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Cytotoxicity of doxorubicin loaded in folate-targeted micelles of dextran/retinoic acid in acute leukemia

J. Varshosaz[1], F. Hasanzadeh[2], H. Sadeghi[3], M. Nayebsadriyan[1,*], M. Banitalebi[1]

[1]Department of Pharmaceutics, School of Pharmacy and Novel Drug Delivery Systems Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Medicinal Chemistry, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Department of Biotechnology, Isfahan University of Medical Sciences, Isfahan, Iran

Background and Aims: The aim of the present study was determination of cytotoxcicity of doxorubicine loaded in the micelles of folate (FA) targeted amphiphilic derivative of retinoic acid-grafted dextran (FA-ATRA-Dex) in KG-1 leukemia cell line.
Methods: FA-ATRA-Dex was synthesized using carbonyldiimidazole and dimethylaminopyridine. The structure of micelle was characterized with 1H NMR, FTIR, and CMC of the copolymer was determined by pyrene fluorescent probe. The particle size and zeta potential of the nanoparticles obtained were determined by Dynamic Light Scattering method. Doxorubicin was loaded in the micelles by dissolving method. Then the mixture was prob-sonicated for about 2 min. The amount of loaded drug was measured from the difference of the total drug and the free un-entrapped drug spectophotometrically. Drug release tests were carried out in dialysis membrane. The cytotoxicity of free doxorubicine was compared with the drug loaded in folate targeted micelles and no-targeted ones by MTT assay on KG-1 cell line in different concentrations of doxorubicin (0.189, 0.377, 0.566 and 0.745 µg/ml).
Results: FA-ATRA-Dex was synthesized successfully. The CMC of copolymer was 12.5 µg/mL when the degree of substitution of 2 and 2.4 mole of FA and ATRA/mol of Dex (Mw10000) was used. The optimized micelles showed particle size of 74.2 nm, zeta potential of -8 mV, drug loading efficiency of 97% and RE of 60%. In the concentration of 0.745 µg/ml of doxorubicine there was no difference between the free drug and drug loaded in micelles without folate ligand ($p>0.05$). However, the difference between cytotoxicity of the drug loaded in the folate targeted micelles and the free drug or drug loaded in the non-targeted micelles were significant ($p<0.05$).
Conclusions: Doxorubicine loaded in folate targeted micelles of ATRA-Dex was approximately 20 fold more toxic than the free drug and seems promising in reducing drug resistance in acute leukemia.

Keywords: Doxorubicin; Cytotoxicity; KG1 cell line; Folate targeted micelles