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Understanding copolymerisation kinetics for the design of functional copolymers *via* free radical polymerisation

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Determining the monomer sequence distribution of copolymers is important when correlating copolymer molecular structure (random, gradient *etc.*) to macroscopic/material properties. We report here the relative monomer reactivities for the copolymerisation of methyl methacrylate (MMA) with functional monomers – poly(ethylene glycol) methyl ether methacrylate (PEGMEM M_n 500 $gmol^{-1}$), acetonide-protected dopamine methacrylamide (ADMA), methacrylic acid (MAA) and glycidyl methacrylate (GMA) – to provide information on monomer sequence distribution and compositional drift. Reactivity ratios were calculated, using non-linear least squares regression analysis, in the cases of the free radical copolymerisation of MMA with i) PEGMEM (r_{MMA}= 1.17 r_{PEGMEM}= 0.62) and ii) ADMA (r_{MMA}= 2.21 r_{ADMA}= 0.17). Additionally, monomer feed depletion as a function of total monomer conversion was monitored by ^{1}H NMR spectroscopy for a series of batch co- and terpolymerisations. This approach offers detailed insight into monomer compositional drift and copolymerisation kinetics. Such information provides a platform for the design of copolymers with specific desired properties *e.g.* adhesion,, solubility or interfacial activity.

Introduction

Copolymerisation is a widely used technique for tuning specific material properties for desired applications. Two or more monomers with differing chemical and physical attributes can, *via* copolymerisation, result in materials with desired targeted properties such as glass transition temperature, durability, solubility, adhesion, chemical reactivity and crystallinity. For this reason, copolymers are widely exploited in the fields of coatings, drug-delivery, cosmetics and agrochemicals. Moreover, in recent years, the theme of "sequence controlled polymers" has emerged, in which a growing number of groups have sought to understand and control or influence the comonomer sequence in chain-growth copolymerisations and understand the limits of precision in these systems.[1-4] It is clear that compositionally identical copolymers with different monomer sequence distributions (e.g. random versus gradient) will have very different properties and the ability to influence monomer sequence distributions offers the possibility to significantly extend the properties and applications of copolymers.[5-9] The first step in this process is to understand the inherent copolymerisation kinetics in systems of interest *via* experimental or computational methods.[10] Such an experimental approach, applied to free radical copolymerisation of methacrylic comonomers, is the primary aim of the current study. Knowledge of the reaction kinetics of specific copolymerisation systems is also directly applicable to model-based engineering of potential industrial processes including feed rates in semi-continuous polymerisation or prediction of polymer chain composition in reversible-deactivation radical polymerisations.[11-13]

Methyl methacrylate (MMA) is a widely used monomer in industry due to its versatile properties and chemical resistance. It is often copolymerised with a range of functional monomers to achieve desired properties.[14] In the present study, a series of functional monomers including poly(ethylene glycol) methyl ether methacrylate (PEGMEM), acetonide-protected dopamine methacrylamide (ADMA), methacrylic acid (MAA) and glycidyl methacrylate (GMA) have each been investigated in free radical copolymerisation with MMA (Figure 1). PEGMEM for example, is commonly utilised with hydrophobic monomers as the water-soluble poly(ethylene) glycol side chain allows tuneable amphiphilicity.[15-17] Deprotected ADMA introduces catechol functionalities which bring widely reported adhesive properties[18] with a surge of interest in utilising this catechol moiety since the first report of the self-polymerisation of catechol-containing dopamine in 2007.[19] Such a library of monomers offers the scope to produce a wide variety of copolymers with diverse potential application in functional adhesives,[18, 20-22] healthcare,[23] pharmaceuticals[24], stabilisation of nanoparticles[25, 26] and in anti-fouling coatings.[27, 28]

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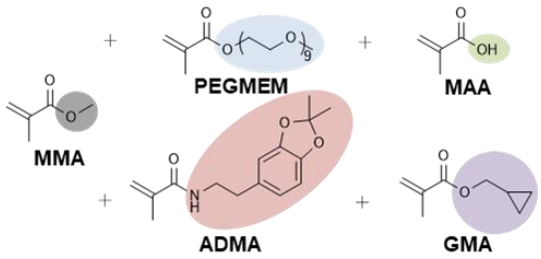

Figure 1 - Chemical structures of the comonomers used for free-radical co- and terpolymerisations of MMA with functional methacrylates (PEGMEM, MAA & GMA) and a functional methacrylamide (ADMA).

Determining the copolymerisation kinetics of MMA with such functional monomers is vital to better understand the monomer distribution and composition in the resulting copolymers. Correlating structure/sequence and properties, can result in copolymers that can be engineered for desired properties.[29] Although such data is surprisingly lacking in the open literature, a number of examples of analogous data for the reaction of MMA with functional monomers have been published.[30-32] The monomer sequence distribution of copolymers is influenced by both the monomer mole fractions (f_1 and f_2, where $f_1 + f_2 = 1$) and reactivity ratios (r_1 and r_2) which are the key variables in the Mayo-Lewis model, also known as the instantaneous copolymerisation equation (eqn 1).[33] In eqn 1, F_1 represents the mole fraction of monomer 1 incorporated in the copolymer, where $F_1 + F_2 = 1$. Using the terminal Mayo-Lewis model, two reactivity ratios can be defined, which describe the individual monomer reactivity in the copolymerisation (eqn 2). The reactivity ratios represent the tendency of monomer 1 and monomer 2 to undergo homopropagation or cross-propagation reactions, where k_{12} represents the rate constant for the addition of monomer 2 to a polymer with a propagating radical species derived from monomer 1.

$$F_1 = \frac{r_1 f_1^{\,2} + f_1 f_2}{r_1 f_1^{\,2} + 2 f_1 f_2 + r_2 f_2^{\,2}} \quad (1)$$

$$r_1 = \frac{k_{11}}{k_{12}} \quad r_2 = \frac{k_{22}}{k_{21}} \quad (2)$$

Linear and non-linear parameter estimation methods can be used to calculate the reactivity ratio values. The most widely-used linear methods to estimate reactivity ratios are the Fineman-Ross[34] and Kelen-Tüdös[35] methods. However, linear methods have been shown to lack statistical rigour for all systems due to assumptions made in their definition and non-linear methods such as non-linear least squares regression analysis (NLLS) and the errors in variables method (EVM) are more statistically sound.[36] The determination of reactivity ratios is most commonly achieved experimentally by limiting the copolymerisation to a low conversion (<10 %) for a variety of different monomer feed ratios which satisfies the assumption, based on the Mayo-Lewis model, that the monomer feed ratio stays constant. Instantaneous copolymer composition can then be determined by ^{1}H NMR, quantitative ^{13}C NMR, FTIR or gas chromatography. Monomer reactivity in copolymerisations can also be analysed by cumulative models based on integration of the Mayo-Lewis equation. NMR spectroscopy, gas chromatography and mass spectrometry,[37, 38] have been used to track monomer depletion, either by reaction sampling or using real-time in-situ NMR spectroscopy to monitor monomer consumption, although real-time methods were not used in the current study.[7, 27, 39-43]

