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Double-stimulus sensitive (temperature and pH) self-assemblable polymers

TESI DI LAUREA SPERIMENTALE

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Acronysm

2-N,N-dimethylaminoethyl methacrylate (DMAEMA)

2-N,N-diethylaminoethyl methacrylate (DEAEMA)

2-N,N-diisopropylaminoethyl methacrylate (DIAEMA)

Poly(ethylene glycol) methyl ether (PEG_OH)

Poly(ethylene glycol) (PEG_bOH)

Pluronic f127 (PLUR_bOH)

Poly(ethylene glycol) methyl ether 2-bromoisobutyrate (PEG_Br)

Poly(ethylene glycol) bis(2-bromoisobutyrate) (PEG_bBr)

Pluronic f127 bis(2-bromoisobutyrate) (PLUR_bBr)

Poly(2-N,N-dimethylaminoethyl methacrylate) (PDMAEMA)

Poly(2-N,N-diethylaminoethyl methacrylate) (PDEAEMA)

Poly(2-N,N-diisopropylaminoethyl methacrylate) (PDIAEMA)

Critical micellar concentration (CMC)

Atom Transfer Radical Polymerization (ATRP)

2,2,6,6-tetramethyl-1-piperidynyl-N-oxy (TEMPO)

Nitroxide mediated polymerization (NMP)

Reversible Addition–Fragmentation chain Transfer (RAFT)

Degree of polymerization (DP)

Gel permaetion cromatography (GPC)

Nuclear magnetic resonance (NMR)

Monomer (M)

Growing radical ($P^{\cdot}$)

Average molecular weight ($\overline{M_n}$)

Molecular weight (MW)

Rate constant of polymerization (k_p)

Rate of polymerization (r_p)

Rate constant of termination (k_{ter})

Rate of termination (r_{ter})

Rate constant of activation (k_{act})

Rate constant of activation (k_{deact})

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1 Introduction

1.1 Controlled/living Radical Polymerization

Free radical polymerization is a versatile technique that can be applied to obtain omo- and copolymers with various monomers in relatively simple conditions; despite this, the low control over the reaction does not permit to obtain polymers with low polydispersity and with a well-defined structure [1].

During a free radical polymerization the growing radical chain adds monomer from the less substituted atoms of the monomer, resulting in a head-to-tail structure and region-selectivity of the reaction. Unfortunately stereo-selectivity could not be achieved in normal conditions. A typical kinetic rate constant of propagation in a free radical polymerization is around 10^3 l/(mol*s) and it is very low respect to the magnitude of coupling and termination's kinetic rate constant, that are around 10^8 l/(mol*s). This is the most important reason why the control over the reaction is not achieved during a free radical polymerization. The fact that the kinetic of propagation and termination reaction depends in a different way on the concentration of growing radical species could be used to control the reaction.

Currently over the 50% of polymers production is based on free radical polymerization process, such as those of ethylene, propylene, vinyl chloride, styrene and its copolymers (with acrylonitrile, butadiene, etc.), polyacrylates and so on, but at the moment it is not possible to obtain them on large scale with high control over the reaction [2].

During the last twenty years much efforts were made to develop polymerization mechanisms that could permit to obtain polymers with pre-determined chain length, structure and polydispersity and this has been achieved developing different 'living' radical polymerization mechanisms [3]. Living polymerization is defined as '' a chain-growth polymerization that propagates with no irreversible chain-transfer or chain-termination reactions''[3d], and anionic and cationic living polymerization were well known in the first years of the ninety's [1b]. It was just during those years that Matyjaszewski and co-authors said that ''free radicals, which are the growing species in radical polymerization, very easily react with another one via coupling and/or disproportionation. Thus, it is inherently impossible to imagine a living radical polymerization. However by careful adjustment of the reaction conditions it is possible to prepare well-defined polymers by a radical mechanism''[4]. Furthermore, the most important goal to reach is to obtain chemoselectivity during the progress of the reaction,

because it affects the dimension of the molecules and defines the end-group of the polymer chain [4]. In subsequent years, the studies made over this type of polymerization have led to different techniques that permit nowadays to synthesize polymers with well-defined structure mediating controlled radical polymerization (Figure 1-1) [5].

A well-defined structure is important because only if the polymers have uniform length, topology, composition and functionality it is possible to control their assembly in nanostructured materials [2]. And it was so important to find a controlled/living radical polymerization because not all the polymers could be synthesized using anionic or cationic living polymerization.

In a radical polymerization, to maximize the control over the reaction and obtain polymers with the desired structure and polydispersity, the reactions of termination by combination and disproportionation need to be reduced as much as possible but they cannot be completely eliminated, as it is for cationic and anionic living polymerization [1].

As shown from Matyjaszewski, "radical polymerizations can become controlled under conditions in which a low, stationary concentration of the active species is maintained and a fast, dynamic equilibrium is established between the active and dormant species''[4].

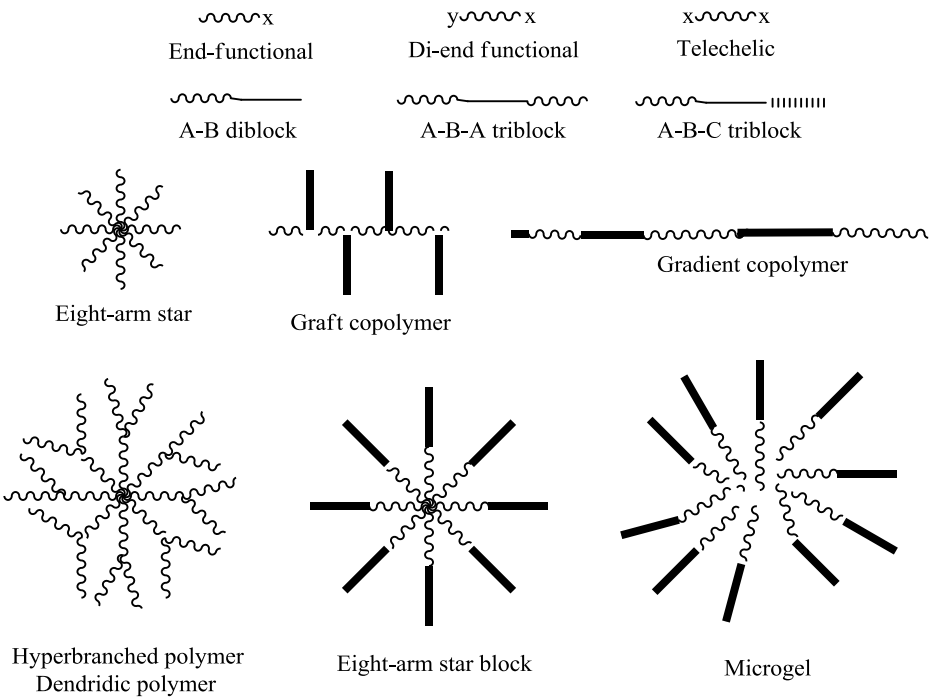


Figure 1-1: Polymer architectures

The dormant species mentioned by Matyjaszewski are not able to react with monomers but they are in equilibrium with the active species, in a system in which the propagating

radicals are formed intermittently. In a controlled radical polymerization, each time a dormant specie is converted into an active specie, this latter should react only with few units of monomer and then return in the inactive dormant specie. What is common to all the controlled radical polymerization is the fast equilibrium between the dormant species and the growing radical, but how it is established is different in each type of controlled radical polymerization [2]. ATRP, TEMPO and RAFT are three types of 'living' radical of polymerizations that in the last years have received the greatest attention.

1.1.1 ATRP-Atom Transfer Radical Polymerization

ATRP has led to the development of several science materials during the last years, because it permits to obtain polymers with well-defined microstructure, functionality and composition, and some of the products obtained with ATRP have interesting potential commercial applications. Despite to this the production on a large scale is rather limited, mainly for three reasons:

- All the oxidants should be removed from the reactor in which the reaction occurs.
- The catalyst should be removed from the resulting polymers and this could be expensive [6].
- The transition metal catalysts used in this technique are toxic (i.e. Cu complex…) and the disposal of huge quantity of this toxic material could be dangerous for the environment [7].

ATRP is one of the controlled living radical polymerization in which the control over the concentration of the active species is based on the equilibrium between the growing radical and a transition metal complex.

In a typical ATRP reaction four components are needed: monomer, initiator, transition metal with two stable state of oxidation in the reaction conditions and ligand to complex the transition metal [8].

The first stage of the reaction is the oxidation of the metal complex from the initiator which at the end of this reaction is in form of radical; this is a reversible reaction and it is shown in scheme 1.

The rate of the reaction and the concentration of its product depend on the two constants k'_{act} and k'_{deact}.

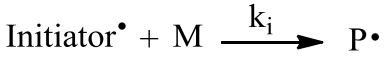
$$\text{Initiator-X} + M^{(n+)}(\text{ligand})_{x'} \underset{k'_{deact}}{\overset{k'_{act}}{\rightleftharpoons}} M^{(m+)}(X)(\text{ligand})_{y'} + \dot{R}$$

Scheme 1

In most of the systems used, the X is an halide such brome or chloro, and these types of atoms could be already present in the complex of the transition metal in its lower oxidation state, as Cu(Br)(bpy) [3b, 8-9].

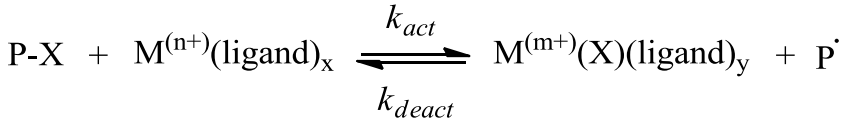
The stability of the complex between the transition metal and the ligands [3b], the temperature, the type of initiator, the stability of the two states of oxidation of the metal, the stability of the radical product, the solvent and so on, affect the entity of the two constant involved in the reaction.

The radical produced can react with the monomer present in solution and the reaction of polymerization can start.



Scheme 2

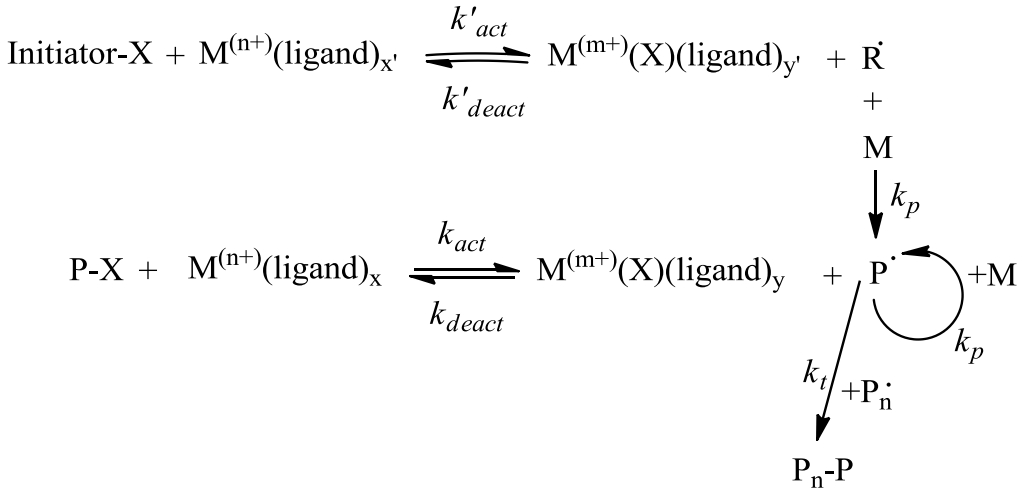
The polymer chain that is growing up is also involved in another redox reaction with the oxidized metal that convert the radical chain into a dormant species as shown in scheme 3 [4, 10].



Scheme 3

The ratio between k_{act} and k_{deact} could be also called k_{ATRP} and it is strictly correlated to other four constants: the constant of oxidation of the metal complex (k_{ox}), the constant of reduction of the halogen into halide ion (*kea*), the constant of homolysis of C-X bond in the alkyl halide (k_{bh}) and the constant of association of the halide ion to the metal complex (k_x). How these constants affect the value of k_{ATRP} will be shown later on [11].

Unfortunately these are not the only reactions that occur in the reaction mixture but, for kinetic reasons, some reactions of termination take place [12]. The overall process is shown in scheme 4 [3b, 12b].



Scheme 4: X(halide), M (metal), R· (radical), P· and Pn· (growing radicals), M(monomer), P-X (dormant specie), k_{act}, k_{deact}, k_p and k_t (rate constant of activation, deactivation, propagation and termination)

It has been demonstrated that the absence of one component among ligand, initiator and transition metal leads to a broader polydispersity and an ill-control over the molecular weight, showing that these three components are equally important for the control over the reaction as desired [8].

The transition metal acts as halogen (or pseudo-halogen) carrier whilst the ligand's task is to solubilize the inorganic salt in the reaction mixture but it also affects the value of the equilibrium constant involved in the process [8].

The goal to reach to obtain a good control over the polymerization reaction is to achieve a low concentration of growing radicals, a fast redox reaction compared to those of termination and disproportionation, and a rate of conversion in the dormant species comparable to that of polymerization. In this way the growth of the polymeric chain is uniform and no more than a few percent of the polymer chains undergo termination.

Practically, less is the concentration of radical species in the reaction mixture, less is the rate of the reaction of termination and disproportionation [8, 13]. Unfortunately, the context is more complicated; in fact, the k_t has the same magnitude order of the diffusion controlled limit and it is higher than the propagation rate constant (k_t = $10^7 \div 10^9$ l/(mol*s) and *kp* $10^2 \div 10^4$ l/(mol*s)). Furthermore the value of k'_{act} is in the range of $10^{-4} \div 10^{-6}$ s^{-1}, the average value of decomposition of a classic radical initiator, and these are the reasons why it is impossible to prevent some reactions of termination [3b, 12a] .

Once the conditions that lead to an overall control over the reaction are reached, several demonstrations can confirm the success of the procedure.

The average molecular weight should follow the following equation:

$$\overline{M_n}, th = \frac{[M]_0}{1-[Iniz]_0} * MW_0 * conv \quad (1)$$

Mn,th= Average theoric molecular weight - [M]0=Concentration of monomer at the beginning - [Init]0=Concentration of initiator at the beginning - (MW)0=Molecular weight of the monomer - conv=conversion

And the result is a polymer with polydispersity lower than 1,5-1,4 [8].

For a well-controlled reaction I mean a reaction which leads to polymer with the desired structure, molecular weight and low polydisperisty.

Plotting ln of $[M]_0/[M]$ as function of time, if the reaction is well controlled, a linear plot should be the result, leading to the statement that the concentration of growing radical is constant during the reaction[9, 12b]. The slope of the line is the k_{app} of the reaction. In fact, the reaction of polymerization is of the first order for both the concentration of radical species and the concentration of monomer, but in ATRP conditions, the concentration of radical species could be considered constant and included in the k_{app} value [12b].

$$r_p = k_p * [P\cdot] * [M] = k_{app} * [M] \quad (2)$$

If it is seen a deviation from the linearity it means that some reactions have reduced the concentration of radical species and the polymerization is not controlled as desired.

If the conditions of the reaction are such as to allow a fast pre-equilibrium and therefore a low polydispersity, the kinetic laws are the following [14].

$$K_{eq} = \frac{k_{act}}{k_{deact}} = \frac{[P\cdot][M^{(m+)}(X)(L)_y]}{[M^{(n+)}(L)_x][PX]} \quad (3)$$

$$r_p = k_{app}[M] = k_p[P\cdot][M] = k_p k_{eq}[Iniz]\frac{[M^{(n+)}(L)_x][PX][M]}{[M^{(m+)}(X)(L)_y]} \quad (4)$$

In these kinetic laws the termination by radical coupling is not considered, but it is a phenomena that happens at the beginning of the polymerization and permits the establishment of the so called ‘’persistent radical effect’’. At time ‘’0’’ the concentration of oxidized metal end radicals is zero. During the initial stages of the polymerization the concentration of radical is such that the rate of the coupling reaction (scheme 5) is faster than the reaction that carries the radical to the dormant species, because they are subject to two different kinetics. The fact that the coupling reaction is irreversible, implies that the more coupling reactions occur the more the concentration of $[M^{(m+)}(X)(L)y]$ increases. As a consequence of the fact that the product $[M^{(m+)}(X)(L)y]*[R\cdot]$ must be constant, the concentration of radicals decreases. By lowering the concentration of

radicals, the rate of coupling reaction becomes gradually slower and for low concentration of radical species the rate of termination reaction is smaller than the rate of the propagation. This is possible for their different dependence from the concentration of radical (equations 4 and 5) [3b]. This system reaches an equilibrium in which the concentration of oxidized metal is sufficient to render the rate of coupling reaction slow enough for a controlled polymerization to occur [12b].

$$2R^{\cdot} \xrightarrow{k_{ter}} R\text{-}R$$

Scheme 5

$$r_{ter} = k_{ter} * [R]^2 \quad (5)$$

If termination reactions are negligible respect to the propagation reactions during the polymerization, and the rate of the reaction that carries the growing radical to the dormant species is fast, the degree of polymerization could be predetermined, because it is directly related to the consumed monomer and the initial concentration of initiator:

$$DP_n = \frac{\Delta[M]}{[Iniz]_0} \quad (6)$$

Another proof that the conditions in which the reaction has occurred has led to a controlled reaction should be provided by ^{1}H-NMR analysis. In fact, the result of such analysis should show the presence of the halide(or pseudo halide) on each end of the macromolecules; this indicates that no reaction of termination (or just a negligible amount) has occurred [9].

1.1.1.1 Reaction conditions

Matyjaszewski has been one of the first to study the ATRP method, and he has found that a system consisting of 1-phenylethyl chloride as initiator, CuCl complexed by 2,2'-bipyridine as catalyst and monomers is able to perform polymerization in which the resulting polymer has a narrow polydispersity (Mw/Mn< 1,5) and a predetermined molecular weight [8]. The combination of initiator, transition metal and ligand proposed in that article is not the only combination possible; a lot of parameters can be changed to tune the reaction with the aim to obtain the goal researched [12b, 13]. The tuning of the reaction should be done because each monomer has its own rate of polymerization, each couple metal/monomer has a different transition state and different value of equilibrium constant and each metal-ligand complex has different solubility in reaction mixture; all these parameters, together with the concentration of every single species, affect the

concentration of growing radicals in solution [3b, 9]. Furthermore, side reactions must be taken into account before and during the study of a new reaction mixture.

Once it has been chosen what species use as initiator, catalyst combined with the leaving group, ligand and monomer, the molar ratio has to be chosen. The correlation between the constant of the reaction and the initial concentration of the species is described by the following equation:

$$k_{app} = \left\{\frac{d[M]}{dt}\right\} \Big/ _{[M]} = k * [Iniz]_0^x * [MetX]_0^y * [ligand]_0^z \quad (7)$$

$$\ln k_{app} = \ln k + x * \ln[Iniz]_0 + y * \ln[MetX]_0 + z * \ln[ligand]_0 \quad (8)$$

The value of x, y and z show how the initial concentration of each component affects the k_{app} and therefore the rate of the reaction. To determine how each initial concentration affects the rate of the reaction, ln(k_{app}) versus the natural logarithm of the concentration of the species under investigation should be plotted. The slope of the resulting plot represents the value of x, y or z depending on the type of plot. The initial concentration of the initiator is linearly related to the value of k_{app} because it affects the concentration of growing radical and its value for x is equal to one. On the other hand, as the transition metal acts as a catalyst, only low concentration of the metal in solution is needed to control the reaction[3b]. It is also true that the polydispersity, in ATRP, is related to the concentration of the oxidized metal with the following equation [15]:

$$PDI = \frac{\overline{M_w}}{\overline{M_n}} = 1 + \frac{1}{DP_n} + \left(\frac{[Iniz]_0 * k_p}{k_{deact}\left[M^{(m+)}(X)(L)_y\right]}\right) * \left(\frac{2}{conv} - 1\right) \quad (9)$$

For the fact that the concentration of the oxidized metal is dependent on the concentration of the reduced metal (equation 3), the concentration of the latter should be enough to obtain a low polydispersity, even if it has no effect on the rate of polymerization because it is related to the ratio of the reduced and oxidized species (equation 4).

1.1.1.1.1 Transition metal

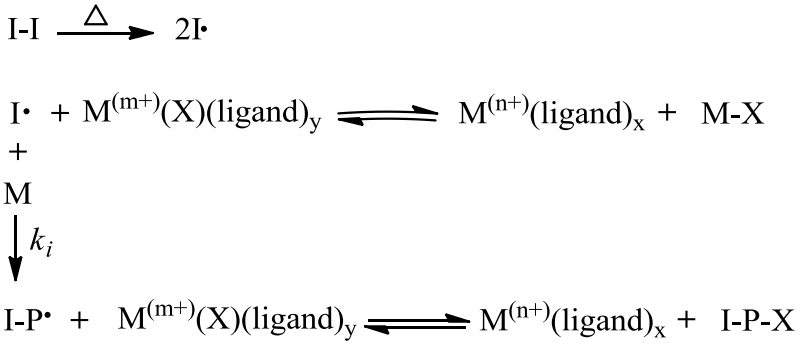
The transition metal should be able to expand its coordination sphere and simultaneously to be oxidized during the progress of the reaction[13].

The metal in the lower oxidation state has the exclusive role to remove the halogen atoms from the inactive chains, in fact it does not react with the radical species present in solution. The metal in the higher state of oxidation is the species that control the

concentration of radicals in solution, and consequently its presence is necessary to control the polymerization.[12b]

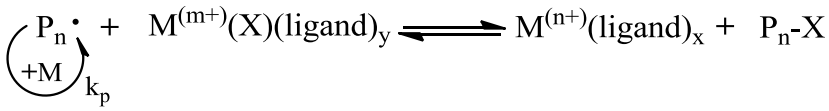
To determine the importance of the oxidized metal an experiment has been made in which the transition metal in the lower oxidation state was replaced with a conventional radical initiator and the same transition metal but in its higher oxidation state. The result has been that the reaction was controlled, demonstrating that the oxidized metal has a more important role respect to the metal in its lower oxidation state . The pathway of the reaction results so modified[9]:

Initiation:



Scheme 6

Propagation:



Scheme 7

In this case, the control over the reaction, as the initiator's efficiency, is enhanced with the concentration of transition metal in the higher oxidation state, proving its central role in ATRP [9].

For its important role in this type of polymerization, to get more control over the reaction, it is possible to add a small amount (1%) of oxidized metal, or leave traces of oxygen in the initial reaction mixture [3b].

Even if copper is the most efficient catalyst in ATRP of a broad range of monomers in different media, a variety of transition metals, as Ti, Mo, Re, Fe, Ru, Os, Co, Ni, Pd and Rh could successfully be used as catalysts [3b, 16].

1.1.1.1.2 Monomer

The monomer used should have one double bond that permit to react with the radical, maintaining the radical specie still able to react with other monomers, and with

substituent able to stabilize the radical after its formation. Also the monomer should not be able, with its functional group, to coordinate the metal catalyst.[9, 12b]

One of the system that has been studied and that can lead to a controlled/living radical polymerization is the one composed by R-X/CuX/bipyridine for the polymerization of styrene or methacrylate. This reaction mixture, tuned with the correct ratio of reagents, catalyst, initiator and ligand, can carry out to polymers with M_w/M_n from 1,50 to 1,10 and $\overline{M_n}$ of the order of 10^5 [3b].

Each monomer has its constant of homolysis of C-X bond (k_{bh}), and as said, this influences the value of k_{ATRP}. As each k_{bh} could be significantly different from monomer to monomer, it might happen that, in the same reaction conditions, different monomers have different values of k_{ATRP}, leading to completely different reaction time to reach the same conversion [17]. So, for each specific monomer the best conditions to reach in reasonable times the conversion desired should be found.

1.1.1.1.3 Solvent

The reaction could be carried out without or with solvent; in the latter case a various combination of solvent could be used and a different initial concentration of the system could be obtained. As the rate of the reactions depends on the concentration, adding solvent means slow down the reaction but it could be useful to solubilize the initial compounds. The choice of what type of solvent and in which quantities should be determined in function of the system under investigation[8].

In all the cases, the reaction of polymerization must be of the first order respect to the monomer and the concentration of radical species should be considered constant; otherwise the reaction is not well controlled[12b].

The solvent has a strong effect on the value of two constants: the constant of reduction of the halogen into halide ion (k_{ea}), and the constant of association of the halide ion to the metal complex (k_x). As said, these two constants affect the value k_{atrp} which becomes itself solvent dependent [18].

As halide ions are stabilized trough solvation, the value of k_{ea} increases in polar solvents [19]. For the same reason k_x decreases with the polar property of the solvent, because of the stabilization of halide ion in the solution [20]. These two considerations are in agreement with the results of experiments in which, using protic solvents, the control over the reaction was lost. This happens because the halide is slightly coordinated with

the deinitiator and the overall process of deactivation does not happen with the frequency needed to control the reaction [21].

1.1.1.1.4 Ligand

Also the relative concentration among initiator, catalyst, ligand and monomer is important.

Ligands are used to solubilize the transition metal salt in the reaction mixture but also they influence the value of the constants involved in the equilibrium between the dormant and the active specie. The exact ratio depends on the reaction conditions and on the solubilizing ability of the ligand, and it could be found doing different measures of the k_{app} maintaining constant all the parameters of the reaction except the concentration of ligand. Plotting the value of k_{app} versus the concentration of ligand it could be noted that the constant rise since it reaches a constant value corresponding to the optimum concentration of ligand in the experimental condition [12b].

The ligand to metal stoichiometry affects also the structure of the complex in solution. The equilibrium established in solution are dynamic and several metal species could be involved in rapid equilibrium in which a specie could have a concentration that is significantly higher than the concentration of the other species. For example, using CuBr and bi-pyridine in 1:2 molar ratio, the major species present in solution is the monomeric complex [L_2CuBr] (Figure 1-2). However, if a 1:1 molar ratio is used, the major species in solution is not L_2CuBr but either bridged dimers [LCu($\acute{\imath}$-X)$_2$CuL], or 2:1 ligand-to-copper cations with a dihalocuprate counteranion, $[L_2Cu]^+[CuX_2]^-$[22].

The relative stability of the complexes formed between the metal, in both the oxidations states, and ligands, affects the potential of oxidation of the catalyst and the value of k_{ATRP}. As consequence of this, different ligands lead to different potential of oxidation and different k_{ATRP}. The more stable is the higher state of oxidation, the more the metal in its lower state of oxidation is a strong reducing agent thus catalytically active in ATRP. As already said, also the potential of reduction should lead to a fast reaction of oxidation of the growing chain, carrying it to the dormant species.

To minimize the risk of ligand substitution with all the other species present in the reaction mixture (monomers, polymers, solvents), to have both the state of oxidation of the metal strongly stabilized from the ligands could help [21, 23].

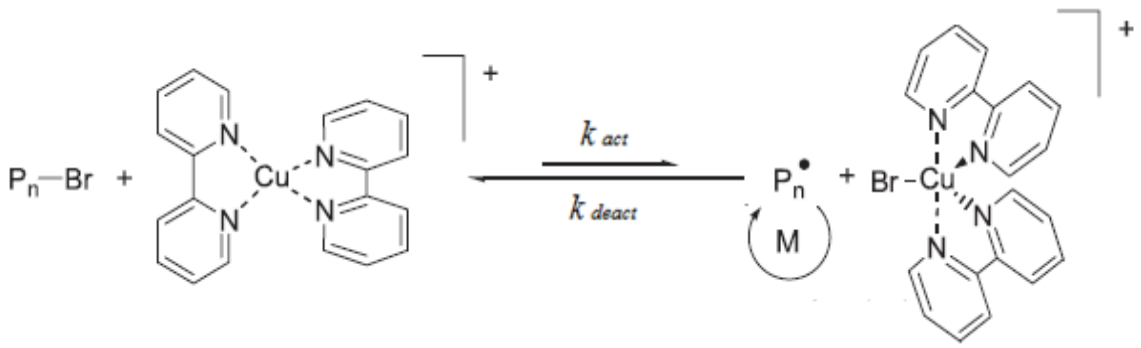


Figure 1-2

1.1.1.2 Initiator

As said, for the success of the reaction, it is very important to find the conditions that allow the optimum combination of equilibrium constants involved in the reaction pattern. As the equilibrium constant is affected by the stability of the species involved in the reaction, to obtain the proper number of radical species that start the reaction of addiction of monomer, the stability of the radical derived from the initiator must be evaluated. The initiators that lead to a proper number of radical species in the reaction mixture are the ones which stabilize the radical product, as initiator with inductive or resonance stabilizing. It has been demonstrated, in fact, that initiator like dichoromethane or buthyl chloride have poor efficiency at the initial step of the reaction, leading to polydispersity higher than 1,6 . The efficiency could be read as the capacity of the initiator to transfer the halide to the transition metal in the redox reaction; if the C-X bond is strong the formation of the radical is less favored and the efficiency of the initiator is low [3b].

1.1.1.3 Leaving Group

As the efficiency of the initiator is related to the bond strength, it is clear that also the leaving group of the initiator plays an important role in determining the efficiency of the process. In their article, Jin-Shan Wang and Krzysztof Matyjaszewski, have shown as the same reaction, made with two initiators that differ only for the leaving group, cause different control over the reaction. This behavior is due to the lower C-Br bond strength respect to C-Cl and lead to a faster reaction and a lower polydispersity [3b].

The halide ions are the most used leaving group, but also pseudohalides, carboxylates and non-coordinating triflate and hexafluorophosphate anions could be used [24].

1.1.1.4 Additives

Additives can be added to or be already present in the reaction mixture; it is important to know if and how they affect the polymerization process.

Matyjaszewski has shown as polar and non-polar additives have a little effect on the polymerization of styrene using 1-phenylethyl bromide [1-PEBr] as initiator in a [styrene : 1-PEBr]100:1 mole ratio, 1 equiv of CuBr relative to initiator as catalyst , and 2 equivs of 4,4-di-(5-nonyl)-2,2-bipyridine [dNbipy] per copper as ligand at 110°C. On the other hand, additives with strongly coordinating property, like PPh_3 and pyridine, decrease the control over the reaction and as a consequence the rate of polymerization is much lower and the polydispersity higher. This happens because these compounds could saturate the coordination sphere of the catalyst or form complexes with the metal that are not sufficiently active for atom transfer [12b].

1.1.1.5 The better conditions for ATRP polymerization

The k_{ATRP} is influenced by different component present in the ATRP system, and it is not possible to determine what are the best catalyst, the best solvent, the best ligand and so on for all the ATRP polymerization, because each parameter has a different influence on k_{ATRP}. To find the optimal conditions of reaction, and the best species to use to obtain the maximum control over the reaction, a screening should be done, changing one parameter in each experiment. At the end of this screening, we should be able to say what are the best conditions to polymerize one specific monomer [2].

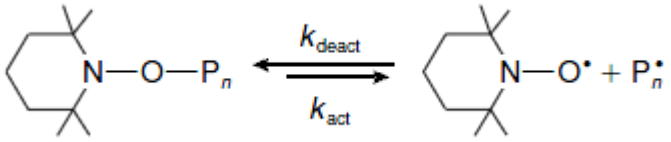
1.1.2 NMP – Nitroxide mediated polymerization

TEMPO reaction is one type of controlled radical polymerization that, if done in the proper way, could permit to obtain homo and copolymers with low polydispersity and defined structures [25].

2,2,6,6-tetramethyl-1-piperidynyl-N-oxy (TEMPO) is the most used agent for this type of reaction but other nitroxide could be used for nitroxide mediated radical polymerization (NMP) [2].

The first example of controlled polymerization using TEMPO in which the resulting polymer had high molecular weight has been reported by Georges and co-authors in 1993 [25a]. The principle on which the TEMPO reactions are based is the same of ATRP reactions: they have very low concentration of radical growing species in solution in order to lower as much as possible bimolecular reaction between two growing radicals (termination). The two systems are different on how this low concentration is achieved.

In a TEMPO reaction an equilibrium between a dormant and a growing specie is still present and this is established through a reaction between the growing radicals and a stable nitroxyl radical as shown in scheme 8 [3e, 25a].

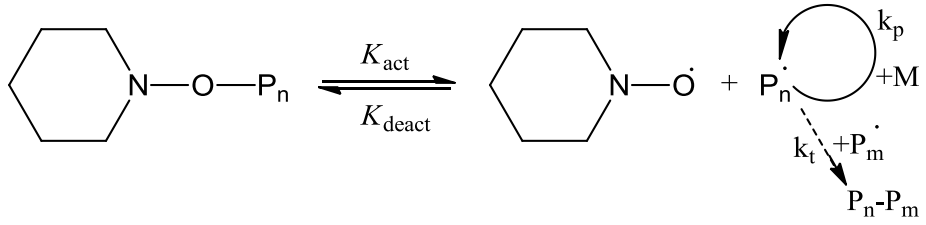


Scheme 8

Compared to ATRP, in TEMPO reactions the formation of the first radical in solution is not formed from the reaction between the initiator and the catalyst (scheme 1) but another way is followed. Polymerization of styrene was one of the first TEMPO reaction studied and, in that case, the formation of the first radical in solution was due to the spontaneous thermal initiation of styrene at ca. 120°C [26]. Instead of spontaneous thermal initiation, to generate the radicals in solution a radical initiator and its redox reaction with the monomer could be employed to form the radicals. Using this latter technique other monomers like methyl methacrylate, methyl acrylate vinyl acetate and so on can be synthesized with TEMPO scavenger [3e, 25d].

Once the radicals have been formed they can react with the nitroxyl radicals, form the alkoxyamines in situ, and establish the equilibrium that permits to maintain a low concentration of growing species in solution and start the controlled radical polymerization [3e, 27]. The dormant species is not directly involved in the polymerization

reactions whilst the radical derived from the dormant specie can undergo two reactions: the polymerization, or the recombination with the nitroxyl radical to form again the dormant specie (scheme 9).



Scheme 9

$$K = \frac{[P_{\dot{n}}]*[ONR_{\dot{2}}]}{[P_n ONR_2]} \quad (10)$$

As it is for ATRP the rate of the two reactions involved in the formation of the dormant species (k_{deact} and k_{act}), the concentration of the species and the value of the equilibrium constant affect the control over the reaction and the rate of polymerization. This happens because the concentration of the growing radicals is very important for the control over the reaction and it depends on all the parameters listed. The position of the equilibrium depends on the nature of the species involved, on the temperature and on the solvent [3e].

The nitroxyl radical acts as a scavenger and its concentration remains constant during the polymerization; the fact that its concentration is present in the formula of the equilibrium involves that the rate of polymerization decreases with an increase of initial scavenger concentration. So, too high concentration of scavenger leads to slow reaction but too low concentration of scavenger does not permit to control the reaction and the polydispersity. For this reason the nitroxyl radicals to initiator molar ratio is to be confined between two values: the lower one represents the minimum ratio that leads to sufficient initiation to control the reaction and the higher one represents the concentration over which some transfer reactions occur.

A too high concentration of nitroxyl radicals is not desirable because in this case the equilibrium in scheme 9 is too shifted to the dormant specie and the concentration of growing radicals is so low that the rate constant of polymerization is so low to inhibit the polymerization.

The proof that the value of the equilibrium constant K is affected by the type of species involved in the reaction is that, using TEMPO-like scavengers, the rate of polymerization and the polydispersity change. In fact, the rate of the homolytic cleavage of the dormant specie and the relative reactivity of the scavengers towards the growing radical affect the

value of K and so the control over the reaction and the rate of polymerization [25c, 28]. Some example of nitroxides employed in nitroxides mediated radical polymerization are shown in Figure 1-3.

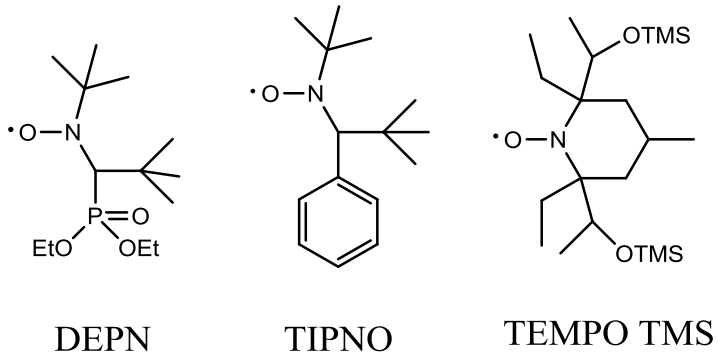


Figure 1-3[2]

Particular attention must be paid during the tuning of the structure of the nitroxyl radical used as scavenger because the C-O dissociation energy of the alkoxyamine and the intrinsic reactivity of the nitroxyl radical could be changed modifying the structure of the scavenger [28-29]. If the steric hindrance of the nitroxyl radical is increased the C-O dissociation energy of the alkoxyamine is lowered. A low dissociation energy leads to higher concentration of growing radicals in solution because this changing affects the K value shifting the position of the equilibrium to the dissociated form (nitroxyl and growing radicals). The higher is the concentration of growing species the lower temperature is needed to obtain a polymerization in reasonable time. On the other hand, if the C-O dissociation energy of the dormant specie is too low the polymerization reaction is not controlled anymore because the concentration of growing radical in solution is higher respect to the one that should be used to avoid termination reactions [30]. The other thing that should be watched is the intrinsic reactivity of the nitroxyl radical towards the monomer used because it might happen that undesired reactions, as the abstraction of H atoms, occur or too low reaction rate between the growing radical and the nitroxyl radical does not permit to control the polymerization [31].

Due to the fact that also the organic radical is directly involved in the equilibrium between dormant and growing species, its structure could affect the equilibrium constant and different organic radicals could lead to different side reactions. Each monomer has its own reactivity and it could be seen that the radicals of methyl methacrylate could be involved in transfer reactions that could not permit to the polymer to reach high molecular weight. If this transfer reactions do not occur the molecular weight should increase with conversion [3e, 25c].

So, before to change the structure of the nitroxyl radical all the possible consequences should be evaluated trying to obtain the best component for each specific monomer and reaction conditions.

1.1.2.1 Kinetic of NMP

A typical mixture for NMP consist of 3 main components: monomer, radical initiator and TEMPO or TEMPO-like radicals. The reaction could occur in bulk solution or with a certain amount of solvent. All the procedures should be carried out in a glass tube, degassed with several freeze-thaw cycles, and sealed off under vacuum [25c, 32].

