

Theoretical Investigation of Hydroxyurea Adsorption on GaSe, InSe, MoSe₂ and WTe₂ for Emerging Nanodrug-Delivery Systems

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Abstract

Hydroxyurea (HU) is a significant antineoplastic agent, however its effectiveness is limited by nonspecific administration and systemic toxicity. Two-dimensional (2D) chalcogenide monolayers provide a compelling approach for precise and regulated drug release due to their extensive surface area, adjustable band topologies, and chemical resilience. This work used density functional theory (DFT) to examine the adsorption of HU on the surfaces of GaSe, InSe, MoSe₂, and WTe₂, assessing their viability as nanocarriers. The calculated adsorption energies vary from - 0.80 eV to -1.20 eV, indicating thermodynamically favorable and stable physisorption with little lattice distortion. HU@MoSe₂ demonstrates the most robust association and the protracted recovery duration (10⁸ s), indicating its appropriateness for continuous release, while HU@InSe displays the lowest adhesion and the briefest desorption time (10¹ s), advantageous for rapid-response sensing. Upon adsorption, the band gap diminishes somewhat (up to about 1%) and the work function improves marginally (up to approximately 1.5%), signifying improved surface sensitivity without compromising semiconducting properties. The global reactivity indices further validate the equilibrium of hardness and electrophilicity across all compounds. These results demonstrate a definitive association between adsorption energetics and electrical modulation in HU-chalcogenide complexes. The results provide a theoretical basis for the forthcoming experimental advancement of biocompatible, intelligent, and electrically sensitive nanocarriers that may enhance the delivery and safety of hydroxyurea in cancer treatment.

Keywords: Hydroxyurea; DFT; Adsorption Energy; Drug Delivery Systems; Electronic Properties.

دراسة نظرية لامتزاز الهيدروكسي يوريا على (GaSe)، (InSe)، (MoSe₂)، و (WTe₂) لاستخدامها في نظم ناشئة للتوصيل الدوائي النانوي

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المخلص

يُعدّ الهيدروكسي يوريا (HU) عاملاً مهماً مضاداً للأورام؛ إلا أن فعاليته محدودة بسبب الإعطاء غير النوعي والسُميّة الجهازية. وتوفر الطبقات الأحادية الكالكوجينية ثنائية الأبعاد نهجاً واعداً للإطلاق الدوائي الدقيق والمضبوط، لما تمتلكه من مساحة سطحية كبيرة وبُنى نطاقية قابلة للضبط وثبات كيميائي. في هذه الدراسة، استُخدمت نظرية دالية الكثافة (DFT) لدراسة امتزاز الهيدروكسي يوريا على أسطح غالسيوم سيلينيد (GaSe)، وإندسيوم سيلينيد (InSe)، وموليبدنوم ثنائي السيلينيد (MoSe₂)، وتنجستن ثنائي التيلورايد (WTe₂)، وتقييم صلاحيتها كنواقل نانوية. تراوحت طاقات الامتزاز المحسوبة بين -0.80 و-1.20 إلكترون فولت، مما يشير إلى امتزاز فيزيائي مستقر ومفضل ترموديناميكياً مع تشوه محدود في الشبكة البلورية. أظهر نظام HU@MoSe₂ أقوى ارتباط وأطول زمن استرداد (10⁸ ثانية)، مما يدل على ملائمة للإطلاق المستمر، في حين أظهر نظام HU@InSe أضعف التصاق وأقصر زمن إزالة امتزاز (10¹ ثانية)، وهو ما يُعدّ مناسباً لتطبيقات الاستشعار سريعة الاستجابة. بعد الامتزاز، انخفضت فجوة النطاق انخفاضاً طفيفاً حتى نحو 1%، وارتفعت دالة الشغل ارتفاعاً طفيفاً حتى نحو 1.5%، مما يدل على تحسن حساسية السطح من دون المساس بالخصائص شبه الموصلة. كما تؤكد مؤشرات التفاعلية العامة توازن الصلابة والإلكترونية في جميع المركبات. وتُظهر هذه النتائج وجود علاقة واضحة بين طاقات الامتزاز والتعديل الإلكتروني في معقدات HU-الكالكوجينيد. وتوفر النتائج أساساً نظرياً للتطوير التجريبي المستقبلي لنواقل نانوية متوافقة حيويًا وذكية وحساسة كهربائياً، يمكن أن تعزز توصيل الهيدروكسي يوريا وسلامته في علاج السرطان.