Despite the wide utility of the aforementioned functional monomers, to the best of our knowledge, no reactivity ratios or kinetic data for the described radical copolymerisations have been previously reported. This is surprising, since the comonomer sequence will have a fundamental impact on copolymer performance in certain industrial applications and knowledge of the reactivity ratios could be exploited to modify the resulting sequence and thus optimise properties and performance. Thus, we report here the outcome of the free radical co- and terpolymerisations of the above-mentioned functional monomers with MMA. This includes a calculation of reactivity ratios for PEGMEM/MMA and ADMA/MMA, and the full conversion analysis of individual monomer kinetics for copolymerisation of MMA with the functional monomers.

Experimental

Materials

Methyl methacrylate (MMA, 99 %), poly(ethylene glycol) methyl ether methacrylate (PEGMEM, average molar mass 500 g mol^{-1}), methacrylic acid (MAA, 99 %), glycidyl methacrylate (GMA, 97 %), 1,4-dioxane (99 %) and dimethylformamide (DMF, 99.8 %), were all supplied by Sigma-Aldrich and passed through an activated alumina column prior to use. Dopamine hydrochloride (99 %), sodium carbonate monohydrate (99.5 %), sodium tetraborate (99.5 %), *p*-toluenesulfonic acid (98 %), 2,2-dimethoxypropane (98 %), methacrylic anhydride (94 %), hydroquinone (99.5 %), trimethylsilyldiazomethane (2.0 M in hexane) and 1,2-propanediol were

supplied by Sigma-Aldrich and used as received. Hydrochloric acid (37 %) was supplied by Fisher Scientific and used as received. 2,2'-Azodi(2-methylbutyronitrile) (AMBN, 98 %) was supplied by AkzoNobel and used as received. Azobisisobutyronitrile (AIBN, 98 %) was supplied by Sigma-Aldrich and recrystallized from methanol prior to use. Dimethyl sulfoxide d_6 (99.9 % D atom) and 1,4-dinitrobenzene (DNB, 98 %) were supplied by Sigma-Aldrich and used as received, deuterated chloroform (99.8 % D atom) was supplied by Apollo Scientific, UK, and used as received. Benzoylated dialysis tubing (MWCO 2000 $gmol^{-1}$) was supplied by Sigma-Aldrich.

Methods

^{1}H NMR spectra were recorded on a Bruker-400 MHz spectrometer using $CDCl_3$ or DMSO d_6 as a solvent. Spectra were referenced to the trace proton peaks present in $CDCl_3$ (7.26 ppm) or DMSO d_6 (2.50 ppm). NMR spectra were analysed using MestReNova (Mestrelab Research, Spain). Dinitrobenzene (DNB) or dimethylformamide (DMF) were used as internal standards in NMR experiments.

Molecular weights were obtained by size exclusion chromatography (SEC) on a Viscotek TDA 302 with refractive index, viscosity, and light scattering detectors. 2 × 300 mm PLgel 5 µm mixed C-columns (with a linear range of molecular weight from 200 to 2,000,000 g mol^{-1}) were used and THF as the eluent with a flow rate of 1.0 mL min^{-1} at a temperature of 35 °C. In all cases the molecular weights were obtained by triple detection SEC with light scattering, using a d*n*/d*c* value of 0.085 mL g^{-1} for methyl methacrylate (obtained from Viscotek). The M_n values are therefore not absolute values as the d*n*/d*c* of PMMA in THF was used throughout.

Synthesis of acetonide-protected dopamine methacrylamide (ADMA)

ADMA was synthesised in two steps using the method of Detrembleur[28] (building on the work of Messersmith and coworkers[18]). A two-necked round-bottomed flask was charged with sodium tetraborate (40.4 g, 105 mmol), sodium carbonate (21.1 g, 168 mmol) and 1 L of water. The solution was deoxygenated by sparging with nitrogen for 4 h, before dopamine hydrochloride (10.0 g, 53 mmol) was added. The mixture was stirred and deoxygenated for a further 15 minutes. The resulting solution was then cooled to 0 °C in an ice-water bath, and methacrylic anhydride (16.8 mL, 105 mmol) was added dropwise over 5 minutes. The reaction mixture was allowed to return to room temperature and stirred for 24 h under nitrogen. The solution was maintained at pH 9–10 by the addition of a further 21.1 g of sodium carbonate during the reaction. The reaction solution was then acidified to pH 2 with aqueous hydrochloric acid, causing a colour change from pink to yellow, and extracted with acetic acid (5 x 40 mL). The combined organic layers were washed twice with 0.1 M hydrochloric acid, once with brine, and dried over magnesium sulfate. Vacuum filtration was used to remove the magnesium sulfate and the solvent was evaporated under reduced pressure to give a light-yellow powder. This was purified by silica gel column chromatography (dichloromethane/methanol, 9:1) to give a white powder of dopamine methacrylamide. Yield 6.51 g, 56 %.

^{1}H NMR (400 MHz, DMSO d_6, δ (ppm)): 8.76, 8.65 (s, -OH, 2H), 7.93 (t, -NH-, 1H), 6.64–6.44 (m, Ph, 3H), 5.62, 5.31 (t, 1H, C**H$_2$**=C-CH_3), 3.22 (q, 2H, -CH_2-C**H$_2$**-NH-), 2.55 (t, 2H, -C**H$_2$**-CH_2-NH-), 1.84 (s, 3H, CH_2=C-C**H$_3$**).
^{13}C NMR (400 MHz, DMSO d_6, δ (ppm)): 167.8 (1C, -NH-C=O), 145.5 (1C, Ph-OH), 143.9 (1C, Ph-OH), 140.5 (1C, CH_2=**C**-CH_3), 130.7 (CH_2-**Ph**), 119.6 (1C, **C**H_2=C-CH_3), 119.2 (1C, Ph), 116.4 (1C, Ph), 115.9 (1C, Ph), 41.4 (-CH_2-NH-), 35.1 (Ph-**C**H_2-CH_2-), 19.1 (1C, CH_2=C-**C**H_3).