In scheme 9 it is shown the main reaction but this is not the only one that occurs in the reaction mixture. The first reaction is the formation of the first radical ($R^{\cdot}$) from the radical initiator in solution (scheme 10).

$$I \xrightarrow{k_d} 2R^{\bullet}$$

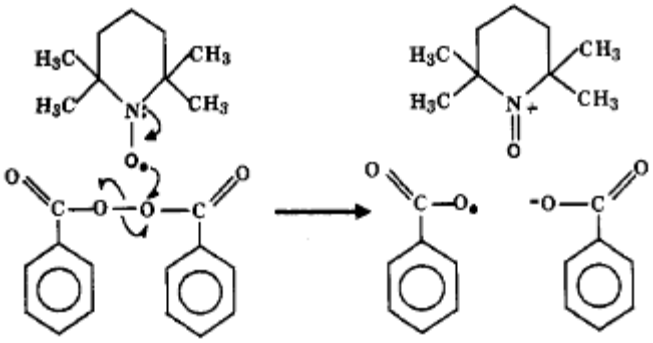
Scheme 10

The radical $R^{\cdot}$ reacts with the monomer forming the growing radical specie $Pn^{\cdot}$ (scheme 11).

$$M + R \xrightarrow{k_i} P_n^{\bullet}$$

Scheme 11

The radical $Pn^{\cdot}$ could be also formed by the thermal self-initiation of the monomer, like in the case of styrene polymerization[33]. Once the radical $Pn^{\cdot}$ has been formed the equilibrium shown in scheme 9 can be established and the polymerization can start [27, 32]. Negligible amount of termination reactions occur even if the polymerization is well controlled. Some side reactions as the one shown in scheme 12 could occur, but these could be avoided using reactants and reaction conditions that do not lead to undesired reactions.



Scheme 12[27]

In a well-controlled TEMPO reaction the kinetic of polymerization is of the first order respect to the monomer concentration [M] and during the polymerization the concentration of growing species is constant; if it is so a linear ln[M]/[M_0] versus time plot is obtained, with the slope depending on the concentration of radical initiator [25c].

The slope of the mentioned semilogarithmic graph is the rate coefficient of polymerization that express how rapidly the concentration of monomer is lowered during the polymerization. If the reaction is not made in a continuous system but in a batch system and the only reaction that lowers the concentration of the monomer is the polymerization, the concentration of monomer evolved following the equation 11 [32].

$$\frac{d[M]}{dt} = k_p * [M] * [P_n^{\cdot}] \quad (11)$$

If there are not side reactions the molecular weight should be directly proportional to the conversion, and the slope of the straight line in the graph which correlate the average molecular weight and the conversion should be influenced from the temperature and specifically it should increase with the temperature of the polymerization. Also, during the entire process the polydispersity should stay below the value of 1.4-1.5 [25c, 32].

During the polymerization the concentration of growing radicals is affected from different reactions but at stationary conditions it should stay constant. The evolution of the growing radicals in solution could be expressed using the following equation 12[32], where r_i is the rate of initiation that could be promoted from the radical initiator or by thermal initiation or both simultaneously as for styrene.

$$\frac{d[P_n^{\cdot}]}{dt} = r_i - k_t * [P_n^{\cdot}]^2 + k_{act} * [P_n ONR_2] - k_{deact} * [P_n^{\cdot}] * [ONR_2^{\cdot}] \quad (12)$$

As it could be seen from equation 12 the concentration of growing radicals (equiation 13) is enhanced from the two reactions of activation, the one of the monomer and the one of the dormant specie whilst it is depleted from the reaction of termination and the reaction that forms the dormant specie.

The concentration of TEMPO in solution is only affected by two members of equation 12 and exactly from the reactions involved in the intermittent formation of the dormant specie [32].

$$\frac{d[ONR_2^{\cdot}]}{dt} = k_{act} * [P_n ONR_2] - k_{deact} * [P_n^{\cdot}] * [ONR_2^{\cdot}] \quad (13)$$

The concentration of nitroxyl radicals depends only on the equilibrium shown in scheme 9. To explain how the system evolves during the first time of the polymerization I will consider a system in which only monomer and Pn-ONR_2 are present, without free

nitroxyl radical. When the temperature is increased enough the adduct Pn-ONR_2 dissociate and form the two radicals $Pn^{\cdot}$ and $ONR_2^{\cdot}$. Only with a certain amount of radical initiator a stationary concentration of growing radical could be reached because: if no new radicals were introduced in the system, the termination reactions, that lead to Pn-Pm and that lower the concentration of growing radicals in solution, let the nitroxyl radicals to accumulate in the system, shifting the equilibrium in scheme 9 to the dormant specie and stopping the polymerization. Only when new radicals are introduced in the system, through the reaction in scheme 10-11 or with thermal self-initiation of the monomer, this one can react with the nitroxyl radicals preventing its accumulation and permitting to the system to reach a stationary state in which the concentration of nitroxyl and growing radicals are stable. These two latter concentrations can be derived from equations 12 and 13 [32].

$$[P_n^{\cdot}] = \left(\frac{r_i}{k_t}\right)^{1/2} \quad (12.1)$$

$$[ONR_2^{\cdot}] = K * \left(\frac{[P_n ONR_2]}{[P_n^{\cdot}]}\right)^{1/2} \quad (13.1)$$

The rate of polymerization is defined as:

$$r_p = k_p * [P_n^{\cdot}] * [M] \quad (14)$$

The stationary rate of polymerization is:

$$r_p{}^{stat} = \left(\frac{{k_p}^2 * R_i}{k_i}\right)^{1/2} * [M] \quad (14.1)$$

Due to the fact that coupling reactions between radicals are fast, the stationary state is reached at a relatively early stage of polymerization.

As TEMPO reactions are very similar to ATRP reactions and both these techniques are based on the same principle. The ‘’persistent radical effect’’ is present also in TEMPO reactions and permits to keep a stationary concentration of growing radicals and a negligible amount of termination reactions during the stationary state of polymerization [14].

1.1.3 RAFT- Reversible Addition–Fragmentation chain Transfer

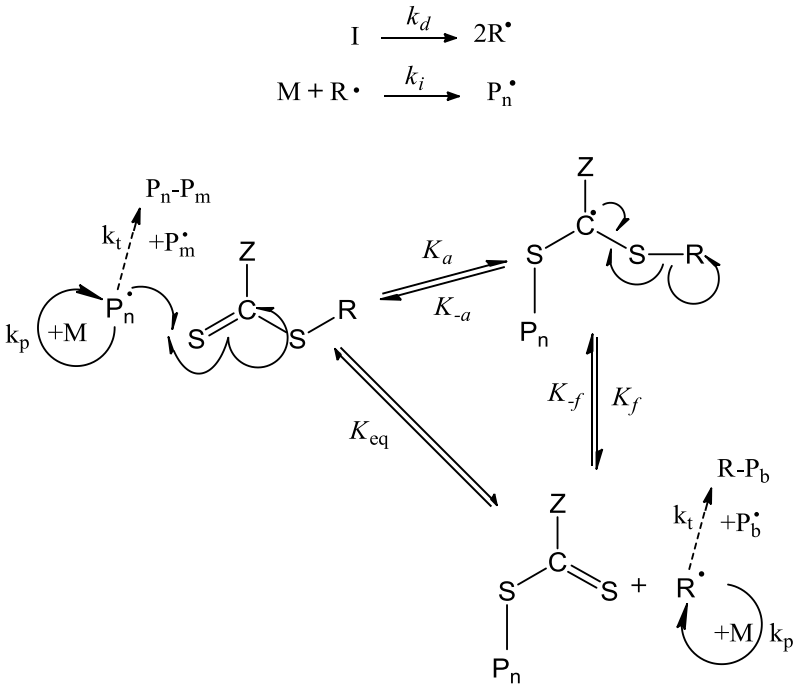
Reversible addition–fragmentation chain transfer (RAFT) is part of a set of reactions in which a degenerative transfer process is involved and allows to obtain polymers with controlled molecular weight and narrow polydispersities (usually < 1.2) [3a]. Respect to the other two systems seen until now, in a degenerative transfer process an equilibrium

between a dormant and a growing radical is still present but the reactions and the way in which the polymerization is controlled are completely different.

In ATRP and TEMPO reactions the rate of polymerization is determined by the value of the equilibrium constant of the activation and deactivation reaction and by the persistent radical effect. In RAFT reaction there is no persistent radical effect and the activation and de-activation reactions are chain-transfer reactions [34].

The three fundamental elements for a degenerative transfer process are: monomer, classic radical initiator and a transfer agent. The different types of degenerative transfer process are different according to the types of transfer agent used [35]. In a RAFT process various dithioesters, dithiocarbamates, trithiocarbonates and xanthates could be used as transfer agent [3a, 34].

The role of the radical initiator in the solution has the role to form radicals in solution that react with the monomers. Once the radicals derived from the monomers are present in solution these can react with the transfer agent and give rise to that equilibrium that characterizes the reversible addition–fragmentation chain transfer (scheme 13) [3a].



Scheme 13

If the starting monomer is capable to thermal self-initiation, such as styrene, no radical initiator is needed [34, 36]. The growing radicals, obtained by radical initiation, could both react with the monomer or with the RAFT agent that acts as a scavengers. Once it reacts with the scavengers it is carried in a dormant form and simultaneously a new radical (R•) is formed and it can react with the monomer continuing the polymerization. To avoid as

much as possible termination reactions, the reaction between growing radical and scavenger should be faster respect to coupling reaction, so it should be very high. Only if the exchange between dormant and active species is very high the polymerization has a living character, resulting in polymers with defined and pre-determined structure, molecular weight and polydispersity [3a]. As a consequence of its living character the resulting product still has the RAFT end groups at the ends of the chain [37].

The reactions conditions used during a RAFT process are the same as those used for a conventional free-radical polymerization, so it can be carried out in bulk, solution, emulsion or suspension, using well known radical initiators and a wide range of molecular weight can be obtained [3a].

1.1.3.1 Choice of the correct RAFT agent

Both Z and R groups are very important for the good control of the reaction and they should be chosen properly according to the type of monomer that should be polymerized [34, 38]. The Z group should activate the transfer agent toward radical addiction, stabilizing the formation of the intermediate radical, and its nature affects the addiction and fragmentation rates [34].

Unfortunately there is not a Z group suitable for all the monomers. For example, for RAFT reactions of methacrylate or styrene, alchyl or aryl group are suitable whilst dialkylamino or alkoxy groups have too low transfer constant; on the other hand the RAFT polymerization of vinyl esters is inhibited if the Z group is an aryl group whilst if it is a dialkylamino or alkoxy groups the polymerization occurs well [2-3].

In Figure 1-4 some possible Z groups arranged in descending order of rates of addiction are shown. There are also some guidelines for selection of the best Z group depending on the type of monomer.

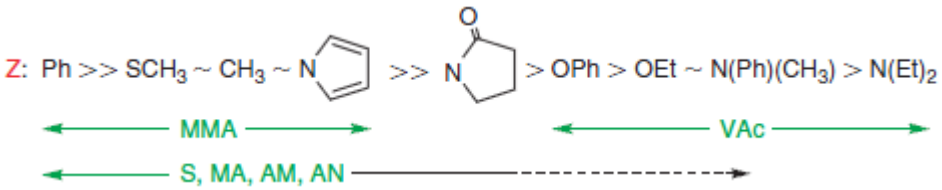


Figure 1-4 [34]

The fact that O-alkyl xanthates or N,N-dialkyl dithiocarbamate are less active as RAFT agents respect to the corresponding Z groups on which the oxygen or the nitrogen atoms are in alpha to an aromatic system or to an electron-withdrawing group, could be explained watching how the C=S double bond is involved in resonance equilibria. In O-

alkyl xanthates or N,N-dialkyl dithiocarbamate the lone pairs of electron interact with the C=S double bond forming the zwitterionic form of the RAFT agent (see Figure 1-5). The delocalization of the negative charge on the sulfur atom retards the radical addiction reaction. If instead of the alkyl groups there was a system capable to withdraw the lone pairs of electrons, this latter could always interact with the C=S double bond but weaker, because it is involved in more equilibria. Following these observations, the Z group could be changed in order to tune activity of the RAFT agent towards radical addiction [34, 39]. Also the R group should be chosen properly to achieve a good control over the reaction. To obtain a rapid and efficient fragmentation of the intermediate the radical derived from the R group ($R^{\cdot}$) should be a good leaving group and it should be more stable than the starting radical $Pn^{\cdot}$.

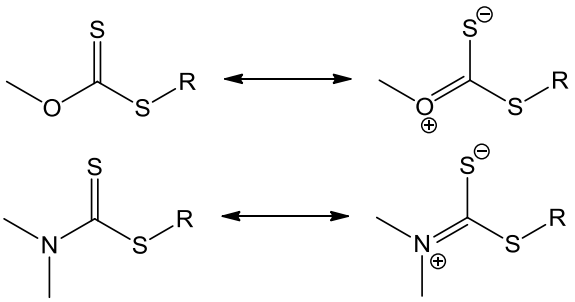


Figure 1-5 [34]

This happens because the intermediate radical should evolve rapidly towards the product and not go back to the starting molecule. For this reason the R group should be chosen in function of what kind of polymer needs to be synthesized and watching the stability of the growing radicals [34, 38].

To increase the rate of fragmentation of the intermediate radical two things can be done:

- Enhance the hindrance of the R group
- Use substituents on R that are capable to stabilize the radical once it has been formed [34]

The fact that $R^{\cdot}$ reacts with the monomer and establish the equilibrium with the dormant specie should also be taken into account. So, as R group a molecule capable to re-initiate the polymerization rapidly should be chosen [34, 38]. In Figure 1-6 some leaving groups (R), arranged in descending order of leaving ability are shown.

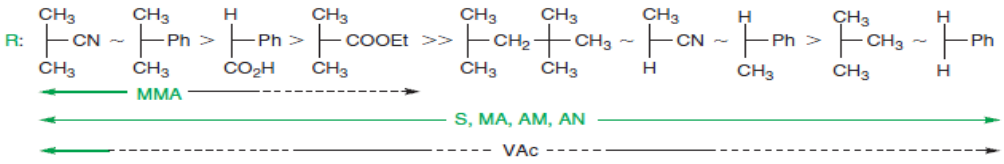
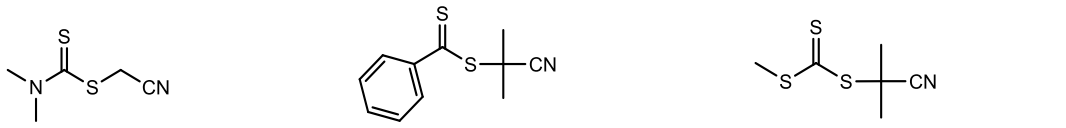


Figure 1-6[34]

Once established that Z and R groups have to be chosen in function of the monomer to be polymerized, some rules could be followed to obtain a good control over the reaction:

- The C=S bond is strongly reactive towards the growing radical, and this should be true for both the thiocarbonylthio compounds. When this is true the k_a is high.
- The intermediate radical should not give side-reactions. This means that it has to fragment rapidly, before all the possible side reactions, and this is possible only if the S-R bond is weak. Also this intermediate should partition in favor of the products, so k_f should be higher than k_a.
- The radical R· derived from the chain-transfer reaction should efficiently re-initiate the polymerization [34].

Although al lot of RAFT agents could be used, the most part of the RAFT polymerization could be carried out using three RAFT agent (Figure 7): N,N-dimethy dithiocarbamate for vinyl monomers and cyanoisopropyl dithiobenzoate or cyanoisopropyl methyl trithiocarbonate for almost all the other monomers [34, 39].



N,N-dimethyl dithiocarbamate cyanoisopropyl dithiobenzoate cyanoisopropyl mehtyl trithiocarbonate

Figure 1-7[39]

The non-correct choice of the monomer/RAFT agent couple could lead to undesired side reactions. These could be caused by the reactivity of the intermediate radical; in fact, if its life-time is not very low it could react with some other radicals present in solution as M·, I· or Pn·. These side-reactions lead to the three or four-armed stars in the resulting reaction mixture [40].

The life-time of the intermediate radical is related to its stability and the more the radical is stable the longer is its life-time. For example, to choose a phenyl as Z group should activate the C=S bond towards radical addiction but at the same time it could stabilize by delocalization the intermediate radical enhancing its life-time (figure 1-8) [39].

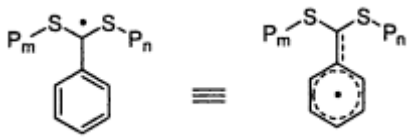


Figure 1-8[39]

To avoid side reactions the life-time of the intermediate radical should be the lowest possible and whenever this is not possible,all the possible reactions between the

intermediate and the other radical in solution should be taken into account and their rates should be evaluated.

1.1.3.2 Properties of the final product obtained with RAFT reaction

When the reaction conditions lead to a living character of the polymerization, the molecular weight and the number of living chains could be pre-determined knowing the concentration and the composition of the mixture. Equations 15 and 16 show how to calculate the theoretical molecular weight and the fraction of living chain respectively. $[M]_0 - [M]_t$ is the difference between the initial concentration of the monomer and the concentration of the monomer at t time, $[I]_0$ is the initial concentration of initiator and MMm is the molecular weight of the monomer. Equation 15 does not take into account the fraction of dead chains formed during the polymerization.

$$\overline{M_{n(calc)}} \approx \frac{([M]_0 - [M]_t) * MM_m}{[I]_0} \quad (15)$$

$$L = \frac{[I]_0}{[I]_0 + df * ([I]_0 - [I]_t)} \quad (16)$$

In equation 16 *d* is the number of chain produced from radical-radical termination $[I]_0$-$[I]_t$ is the concentration of initiator consumed and *f* is the initiator efficiency.

When the theoretical molecular weight is lower than the one of the resulting polymer it means that not all the RAFT agent has been used whilst if it is higher it means that in the reaction mixture there are other sources of polymer chains [34].

As in all the living radical polymerization the $\overline{Mn}$ should increase linearly and the polydispersity should decrease reaching a constant value with increasing of the conversion.

1.1.4 Advantages and disadvantages of ATRP, NMP and RAFT polymerization

All the controlled radical polymerization seen have one thing in common: the control over the reaction is achieved establishing an intermittent equilibrium between dormant and propagating radical, but each technique is different respect to the other.

The advantage of TEMPO reactions compared to ATRP reactions is that a purely organic system could be used whilst in ATRP an organic-metal compound should be used. On the other hand bi-substituted methacrylate are difficult to polymerize with TEMPO, high temperatures are often required and it is not easy to introduce end-functionality to the polymers.

ATRP has the advantage that is a versatile technique that permits to polymerize various type of monomers, it permits to use commercial initiators and it is possible to end-functionalize the polymers easily. The disadvantages are that the catalyst should be removed from the resulting product after the reaction and acidic monomers need to be protected to be polymerized with ATRP [2, 9].

Maybe, RAFT is the most versatile and convenient technique of the three seen. It can be performed with various monomers and different conditions, the kinetic is very similar to that of radical polymerization and the only difference respect to the normal radical polymerization is the addition of the RAFT agent.

Unfortunately the RAFT agents are not commercially available and are not always stable for long time.

Moreover the dithioester introduced in the system should be removed from the resulting product because they could be toxic or they could have a bad smell [2, 39].

1.2 Pluronic block copolymers

Pluronic is the commercial name of ABA triblock copolymers, where A is poly(ethylene glycol) (PEG) and is poly(propylene glycol) (PPG). Different Pluronic are commercial available and they differ for the total molecular weight and for the PPG/PEG molar ratio [41]. Table 1-1 provides name, molecular formulas and average molecular weight and other physiochemical characteristics of some commercially available Pluronics.

Table 1-1 [42]: Characteritics of some commercially available Pluronic polymers.

Copolymer	$\overline{M_n}$ (g/mol) [a]	Average no. of EG units [b]	Average no. of PG unit [b]	Cloud point in 1% aqueous solution (°C) [c]	CMC (M) [d]
L35	1900	12.59	16.38	73	$5.3 * 10^{-3}$
L43	1850	12.61	22.33	42	$2.2 * 10^{-3}$
L44	2200	20.00	22.76	65	$3.6 * 10^{-3}$
L61	2000	4.55	31.03	24	$1.1 * 10^{-4}$
L62	2500	11.36	34.48	32	$4.0 * 10^{-4}$
L64	2900	26.36	30.00	58	$4.8 * 10^{-4}$
F68	8400	152.73	28.97	>100	$4.8 * 10^{-4}$
L81	2750	6.25	42.67	20	$2.3 * 10^{-5}$
P84	4200	38.18	43.45	74	$7.1 * 10^{-5}$
P85	4600	52.27	39.66	85	$6.5 * 10^{-5}$
F87	7700	122.50	39.83	>100	$9.1 * 10^{-5}$
F88	11400	207.27	39.31	>100	$2.5 * 10^{-4}$
L92	3650	16.59	50.34	26	$8.8 * 10^{-5}$
F98	13000	236.36	44.83	>100	$7.7 * 10^{-5}$
L101	3800	8.64	58.97	15	$2.1 * 10^{-6}$
P103	4950	33.75	59.74	86	$6.1 * 10^{-6}$
P104	5900	53.64	61.03	81	$3.4 * 10^{-6}$
P105	6500	73.86	56.03	91	$6.2 * 10^{-6}$
F108	14600	265.45	50.34	>100	$2.2 * 10^{-5}$
L121	4400	10.00	68.28	14	$1.0 * 10^{-6}$
P123	5750	39.20	69.40	90	$4.4 * 10^{-6}$
F127	12600	200.45	65.17	>100	$2.8 * 10^{-6}$

[a] The average molecular weight provided by the manufacturer (BASF, Wyandotte, MI).
[b] The average numbers of EG and PG units in the polymer were calculated using the average molecular weights.
[c] Determined by the manufacturer.
[d] CMC (critical micellar concentration) values were determined using pyrene probe.

1.2.1 Behavior of Pluronic amphiphiles in water

1.2.1.1 Formation of micelles

The PPG blocks act as hydrophobic part in all Pluronic structures. The PPG methyl group reduces the interactions of that chain with water due both to its own hydrophobicity and to steric effects, and as a result PPG chains are fully segregated in water at any temperature > 15°C and room pressure. The different hydrophilicity of PEG and PPG makes Pluronic behaving as surfactants in water and allows them to form micelles, micro-emulsions and liquid-crystalline phases, whose properties can be modulated by changing the PEG to PPG ratio and the molecular weight of the copolymer [41, 43].

The basic parameters to characterize the amphiphilic behavior of a compound are its critical micellar concentration (CMC) and its critical micelle temperature (CMT). The CMC is the concentration at which, at a constant temperature, the micelles start to be formed in solution. The CMT is the temperature at which, at a given concentration, the micelles start to be formed in solution. Typically, CMT decreases with increasing concentration of the amphiphile, and CMC decreases with increasing temperature. CMC or CMT can be determined by a variety of techniques, e.g. DSC,surface tension measurements, chromatography, light scattering, small angle neutron scattering (SANS), small angle X-ray scattering (SAXS), differential scanning calorimetry, viscosimetry etc…. Different techniques, however, may provide different value of CMC for the same samples [42].

In Pluronics, both CMC and CMT decrease by increasing the average number of PG units in the PPG segments. Also the length of the PEG chain affects CMC and CMT, but its effect is less remarkable respect to the effect of hydrophobic chain and the hydrophobic PPG chain length is the primary factor that affects the micellization process. CMT and CMC also depend on the molecular weight of the copolymer and they decrease with increasing molecular weight [41].

At low temperature (<15°C) both PEG and PPG blocks are water-soluble and Pluronic macromolecules are present as unimers. Since the less hydrophilic PPG adopts a more compact conformation than the more soluble PEG chain, unimers can also be seen as unimolecular micelles. Increasing the temperature above the CMT, PPG becomes insoluble in water producing spherical micelles where a 4-5 nm PPG core is surrounded by a corona of hydrated PEG [41, 44].

The thermodynamics of the micellization process could be modeled using the mass-action model that considers micelles and unassociated unimers to be in an association-dissociation equilibrium. The free energy of micellization (ΔG) is defined as the standard free energy change for the transfer of one mole of amphiphilc from solution to the micellar phase; in the approach above, the free energy of micellization is expressed as:

$$\Delta G = RT \ln(X_{CMC}) \quad (17)$$

where R is the gas law constant, T is the absolute temperature, and X_{CMC} is the critical micellization concentration expressed as a mole fraction. The standard enthalpy of micellization could be derived from the following equation:

$$\frac{H}{R*T} = -T * \left[\frac{d(G/R*T)}{dT}\right]_{P,n} \quad (18)$$

Assuming that the aggregation number is not dependent on the temperature, the standard enthalpy of micellization could be defined as:

$$\Delta H = -R * T^2 * \left[\frac{d \ln(X_{CMC})}{dT}\right]_{P,n} = R * \left[\frac{d \ln(X_{CMC})}{d(1/T)}\right]_{P,n} \quad (19)$$

Equations 17 and 19 are derived assuming that the micelle aggregation number is sufficiently large.

Plotting CMT^{-1} versus the natural logarithm of the copolymer concentration (in mole fraction) a linear plot is obtained confirming the good fitting between experimental and theoretical values derived from eq.19 [41]. The entropy change associated to the micellization process could be derived from its dependence from ΔG and ΔH.

$$\Delta S = (\Delta H - \Delta G)/T \quad (20)$$

The micellization process is an endothermic process (ΔH>0) whilst the formation of the micelles is thermodynamically favored (ΔG<0); this means that, despite unimers having forced in a defined structure into the micelles, the micellization is a entropy favored process (ΔS<0). This apparently strange behavior is due to the fact that the solubilization of unimers in water causes a significant decrease in the entropy of the water, suggesting an increase in the degree of structuring of the water molecules. When unimers aggregate to form a micelle, the release of water bound around the PPG blocks increases the water entropy increases, overcoming the entropy loss due to the localization of the hydrophobic chains in the micelles [41].

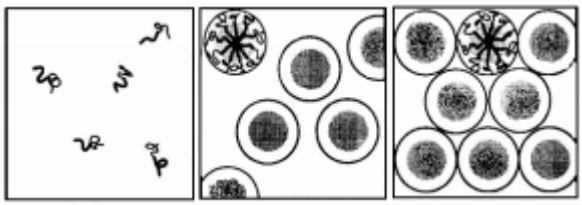


Figure 1-9. Illustration of the critical micelle concentration (CMC) and critical gel concentration (CGC) in a block copolymer solution [45].

The aggregation number, that is the number of unimers forming a micelle, and the micellar size are independent on polymer concentration, while temperature affects the Pluronic micellar size (increasing temperature the size increases), but also their assembly in 3D structure, which are generally referred to as micellar gels.

1.2.1.2 Formation of micellar gels

Figure 1-10 reports a contour plot showing a typical dependency of micellar volume fraction on polymer concentration and temperature; above a critical combination of the two parameters, the system reaches an arrested state, which often exhibits a long-range order, ie a crystalline or paracrystalline organization (Figure 1-11). It is noteworthy that upon temperature increase, a first order phase transition occurs leading to a crystal phase [44, 46], but there is no specific micellar volume fraction at which the system becomes completely crystalline, whereas there exists a transition interval in which liquid and crystalline domain coexist. The presence of transition regions is not unexpected: for Pluronics, as much for most polymer amphiphiles, also micellization is not a sharp process and both CMC and CMT should be better described as concentration and temperature "windows".

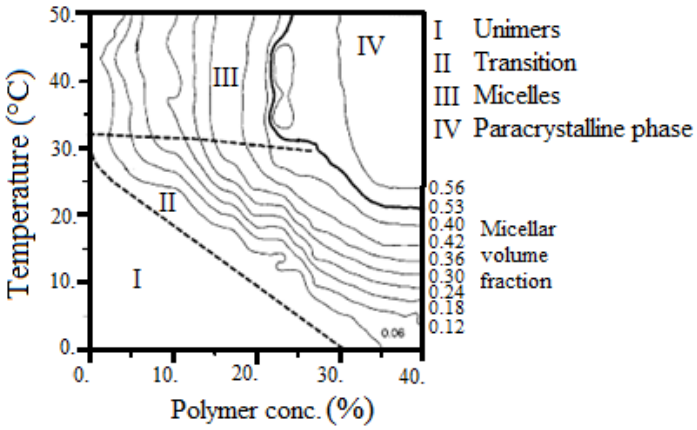


Figure 1-10[44]

Using Figure 1-10, the effect of Pluronic concentration is easy to explain (the more chains, the more volume occupied by the polymer), but the molecular interpretation of

the effect of temperature is more controversial and may involve several factors, e.g. degree of entanglement between loose PEG chains, possible release of bound water from PEG chains and/or increased solubility of free water (this is favored by entropy, as opposed to the presence of bound water) in PPG domains; the latter two effects may increase the volume of the micelles or increase their hardness. Related systems have been studied, showing that Pluronic F127 cross-linked micelles still exhibit a thermally induced gelation, therefore excluding any significant contribution of chain entanglements [47], and that Pluronic-based nanoparticles exhibit it although they have an overall volumetric contraction [48]. As a result of these evidences, more than other factors an increase of hardness of individual micelles may be seen as the likely main cause of macroscopic gelation.

It is noteworthy that in these micellar assemblies the gelation is reversible, because of the purely physical nature of the transition: the latter is based on a change in micellar dynamics. Compared to a chemical gelation the strength of the interactions involved is weaker but on the other hand the gel formation is totally and rapidly reversible.

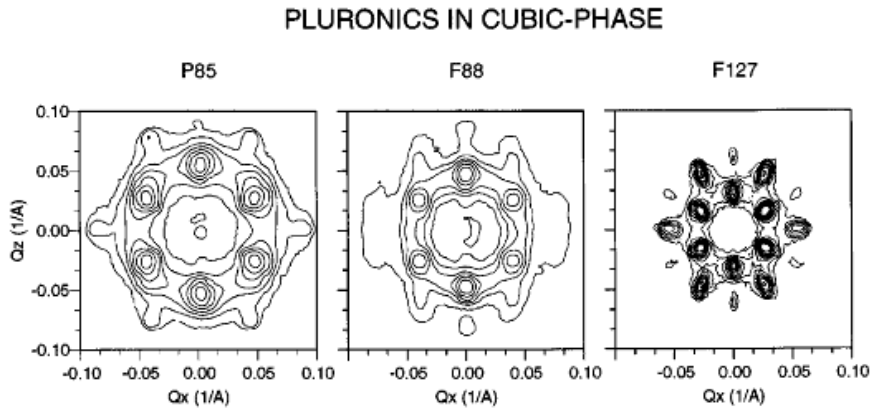


Figure 1-11 [46]

In the gels Pluronic micelles arrange in a cubic geometry (see Figure 1-11 for the two-dimensional scattering functions of P85, F88, and F127), which most often is supposed to correspond a body-centered cubic (BCC) lattice. These ordered phases are often associated to shear moduli in the order of 10^4-10^5 Pa [44].

It is noteworthy that the temperature in the gel phase can also affect the micellar shape (not only their size, as previously mentioned), with higher temperatures sometimes inducing a transition from spherical micelles via prolate ellipsoids to rod-like micelles. At high temperature, the micelles have a core diameter that is almost the size of a fully stretched PPG chain and the system evolves forming micelles with rod-like shape, decreasing intermicellar interaction [41, 44].

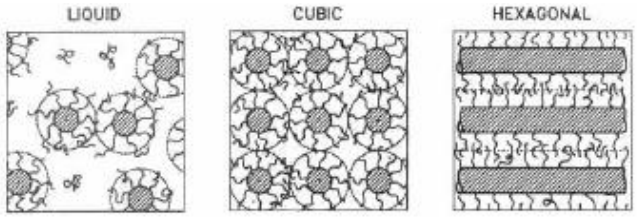


Figure 1-12. Schematic illustration of micellar phases formed by the Pluronics [45].

1.2.2 Applications of Pluronics

When a drug molecule is taken it has to overcome enormous barriers to reach the site into the body where it can perform its biological role, and during its travel through the body it can be absorbed in non-desired sites or it can partially react forming a non-active product. Another important problem that should be taken into account during the development of a new drug is its solubility and stability: it can happen that a good drug against a particular disease cannot be used because it is not stable or it is not soluble in our body. Using drug delivery technologies this problems can be overlapped and the current therapies can be improved. A growing number of therapeutic polymers are approved by the regulatory authorities in North America, Europe and Asia for clinical use in treatment of cancer, infectious and genetic diseases[42].

Most applications of Pluronic are derived from the ability of this A-B-A block copolymer to enhance the solubility of hydrophobic compounds in water solution combined with the fact that the formation of the gel phase is thermo-reversible [49]. The possibility to enhance the solubility in water of compounds that are water-insoluble is due to the ability of the hydrophobic PPG core of the micelles to solubilize hydrophobic compounds.

This particular behavior makes the micelles of Pluronic micro-containers for molecules which exhibit poor water solubility, undesired pharmacokinetics and low stability in a physiological environment [41-42]. Another important aspect that differs Pluronic-based drug delivery system is that they have the ability to enhance drug performance by acting as biological response-modifying agents, which act directly upon the target cells [42].

The preferred size range for many pharmaceutical applications using nanoscale particles is from 10 to 100 nm and Pluronic micelles are usually within this range. This range is determined by the fact that using particles with diameters larger than 200 nm they are sequestered by the spleen and particles with diameter of 5-10 nm are removed through extravasation and renal clearance. The result of this two different phenomena related to the size of micelles is the same and specifically the decreasing of the circulation time of the micelles in the blood.

Pluronic F-127 is one of the most studied copolymers to create drug delivery systems to administer drugs through different form of administration [50].

When a molecule is solubilized in the PPG core of a micelle, an equilibrium between its concentration in water solution and in the PPG core is established. The ratio between the drug concentration in the micelles and the drug concentration in the external water, once the equilibrium has been reached, is defined as partition coefficient (equation 21). It quantifies numerically the dynamic exchange between solubilized molecules into the micelle's core and those dissolved in water when the system has reached the equilibrium (figure 1-13).

$$P = \frac{[Dm]}{[Dw]} \quad (21)$$

$[Dm]$ = conc. of drug into the external water

$[Dw]$ = conc. of drug into the external water

Although the equilibrium is usually not reached in the body, the partitioning value allows a rough estimate of the drug that could be released into the body after the dilution in the body fluids [42]. If the molecule has a too low P value, once the drug solubilized in the micelles has been given to the patient, the drug is released from the micelles before the micelles have reached the desired site.

The solubility of a specific molecule in water solutions containing Pluronic could be tuned with the aim to obtain the researched solubility acting on the molecular weight of Pluronic [41].

To permit the solubilization of drugs into the PPG core of the micelles, the system have to be above the CMT. Pluronic-based system are suitable to be used as drug delivery system because they have a CMT near to body temperature.

On the other hand it should be taken into account that once the drug has been incorporated into the micelles the system should not be left in a temperature in which the micelles destroy. If it happens, the drug could not be soluble in the system constituted from solvent and unimers and the drug could precipitate and it is not sufficient to increase again the temperature to obtain the previous drug delivery system [42].

The drug incorporation in Pluronic micelles is most often accomplished by exposing a micellar dispersion of Pluronic in water to solid drug dispersion or to a small volume of a drug solution in a water-miscible or volatile organic solvent. As said, the drug is solubilized into the hydrophobic core of the micelles so, to determine if a drug could be hosted into the micelle's core, the compatibility between the drug and the core of the

micelles and the hydrophilicity of the specific drug should be evaluated. It could be seen that to obtain a good solubilization of the drug into the micellar dispersion of Pluronic in water there should be interactions between the core of the micelles and the drug and the solubilized-water surface tension should be low [42].

It should be taken into account that after administration and before the drug (contained into the micelles) reaches the desired site, the system could interact with other sites and can undergo changing of structure as consequence of the fact that pH and temperature can change during the trip to the desired site [42]. To enhance the efficiency of the recognition mechanism between the micelles and the site where the pharmacologic action should be carried out, proteins could be attached covalently to Pluronic molecules, using the free hydroxyl groups present in this latter. The drug delivery system could be built mixing unmodified Pluronic with functionalized Pluronic macromolecules, obtaining micelles that are able to interact selectively with specific sites or receptors in function of what type of protein is bonded to Pluronic [42, 51].

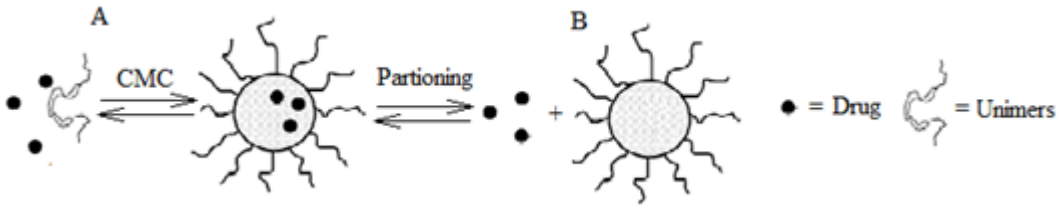


Figure 1-13 [42]: Mechanisms of drug release from micelle: (A) disintegration of the micelles below CMC; (B) release of the drug as a result of partitioning.

Pluronic can be used in form of gel or micelles to administrate drugs. In addition to facilitating the overcoming of the drug throw the barriers present into the body, as the ones posed by the gastrointestinal tract, Pluronic micelles can also enhance the activity of the drugs. For example, it has been shown that doxorubicin administrated with Pluronic micelles enhances its cytotoxic activity compared to doxorubicin alone, by two or three order of magnitude against tumors with multidrug-resistant phenotype. The administration of doxorubicin with Pluronic demonstrated that Pluronic micelles are able to sensitize the resistant cells, improving the treatment of drug-resistant cancers [52].

Pluronic micelles containing risperidone transport it across the intestinal membrane, achieving a bioavailability of 40%. Risperidone is a poorly soluble drug and to obtain good level of bioavailability was administrated by intravenous delivery. It has been demonstrated that oral delivery of risperidone in formulation with polymeric micelles exhibit similar delivery properties to intravenous delivery. Oral administration is preferred to intravenous administration because it is more convenient when repeated

administration is required. Pluronic drug formulations have the characteristic to replace intravenous administration for that poorly water soluble drugs that cannot overlap the barriers present into the human body [53].

Pluronic gels can be used for topical drug delivery systems in formulation with analgesic, anti-inflammatory drugs, anti-cancer agents and so on. The possibility to deliver the drug through the skin, exactly where it is needed, permits to use a lower amount of drug compared to other ways of administration (e.g. oral administration). Sometime, in formulations for topical application, penetration enhancers are necessary to permit the drug to pass through the skin. Administration through topical application has been study for indomethacin (anticancer agent), ketoprofen, fenantyl, sodium naproxen, insulin and so on. In topical application, diffusion of Pluronic controls the release rate of the drug, accelerating the process of solute diffusion within lipid bilayers [49, 54].

