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Synthesis of Polysulfone Based Amphiphilic Graft Copolymers by a 'Grafting to' Approach

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Abstract: Synthesis of amphiphilic polysulfone graft copolymers by "Click" chemistry is described. First, a commercial PSU was chloromethylated to give chloro-funtional PSU (PSU-Cl). Subsequently, chloride groups were converted into azide moieties by nucleophilic substitution. Hydrophilic poly(*N,N*-dimethylacrylamide) (PDMA) side chains were then attached via a "grafting to" approach by using copper-catalyzed azide–alkyne cycloaddition (CuAAC). Precursor polymer and the final amphiphilic copolymers were characterized by proton nuclear magnetic resonance (^{1}H NMR), fourier-transform infrared spectroscopy (FT-IR), gel permeation chromatography (GPC) and contact angle measurements.

Keywords: Polysulfone, grafting to, graft copolymers, amphiphilic materials.

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INTRODUCTION

Based on their outstanding properties, such as superb thermal and chemical stability, mechanical strength, and resistance to radiation degradation (1, 2), polysulfones (PSU) have been widely employed in numerous industrial applications such as food processing, fuel cells, and electronics (3, 4). Moreover, based on their biocompatible and non-degradable nature, they have also been used in bio-applications including bioreactors, hemodialysis, etc. (5, 6). However, their poor tracking resistance and weathering properties remains as the major challenges limit their even wider utilization (7). Not only to overcome these problems, but also to fulfill the necessities of the application, functionalization of suitable PSU precursors have gained growing interest recently (8). Using functional co-monomers through the polymerization or post-modification approaches are the two main approaches utilized for this purpose. However, the latter method, in which the desired functionalities are incorporated to the PSU chains, appears to be a more powerful approach, since polymerizations may be inhibited in the direct polymerization case as a result of limited functional-group tolerance of the polymerization procedures (9).

The post-modification concept has made a great progress by the development of "Click Chemistry" (10). Basically, click chemistry term covers the chemical approaches with several advantageous properties including high yields, tremendous orthogonality and selectivity (11). Although here exist different type of click reactions including Diels-Alder and thiol-ene reactions, the pioneering approach, copper-catalyzed azide–alkyne cycloaddition (CuAAC) has gained broad interest and has been extensively utilized for the preparation of numerous complex macromolecular structures (12). For instance, it has been established that many macromolecular architectures such as graft/block and star copolymers, polymeric networks, functional polymers and hyperbranched polymers can be prepared by CuAAC click reactions (13). Moreover, CuAAC has been also demonstrated to be a powerful tool for the modification/ functionalization of different polymeric materials (14, 15).

Amphiphilic polymeric materials have been the basis of different bio-applications ranging from drug delivery systems to membranes (16-18). As a result of their unique chemical structure, they form polymeric micelles with a hydrophobic core and hydrophilic shell where the core act as a reservoir for hydrophobic drugs and the hydrophilic part stabilizes the core by serving as an interface between aqueous phase and the hydrophobic domain. This exceptional property makes them perfect materials for encapsulation and delivery of hydrophobic drugs (19, 20). Among the various polymers employed as hydrophilic domains for amphiphilic polymers, poly(*N,N*-dimethylacrylamide) (PDMA) is one of the most widely used one due to their hydrophilic in the absence of ionic functionalities and inertness to biomolecules (21, 22).

In the current study, a "grafting to" approach is described for the synthesis of PSU-based graft copolymers through CuAAC. PDMA was purposely chosen as the side chain to obtain amphiphilic polysulfone graft copolymers. Thus, the obtained polymer scaffold is believed to be a suitable candidate for biomedical applications and drug delivery systems.

EXPERIMENTAL SECTION

Materials

Polysulfone (PSU, Udel® P-1700, Solvay), paraformaldehyde (95%, Merck), tin(IV) chloride (98%, Alfa Aesar), trimethylsilyl chloride (≥ 99.0%, Aldrich), sodium azide (97%, Aldrich), N,N'-dicyclohexylcarbodiimide (DCC, 99%, Aldrich), 4-(dimethylamino)pyridine (DMAP, 98%, Aldrich), propargyl alcohol (99%, Aldrich), copper (I) bromide (98%, Acros), *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylene triamine (PMDETA, 99%, Aldrich), N,N-dimethylacrylamide (99%, Aldrich), N,N-dimethylformamide (DMF, ≥ 99.8%, Merck), and methanol (100%, VWR) were used as received. Alkyne functional RAFT agent (RAFT-alkyne) was synthesized according to previous literature (23).

