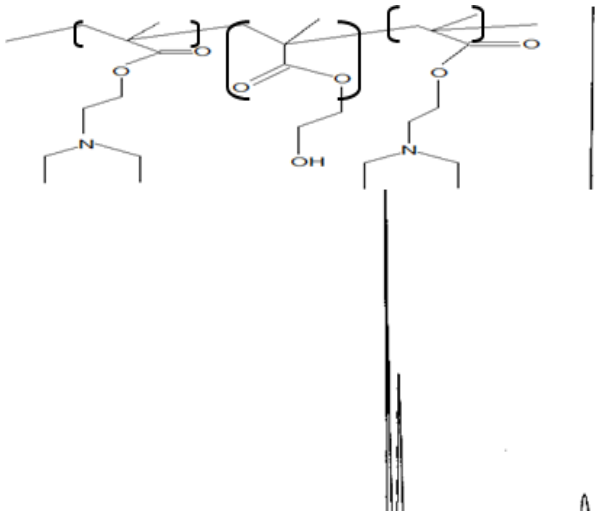


Figure 4. Two Representative ^{1}H NMR Spectra of Poly (DEA-HEMA-DEA) in CD3O

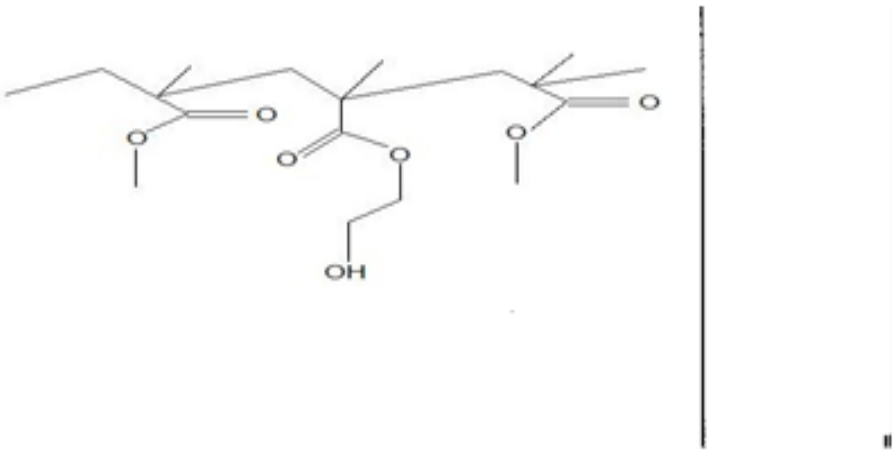
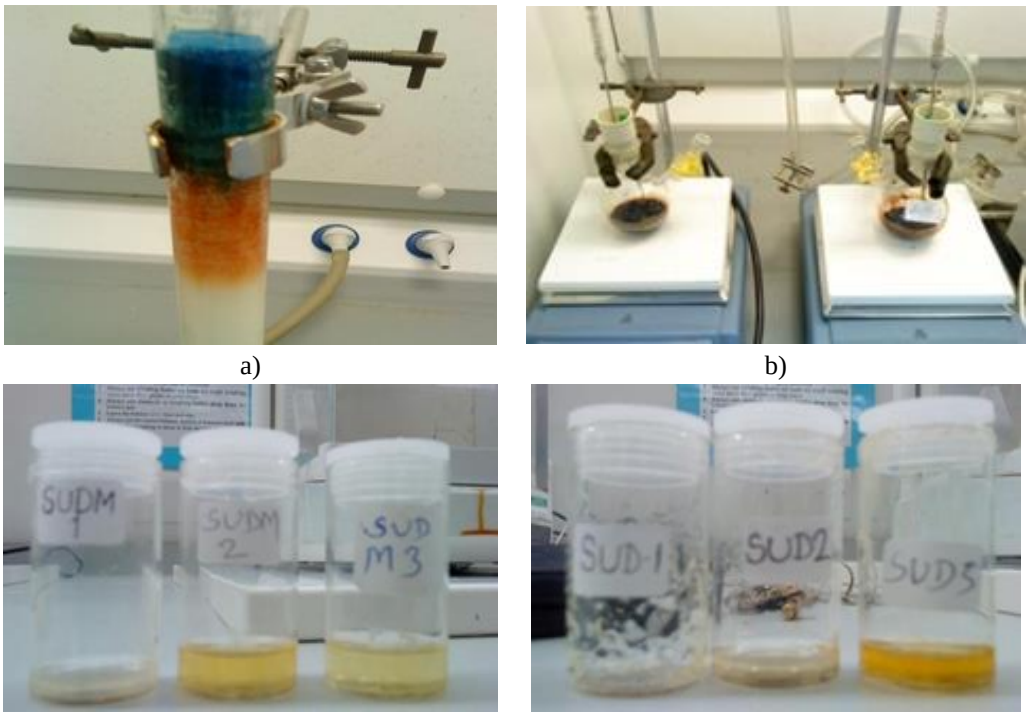


Figure 5. ^{1}H NMR Spectrum of Poly (MMA-HEMA-MMA) in CD3OD



a) b)

c) d)

Figure 6. Images of Samples

CONCLUSION

Atom transfer radical polymerization of 2-hydroxyethyl Methacrylate has been successfully carried out with two different monomers, diethylamino ethyl methacrylate (DEA) and methylmethacrylate (MMA) in two separate batches from diethyl meso-2,5-dobromoadipate bifunctional ATRP initiator and Cu(I)Br catalyst. Different length linear ABA triblock copolymers with predetermined molecular weights have been effectively synthesized with sequential two-step monomer addition, first with HEMA and then DEA in the first batch. In contrast, DEA was replaced in the second batch. The analysis of both block copolymers was obtained around sixty spectra of proton NMR. Proton NMR (1 H NMR) analysis showed 100% conversion of polymers. The micelle formations were analyzed using the 1H NMR technique by changing solvents (D2O, CDCl3).

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ETHICS STATEMENT : None

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