Pluronic gels can also be used for buccal, rectal, subcutaneous and intramuscular applications. The interesting thing in this systems is that gels act as reservoirs of drug. Drugs given in this way have the following advantages:

- they have a prolonged action and reduced side-affects;
- they can be designed to interact with specific target and release the drug only in a specific part of the body;
- they permit to obtain constant drug levels in the desired part for all the time the gel performs its action.

All these advantages allow to administrate the drug only once in a certain period of time [55].

Upon administration, the stability of the micelles affects the circulation time and the drug release rate. Two parameters that could help during the evaluation of the pharmacokinetic are the critical micelles concentration (CMC) (that for Pluronic is in the range of $5x10^{-3}$÷1 % wt) and the partition coefficient. In fact, the drug contained into the micelles can be released in the external media when the micelles are destroyed as consequence of dilution to a concentration lower than CMC or as result of portioning of the drug between the internal core of the micelle and the external media. The critical micelles concentration is a value related to the thermodynamic of the system but it does not consider the kinetic stability of the micelles: micelles formed with hydrophobic core that have glass transition temperature higher than 37-38°C exhibit long lasting relaxation process that results in slow dissociation kinetic when the system reaches a concentration lower than the CMC. This behavior is due to the fact that if the polymeric chains in the

core of the micelles are above the glass transition temperature, they are physically attached to each other and the drug diffuses slowly. The low drug release rate resulting from systems with micelle's core with glass transition temperature near to 37-38°C permits to obtain system with high blood circulation time and slow release of the drug in the body [42]. Studies made on Pluronic-based systems prove that the concentration of the block copolymers in the plasma could be sufficient to form micelles [56]. The possibility to change the composition and the structure of Pluronic-based drug delivery system just by changing the length of hydrophobic and hydrophilic part and their ratio in each macromolecular chain, permits to obtain different systems suitable for different type of drug and with different type of pharmacokinetic (figure 1-14). Once the drug and the site where the pharmacologic action should be carried out are known, the drug delivery system has to be chosen and to do that two important parameters should be taken into account:

- the incorporation of the drug into the carrier should lead to an increase in stability and circulation time of the drug into the body;
- the release of the drug into the critical site of action should be effective.

These two listed behavior lead to the maximal therapeutic index but obtain them is not so easy. Too high stability of the drug into the micelle's core leads to a great stability of the drug delivery system and to high circulation time but the bioavailability of the drug in the desired site could not be sufficient to obtain the pharmacologic action. Said this, a good ratio between the stability of the drug delivery system and the release of the drug into the desired site should be achieved. This compromise could be obtained changing the characteristic of the block-copolymer used to build the drug delivery system [42].

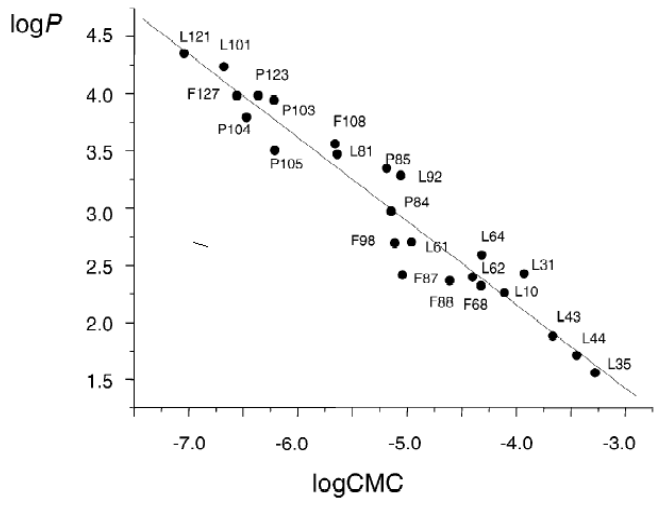


Figure 1-14[57]: Relationship between the partitioning coefficients of pyrene and CMC in different commercial Pluronic block copolymer systems.

2 THE PROJECT

This project aims to develop polymers that are capable to exhibit a double responsiveness to pH and temperature in a water environment.

More specifically, the main question this study is designed to address is whether extending Pluronic F127 with hydrophobic blocks with different macromolecular chains (methacrylics instead of polyethers) may lead to further aggregation of Pluronics micelles. This may happen due to the incompatibility (immiscibility) of methacrylic and polyether chains, which would cause the two kinds of macromolecules to associate in distinct hydrophobic domains. If this occurs, if the hydrophobicity of these chains is pH-dependent, and further considering that Pluronic aggregation is temperature-dependent, one would obtain a gel-forming system with double responsiveness.

On the other hand, if the two kinds of chains are miscible and the hydrophobic extensions can fold back into the hydrophobic core of a micelle, one would imagine that this may significantly affect the size and dynamics (and thus also temperature dependence) of the Pluronic micelles.

The two possible situations are depicted in Figure 2-1.

This study focuses on the use of Pluronic F127 as a temperature-sensitive unit and methacrylic tertiary amines with different alkyl residues as pH-sensitive ones.

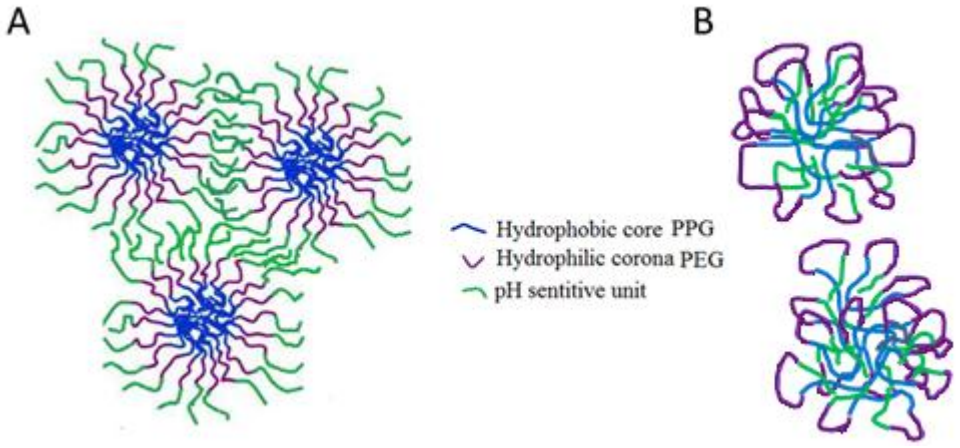


Figure 2-1 – Ideal representation of the two possible consequences of the extension of Pluronic chains with hydrophobic blocks. A. Incompatibility of the blocks leads to phase segregation and inter-micellar aggregation. B. Compatibility between the hydrophobic core of Pluronic (i.e. poly(propylene glycol)) and the methacrylic blocks lead to flower-like micelles.

In particular, we have used three different amine residues (2-N,N-dimethylaminoethyl, 2-N,N-diethylaminoethyl, 2-N,N-diisopropylaminoethyl) that are characterized by different basicity, which decreases with increasing steric hindrance on the nitrogen centre (Figure 2-2).

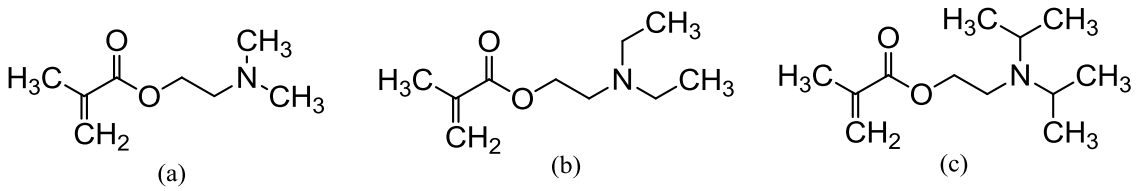


Figure 2-2: Structures of (a) 2-(N,N-dimethylamino)ethyl methacrylate (b) 2-(N,N-diethylamino)ethyl methacrylate and (c) 2-(N,N-diisopropylamino)ethyl methacrylate

The macromolecular architectures investigated in this study are three: A) Pluronic F127 as a central, bifunctional and amphiphilic block, which provides self-assembly in water, B) bifunctional PEG with length identical to that of the combined PEG blocks in Pluronic ($\overline{M_n}$=9,000 g/mol), which is a negative control for the behavior of the block copolymers, since it is incapable of hydrophobic aggregation, C) monofunctional PEG with half of that size ($\overline{M_n}$=5,000 g/mol), which provides a further negative control corresponding to a single PEG arm of Pluronic (figure 2-3).

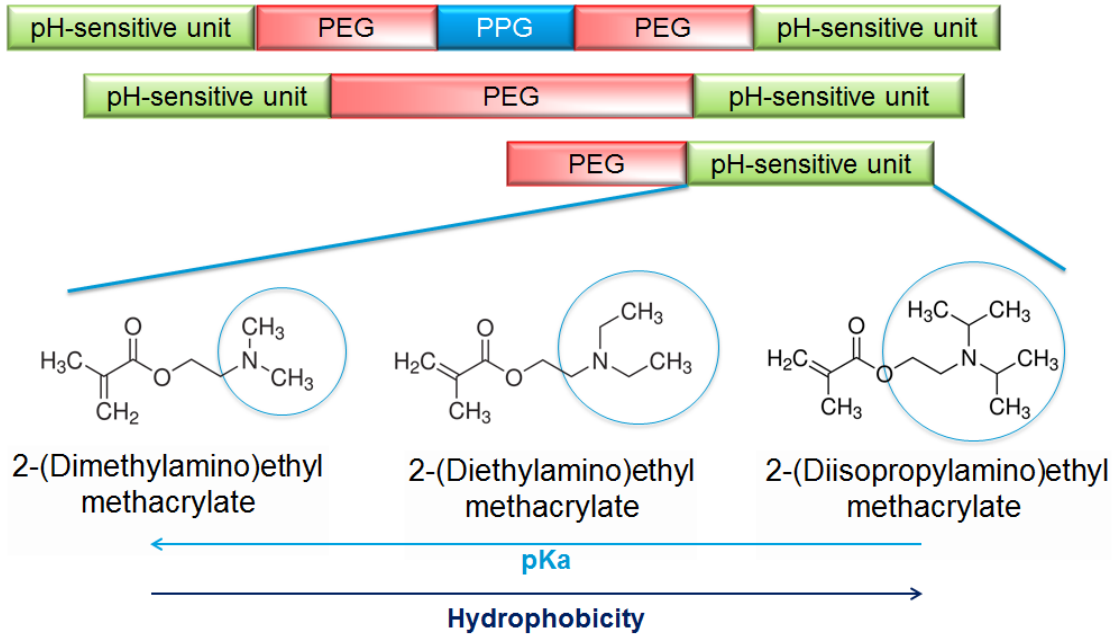


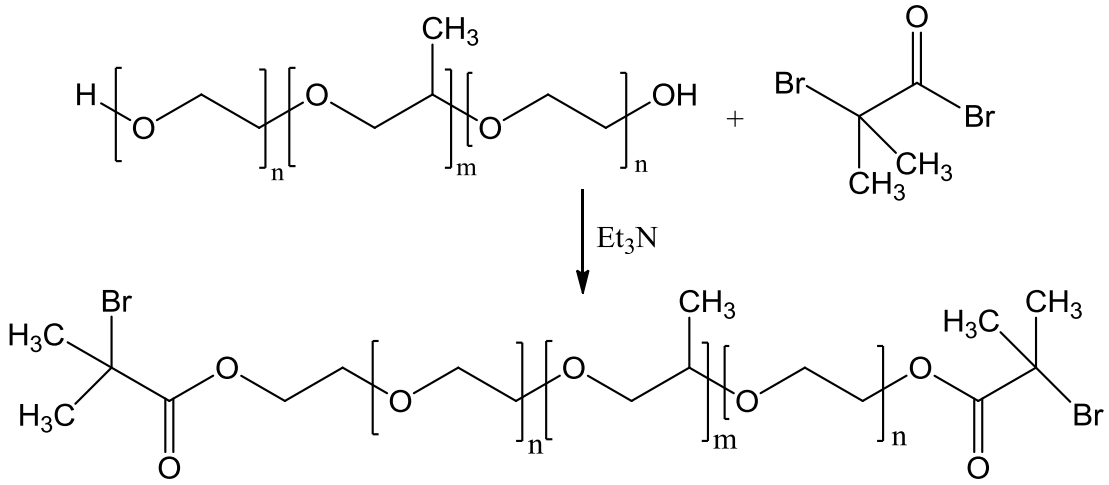
Figure 2-3: Schematic structures of the polymers obtained mediating ATRP using mono- and bi-functionalized initiators.

Pluronic and PEG chains were extended at their functional ends, using (2-bromoisobutyryl) derivatives as macroinitiators for ATRP of polymeric chains of methacrylic amines; this mechanism of controlled radical polymerization was chosen because of the need to minimize polydispersity and avoid transfer reactions possibly leading to homopolymeric inpurities.

In this way, a library of polymers can be prepared, where three variables can be independently controlled: macromolecular architecture (and hydrophobically driven self-

assembly), chain-length of amine methacrylate blocks and basicity of the amine groups in the side-chain.

We will use polymer chains with different basicity and degree of polymerization to link any possible effect of their presence to the conditions under which they become hydrophobic: the longer the chain and the less basic the amine, the more likely the polymer to be hydrophobic throughout an extend pH range and therefore to produce effects linked to hydrophobic aggregation. The latter can proceed either in an inter-micellar or in an intra-micellar direction only for Pluronic derivatives, whereas for PEG derivatives it is expected only to observe micelle formation (or solubilization) as a function of pH.



Scheme 14: Esterification of Pluronic F127 leading to its bis(2-bromoisobutyryl) derivative. The same reaction was performed on mono- and bifunctional PEG.

The project was articulated in two parts. In the first one, we have synthesized Pluronic and PEG macroinitiators and studied the ATRP polymerization for the three methacrylic amines, showing this to have a controlled character. In the second part, we focused on the rheological characterization of the produced materials.

3 Experimental section

3.1 Materials

Poly(ethylene glycol) monomethyl ether (PEG_OH), poly(ethylene glycol) diol (PEG_bOH) and Pluronic F127 (PLUR_bOH), with $\overline{M_n}$= 5,292 g/mol, 8,878 g/mol and 13,322 g/mol respectively (from MALDI measurements) were purchased from Aldrich and used as supplied. Triethylamine (99.5%), toluene (99.5%, d=0.865 g/mL), n-hexane (>95%), 2-bromoisobutyryl bromide (98%), dichloromethane (>99.8%), copper (I) chloride (>99%), 2,2′-bipyridyl (>99%) and ethylenediaminotetraacetic acid (EDTA) (>98.5%) were all purchased from Aldrich and were used as supplied. 2-(N,N-dimethylamino)ethyl methacrylate (98%, d=0.933 g/mL), 2-(N,N-diethylamino)ethyl methacrylate (99%, d=0.922 g/mL) and 2-(N,N-diisopropylamino)ethyl methacrylate (97%, d=0.900 g/mL) were all purchased from Aldrich and passed through a column filled with neutral alumina, just before use.

Table 3-1: MW, ($\overline{Mn}$ for polymers), formula and purity of reactants used during the project.

Reactant	MW($\overline{Mn}$) [a] (g/mol)	Formula	Assay (%)
Poly(ethylene glycol) monomethyl ether	5000	$CH_3(OCH_2CH_2)_nOH$	-
Poly(ethylene glycol) diol	9000	$H(OCH_2CH_2)_nOH$	-
Pluronic F127	12500	$H(OCH_2CH_2)_n[OCH(CH_3)CH_2]_m(OCH_2CH_2)_nOH$	-
Triethylamine	101.19	$(C_2H_5)_3N$	99.5
2-bromoisobutyryl bromide	229.90	$(CH_3)_2CBrCOBr$	98
Copper (I) chloride	99.00	CuCl	>99
2,2′-bipyridyl	156.18	$C_{10}H_8N_2$	>99
Ethylenediaminotetraacetic acid	292.24	$(HO_2CCH_2)_2NCH_2CH_2N(CH_2CO_2H)_2$	>98.5
2-(N,N-dimethylamino)ethyl methacrylate	157.21	$CH_2=C(CH_3)COOCH_2CH_2N(CH_3)_2$	98
2-(N,N-diethylamino)ethyl methacrylate	185.26	$H_2C=C(CH_3)CO_2CH_2CH_2N(C_2H_5)_2$	99
2-(N,N-diisopropylamino)ethyl methacrylate	213.32	$H_2C=C(CH_3)CO_2CH_2CH_2N(C_3H_7)_2$	97

[a] The average molecular weight of the polymers as provided by the manufacturer (Sigma-Aldrich).

3.2 Physico-chemical Characterization

^{1}H NMR spectra were recorded on polymer solutions in deuterated solvents using a DRX 500 Avance, Bruker Biospin GmbH (Rheinstetten Germany) spectrometer.

FT-IR spectra were recorded in ATR mode on a Shimadzu FTIR-8400S (Duisburg, Germany) spectrometer.

MALDI spectra were recorded on 1 mg/mL polymer solutions in N,N-dimethylformamide using a Bruker ultrafleXtreme mass spectrometer.

GPC analysis was performed on polymer solutions in DMF containing 0.05% of BHT using a GPC JASCO 851-AS Intelligent sampler (with PSS column) (UK) equipped with refractive index and viscosity detectors, using universal calibration with poly(styrene) standards.

Rheological measurements were performed on a Haake Mars Rotational Rheometer in parallel plate configuration (20 mm upper plate diameter; gap: 300 µm; volume applied: 200 µL). The solutions were prepared as follows: 0.30 grams of solid were dispersed in 1.5 mL of deionized water (16.7% (wt)) adjusted at pH = 4 with concentrated HCl and left overnight at 3°C. The solution was finally split in three 0.5 mL aliquots and their pH adjusted to 5.5, 6.5, 7.5 using concentrated NaOH (addition of less than 25 µL, i.e. insignificant variations in the polymer concentration). Loss (G'') and storage (G') moduli were recorded on the solutions as a function of temperature (5 to 60 °C homogeneously increased within 45 minutes at a rate of about 1.2 °C/min) applying a shear stress of 10 Pa with a frequency of 1 Hz.

3.3 Preparative procedures

3.3.1 Synthesis of macroinitiators

The same procedure was followed for the three macroinitiators (PEG_Br, PEG_bBr, PLUR_bBr). In a typical procedure, 11 g of precursor (corresponding to 2.1 mmol OH groups for PEG_OH, 2.5 mmol for PEG_bOH and 0.8 mmol for PLUR_bOH) and 300 mL of toluene were introduced under inert Ar atmosphere into a 500 mL two-necked flask connected to Soxhlet apparatus filled with activated molecular sieves and a cooling tower. The solution was azeotropically dried for two hours, cooled at room temperature and further cooled to 5°C into an ice bath. 6.7 equivalents of triethylamine and 5 equivalents of 2-bromoisobutyryl bromide dissolved in 20 mL of dichloromethane were then added dropwise, stirring the heterogeneous mixture for one hour. At the end of the reaction 0.3 mL of water were added to the reaction mixture. Sodium carbonate was

added to the reaction mixture, stirred and then removed by filtration; the solvents were almost completely removed at the rotary evaporator. 40 mL of dichloromethane were added to the residual solution and this latter was extracted with 5x10 mL of acetic acid solution (5% wt in water). The acid water phases were extracted with 2x10 mL of dichloromethane. The organic phase were collected and extracted with 10x10 mL of sodium bicarbonate solution (5%wt in water). The basic water phases were extracted with 2x10mL of dichloromethane. The organic phases were collected and finally dried over sodium sulfate. The solvent was removed until the solution reached a volume of 20 mL, precipitated twice in excess hexane (10:1 v:v hexane:dichloromethane) and filtered through a paper filter. The resulting solid was solubilized in 20 mL if dichloromethane and finally the solvent was removed under vacuum to yield a white powder.

Yields: 87 %wt. (PEG_Br), 98 %wt. (PEG_bBr) and 95% (PLUR_bBr). Conversion: 98 %mol (PEG_Br), 95 %mol. (PEG_bBr) and 100 %mol (PLUR_bBr).

^{1}H-NMR ($CDCl_3$): **PEG_OH**: 3.37 (s, 3H, -$CH_2CH_2OC\mathbf{H_3}$), 3.49 and 3.78 (side band of the peak at 3.64 ppm), 3.54 (t, 2H, -$C\mathbf{H_2}OCH_3$), 3.64 (broad, PEG chain proton, -$C\mathbf{H_2}C\mathbf{H_2}$O-), 3.72 (t, 2H,-$OCH_2C\mathbf{H_2}$OH) ppm. **PEG_Br**: 1.87 (s, 6H, -C(Br)($C\mathbf{H_3}$)$_2$), 3.31 (s, 3H, -$CH_2CH_2OC\mathbf{H_3}$), 3.43 and 3.72 (side band of the peak at 3.58 ppm), 3.48 (t, 2H, -$C\mathbf{H_2}OCH_3$), 3.58 (broad, PEG chain proton, -$C\mathbf{H_2}C\mathbf{H_2}$O-), 3.68 (t, 2H, -$OC\mathbf{H_2}CH_2OC$(O)C(Br)($CH_3$)$_2$), 4.25 (t, 2H,-$CH_2C\mathbf{H_2}OC$(O)C(Br)($CH_3$)$_2$) ppm. **PEG_bOH**: 3.42 and 3.71 (side band of the peak at 3.57 ppm), 3.57 (broad, PEG chain proton,-$C\mathbf{H_2}C\mathbf{H_2}$O-), 3.65 (t, 2H, -$OCH_2C\mathbf{H_2}$OH) ppm. **PEG_bBr**: 1.87 (s, 12H, -C(Br)($C\mathbf{H_3}$)$_2$), 3.43 and 3.71 (side band of the peak at 3.57 ppm), 3.57 (broad, PEG chain proton, -$C\mathbf{H_2}C\mathbf{H_2}$O-), 3.67 (t, 4H, -$OC\mathbf{H_2}CH_2OC$(O)C(Br)($CH_3$)$_2$), 4.25 (t, 4H, $OCH_2C\mathbf{H_2}OC$(O)C(Br)(CH_3)$_2$) ppm. **PLUR_bOH**: 1.14 (broad, PPG chain proton,, -$CH_2CH(C\mathbf{H_3})$O-), 3.41 (broad, PPG chain proton, -$CH_2C\mathbf{H}(CH_3)$O-), 3.56 (broad, PPG chain proton,-$C\mathbf{H_2}CH(CH_3)$O-), 3.65 (broad, PEG chain proton, -$C\mathbf{H_2}C\mathbf{H_2}$O-), 3.73 (t, 2H, -$OCH_2C\mathbf{H_2}$OH), 3.78 (side band of the peak at 3.65 ppm) ppm. **PLUR_bBr**: 1.07 (broad, PPG chain proton,, -$CH_2CH(C\mathbf{H_3})$O-), 1.87 (s, 12H, C(Br)($C\mathbf{H_3}$)$_2$), 3.32 (broad, PPG chain proton,-$CH_2C\mathbf{H}(CH_3)$O-), 3.48 (broad, PPG chain proton,-$C\mathbf{H_2}CH(CH_3)$O-), 3.57 (broad, PEG chain proton, -$C\mathbf{H_2}C\mathbf{H_2}$O-), 3.67 (t, 4H, -$OC\mathbf{H_2}CH_2OC$(O)C(Br)($CH_3$)$_2$), 3.71 (side band of the peak at 3.65 ppm), 4.25 (t, 4H, $OCH_2C\mathbf{H_2}OC$(O)C(Br)(CH_3)$_2$) ppm.

FT-IR (polymer in powder): **PEG_OH**: shoulder at 2945 (ν_{as} CH_2), 2882 (ν_s CH_2), 1466 (δ_s CH_2), 1340 (ν_s OH), 1279, 1240, 1096 (ν_{as} C-O-C), 947, 841 cm^{-1}. **PEG_Br**: shoulder

at 2945 (ν_{as} CH_2), 2882 (ν_s CH_2), 1734 (ν_s C=O),1466 (δ_s CH_2), 1340 (ν_s OH), 1279, 1240, 1098 (ν_{as} C-O-C), 947, 841 cm^{-1}.

PEG_bOH: shoulder at 2945 (ν_{as} CH_2), 2880 (ν_s CH_2), 1466 (δ_s CH_2), 1341 (ν_s OH), 1279, 1242, 1094 (ν_{as} C-O-C), 947, 841 cm^{-1} (in bold the absorptions characteristic of PEG). **PEG_bBr**: shoulder at 2945 (ν_{as} CH_2), 2880 (ν_s CH_2), 1734 (ν_s C=O), 1466 (δ_s CH_2), 1342 (ν_s OH), 1279, 1242, 1098 (ν_{as} C-O-C), 947, 841 cm^{-1}.

PLUR_bOH: shoulder at 2970 (ν CH_3), 2883 (ν_s CH_2), 1467 (δ_s CH_2), 1342 (ν_s OH), 1280, 1241, 1099 (ν_{as} C-O-C), 946, 841 cm^{-1}. **PLUR_bBr**: shoulder at 2968 (ν_{as} CH_2), 2880 (ν_s CH_2), 1734 (ν_s C=O),1466 (δ_s CH_2), 1342 (ν_s OH), 1279, 1242, 1101 (ν_{as} C-O-C), 947, 841 cm^{-1}.

3.4 Study of the kinetic of the ATRP reactions

The same procedure was followed to study the polymerization kinetic of 2-N,N-dimethylaminoethyl methacrylate (DMAEMA), 2-N,N-diethylaminoethyl methacrylate (DEAEMA), 2-N,N-diisopropylaminoethyl methacrylate (DIAEMA) with the three macroinitiators (PEG_Br, PEG_bBr, PLUR_bBr). The products of the reactions were:

- PLUR_bPDMAEMA
- PLUR_bPDEAEMA
- PLUR_bPDIAEMA
- PEG_bPDMAEMA
- PEG_bPDEAEMA
- PEG_bPDIAEMA
- PEG_PDMAEMA
- PEG_PDEAEMA
- PEG_PDIAEMA

Macroinitiator, catalyst CuCl and 2,2′-bipyridyl ligand were placed in a schlenk tube with a stirring bar. The schlenk tube was closed with a glass cap and placed under argon atmosphere with three vacuum/argon cycle. The solids were weighted in order to have the following molar ratio: 70:2:1:1 (monomer: ligand: catalyst: initiator groups). Monomer was degassed with argon purge for at least 30 min at room temperature into a calibrated schlenk. Toluene was simultaneously degassed using argon purge and was added to the schlenk containing the solids. The amount of toluene added into the schlenk was calculated in order to have an initial concentration of monomer about of 25% (vol). The flask was placed in a thermostated oil bath at 60 °C and stirred until all the solids

were solubilized. Finally the monomer was added to the schlenk containing the solution of macroinitiator and the mixture was stirred at 60°C until the end of the experiment. The molar amount of monomer added into the schlenk was determined in order to have the previously mentioned molar ratio. Two samples for each derived product were prepared in the same way and the reactions were carried out in parallel.

An initial sample was taken from the two schlenks in order to determine experimentally the initial concentration of monomer. For kinetic studies, 0.15 mL of solution were withdrawn with a syringe at different intervals of time; in the syringe the reaction was terminated by exposure to air. From one schlenk, samples were withdrawn after 20, 40 and 60 minutes whilst from the other schlenk, samples were withdrawn after 30, 60, 90, 120, 150 minutes.

The withdrawn sample was introduced onto a micro-column, fabricated with a glass Pasteur pipette packed with 0.35 g of basic alumina and filled with cotton on the bottom. The content was eluted by a total of 1 mL of $CDCl_3$ to remove the catalyst and the resulting solution was used to determine the monomer concentration and copolymer composition by ^{1}H-NMR analysis.

^{1}H-NMR ($CDCl_3$): **PLUR_bPDMAEMA** in solution with toluene and unreacted monomer: 0.93 (broad, -C**H$_2$**C(CH_3)- in the repeating units of the polymer), 1.14 (t, 3H, CH_2-CH(C**H$_3$**)-O of PPG chain), 1.85 (broad, -CH_2C(C**H$_3$**)- in the repeating units of the polymer)**,** 1.93 (s, 3H, -CH_2C(C**H$_3$**)- in the monomer), 2.26 (s, 6H, -N(C**H$_3$**)$_2$), 2.57 (t, 2H, O-CH_2-C**H$_2$**-N-), 3.40, 3.55, 3.62 (CH_2-C**H**(CH_3)-O and C**H$_2$**-CH(CH_3)-O in the PPG chain, C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.06 (broad, O-C**H$_2$**-CH_2-N-), 4.23 (t, 2H, O-C**H$_2$**-CH_2-N-), 5.52 (t, 1H, **H$_2$**C=C(CH_3)- cis to methyl group in the monomer) and 6.10 (s, 1H, **H$_2$**C=C(CH_3)- trans to methyl group in the monomer) ppm. **PLUR_bPDEAEMA** in solution with toluene and unreacted monomer: 0.84 (broad, -C**H$_2$**C(CH_3)- in the repeating units of the polymer), 1.03 (t, 6H, -N(CH_2C**H$_3$**)$_2$), 1.14 (t, 3H, CH_2-CH(C**H$_3$**)-O of PPG chain), 1.87 (broad, -CH_2C(C**H$_3$**)- in the repeating units of the polymer)**,** 1.93 (s, 3H, -CH_2C(C**H$_3$**)- in the monomer), 2.56 (q, 4H, N(C**H$_2$**CH_3)$_2$), 2.63 (broad, O-CH_2-C**H$_2$**-N- in the repeating units of the polymer), 2.73 (t, 2H, O-CH_2-C**H$_2$**-N- in the monomer), 3.40, 3.55, 3.62 (CH_2-C**H**(CH_3)-O and C**H$_2$**-CH(CH_3)-O in the PPG chain, C**H$_2$**-C**H$_2$**-O in the PEG chain), 3.93 (broad, O-C**H$_2$**-CH_2-N-), 4.20 (t, 2H, O-C**H$_2$**-CH_2-N-), 5.52 (t, 1H, **H$_2$**C=C(CH_3)- cis to methyl group in the monomer) and 6.10 (s, 1H, **H$_2$**C=C(CH_3)- trans to methyl group in the monomer) ppm. **PLUR_bPDIAEMA** in solution with toluene and unreacted monomer: 0.84 (broad, -C**H$_2$**C(CH_3)- in the

repeating units of the polymer), 1.00 (d, 12H, -N(CH(C**H$_3$**)$_2$)$_2$), 1.14 (t, 3H, CH_2-CH(C**H$_3$**)-O of PPG chain), 1.75 (broad, -CH_2C(C**H$_3$**)- in the repeating units of the polymer)**,** 1.92 (s, 3H, -CH_2C(C**H$_3$**)- in the monomer), 2.54 (broad, O-CH_2-C**H$_2$**-N- in the repeating units of the polymer), 2.66 (t, 2H, O-CH_2-C**H$_2$**-N- in the monomer), 2.98 (m, 2H, -N(C**H**$(CH_3)_2)_2$), 3.40, 3.55, 3.62 (CH_2-C**H**(CH_3)-O and C**H$_2$**-$CH(CH_3)$-O in the PPG chain, C**H$_2$**-C**H$_2$**-O in the PEG chain), 3.76 (broad, O-C**H$_2$**-CH_2-N-), 4.07 (t, 2H, O-C**H$_2$**-CH_2-N-), 5.49 (t, 1H, **H$_2$**C=$C(CH_3)$- cis to methyl group in the monomer) and 6.10 (s, 1H, **H$_2$**C=$C(CH_3)$- trans to methyl group in the monomer) ppm.

PEG_bPDMAEMA in solution with toluene and unreacted monomer: 0.92 (broad, -C**H$_2$**$C(CH_3)$- in the repeating units of the polymer), 1.85 (broad, -CH_2C(C**H$_3$**)- in the repeating units of the polymer)**,** 1.94 (s, 3H, -CH_2C(C**H$_3$**)- in the monomer), 2.28 (s, 6H, -N(C**H$_3$**)$_2$), 2.56 (broad, O-CH_2-C**H$_2$**-N- in the repeating units of the polymer), 2.61 (t, 2H, O-CH_2-C**H$_2$**-N- in the monomer), 3.63, (broad, C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.06 (broad, O-C**H$_2$**-CH_2-N-), 4.25 (t, 2H, O-C**H$_2$**-CH_2-N-), 5.55 (t, 1H, **H$_2$**C=$C(CH_3)$- cis to methyl group in the monomer) and 6.11 (s, 1H, **H$_2$**C=$C(CH_3)$- trans to methyl group in the monomer) ppm. **PEG_bPDEAEMA** in solution with toluene and unreacted monomer: 0.83 (broad, -C**H$_2$**$C(CH_3)$- in the repeating units of the polymer), 0.96 (t, 6H, -N(CH_2C**H$_3$**)$_2$), 1.74 (broad, -CH_2C(C**H$_3$**)- in the repeating units of the polymer)**,** 1.86 (s, 3H, -CH_2C(C**H$_3$**)- in the monomer), 2.49 (q, 4H, N(C**H$_2$**CH_3)$_2$), 2.62 (broad, O-CH_2-C**H$_2$**-N- in the repeating units of the polymer), 2.67 (t, 2H, O-CH_2-C**H$_2$**-N- in the monomer), 3.56 (broad, C**H$_2$**-C**H$_2$**-O in the PEG chain), 3.92 (broad, O-C**H$_2$**-CH_2-N-), 4.13 (t, 2H, O-C**H$_2$**-CH_2-N-), 5.46 (t, 1H, **H$_2$**C=$C(CH_3)$- cis to methyl group in the monomer) and 6.02 (s, 1H, **H$_2$**C=$C(CH_3)$- trans to methyl group in the monomer). **PEG_bPDIAEMA** in solution with toluene and unreacted monomer: 0.85 (broad, -C**H$_2$**$C(CH_3)$- in the repeating units of the polymer), 0.91 (d, 12H, -N(CH(C**H$_3$**)$_2$)$_2$), 1.75 (broad, -CH_2C(C**H$_3$**)- in the repeating units of the polymer)**,** 1.85 (s, 3H, -CH_2C(C**H$_3$**)- in the monomer), 2.54 (broad, O-CH_2-C**H$_2$**-N- in the repeating units of the polymer), 2.59 (t, 2H, O-CH_2-C**H$_2$**-N- in the monomer), 2.91 (m, 2H, -N(C**H**$(CH_3)_2)_2$), 3.54 (broad, C**H$_2$**-C**H$_2$**-O in the PEG chain), 3.76 (broad, O-C**H$_2$**-CH_2-N-), 3.99 (t, 2H, O-C**H$_2$**-CH_2-N-), 5.43 (t, 1H, **H$_2$**C=$C(CH_3)$- cis to methyl group in the monomer) and 6.02 (s, 1H, **H$_2$**C=$C(CH_3)$- trans to methyl group in the monomer) ppm.

PEG_PDMAEMA in solution with toluene and unreacted monomer: 0.85 (broad, -C**H$_2$**$C(CH_3)$- in the repeating units of the polymer), 1.77 (broad, -CH_2C(C**H$_3$**)- in the repeating units of the polymer)**,** 1.84 (s, 3H, -CH_2C(C**H$_3$**)- in the monomer), 2.18 (s, 6H,

-N(C**H₃**)₂), 2.49 (t, 2H, O-CH₂-C**H₂**-N- in the monomer), 3.26 (s, 3H, -OC**H₃** at the end of the macroinitiator polymer chain), 3.53 (broad, C**H₂**-C**H₂**-O in the PEG chain), 3.97 (broad, O-C**H₂**-CH₂-N-), 4.14 (t, 2H, O-C**H₂**-CH₂-N-), 5.43 (t, 1H, **H₂**C=C(CH₃)- cis to methyl group in the monomer) and 6.02 (s, 1H, **H₂**C=C(CH₃)- trans to methyl group in the monomer) ppm. **PEG_PDEAEMA** in solution with toluene and unreacted monomer: 0.86 (broad, -C**H₂**C(CH₃)- in the repeating units of the polymer), 0.97 (t, 6H, -N(CH₂C**H₃**)₂), 1.77 (broad, -CH₂C(C**H₃**)- in the repeating units of the polymer)**,** 1.87 (s, 3H, -CH₂C(C**H₃**)- in the monomer), 2.50 (q, 4H, N(C**H₂**CH₃)₂), 2.62 (broad, O-CH₂-C**H₂**-N- in the repeating units of the polymer), 2.67 (t, 2H, O-CH₂-C**H₂**-N- in the monomer), 3.30 (s, 3H, -OC**H₃** at the end of the macroinitiator polymer chain), 3.57 (broad, C**H₂**-C**H₂**-O in the PEG chain), 3.94 (broad, O-C**H₂**-CH₂-N-), 4.15 (t, 2H, O-C**H₂**-CH₂-N-), 5.46 (t, 1H, **H₂**C=C(CH₃)- cis to methyl group in the monomer) and 6.04 (s, 1H, **H₂**C=C(CH₃)- trans to methyl group in the monomer) ppm. **PEG_PDIAEMA** in solution with toluene and unreacted monomer: 0.93 (broad, -C**H₂**C(CH₃)- in the repeating units of the polymer), 1.01 (d, 12H, -N(CH(C**H₃**)₂)₂), 1.84 (broad, -CH₂C(C**H₃**)- in the repeating units of the polymer) 1.93 (s, 3H, -CH₂C(C**H₃**)- in the monomer), 2.66 (t, 2H, O-CH₂-C**H₂**-N-), 2.99 (m, 2H, -N(C**H**(CH₃)₂)₂), 3.35 (s, 3H, -OC**H₃** at the end of the macroinitiator polymer chain), 3.62 (broad, C**H₂**-C**H₂**-O in the PEG chain), 3.84 (broad, O-C**H₂**-CH₂-N-), 4.07 (t, 2H, O-C**H₂**-CH₂-N-), 5.50 (t, 1H, **H₂**C=C(CH₃)- cis to methyl group in the monomer) and 6.09 (s, 1H, **H₂**C=C(CH₃)- trans to methyl group in the monomer) ppm.

In cap. 3.4.1 – 3.4.9 are reported the graphs that correlate ln([M_0]/[M]) with the time for each couple of monomer and macroinitiator. ATRP should follow a first order kinetic respect to the monomer (see eq.4 pag. 7). k_p is constant with the temperature which was kept constant during the experiment and [$P^{\cdot}$] should be kept constant with the equilibrium that is established between the growing radicals and the catalyst (scheme 3 pag.9).

