CURCUMIN LOADED FUNCTIONAL POLYMERIC NANOCARRIERS FOR IMPROVED DRUG TARGETING AND CANCER TREATMENT

Marta Slavkova[a], Denitsa Momekova[a], Georgi Momekov[a], Georgy Grancharov[b], Valeria Gancheva[b], Marya Kyulavska[b], Petar Petrov[b]

[a]Faculty of Pharmacy, Medical University-Sofia, 2 Dunav Str. 1000 Sofia, Bulgaria
[b]Institute of Polymers, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria

The intracellular drug targeting achieved by passive or active mechanisms provide the potential to increase the therapeutic efficiency of different APIs, especially ones with low aqueous solubility and limited cell uptake such as curcumin. This phytochemical can be successfully used in the cancer treatment due to its pleiotropic activity.

In the present study novel functional multilayer polymeric nanocarriers based on a binary blend of amphiphilic poly(ethylene oxide)-poly(ε-caprolactone)-b-poly(ethylene oxide) and poly(2-(dimethylamino)ethyl methacrylate)-b-poly(ε-caprolactone)-b-poly(2-(dimethylamino)ethyl methacrylate), with triphenylphosphonium ligands, were obtained and tested for targeted cell delivery of curcumin. Nanocarriers were prepared and loaded with curcumin by the solvent evaporation technique. DLS and TEM analysis confirmed formation of spherical mixed micelles with monomodal particle size distribution and mean hydrodynamic diameter of 120 nm. The drug was successfully incorporated into the hydrophobic micellar core with high loading efficiency. The *in vitro* dissolution tests revealed an initial "burst" release, followed by controlled release of up to 30 % of the API within 24 hours. The cytotoxicity and biocompatibility were tested using a MTT-dye reduction assay on HEK-293 (human embryonal kidney, non-tumorogenic), HEP-G2 (human hepatocellular carcinoma), HL-60 (acute myeloid leukemia) cell lines and on HL-60 multidrug resistant (HL-60/DOX) and cisplatine-resistant (HL-60/CDDP) sublines. In addition, the apoptosis, NF-κB activity and *in vitro* cellular uptake were evaluated. The blank micelles were practically devoid of cytotoxicity while curcumin loaded counterparts were possessed antiproliferative effect 1.5 to 5 times higher compared to the free API. Curcumin loaded micelles also successfully circumvented the resistance mechanisms and achieved lower IC_{50} values in the HL-60/DOX and HL-60/CDDP sublines compared to sensitive HL-60 cell line. The nanocarriers were also superior in the apoptogenic activity and NF-κB inhibition as opposed to the free drug due to improved cell internalization. Taking all results into account, one may conclude that the developed functional polymeric nanocarriers are promising candidates for effective intracellular drug delivery in anticancer treatment.

This research was supported by the Bulgarian National Science Fund (T02-21/2014).