POLYESTER-CAMPTOTHECIN CONJUGATES FOR CONTROLLED RELEASE

MARCIN SOBCZAK[1]*, EWA OLĘDZKA[1], MARZENA KURAS[1], URSZULA LUCHOWSKA[1], LUCYNA ŚWINIARSKA[1], RAFAŁ WYRĘBIAK[1], GRZEGORZ NAŁĘCZ-JAWECKI[2]

[1] DEPARTMENT OF INORGANIC AND ANALYTICAL CHEMISTRY, FACULTY OF PHARMACY AND DIVISION OF LABORATORY MEDICINE, MEDICAL UNIVERSITY OF WARSAW, POLAND
[2] DEPARTMENT OF ENVIRONMENTAL HEALTH SCIENCE, FACULTY OF PHARMACY AND DIVISION OF LABORATORY MEDICINE, MEDICAL UNIVERSITY OF WARSAW, POLAND
*E-MAIL: MARCIN.SOBCZAK@WP.PL

[ENGINEERING OF BIOMATERIALS 138 (2016) 45]

Introduction

Camptothecin (CMPT) (FIG. 1) belongs to the family of monoterpene indole alkaloids, isolated from *Camptotheca acuminata* tree [1]. CMPT and its derivatives commonly used in antitumor therapy, exhibit a broad range of antitumor and antileukaemia activity leading to the inhibition of topoisomerase I, subsequent damage of DNA and thus cell death. However, the clinical use of CMPT is limited by its low solubility in water, high toxicity and inactivation through lactone ring hydrolysis at a physiological pH [2]. From this point of view, the disadvantage of CAMPT might be overcome by its attaching to the macromolecular conjugates [3-4].

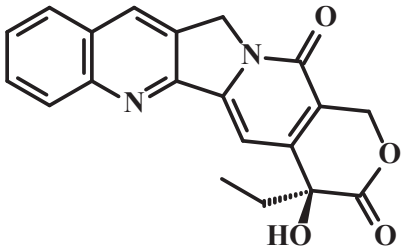

FIG. 1. Camptothecin.

The aim of this study was to prepare new polyester conjugates of CMPT. The polyester matrices were obtained by the ring-opening polymerization (ROP) of ε-caprolactone (CL), glycolide (GL) and *rac*-lactide (LA) in the presence of a new zinc-catalytic system. The preliminary studies of the influence of the polymeric chain structure on the release process of CMPT were described.

Materials and Methods

The ROP of cyclic esters was carried out under an argon atmosphere. The toxicity test was carried out according to the procedure described in our early paper [5]. Polymeric conjugates of CMPT were synthesized using 1,6-diisocyanatohexane (HDI) as linker under argon atmosphere. The polymerization products were characterized by means of ^{1}H- and ^{13}C-NMR (300 MHz, recorded in $CDCl_3$) spectroscopy. Number-average molecular weight (M_n) and polydispersity were determined by gel permeation chromatography (GPC). The zinc concentration in the obtained polymers was determined by Flame Atomic Absorption Spectrometry. The *in vitro* release study of CMPT from the synthesized conjugates was investigated by measuring the concentration of CMPT released at pH 7. The absorption in a buffer solution was determined by a UV-Vis spectrophotometer at the absorbance peak with a wavelength at 355 (lactone form) or 368 nm (carboxyl form) [4].

Results and Discussion

The macromolecular conjugates of anticancer drug were obtained from the copolymers of CL, LA and GL. The polymeric matrices and CMPT were coupled *via* HDI. The ROP process was carried out in the presence of diethylzinc/phenylalanine catalytic system (FIG. 2).

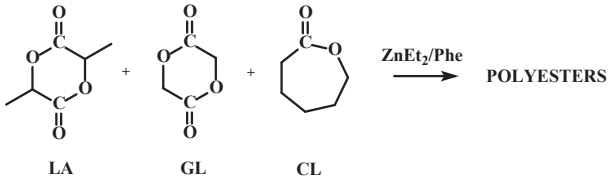

FIG. 2. Scheme of polyester matrices synthesis.

The M_n values of CL/LA and GL/LA copolymers determined by the GPC were in the range of 1900-6800 g/mol and 1600-5700 g/mol, respectively.

The cytotoxicity evaluation of the obtained polymers was studied using the luminescent bacteria *V. fischeri*. It was found that the obtained matrices were not toxic to the test biont. Four kinds of macromolecular conjugates of CMPT were prepared from CL/LA (63:37), CL/LA (42:58), GL/LA (56:44) and GL/LA (32:68). *In vitro* CMPT release from the macromolecular conjugates was carried out in PBS buffer at 37°C for 4 weeks. The percentage of the CMPT released after 4 weeks of incubation was about 62% for GL/LA (56:44), 57% for GL/LA (32:68), 42% for CL/LA (42:58) and 33% for CL/LA (63:37). The rate of *in vitro* drug release increased as the GL or LA content in the chain of copolymers decreased.

Conclusions

The synthesized biodegradable polymeric matrices were not toxic. The rates of CMPT release were shown to be directly dependent on the nature of the obtained copolymers. The kinetic rates of CMPT released were seen to be faster for the polymeric conjugates contained GL units as compared to those with CL units. Importantly, in some cases, drug "burst release" was not observed during the degradation process. The obtained results demonstrate that the macromolecular conjugates are interesting and promising materials for the controlled release of CMPT.

Acknowledgments

This work was financially supported by National Science Centre of Poland (Project NCN OPUS-5 DEC-2013/09/B/ST5/03480 entitled: "Elaboration of anti-cancer drug implantational delivery system immobilized on polymer matrix").

This work was also financially supported by the Medical University of Warsaw (The Student Grant – Mini-grant Studencki WUM 2015, Urszula Luchowska: "Innowacyjne biodegradowalne nośniki cytostatyków - synteza i badania strukturalne").

References

[1] S-F. Wu, P-W. Hsieh *et al.,* Molecules 13 (2008) 1361-1671.
[2] H. Fan, J. Huang *et al.,* Polymer 51 (2010) 5107-5114.
[3] E. Oledzka, P. Horeglad *et al.,* Molecules 19 (2014) 19460-19470.
[4] M. Sobczak, E. Oledzka *et al.,* J. Macromol. Sci. Pure and Appl. Chem. 51 (2014) 254–262.
[5] M. Sobczak, W. Kamysz *et al.,* React. Funct. Polym. 83 (2014) 54-61.