When points in the different graphs are not in agreement with a linear correlation between ln([M_0]/[M]) and the time means these samples are partially oxidized. During the sampling the schlenk was opened and, even if argon was purged into the schlenk continuously, it might happened that some oxygen entered into the system. When this happens the catalyst is oxidized and the equilibrium between the dormant and the growing specie is shifted towards the dormant specie, leading to the lowering of the concentration of the growing radicals in solution. When the concentration of the growing

specie decreases, also the rate of polymerization decreases, leading to a non-directly dependence of ln([M_0]/[M]) from time.

Several devices were tried but the system used was the best possible.

Some sample have higher ln([M_0]/[M]) compared to samples withdrawn previously. This is not possible because even if the reaction stops the concentration should remain constant but it cannot increase. This can be explained assuming that some polymer was retained in the basic alumina column whilst all the monomer, which is more soluble in the solvent, passed completely throw the column. If this happen, the ratio between the concentration of monomer and the concentration of polymer is not the same as the one in the Shlenk where the reaction was carried out, but it is higher.

3.4.1 Study of the polymerization kinetics using Poly(ethylene glycol)methylether (2-bromoisobutyrate) as initiator and 2-N,N-dimethylaminoethyl methacrylate as monomer

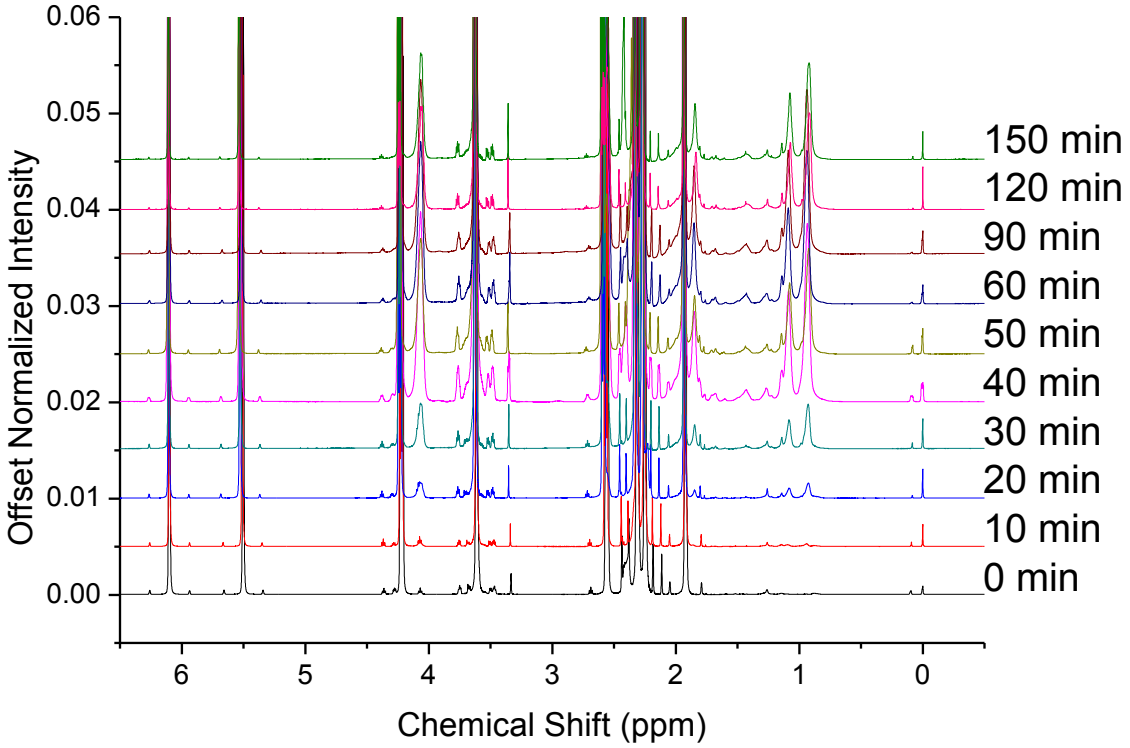


Figure 3-1: ^{1}H-NMR of the samples withdrawn to study the ATRP kinetic using Poly(ethylene glycol)methylether (2-bromoisobutyrate) as initiator and 2-N,N-dimethylaminoethyl methacrylate as monomer.

In Figure 3-1 the ^{1}H-NMR of the samples withdrawn during the study of the polymerization kinetic are shown. It can be seen that the intensity of the two peaks at 6.02 and 5.43 ppm, that are related to the monomer, decreases with the time whilst the

intensity of the other peaks, related to the product, as the ones at 3.97, 1.00 and 0.85 ppm, increases with time.

Plotting ln([M_0]/[M]) versus the time, the graph shown in Figure 3-2 is obtained.

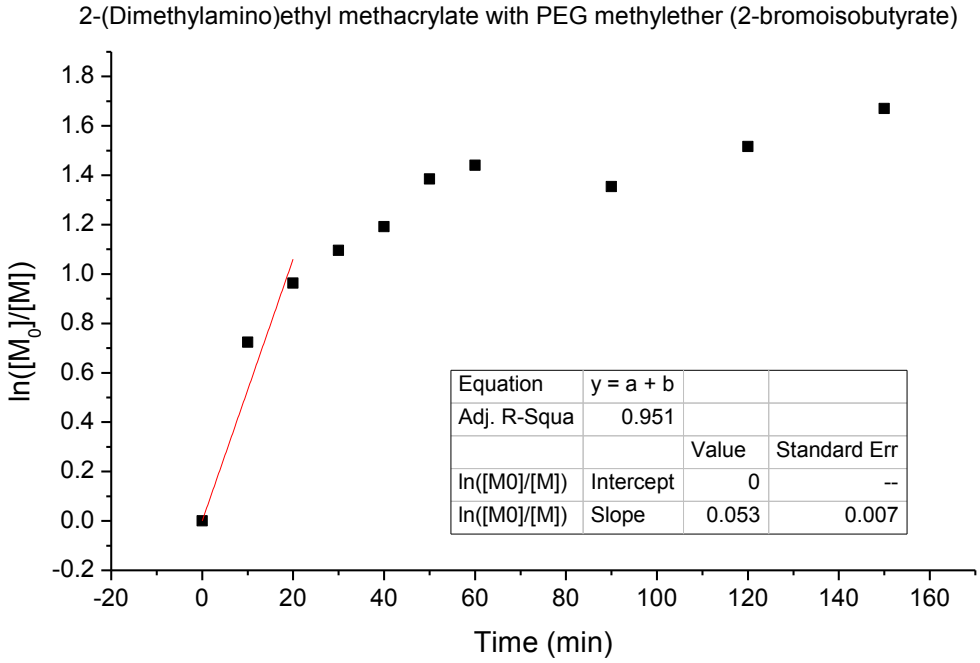


Figure 3-2: Graph that correlates ln([M_0]/[M]) with time during the study of the polymerization of 2-N,N-dimethylaminoethyl methacrylate using PEGOMe (2-bromoisobutyrate) as initiator.

Only the slope of the fitting line of the point within the first 20 minutes was used to be compared with the slopes calculated from the kinetic studies of the other couples of monomer and initiator. The same value was used to calculate the time needed to obtain polymers with pre-determined chain length using PEG_Br as initiator and DMAEMA as monomer. During the synthesis of these compounds with pre-determined chain length the schlenk was not opened and argon was purged into the shlenk during the polymerization. It is reasonable to think that the catalyst did not undergo oxidation from atmospheric oxygen during the polymerization.

3.4.2 Study of the polymerization kinetics using Poly(ethylene glycol)methylether (2-bromoisobutyrate) as initiator and 2-N,N-diethylaminoethyl methacrylate as monomer

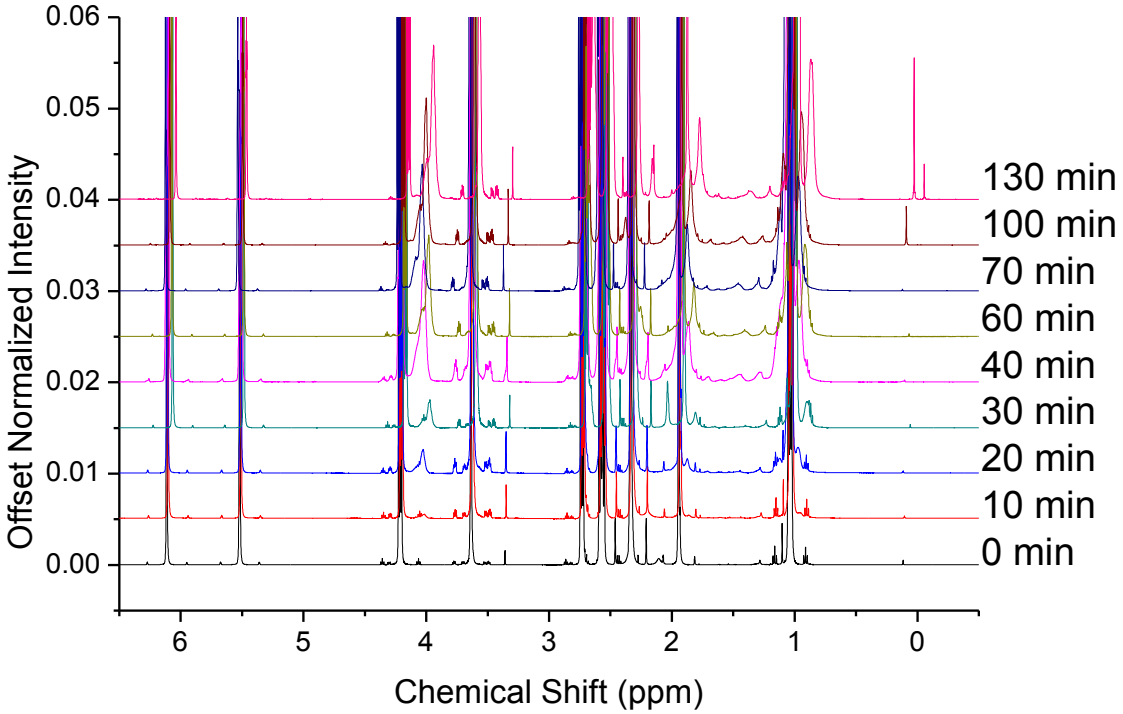


Figure 3-3: ^{1}H-NMR of the samples withdrawn to study the ATRP kinetic using Poly(ethylene glycol)methylether (2-bromoisobutyrate) as initiator and 2-N,N-diethylaminoethyl methacrylate as monomer.

In Figure 3-3 the ^{1}H-NMR of the samples withdrawn during the study of the polymerization kinetic are shown. Also in this case it can be seen that the intensity of the peaks of the product increases with the time. Plotting $\ln([M_0]/[M])$ versus the time the graph shown in Figure 3-4 is obtained.

During the first hour a correlation which is close to a linear correlation between $\ln([M_0]/[M])$ and the time is achieved.

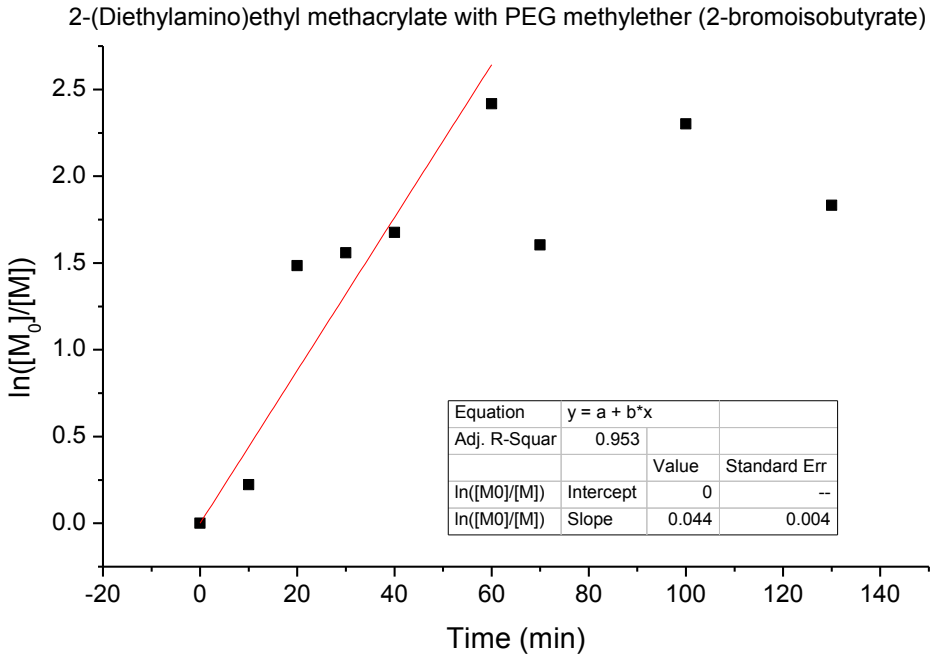


Figure 3-4: Graph that correlates ln([M_0]/[M]) with time during the study of the polymerization of 2-N,N-diethylaminoethyl methacrylate using PEGOMe (2-bromoisobutyrate) as initiator.

Only the slope of the fitting line of the point within the first 60 minutes was used to be compared with the slopes calculated from the kinetic studies of the other couples of monomer and initiator. The same value was used to calculate the time needed to obtain polymers with pre-determined chain length.

3.4.3 Study of the polymerization kinetics using Poly(ethylene glycol)methylether (2-bromoisobutyrate) as initiator and 2-N,N-diisopropylaminoethyl methacrylate as monomer

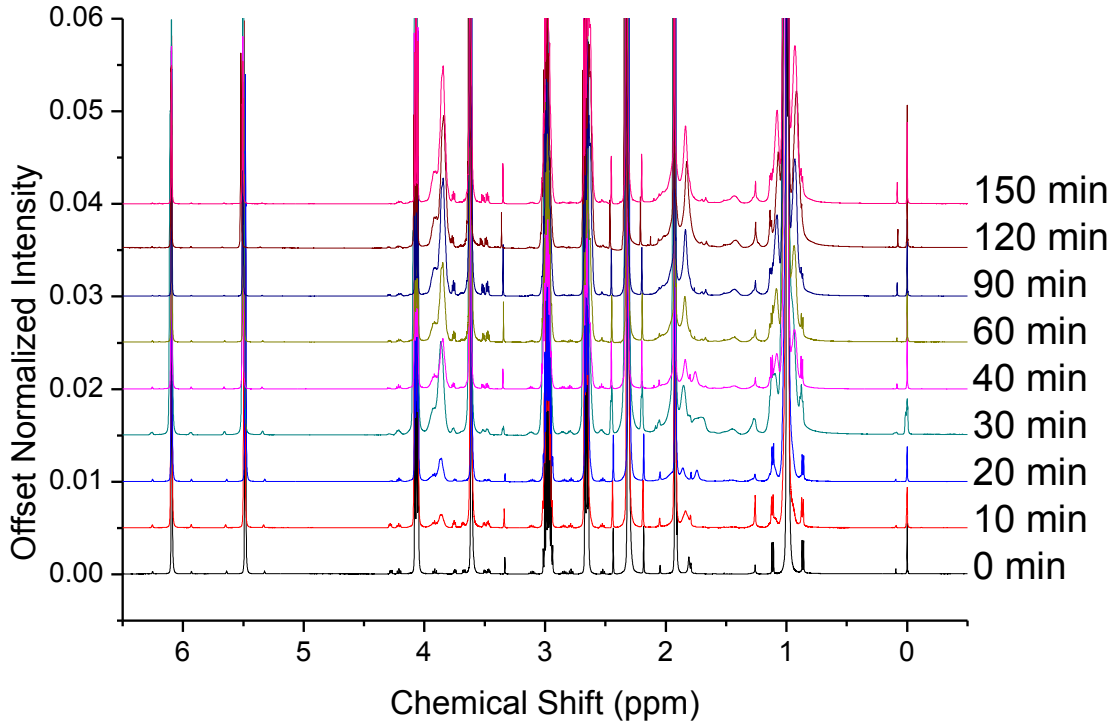


Figure 3-5: ^{1}H-NMR of the samples withdrawn to study the ATRP kinetic using Poly(ethylene glycol)methylether (2-bromoisobutyrate) as initiator and 2-N,N-diisopropylaminoethyl methacrylate as monomer.

In Figure 3-5 ^{1}H-NMR of the samples withdrawn during the study of the polymerization kinetic are shown. Also in this case it can be seen that the intensity of the peaks of the product increases with the time. Plotting ln([M_0]/[M]) versus the time the graph shown in Figure 3-6 is obtained. It can be noticed that for the first 90 minutes the concentration of the monomer decreases according with a first order kinetic. Only the slope of the fitting line of the point within the first 90 minutes was used to be compared with the slopes calculated from the kinetic studies of the other couples of monomer and initiator. The same value was used to calculate the time needed to obtain polymers with pre-determined chain length.

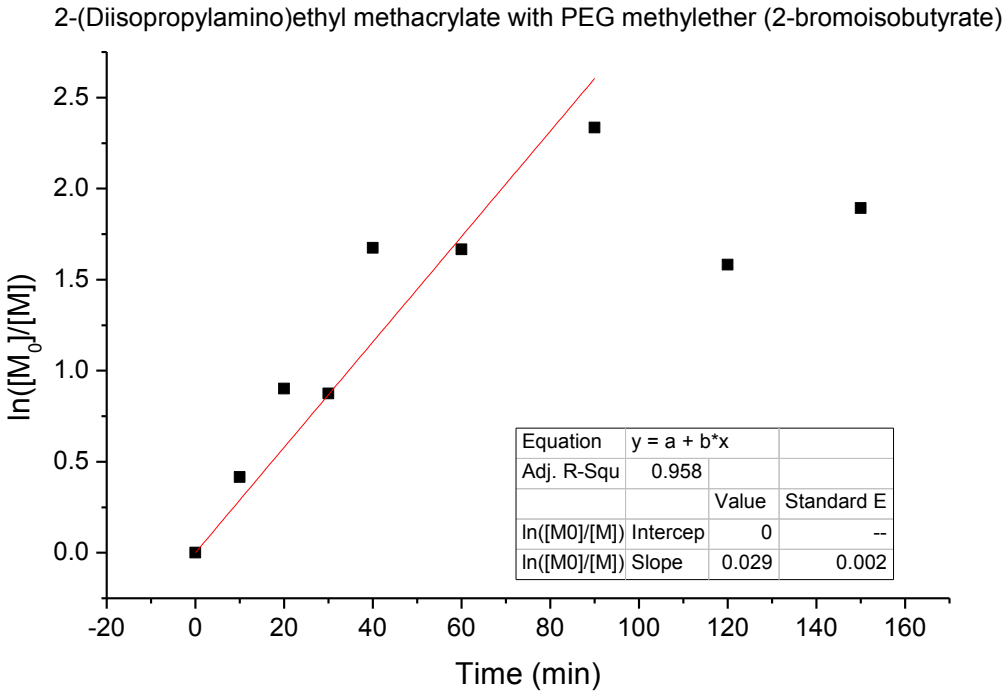


Figure 3-6:Graph that correlates ln([M0]/[M]) with time during the study of the polymerization of 2-N,N-diisopropylaminoethyl methacrylate using PEGOMe (2-bromoisobutyrate) as initiator.

3.4.4 Study of the polymerization kinetics using Poly(ethylene glycol) bis(2-bromoisobutyrate) as initiator and 2-N,N-dimethylaminoethyl methacrylate as monomer

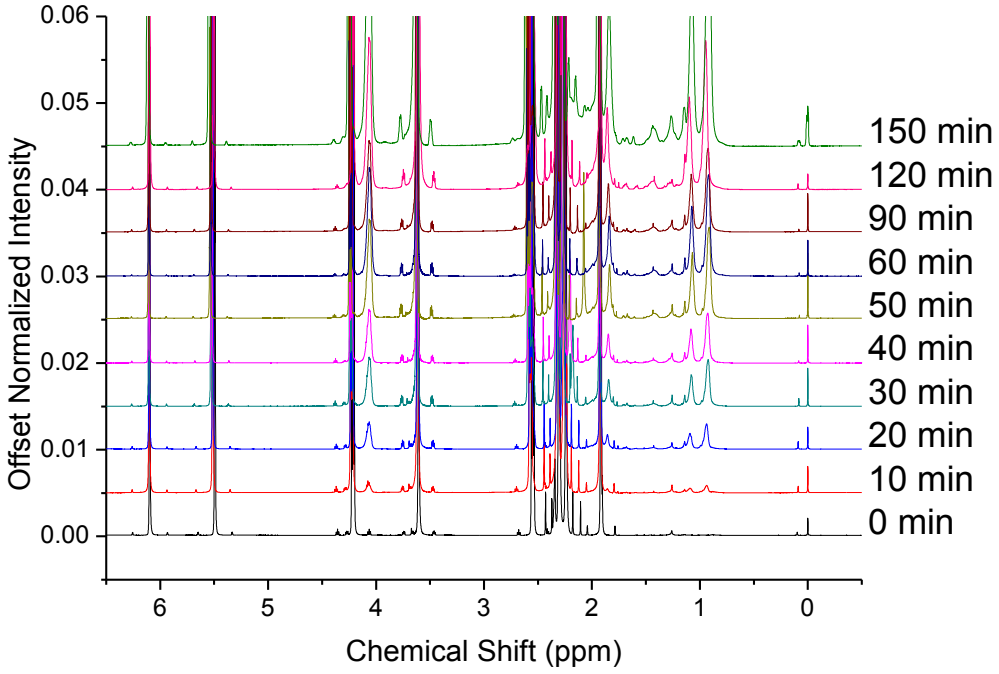


Figure 3-7: ^{1}H-NMR of the samples withdrawn to study the ATRP kinetic using Poly(ethylene glycol) bis(2-bromoisobutyrate) as initiator and 2-N,N-dimethylaminoethyl methacrylate as monomer.

In Figure 3-7 the ^{1}H-NMR spectra of the samples withdrawn during the polymerization kinetic study are shown. It can be clearly seen that the peaks of the product increase with the time whilst the relative intensity of the peaks of the monomer decreases. Calculating the concentration of monomer in each sample and plotting ln([M_0]/[M]) versus the time the graph shown in Figure 3-8 is obtained.

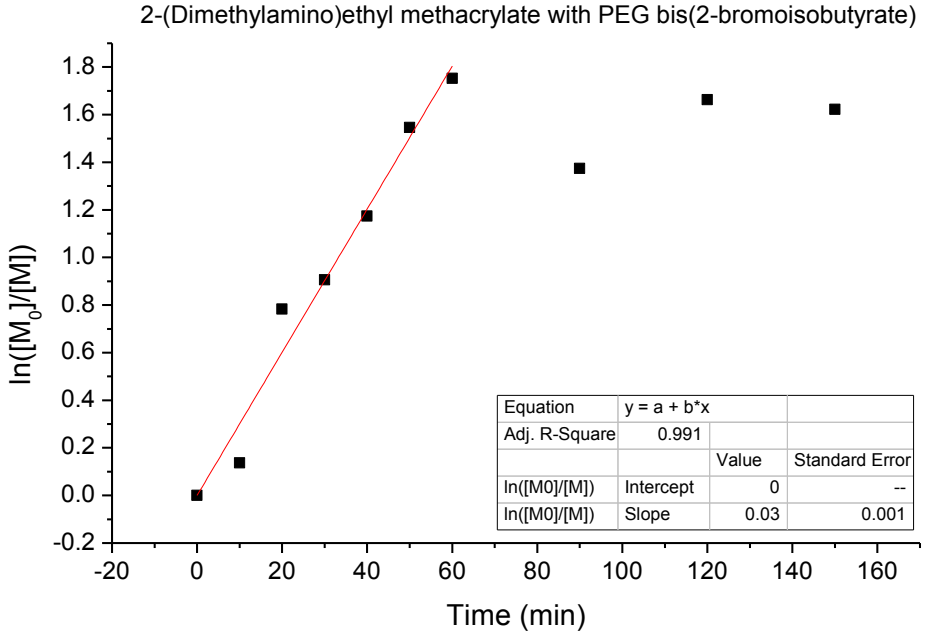


Figure 3-8: Graph that correlates ln([M0]/[M]) with time during the study of the polymerization of 2-N,N-dimethylaminoethyl methacrylate using PEG bis(2-bromoisobutyrate) as initiator.

For the first 60 minutes ln([M_0]/[M]) increases linearly with time, confirming the fact that the system, at least for the first hour, follows the kinetic shown in equation 4 (pag. 11).

Only the slope of the fitting line of the point within the first 60 minutes was used to be compared with the slopes calculated from the kinetic studies of the other couples of monomer and initiator. The same value was used to calculate the time needed to obtain polymers with pre-determined chain length.

3.4.5 Study of the polymerization kinetics using Poly(ethylene glycol) bis(2-bromoisobutyrate) as initiator and 2-N,N-diethylaminoethyl methacrylate as monomer

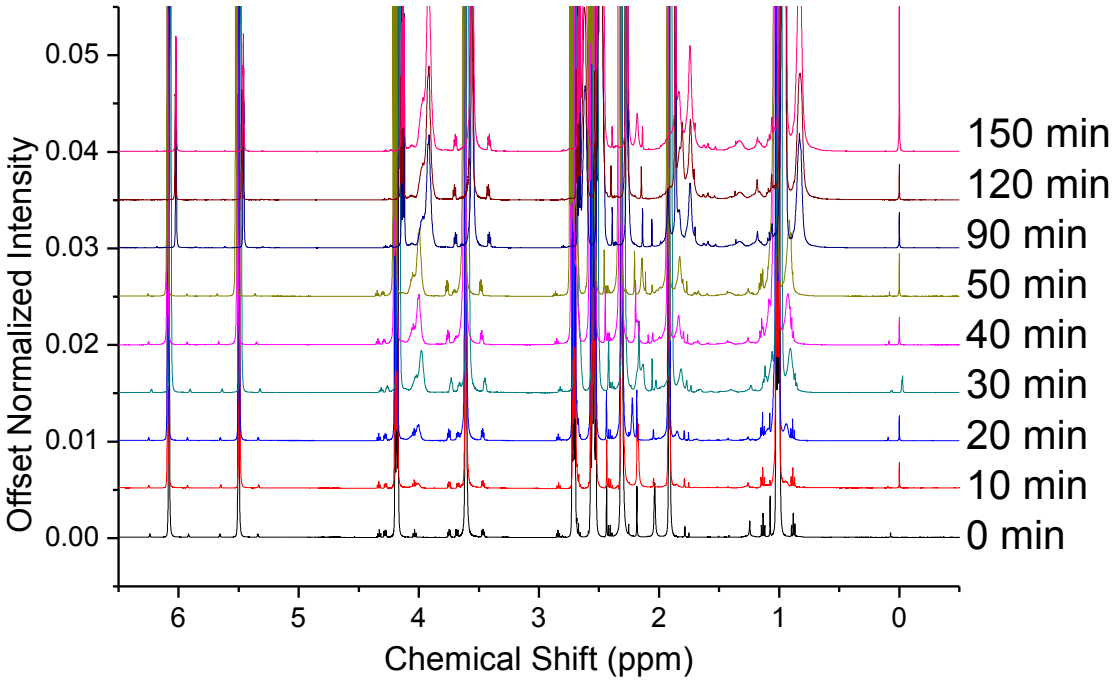


Figure 3-9: ^{1}H-NMR of the samples withdrawn to study the ATRP kinetic using Poly(ethylene glycol) bis(2-bromoisobutyrate) as initiator and 2-N,N-diethylaminoethyl methacrylate as monomer.

In Figure 3-9 the ^{1}H-NMR spectra of the samples withdrawn during the polymerization kinetic study are shown. It can be clearly seen that the peaks of the product increase with the time whilst the relative intensity of the peaks of the monomer decreases with the time. Calculating the molar ratio between the concentration of monomer and the concentration of the initiator in each sample and plotting $\ln([M_0]/[M])$ versus the time the graph shown in Figure 3-10 is obtained.

Even if the points are not strictly on the same line it can be seen that the correlation between $\ln([M_0]/[M])$ and the time is almost linear with a slope of 0.018 min^{-1}.

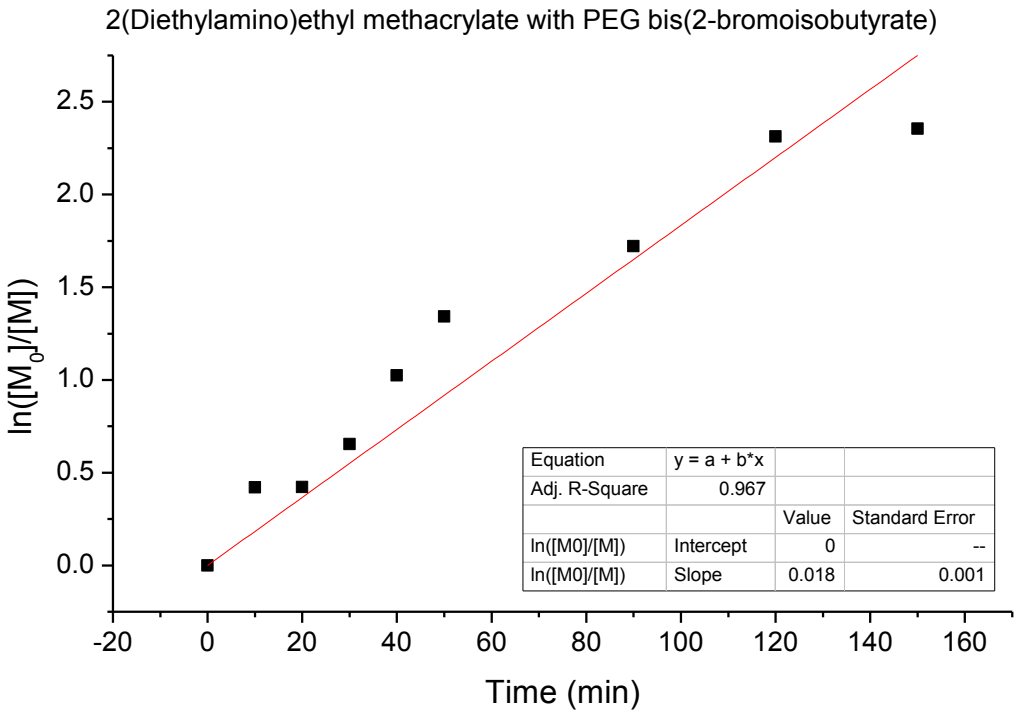


Figure 3-10: Graph that correlates ln([M_0]/[M]) with time during the study of the polymerization of 2-N,N-diethylaminoethyl methacrylate using PEG bis(2-bromoisobutyrate) as initiator.

All the points shown in Figure 3-10 were used to calculate the fitting line and its slope used to be compared with the slopes calculated from the kinetic studies of other couples of monomer and initiator. The same value was used to calculate the time needed to obtain polymers with pre-determined chain length.

3.4.6 Study of the polymerization kinetics using Poly(ethylene glycol) bis(2-bromoisobutyrate) as initiator and 2-N,N-diisopropylaminoethyl methacrylate as monomer

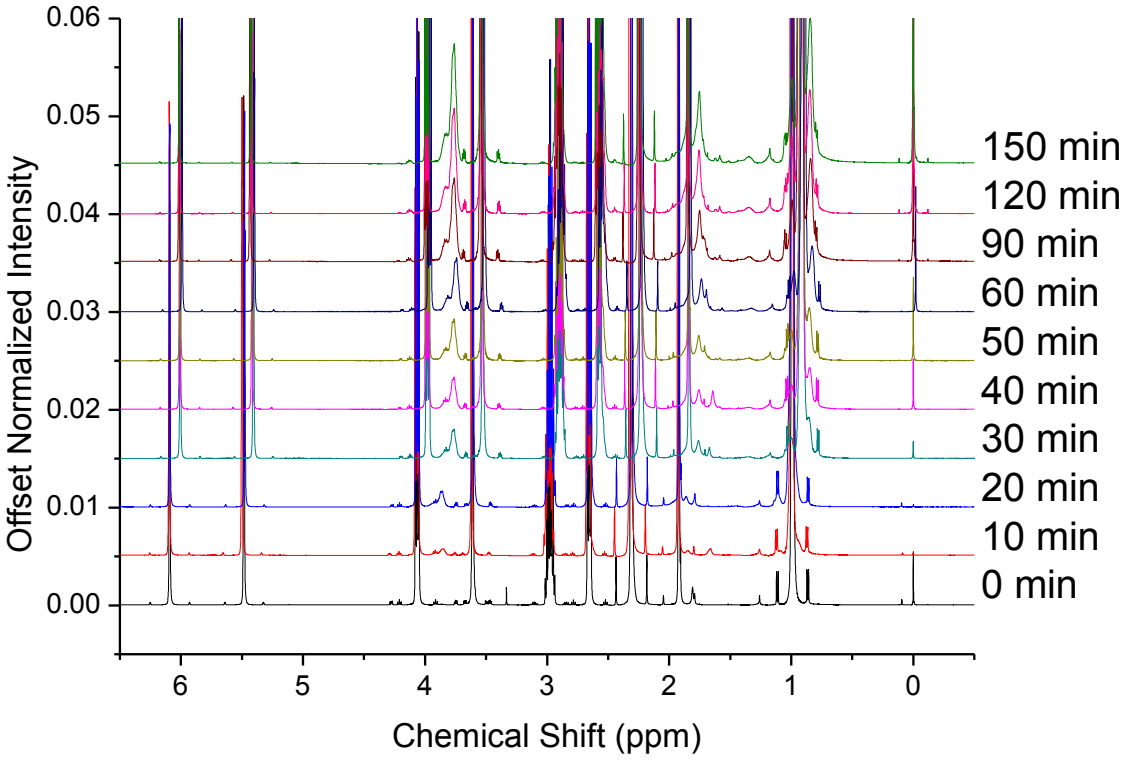


Figure 3-11: ^{1}H-NMR of the samples withdrawn to study the ATRP kinetic using Poly(ethylene glycol) bis(2-bromoisobutyrate) as initiator and 2-N,N-diisopropylaminoethyl methacrylate as monomer.

In Figure 3-11 the ^{1}H-NMR spectra of the samples withdrawn at different time during the polymerization kinetic study are shown. It can be clearly seen that the peaks of the product increase with the time whilst the relative intensity of the peaks of the monomer decreases with the time. Calculating the molar ratio between the concentration of monomer and the concentration of the initiator in each sample and plotting $\ln([M_0]/[M])$ versus the time the graph shown in Figure 3-12 is obtained.

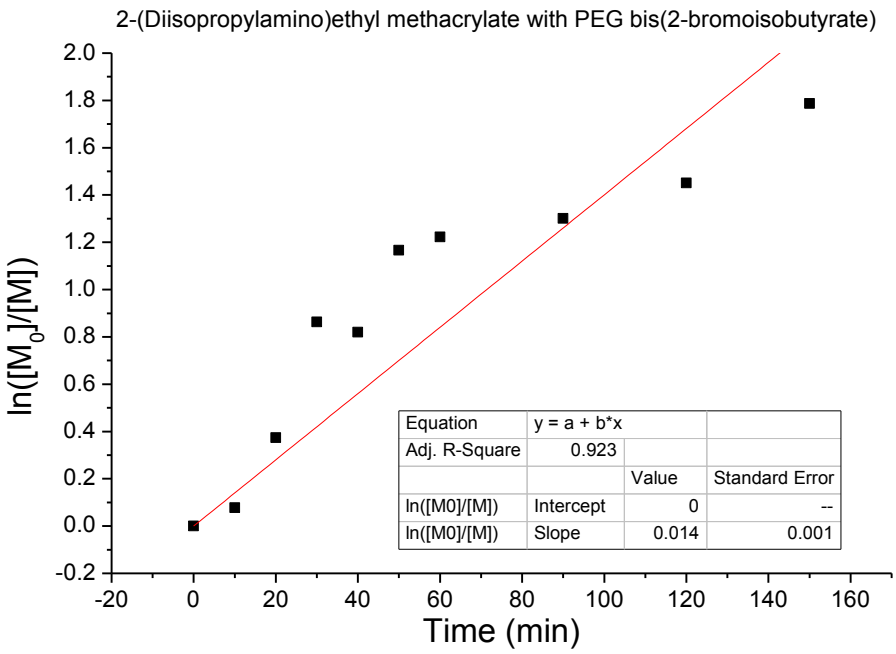


Figure 3-12: Graph that correlates ln([M_0]/[M]) with time during the study of the polymerization of 2-N,N-diisopropylaminoethyl methacrylate using PEG bis(2-bromoisobutyrate) as initiator.

Graph shown in Figure 3-12 shows the correlation between ln([M_0]/[M]) and the time using PEG_bBr as initiator and DIAEMA as monomer. Even if the points are not strictly on the same line it can be seen that the correlation between ln([M_0]/[M]) and the time is almost linear with a slope of 0.014 min^{-1}. It can also be seen that if the fitting line was calculated only using the points within the first 60 minutes instead of using all the points within the entire range of time in which the kinetic study was carried out (150 minutes), the slope of the fitting curve would have been higher and the correlation would have been better. Despite to this, all the points shown in Figure 3-12 were used to calculate the fitting line and its slope was used to be compared with the slopes calculated from the kinetic studies of the other couples of monomer and initiator. The same value was used to calculate the time needed to obtain polymers with pre-determined chain length. It was done like that to avoid deleting data that were not affected from error for sure.

