Nanocomposites of two-dimensional transition metal dichalcogenides with anticancer drug 5-fluorouracil: biophysical examination of drug delivery applicability

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Introduction

Two-dimensional (2D) transition metal dichalcogenides (TMDs), notably MoS_2 and WS_2, are considered and deeply studied as efficient, biocompatible nanocarriers for drug delivery and cancer therapy due to their high surface area, excellent photothermal conversion, and other physico-chemical peculiarities. At the same time, TMDs are characterized by high catalytic activity, in particular edge-site activity and defects stimulated catalysis, that can affect the drugs transported. Therefore, the study of the peculiarities of biophysical interactions between nanoparticles and drug molecules can become the basis for the development and understanding of the controllability of processes of drug compound loading and release, as well as provide the opportunity to assess the applicability of TMDs for specific drug delivery. Our previous recent study focused on the combined – experimental&theoretical – characterization of interactions between the components of a nanocomposite of MoS_2 with anticancer thioderivatives of purine nucleobases 6-thiopurine (TP), and 2-thioadenine (TA) [2]. The biologically significant noncovalent and covalent interactions of TP and TA with MoS_2 nanosheets were revealed. In the current study, we used the same approach combining laser desorption/ionization (LDI) mass spectrometry and ab initio DFT/M06-2X calculations to characterize the nanocomposites of **TMD (MoS_2 or WS_2)** with the widely used anticancer drug **5-fluorouracil (FU)**.

LDI MS of TDMs + FU nanocomposites

The LDI data show the presence of appropriate peaks of intact molecular ions of FU in the positive and negative ion modes spectra for both (MoS_2 + FU) and (WS_2 + FU) nanocomposites (Fig. 2). These results confirm the effective drug loading on the TMD nanoparticles during the composites production by ultrasonic treatment and effective drug release under the LDI. Note, that LDI conditions can be considered as modeling the other light-activated drug release conditions such as the conditions of photothermal cancer treatment with TMD nanomaterials usage. Preservation of intensive peak of FU molecular ion in the spectra of nanocomposites (TMD+FU) testifies to the preservation of the drug`s molecular structure and anticancer activity within the nanocomposites.

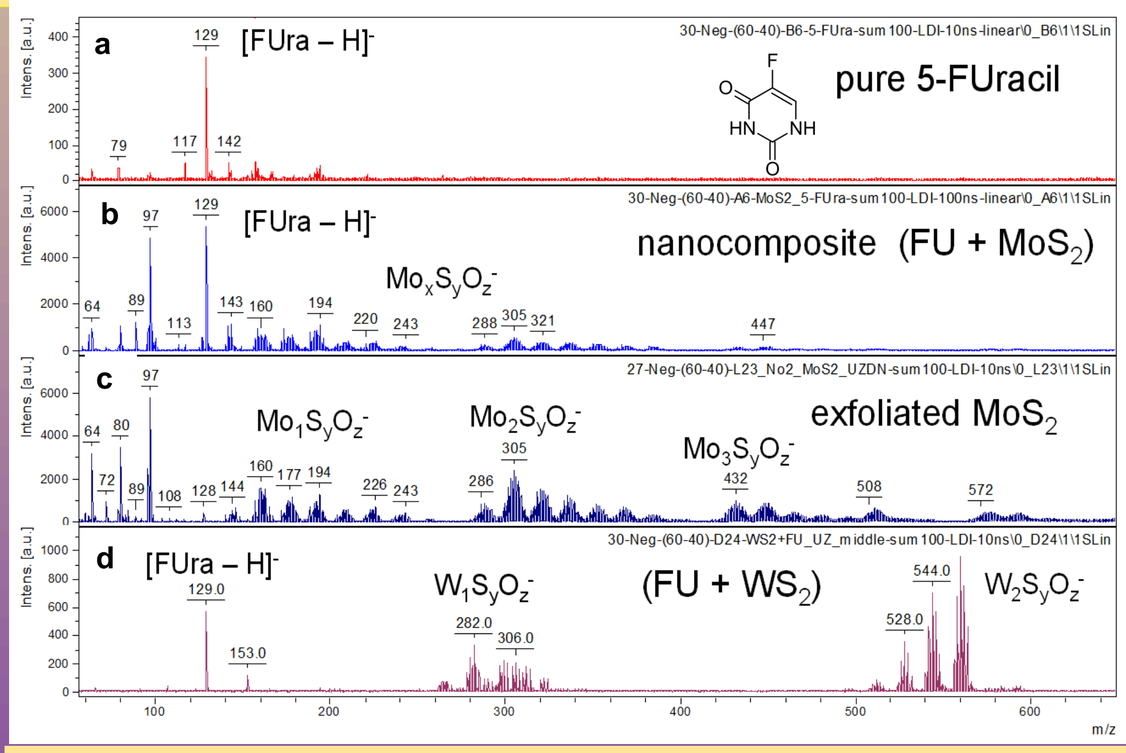


Fig.2 .LDI mass spectra of the systems studied: a) dried aqueous solution of FU; b) nanocomposite (FU+ MoS_2); c) pure exfoliated MoS_2 aqueous suspension; d) nanocomposite (FU+ WS_2).