400 mL of anhydrous toluene was transferred to a round-bottomed flask and sparged with nitrogen for 2 hours. Dopamine methacrylamide (4.00 g, 18 mmol) and *p*-toluene sulfonic acid (0.17 g, 1 mmol) were added, and the mixture was refluxed for 3 hours with Dean-Stark apparatus. The resulting solution was cooled to 0 °C in an ice-water bath and 2,2-dimethoxypropane (16.80 mL, 137 mmol) was added. A Soxhlet extractor (thimble filled with $CaCl_2$) was fitted and the solution was refluxed for 4 hours in the dark with vigorous stirring. The reaction mixture was washed with water and brine twice, then dried over magnesium sulfate. The remaining solvent was removed under reduced pressure and the solid product was purified by silica gel column chromatography (hexane/ethyl acetate 1:1). Acetonide-protected dopamine methacrylamide (ADMA) was collected as a white powder. Yield 4.16 g, 88 %.

^{1}H NMR (400 MHz, $CDCl_3$, δ (ppm)): 6.69–6.60 (**Ph**, 3H), 5.8 (broad) (-CH_2-CH_2-N**H**-), 5.64, 5.32 (1H, C**H$_2$**=C-CH_3), 3.53 (2H, -CH_2-C**H$_2$**-NH-), 2.77 (2H, -C**H$_2$**-CH_2-NH-), 1.94 (3H, CH_2=C-C**H$_3$**), 1.69 (6H, O-C-C**H$_3$**).
^{13}C NMR (400 MHz, $CDCl_3$, δ (ppm)): 168.4 (1C, -NH-**C**=O), 147.7 (1C, **Ph**-O(C(Me)$_2$)), 146.0 (1C, **Ph**- O(C(Me)$_2$)), 140.1 (1C, CH_2=**C**-CH_3), 132.0 (CH_2-**Ph**), 121.0 (1C, **Ph**), 119.3 (1C, **C**H_2=C-CH_3), 117.8 (1C, **C**(Me)$_2$), 108.8 (1C, **Ph**), 108.1 (1C, **Ph**), 41.0 (1C, -**C**H_2-NH-), 35.4 (1C, Ph-**C**H_2-CH_2-), 25.8 (2C, -C(**C**H_3)$_2$), 18.6 (1C, CH_2=C-**C**H_3).

Typical procedure for the synthesis of P(MMA-co-PEGMEM$_{500}$)

The following procedure uses an equimolar monomer feed ratio. MMA (0.50 g, 5.00 mmol) and $PEGMEM_{500}$ (2.50 g, 5.00 mmol) were added to 1,2-propanediol (30 mL) in a 100 mL two-necked, round-bottomed flask fitted with a condenser; the other neck was sealed with a rubber septum. The solution was sparged with nitrogen for 60 minutes. It was then heated to 70 °C in an oil bath under a nitrogen blanket. An initial reaction sample was collected in a vial for analysis using a syringe and rapidly cooled by submersion into liquid nitrogen. AMBN (29 mg, 0.15 mmol) was then added to the reaction. For the estimation of reactivity ratios: a sample was taken after 7 minutes and quenched using liquid nitrogen (to ensure the conversion was kept to <10 %, it was checked using ^{1}H NMR spectroscopy). Hydroquinone (0.15 g) was then added to the remaining reaction mixture which was then allowed to cool and was dialysed (benzoylated dialysis tubing, 2000 MWCO) in water for three days. The water was then removed under reduced pressure, yielding a colourless solid. For the analysis of copolymerisation reactions that were allowed to run to full conversion, further samples were removed and quenched every 10 minutes until 60 minutes, then every 30 minutes until 180 minutes and then every 60 minutes until 360 minutes. The reaction was quenched with hydroquinone, dialysed and dried overnight under vacuum. M_n 90,300 g mol^{-1}, Đ 1.62.

Typical procedure for the synthesis of P(MMA-*co*-ADMA)

The following procedure uses an equimolar monomer feed ratio. MMA (0.10 g, 1.00 mmol) and ADMA (0.26 g, 1.00 mmol) were added to 1,4-dioxane (3 mL) in a 50 mL two-necked, round-bottomed flask fitted with a condenser; the other neck was sealed with a rubber septum. The solution was sparged with nitrogen for 60 minutes. It was then heated to 70 °C in an oil bath under a nitrogen blanket. An initial reaction sample was collected in a vial for analysis using a syringe and rapidly cooled by submersion into liquid nitrogen. AIBN (3.20 mg, 0.02 mmol) was dissolved in 0.1 mL 1,4-dioxane and injected into the reaction. For the estimation of reactivity ratios: a sample was collected after 10 minutes and quenched using liquid nitrogen (to ensure the conversion was kept to <10 %, it was checked using 1H NMR spectroscopy). Hydroquinone (0.30 g) was then added to the remaining reaction mixture which was allowed to cool and was then dialysed (benzoylated dialysis tubing, 2000 MWCO) in methanol for three days. The methanol was removed under reduced pressure, yielding a white solid. In subsequent reactions monomer feed ratios were adjusted as required. For the full conversion reactivity analysis: further samples were removed and quenched after 20 minutes (then every 20 minutes until 60 minutes), 90 minutes (then every 30 minutes until 180 minutes), 240 minutes (then every 60 minutes until 360 minutes) and 15 hours. The reaction was allowed to proceed for 20 hours, before being quenched with hydroquinone. The polymer was precipitated in methanol, yielding a white solid, which was collected and dried overnight under vacuum. M_n 142,700 g mol^{-1}, Đ 2.30.

Typical procedure for the synthesis of P(MMA-co-$PEGMEM_{500}$-co-PMAA)

The following procedure uses an equimolar monomer feed ratio. MMA (0.50 g, 5.00 mmol), $PEGMEM_{500}$ (2.50 g, 5 mmol) and MAA (0.43 g, 5.00 mmol) were added to 1,2-propanediol (30 mL) in a 100 mL two-necked round-bottomed flask, fitted with a condenser and the other neck sealed with a rubber septum. The solution was sparged with nitrogen for 60 minutes. It was then heated to 70 °C in an oil bath under a nitrogen blanket. An initial reaction sample was collected for analysis using a syringe and rapidly cooled using liquid nitrogen. AMBN (43.0 mg, 0.23 mmol) was added to initiate the reaction. Further samples were removed and quenched every 10 minutes until 60 minutes, then every 30 minutes until 180 minutes and then every 60 minutes until 360 minutes. The reaction was quenched with hydroquinone, dialysed and dried overnight under vacuum. M_n 96,900 g mol^{-1}, Đ 1.81.