Characterization

^{1}H NMR spectra were recorded on a Bruker Advance III, 300 MHz spectrometer at room temperature in $CDCl_3$ with tetramethylsilane as an internal standard. Molecular weights and distributions were determined by GPC using Viscotek GPC max system including a pump module (GPC max, Viscotek, Houston, TX) and a refractive index (RI) detector (VE 3580, Viscotek). In the analyses, 1 mL/min flow rate and 50 µL injection volume were used with autosampler system. The calibration of RI detector was done by narrow molecular weight polystyrene standards. Two columns (LT5000L, Mixed, Medium Organic 300×8 mm and LT3000L, Mixed, Ultra-Low Organic 300 × 8 mm) with a guard column (TGuard, Organic Guard Column 10 × 4.6 mm) were used for the tetrahydrofuran eluent at 35 °C. Viscotek OmniSEC Omni01 software was used to analyze the data. Fourier transformed infrared spectroscopy (FTIR) studies were performed by using a Perkin-Elmer Spectrum Two Spectrometer (Lambda 25, Waltham, MA) equipped with a diamond attenuated total reflectance (ATR) device at ambient temperature.

Chloromethylation of polysulfones

PSU-Cl was synthesized by following a literature protocol. Briefly, PSU (10 g, 0.25 mmol) was dissolved in chloroform (300 mL) by using an ultrasonic bath and then paraformaldehyde (29 mL, 225 mmol) and trimethylsilyl chloride (29 mL, 225 mmol) were added. After stirring for a while, tin(IV) chloride (0.26 mL, 2.25 mmol) was added and the mixture was stirred at room temperature for 72 hours. At the end of the given time, the product was precipitated by pouring into excess methanol. Then, the precipitate was filtered and dried in a vacuum oven at room temperature.

Azidation of polysulfones

PSU-Cl was synthesized by following a literature protocol. Briefly, PSU (10 g, 0.25 mmol) was dissolved in chloroform (300 mL) by using ultrasonic bath and then paraformaldehyde (29 mL, 225 mmol) and trimethylsilyl chloride (29 mL, 225 mmol) were added. After stirring for a while, tin(IV) chloride (0.26 mL, 2.25 mmol) was added and the mixture was stirred at room temperature for 72 hours. End of the given time, the product was precipitated into excess methanol. Then, the precipitate was filtered and dried in a vacuum oven at room temperature.

Synthesis of alkyne functional PDMA (PDMA-alkyne)

PDMA-alkyne was synthesized by reversible addition–fragmentation chain-transfer (RAFT) polymerization according to previous literature. Briefly, DMA (50 eq.), RAFT agent (1 eq.), and AIBN (0.01) were dissolved in DMSO. After deoxygenation by purging with N_2, the mixture was heated at 60 °C. After given time the reaction was terminated by cooling to 0 °C and exposed to air. The mixture was dissolved in a large excess of DCM and extracted twice by distilled water. The organic phase removed by reduce pressure, the concentrated mixture was precipitated in ten-fold excess of Et_2O and dried under reduced pressure.

Click Reactions

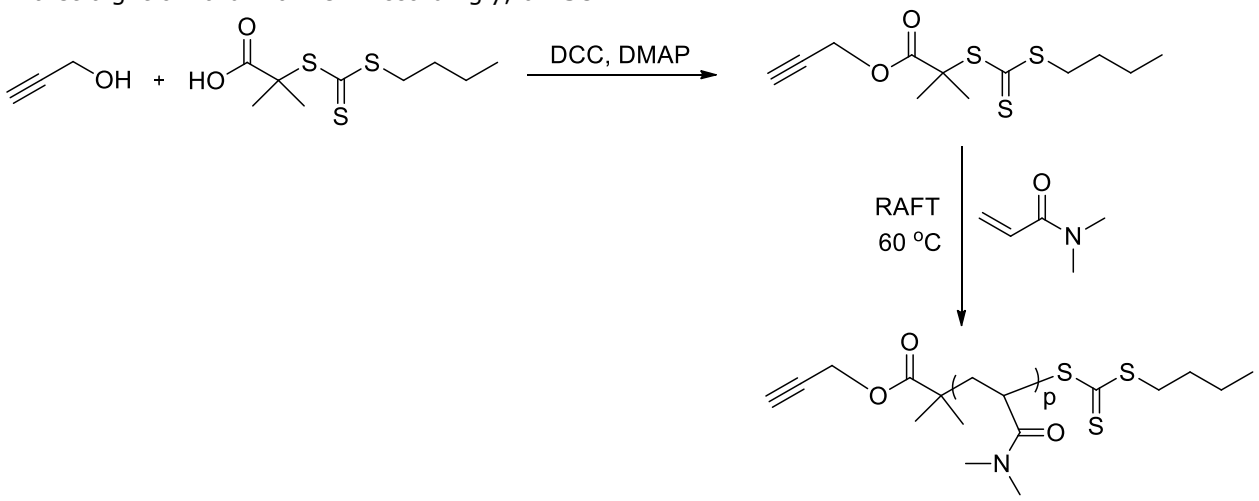
In a typical click reaction, azide functional PSU (50 mg), PDMA-alkyne (3×10^{-4} mol), catalyst (Cu^IBr, 3×10^{-4} mol), ligand (PMDETA, 6×10^{-4} mol), and 4 mL of toluene were placed in a Schlenk tube. The reaction mixture was degassed by three freeze−pump−thaw cycles and stirred at room temperature for 24 h. After the click reaction, the reaction mixture was passed through a column filled with neutral alumina to