3.4.7 Study of the polymerization kinetics using Pluronic F127 bis(2-bromoisobutyrate) as initiator and 2-N,N-dimethylaminoethyl methacrylate as monomer

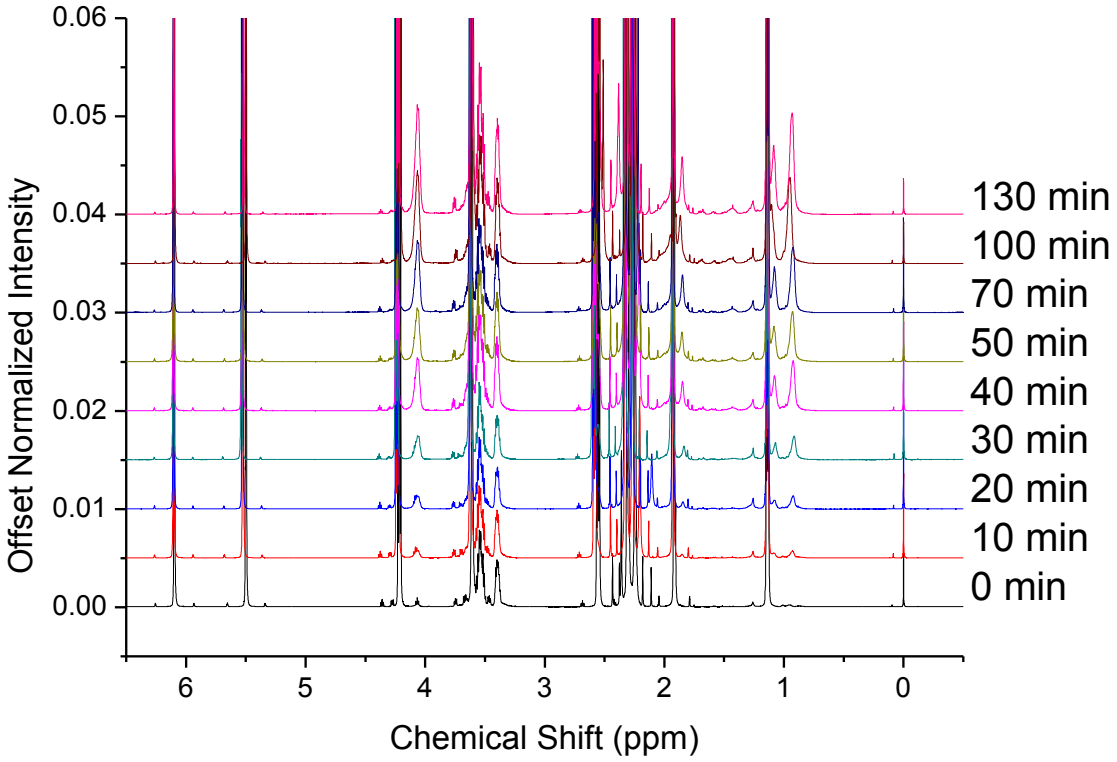


Figure 3-13: ^{1}H-NMR of the samples withdrawn to study the ATRP kinetic using Pluronic F127 bis(2-bromoisobutyrate) as initiator and 2-N,N-dimethylaminoethyl methacrylate as monomer.

In Figure 3-13 the ^{1}H-NMR spectra of the samples withdrawn at different time during the polymerization kinetic study are shown. It can be clearly seen that the peaks of the product increase with the time whilst the relative intensity of the peaks of the monomer decreases with the time. Calculating the molar ratio between the concentration of monomer and the concentration of the initiator in each sample and plotting $\ln([M_0]/[M])$ versus the time the graph shown in Figure 3-14 is obtained.

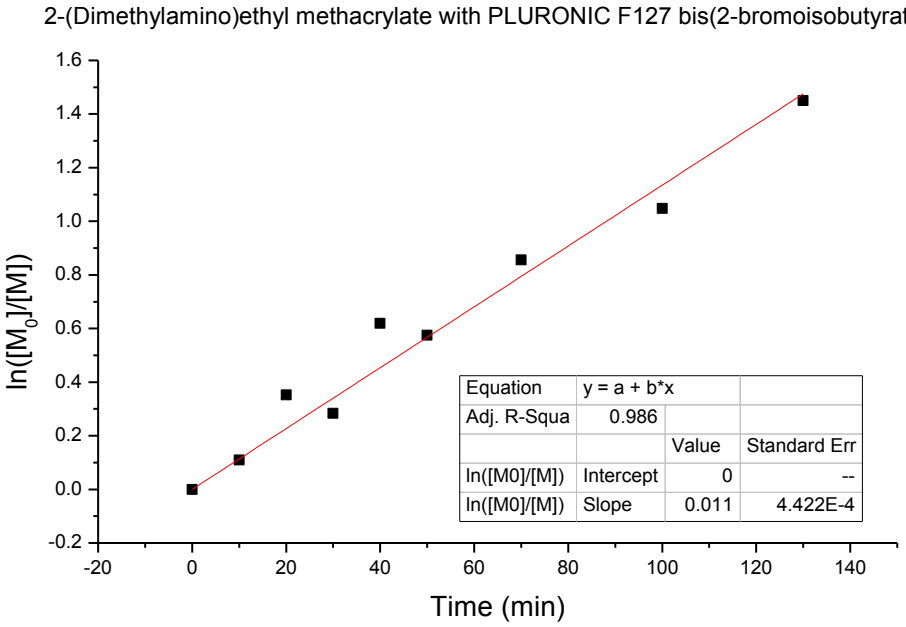


Figure 3-14: Graph that correlates ln([M_0]/[M]) with time during the study of the polymerization of 2-N,N-dimethylaminoethyl methacrylate using Pluronic F127 bis(2-bromoisobutyrate) as initiator.

Graph shown in Figure 3-14 shows the correlation between ln([M_0]/[M]) and the time using PLUR_bBr as initiator and DMAEMA as monomer. Even if the points are not strictly on the same line it can be seen that the correlation between ln([M_0]/[M]) and the time is almost linear with a slope of 0.011 min^{-1}. It can also be seen that the slope of the fitting line remains constant for the entire range in which the kinetic study was carried out, showing that the catalyst did not oxidize during the experiment, leading to a good linear correlation between ln([M_0]/[M]) and the time.

The fitting line was calculated using all the experimental points shown in figure 3-14 and its slope was used to be compared with the slopes calculated from the kinetic studies of the other couples of monomer and initiator. The same value was used to calculate the time needed to obtain polymers with pre-determined chain length.

3.4.8 Study of the polymerization kinetics using Pluronic F127 bis(2-bromoisobutyrate) as initiator and 2-N,N-diethylaminoethyl methacrylate as monomer

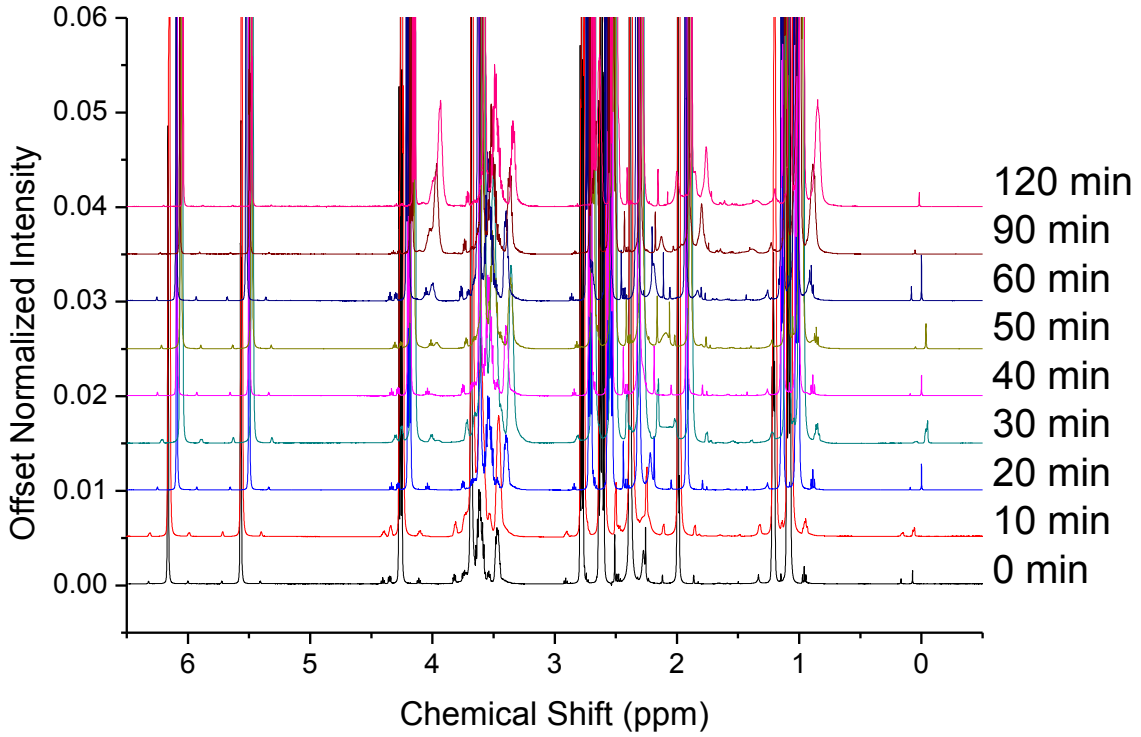


Figure 3-15: ^{1}H-NMR of the samples withdrawn to study the ATRP kinetic using Pluronic F127 bis(2-bromoisobutyrate) as initiator and 2-N,N-diethylaminoethyl methacrylate as monomer.

In Figure 3-15 the ^{1}H-NMR spectra of the samples withdrawn at different time during the polymerization kinetic study are shown. It can be clearly seen that the peaks of the product increase with the time whilst the relative intensity of the peaks of the monomer decreases with the time. Calculating the molar ratio between the concentration of monomer and the concentration of the initiator in each sample and plotting $\ln([M_0]/[M])$ versus the time the graph shown in Figure 3-16 is obtained.

Graph shown in Figure 3-16 shows the correlation between $\ln([M_0]/[M])$ and the time using PLUR_bBr as initiator and DEAEMA as monomer. Even if the points are not strictly on the same line it can be seen that the correlation between $\ln([M_0]/[M])$ and the time is almost linear with a slope of 0.011 min^{-1}. It can also be seen that the slope of the fitting line remains constant for the entire range in which the kinetic study was carried out, showing that the catalyst did not oxidize during the experiment, leading to a good linear correlation between $\ln([M_0]/[M])$ and the time.

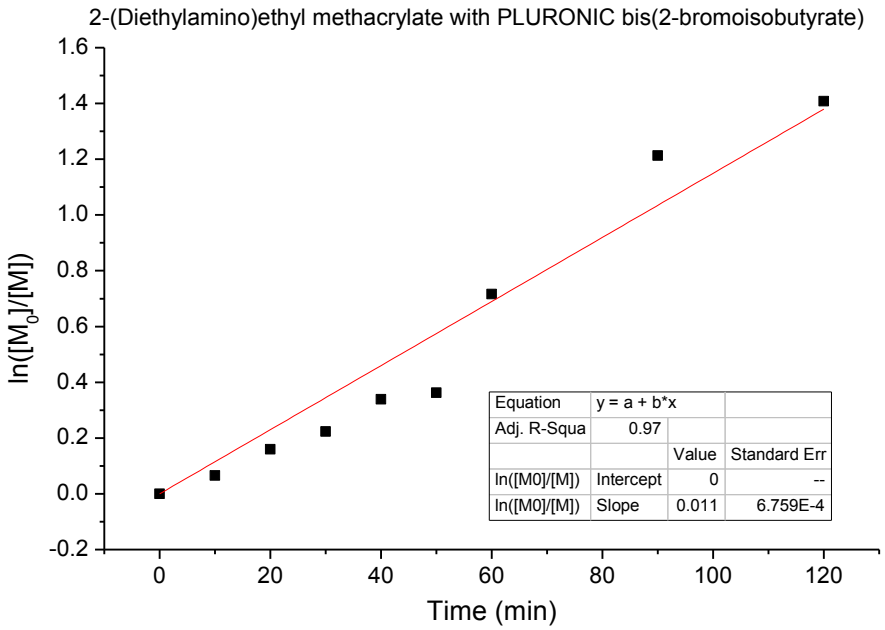


Figure 3-16: Graph that correlates ln([M_0]/[M]) with time during the study of the polymerization of 2-N,N-diethylaminoethyl methacrylate using Pluronic F127 bis(2-bromoisobutyrate) as initiator.

The fitting line was calculated using all the experimental points shown in Figure 3-16 and its slope was used to be compared with the slopes calculated from the kinetic studies of the other couples of monomer and initiator. The same value was used to calculate the time needed to obtain polymers with pre-determined chain length.

3.4.9 Study of the polymerization kinetics using Pluronic F127 bis(2-bromoisobutyrate) as initiator and 2-N,N-diisopropylaminoethyl methacrylate as monomer

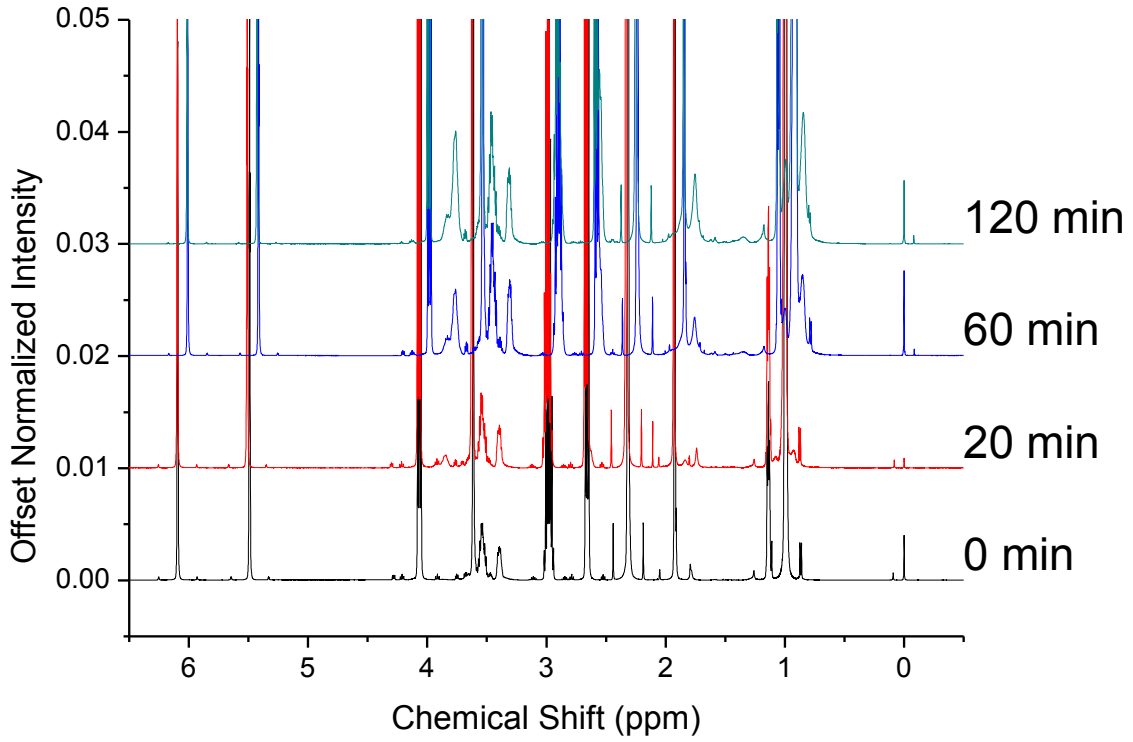


Figure 3-17: 1H-NMR of the samples withdrawn to study the ATRP kinetic using Pluronic F127 bis(2-bromoisobutyrate) as initiator and 2-N,N-diisopropylaminoethyl methacrylate as monomer.

In Figure 3-17 the ^{1}H-NMR spectra of the samples withdrawn at different time during the polymerization kinetic study are shown. It can be clearly seen that the peaks of the product increase with the time whilst the relative intensity of the peaks of the monomer decreases with the time. Calculating the molar ratio between the concentration of monomer and the concentration of the initiator in each sample and plotting $\ln([M_0]/[M])$ versus the time the graph shown in Figure 3-18 is obtained.

Graph shown in Figure 3-18 shows the correlation between $\ln([M_0]/[M])$ and the time using PLUR_bBr as initiator and DIAEMA as monomer. The points are on the same line and the correlation between $\ln([M_0]/[M])$ and the time is linear with a slope of 0.013 min^{-1}. All the points shown in figure 3-18 were used to calculate the fitting line and its slope was used to be compared with the slopes calculated from the kinetic studies of the other couples of monomer and initiator. The same value was used to calculate the time needed to obtain polymers with pre-determined chain length.

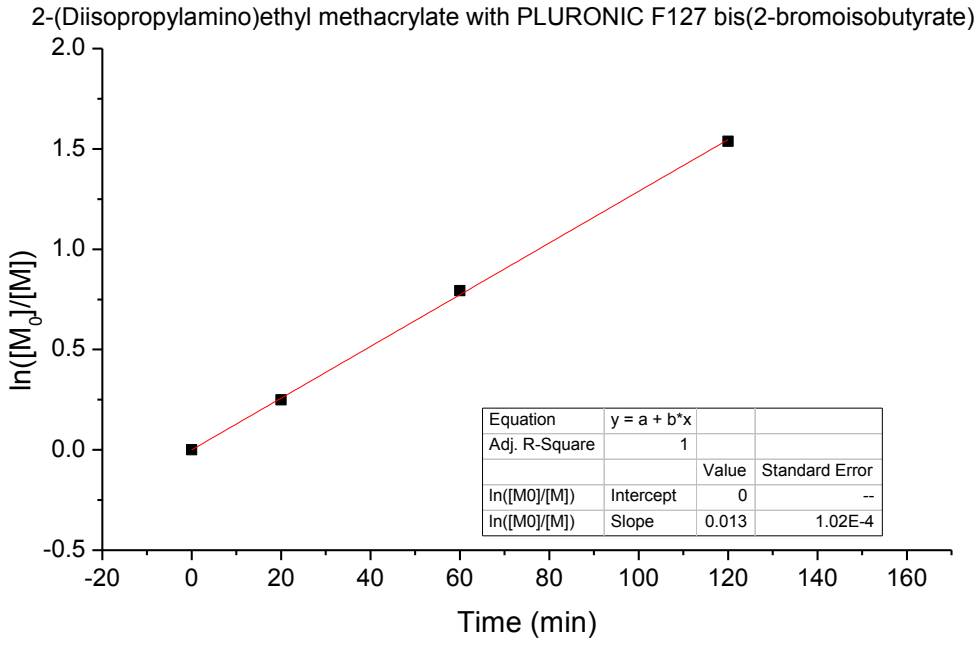


Figure 3-18: Graph that correlates ln([M_0]/[M]) with time during the study of the polymerization of 2-N,N-diisopropylaminoethyl methacrylate using Pluronic F127 bis(2-bromoisobutyrate) as initiator.

3.5 Polymer chain extension with pH-sensitive units

The same procedure was followed to synthesize all the 18 polymers. For each couple of monomer and initiator two products with different degree of polymerization were obtained.

Polymers were synthesized according to procedure reported in cap 3.4 but no samples were withdrawn at the beginning and during the experiment. The schlenk was kept closed with a glass cap and a constant pressure of argon was kept into the shlenk.

The right reaction time was predetermined from the kinetic studies and it depend on the couple of monomer-initiator and on the desired degree of polymerization. At the end of the reaction the schlenk was exposed to air and the catalyst oxidized from the atmospheric oxygen.

Sample was brought at room temperature and extracted with 8x10 mL of water acidic (pH=5 for HCl) solution. During the extraction, the pH of the water solution resulting from the extraction was checked and bring again at pH 5 with HCl solution in water. After extraction the water phases were collected and submitted to dialysis using a membrane that allows the passage of everything with weight lower than 3000gr/mol. The initial solution used for the dialysis was a HCl solution in water at pH 5 containing EDTA 10 mM. After two hours the solution for dialysis was changed with fresh acidic solution. After two hours the solution for dialysis was replaced with a bicarbonate water

solution at pH 8 containing 10mM of EDTA. After two hours the bicarbonate solution was changed and replaced with deionized water. Finally the solution for dialysis was replaced with fresh deionized water every two hours until the conductivity remained constant and equal to the one of the starting deionized water. At the end of the dialysis the water has been removed mediating sublimation to yield a white powder.

^{1}H-NMR (Toluene - d8): **PLUR_bPDMAEMA**: 1.14 (CH_2-CH(C**H_3**)-O of PPG chain), 1.30 (-CH_2C(C**H_3**)- of methacrylic chain), 1.41 (-C**H_2**C(CH_3)- of methacrylic chain), 1.74 (-PEG-O-C(O)C(C**H_3**)$_2$-CH_2-), 2.11 (-N(C**H_3**)$_2$), 2.39 (O-CH_2-C**H_2**-N-), 3.35, 3.46, 3.52(CH_2-C**H**(CH_3)-O and C**H_2**-CH(CH_3)-O in the PPG chain, C**H_2**-C**H_2**-O in the PEG chain), 4.06 (O-C**H_2**-CH_2-N-) ppm. **PLUR_bPDEAEMA**: 1.00 (-N(CH_2-C**H_3**)$_2$), 1.15 (CH_2-CH(C**H_3**)-O of PPG chain), 1.33 (-CH_2C(C**H_3**)- of methacrylic chain), 1.43 (-C**H_2**C(CH3)- of methacrylic chain), 1.74 (-PEG-O-C(O)C(C**H_3**)$_2$-CH_2-), 2.45 (-N(C**H2**-CH_3)$_2$), 2.62 (O-CH_2-C**H_2**-N-), 3.37, 3.46, 3.52 (CH_2-C**H**(CH_3)-O and C**H_2**-CH(CH_3)-O in the PPG chain, C**H_2**-C**H_2**-O in the PEG chain), 4.07 (O-C**H_2**-CH_2-N-) ppm. **PLUR_bPDIAEMA**: 0.99 (-N((CH-(C**H_3**)$_2$)$_2$), 1.16 (CH_2-CH(C**H_3**)-O of PPG chain), 1.36 (-CH_2C(C**H_3**)- of methacrylic chain), 1.46 (-C**H_2**C(CH_3)- of methacrylic chain), 2.71 (-N((C**H**-(CH_3)$_2$)$_2$), 2.91 (O-CH_2-C**H_2**-N-), 3.35, 3.47, 3.52 (CH_2-C**H**(CH_3)-O and C**H_2**-CH(CH_3)-O in the PPG chain, C**H_2**-C**H_2**-O in the PEG chain), 4.04 (O-C**H_2**-CH_2-N-) ppm.

PEG_bPDMAEMA: 1.31 (-CH_2C(C**H_3**)- of methacrylic chain), 1.41 (-C**H_2**C(CH_3)- of methacrylic chain), 1.74 (-PEG-O-C(O)C(C**H_3**)$_2$-CH_2-), 2.12 (-N(C**H_3**)$_2$), 2.40 (O-CH_2-C**H_2**-N-), 3.46, (C**H_2**-C**H_2**-O in the PEG chain), 4.07 (O-C**H_2**-CH_2-N-) ppm. **PEG_bPDEAEMA**: 0.99 (-N(CH_2-C**H_3**)$_2$), 1.32 (-CH_2C(C**H_3**)- of methacrylic chain), 1.42 (-C**H2**C(CH3)- of methacrylic chain), 1.74 (-PEG-O-C(O)C(C**H_3**)$_2$-CH_2-), 2.44 (-N(C**H2**-CH_3)$_2$), 2.61 (O-CH_2-C**H_2**-N-), 3.46 (C**H_2**-C**H_2**-O in the PEG chain), 4.07 (O-C**H_2**-CH_2-N-) ppm. **PEG_bPDIAEMA:** 0.97 (-N((CH-(C**H_3**)$_2$)$_2$), 1.34 (-CH_2C(C**H_3**)- of methacrylic chain), 1.42 (-C**H_2**C(CH_3)- of methacrylic chain), 1.74 (-PEG-O-C(O)C(C**H_3**)$_2$-CH_2-), 2.69 (-N((C**H**-(CH_3)$_2$)$_2$), 2.89 (O-CH_2-C**H_2**-N-), 3.46 (C**H_2**-C**H_2**-O in the PEG chain), 4.02 (O-C**H_2**-CH_2-N-) ppm.

PEG_PDMAEMA: 1.32 (-CH_2C(C**H_3**)- of methacrylic chain), 1.42 (-C**H_2**C(CH_3)- of methacrylic chain), 1.75 (-PEG-O-C(O)C(C**H_3**)$_2$-CH_2-), 2.15 (-N(C**H_3**)$_2$), 2.41 (O-CH_2-C**H_2**-N-), 3.13 (-O-C**H_3**), 3.47, (C**H_2**-C**H_2**-O in the PEG chain), 4.08 (O-C**H_2**-CH_2-N-) ppm. **PEG_PDEAEMA:** 1.32 (-CH_2C(C**H_3**)- of methacrylic chain), 1.42 (-C**H_2**C(CH_3)- of methacrylic chain), 1.75 (-PEG-O-C(O)C(C**H_3**)$_2$-CH_2-), 2.15 (-N(C**H_3**)$_2$), 2.41 (O-

CH_2-C**H$_2$**-N-), 3.13 (-O-C**H$_3$**), 3.47, (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.08 (O-C**H$_2$**-CH_2-N-) ppm. **PEG_PDIAEMA:** 1.32 (-CH_2C(C**H$_3$**)- of methacrylic chain), 1.42 (-C**H$_2$**C(CH_3)- of methacrylic chain), 1.75 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH_2-), 2.15 (-N(C**H$_3$**)$_2$), 2.41 (O-CH_2-C**H$_2$**-N-), 3.13 (-O-C**H$_3$**), 3.47, (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.08 (O-C**H$_2$**-CH_2-N-) ppm.

^{1}H-NMR (CD_3OD): **PLUR_bPDMAEMA**: 0.90 (-CH_2C(C**H$_3$**)- of methacrylic chain) 1.09 (CH_2-CH(C**H$_3$**)-O of PPG chain), 1.85 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH_2-), 1.93 (-C**H$_2$**C(CH_3)- of methacrylic chain), 2.31 (-N(C**H$_3$**)$_2$), 2.75 (O-CH_2-C**H$_2$**-N-), 3.42, 3.47, 3.60 (CH_2-C**H**(CH_3)-O and C**H$_2$**-CH(CH_3)-O in the PPG chain, C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.07 (O-C**H$_2$**-CH_2-N-) ppm.

^{1}H-NMR (D_2O with NaOD and HCl pH, 5.5): **PLUR_bPDMAEMA short**: 1.01 (CH_2-CH(C**H$_3$**)-O of PPG chain), 1.82 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH_2-), 2.85 (O-CH_2-C**H$_2$**-N-), 3.56 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.21 (O-C**H$_2$**-CH_2-N-) ppm. **PLUR_bPDMAEMA long:** 1.01 (CH_2-CH(C**H$_3$**)-O of PPG chain), 2.84 (O-CH_2-C**H$_2$**-N-), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.26 (O-C**H$_2$**-CH_2-N-) ppm. **PLUR_bPDEAEMA short**: 1.02 (CH_2-CH(C**H$_3$**)-O of PPG chain), 1.22 (-N(CH_2-C**H$_3$**)$_2$), 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH_2-), 3.18 (-N(C**H$_2$**-CH_3)$_2$), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.23 (O-C**H$_2$**-CH_2-N-) ppm. **PLUR_bPDEAEMA long**: 1.02 (CH_2-CH(C**H$_3$**)-O of PPG chain), 1.26 (-N(CH_2-C**H$_3$**)$_2$), 1.82 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH_2-), 3.20 (-N(C**H$_2$**-CH_3)$_2$), 3.56 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.26 (O-C**H$_2$**-CH_2-N-) ppm. **PLUR_bPDIAEMA short** : 1.02 (CH_2-CH(C**H$_3$**)-O of PPG chain), 1.26 (-N((CH-(C**H$_3$**)$_2$)$_2$), 1.78 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH_2-), 3.17 (-N((C**H**-(CH_3)$_2$)$_2$), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.22 (O-C**H$_2$**-CH_2-N-) ppm. **PLUR_bPDIAEMA long**: 1.02 (CH_2-CH(C**H$_3$**)-O of PPG chain), 1.28 (-N((CH-(C**H$_3$**)$_2$)$_2$), 3.56 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.24 (O-C**H$_2$**-CH_2-N-) ppm.

PEG_bPDMAEMA short: 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH_2-), 2.85 (-N(C**H$_3$**)$_2$), 3.57, (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.24 (O-C**H$_2$**-CH_2-N-) ppm. **PEG_bPDMAEMA long**: 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH_2-), 2.83 (-N(C**H$_3$**)$_2$), 3.55, (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.25 (O-C**H$_2$**-CH_2-N-) ppm. **PEG_bPDEAEMA short**: 1.23 (-N(CH_2-C**H$_3$**)$_2$), 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH_2-), 3.19 (-N(C**H$_2$**-CH_3)$_2$), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.27 (O-C**H$_2$**-CH_2-N-) ppm. **PEG_bPDEAEMA long**: 1.22 (-N(CH_2-C**H$_3$**)$_2$), 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH_2-), 3.19 (-N(C**H$_2$**-CH_3)$_2$), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.27 (O-C**H$_2$**-CH_2-N-) ppm. **PEG_bPDIAEMA short**: 1.30 (-N((CH-(C**H$_3$**)$_2$)$_2$), 1.73 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH_2-), 2.70 (-N((C**H**-(CH_3)$_2$)$_2$), 3.57 (C**H$_2$**-C**H$_2$**-O in the

PEG chain), 4.27 (O-C**H$_2$**-CH$_2$-N-) ppm. **PEG_bPDIAEMA long:** 1.27 (-N((CH-(C**H$_3$**)$_2$)$_2$), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.23 (O-C**H$_2$**-CH$_2$-N-) ppm.

PEG_PDMAEMA short: 2.85 (-N(C**H$_3$**)$_2$), 3.23 (-O-C**H$_3$** at the end of the macroinitiator chain), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.26 (O-C**H$_2$**-CH$_2$-N-) ppm. **PEG_PDMAEMA long:** 2.84 (-N(C**H$_3$**)$_2$), 3.23 (-O-C**H$_3$** at the end of the macroinitiator chain), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.26 (O-C**H$_2$**-CH$_2$-N-) ppm. **PEG_PDEAEMA short:** 1.24 (-N(CH$_2$-C**H$_3$**)$_2$), 1.76 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH$_2$-), 3.21 (-N(C**H$_2$**-CH$_3$)$_2$), 3.24 (-O-C**H$_3$** at the end of the macroinitiator chain), 3.56 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.29 (O-C**H$_2$**-CH$_2$-N-) ppm. **PEG_PDEAEMA long:** 1.22 (-N(CH$_2$-C**H$_3$**)$_2$), 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH$_2$-), 3.19 (-N(C**H$_2$**-CH$_3$)$_2$), 3.23 (-O-C**H$_3$** at the end of the macroinitiator chain), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.26 (O-C**H$_2$**-CH$_2$-N-) ppm. **PEG_PDIAEMA short:** 1.26 (-N((CH-(C**H$_3$**)$_2$)$_2$), 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH$_2$-), 2.83 (-N((C**H**-(CH$_3$)$_2$)$_2$, 3.23 (-O-C**H$_3$** at the end of the macroinitiator chain), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.22 (O-C**H$_2$**-CH$_2$-N-) ppm. **PEG_PDIAEMA long:** 1.25 (-N((CH-(C**H$_3$**)$_2$)$_2$), 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH$_2$-), 3.23 (-O-C**H$_3$** at the end of the macroinitiator chain), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.22 (O-C**H$_2$**-CH$_2$-N-) ppm.

^{1}H-NMR (D$_2$O with NaOD and HCl, pH 7.5): **PLUR_bPDMAEMA short**: 1.01 (CH$_2$-CH(C**H$_3$**)-O of PPG chain), 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH$_2$-), 2.70 (O-CH$_2$-C**H$_2$**-N-), 3.56 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.21 (O-C**H$_2$**-CH$_2$-N-) ppm. **PLUR_bPDMAEMA long:** 1.02 (CH$_2$-CH(C**H$_3$**)-O of PPG chain), 2.70 (O-CH$_2$-C**H$_2$**-N-), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.18 (O-C**H$_2$**-CH$_2$-N-) ppm. **PLUR_bPDEAEMA short**: 1.02 (CH$_2$-CH(C**H$_3$**)-O of PPG chain), 1.18 (-N(CH$_2$-C**H$_3$**)$_2$), 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH$_2$-), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.22 (O-C**H$_2$**-CH$_2$-N-) ppm. **PLUR_bPDEAEMA long**: 1.02 (CH$_2$-CH(C**H$_3$**)-O of PPG chain), 1.19 (-N(CH$_2$-C**H$_3$**)$_2$), 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH$_2$-), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.24 (O-C**H$_2$**-CH$_2$-N-) ppm. **PLUR_bPDIAEMA short**: 1.02 (CH$_2$-CH(C**H$_3$**)-O of PPG chain), 1.76 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH$_2$-), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain) ppm. **PLUR_bPDIAEMA long**: 3.56 (C**H$_2$**-C**H$_2$**-O in the PEG chain) ppm.

PEG_bPDMAEMA short: 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH$_2$-), 2.85 (-N(C**H$_3$**)$_2$), 3.56 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.24 (O-C**H$_2$**-CH$_2$-N-) ppm. **PEG_bPDMAEMA long**: 2.70 (-N(C**H$_3$**)$_2$), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.18 (O-C**H$_2$**-CH$_2$-N-) ppm. **PEG_bPDEAEMA short**: 1.17 (-N(CH$_2$-C**H$_3$**)$_2$), 1.81 (-PEG-O-C(O)C(C**H$_3$**)$_2$-CH$_2$-), 3.12 (-N(C**H$_2$**-CH$_3$)$_2$), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.22 (O-C**H$_2$**-CH$_2$-N-) ppm.

PEG_bPDEAEMA long: 1.16 (-N(CH_2-C**H$_3$**$)_2$), 1.81 (-PEG-O-C(O)C(C**H$_3$**$)_2$-CH_2-), 3.10 (-N(C**H$_2$**-$CH_3)_2$), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.27 (O-C**H$_2$**-CH_2-N-) ppm. **PEG_bPDIAEMA short**: 1.27 (-N((CH-(C**H$_3$**$)_2)_2$), 1.73 (-PEG-O-C(O)C(C**H$_3$**$)_2$-CH_2-), 3.56 (C**H$_2$**-C**H$_2$**-O in the PEG chain) ppm. **PEG_bPDIAEMA long:** 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain) ppm.

PEG_PDMAEMA short: 2.69 (-N(C**H$_3$**$)_2$), 3.23 (-O-C**H$_3$** at the end of the macroinitiator chain), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.26 (O-C**H$_2$**-CH_2-N-) ppm. **PEG_PDMAEMA long:** 2.84 (-N(C**H$_3$**$)_2$), 3.23 (-O-C**H$_3$** at the end of the macroinitiator chain), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.20 (O-C**H$_2$**-CH_2-N-) ppm. **PEG_PDEAEMA short:** 1.21 (-N(CH_2-C**H$_3$**$)_2$), 1.73 (-PEG-O-C(O)C(C**H$_3$**$)_2$-CH_2-), 3.24 (-O-C**H$_3$** at the end of the macroinitiator chain), 3.56 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.27 (O-C**H$_2$**-CH_2-N-) ppm. **PEG_PDEAEMA long:** 1.16 (-N(CH_2-C**H$_3$**$)_2$), 1.81 (-PEG-O-C(O)C(C**H$_3$**$)_2$-CH_2-), 3.10 (-N(C**H$_2$**-$CH_3)_2$), 3.23 (-O-C**H$_3$** at the end of the macroinitiator chain), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.20 (O-C**H$_2$**-CH_2-N-) ppm. **PEG_PDIAEMA short:** 1.81 (-PEG-O-C(O)C(C**H$_3$**$)_2$-CH_2-), 3.23 (-O-C**H$_3$** at the end of the macroinitiator chain), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.23 (O-C**H$_2$**-CH_2-N-) ppm. **PEG_PDIAEMA long:** 1.25 (-N((CH-(C**H$_3$**$)_2)_2$), 1.81 (-PEG-O-C(O)C(C**H$_3$**$)_2$-CH_2-), 3.23 (-O-C**H$_3$** at the end of the macroinitiator chain), 3.55 (C**H$_2$**-C**H$_2$**-O in the PEG chain), 4.23 (O-C**H$_2$**-CH_2-N-) ppm.

4 Results and discussion

4.1 Macroinitiators

The characterization data of the three macroinitiators synthesized in this work are reported in table 4-1. In all cases ^{1}H-NMR showed a substantially quantitative conversion of the OH groups; a corresponding increase in the polymer molecular weight was noticed both from ^{1}H NMR and MALDI-ToF, and a decrease in PEG melting temperature.

Comparing the $\overline{M_n}$ of PEG_Br and PEG_OH obtained by Maldi-TOF analysis it was expected that, after the esterification, PEG_Br weights 144 g/mol more than PEG_OH. MALDI_ToF analysis shows a 141 g/mol higher molecular weight for PEG_Br compared to its precursor. The difference between the experimental result and the theoretical value is mainly due to the fact that polymer chains with different chain length have different volatility and this leads to the fact that the composition of the vapor in the instrument during the analysis is not the same as the composition of the compound in the solid state. If the hydroxyl groups conversion was not over 95% in the MALDI spectrum of PEG_Br two different peaks distribution should be seen, showing the peaks of the product and the peaks of the starting material with a difference in the molecular weight of 144 g/mol. In the MALDI spectrum of PEG_Br, under 4700 g/mol the peaks are slightly broader. This is maybe due to a little part of un-converted material but the amount of this latter is negligible respect the amount of 100% converted material. Analogous results have been obtained with PEG_bBr and PEG_bOH.

The MALDI spectra of PLUR_bBr and PLUR_bOH do not show separate peaks as PEG polymers, and also the intensity of the signal is not zero for molecular weight lower than 12,000 g/mol. Even if the spectra are not as good as the spectra obtained for the other samples, it can be seen that after the functionalization the molecular weight increases from 13322 g/mol to 13797 g/mol.

Table 4-1: Characterization data of three macroinitiators.

	$\overline{M_n}$ (g/mol)		OH conv. (%mol)	T_m (°C)	Water content (%wt.)
	^{1}H NMR	MALDI			
PEG_OH → PEG_Br	5141 / 5287 [a]	5292 / 5434	98 [b] (4.25ppm-2.97, 3.58ppm- 711) [c]	62/61 [d]	1.2/2.4 [e]
PEG_bOH → PEG_bBr	8756 / 9054 [a]	8878 / 9194	95 [b] (4.25ppm-3.36, 3.57ppm- 700) [c]	65/62 [d]	1.0/1.2 [e]
PLUR_bOH → PLUR_bBr	15956 (0.71 PEG weight fraction) / 16254 [a]	13322 / 13797 [f]	100 [b] (4.25ppm-1.9, 3.58ppm- 500) [c]	58/52 [d]	1.5/1.5 [g]

[a] Calculated from the comparison of the EG CH_2 signal (PEG chain) at 3.64 ppm and that at 3.72 ppm, which is assigned to the terminal CH_2OH groups. The latter is heavily overlapped with the main CH_2 peak and was corrected by the use of a baseline, but it is likely much affected by errors.