Acknowledgements. **This work was supported by the NAS of Ukraine grant 0126U001857**

Expetimental&theoretical methods

In the current study, LDI MS was applied for an experimental characterization of the exfoliated MoS_2 (or WS_2) and nanocomposites obtained by ultrasound treatment (using piezoelectric oscillator generating 1700 kHz frequency) of aqueous dispersions of MoS_2 (or WS_2) with FU. LDI mass spectrometric experiments were performed with MALDI-TOF Autoflex II LRF20 instrument applying UV laser operating at 337 nm.

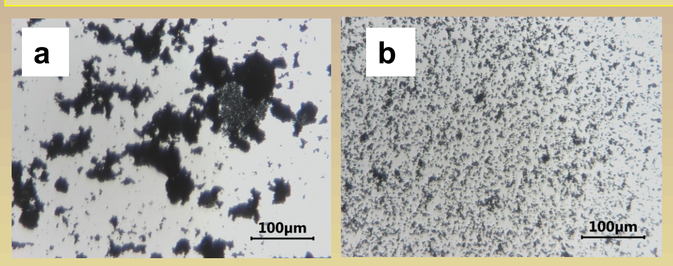


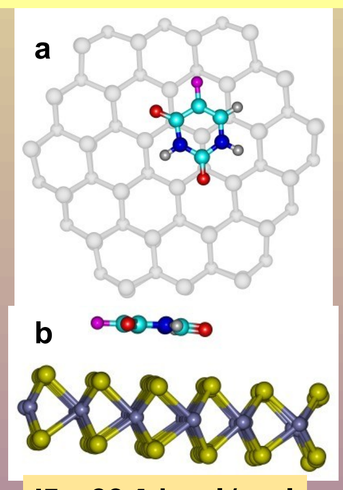
Fig.1 . Optical microscopy images of a) MoS_2 powder aqueous suspension; b) (MoS_2+FU) nanocomposite.

The nanocomposite samples were also examined by the optical microscopy method (Fig. 1) to confirm the effective TMDs particles exfoliation.

We used the DFT/M06-2X/LanL2DZ(Mo)/LanL2DZdp(S)/6-31++G** method for theoretical modelling of nanocomplexes of MoS_2 nanosheets with FU to examine the possible structures and energetic parameters of such nanocomplexes. For the modelling of MoS_2 nanoparticles we took the nanosheets containing 27 atoms of Mo and 54 atoms of S.

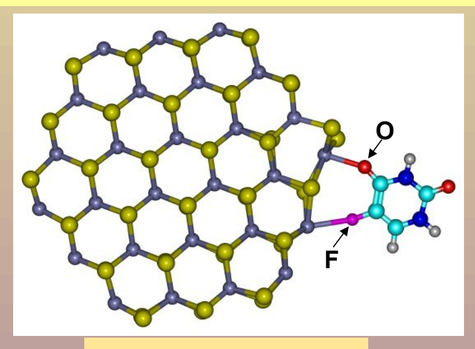
Quantum chemical modeling of MoS_2 nanocomplexes with FU

DFT/M06-2X modelling of nanocomplexes of MoS_2 nanosheets with FU allowed us to obtain the structural and energetic parameters of biophysical interactions of the drug molecules with the nanoparticles. It was shown that FU can form stable staked complexes with the MoS_2 nanosheet surface. Some FU molecules can form covalent complexes with the nanosheets` edges.



IE=-20.1 kcal/mol

Fig.3. Structure of the most stable noncovalent staked complex of (MoS_2+FU) : a) top view; b) side view.



IE=-46.8 kcal/mol

Fig.4. Structure of the most stable covalent complex of (MoS_2+FU) – initial geometry when the drug molecule contacts with the nanoflake edge. The complex is stabilized by two covalent bonds O-Mo, F-Mo.

Conclusions

In the LDI mass spectra of studied (TDM+FU) nanocomposites we did not find the spectral indications of the structural transformations of FU molecules which would be crucial for its anticancer effect in contrast to the situation with nanocomposites of (MoS_2 +TP) or (MoS_2 +TA) [2] that testifies to the TDMs applicability for the FU drug delivery. DFT calculations revealed the formation of stable staked complexes of FU with MoS_2 nanosheet`s surface as well as possibility of the covalent bonding of FU molecules to the nanoparticle`s edges.

Reference. [1] R. Zhang, Z. Yan, M. Gao, et al, J. Mater. Chem. B, 12, 12437 (2024).
[2] V. A. Pashynska, M. V. Kosevich, et al., Low Temp. Phys, 52, N 5 (2026).