Typical procedure for the synthesis of P(MMA-co-ADMA-co-GMA)

The following procedure uses an equimolar monomer feed ratio. MMA (0.08 g, 0.8 mmol), GMA (0.11 g, 0.8 mmol) and ADMA (0.21 g, 0.08 mmol) were added to 1,4-dioxane (6.30 mL) in a 50 mL two-necked round-bottomed flask, fitted with a condenser; the other neck was sealed with a rubber septum. The solution was sparged with nitrogen for 60 minutes and then heated to 70 °C in an oil bath under a nitrogen blanket. An initial reaction sample was collected for analysis using a syringe and rapidly cooled using liquid nitrogen. AIBN (3.94 mg, 0.02 mmol) was dissolved in 0.1 mL 1,4-dioxane and injected into the flask to initiate the reaction. Further samples were removed and quenched after 20 minutes (then every 20 minutes until 60 minutes), 90 minutes (then every 30 minutes until 180 minutes), 240 minutes (then every 60 minutes until 360 minutes) and 15 hours. The reaction was allowed to proceed for 20 hours before being quenched with hydroquinone. The polymer was precipitated in methanol, yielding a white solid, which was collected and dried overnight under vacuum. M_n 85,400 g mol^{-1}, Đ 1.47.

Results and Discussion

Reactivity ratios for the free-radical copolymerisation of MMA with functional monomers PEGMEM and ADMA were determined. The reactivity ratio values alone allow for a better understanding of comonomer sequence distribution and compositional drift for given monomer feed ratios. To verify the impact of copolymerisation kinetics and compositional drift in copolymer microstructure, a series of copolymerisation reactions were also carried out and allowed to proceed to full conversion. In these reactions the instantaneous monomer feed ratio was monitored by the withdrawal of samples for analysis as the reaction proceeded. This study

was extended to include additional functional monomers, MAA and GMA, in terpolymerisations, to determine copolymer composition as a function of total monomer conversion.

Reactivity Ratio Estimation

To determine reactivity ratios, a series of free radical solution copolymerisation reactions of MMA with PEGMEM M_n= 500 $gmol^{-1}$ (in 1,2-propanediol) and MMA with ADMA (in 1,4-dioxane) at 70 °C, were carried out with monomer (molar) feed ratios (f_{MMA}) ranging from 0.1 to 0.9 (Table 1). 2,2'-Azodi(2-methylbutyronitrile) (AMBN) was used as the initiator for the MMA/PEGMEM system and azobisisobutyronitrile (AIBN) for the MMA/ADMA system. AIBN and AMBN have very similar thermal decomposition rates, with a 10 hour half-life at 67 °C and 63 °C respectively. As such, we do not anticipate the variation of initiator, and any small change in the rate of initiation, will have a significant impact on the copolymerisation kinetics. 1,2-Propanediol was selected for the polymerisation of MMA with PEGMEM as it is considered to be a green solvent and is widely used by industry. Due to the limited solubility of PMMA in 1,2-propanediol, f_{MMA} was limited to <0.66 for the copolymerisation with PEGMEM. ADMA has extremely low solubility in 1,2-propanediol and for this reason 1,4-dioxane was selected as an alternative solvent for the copolymerisation of ADMA. As reaction concentration can affect reactivity ratios,[44] all reactions were carried out using a 10% (w/v) monomer concentration, to eliminate any error in reactivity ratio due to inconsistencies in concentration. All reactions used to determine reactivity ratios were quenched at low conversion (<10%), which satisfied the requirements of the Mayo-Lewis model. To determine at what time the polymerisations needed to be quenched to achieve <10 % total conversion, several preliminary reactions were carried out and conversion was measured. The total monomer conversion was checked after each polymerisation was quenched. Data on the total monomer conversion as a function of time up to 23 % conversion is included as electronic supporting information, Figure S1. The fractional monomer composition (f_{mon}) and copolymer composition (F_{mon}) were calculated using ^{1}H NMR spectroscopy (Figures S2 and S3).

To give an initial indication of copolymer composition as a function of feed ratio, a Mayo-Lewis plot (Figure 2) was created using the f_{MMA} and F_{MMA} data (Table 1) for each monomer pair. This plot shows that for the MMA/PEGMEM copolymerisation, the mole fraction of MMA is slightly higher in the copolymer than the monomer feed ($F_{MMA} > f_{MMA}$), and this is the case for all monomer feed ratios. A similar but more pronounced behaviour can be seen for the MMA/ADMA system, where once again $F_{MMA} > f_{MMA}$. This data would suggest that in each case, there is a greater tendency to incorporate MMA and this tendency is more pronounced in the MMA/ADMA copolymerisation. A fit of the data in Table 1 was obtained using the non-linear least squares (NLLS) method to estimate the reactivity ratios (r_1 and r_2) from the instantaneous copolymerisation equation (eqn 1). The lines generated by this fit are shown on the Mayo-Lewis plot (Figure 2).

Table 1. Monomer mole fraction (f_{mon}) values and the resulting copolymer composition data (F_{mon}) obtained by ^{1}H NMR spectroscopy for the MMA/$PEGMEM_{500}$ copolymerisation in 1,2-propanediol at 70 °C, and the MMA/ADMA copolymerisation in 1,4-dioxane at 70 °C.

MMA/PEGMEM		MMA/ADMA	
f_{MMA}	F_{MMA}	f_{MMA}	F_{MMA}
0.09	0.13	0.05	0.22
0.14	0.23	0.17	0.44
0.21	0.28	0.33	0.56
0.26	0.33	0.45	0.70
0.35	0.41	0.56	0.82
0.43	0.50	0.70	0.83
0.46	0.54	0.78	0.91
0.52	0.59	0.94	0.96
0.56	0.63		
0.64	0.67		
0.66	0.75		

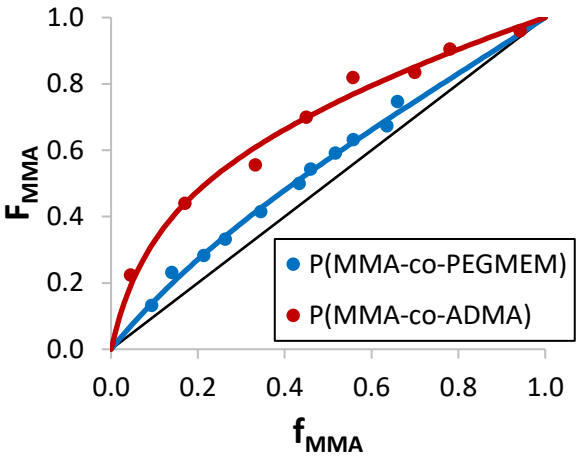

Figure 2. Mayo Lewis plot showing MMA mole fraction in copolymer as a function of feed ratio for both the MMA/PEGMEM$_{500}$ (blue) and MMA/ADMA (red) copolymerisations. A non-linear least squares method was used to fit the data. The black line with the equation x = y represents the expected result in an ideal polymerisation (where $r_1 = r_2 = 1$).

