aggregation leads also to the loss of mTHPC fluorescent ability and affects on their affinity to biological structures, such as plasma proteins and cell membranes. Therefore, mTHPC aggregation limits the range of methods to determine the quantitative characteristics of mTHPC distribution processes in blood serum.

In our study we used cyclic oligosaccharides (cyclodextrins) to prevent the photosensitizer aggregation and to calculate the binding constants of mTHPC to the main serum proteins. It is widely known that cyclodextrins readily form inclusion complexes with many drugs by incorporating a drug molecule or more commonly a lipophilic moiety of the molecule into the central cavity. It has been shown, that CDs efficiently form an inclusion complexes with mTHPC [3] and can be used in indirect techniques of binding constants determination.

To determine the mTHPC affinity to biological structures we have analysed the processes of mTHPC binding to methyl-β-cyclodextrin in the serum proteins solutions (human serum albumin, low and high density lipoproteins) and in the lipid vesicles suspensions. The obtained titration curves and previously determined binding constants values for the mTHPC association with methyl-β-cyclodextrin process were used to estimate relative mTHPC affinity to biological structures. The following values of the distribution coefficient were obtained: 2.6 $(mg/ml)^{-1}$ for human serum albumin, $4.8x10^2$ $(mg/ml)^{-1}$ for low density lipoproteins and $1.0x10^3$ $(mg/ml)^{-1}$ for high density lipoproteins. The ratios of mTHPC distribution coefficients in plasma com-pounds were in a good accordance to the data obtained by means of the gel-chromatography [4].

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# ВЛИЯНИЕ ПРОИЗВОДНЫХ В-ЦИКЛОДЕКСТРИНА НА БИОДОСТУПНОСТЬ И БИОРАСПРЕДЕЛЕНИЕ ТЕТРАПИРРОЛЬНЫХ СОЕДИНЕНИЙ

# INFLUENCE OF B-CYCLODEXTRIN DERIVATIVES ON THE BIOAVAILABILITY AND BIODISTRIBUTION OF TETRAPYRROLE COMPOUNDS

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Цель данной работы – оценить влияние β-циклодексринов на биодоступность и биораспределение мТГФХ в различных биологических системах, включая процессы распределения в мышах-опухоленосителях.

The aim of this work was to evaluate the effect of β-cyclodextrins on mTHPC bioavailability and biodistribution in various biological systems including tumor-bearing mices.

*Ключевые слова:* мТГФХ, β-циклодекстрины, комплексы включения, фотодинамическая терапия, биораспределение.

*Keywords*: mTHPC, β-cyclodextrins, inclusion complexes, photodynamic therapy, biodistribution.

The application of many drugs is hampered by their non-optimal pharmacological properties, such as low aqueous solubility, irritating nature, lack of stability, rapid metabolism and non-selective drug distribution. Nanocarriers were developed to palliate these problems by improving drug delivery, opening the era of nanomedicine in oncology [1, 2]. Significant efforts have been made toward this goal by developing nanoparticle drug delivery systems, having particle diameters up to 200 nm [1]. Nanocarriers can deliver drugs in a spatiotemporally controlled manner that potentially increase therapeutic efficacy of the drugs, reduce their systemic side effects, and improve patient's adherence to regimen by reducing the dose and administration frequency [2].

Cyclodextrins (CDs) of biomedical and pharmaceutical interest are a family of cyclic oligosaccharides with a hydrophobic internal cavity and a hydrophilic outer surface. The most notable CD feature is their ability to form stable inclusion complexes ("host – guest" complexes) with a very wide range of solid, liquid and gaseous compounds by a molecular complexation [3]. The inclusion complexes based on CDs are of interest from the unique properties of CDs enables using them as additives to improve the properties of various substances. As a result CDs have been explored as additives in the food, cosmetic and pharmaceutical industries to improve product stability and solubility [3, 4]. CDs applications in the pharmaceutical industry are constantly expanding. To date there are above 40 products or formulations containing various CDs, especially β-CD and its derivative [4]. Moreover, CDs are promising delivery systems for photodynamic therapy (PDT) purpose [5].

Of special interest for this study is mTHPC, which is a potent, clinically approved tetrapyrrole photosensitizer (PS) for PDT purpose that used as a solvent-based formulation for the treatment of head and neck cancers [6]. The main limitation of mTHPC application is related to its low water solubility necessitating the use of special delivery systems including CDs. The aim of this work was to evaluate the effect of β-cyclodextrins on mTHPC bioavailability and biodistribution in various biological systems.

It was shown that association of mTHPC with the β-CDs completely abolishes its aggregation after introduction into blood that should improve pharmacokinetics and bioavailability of mTHPC. It was demonstrated that β-CDs have a concentration-dependent effect on the process of mTHPC distribution in blood serum. Besides, β-CDs increase diffusion movement of mTHPC molecules that can significantly accelerate the delivery of PS to the targets cells and tissues. *In vivo* study confirms the fact that the use of β-CDs allows modifying mTHPC distribution processes in tumor bearing animals that is reflected in the decreased level of PS accumulation in skin and muscles, as well as in the increased PS accumulation in tumor. Taken as a whole, complexation of mTHPC with β-CDs leads to increased water solubility, accelerated delivery of PS to the targets cells and tissues, improved the tumor-to-muscles ratio and expected low skin photosensitivity. Thus, β-CDs are very attractive delivery system for tetrapyrrole photosensitizers and these findings might have potential relevance in the improvement of PDT treatment with mTHPC.

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