remove the copper salt, 10-fold excess of methanol and dried under reduced pressure.

RESULTS AND DISCUSSION

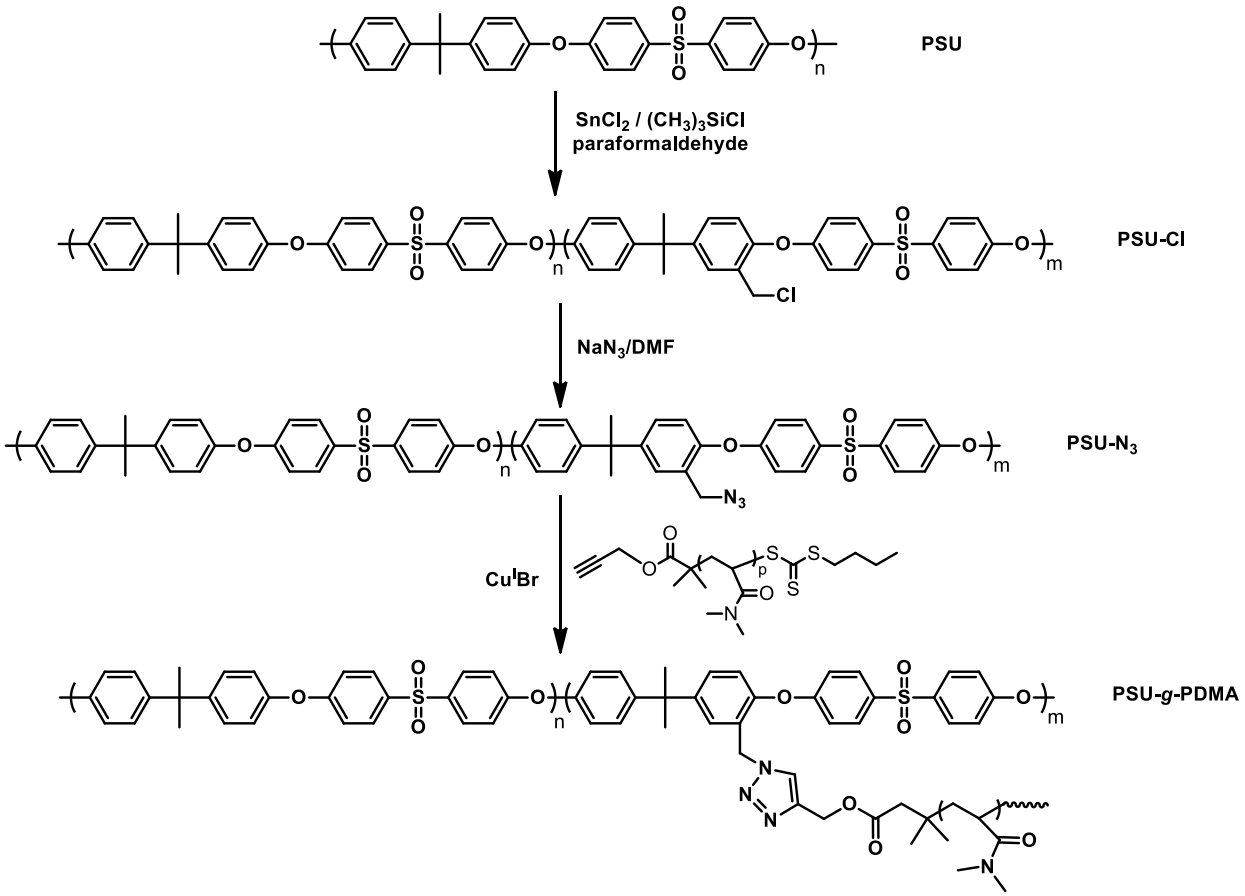
Among the various potential approaches that could be employed for the synthesis of PSU graft copolymers, CuAAC appeared to be the most appropriate one for numerous motives. In addition to its orthogonality and excellent yields, the procedure is also compatible the functional groups existing in the PSU backbone.(24) Thus, it enables the attachment of the desired side chains in a straightforward manner. Accordingly, a PSU with pendant chloro-groups was prepared by using a chloromethylation procedure. Then, chloro- units were converted into azide groups by a nucleophilic substitution reaction using NaN_3 to give the azide-functional PSU (PSU-N_3).

