Encapsulation of Resveratrol in Poly(ε-caprolactone)-Poly(methacrylic acid) Copolymeric Micelles for Oral Delivery

L. Radeva[1*], K. Kamenova[2], S. Konstantinov[1], P. D. Petrov[2], K. Yoncheva[1]

[1]*Faculty of Pharmacy, Medical University of Sofia, Sofia, Bulgaria*
[2]*Institute of Polymers, Bulgarian Academy of Sciences, Sofia, Bulgaria*
[*]*l.radeva@pharmfac.mu-sofia.bg*

The application of nanosized drug delivery systems such as polymeric micelles in medicine is of a particular interest since they could provide targeted drug delivery, increased solubility and stability of the loaded substance as well as enhanced bioavailability and pharmacological effects [1, 2]. The natural polyphenol resveratrol exerts anrioxidant and anti-inflammatory effects, however, its poor aqueous solubility hinders its application [3, 4]. Therefore, its encpasulaition in nanoparticles could be considered an appropriate strategy. Taking this into consideration we developed novel micellar copolymeric carrier for resveratrol based on poly(methacrylic acid) and poly(ε-caprolactone) (PMAA-b-PCL-b-PMAA). Atom transfer radical polymerization (ATRP) of tert-butyl methacrylate (t-BMA), initiated from a bifunctional PCL macroinitiator, followed by hydrolysis of t-BMA groups, was applied for sythesizing central PCL hydrophobic block and two outer PMAA hydrophilic blocks amphiphilic block copolymer. The micelles were then obtained via self-assembly of the copolymer in aqueous media. The critical micelle concentration (CMS) was found to be 0.076 g/L and the system was characterized with mean diameter of 102 nm. Resveratrol was loaded via the solvent evaporation method at a mass ratio between the drug and the polymer 1:15. Encapsulation efficiency of 72% and loading degree of 67 μg/mL were achieved. The mean diameter of the loaded micelles was lower, namely 78 nm. TEM confirmed the small size and showed spherical shape of the micelles. The in vitro release tests showed burst release followed by sustained release which was slightly faster in media with pH=6.8 in comparison with pH=1.2. This was in agreement with the founding that the micelles aggregated in the acidic media due to protonation of the PMMA chains. Kinetic analysis showed that the release in the buffer with pH=6.8 followed first order kinetic while the process in the slightly acidic medium correlated with the Higuchi model. More importantly, 100% resveratrol was released from the system for 24 h in comparison with the free drug which showed dissolution of only 10% for the same period. Albumin denaturation assay confirmed the anti-inflammatory activity of both encapsulated and free resveratrol. In vitro co-culture model of inflammation revelaed that only pretreatment with the encpasulated resveratrol at 5 and 10 μM concentrations showed anti-inflammatory effect. Therefore, the PMAA-b-PCL-b-PMAA triblock copolymer micelles could be considered appropriate carriers for the oral delivery of the hydrophobic polyphenol resveratrol.

Keywords: polymeric micelles, resveratrol, anti-inflammatory activity

Acknowledgments
This research was funded by the European Union-NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, Project BG-RRP-2.004-0004-C01.

References

[1] Kawabata, Y.; Wada, K.; Nakatani, M.; Yamada, S.; Onoue, S. Formulation Design for Poorly Water-Soluble Drugs Based on Biopharmaceutics Classification System: Basic Approaches and Practical Applications. *Int. J. Pharm.* **2011**, *420*, 1–10.
[2] Suchaoin, W.; Bernkop-Schnürch, A. Nanocarriers Protecting toward an Intestinal Pre-Uptake Metabolism. *Nanomed.* **2017**, *12*, 255–269.
[3] Yang, G.; Chang, C.-C.; Yang, Y.; Yuan, L.; Xu, L.; Ho, C.-T.; Li, S. Resveratrol Alleviates Rheumatoid Arthritis via Reducing ROS and Inflammation, Inhibiting MAPK Signaling Pathways, and Suppressing Angiogenesis. J. *Agric. Food Chem.* **2018**, *66*, 12953–12960.
[4] Robinson, K.; Mock, C.; Liang, D. Pre-Formulation Studies of Resveratrol. *Drug Dev. Ind. Pharm.* **2015**, *41*, 1464–1469.