[b] Calculated from the comparison of the CH_2-O-CO signal at 4.25ppm and the value that this signal should have if the conversion was 100%. The same result is obtained using the peak at 1.87 ppm that is assigned to the CH_3 groups of isobutyrate.

[c] Chemical shift (ppm) and integral values of the peaks used to determine the conversion.

[d] Determined by DSC.

[e] Calculated from the comparison of the signals at 2.42 and 2.74 ppm (broad signal attributed to water) and the OCH_3 signal at 3.37 ppm.

[f] The spectra are very poorly defined (see cap.6, Figure 6-6) and these figures reflect the signal value rather than the $\overline{M_n}$.

[g] Calculated from the comparison of the signal at 2.05-2.2 (broad signal attributed to water) and the EG CH_2 signal at 3.65 ppm.

The Differential Scanning Calorimetry thermograph shown in figure 4-1 suggests that the introduction of the isobutyryl group at one side of the chain leads to the lowering in the melting temperature of the polymer. This result is in agreement with what it was expected because the isobutyryl group is bigger respect the hydroxyl group and decreases the degree of order in the crystal. The glass transition temperature cannot be seen because the increase in the specific heat of the solid is too low.

Introducing two isobutyrate groups at both ends of the polymeric chains of PEG_bOH and PLUR_bOH leads to the decrease of the melting temperature. In this cases, the effect is bigger compared to the effect seen for PEG_Br and PEG_OH because both the two end-groups have been substituted with two more hindered groups.

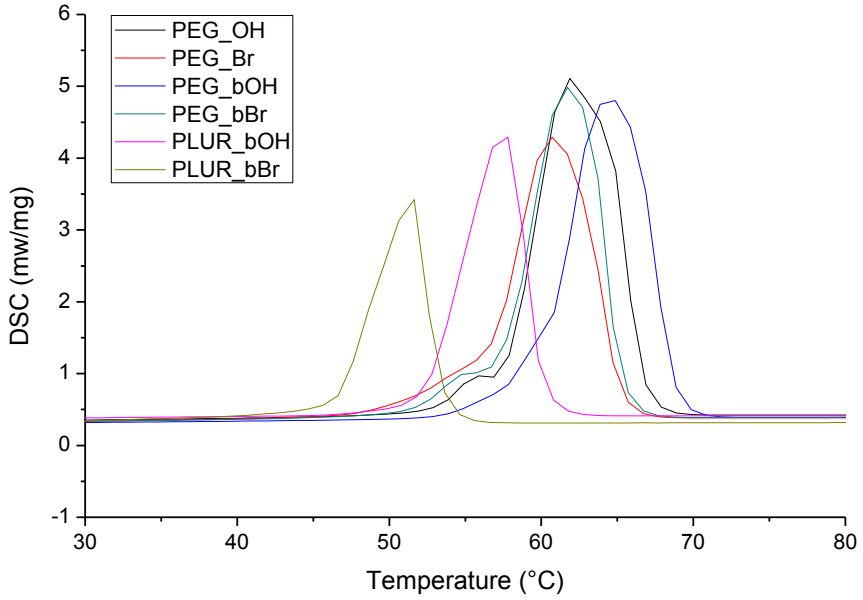


Figure 4-1: DSC of the polymers obtained after esterification compared with DSC of the starting materials.

4.2 kinetic studies

The same procedure was followed for all the kinetic studies. The quantities of initiator (bromide groups), monomer, catalyst, ligand and solvent were chosen in order to keep the monomer concentration and the initiator/monomer ratio constant in all experiments. Keeping constant, in all the experiments, the concentration of initiator groups it is possible to compare the different rate of polymerization just by comparing the slopes of the different graphs that correlate $\ln([M_0]/[M])$ with the time, where $[M_0]/[M]$ is the ratio between the initial concentration of monomer and the concentration of monomer after a certain time.

The monomer concentration in each sample at the time ''t'' was calculated by ^{1}H-NMR analysis using the ratio between the integral of the two signals around 6 and 5.5 ppm assigned to C**H$_2$**=C- in the monomers and the signal of PEG chain of the initiator (at 3.46 ppm) (Figure 4-2).

As an example, in Figure 4-2 are reported all the ^{1}H-NMR spectra of the samples withdrawn at different time during the polymerization kinetic study of 2-N,N-dimethylaminoethyl methacrylate (DMAEMA) using Pluronic F127 bis(2-bromoisobutyrate) (PLUR_bBr) as macroinitiator. It can be seen that the intensity of the two peaks at 6.02 and 5.43 ppm, that are related to the monomer, decreases with the time whilst the intensity of the other peaks, related to the product, as the ones at 3.97, 1.00 and 0.85 ppm, increases with time.

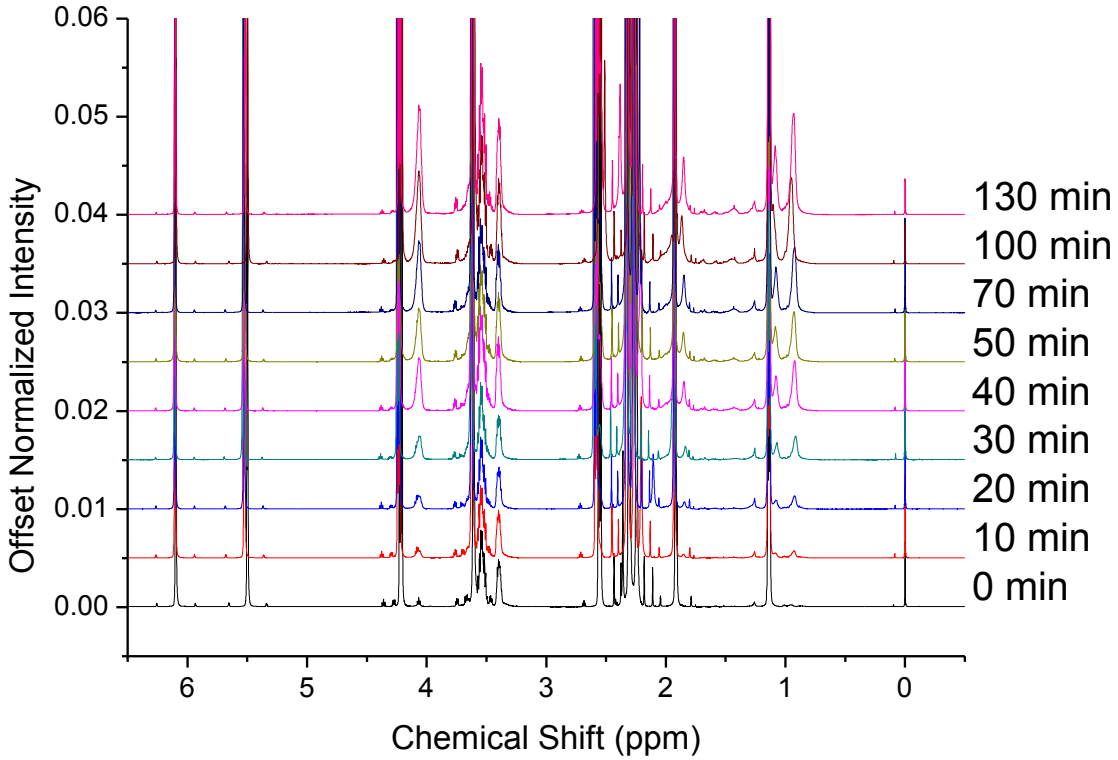


Figure 4-2: ^{1}H-NMR of the samples withdrawn to study the ATRP kinetic using Pluronic F127 bis(2-bromoisobutyrate) as initiator and 2-N,N-dimethylaminoethyl methacrylate as monomer.

Plotting ln([M_0]/[M]) versus the time, the graph shown in Figure 4-3 is obtained.

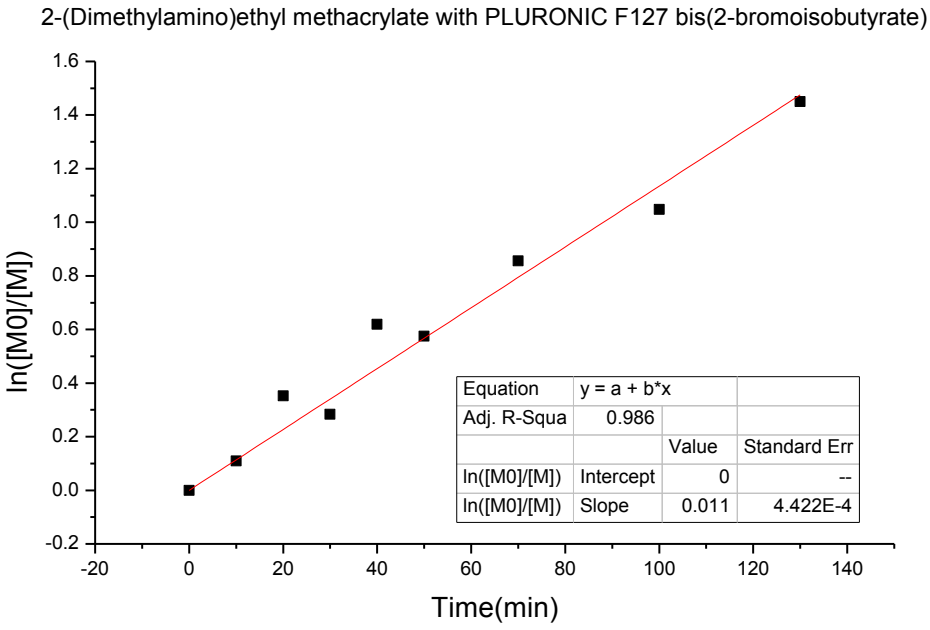


Figure 4-3: Graph that correlates ln([M_0]/[M]) with time during the study of the polymerization of 2-N,N-dimethylaminoethyl methacrylate using Pluronic F127 bis(2-bromoisobutyrate) as initiator.

Graph shown in Figure 4-3 shows the correlation between ln([M_0]/[M]) and the time using PLUR_bBr as initiator and DMAEMA as monomer. Even if the points are not

strictly on the same line it can be seen that the correlation between ln([M_0]/[M]) and the time is almost linear with a slope of 0.011 min^{-1}. It can also be seen that the slope of the fitting line remains constant for the entire range in which the kinetic study was carried out, showing that the catalyst did not oxidize during the experiment, leading to a good linear correlation between ln([M_0]/[M]) and the time.

All the experimental kinetics data obtained are reported in experimental section (cap. 3.4.1 - 3.4.9).

During a living radical polymerization ln([M_0]/[M]) should increase linearly with time and in the case of ATRP the rate of polymerization is directly proportional to the concentration of monomer by the concentration of growing radicals (see eq.4 pag. 7).

k_p is constant with the temperature which was kept constant during the experiment and [$P^{\cdot}$] should be kept constant with the equilibrium that is established between the growing radicals and the catalyst (scheme 3 pag.9).

Figure 4-4 shows the comparison of the different kinetic constant by the concentration of growing specie in function of the types of monomers and initiators used for the polymerization.

As already said, the concentration of growing specie was kept constant in all the experiment and this permits to compare the different k_p by comparing the values of k_p*[$P^{\cdot}$]. The black dots in Figure 4-4 are the values of k_p*[$P^{\cdot}$] for the polymerization in which PEG_Br was used as initiator. The red dots are the values of k_p*[$P^{\cdot}$] for the polymerization in which PEG_bBr was used as initiator, and the green ones are the dots that represent the values of k_p*[$P^{\cdot}$] for the polymerization in which PLUR_bBr was used as initiator. A general trend can be seen.

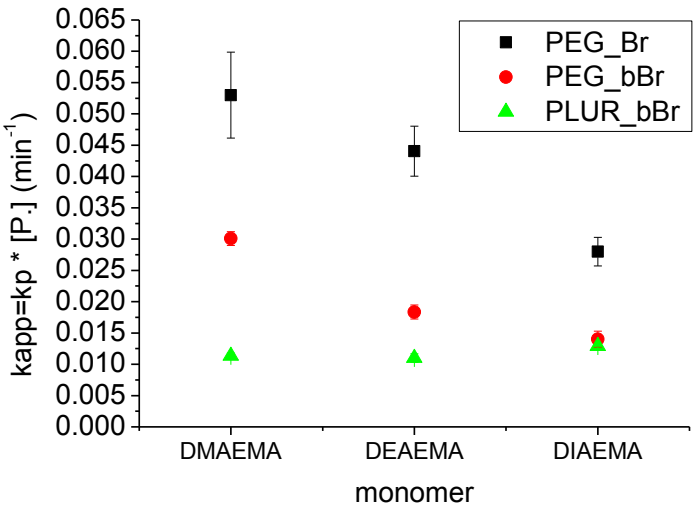


Figure 4-4: Comparison of the kinetic constant by the concentration of growing specie for each couple of monomer-initiator

For PEG_Br and PEG_bBr, the rate of polymerization decreases, changing the monomer polymerized, in the following order: DMAEMA>DEAEMA>DIAEMA. This trend follows exactly the order of steric hindrance in the monomer: the more the monomer is sterically hindered the slower the kinetic reaction is. The steric hindrance on the nitrogen atom of the monomer can have two effect:

- Lowering the steric hindrance the monomer can react faster with the growing specie.
- Less hindered monomers can form complex with copper(I) and increase the catalyst concentration in solution. This can increase the polymerization rate only if the complex between the monomer and the catalyst is not so strong to prevent the reaction between the monomer and the growing radicals.

For each monomer it can be seen that the rate of polymerization decreases increasing the molecular weight of the initiator. The fastest reactions are the ones with PEG_Br which has a molecular weight of about 5000 g/mol. The slowest kinetic reactions are the ones with PLUR_bBr which has a molecular weight of about 12500 g/mol. This trend was expected because increasing the molecular weight the reactive end groups are less available to react with the monomer and this leads to slower kinetic reactions.

For kinetic studies made with PLUR_bBr the same trend seen for PEG_BBR and PEG_Br cannot be seen. For polymerization in which PLUR_bBr was used as initiator, changing the monomer the rate of polymerization did not change so much. This is maybe due to the fact that when the molecular weight of the initiator is high, the rate of

polymerization is mainly determined from the difficulty of the reactive end groups to react with the monomer and not from the reactivity of the monomer.

These values were used to calculate the time needed to obtain polymers with pre-determined chain length.

4.3 Compounds with pH-sensitive units

Polymers were synthesized according to procedure reported in cap 3.4 but no samples were withdrawn at the beginning and during the experiment. The schlenk was kept closed with a glass cap and a constant pressure of argon was kept into the shlenk.

The right reaction time was predetermined using the values of k_{app} obtained from the kinetic studies and it depend on the couple of monomer-initiator and on the desired degree of polymerization. For each couple of monomer and initiator two products were synthesized: one with DP close to 10 that has *short* methacrylic chains and one with DP close to 70 that has *long* methacrylic chains. In this way it is possible to investigate the influence of the methacrylic chain length on the properties of the resulting materials. The degree of polymerization is referred to the initiators groups.

At the end of the reaction the schlenk was exposed to air and the catalyst oxidized from the atmospheric oxygen. Sample was brought at room temperature and extracted with 8x10 mL of water acidic (pH=5 for HCl) solution. During the extraction, the pH of the water solution resulting from the extraction was checked and bring again at pH 5 with HCl solution in water. After extraction the water phases were collected and submitted to dialysis using a membrane that allows the passage of everything with weight lower than 3000gr/mol. The initial solution used for the dialysis was a HCl solution in water at pH 5 containing EDTA 10 mM. After two hours the solution for dialysis was changed with fresh acidic solution. After two hours the solution for dialysis was replaced with a bicarbonate water solution at pH 8 containing 10mM of EDTA. After two hours the bicarbonate solution was changed and replaced with deionized water. Finally the solution for dialysis was replaced with fresh deionized water every two hours until the conductivity remained constant and equal to the one of the starting deionized water. At the end of the dialysis the water has been removed mediating sublimation to yield a white powder.

The principal characteristic data of synthesized copolymers are reported in Table 4-2.

Table 4-2: $\overline{Mn}$ determined with ^{1}H-NMR and GPC and polydispersity determined with GPC.

Compound	DP	Degree of hydrolysis (%)	$\overline{Mn}$ (g/mol)		PD [a]
			^{1}H-NMR	GPC	
PLUR_bBr			16254	16600	1.30
PLUR_bPDMAEMA short	13.2 [b]	65 [c]	17634 [d]	15900	1.45
PLUR_bPDMAEMA long	46.4 [e]	[f]	28062 [d]	25500	1.47
PLUR_bPDEAEMA short	15.3 [b]	57 [c]	19127 [d]	19250	1.87
PLUR_bPDEAEMA long	39.5 [b]	55 [c]	28230 [d]	18750	1.41
PLUR_bPDIAEMA short	21.6 [e]	[f]	22690 [d]	16650	1.34
PLUR_bPDIAEMA long	80.8 [e]	[f]	47912 [d]	19200	1.41
PEG_bBr			9054	14950	1.14
PEG_bPDMAEMA short	8.6 [b]	54 [c]	12035 [d]	15750	1.18
PEG_bPDMAEMA long	51.4 [b]	69 [c]	25480 [d]	19200	1.28
PEG_bPDEAEMA short	13.3 [b]	46 [c]	14251 [d]	16300	1.20
PEG_bPDEAEMA long	34.3 [b]	47 [c]	22040 [d]	17750	1.30
PEG_bPDIAEMA short	11.6 [b]	59 [c]	14260 [d]	15100	1.18
PEG_bPDIAEMA long	74.0 [b]	62 [c]	40757 [d]	17800	1.36
PEG_Br			5287	9450	1.09
PEG_PDMAEMA short	18.7 [b]	85 [c]	8301 [d]	10000	1.14
PEG_PDMAEMA long	145.6[b]	86 [c]	28252 [d]	13450	2.02
PEG_PDEAEMA short	1.9 [b]	10 [c]	5709 [d]	9800	1.12
PEG_PDEAEMA long	25.0 [b]	48 [c]	9994 [d]	11450	1.24
PEG_PDIAEMA short	2.0 [b]	25 [c]	5802 [d]	9650	1.16
PEG_PDIAEMA long	95.8 [b]	77 [c]	25797 [d]	12400	1.24

[a] Determined with GPC

[b] Calculated comparing the integral of the signal at 1.74 ppm(methyl groups in the isobutyrate) to the integral of the signal at 4.06 ppm (signal attributed to the CH_2 in the monomer).

[c] Calculated comparing the integral of the signal at 1.74 ppm (methyl groups in the isobutyrate) to the integral that this peak should have if hydrolysis did not occur.

[d] Calculated using the $\overline{M_n}$of the starting material calculated with MALDI and the degree of polymerization (DP) calculated with NMR.

[e] Calculated comparing the integral of the signal at 1.09 ppm (methyl groups in PPG chain) to the integral of the signal at 4.07 ppm (signal attributed to the CH_2 in the monomer).

[f] It cannot be calculated because the peak at 1.74 is too low and partially overlapped with other peaks.

During the purification, the compounds underwent acidic hydrolysis and part of the solids obtained after the purification were the hydrolysis products and not the desired compounds. The molecular weight and the degree of poly Determined with GPCmerization of the synthesized compounds, determined with ^{1}H-NMR, are not always as expected, especially when an high degree of polymerization was desired. The membrane used for the dialysis during the purification of the synthesized compounds (see pag.67) had a molecular weight cut-off of 3000 g/mol. This means that if hydrolysis occurred during the dialysis, methacrylate chains and initiator chains with molecular weight higher than 3000 g/mol were retained into the membrane and they were not separated from the desired compounds. On the other hand, methacrylate chains with a molecular weight lower than 3000 g/mol (corresponding to DP<13) resulting from the degradation of the desired product passed throw the membrane, leaving an higher initiator/methacrylate chain molar ratio in the membrane and in the resulting solid. Thus the solids analyzed with NMR and GPC were constituted by the desired compounds, initiator and methacrylate chains resulting from the degradation.

With ^{1}H-NMR it is not possible to distinguish signals of methacrylate chains that are still bonded to the initiator from signals of methacrylate chains that underwent hydrolysis. This impossibility to distinguish the signals does not permit to establish:

- How long is the methacrylate chain still bonded to the initiator
- How much is the quantity of methacrylate chains separated from the initiator.

As a consequence, the molecular weight calculated with the NMR is not the average molecular weight of the compound made with the methacrylate chains bonded to the initiator.

Also the molecular weight calculated with GPC is not the average molecular weight of the compound made with the methacrylate chains bonded to the initiator but it takes into account also the molecular weight of initiator and methacrylate chains that have a lower molecular weight compared with the molecular weight of the desired compound.

Maybe a better purification would have been the precipitation into a non-solvent for the polymer. Unfortunately the solubility changes a lot changing the degree of polymerization and the type of polymer, and there is not a common solvent in which all the synthesized polymers were insoluble. Another possible way to follow for the purification was the evaporation of the liquid from the solution containing the polymers. Unfortunately the low volatility of the monomers forces to increase the temperature to eliminate them completely and, without inhibitor, the self-polymerization of the

methacrylate monomers could occur. If the self-polymerization of the methacrylate monomers occurred the resulting products would have uncontrolled molecular weights and polydispersities. These are the reasons why we chose the extraction with water acidic solution to purify the polymers.

Furthermore, ATRP is a technique that permits to obtain polymers with pre-determined molecular weight and polydispersity but, especially using macromolecules as initiator, these goals are not so easy to reach. During an ATRP the equilibrium between dormant and growing specie is very important. This equilibrium is based on the equilibrium between copper(I) and copper(II). The amount of catalyst used in the synthesis was so low that even if a very low amount of copper(I) was oxidized from oxigen during the reaction, the equilibrium between dormant and growing radical was shifted towards the dormant specie, lowering the reaction. Also, during the polymerization the viscosity of the solution increases, lowering the diffusion coefficient of the molecules during the reaction. The lower mobility of the molecules can lower the rate of polymerization even if oxidation did not occur. Furthermore, when the molecular weight of the growing radical increases the reactive end-groups are less available to react with the monomer and this can affect the rate of polymerization.

One more thing that slows the polymerization rate down is the self-polymerization of the monomer that can happen at 60°C. Once the self-polymerization of the monomer occurs, the ATRP is not the only reaction that slows down the concentration of monomer and $\ln([M_0]/[M])$ does not increases linearly with the time.

4.3.1 GPC analysis

All the samples were submitted to GPC analysis using DMF as solvent.

Unfortunately none of the polymeric solids was completely soluble neither in DCM nor in DMF, the only two solvents available for GPC. We chose DMF because it gave relatively better results than DCM.

The samples were prepared dissolving the solid in DMF containing 0.05% of BHT as standard. The amount of solvent added to the solid was equal to the quantity needed to obtain a concentration of 2 g/l. The fact that the solids did not dissolve completely leaded to solution with an unknown concentration, lower than 2 g/l. The samples were left four hours at 60°C in order to have the maximum concentration possible in the analyzed solutions.

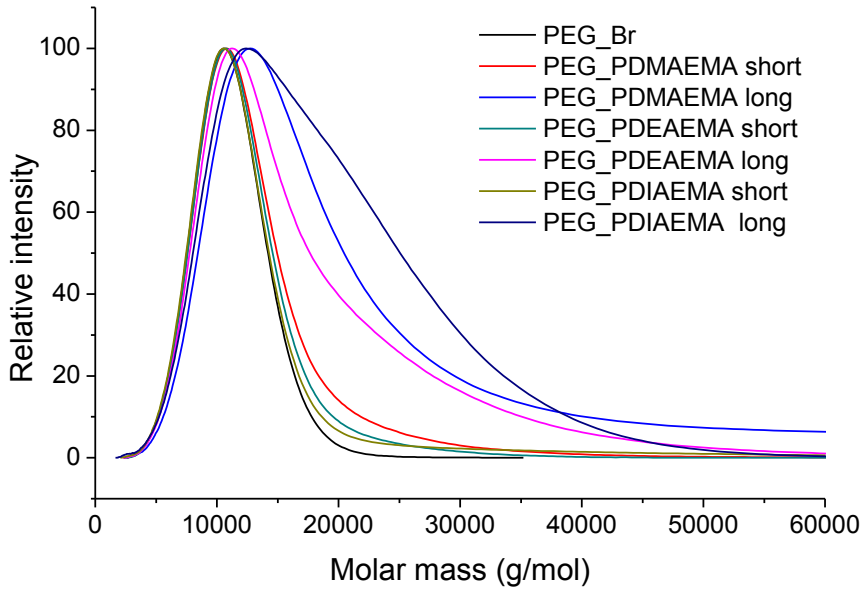


Figure 4-5:GPC traces, of samples PEG_PDMAEMA short and long, PEG_PDEAEMA short and long and PEG_PDIAEMA short and long compared with the molecular weight distribution of PEG methylether (2-bromoisobutyrate)

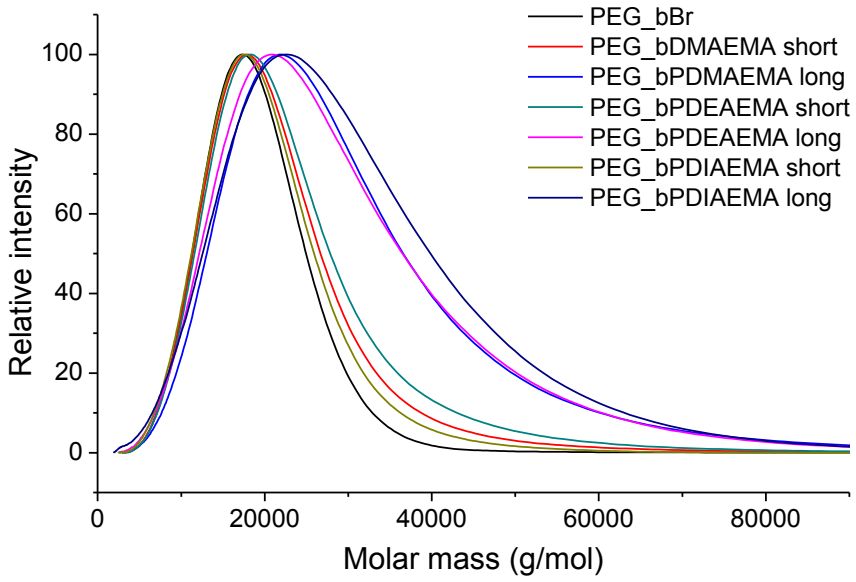


Figure 4-6: GPC traces, of samples PEG_bPDMAEMA short and long, PEG_bPDEAEMA short and long and PEG_bPDIAEMA short and long compared with the molecular weight distribution of PEG bis(2-bromoisobutyrate)

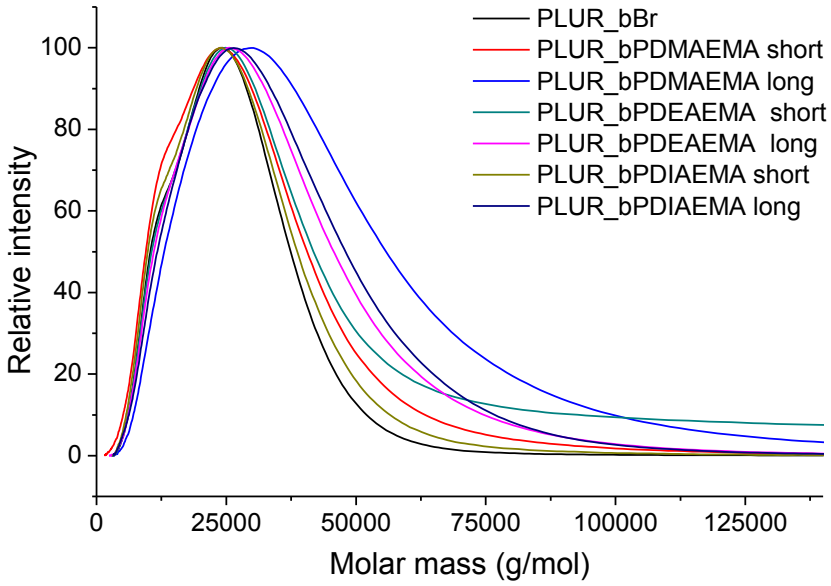


Figure 4-7: GPC traces, of samples PLUR_bPDMAEMA short and long, PLUR_bPDEAEMA short and long and PLUR_bPDIAEMA short and long compared with the molecular weight distribution of Pluronic F127 bis(2-bromoisobutyrate)

In Figures 4-5, 4-6, 4-7 are reported the GPC traces of the synthesized compounds, compared with the GPC chromatogram of the starting materials. It can be seen that the synthesized compounds have an higher molecular weight and an higher polydispersity compared with the starting material. Unfortunately, the products of hydrolysis present in the sample and the low solubility of the solids in DMF do not permit to know the exact molecular weight of the compounds that did not undergo hydrolysis.

Comparing the molecular weight of PLUR_bBr, that is completely soluble in DMF, with the molecular weight determined by GPC of sample PLUR_bDMAEMA short, this latter has a lower molecular weight. This might be due to the fact that sample PLUR_bDMAEMA short was in a lower concentration compared to Pluronic F127 bis(2-bromoisobutyrate) and the two measurement cannot be compared. The $\overline{M_n}$ of sample PLUR_bDMAEMA short might be also lowered from the presence in the sample of the products of hydrolysis that have a lower molecular weight.

With GPC it is not possible to separate compounds that underwent hydrolysis and compounds that did not undergo hydrolysis, especially if their molecular weight is similar. In this way, in the molecular weight determined by GPC, the signals from the hydrolysis products are also taken into account, decreasing the values of $\overline{M_n}$ and increasing the polydispersity.

Even if the measurements have been affected from the already said errors, watching the data shown in Table 4-2 it can be seen that, for almost all the samples, the molecular

weight of the samples with the higher degree of polymerization are higher compared to the molecular weight of the corresponding samples with lower degree of polymerization.
The discordance between the expected $\overline{M_n}$, the $\overline{M_n}$determined with ^{1}H-NMR and the $\overline{M_n}$ determined with GPC could also be due to the fact that GPC analysis is based on the volume occupied from the molecules in the solvent during the elution. The molecular weight of the molecule is determined comparing the retention times of the molecules with the retention times of standard samples containing styrene of known molecular weight. The synthesized polymers have a structure designed in order to make the polymers able to self-aggregate. The aggregation of the synthesized compounds may lead to an underestimation of their $\overline{M_n}$ because of the lower volume occupied from polymeric aggregates compared to styrene. Furthermore, in the synthesized polymers with *long* methacrylic chains, the aggregation increases because of the enhanced interactions that occur between the methacrylic chains.
Even if the concentration of the samples was lower than it should be, the results by GPC could be useful to calculate the polydispersity. It can be seen that for almost all the samples the polydispersity is lower than 1.4-1.5, as it should be for a radical living polymerization. Also there are no samples with a polydispersity lower or equal to the starting material, which is in agreement with the expectation because with ATRP reaction the initial polymeric chains have been extended. Sample PEG_PDMAEMA long is the one with the highest polydispersity and this is maybe due to the fact that the degree of polymerization is high but also the degree of hydrolysis is high, leading to a very broad peak and an high polydispersity.

4.3.2 ^{1}H-NMR analysis in different solvents and pH

4.3.2.1 Compounds containing Pluronic

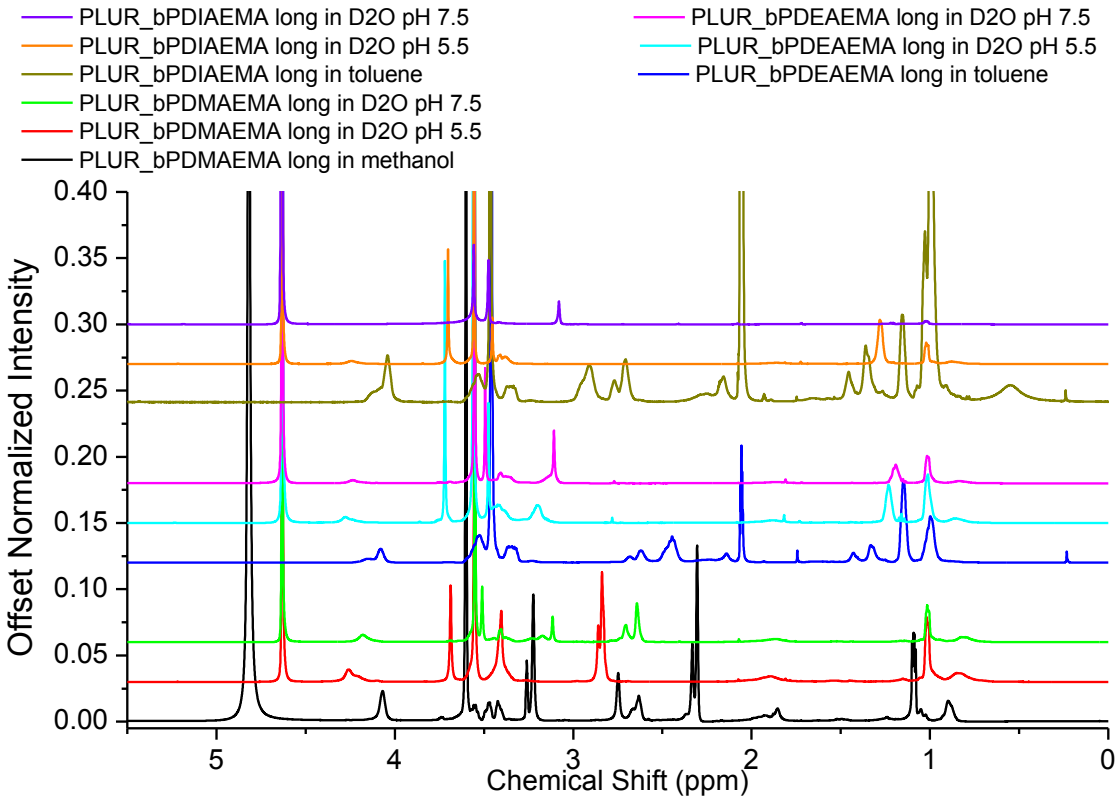


Figure 4-8: ^{1}H-NMR of samples PLUR_bPDMAEMA long, PLUR_bPDEAEMA long and PLUR_bPDIAEMA long in deuterated toluene and in D_2O at pH 5.5 and 7.5.

In Figure 4-8 the ^{1}H-NMR spectra of samples PLUR_bPDMAEMA long, PLUR_bPDEAEMA long and PLUR_bPDIAEMA long in toluene and in D_2O at pH 5.5 and 7.5 are shown.

In toluene PLUR_bPDIAEMA long does not form micelles and the peaks that can be seen are the peaks of the five block copolymer with the following structure: PDIAEMA-PEG-PPG-PEG-PDIAEMA. When the solid is dissolved in water it forms micelles and the structure of the micelles depends on the pH of the solution. In ^{1}H-NMR spectrum at pH 5.5 the signal of CH_3 in the isopropryl in the pH-sensitive repeating units can be seen at 1.02 ppm. These two latter peaks have a lower relative intensity compared to the same signal in the ^{1}H-NMR spectra registered in toluene and they completely disappear in the spectrum made in D_2O at pH 7.5.

The same trend shown from samples of PLUR_bPDIAEMA long can be seen for samples from PLUR_bPDEAEMA long: the relative intensity of the characteristic peaks in the methacrylate chains decreases passing from the sample solubilized in toluene to the sample solubilized in D_2O at pH 5.5 and 7.5. The difference between the spectra of

samples PLUR_bPDIAEMA long and PLUR_bPDEAEMA long is that at pH 7.5 the signals of the methacrylate chains do not disappear in the spectrum of PLUR_bPDEAEMA long as it is in the spectrum of PLUR_bPDIAEMA long.

The same can also be seen for samples from PLUR_bPDMAEMA long. In this latter case, the spectra recorded in D_2O at pH 7.5 still shows some peaks of the methacrylate chains (at 4.18, 3.12, 2.64 ppm), confirming that hydrophilicity of the methacrylate chains increases in the following order: PDIAEMA<PDEAEMA<PDMAEMA.

The same trend seen in these three samples, that are the ones with the highest degree of polymerization in which PLUR_bBr was used as initiator, can also be seen for the other samples with a lower degree of polymerization.

The fact that decreasing the hydrophobicity of the methacrylate chains their signals disappear suggests that the structure of the micelles changes with the pH in the way shown in the following figure:

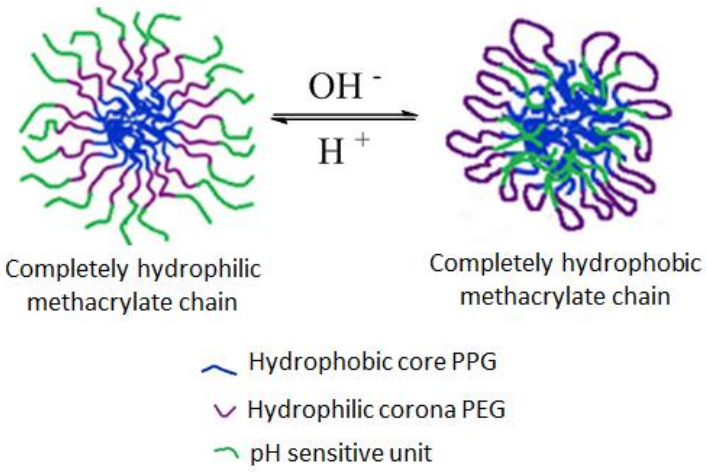


Figure 4-9: Schematic representation of the behavior of synthesizd Pluronic based block copolymers in water solution

When the methacrylate chains are highly protonated, at acidic pH, they are hydrophilic and the micelles are formed from a core of PPG and a corona of PEG and methacrylate chains. In this way the peaks of the methacrylate are visible in the ^{1}H-NMR. Increasing the pH the hydrophilicity of the methacrylate chain decreases and when they are completely hydrophobic the micelles are formed from a core of PPG and methacrylate chain and an external corona of PEG. In this latter case the peaks of the methacrylate are not visible in the ^{1}H-NMR.

As already said, the studied polymer chains are made from five blocks and, when the methacrylate chains are hydrophobic, hydrophobic parts alternate with hydrophilic parts

along the chain. To permit to the PEG part to interact with water and simultaneously permit to the methacrylate chain to interact with the PPG core, the polymer chains have to fold back on themselves. The micelle's structure obtained in this way is more compact compared to the structure of micelles made only from Pluronic F127.