On the other hand, alkyne functional PDMA (PDMA- alkyne) was prepared following a literature procedure with slight changes (Scheme 1). Accordingly, an alkyne functional RAFT agent was synthesized by esterification reaction, which was then used to mediate RAFT polymerization of DMA to access the anticipated PDMA-alkyne.



Scheme 1: Synthetic route to PDMA-alkyne.

Finally, the PDMA chains were grafted to the PSU main chain via CuAAC reactions to give the desired amphiphilic polysulfone graft copolymers. Overall process for the synthesis of graft copolymers is summarized in Scheme 2.



Scheme 2: Overall process for synthesis of PSU-*g*-PDMA copolymers by CUAAC.

As can be seen from Table 1, molecular weights, and thus, hydrophilicities of the formed graft copolymers could be manipulated by using different PDMA-alkyne with diverse molecular weights.

Table 1: "Grafting to" of PDMAs to PSU-N_3[a].

Sample	M_n (g mol^{-1})[b]	M_w/M_n[b]	WCA (°)
PSU-*g*-PDMA-1[c]	39 300	1.77	72
PSU-*g*-PDMA-2[d]	46 100	1.79	65

[a] M_n(PSU-N_3) = 30,200 g mol^{-1}, M_w/M_n = 1.74, [b] Determined by GPC, [c] PDMA-1 (M_n = 1,300 g mol^{-1}, M_w/M_n = 1.09) was used as the antagonist click component, [d] PDMA-2 (M_n = 2,100 g mol^{-1}, M_w/M_n = 1.09) was used as the antagonist click component.

Each step of the process was followed by ^{1}H-NMR analysis. The degree of the chloromethylation was determined as 10 mol% by comparison of the integration area of–CH_2Cl protons of the chloromethyl at δ = 4.55 ppm with the aromatic signals of PSU backbone (Figure 1). Subsequent to the azide substitution, the mentioned methylene signals were entirely shifted to δ = 4.35 confirming quantitative azidation. The successful click process was also confirmed as can be seen from the spectra of the graft copolymer. Thus, a new signal appeared, in addition to the aromatic peaks of PSU segment, around δ = 2.87 corresponding to characteristic signals of –CH_3 moieties of PDMA.

