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Application of Low Frequency Ac Magnetic Field for Controlled Delivery of Drugs by Magnetic Nanoparticles

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Abstract : Introduction:Nowadays pharmaceutical medicine is aimed to create systems for combined therapy, diagnostic, drug delivery and controlled release of active molecules to target cells. Magnetic nanoparticles (MNPs) are used to achieve this aim. MNPs can be applied in molecular diagnostics, magnetic resonance imaging (T1/T2 contrast agents), drug delivery, hyperthermia and could improve therapeutic effect of drugs. The most common drug containers, containing MNPs, are liposomes, micelles and polymeric molecules bonded to the MNPs surface. Usually superparamagnetic nanoparticles are used (the general diameter is about 5-6 nm) and all effects of high frequency magnetic field (MF) application are based on Neel relaxation resulting in heating of surrounded media. In this work we try to develop a new method to improve drug release from MNPs under super low frequency MF. We suppose that under low frequency MF exposures the Brown's relaxation dominates and MNPs rotation could occur leading to conformation changes and release of bioactive molecules immobilized on MNPs surface.The aim of this work was to synthesize different systems with active drug (biopolymers coated MNPs nanoclusters with immobilized enzymes and doxorubicin (Dox) loaded magnetic liposomes/micelles) and investigate the effect of super low frequency MF on these drug containers. Methods: We have synthesized MNPs of magnetite with magnetic core diameter 7-12 nm . The MNPs were coated with block-copolymer of polylysine and polyethylene glycol. Superoxide dismutase 1 (SOD1) was electrostatically adsorbed on the surface of the clusters. Liposomes were prepared as follow: MNPs, phosphatidylcholine and cholesterol were dispersed in chloroform, dried to get film and then dispersed in distillated water, sonicated. Dox was added to the solution, pH was adjusted to 7.4 and excess of drug was removed by centrifugation through 3 kDa filters. Results: Polylysine coated MNPs formed nanosized clusters (as observed by TEM) with intensity average diameter of 112±5 nm and zeta potential 12±3 mV. After low frequency AC MF exposure we observed change of immobilized enzyme activity and hydrodynamic size of clusters. We suppose that the biomolecules (enzymes) are released from the MNPs surface followed with additional aggregation of complexes at the MF in medium. Centrifugation of the nanosuspension after AC MF exposures resulted in increase of positive charge of clusters and change in enzyme concentration in comparison with control sample without MF, thus confirming desorption of negatively charged enzyme from the positively charged surface of MNPs. Dox loaded magnetic liposomes had average diameter of 160±8 nm and polydispersity index (PDI) 0.25±0.07. Liposomes were stable in DW and PBS at pH=7.4 at 370C during a week. After MF application (10 min of exposure, 50 Hz, 230 mT) diameter of liposomes raised to 190±10 nm and PDI was 0.38±0.05. We explain this by destroying and/or reorganization of lipid bilayer, that leads to changes in release of drug in comparison with control without MF exposure. Conclusion: A new application of low frequency AC MF for drug delivery and controlled drug release was shown. Investigation was supported by RSF-14-13-00731 grant, K1-2014-022 grant.

Keywords : magnetic nanoparticles, low frequency magnetic field, drug delivery, controlled drug release
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