Between the two extreme structures shown in Figure 4-9 there are several intermediate states. Passing from an acidic pH to a basic pH the hydrophilicity of the methacrylate chains gradually decreases and it might happen that some part of the methacrylate chains try to interact with the PPG even if the chain is not completely hydrophobic.

Also comparing ^{1}H-NMR of samples PLUR_bDIAEMA long, PLUR_bDEAEMA long and PLUR_bDMAEMA long in toluene and in D_2O at different pH it can be seen that at pH 7.5 PDIAEMA chains are completely hydrophobic and they are completely into the PPG core. On the other hand PDEAEMA and PDMAEMA are not completely hydrophobic at pH 7.5 and an higher pH should be reached to make them completely hydrophobic.

4.3.2.2 Compounds containing PEG

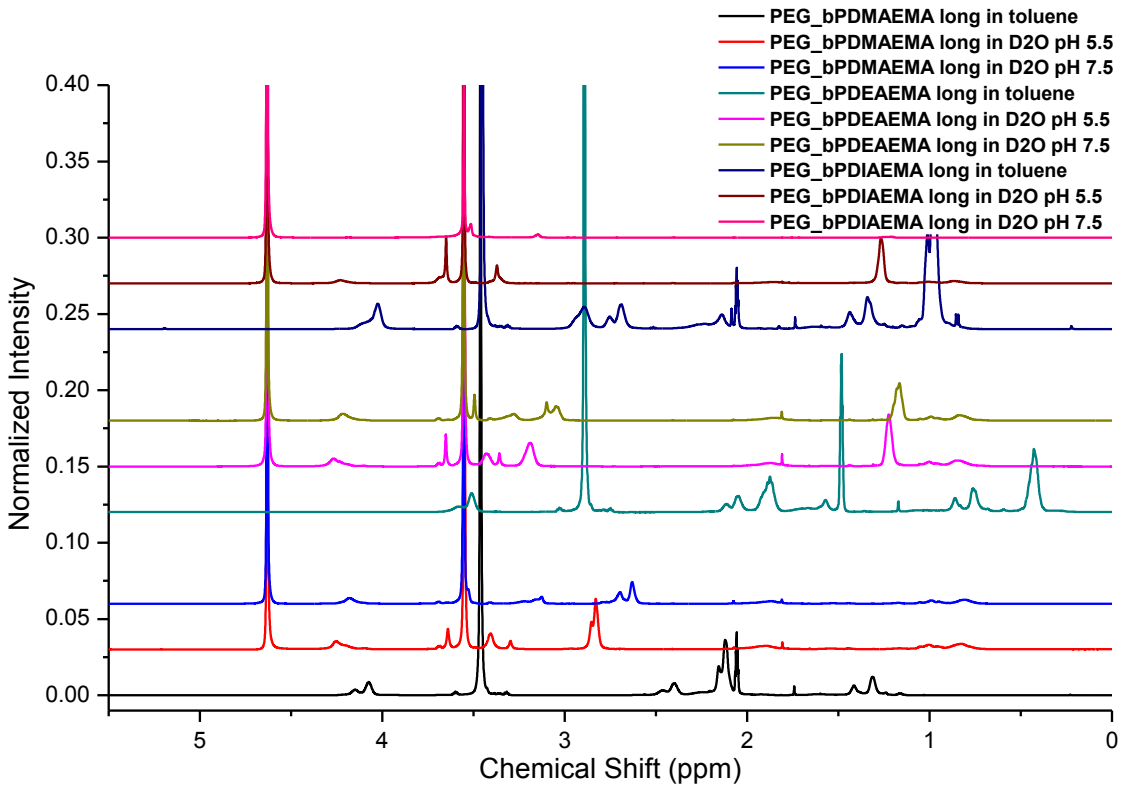


Figure 4-10: ^{1}H-NMR of samples PEG_bPDMAEMA long, PEG_bPDEAEMA long and PEG_bPDIAEMA long in deuterated toluene and in D_2O at pH 5.5 and 7.5.

In Figure 4-10 the ^{1}H-NMR of samples PEG_bPDMAEMA long, PEG_bPDEAEMA long and PEG_bPDIAEMA long in toluene and in D_2O at pH 5.5 and 7.5 are shown. It

can be seen that in each sample, dissolving the solid in D_2O at pH 5.5 the intensity of the peaks of the methacrylate chain have a lower relative intensity compared with the peaks of the methacrylate chain when the solid is dissolved in toluene - d8. The intensity of the peaks of the methacrylate chains decreases again when the sample is dissolved in D_2O at pH 7.5. The three samples were synthesized using PEG_bBr as initiator and they differ for the methacrylate chain. These three samples are analogous to samples PEG_bPDMAEMA short, PEG_bPDEAEMA short and PEG_bPDIAEMA short but they have an higher degree of polymerization. For sample PEG_bPDIAEMA long in D_2O at pH 7.5 the peaks of the methacrylate chains completely disappear, leaving in the spectrum only the peaks of the PEG chain at 3.55 ppm. For samples PEG_bPDEAEMA long and PEG_bPDMAEMA long the relative intensity of the peaks of the methacrylate chains decreases passing from pH 5.5 to pH 7.5 but they do not disappear, confirming that the hydrophilicity of the methacrylate chains follows the following trend: PDIAEMA< PDEAEMA< PDMAEMA.

Samples PEG_bPDMAEMA short, PEG_bPDEAEMA short and PEG_bPDIAEMA short follow the same trend shown for samples PEG_bPDMAEMA long, PEG_bPDEAEMA long and PEG_bPDIAEMA long but the methacrylate chain peaks intensity is lower due to the lower degree of polymerization.

The results of ^{1}H-NMR in toluene and in D_2O at different pH show that when polymers are dissolved in water and the methacrylate chains are completely hydrophilic (at acidic pH), the polymer chains are solubilized and no micelles are formed. On the other hand, when methacrylate chains are completely hydrophobic the polymers chains arrange in micelles (Figure 4-11) and in the ^{1}H-NMR the signals of the methacrylate chains disappear. Between these two extreme behaviors, when the methacrylate chains are partially protonated, it might happen that the hydrophobic part of the methacrylate chains tries to form micelles to avoid contact with water molecules but part of the methacrylate chain (the more hydrophilic) interacts in water.

The fact that these macromolecules are lock copolymers with the block in the middle made of PEG forces the PEG chains to fold back on themselves when the methacrylate chains are hydrophobic. In this way the micelles are made from an hydrophobic core and a compact hydrophilic corona (Figure 4-11).

The PEG block cannot move as in a micelle made from Pluronic F127 that is also a tri-block copolymer but with the PEG hydrophilic chains as external block. In Pluronic F127 micelles, the structure of the polymer leaves the end of the PEG chains free to move

without forcing it in a specific structure. When the hydrophilic part of a tri-block copolymers is the block in the middle, it is forced to fold back on itself to permit to the external hydrophobic block to form the micelle's core. Micelles built in this way are more compact compared to micelles made from Pluronic F127.

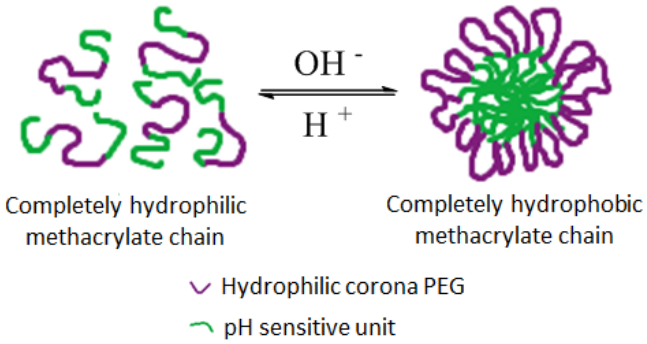


Figure 4-11: Schematic representation of the behavior of synthesized PEG based difunctional copolymers in water solution

4.3.2.3 Compounds containing PEGOMe

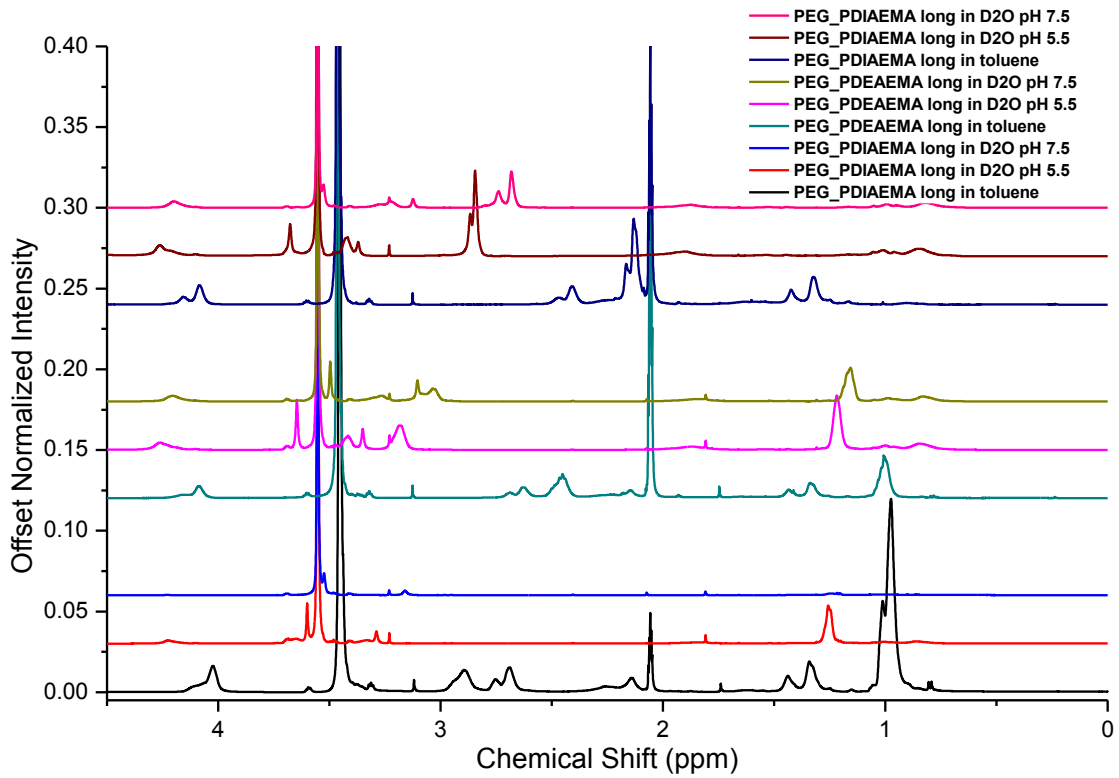


Figure 4-12: ^{1}H-NMR of samples PEG_PDMAEMA long, PEG_PDEAEMA long and PEG_PDIAEMA long in deuterated toluene and in D_2O at pH 5.5 and 7.5.

In Figure 4-12 the ^{1}H-NMR of samples PEG_PDMAEMA long, PEG_PDEAEMA long and PEG_PDIAEMA long in toluene and in D_2O at pH 5.5 and 7.5 are shown. It can be seen that in each sample, dissolving the solid in D_2O at pH 5.5, the intensity of the peaks of the methacrylate chain have a lower relative intensity compared with the peaks of the

methacrylate chain when the solid is dissolved in toluene - d8. The intensity of the peaks of the methacrylate chains decreases again when the sample is dissolved in D_2O at pH 7.5. The three samples were synthesized using PEG_Br as initiator and they differ for the type of methacrylate chain. Samples GM-12-041, GM-12-036, GM-12-039 are analogous to samples GM-12-052, GM-12-035 and GM-12-047 but they have an higher degree of polymerization. The relative intensity of the peaks of the methacrylate chains that decreases passing from pH 5.5 to pH 7.5 confirm that the hydrophilicity of the methacrylate chains follows the following trend: PDIAEMA<PDEAEMA< PDMAEMA. Samples PEG_PDMAEMA short, PEG_PDEAEMA short and PEG_PDIAEMA short follow the same trend shown from samples PEG_PDMAEMA long, PEG_PDEAEMA long and PEG_PDIAEMA long but the intensity of the methacrylate chains is lower due to the lower degree of polymerization.

At pH 7.5 the peaks of the methacrylate chains in PEG_PDIAEMA long do not disappear completely as it is for samples PLUR_bPDIAEMA long and PEG_bPDIAEMA long. This demonstrate that for di-block copolymers is more difficult to form micelles in water solution, compared to the other polymers discussed previously.

4.3.3 Rheological measurements

During the measurement, G', G'' and η were measured in function of the temperature of the sample.

η is the viscosity and G' and G'' are defined as:

$$G' = G^* \cos\delta = (\tau_0/\gamma_0) \cos\delta \quad (22)$$

$$G'' = G^* \sin\delta = (\tau_0/\gamma_0) \sin\delta \quad (23)$$

$$G^* = \tau_0/\gamma_0 = G' + i * G'' \quad (24)$$

Where G' and G'' are the elastic modulus and the loss modulus respectively and G^* is the total resistance of the substance against the applied strain.

δ is the phase shift angle: when its value is zero there is no delay between the applied stress and the response of the material, sinδ is zero, $G' = G^*$ and the material is completely elastic. When δ is 90° cosδ is zero, $G'' = G^*$ and the material is completely viscous. When $0° < \delta < 90°$ the material is viscous-elastic. The gels have G' higher than G''. The critical gelation temperature is the lower temperature at which G' is higher than G''.

The analyzed samples have one or two pH-sensitive methacrylate chains in which the hydrophobic/hydrophilic behavior depends on the pH of the solution: at acidic pH the

methacrylate chains are hydrophilic, and the hydrophilicity depends on the pH value and on the steric hindrance of the groups attached to the nitrogen atom. Increasing the pH the hydrophilicity of the methacrylate chains decreases until they become hydrophobic. Once again, the pH value at which the methacrylate chains become hydrophobic depends on the steric hindrance of the groups attached to the nitrogen atom. In the methacrylate chains the nitrogen groups are close to each other and the protonation state of one nitrogen atom is influenced from the pH and from the protonation state of the nitrogen atoms next to it.

The hydrolysis that occurred during the purification of the compounds do not permit to compare results of the rheological measurements of different samples. It is only possible to compare data obtained from rheological measurements done using the same sample in different measurement conditions. It is so because each sample has a different degree of hydrolysis and even if the concentration of solid in the solution was kept constant in all the measurements, the concentration of compound in which the methacrylate chain is still bonded to the initiator is different from sample to sample. Furthermore, samples in which the investigated compound is solubilized with the degradation products (initiator and methacrylate chains) are inhomogeneous. This inhomogeneity can disturb the order that is established between the micelles when the gelation occurs, leading to gelation temperatures that could be higher than the gelation temperature of samples made using only the desired compound (with the methacrylate chains bonded to the initiator).

To conclude, it is not possible to compare results from rheological measurements done using different samples. It is also not possible to compare results from rheological measurements done using one of the synthesized compounds with results of rheological measurements done using PLUR_bOH.

4.3.3.1 Rheological measurements of samples containing Pluronic

4.3.3.1.1 Rheological measurements of Pluronic f127

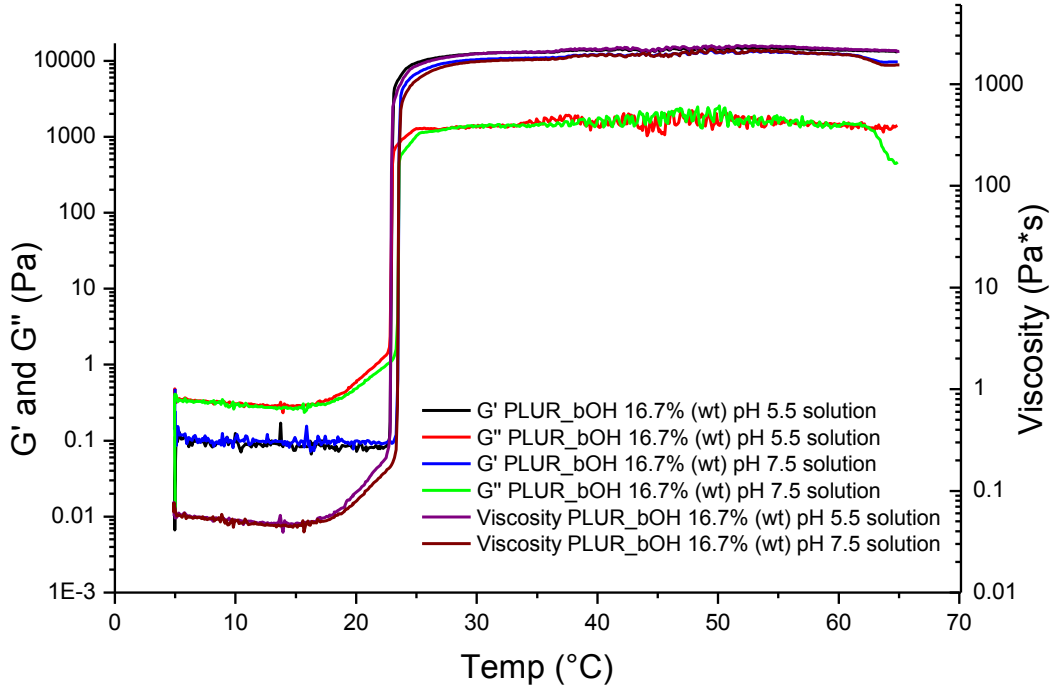


Figure 4-13: Values of G', G'' and η of 16.7% (wt) Pluronic F127 solutions at pH 5.5 and 7.5.

To show the rheological behavior of Pluronic F127, different measurements were carried out. Figure 4-13 shows the results of two different rheological dynamic measurements. The black, red and violet dots are the values of G', G'' and η respectively between 5 and 65°C of a 16.7% (wt) Pluronic F127 at pH 5.5. The blue, green and brown dots are the values of G', G'' and η respectively between 5 and 65°C of a 16.7% (wt) Pluronic F127 at pH 7.5. In both samples it can be seen that at 23°C a gel-phase transition occurs. Before the gel-phase transition G' is lower than G'' whilst after 23°C G' is higher than G'' and a significant increase in G' and G'' values can be seen. Values of G' and G'' do not change significantly between 5 and 15°C and between 30 and 60°C. The values of G', G'' and η are constant, showing that the pH of the solution does not affect the rheological properties of Pluronic F127 solutions.

4.3.3.1.2 Rheological measurements of samples PLUR_bPDMAEMA short and PLUR_bPDMAEMA long

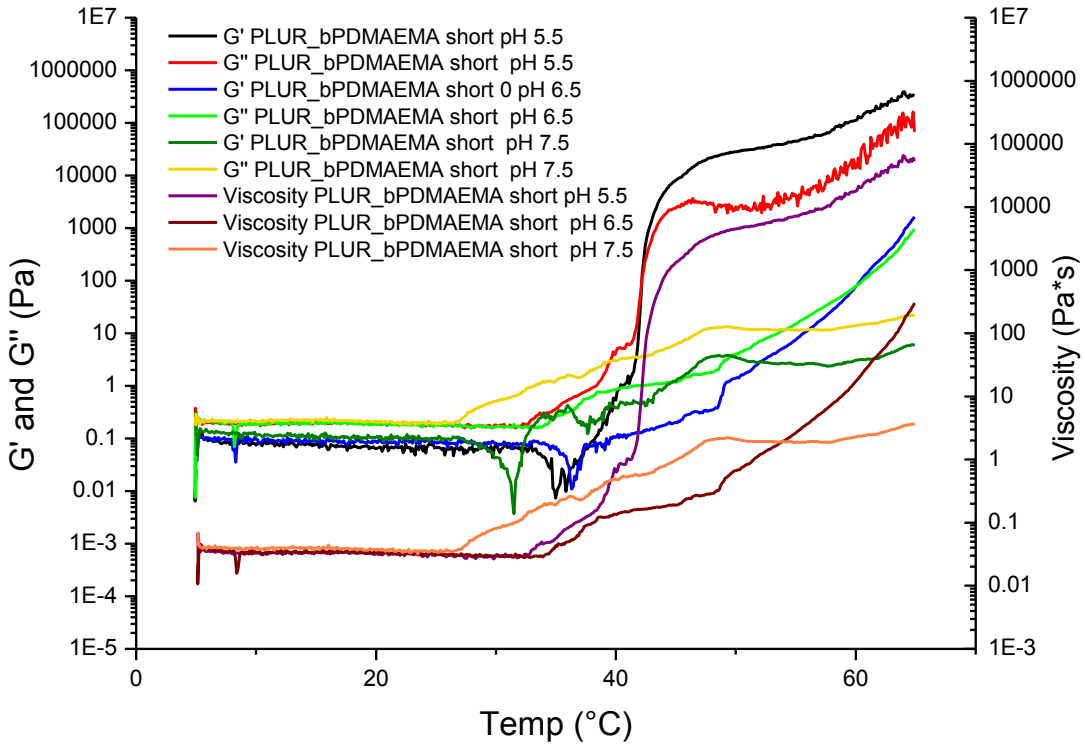


Figure 4-14: Values of G', G'' and η of 16.7% (wt) of PLUR_bPDMAEMA short at pH 5.5, 6.5 and 7.5.

Figure 4-14 and Figure 4-15 show how the values of G', G'' and η change with the temperature when a stress of 10 Pa with a frequency of 1 Hz is applied to their 16.7% (wt) water solutions of sample PLUR_bPDMAEMA short and PLUR_bPDMAEMA long, respectively, at pH 5.5, 6.5 and 7.5. For sample short at pH 5.5 a gel-phase transition can be seen at 42.28 °C, accompanied by a great increase in the values of G', G'' and η. These three values at 64°C, are ten times the values of G', G'' and η at the same temperature shown from 16.7% (wt) Pluronic F127 water solution (fig. 4-27). For sample at pH 6.5 a gel-phase transition can be seen at 60.08 °C but at 65 °C it is still not finished. For this sample the gel-phase transition is slower than for sample at pH 5.5 and also it occurs at higher temperature. For sample at pH 7.5 no gel-phase transition can be seen before 65 °C (Figure 4-14).

Analyzing the graphs shown in Figure 4-14 it can be seen that decreasing the hydrophilicity of the methacrylate chains the gel-phase transition temperature increases, until at pH 7.5 the gel-phase transition does not occur, at least until 65°C.

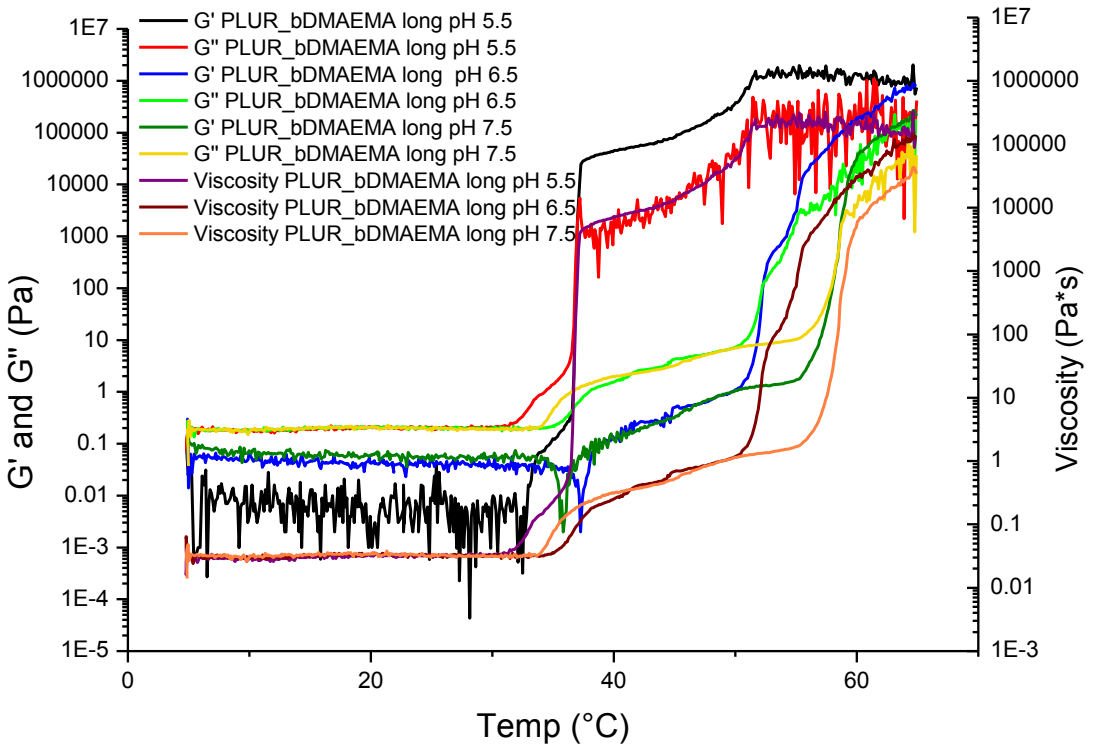


Figure 4-15: : Values of G', G'' and η of 16.7% (wt) of PLUR_bPDMAEMA long at pH 5.5, 6.5 and 7.5.

In the case of PLUR_bPDMAEMA long all the three samples show a phase-transition influenced from the pH. The gel-phase transition is 37.02°C when the pH is 5.5; it increases to 52.40°C increasing the pH to 6.5 and it reach 58.53°C when the pH of the solution is 7.5.

Samples PLUR_bPDMAEMA short and PLUR_bPDMAEMA long have the same block structure (PDMAEMA-PEG-PPG-PEG-PDMAEMA), but they differ for the degree of polymerization of the pH sensitive units (PDMAEMA). PLUR_bPDMAEMA short have a DP of 13.2 whilst sample PLUR_bPDMAEMA long have a DP of 46.4. For both samples, increasing the pH, the gel-phase transition temperature increases but when the DP is higher, the gel-phase transition occurs at lower temperature compared with the sample at the same pH but with lower degree of polymerization. This is due to the fact that increasing the hydrophilic chain length the micelles are bigger and the gel-phase transition occurs at lower temperature.

Increasing the pH, the block of PDMAEMA becomes less hydrophilic and part of this block interact with the PPG hydrophobic core. The more the PDMAEMA block becomes hydrophobic, the more the PEG chains have to fold back on themselves and the more the

micelles are small and compact. Decreasing the diameter of the micelles (increasing the pH) the gelation occurs at higher temperatures.

The fact that the micelles are more compact results in the higher G' and G'' values of the gels, compared to Pluronic F127 16.7% (wt) water solutions. Samples with the higher degree of polymerization have the highest G' and G'' values because of the more compact micelles generated by the higher length of the pH-sensitive block.

4.3.3.1.3 Rheological measurements of sample PLUR_bPDEAEMA short and PLUR_bPDEAEMA long

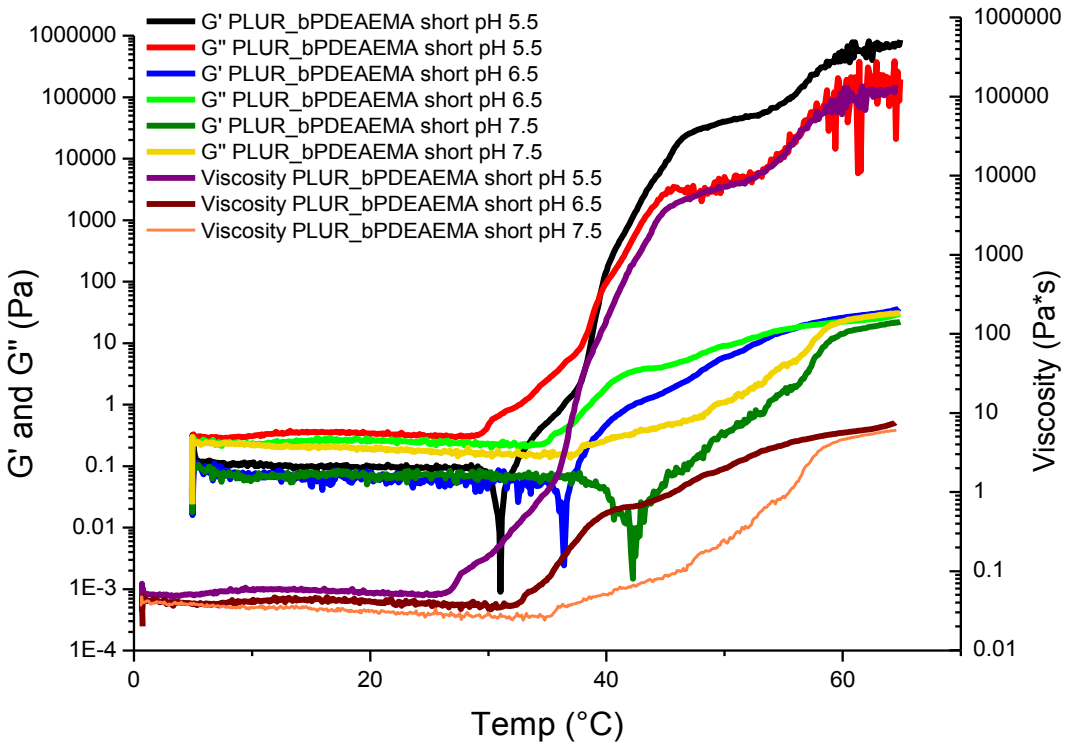


Figure 4-16: Values of G', G'' and η of 16.7% (wt) of PLUR_bPDEAEMA short at pH 5.5, 6.5 and 7.5.

Figure 4-16 shows how the values of G', G'' and η change with the temperature when a stress of 10 Pa with a frequency of 1 Hz is applied to three 16.7% (wt) water solutions of sample PLUR_bPDEAEMA short at pH 5.5, 6.5 and 7.5.

The gel-phase transition passes from 39.55 °C for sample at pH 5.5, to 56.31 °C for sample at pH 6.5. At pH 7.5 the sample does not show a gel-phase transition into the analyzed temperature range.

The rheological measurements of sample PLUR_bPDEAEMA long, compared to sample PLUR_bPDEAEMA short show the same trend. For sample at pH 5.5 gelation occurs at 44.00 °C; for sample at pH 6.5 gelation occurs at 59.82 °C whilst for sample at pH 7.5

gelation does not occur. Analyzing the change in the gelation temperature with the pH the same trend seen for samples PLUR_bPDMAEMA short and PLUR_bPDMAEMA long can be seen: increasing the pH the gelation temperature increases. This is due, as it was for the other samples, to the fact that increasing the pH the micelles are smaller and the gelation occurs at higher temperatures.

On the other hand, the opposite trend is seen when the influence of the chain length on the gelation temperature is analyzed. Comparing the gelation temperatures of samples at the same pH and concentration from samples PLUR_bPDEAEMA short and PLUR_bPDEAEMA long, it can be seen that increasing the pH-sensitive block length, the gelation temperature increases.

This opposite trend can be explained assuming that PDMAEMA is mainly hydrophilic in the pH range between 5.5 and 7.5 and the increased pH-sensitive block length leads to bigger micelles. In samples where PDMAEMA has been substituted with PDEAEMA, the pH-sensitive block is mainly hydrophobic (due to the higher steric hindrance on the nitrogen atom) and once the pH-sensitive unit is extended, the result is that most of the chain tries to interact with the PPG hydrophobic core. This behavior lead to smaller and more compact micelles that form gel at higher temperature. This difference in the hydrophilicity is confirmed from the fact that DMAEMA is soluble in water at pH 7.00 whist DEAEMA is not soluble in water at the same pH.

4.3.3.1.4 Rheological measurements of sample PLUR_bPDIAEMA short and PLUR_bPDIAEMA long

For sample PLUR_bPDIAEMA short, the gelation occurs at 43.40, 58.63 and 64.69 °C when the pH is 5.5, 6.5 and 7.5, respectively. For sample at pH 7.5 is not possible to see a real gelation because the phase transition starts at 64.80 °C .

For sample PLUR_bPDIAEMA long, the gelation can be seen only for the sample at pH 5.5 which has a gelation temperature of 57.91 °C.

Comparing samples PLUR_bPDIAEMA short and PLUR_bPDIAEMA long with samples PLUR_bPDEAEMA short and PLUR_bPDEAEMA long, at the same pH, it can be seen that passing from PDEAEMA to PDIAEMA the gelation temperatures increase. This confirms that increasing the hydrophobicity of the pH-sensitive block micelles become smaller leading to higher gelation temperatures.

4.3.3.2 Comments regarding compounds derived from Pluronic F127

It can be seen that when gelation occurs, before to reach the gelation temperature G' and G'' increase without G' exceeds G'', as if the gelation phase transition is divided in two steps. Figure 4-17 shows how the gelation temperature changes with the pH for all samples containing Pluronic F127. The gel-phase transition temperature is influenced from the pH of the solution and from the length of the pH-sensitive block. The pH affects the hydrophilicity of the methacrylic chains and the way in which they arrange into the micelles.

The obtained results show that there is a direct correlation between the pH values and the gelation temperatures: for each sample, increasing the pH the gelation temperature increases (Figure 4-17).

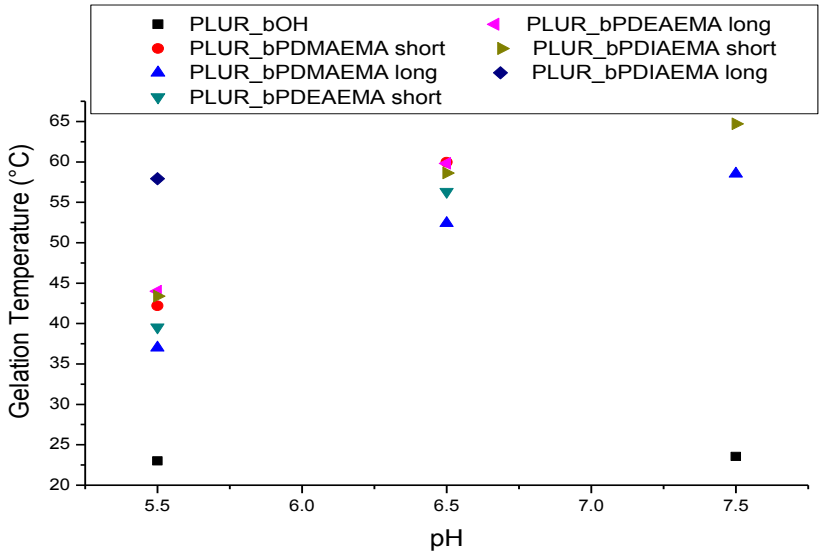


Figure 4-17: Comparison of gelation temperatures of block copolymers containing Pluronic f127.

Decreasing the hydrophilicity of the pH-sensitive chains in 16.7% (wt) water solutions of these six samples, the gel-phase transition temperature increases, showing that the chain extension of PLUR_bOH molecules with pH-sensitive chains leads to compounds that show pH-sensitive behavior in water solution. The results of the rheological measurements show that is possible to tune the gelation temperature of the compounds changing the hydrophilicity of the pH-sensitive block. If it is desired to obtain big micelles with low gelation temperature Pluronic F127 chains have to be extended with blocks that are hydrophilic.

If compact micelles with high gelation temperature are desired, Pluronic F127 chains have to be extended with hydrophobic blocks on both ends of the chain. We have demonstrated that it is possible to obtain both the mentioned results extending the

Pluronic chains with pH-sensitive blocks that can be hydrophilic or hydrophobic tuning the pH of the water solution where they are solubilized.

In Table 4-3 are summarized the results obtained from the rheological measurements of samples containing Pluronic f127 that form gels.

Table 4-3: Rheological properties comparison of samples derived from Pluronic f127

Compound	DP	pH	GT [a](°C)	G'/G'' at 20°C (Pa)		G'/G'' at 65°C (Pa)		μ at 20°C (Pa*s)	μ at 64°C (Pa*s)
				G'	G''	G'	G''		
PLUR_bOH		5.5	23.0	0.0809	0.723	13300	1340	0.116	2120
		7.5	23.6	0.0968	0.611	12100	1500	0.0984	1940
PLUR_bPDMAEMA short	13.2	5.5	42.2	0.0666	0.191	341000	111000	0.0322	54900
		6.5	60.0	0.0873	0.188	1180	788	0.0331	245
PLUR_bPDMAEMA long	46.4	5.5	37.0	0.0010	0.200	1170000	941000	0.0310	239000
		6.5	52.4	0.0400	0.200	889000	206000	0.0310	145000
		7.5	58.5	0.0610	0.202	208000	38900	0.0335	36300
PLUR_bPDEAEMA short	15.3	5.5	39.6	0.0969	0.336	707900	193000	0.0555	122000
		6.5	56.3	0.0631	0.262	35.2	29.0	0.0430	7.25
PLUR_bPDEAEMA long	39.5	5.5	44.0	0.0243	0.264	513000	109000	0.0420	72400
		6.5	59.8	0.0388	0.216	2370	1190	0.0349	422
PLUR_bPDIAEMA short	21.6	4.6	41.2	0.0895	0.181	844000	187000	0.0321	140000
		5.5	43.4	0.0514	0.325	1390000	321000	0.0529	232000
		6.5	58.6	0.0770	0.214	318000	110000	0.0361	53500
		7.5	64.7	0.0753	0.166	223	209	0.0289	48.7
PLUR_bPDIAEMA long	80.8	5.5	57.9	0.112	0.182	23900	5850	0.0339	4090

[a] Gelation Temperature (GT)

4.3.3.3 Rheological measurements of samples samples containing PEG: PEG_bPDMAEMA short, PEG_bPDMAEMA long, PEG_bPDEAEMA short, PEG_bPDEAEMA long, PEG_bPDIAEMA short and PEG_bPDIAEMA long

Samples PEG_bPDMAEMA short, PEG_bPDMAEMA long, PEG_bPDEAEMA short, PEG_bPDEAEMA long, PEG_bPDIAEMA short and PEG_bPDIAEMA long differ for the type of pH-sensitive blocks and for the degree of polymerization. They are all tri-block copolymers with the following structure: PDxAEMA-PEG-PDxAEMA. Only the samples with higher degree of polymerization show a gel-phase transition.

For sample PEG_bPDMAEMA long at pH 5.5 no gelation can be seen whilst for sample at pH 6.5 gelation occurs at 54.45 °C. Sample PEG_bPDMAEMA long was not completely soluble at pH 7.5 and it does not make sense to compare its rheological results with results from samples at different pH because the concentration would not be the same. At 64°C values of G' and G'' are higher for 16.7% (wt) water solution of sample PEG_bPDMAEMA long at pH 6.5 then for 16.7% (wt) water solution of Pluronic F127.

