NONCOVALENT NANOCOMPLEXES BETWEEN DRUGS AND TRANSMEMBRANE TRANSFER FACILITATING AGENTS: FORMATION, STRUCTURE AND APPLICATION FOR DRUG DELIVERY PURPOSES

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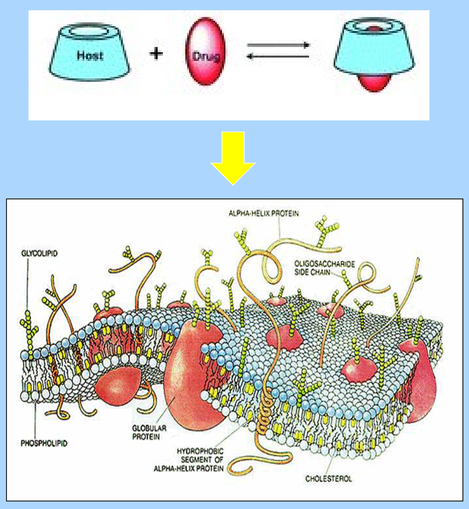
INTRODUCTION

Searching for the new prospective drug delivery approaches is an urgent challenge of the modern biomedical science and technology areas, including molecular medicine, molecular pharmacology, molecular biophysics and nanotechnology. Among effective ways to promote drug molecules administration into the targeting cells there is a way when penetration enhancing agents' molecules or specially created drug delivery molecular systems (liposomes, nanosomes) form noncovalent complexes with the drug to be delivered. Such complexes can penetrate the cell membranes easier due to physico-chemical properties of the delivery assisting substances: here the molecule or molecular cluster of facilitating compound works as a vehicle.



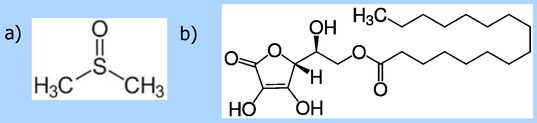
In the current combined mass spectrometry and quantum chemical study, we examined the intermolecular interactions of the molecules of selected anticancer mercapto-derivatives of nucleobases with drug delivery facilitating agent dimethyl sulfoxide (DMSO known as a transdermal and transmembrane drugs penetration enhancer) or ascorbyl palmitate (AP, fat soluble form of vitamin C, known as an agent forming nanosomes called aposomes with potential applicability in the drug delivery area).

EXPERIMENTAL

Mass spectral data were obtained in the positive ion mode using triple quadruple (QqQ) Micromass Quattro Micro mass spectrometer (Waters, Manchester, UK) which was equipped with the electrospray ion source. This source was operated in the standard ESI mode. The ESI source temperature was set to 120°C and the desolvation temperature was 200°C. The capillary was operated at 3.5 kV. The cone voltage (CV) values of 20 and 10 V were used. ESI spectra were recorded in the mass range of *m/z* 100-2000. Data acquisition and processing were performed using MassLynx 4.1 software (Waters, Manchester, UK).

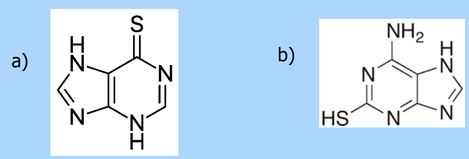
Objects of investigations

Drugs delivery facilitating agents



Scheme 1. Chemical structures of the facilitating agents a) dimethyl sulfoxide; b) ascorbyl palmitate .

Anticancer drugs



Scheme 2. Chemical structures of the medications under study: a) 6-mercaptopurine; b) 2-mercaptoadenine.

The objects of study are the following drug delivery facilitating agents: dimethyl sulfoxide (DMSO, C_2H_5OS, MW=78.13 Da) and Ascorbyl Palmitate (AP, other names 6-O-palmitoylascorbic $C_{22}H_{38}O_7$, MW = 414.5 Da), whose chemical structure is presented in Scheme 1.

The medications under study are anticancer mercapto-derivatives of nucleobases : 6-mercaptopurine (MP, $C_5H_4N_4S$, MW=152.2 Da); 2-mercaptoadenine (MA, $C_5H_5N_5S$, MW=167.2 Da), whose chemical structure is presented in Scheme 2.