الكلمات المفتاحية: الهيدروكسي يوريا؛ نظرية دالية الكثافة؛ طاقة الامتزاز؛ نظم توصيل الدواء؛ الخواص الإلكترونية.

1. Introduction

In 2020, the World Health Organization identified cancer as the primary cause of mortality on a global scale, with an estimated 10 million fatalities [1, 2]. Cancer is the second most common cause of mortality on a global scale, according to research conducted by the Centers for Disease Control and Prevention. There are several prominent subtypes of cancer, including breast, lung, prostate, colon, and rectal cancer [3]. The treatment of cancer, a highly fatal illness, necessitates the use of medications that are both highly effective and less hazardous to patients. To accomplish this goal, numerous antineoplastic medications have been assessed for their efficacy in eliminating malignant cells [3, 4]

The use of nanostructures for the targeted delivery of therapeutic compounds is a pivotal application of nanotechnology in the medical field. Researchers are concentrating on developing drug delivery systems (DDS) using nanostructures for tailored medicine administration [5]. The drug molecule is liberated from drug delivery systems after being adsorbed onto the nanocarrier and conveyed to the target tissue. This method may reduce the probability of adverse drug effects. Moreover, DDSs may regulate and selectively modify drug release, enhancing the efficacy of the therapeutic molecules [6]. Owing to its exceptional features as a two-dimensional nanomaterial, including a high specific surface area, low toxicity, notable biocompatibility, and drug accessibility. Its competitive advantage over other distribution techniques is further augmented by its ability to traverse cellular boundaries.

Two-dimensional (2D) materials are increasingly favored for their distinctive features. Due to their compact size, high surface area-to-volume ratio, superior biocompatibility, exceptional stability and permanence, and easily modifiable surface, they offer the advantages of adjustable lifespan, permeability augmentation, and receptor targeting specificity [7, 8].

Transition metal dichalcogenides (TMDs) are multifaceted two-dimensional materials characterized by tunable band gaps and extensive surface areas, rendering them suitable for biological applications, including drug delivery [9].

Hydroxyurea (HU) is a prevalent pharmacological substance used in chemotherapy for many severe conditions, including breast cancer, gastric cancer, intestinal cancer, head and neck cancer, and chronic myelocytic leukemia [10, 11]. Nevertheless, research has shown that the administration of the HU medication may result in adverse effects, including rashes, leukopenia, and leg ulcers throughout therapy [12]. The potential use of HU in cancer therapy is somewhat constrained by these detrimental consequences [13]. Moreover, medication encounters challenges due to its inadequate solubility and diminished potency in vivo studies. Drug delivery systems that facilitate the accurate and controlled flow of medications to the affected tissue may mitigate these adverse effects. Recent studies have concentrated on examining the interactions between Cisplatin (CP) and other two-dimensional (2D) materials to assess their viability as efficient drug delivery carriers [14, 15]. Munny et al. [3] observed that boron-doped graphene quantum dots had a better capacity for hydroxyurea adsorption compared to their undoped counterparts, suggesting an increased drug loading capability. Muktadir et al. [16] investigated several nanostructures and demonstrated that materials consisting of C12-B6N6, C12-AL6N6, and B6N6-AL6N6 exhibited significant interactions with hydroxyurea, indicating their potential as viable candidates for drug delivery applications.