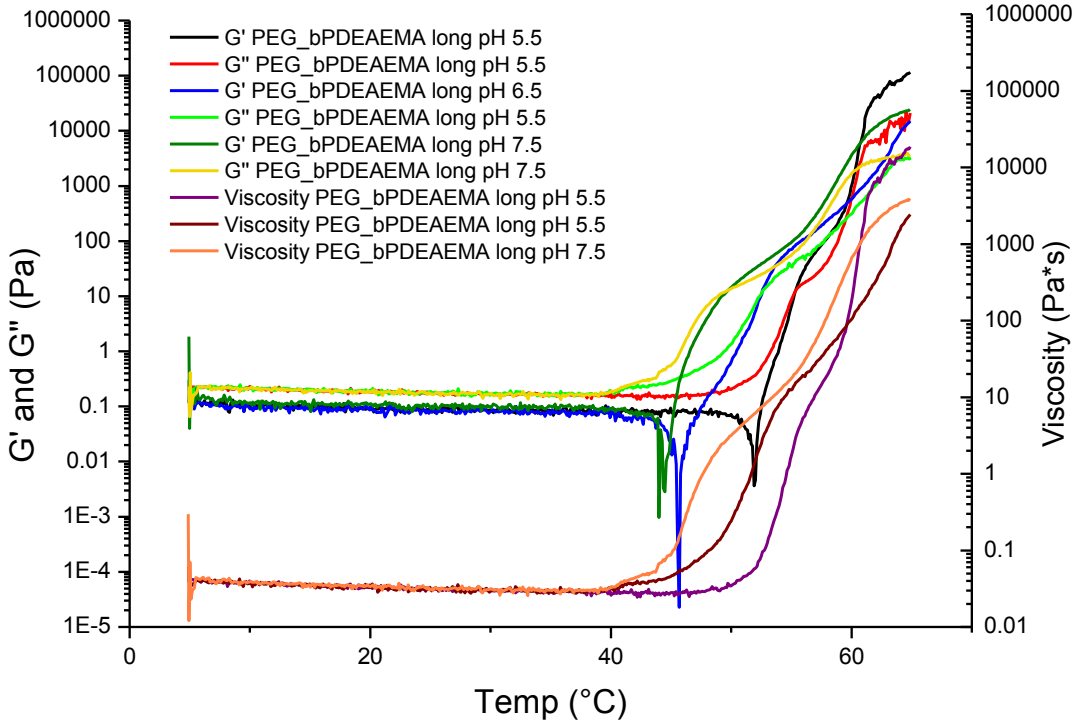


Figure 4-18: Values of G', G'' and η of 16.7% (wt) of PEG_bPDEAEMA long at pH 5.5, 6.5 and 7.5.

Figure 4-18 shows the values of G', G'' and η at different temperatures for sample PEG_bPDEAEMA long at pH 5.5, 6.5 and 7.5. Gelation can be seen in all the three

samples. At pH 5.5 gelation occurs at 55.38 °C, at pH 6.5 gelation occurs at 52.60 °C whilst at pH 7.5 gelation occurs at 49.75 °C.

For sample PEG_bPDIAEMA long at pH 5.5 gelation occurs at 56.96 °C whilst for sample at pH 6.5 gelation occurs at 55.29 °C. Sample PEG_bPDIAEMA long was not completely soluble at pH 7.5 and it does not make sense to compare its rheological results with results from samples at different pH because the concentration would not be the same. At 64°C values of G' and G'' are higher for 16.7% (wt) water solution of sample PEG_bPDIAEMA long at pH 6.5 then for 16.7% (wt) water solution of Pluronic F127.

4.3.3.4 Comments regarding compounds derived from di-functional PEG

As it was for samples containing Pluronic F127 also in samples containing di-functionalized PEG it seems that the gelation process is divided in two steps.

In polymers derived from PEG_bBr a general trend can be seen: when the sample is soluble and the pH-sensitive units is long enough, as shown in Figure 4-19, the gelation temperature decreases increasing the pH. This behavior is exactly the opposite compared to samples derived from PLUR_bBr. The reason of the opposite trend derives from the structure of the polymeric chain. When the methacrylic chains are hydrophilic (at acidic pH), the entire polymeric chain is hydrophilic and it does not form micelles because there are no hydrophobic blocks that prefer to avoid interactions with water. Increasing the pH, the methacrylate external chains become more and more hydrophobic and, to avoid interactions with water, they force the PEG chains to fold back on themselves to form micelles. Increasing the pH, the methacrylate chains become always more hydrophobic, increasing the diameter of the hydrophobic core and forming bigger micelles that form gels at lower temperature.

The samples synthesized using PEG_bBr that show a gel-phase transition have values of G' and G'' at 64°C that are higher than the values shown from Pluronic F127 16.7% (wt) water solutions but that are lower than the values of G' and G'' at 64°C shown from five block copolymers of structure PDxAEMA-PEG-PPG-PEG-PDxAEMA. This is in agreement with the structure of micelles shown in Figure 4-9 and Figure 4-11.

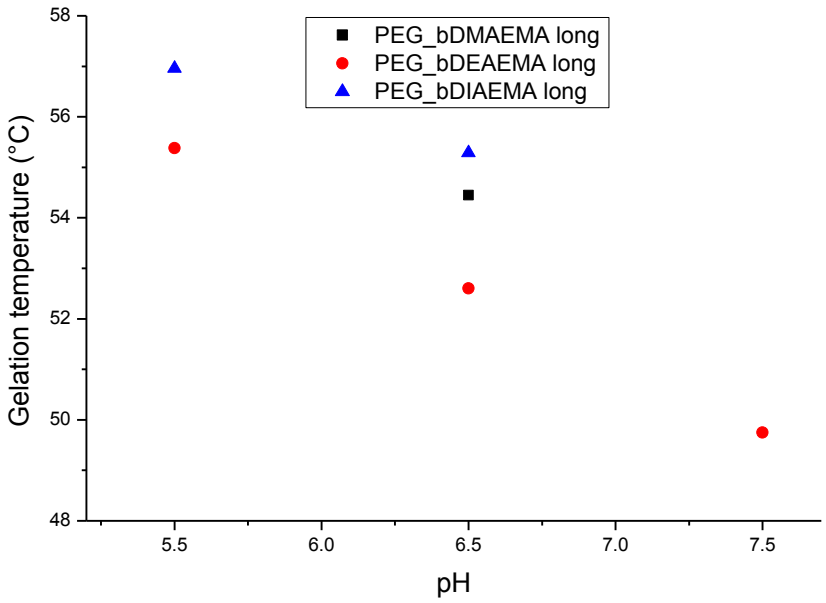


Figure 4-19: : Comparison of gelation temperatures of block copolymers containing di-functional PEG.

When micelles are formed only from Pluronic F127 the ends of the PEG chains are not forced into rigid structure and they are free to move as long as the PPG chains remain into the hydrophobic core.

If micelles are formed from structures as PDxAEMA-PEG-PDxAEMA, in which each PEG chain has a molecular weight of about 9000 g/mol, PEG chains are forced to fold back on themselves and micelles formed in this way are more compact compared to micelles formed from Pluronic F127. Also in micelles formed from structures as PDxAEMA-PEG-PPG-PEG-PDxAEMA, in which each PEG chain has a molecular weight of about 4000 g/mol, PEG chain fold back on themselves to permit the interaction of the methacrylate chains with the hydrophobic core. Gels made with micelles that contain shorter hydrophilic PEG chains have the highest values of G' and G'' because of the length of the external PEG corona. The lower molecular weight of the PEG chain, compared with the molecular weight of PEG in micelles with structure as PDxAEMA-PEG-PDxAEMA, lead to micelles with a smaller and more rigid hydrophilic corona. This more rigid structure of the micelles permits to obtain gels with higher values of G' and G''.

In Table 4-4 are summarized the results obtained from the rheological measurements of samples containing di-functional PEG that form gels.

Table 4-4: Rheological properties comparison of samples derived from di-functional PEG

Compound	DP	pH	GT [a] (°C)	G'/G'' at 20°C (Pa)		G'/G'' at 65°C (Pa)		μ at 20°C (Pa*s)	μ at 64°C (Pa*s)
				G'	G''	G'	G''		
PEG_bPDMAEMA long	51.4	6.5	54.4	0.0862	0.206	19300	5430	0.0355	3190
PEG_bPDEAEMA long	34.3	5.5	55.4	0.0893	0.186	97300	16200	0.0329	15700
		6.5	52.6	0.0854	0.189	11800	3090	0.0330	1940
		7.5	49.8	0.105	0.183	22400	3650	0.0336	3610
PEG_bPDIAEMA long	74.0	5.5	57.0	0.0195	0.188	94000	23500	0.0300	15400
		6.5	55.3	0.0427	0.178	79700	12500	0.0291	12900

[a] Gelation Temperature

4.3.3.5 Rheological measurements of samples containing PEGOMe: PEG_PDIAEMA short, PEG_PDMAEMA long, PEG_PDEAEMA short, PEG_PDEAEMA long, PEG_PDIAEMA short and PEG_PDIAEMA long

Samples PEG_PDIAEMA short, PEG_PDMAEMA long, PEG_PDEAEMA short, PEG_PDEAEMA long, PEG_PDIAEMA short and PEG_PDIAEMA long were all synthesized using PEG_Br as initiator. The PEG chain has a molecular weight of about 5000 g/mol which is the half of the molecular weight of the PEG chain in PEG_bBr. This lower molecular weight of the hydrophilic PEG chain lead to the fact that, when the methacrylate chains are hydrophobic, the polymer is not soluble in water solution. For this reason, for most of the samples could not have been determined the rheological properties of their 16.7 % (wt) water solution (Figure 4-20).

Sample PEG_PDMAEMA short shows a gel-phase transition at 60.57 °C, sample PEG_PDEAEMA short shows gelation at 56.35 °C, sample PEG_PDIAEMA short shows the gel-phase transition at 64.03°C and sample PEG_PDIAEMA long shows gelation at 62.72°C. For all these samples gelation occurs only when the pH of the measured solution is 5.5 (Figure 4-20). A general behavior cannot be seen because only few samples are soluble and form gel. It is reasonable to think that some polymers form micelles in solution but not all materials that form micelles give gels increasing the temperature.

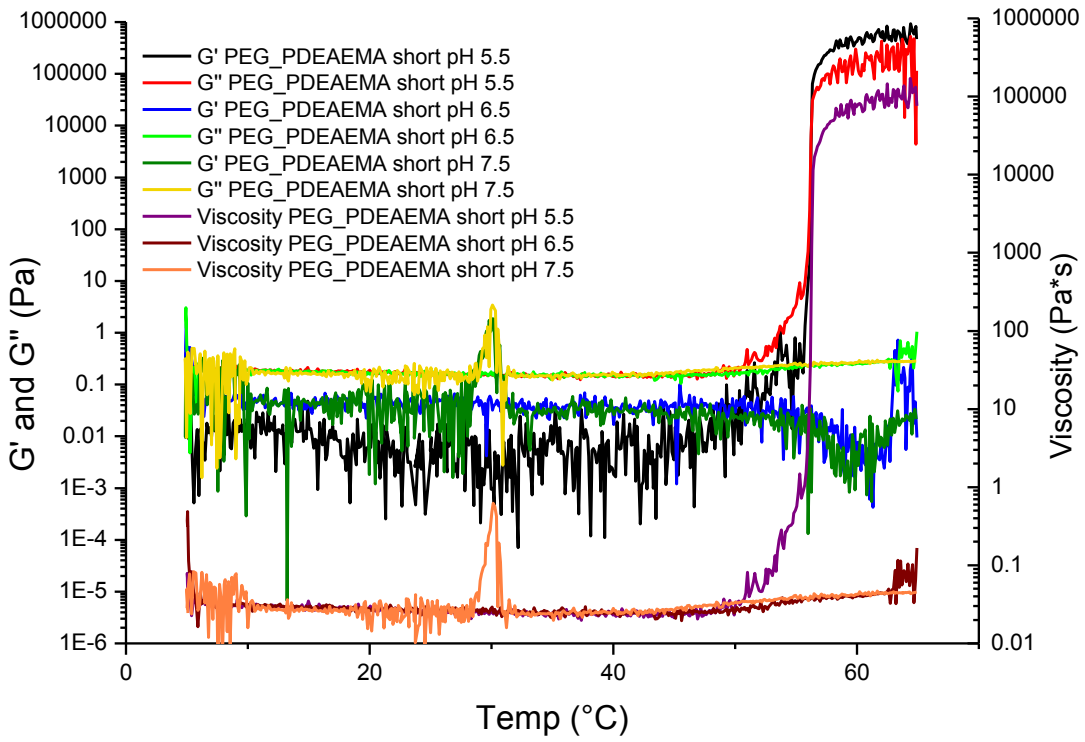


Figure 4-20: Values of G', G'' and η of 16.7% (wt) of PEG_PDEAEMA short at pH 5.5, 6.5 and 7.5.

Only for samples PEG_PDIAEMA short and PEG_PDIAEMA long it can be seen that increasing the length of the pH-sensitive block the gelation temperature decreases. Unfortunately the absence of other samples that confirm the same trend does not permit to see a general behavior for water solutions containing PDxAEMA-PEGOMe.

In Table 4-5 are summarized the results obtained from the rheological measurements of samples containing di-functional PEG that form gels.

Table 4-5: Rheological properties comparison of samples derived from mono-functional PEG

Compound	DP	pH	GT [a](°C)	G'/G'' at 20°C (Pa)		G'/G'' at 65°C (Pa)		μ at 20°C (Pa*s)	μ at 64°C (Pa*s)
				G'	G''	G'	G''		
PEG_PDMAEMA long	18.7	5.5	60.6	0.0713	0.181	378000	214000	0.0309	72000
PEG_PDEAEMA short	1.9	5.5	56.4	0.0078	0.174	602000	232000	0.0277	106000
PEG_PDIAEMA short	2.0	5.5	64.0	0.0550	0.170	85900	25400	0.0284	14300
PEG_PDIAEMA long	95.8	5.5	62.7	0.0086	0.1564	46100	11900	0.0250	7600

[a] Gelation Temperature

5 Conclusions

The aim of the project is to study the rheological properties of five block copolymers based on di-functionalized PLUR_bOH, a polymer that gives micelles and gel formation in water solution. The gel formation from PLUR_bOH solution depends only on the concentration and on the temperature. The pH value of PLUR_bOH solutions has no influence on their rheological property. Other two polymers were used as model to see how the different blocks of PLUR_bOH affect the property of the resulting material. These polymers used as model are:

- PEG_bOH ($\overline{M_n}$ ≈ 9000 g/mol) that represent the two hydrophilic blocks in PLUR_bOH without the PPG in the middle of the chain.
- PEG_OH ($\overline{M_n}$≈ 5000 g/mol) that represent only one side of the hydrophilic block in PLUR_bOH.

PLUR_bOH, PEG_bOH and PEG_OH were used as starting material and they underwent the same reactions. The goal we wanted to reach was to obtain polymers that were temperature and pH sensitive, extending the polymer chains of the starting materials with pH-sensitive units. We synthesized polymers with different pH-sensitive units, using DMAEMA, DEAEMA and DIAEMA as monomers. Also the influence that the pH-sensitive units length has on the property of the resulting materials was investigated.

We decided to use ATRP to extend the polymers chains, in order to obtain polymers with low polydispersity. To use the starting materials as initiators for ATRP they were functionalized with an esterification reaction with 2-bromoisobutyril bromide. The resulting products have been characterized with IR, MALDI, ^{1}H-NMR and DSC, and the complete conversion of -OH end groups in the polymer chains was confirmed.

In order to obtain polymers with different chain length, the kinetic of the ATRP of each couple of monomer and initiator was studied. Once the kinetics were studied we should have been able to obtain polymers with pre-determined chain length stopping the reaction after a previously calculated period of time.

Knowing the kinetic of the reaction, 18 different final polymers were synthesized. The polymer chains of each initiator were extended with the three monomers and for each monomer two different degree of polymerization were obtained. These polymers were characterized using ^{1}H-NMR and GPC and the rheological properties of 16.7 % (wt) water solutions at different pH were measured.

Even if the study of the kinetics has been complicated, the different values of the constant of polymerization are in line with the expectation. Increasing the molecular weight of the initiator or increasing the hindrance on the nitrogen atom in the monomer the rate of the polymerization slows down. For each monomer the fastest reaction is the one in which PEG_Br was used as initiator whilst the slowest reaction is the one in which PLUR_bBr was used as initiator.

From the molecular weight values, calculated with NMR and GPC it cannot be said if the compounds have the expected molecular weight because these measurements are affected from errors. These errors are due to the presence into each sample of the product of acidic hydrolysis that occurred during the purification. As consequence of this, it might be that the polymers that did not undergo hydrolysis have the expected molecular weight but the presence in the sample of polymers with lower molecular weight do not permit to determine the exact molecular weight of the compounds with the methacrylic chains bonded to the initiator chain.

The polydispersity measured with GPC is in the expected range for an ATRP but it is not sufficient to be sure that the synthesized compounds that did not undergo hydrolysis have the expected molecular weight.

In Table 4-3, Table 4-4 and Table 4-5 are summarized the results obtained from rheological measurements. Unfortunately, the fact that the solids weighted to prepare the sample for the rheological measurements were partially degraded does not permit to compare samples prepared from different solids. It is so because it is not possible to know the concentration in solution of the solid that did not undergo hydrolysis. Despite to this a general behavior can be seen and it has been demonstrated that the synthesized compounds are pH-sensitive.

Five block copolymers with structure PDxAEMA-PEG-PPG-PEG-PDxAEMA are pH sensitive and the gelation temperature increases increasing the pH of the solution.

It is interesting to see that tri-block copolymers with structure PDxAEMA-PEG-PDxAEMA are pH sensitive and the gelation temperature decreases increasing the pH of the solution. This is completely the opposite behavior shown from five block copolymers with structure PDxAEMA-PEG-PPG-PEG-PDxAEMA.

A general behavior from mono-functionalized PEG polymers cannot be determined.

It can also be seen that the chain length of the hydrophilic block and the structure of the micelles in solution affect G’ and G’’ values of gels. When the hydrophilic blocks are forced to fold back on themselves to form micelles, gels with higher values of G’ and G’’

are obtained. Furthermore, decreasing the hydrophilic PEG chain length the values of G' and G'' are increased. Obviously, the hydrophilic chain length cannot be decreased too much because it should be long enough to permit to the system to form micelles in solution.

PEG_bOH was used as starting material to see how the structure of PLUR_bOH affects the property of the resulting material and it can be seen that systems formed from these two polymers, after their chains have been extended with pH-sensitive units, behave in a completely different way.

In three blocks copolymers derived from PEG_bOH, when chains are completely hydrophilic no micelles are formed. To permit to the system to form micelles it is necessary to make hydrophobic the pH-sensitive blocks. In this way micelles are formed only above a certain pH, depending on the intrinsic hydrophilicity of the pH-sensitive units. Increasing the pH, the diameter of the hydrophobic core is increased, and the PEG chains forced to fold back on themselves more strongly.

In five blocks copolymer derived from PLUR_bOH, an hydrophobic core made with PPG is already present in the starting material and micelles are formed even if the pH-sensitive units are hydrophilic. Increasing the pH the pH-sensitive units become hydrophobic and they try to interact with the PPG core. When the methacrylate chains interact with the PPG core the space occupied from the hydrophilic corona is decreased because the PEG chains are forced to fold back on themselves. In this way, increasing the pH the gelation temperature increases.

The synthesized five or tri-blocks copolymers with PDxAEMA-PEG-PPG-PEG-PDxAEMA and PDxAEMA-PEG-PDxAEMA in 16.7% (wt) water solution form gels. The gel-phase transition depends on the temperature and on the pH of the solution in which they are dissolved. The PPG block in five blocks copolymers is necessary to form micelles whatever the pH of the solution is. On the other hand a certain pH is necessary to see the formation of micelles from tri-block copolymers that do not contain PPG. Increasing the pH in five blocks copolymers solution, a change in the structure of the micelles occurs and this change leads to an increase of the gelation temperature of the system.

The project can be continued and improved. The kinetic studies could be done again, trying to eliminate the errors that occurred during the project. The synthesis of the compounds could be improved and some more analysis could be done. Some DLS measurements of the final compounds can help in seeing how the diameter of the

micelles change with the pH of the solution. Also the X-Ray diffraction can help to see how the micelles arrange when the gel is formed and if some other transitions occur after the first gel-phase transition. CMC and CMT can be determined using DSC.

6 Appendix

6.1 Characterization of PEGmethylether (2-bromoisobutyrate)

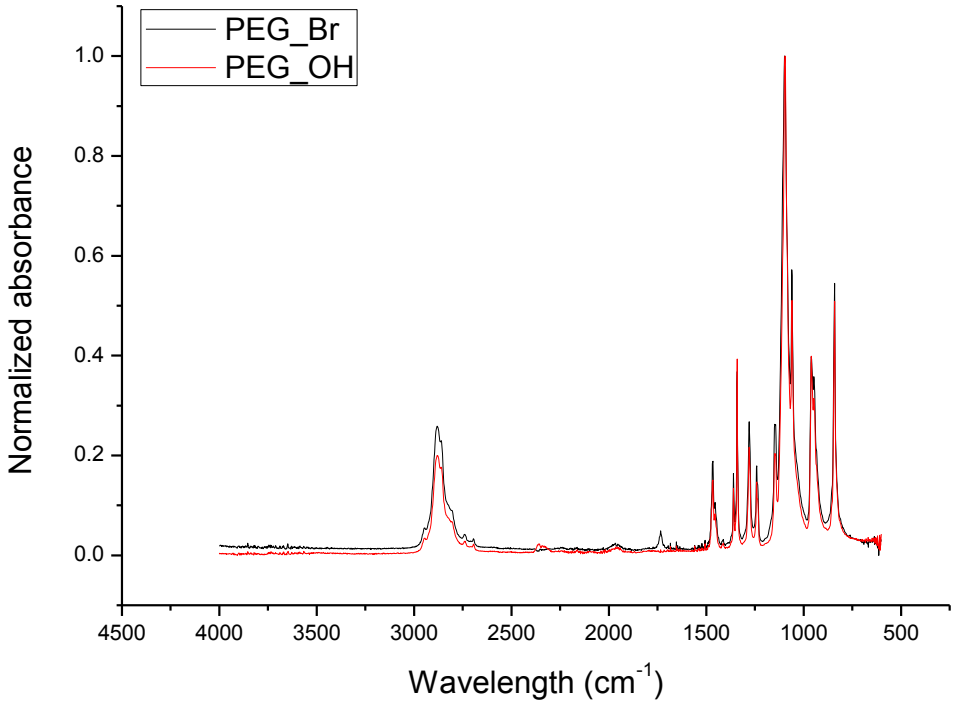


Figure 6-1: IR spectra of PEGmethylether (2-bromoisobutyrate) (black line) obtained using PEGmethylether (red line) as starting material.

In figure 6-1 the IR spectra of PEG_Br and PEG_OH are shown. The main difference between the two spectra is the presence, in the spectrum of PEG_Br, of the carbonyl peak at 1734 cm^{-1}. This peak, that was not present in the starting material, shows that the esterification of the hydroxyl group in the PEG_OH chain occurred, but it was not used to calculate the degree of functionalization because of the low intensity. At 2880 cm^{-1} the peak is related to the C-H stretching and it can be seen that in the spectrum of PEG_Br the absorbance of this peak is increased. This is due to the fact that the group that has been introduced with the esterification reaction contains two CH_3 groups.

Comparing the ^{1}H-NMR spectra of the starting material and the resulting product (figure 6-2 and 6-3) it can be clearly seen that in the latter one there are two more peaks at 4.25 and 1.87 ppm that can be assigned to the group introduced with the esterification.

From the integrals of the peaks at 1.87 and 4.25 ppm the conversion of hydroxyl end-groups can be calculated, comparing the value of their integrals and the value that they should have if the conversion was 100%.

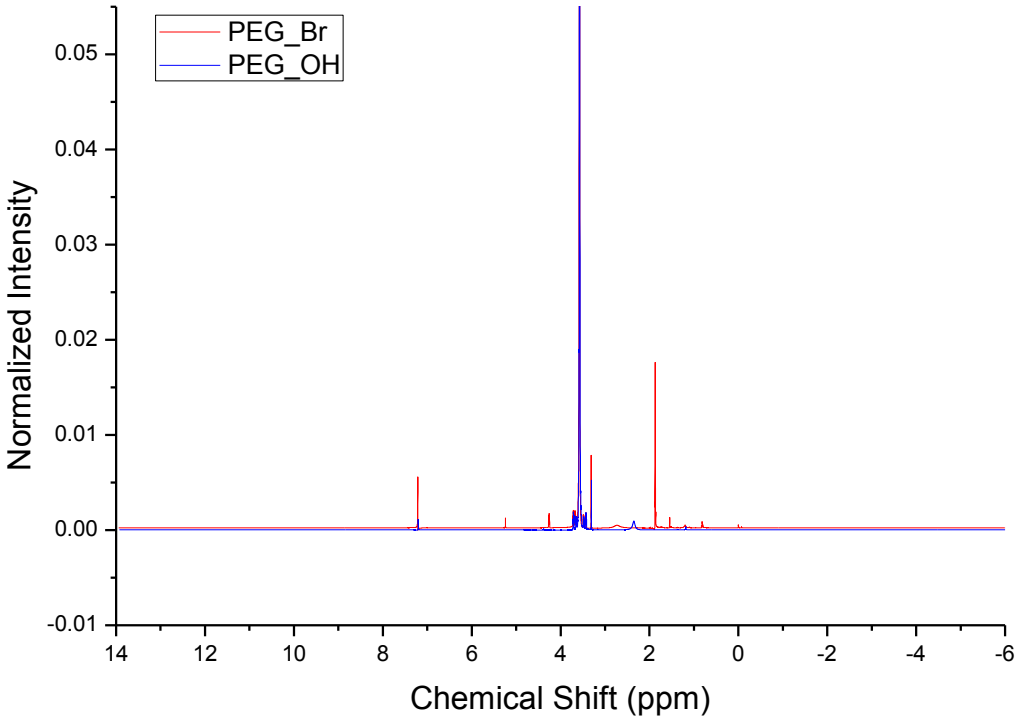


Figure 6-2: 1H-NMR spectra of PEGmethylether (2-bromoisobutyrate) (blue line) obtained using PEGmethylether (red line) as starting material.

.

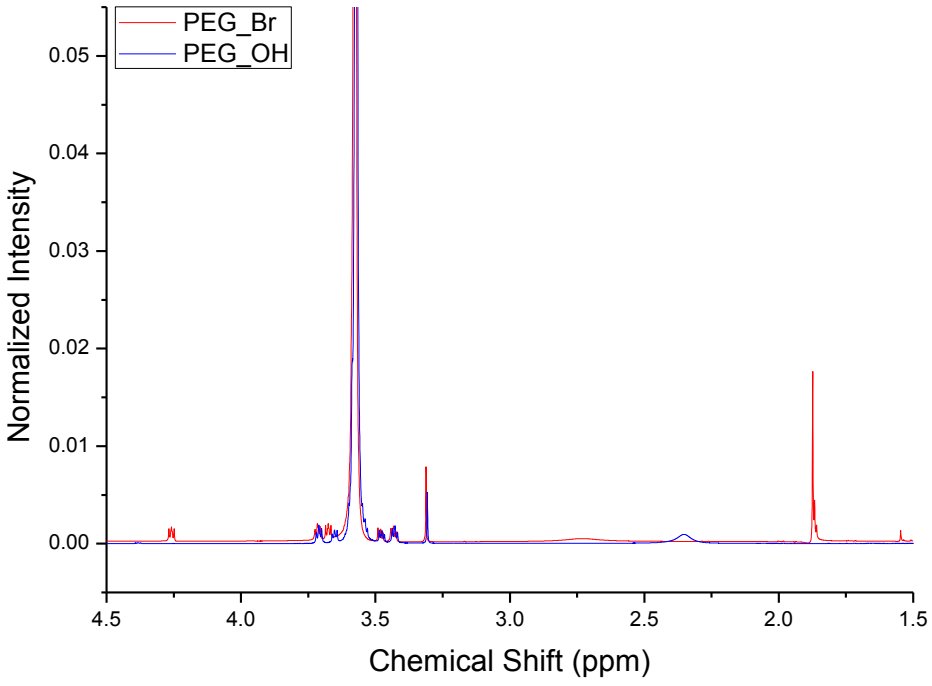


Figure 6-3: Zoom between 1.6 and 4.3 of the ^{1}H-NMR spectra shown in figure 6-2

6.2 Characterization of PEG bis(2-bromoisobutyrate)

In the IR spectrum of PEG_bBr, as in the comparison of PEG_OH and PEG_Br spectra , it can be seen that the peak at 2889 cm^{-1} is bigger than in the spectrum of PEG_bOH and it can also be seen the peak of the carbonyl group at 1735 cm^{-1}. This two latter observations demonstrate that the esterification of the hydroxyl group occurred.

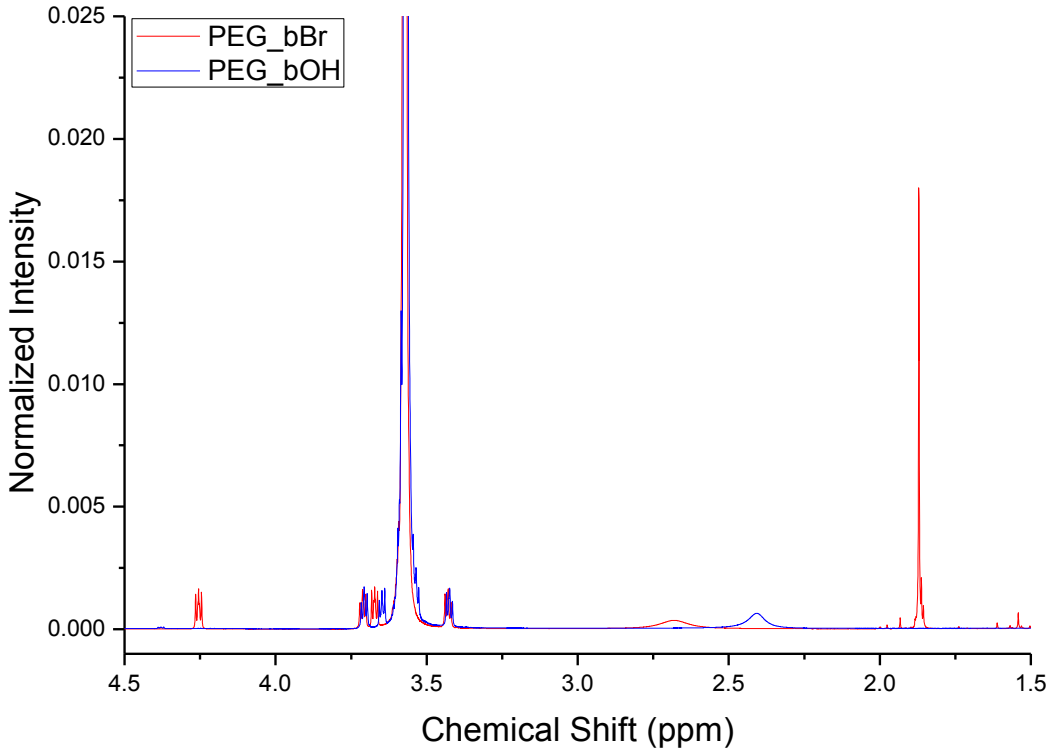


Figure 6-4: Zoom between 1.4 and 4.5 ppmn of 1H-NMR spectra of PEG bis(2-bromoisobutyrate) (red line) obtained using PEG diol (blue line) as starting material.

In figure 6-4 the spectra of PEG_bOH and PEG_bBr are shown. As it was for the PEG_OH and PEG_Br, the main differences between the two spectra are the peaks at 4.25 ppm, that is the signal of the CH_2 before the ester bond, and the peak at 1.87 ppm, that is the signal of the methyl groups introduced with the isobutyryl groups. These peaks were used to calculate the hydroxyl groups conversion.

6.3 Characterization of Pluronic F127 bis(2-bromoisobutyrate)

As shown for PEG_bBr and PEG_bBr, also in the IR spectrum of PLUR_bBr at 1734 cm^{-1} the peak of the carbonyl group, introduced with the esterification reaction, can be clearly seen. Watching the peak at 2887 cm^{-1} no big difference can be seen between the two spectra; this is maybe due to the fact that Pluronic F127 has an higher molecular weight compared to PEG_bOH and PEG_OH and it contains more C-H bonds leading to the fact that the addition of four methyl groups for each molecule does not result in a big

change in the absorbance of the solid at 2887 cm^{-1}. The comparison between the ^{1}H-NMR of PLUR_bBr and PLUR_bOH (figure 6-5), clearly show the two peaks, seen also in the others spectra of the functionalized product, that demonstrate the functionalization of the two hydroxyl groups at the end of the PLUR_bOH chain. The ^{1}H-NMR spectrum of PLUR_bOH is different from the ^{1}H-NMR spectrum of PEG_OH and PEG_bOH because it contains three more peaks. These three peaks are related to the PPG present in the structure of PLUR_bOH and they can be seen at 1.14, 3.40 and 3.56 ppm.

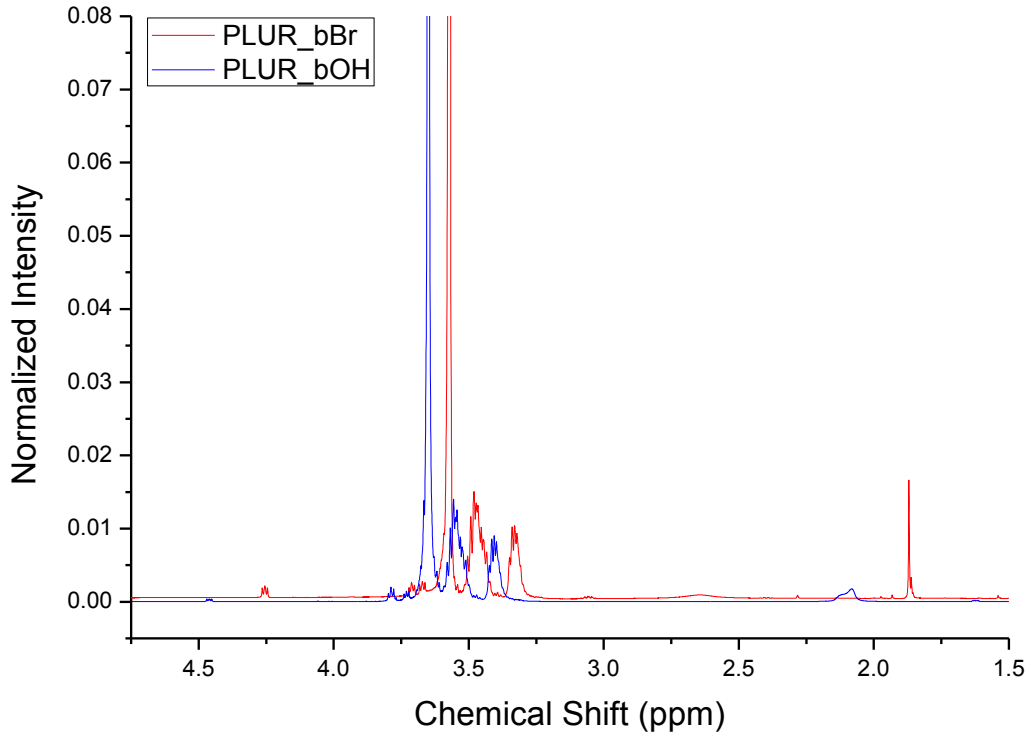


Figure 6-5: Zoom between 0.8 and 4.3 ppm of the 1H-NMR spectra of Pluronic F127 (blue line) and Pluronic F127 bis(2-bromoisobutyrate).

In figure 6-6 the MALDI spectra of PLUR_bOH and PLUR_bBr are shown. The peaks are not clearly separated as it should be and also the signal does not reach zero for $\overline{M_n}$ lower than 10000 g/mol.

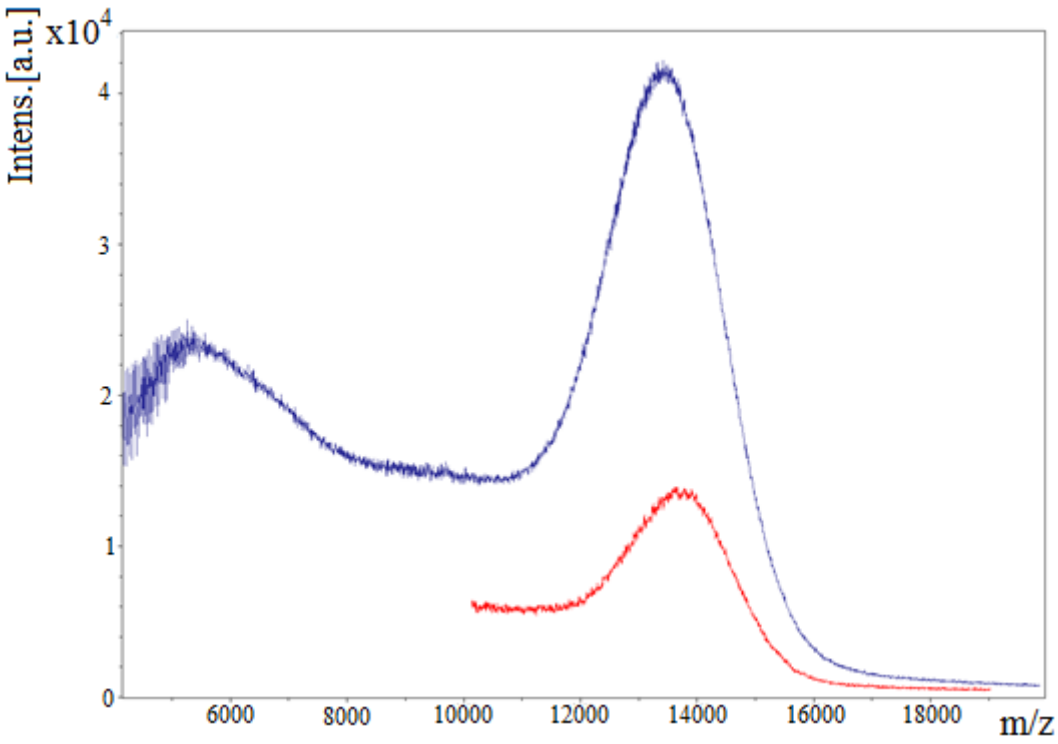


Figure 6-6: Comparision of MALDI spectra of Pluronic F127 bis(2-bromoisobutyrate) (red line) obtained using Pluronic F127 (blue line) as starting material.

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