DOES COMPLEXING OF ANTRACYCLIN BY CYCLODEXTRIN BLOCK THE FORMATION OF FREE RADICALS IN FENTON REACTION?

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Anthracycline drugs have been used for nearly forty years for the treatment of several malignancies. Hundreds of analogs of the first anthracycline antibiotics: doxorubicin and daunorubicin have been synthesized and evaluated. Multiple molecular mechanisms were proposed to explain the cytostatic and cytotoxic effects induced by these drugs.[1,2] The specific toxicity is due to reactive forms of oxygen: aminoradical superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and especially toxic hydroxyl radical ($HO^{\bullet}$), which are produced in redox reactions of anthracyclines such as Fenton reaction.[3] To prevent any adverse action of active oxygen species we can block the quinone group which is responsible for their production until delivery of drug molecules to pathologically changed cells. Blocking can be achieved by the formation of an inclusion complex between the anthracycline molecule and cyclic oligosaccharides such as cyclodextrins (CDs).[4,5]

In the first step of our work, the complexation of anthracycline drugs such as doxorubicin and daunorubicin with several derivatives of β-cyclodextrin (Figure 1) have been investigated using cyclic voltammetry, amperometry and spectroscopy. These experiments indicate that cyclodextrins modified with different functional side groups form significantly more stable complexes with anthracyclines than unmodified CD itself. Electrochemical studies of the reactive oxygen species formation in Fenton reaction were carried out for anthracycline drugs complexed inside the cavities of the β-CD derivatives. These studies allowed to evaluate the extent of the quinone group blocking in case of the drug complexed by derivatives of cyclodextrin.

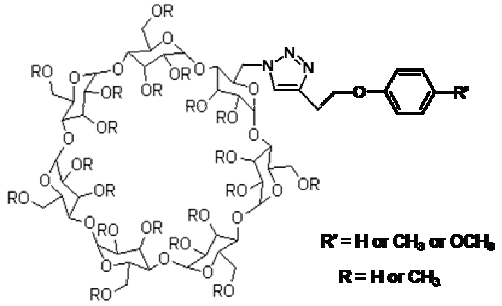

Figure 1

[1] J.B. Chaires, J.E. Herrera, M.J. Waring; *Biochemistry*, **1990**, 29, 6145–6153
[2] L.J. Steinherz, P.G. Steinherz, C.T. Tan, G. Heller, M.L. Murphy; *J.A.M.A.*, **1991**; 266, 1672–1677
[3] T. Šimùnek, M. Štìrba, O. Popelová, M. Adamcová, R. Hrdina, V. Geršl; *Pharmacological Reports*, **2009**, 61, 154–171
[4] O. Bekers, J. J. Kettenes-Van Der Bosch, S. P. Van Helden, D. Seijkens, J. Beijnen, A. Bult, W. J. M. Underberg; J. Incl. Phenom. and Molecular Recognition in Chemistry, 1991, 11, 185-193
[5] C. Thiele, D. Auerbach, G. Joung, G. Wenz;. J. Incl. Phenom. Macrocycl. Chem. 2010,DOI:10.1007/s10847-010-9741-4.