Monolayer GaSe has Se–Ga–Ga–Se layers interconnected by van der Waals forces, and GaSe is classified as a direct bandgap semiconductor [17]. Huang et al. discovered that the defective GaSe material with selenium vacancies has excellent detecting capabilities for carbon monoxide and may serve as a viable carbon monoxide sensor. Jiang et al. report that the V-GaSe sensor exhibits excellent adsorption capabilities for H₂S, SO₂, SO₂F₂, and SOF₂. Consequently, GaSe could serve as a viable substrate material for the detection of several harmful gasses [18]. The InSe exhibits a graphene-like layered architecture consisting of vertically aligned Se–In–In–Se layers interconnected by weak van der Waals interactions. InSe exhibits a low effective mass for electrons, pronounced quantum confinement effects, and elevated electron mobility at ambient temperature ($\sim 103 \text{ cm}^2 \cdot \text{V}^{-1} \cdot \text{s}^{-1}$) [19]. TMD materials are suitable for photothermal-induced therapies, including tumor photothermal and photodynamic therapy, owing to their superior light and heat conversion efficiencies [20]. WTe₂, a member of the transition metal dichalcogenide (TMD) family, exhibits distinctive electrical conductivity, a high surface-to-volume ratio, and remarkable structural stability, rendering it an attractive choice for surface adsorption and gas sensing applications. To improve the sensing and adsorption efficacy of WTe₂ [21]. Arnab and colleagues have examined the interaction of MoSe₂ and Al-Doped MoSe₂ monolayers with anti-tuberculosis medication molecules. Their findings underscore the potential of Al-modified and pristine MoSe₂ as viable carriers for the diagnosis of anti-tuberculosis medications [22]. A team from Peking University created high-transconductance field-effect transistors utilizing InSe channels, with an 83% room-temperature ballistic ratio at an operational voltage of 0.5V [23].

This work seeks to examine the adsorption of Hydroxyurea on several TMD surfaces (GaSe, InSe, MoSe₂, and WTe₂), highlighting the potential of these two-dimensional materials for enhanced drug delivery systems. Our aim is to examine the qualities of geometric parameters, adsorption energies, and other electrical and geometric features via density functional theory (DFT).

2. Computational Detail

The computations were conducted using first-principles density functional theory (DFT) techniques [2, 24, 25] with the nonequilibrium Green's function (NEGF) approach, as implemented in QuantumATK S-2021.06 [26, 27]. The Kohn-Sham equations were resolved, and the electron density was expanded utilizing the Generalized Gradient Approximation of Perdew–Burke–Ernzerhof (GGA-PBE) method, employing a double- ζ polarized basis set, with a force threshold of less than 0.01 eV/Å and a 300 eV cutoff for the plane-wave basis set.

All structures were computed using the fast Fourier transform (FFT) Poisson solver, the Fermi–Dirac occupation method, and the linear combination of atomic orbitals (LCAO) basis set with moderate accuracy [28]. The structures were fully relaxed by the limited-memory Broyden–Fletcher–Goldfarb–Shanno (LBFGS) quasi-Newton method until the forces and stresses on each atom fell below the limits of 0.01 eV/Å and 0.001 eV/Å³, respectively.

Additionally, to achieve a suitable balance between accuracy and computational expense, we have selected a higher energy mesh cutoff of 100 Hartree and used $6 \times 6 \times 3$ k-point sampling for Brillouin zone integration. All simulations used the Fritz-Haber Institute (FHI) kind of pseudopotentials for the exchange-correlation functional [28, 29].

The band gap energy (E_{gap}) and Fermi level (E_{FL}) are computed by using the following equations [30-32]:

$$E_g = E_{LUMO} - E_{HOMO} \quad (1)$$

E_{HOMO} represents the energy level of the highest occupied molecular orbital, while E_{LUMO} indicates the energy level of the lowest unoccupied molecular orbital.

