

SYNTHESIS OF DEGRADABLE POLYPHOSPHOESTER COPOLYMERS FOR TEMPLATING CALCIUM CARBONATE DRUG DELIVERY CARRIERS

Ergul Yilmaz Zeynep¹, Debuigne Antoine¹, Calvignac Brice², Boury Frank², Jerome Christine¹

¹Center for Education and Research on Macromolecules (CERM), University of Liège (ULg), Chemistry Department
Sart Tilman, Building B6a-third floor, Liège, B-4000, Belgium

²INSERM U1066, Micro et Nanomédecines Biomimétiques, IBS, University of Angers,
4 rue Larrey, Cedex 9, Angers, 49933, France

zeynep.ergul@ulg.ac.be

SUMMARY

Degradable acid bearing polyphosphoester (PPE) copolymers were prepared by combination of organocatalyzed ring opening polymerization and click chemistry. Their solution behavior and ability to complex calcium ions were studied as well as their capacity to template CaCO₃ particles dedicated to drug delivery.

INTRODUCTION

The design of drug delivery systems (DDS) often requires biodegradable and biocompatible materials that allow safe retention and controlled release of the drug. In this respect, CaCO₃ particles are appropriate drug carriers that have excellent properties such as low density, high specific surface areas and porosity for drugs and proteins encapsulation.[1] Here, hyaluronic acid usually used for templating CaCO₃ particles was substituted by a degradable synthetic copolymer based on PPE. The latter is a promising candidate due to its biocompatibility, biodegradability and the low toxicity of its degradation products such as phosphates. We also introduced acid functions on the PPE segment in order to enhance its calcium affinity and ability to tune the morphology of the CaCO₃ particles.

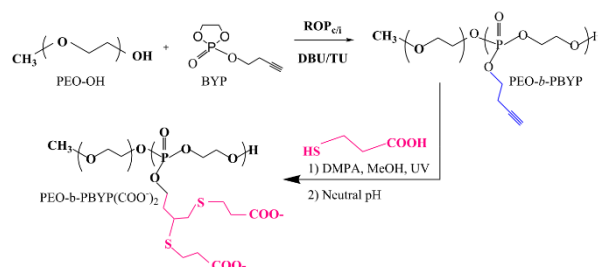
EXPERIMENTAL METHODS

The butynyl phospholane (BYP) polymerization was initiated from poly(ethylene oxide) PEO-OH by organocatalyzed ring opening polymerization (ROP) [2] followed by UV catalyzed thiol-yne addition of 3-mercaptopropionic acid onto the alkyne functions according to ref [3]. CaCO₃ particles were then generated in the presence of the copolymer following a procedure inspired from [4].

RESULTS AND DISCUSSION

Well-defined PPE copolymers bearing pendant alkynyl groups, i.e. PEO-*b*-PBYP (Đ <1.1), were obtained by organocatalyzed ROP of BYP initiated at 0°C from PEO-OH (Scheme 1). The copolymer was then reacted under UV with 3-mercaptopropionic acid in order to introduce carboxylic acid functions along the PPE backbone by thiol-yne reaction.[3] NMR analyses confirmed that full functionalization was reached after 2h. The high density of

acid moieties in PEO-*b*-PBYP(COO⁻)₂ is supposed to facilitate the Ca²⁺ complexation.



SCHEME 1. Synthesis of acid containing PEO-*b*-PBYP.

The solution behavior and self-assembly of PEO-*b*-PBYP(COO⁻)₂ in water was investigated by DLS with and without Ca²⁺ at different pH. Finally, stoichiometric amounts of CaCl₂ and Na₂CO₃ were mixed in water containing the PEO-*b*-PBYP(COO⁻)₂ which strongly influences the size of the CaCO₃ particles (~1.5 μm). (Figure 1)

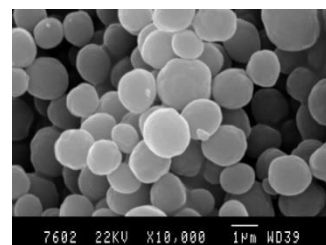


FIGURE 1. SEM image of CaCO₃ particles templated by PEO-*b*-PBYP(COO⁻)₂.

CONCLUSION

The acid-bearing PPE-based copolymers were successfully prepared and used as templating agents for the synthesis of CaCO₃ particles.

ACKNOWLEDGEMENTS

This work is supported by Erasmus Mundus Doctoral School Nanofar from the European Community.

REFERENCES

1. T. Beuvier *et al.*, *J. Mater. Chem.*, 2011, **21**, 9757.
2. B. Clément *et al.*, *Macromolecules*, 2012, **45**, 4476.
3. S. Zhang *et al.*, *J. Am. Chem. Soc.*, 2012, **134**, 18467.
4. H. Colfen *et al.*, 1998, **382**, 582.