Copolymerisation of dimethyl-aminoethyl-methacrylate with poly(ethylene oxide) α-hydroxy, ω-methacrylate adopting Atom Transfer Radical Polymerization (ATRP). A comparison of the reaction performed either in bulk or solution.

M. Counson[1,2,#], B. Abraham[1,2,#], J. Vervecken[1,2], L. Flebus[1], F. Lombart[1], Ch. Sevrin[1] and Ch. Grandfils[1,*]

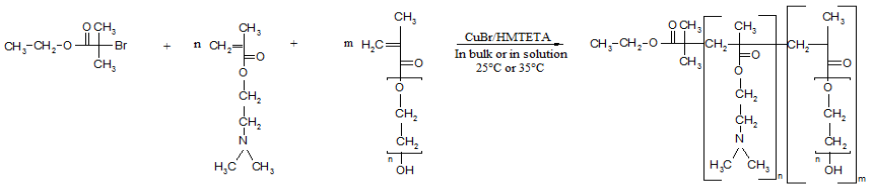
[1] Interfacultary Research Center on Biomaterials (CEIB), University of Liege, Chemistry Institute, B6C, B-4000 Liege (Sart-Tilman)
[2] Haute Ecole de la Province de Liège, Quai Gloesener, 6, B-4020 Liege
*[#] The two co-authors have contributed equally to this work ; * for any correspondence: C.Grandfils@ulg.ac.be.*

INTRODUCTION

Natural or synthetic polycations are daily used in clinic for human and veterinary purposes (Protamine, Eudragit®, Chitosan,..). Other potential applications of polycations could rely on their chemical association with polyethylene oxydel (PEO) in order to mask the antigenic sites of cells for cell therapies, in particular for erythrocytes immunnomasking in blood transfusion or for drug delivery purposes. According to this approach diblock copolymers, made from a polycation sequence that links by ionic interaction to the glycocalyx and from a polyethylene glycol moiety that prevents nonspecific interactions, are able to self-association at the erythrocyte surface (Cerda et al. J. Controlled Release, 2012, in press ; Cerda et al. Biomacromolecules, 2012, in press).

AIM

For this purpose this work aims to generate poly(2-(dimethylamino)ethyl methacrylate-b-poly(ethylene oxide) α-hydroxy, ω-methacrylate) copolymer (P(DMAEMA-b-PEO)) using Atom Transfer Radical Polymerization (ATRP). This pseudo-living radical polymerisation technique has as main advantageous to tailor well-defined copolymers with a control of their molecular features, in particular their architecture, composition, Mw, polydispersity.



ATRP was conducted using copper bromide as catalyst, first complexed with 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) ligand and 2-ethylbromoisobutyrate (EBiB) as initiator. For the sake to simplify the polymerization and to avoid any solvent, we have compared the polymerization realized either in bulk, either in solution (THF or toluene). A 10,000 molecular weight was aimed, considering either a 10 or 30 wt % of poly(ethylene glycol) methacrylate (H2C=C(CH3)CO(OCH2CH2)nOH) as co-macromonomer (Mn : 625).

RESULTS AND DISCUSSIONS

First approach : Polymerization in bulk

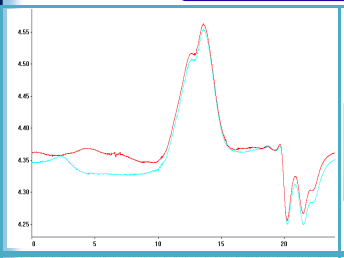


Figure 1 : SEC chromatograms of copolymer containing 10 wt % MAPEO

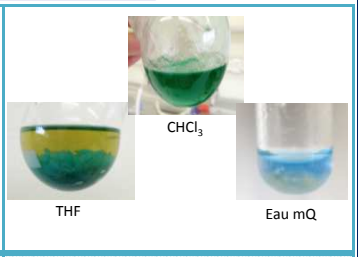


Figure 2 : Solubilisation assay of copolymer containing 30 wt % MAPEO

The high molecular weight observed for the copolymer containing 10% in MAPEO (Mw 55,600) and its bimodal profile (figure 1) do not fit to the typical macromolecular features observed with a homopolymer of PDMAEMA prepared according to the same experimental protocol (figure 5).

Surprisingly enough the copolymer prepared in bullk with 30wt% of MAPEO has been found insoluble in all solubilization assays conducted adjusting solvent quality, temperature and mechanical conditions (see figure 2). The formation of this macrogel can be explained by the formation of hyperbranched macromolecules resulting from the electrophilic attack of the radical of the polymer growing chains on the hydroxyl group present at the extremity of the MAPEO segments.

Second approach : Polymerization in solution

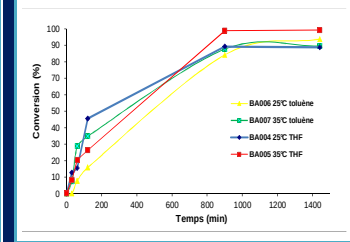


Figure 3: Comparison of conversion rates of polymerization of DMAEMA and MAPEO in function of T° and solvent

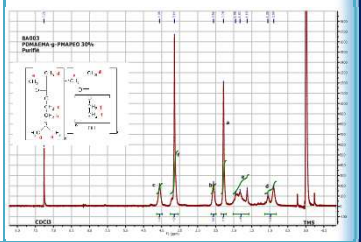


Figure 4 : ^{1}H.NMR spectrum of a PDMAEMA-g-MAPEO (70-30) synthesized in solution

When conducted in solution soluble copolymers with the targeted composition (see ^{1}H.NMR on figure 4) and molecular weight (figure 5) have been obtained for both copolymer composition and solvents. Although some differences in polymerization kinetics have been noticed (with a faster rate in THF and when carried out at 35 °C) these differences are not statistically significant.

Although the kinetics of the polymerizations conducted in solution is definitely slower compared to the same reaction carried out in bulk, a conversion rate of 90 to 99% is achieved when the reaction is conducted overnight.

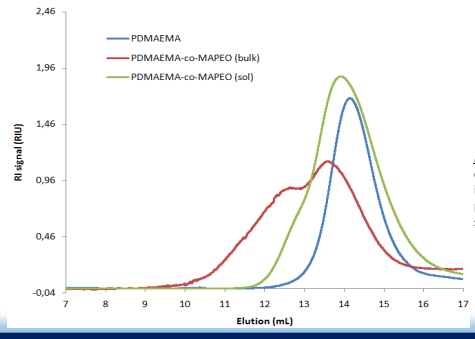
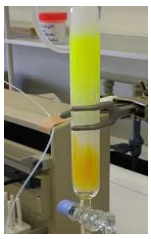


Figure 5 : Comparison of SEC chromatograms of PDMAEMA or its copolymers with MAPEO prepared either in bulk or in solution (10 wt%)



Purification optimization

In view to replace the classical purification techniques reported in literature which are tedious and consume large amount of solvents, we have succeed to replace all of them to one single step based on SEC performed in pure water and within less than 1 hour (see figure 6).

Figure 6 : Semi-preparative SEC chromatography of a fluorescent PDMAEMA (10Ka) in mQ water. The upper fluorescent zone is made from free fluorescein monomer

Acknowledgments

Part of this research has been supported by BioMiMedics Interreg Project.

L. Flebus PhD grant is financed by FRIA.