GRADIENT COPOLYMERS FROM AROMATIC AND ALIPHATIC 2-OXAZOLINES AS PROMISING BIOMEDICAL MATERIALS

JURAJ KRONEK[1]*, NADEŽDA PETRENĆÍKOVÁ[1], ZUZANA KRONEKOVÁ[1], SHUBHASHIS DATTA[2], DANIEL JANCURA[2]

[1] DEPARTMENT FOR BIOMATERIALS RESEARCH, POLYMER INSTITUTE, SLOVAK ACADEMY OF SCIENCES, BRATISLAVA, SLOVAKIA
[2] DEPARTMENT OF BIOPHYSICS, FACULTY OF SCIENCE, P.J. SAFARIK UNIVERSITY, KOŠICE, SLOVAKIA
*JURAJ.KRONEK@SAVBA.SK

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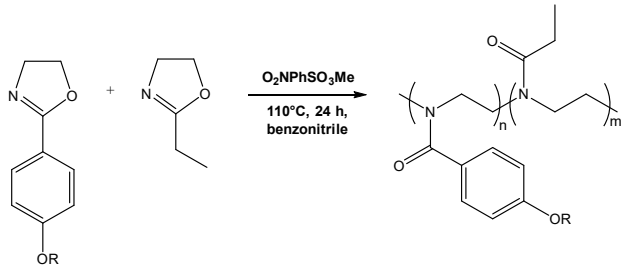
Introduction

Amphiphilic block copolymers play an important role in interfacial and colloid chemistry due to possible to self-assembly processes in solutions or on the surfaces. They play a special role in drug delivery systems as micellar or polymerosome particles encapsulating poorly soluble drugs. Gradient copolymers have been shown as polymeric materials with similar self-assembly properties as in the case of block copolymers. Poly(2-oxazolines) prepared by living cationic ring-opening polymerization (LCROP) represent versatile biomedical polymers with diversity of solubility, functionality, and stimuli responsive behaviour [1]. Block and gradient copolymers from 2-methyl-2-oxazoline and 2-phenyl-2-oxazoline were used for the preparation of stable nanoparticles of different size and particle shape [2]. Recently, we used gradient copolymer of 2-ethyl-2-oxazoline with extremely hydrophobic 2-(4-dodecyloxyphenyl)-2-oxazoline for the encapsulation of curcumin. Prepared nanoparticles exhibited excellent stability, high loading capacity, and efficient cell internalization of encapsulated curcumin [3].
Aim of this contribution is a survey of synthesis, properties and biomedical applications of gradient copolymers of different 2-(4-alkyloxyphenyl)-2-oxazolines with 2-ethyl-2-oxazoline.

Materials and Methods

2-(4-Alkyloxyphenyl)-2-oxazolines were prepared from 2-(4-hydroxyphenyl-2-oxazoline) by the reaction with alkyl halides in the presence of a base. Cationic polymerizations of 2-(4-alkyloxyphenyl)-2-oxazolines with 2-ethyl-2-oxazoline were performed in benzolitrile at 110 C for 24 h using methyl 4-nitrobenzenesulfonate as an initiator (SCHEME 1). Theoretical degree of polymerizations was in all cases equal to 100. Composition of copolymers was determined by NMR spectroscopy.



SCHEME 1. Cationic polymerization of 2-(4-alkyloxyphenyl)-2-oxazolines with 2-ethyl-2-oxazoline initiated by methyl 4-nitrobenzenesulfonate.

Thermoresponsive properties were measured by UV/Vis spectrometry as dependence of transmittance at 700 nm on temperature. Thermal properties were characterized by DSC. Drug-loaded and empty nanoparticles were prepared by dialysis method and characterized by DLS. In vitro cytotoxicity of copolymers and nanoparticles were characterized by a laboratory MTT test. Cell internalization was visualized by CLSM.

Results and Discussion

2-(4-alkyloxyphenyl-2-oxazolines) representing extremely hydrophobic monomers were used in living ring-opening cationic copolymerizations with 2-ethyl-2-oxazolines resulting in the library of amphiphilic copolymers. The composition of copolymers was followed by NMR in different time of polymerization and kinetic plots proved gradient character of prepared copolymers (FIG. 1). The polarity of prepared copolymers was characterized by contact angles measurements. Copolymers with content up to 15 mol % of aromatic comonomer exhibited thermosensitive behaviour.

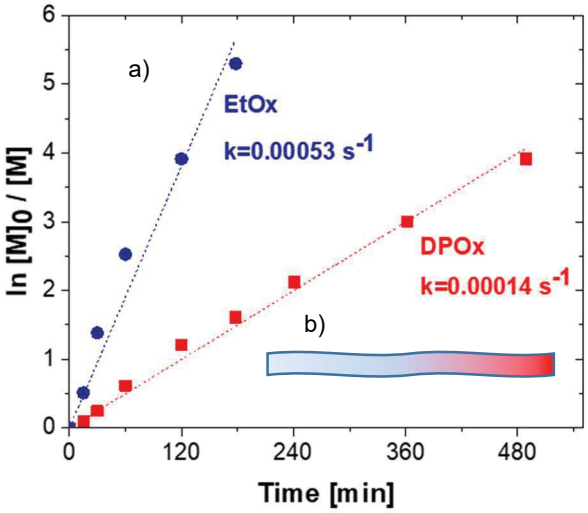


FIG. 1. Difference of polymerization rate of 2-ethyl-2-oxazoline (EtOx) and 2-(4-dodecyloxyphenyl)-2-oxazoline (DPO) during cationic polymerization (a) and schematic illustration of a gradient structure (b)

Copolymers above 12 mol.% of aromatic comonomers were able to form stable micellar nanoparticles. Particle size, shape, and loading capacity of model drugs were dependent on type of aromatic comonomers and composition of copolymers.

Conclusions

Gradient copolymers of different 2-(4-alkyloxyphenyl)-2-oxazolines with 2-ethyl-2-oxazoline represent versatile polymeric materials with thermosensitive properties and self-assembly behaviour.

Acknowledgments

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