Reactivity ratio data was estimated by non-linear least squares (NLLS) regression analysis. NLLS involves estimating the reactivity ratios from a non-linear fit of the data in Figure 2 to the Mayo-Lewis equation. For comparison, reactivity ratios were also estimated using the well-known linearisation methods, namely the Fineman-Ross[29] and the Kelen-Tüdös[30] models. The Fineman-Ross and the Kelen-Tüdös methods are derived from the Mayo-Lewis model and a detailed description of the method is included as electronic supporting information. The reactivity ratios estimated using both non-linear and linear parameter estimation techniques for the copolymerisation of MMA with PEGMEM and ADMA respectively are reported in Table 2. NLLS 95% confidence intervals were obtained using the regression data. 95% confidence intervals for the FR were calculated using a linear least squares regression of the data presented. KTM 95% confidence intervals were calculated according to the method of Kelen, Tüdös and Turcsanyi.[45]

Table 2. Reactivity ratios for the copolymerisation of MMA/PEGMEM and MMA/ADMA using the non-linear least squares method and Fineman-Ross and Kelen-Tüdös linearisation methods.

	$r_{1\,(MMA)}$	$r_{2\,(PEGMEM)}$	$r_1.r_2$	$r_{1\,(MMA)}$	$r_{2\,(ADMA)}$	$r_1.r_2$
Non-linear Least Squares	1.17 ± 0.11	0.62 ± 0.06	0.73	2.21 ± 0.26	0.17 ± 0.03	0.38
Fineman-Ross	1.22 ± 0.08	0.63 ± 0.10	0.77	2.30 ± 0.11	0.22 ± 0.14	0.51
Kelen-Tüdös	1.17 ± 0.23	0.60 ± 0.10	0.70	2.26 ± 0.73	0.21 ± 0.17	0.47

When firstly considering the MMA/PEGMEM copolymerisation, it is clear that regardless of the method chosen to estimate reactivity ratios, the obtained data is rather similar in each case. Namely that r_{MMA} is approximately 1.2, indicating a slight preference for homopropagation and r_{PEGMEM} is approximately 0.6, indicating a slight preference for cross-propagation. Perhaps the similarity of the data (reported in Table 2) obtained by the three methods, is a feature of the system(s) in question, however, this should not diminish the argument for using a NLLS method since in some reported cases, significant differences have been observed in reactivity ratios obtained by linear and non-linear methods.[36, 46] These data are in good agreement with the Mayo-Lewis plot (Figure 2) which indicates that MMA is incorporated into the copolymer in preference to PEGMEM and that some compositional drift will occur. The NLLS data (Table 2) indicates the product of the reactivity ratios ($r_1.r_2$) for the MMA/PEGMEM copolymerisation ($r_{MMA}.r_{PEGMEM}$ = 0.73) is close to 1, indicating a slight deviation from random polymerisation

kinetics (defined as when $r_1.r_2 = 1$). We can therefore expect the polymer sequence to have a nearly random distribution of monomers, with a slight drift from MMA to $PEGMEM_{500}$. Given that both monomers are methacrylates it is not entirely surprising that their reactivity in this instance is very similar.[47, 48] Moreover, these results are consistent with previous reports of similar systems. For example, the (bulk) free radical copolymerisation of MMA with 2-hydroxyethyl methacrylate caprolactone[49] (HEMA-CL_3) (molar mass of 473 $gmol^{-1}$) proceeds with reactivity ratios near unity and the solution free radical copolymerisation of dodecyl methacrylate[50] (DMA) (254 $gmol^{-1}$) with MMA has reactivity ratios r_{MMA}= 1.22 and r_{DMA}= 0.84. In both cases it was observed that the copolymer composition did not vary greatly from the comonomer (feed) composition - indicating nearly random copolymerisation behaviour. Although the differences in reactivity ratio are small, one can speculate about the kinetic behaviour of MMA and PEGMEM. Factors influencing the reactivity ratios, including the solvation of both monomer and the propagating radical[51] and hydrogen bonding[52] may be considered. In this case neither MMA nor PEGMEM contain H-bond donating groups, so H-bonding between monomer molecules or between monomer and polymer can be discounted. 1,2-Propanediol, an H-bond promotor,[47] clearly is capable of H-bonding to either monomer. It could be speculated that the small difference in reactivity ratios may be rationalised by slight differences in monomer solvation. However, PEGMEM having a stronger tendency to H-bond with the solvent will likely be better solvated and a recent report by Schubert *et al*. would suggest differences in solvation is not the cause of differences in reactivity ratio.[53] In that report, which describes the reversible deactivation fragmentation transfer (RAFT) copolymerisation of di(ethylene glycol) methyl ether methacrylate (DEGMEM) and poly(ethylene glycol) methyl ether methacrylate (M_n 1100 $gmol^{-1}$) ($PEGMEM_{1100}$) in ethanol, the rate of consumption of DEGMEM was slower than that of the $PEGMEM_{1100}$, an outcome that was explained by the greater relative solvation of $PEGMEM_{1100}$ in ethanol. That study would suggest that on the basis of solvation alone, in the current study PEGMEM should be consumed more quickly than, whilst the opposite is observed. One might also speculate that the relative rate of monomer incorporation is impacted by the relative size of the two monomers. Whilst there is little in the literature to suggest that the reactivity ratio of a macromonomer such as PEGMEM is directly impacted by steric hindrance, it is possible that the relative rate of diffusion of the two monomers plays a role. There is also evidence to suggest that the relative molar volume of monomer and solvent can play a role.[44, 47] This can be interpreted as a competition between solvent and monomer molecules for access to the propagating site and if the monomer size is greater than the solvent, the concentration of monomer at the propagating site will be lower than the analytical concentration. One might assume that in the copolymerisation of two monomers of significantly differing molar volume, such as MMA and PEGMEM, when all other factors are equal, the larger monomer (PEGMEM) may have a more restricted access to the propagating site and thus a lower reactivity ratio. This assumption would appear to be supported by the data presented. Moreover, this is the subject of an ongoing study involving the copolymerisation of MMA and PEGMEM macromonomers of varying molecular weight and the outcomes will be reported in a future submission. It must again be emphasised that reactivity ratios reported in this manuscript are unique to the systems employed with respect to solvent and monomer concentration.