RESULTS AND DISCUSSION

ESI MS study of intermolecular interactions between DMSO and the anticancer drugs

Formation of stable noncovalent complexes of DMSO with the molecules of 6-mercaptopurine and 2-mercaptoadenine in the polar solvent methanol was revealed by the ESI MS probing of model binary systems containing DMSO and these anticancer drugs (Fig.1 and Fig.2). To evaluate the structure and energetic parameters of the noncovalent complexes of DMSO with the studied drugs, the quantum chemical calculations of the nanocomplexes were performed: the geometry and interaction energy (IE) of the most stable complexed are presented in the inserts of Fig.1 and 2.

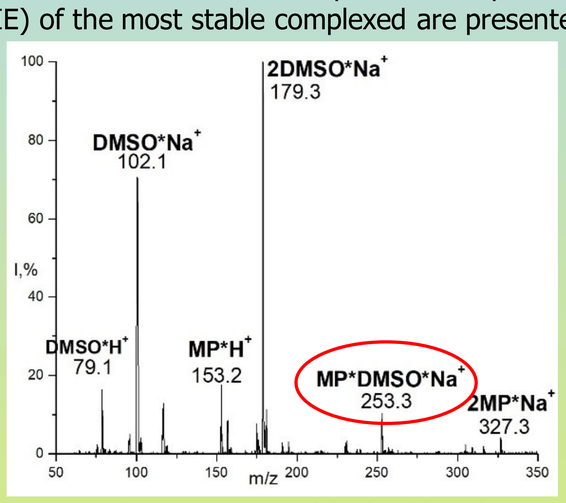
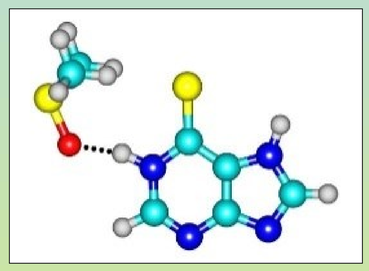


Fig. 1. ESI mass spectrum of the (DMSO+MP) model system (1:3 molar ratio) in methanol.



IE=-15.3 kcal/mol

Fig. 2. Calculated by DFT method optimal structure and interaction energy of noncovalent complex of MP with DMSO.

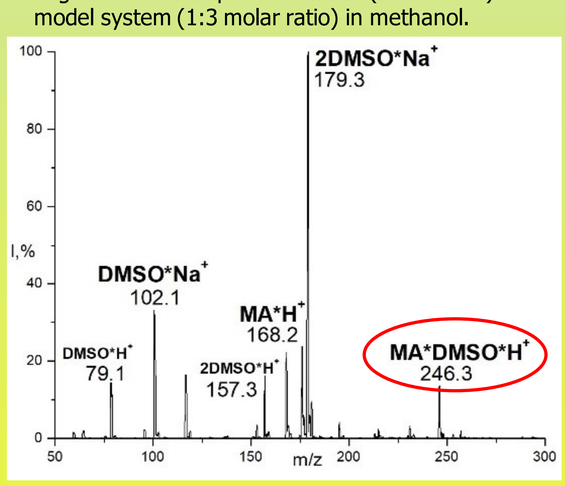
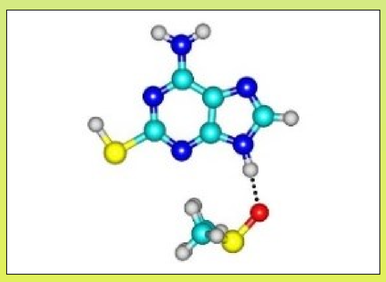


Fig. 3. ESI mass spectrum of the (DMSO+MA) model system (1:3 molar ratio) in methanol.



IE=-15.6 kcal/mol

Fig. 4. Calculated by DFT method optimal structure and interaction energy of noncovalent complex MA with DMSO.

The results of the study as to formation of stable noncovalent nanocomplexes of DMSO with the anticancer mercapto-derivatives of nucleobases are proposed to be considered as one of the possible molecular mechanisms of action of DMSO as transmembrane penetration enhancer for these drugs delivery.

ESI MS study of complexation between AP and the drugs

The following ESI MS measurements confirmed the possibility of stable noncovalent complexes formation between another drug delivery facilitating agent Ascorbyl Palmitate (AP) and 6-mercaptopurine and 2-mercaptoadenine in the polar media (Fig.5 and Fig.6).