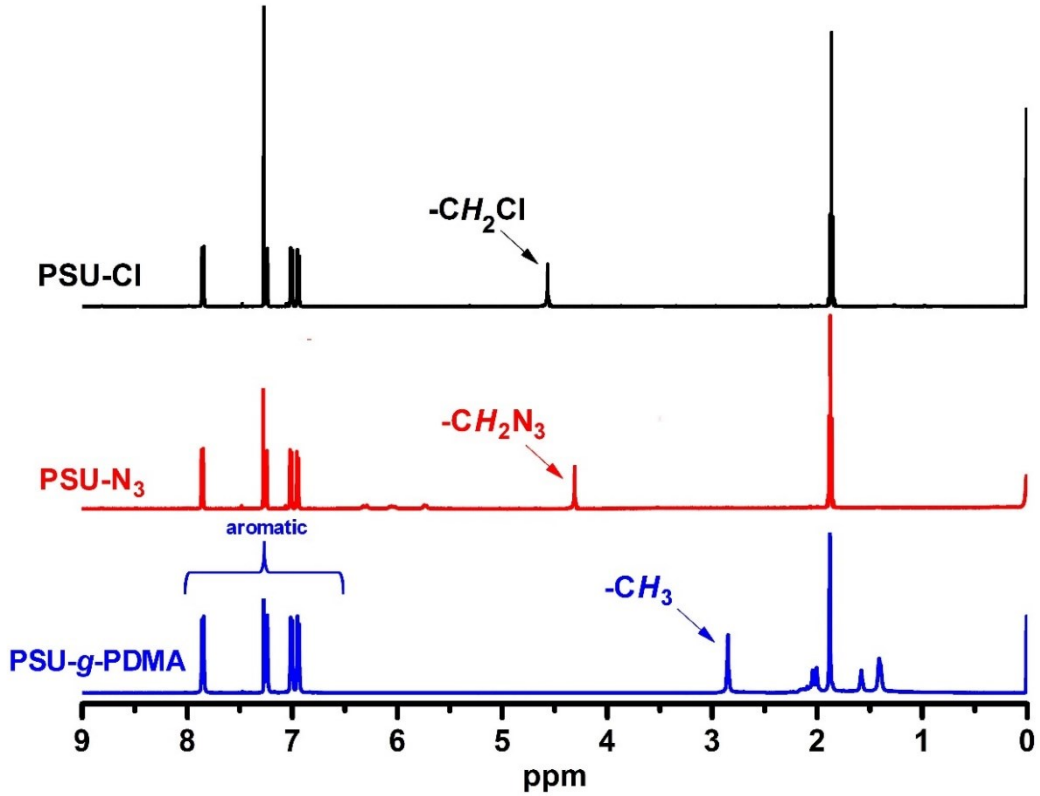


Figure 1: ^{1}H NMR spectra of PSU-Cl, PSU-N_3 and PSU-*g*-PDMA.

FT-IR results also confirmed both azidation and grafting processes (Figure 2). After the azidation, the typical $-N_3$ peak around 2120 cm^{-1} was clearly detectable. On the other hand, the spectrum of the graft copolymer displays the distinguishing carbonyl bands (1720 cm^{-1}) of the PDMA segment in addition to the aromatic stretching bands of PSU units at 1590 and 1480 cm^{-1}. Moreover, the complete disappearance of $-N_3$ signal represents the quantitative yield of the click reaction.

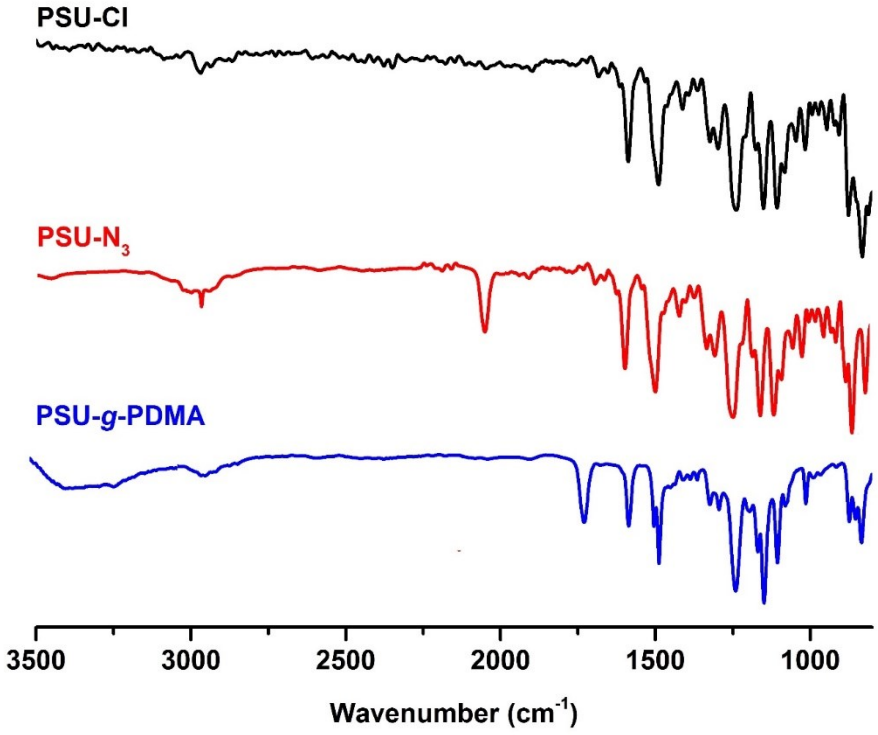


Figure 2: FT-IR spectra of PSU-Cl, PSU-N_3 and PSU-*g*-PDMA.

The GPC curves of the precursor polymer and its corresponding graft copolymer analogues are illustrated in Figure 3. The obvious shift of the graft copolymers towards higher molecular weight region (lower elution volumes), indicates successful grafting.