When considering the MMA/ADMA system, it is clear from the Mayo-Lewis plot (Figure 2) that the copolymerisation kinetics are far from random, which may not be surprising given that we are now considering the copolymerisation of a methacrylate monomer with a methacrylamide monomer. As mentioned above, ADMA shows poor solubility in propanediol and thus the copolymerisation of ADMA reported herein was carried out using 1,4-dioxane due to the excellent solubility of both monomers. As 1,4-dioxane is a polar aprotic solvent and MMA and ADMA are unable to donate H-bonds, the solvent in this case is unlikely to strongly influence the monomer reactivity ratios. The reactivity ratio data reported in Table 2, shows some modest variation for the different models and using the NLLS method (Table 2) we obtain r_{MMA} = 2.21, confirming that MMA shows a strong preference for homopropagation and r_{ADMA} = 0.17, indicating a strong preference for cross-propagation. In this system we would expect therefore that the resulting copolymer will show significant compositional drift with a high fraction of MMA incorporated in the early stages of copolymerisation. The product of the reactivity ratios ($r_1.r_2$ = 0.38) indicates that the rate of monomer addition is far from random and both types of propagating radical show a preference to react with MMA. A survey of the literature for other methacrylate/methacrylamide copolymerisation systems reveals a general agreement with our reported observations, whereby the methacrylate monomer is consumed in preference to the methacrylamide, although such reports describe copolymerisation reactions carried out in a variety of solvents. For example, the free radical copolymerisation of MMA and N-(1-hydroxy-4-methyl-2-pentyl)methacrylamide (HMPMA) in methanol had reported reactivity ratios of r_{MMA} = 2.38 and r_{HMPMA} = 0.50[54] and the free radical copolymerisation of MMA and thiazoyl methacrylamide (TMA) in DMF had reported reactivity ratios of r_{MMA} = 2.72 and r_{TMA} = 0.59.[55] Both of these systems are in broad agreement with the reactivity ratios obtained for the copolymerisation of MMA and ADMA in the current study however, variation in published reactivity ratios for similar comonomer pairs highlights the risk in simply making assumptions about copolymerisation kinetics, especially in the presence of different solvents, and the value of carrying out rigorous experimental studies to obtain accurate reactivity ratio data for each specific system.

In each of the two systems described above, it might be expected that the steric bulk of the substituents on monomers such as PEGMEM and ADMA would sterically inhibit reactivity and impact copolymerisation kinetics. However, as mentioned above there is little evidence in the literature to support that hypothesis. Moreover, a recent report by Frey *et al.* describes the anionic copolymerisation of a series of protected vinyl catechol (4- and 5-vinyl benzodioxole) monomers with styrene.[56] It was found in this case that the bulky ring structure created via the protection of the catechol groups, only impacts monomer reactivity, and

therefore copolymerisation kinetics, when the alkyl moiety of the protecting group is in direct proximity to the propagating site. This observation would appear to agree with the findings of the current study where the PEG substituent of PEGMEM and bulky protected dopamine substituent of ADMA are, in each case, somewhat remote from the propagating radical and has little or no impact on reactivity. Steric bulk of monomers can play a significant role in copolymerisations as demonstrated by previous work from our group on the steric (and electronic) impact on the anionic copolymerisation and terpolymerisation of diphenylethylene (and derivatives) with styrene and butadiene.[57, 58] In these cases the steric bulk of DPE renders it unable to homopolymerise. Our current findings, and these reports, suggest that for bulky substituents to impact monomer addition, the steric bulk must be in direct proximity to the propagating species. It could therefore be suggested that the flexible linking segment between the protected catechol functionality of ADMA and the reactive vinyl group diminishes any steric effects of the side chain on the monomer reactivity. We therefore propose that the extent of spatial separation between the bulky side chain and propagating group is crucial when considering the impact on reactivity.[47]

Study of compositional drift in copolymerisation

Above, the calculation of reactivity ratios for the copolymerisation of MMA/PEGMEM$_{500}$ and MMA/ADMA has been reported. The methods used to calculate these data require that copolymer composition be calculated at low monomer conversion. It is also of interest, however, to obtain a quantitative understanding of the full impact of compositional drift on the heterogeneity of the resulting copolymer systems, and to this end, the copolymerisation reactions described above were repeated and allowed to run to full conversion.

Using ^{1}H NMR spectroscopy, samples collected at different time intervals during the batch copolymerisations were analysed (without work-up) and the consumption of each monomer as a function of total monomer conversion was determined, working on the assumption that all monomer consumed was incorporated into the copolymer. Figure 3 shows a typical set of stacked ^{1}H NMR spectra for the copolymerisation of an equimolar mixture of MMA and PEGMEM. The monomer vinyl group peaks are displayed at chemical shifts 5.63 ppm and 6.19 ppm (MMA) and 5.65 and 6.23 ppm (PEGMEM). At first glance, the two monomers were depleted at similar rates, in line with expectations. Analogous spectra for the copolymerisation of MMA and ADMA (Figure S5) demonstrate a significantly slower rate of conversion of ADMA relative to MMA.

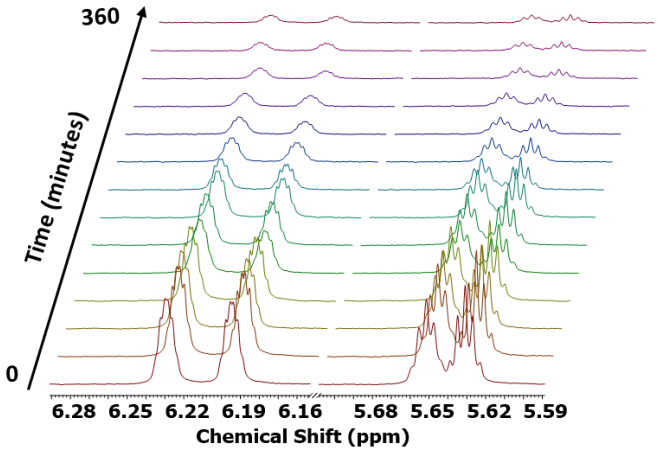

Figure 3. Stacked ^{1}H NMR spectra of samples from 0-360 minutes from the copolymerisation of MMA and PEGMEM in 1,2-propanediol at 70 °C in $CDCl_3$. The monomer vinyl group peaks are displayed: MMA (δ 5.63 and 6.19 ppm) and PEGMEM (δ 5.65 and 6.23 ppm).