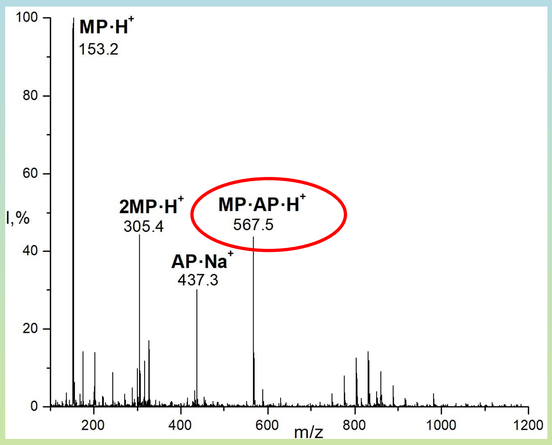


Fig. 5. ESI mass spectrum of the (AP+MP) model system (1:1 molar ratio) in methanol.

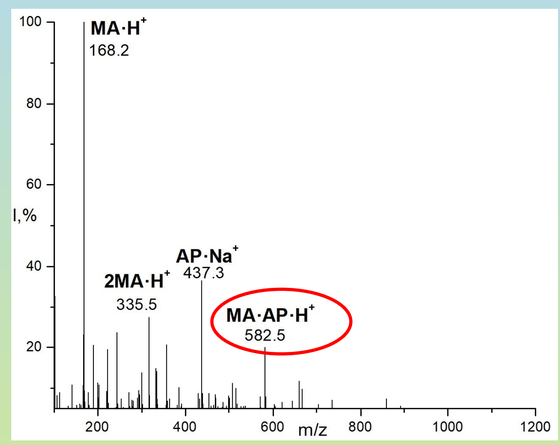


Fig. 6. ESI mass spectrum of the (AP+MA) model system (1:1 molar ratio) in methanol.

ESI MS examining of AP as an agent for nanosomes formation

The ESI experiments reveal the presence in the mass spectrum peaks of protonated and cationized AP molecules as well as the abundant AP clusters of nAP•H$^+$ and nAP•Na$^+$ type (n=2÷4) (Fig.7). This result testifies to the formation of stable noncovalent complexes of the AP molecules in the polar media and confirms the AP effectiveness to form nanosomes for drug delivery. The ESI probing of the model system containing AP and DPPC (Fig. 8) demonstrates the presence in the spectrum a peak of stable complex AP•DPPC•H$^+$ which models the AP intermolecular interactions with the phospholipid components of biomembranes and/or liposomes under AP functioning as a drugs delivery assisting agent.

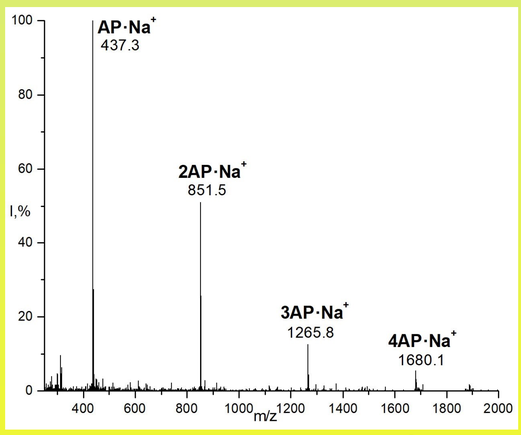


Fig. 7. Positive ion ESI mass spectrum of AP in methanol.

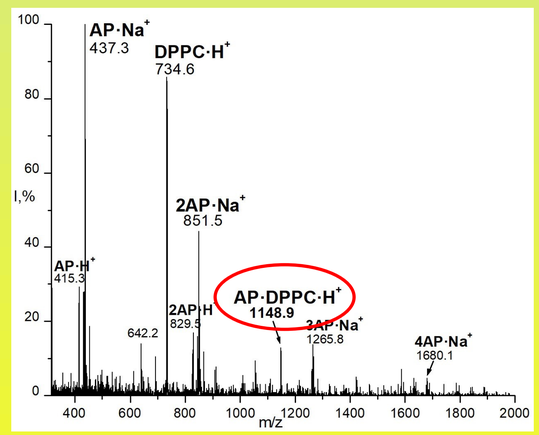


Fig. 8. ESI mass spectrum of the (AP+DPPC) system (1:1 molar ratio).

Conclusions

The results of the study on formation of noncovalent nanocomplexes between the anticancer drug molecules and the delivery facilitating molecules or molecular clusters can be considered as a basis for the development of nanostructures for facilitating of transmembrane transfer of the fat insoluble drugs.

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