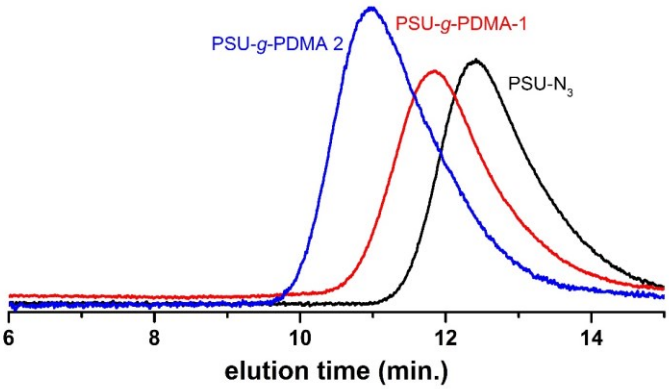


Figure 3: GPC traces of PSU-N_3, PSU-*g*-PDMA-1 and PSU-*g*-PDMA-2.

Hydrophilicity of the graft copolymers were investigated by demonstrated by water contact angle (WCA) measurements. The WCA results of the pristine PSU and corresponding graft copolymer analogues are presented in Figure 4. WCAs of graft copolymers were lower (72° and 65°) then the precursor PSU (81°) as expected. Moreover, as can deduced from the higher WCA of PSU-*g*-PDMA-1 that bears a shorter hydrophilic PDMA side chain compared to PSU-*g*-PDMA-2, the WCAs decreased with the increase of the PDMA side chain content in the structure.

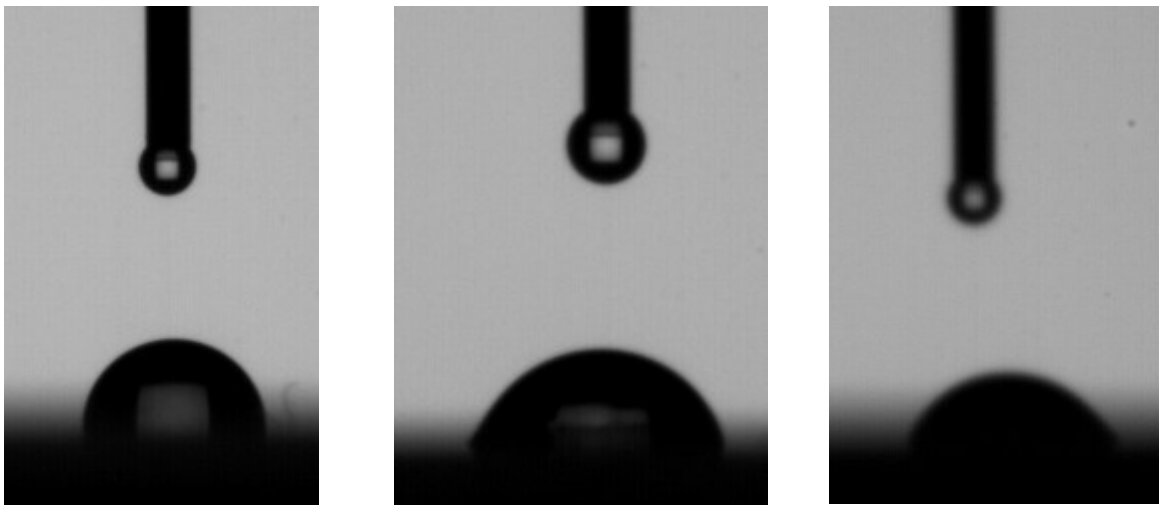


Figure 4. Shapes of water drops on thin films of PSU-N_3 (left), WCA: 83°, PSU-*g*-PDMA-1 (middle), WCA: 72°and PSU-*g*-PDMA-2 (right), WCA: 65°.

In summary, amphiphilic polysulfone graft copolymers, with different hydrophilicities were obtained. In the process, chloro-functional PSUs were synthesized from a commercial PSU then azide groups were then incorporated to the polymer chain. Subsequently, alkyne functional PDMAs, prepared by RAFT polymerization by using functional RAFT agent, were attached via CuAAC to give the amphiphilic polysulfone-*g*-poly(N,N-dimethylacrylamide) (PSU-*g*-PDMA) copolymers. The obtained graft copolymers possessing hydrophobic PSU main chain and hydrophilic PDMA side chains appear as suitable candidates for various application especially biomedical applications.

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