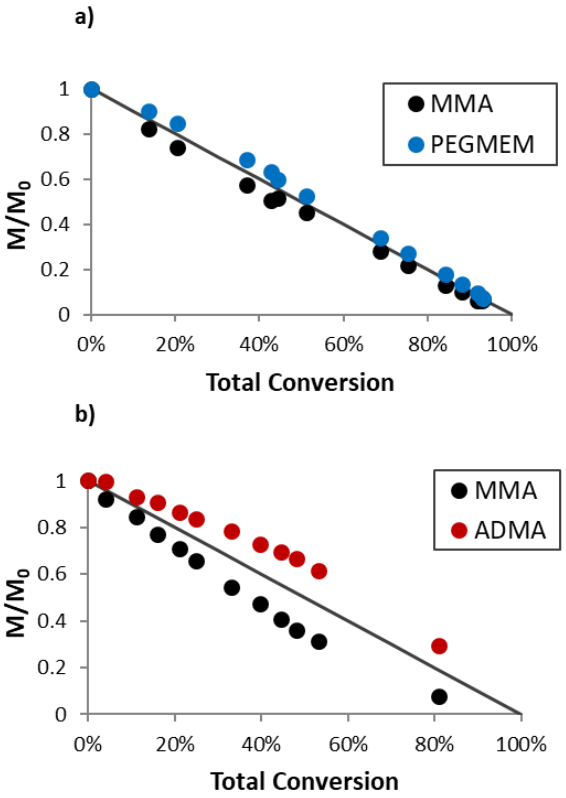

Figure 4. Fraction of residual monomer in feed (M/M_0) as a function of total conversion for the equimolar copolymerisations of a) MMA/$PEGMEM_{500}$ in 1,2-propanediol and b) MMA/ADMA in 1,4-dioxane.

Figure 4a depicts MMA and PEGMEM monomer depletion as a function of total monomer conversion using the NMR data obtained. In line with previous reports[52], depletion is normalised to clearly show the relative incorporation of each monomer, full reaction conversion was achieved after 6 hours. In line with the reactivity ratio estimations above, there is a slight preference for the consumption of MMA at the start of the copolymerisation with $PEGMEM_{500}$. Figure 4b depicts the same relationship, this time for MMA and ADMA. It is important to note that in this case the polymerisation took 24 hours to reach 80% conversion in comparison to 2.5 hrs to reach the same extent of conversion in the MMA/PEGMEM system. This is likely a result of the intrinsically slower propagation rate of methacrylamides compared to methacrylates (in the absence of H-bonding effects).[59] The monomer depletion data is in agreement with the obtained reactivity ratio data, showing that MMA is consumed more rapidly than ADMA. Thus at 53 % total monomer conversion, the instantaneous (residual) monomer feed ratio is 0.33 : 0.67 (MMA : ADMA), indicating a significantly higher residual fraction of ADMA compared to MMA. It is only when approximately 70 % of the MMA has been consumed that the rate of depletion for the two monomers begins to converge. This is to be expected since, although MMA has a higher reactivity and a strong tendency to homopropagate, as the fraction of MMA in the feed diminishes, ADMA becomes the major component in the residual feed. This conversion data combined with the reactivity ratio data clearly illustrates the extent of compositional drift. Understanding this is important for such copolymers, particularly those containing ADMA, in which catechol groups are frequently incorporated to promote binding and adhesion of the copolymer to a surface and the mole fraction of ADMA in the copolymer is critical to adhesive strength.[20] Significant compositional drift implies that the number of catechol groups per chain is likely to vary dramatically depending on conversion (in a batch copolymerisation). This would lead to significant heterogeneity in copolymer properties. Special monomer feed measures may need to be adopted should a truly random/uniform distribution of catechol functionalities be required in the copolymer, which may be supported by modelling of the polymer composition using the reactivity ratios.[60]

Study of compositional drift in terpolymerisations

Terpolymers are important from an academic and industrial perspective due to the potential for incorporating multifunctionality. Each monomer can contribute a particular function to the overall performance of the polymer, depending on the desired application.[21] Understanding the distribution of functionality is crucial when designing a terpolymer.

Two batch terpolymerisation systems were studied. The first introduced methacrylic acid (MAA) into the MMA/$PEGMEM_{500}$ system and the second added glycidyl methacrylate (GMA) into the MMA/ADMA system. In each case the aim was to add additional

functionality to the copolymers. MAA is widely used in adhesives and surface active polymers[26] and can be used as a salt to introduce polyelectrolyte features such as enhanced colloidal stability *via* electrostatic repulsion. GMA is of interest due to the presence of its reactive epoxide ring. Reaction of the epoxide group of GMA with primary amines and thiols can be exploited in surface-active coatings, in which the epoxide acts as a grafting point for layer-by-layer polymer deposition[61] or for binding to biomolecules such as enzymes.[62]

Binary reactivity ratios can be used to estimate terpolymerisation reactivity ratios, however, in doing so, considerable assumptions must be made and the predicted values are not always accurate.[63] Consequently, the binary reactivity ratios were not used to determine terpolymer composition in this study. However, the relative reactivity of each monomer can be illustrated using monomer depletion data and NMR analysis as described above. The ^{1}H NMR spectra and monomer depletion as a function of total monomer conversion for the MMA/PEGMEM/MAA system are depicted in figures 5 and 6a. The stacked ^{1}H NMR spectra show the monomer vinyl group peaks displayed at chemical shifts 5.63 ppm and 6.20 ppm, 5.65 ppm and 6.23 ppm, and 5.67 ppm and 6.25 ppm for MMA, PEGMEM and MAA respectively. It is evident that the rate of monomer consumption as a function of total monomer conversion is almost identical for each of MMA, PEGMEM and MAA under these reaction conditions. This would suggest almost no compositional drift occurs in this case producing an almost perfectly random terpolymer. It has been previously reported that hydroxyl bearing methacrylates, in specific conditions, have enhanced reactivity when compared to their alkyl analogues.[47] This increased reactivity is explained through the formation dimers through specific hydrogen bond associations between monomer and propagating chain. However, in the current work, 1,2-propanediol can act as a H-bond promoter, interacting with all three monomers in this case, but could also be considered a H-bond disruptor, competitively hydrogen-bonding to the propagating polymer chain, disrupting H-bonds between monomer and propagating chain and negating any preferential incorporation of MAA which may occur in non-H-bonding solvents.[44, 47] When considered in a wider context, the copolymerisation of this small family of methacrylate/methacrylic acid monomers suggests that the reactivity of the monomer/propagating radical is rather insensitive to the nature of the substituent, under these conditions. This is in stark contrast to alternative polymerisation mechanisms, such as anionic polymerisation, where the reactivity ratios are extremely sensitive to monomer structure.[64]

Figure 6b depicts the monomer depletion as a function of the total monomer conversion for the MMA/ADMA/GMA system. Consumption of MMA and ADMA is akin to the binary copolymerisation above. GMA depletes at a very similar, but slightly higher rate than MMA, which is not surprising given that MMA and GMA are both (similar) methacrylate monomers. The slightly faster depletion rate of the GMA is in agreement with the reported higher (bulk) homo-propagation rate constant observed for cyclic compared to linear methacrylates[65] and the reported slight preference for GMA incorporation in a free radical copolymerisation.[66] For the MMA/ADMA/GMA system the stacked NMR spectra illustrating the relative rate of monomer depletion of each monomer are shown in Figure S6.

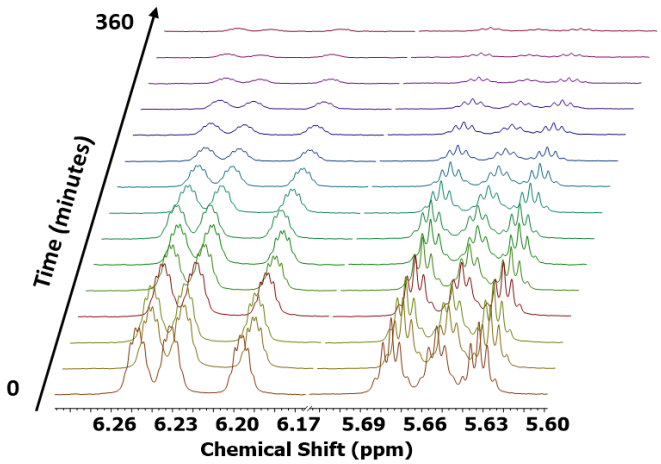

Figure 5. Stacked ^{1}H NMR spectra of samples from 0-360 minutes from the terpolymerisation of MMA, PEGMEM and MAA in 1,2-propanediol at 70 °C in $CDCl_3$. The monomer vinyl group peaks are displayed: MMA (δ 5.63 and 6.20 ppm), PEGMEM (δ 5.65 and 6.23 ppm), and MAA (δ 5.67 and 6.25 ppm).

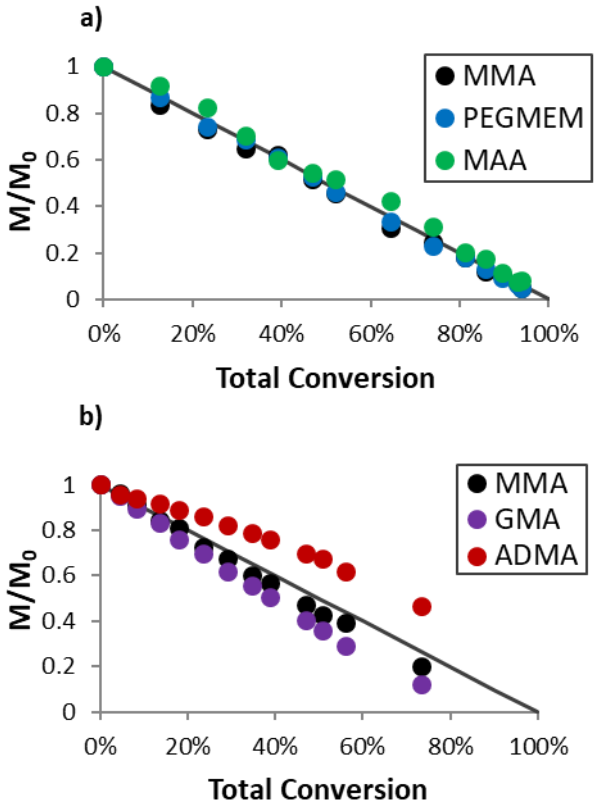

Figure 6. Fraction of monomer in feed as a function of total conversion for the equimolar terpolymerisations of a) MMA/PEGMEM$_{500}$/MAA in 1,2-propanediol and b.) MMA/ADMA/GMA in 1,4-dioxane.

The observed terpolymerisation kinetics of MMA/ADMA/GMA suggests that compositional drift will impact upon copolymer properties at a molecular level, with polymer chains rich in MMA and GMA produced in the initial stages of the polymerisation and ADMA incorporated in the later stages. Practically, this implies that industrial-scale batch copolymerisation may not be appropriate to ensure significant inclusion of ADMA in the copolymers. An alternative would be to use reactivity ratios to model appropriate feed ratios in a semi-batch polymerisation, in which the comonomer feed ratios and rate of monomer addition may be modelled to achieve optimised copolymer composition.[11, 12]

Conclusions

For the first time, to the best of our knowledge, we describe the copolymerisation kinetics for a series of MMA copolymerisations (MMA/PEGMEM and MMA/ADMA) and terpolymerisations (MMA/PEGMEM/MAA and MMA/ADMA/GMA). Moreover, reactivity ratios were estimated for the copolymerisation of the binary mixtures of MMA/PEGMEM and MMA/ADMA.

The reactivity ratios, estimated using a non-linear least squares method, for the MMA/PEGMEM system were r_{MMA} = 1.17 and r_{PEGMEM} = 0.62, indicating that MMA has a slight preference for homopropagation and PEGMEM a slight preference for cross-propagation resulting in a nearly random copolymer with only a low extent of compositional drift. In contrast, the copolymerisation of ADMA/MMA has reactivity ratios that indicate a strong tendency for MMA to be incorporated in preference to ADMA. This will be largely due to the inherently lower reactivity of methacrylamides in a copolymerisation with methacrylates.

These assertions are supported by further copolymerisation reactions which were followed by ^{1}H NMR and allowed to proceed to full conversion. As predicted by the reactivity ratios, MMA and PEGMEM were consumed at a very similar rate, suggesting limited compositional drift and little structural heterogeneity in the resulting copolymers. However, MMA and ADMA showed significant compositional drift with a strong preference for the incorporation of the MMA.

Finally, a series of functional terpolymers were synthesised with promising properties for application as surface active materials. The addition of MAA to the MMA/PEGMEM system appeared to result in an almost random terpolymer. The addition of GMA to the MMA/ADMA system showed that the GMA was consumed at almost the same rate as MMA and both were consumed in preference to ADMA, to result in a (nearly) random copolymer of MMA/GMA with a gradient incorporation of the ADMA. As a result of these studies we have significantly enhanced our understanding of the copolymerisation kinetics and comonomer distribution for the described systems.

Conflicts of interest

The authors declare no conflicts of interest.

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