The adsorption energy has been ascertained, denoted by E_{ads} , as follows [33, 34]:

$$E_{ads} = E_{HU-Substrate} - E_{Substrate} - E_{HU} \quad (2)$$

Where the $E_{HU-Substrate}$, $E_{Substrate}$, E_{HU} represent, respectively, the total energy of the substrate and anticancer drug HU@GaSe, HU@InSe, HU@MoSe₂, and HU@WTe₂, the total energy of the GaSe, InSe, MoSe₂ and WTe₂, the total energy of the anticancer drug HU, respectively.

Employing Koopmans' theorem and the DFT methodology, we examined the reactivity of the analyzed compounds by computing a global reactivity index [35]:

$$IP = -E_{HOMO} \quad (3)$$

$$EA = -E_{LUMO} \quad (4)$$

$$H = \frac{E_{LUMO} - E_{HOMO}}{2} \quad (5)$$

$$S = \frac{1}{2\eta} \quad (6)$$

$$\mu = \frac{E_{LUMO} + E_{HOMO}}{2} \quad (7)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (8)$$

The work function (Φ) is the minimal energy necessary to displace the least tightly bound electron from the Fermi energy level of a solid surface to a vacuum state [36, 37]. Additionally, this measure functions as an auxiliary signal that offers a valuable comprehension of the substrate's sensitivity and reactivity to cisplatin. The subsequent equation can be employed to ascertain this value [38]:

$$\Phi = V_{el(+\infty)} - E_{FL} \quad (9)$$

The symbol $V_{el(+\infty)}$ refers to the electrostatic potential of an electron at a significant distance from the surface, assumed to be zero (i.e., $V_{el(+\infty)} = 0$).

The following equation was employed to calculate the change in work function that resulted from gas adsorption:

$$\Delta\Phi (\%) = \frac{\Phi_b - \Phi_a}{\Phi_b} \times 100 \quad (10)$$

where Φ_b and Φ_a represent the work function before and after the adsorption, respectively.

Φ_b , represent the work function of the anticancer drug HU@GaSe, HU@InSe, HU@MoSe₂ and HU@WTe₂, Φ_a represent the work function of the GaSe, InSe, MoSe₂, and WTe₂, work function of the anticancer drug Hydroxyurea, respectively.

The recovery time (τ) is a crucial parameter for gas sensors and medication delivery systems. It denotes the duration necessary for the drug molecule to dissociate from the nanosheet surface. The correlation between it and the adsorption energy exhibits an exponential pattern, which may be formally expressed by conventional transition state theory as [39, 40]:

$$\tau = \frac{1}{\nu_0} e^{\frac{-E_{ads}}{K_B T}} \quad (11)$$

The deformation energy E_{def} was computed to measure the structural distortion caused by the adsorption process. It is characterized as:

$$E_{def} = E_{surf}^* - E_{HU}^* - E_{surf} - E_{HU} \quad (12)$$

Where E_{surf}^* and E_{HU}^* denote the energies of the substrate and hydroxyurea molecule in their distorted states inside the adsorption complex, respectively, whereas E_{surf} and E_{HU} refer to their completely relaxed isolated configurations. This value indicates the energy expense related to structural deformation during adsorption. Reduced E_{def} values signify less geometric distortion and imply a more advantageous and reversible adsorption process.

3. Results and discussion

3.1. Structure properties

The optimized geometric configurations of the pristine two-dimensional (2D) substrates GaSe, InSe, MoSe₂, and WTe₂ used in this investigation are depicted in Figure 1. These layered materials are the perfect candidates for drug-delivery and adsorption applications due to their hexagonal configuration, which is characterized by covalently bonded atomic planes that are stacked through mild van der Waals forces. The geometry optimization confirms that all pristine substrates are structurally stable, exhibiting no imaginary frequencies or distortions after complete relaxation. GaSe and InSe are group-III monochalcogenides that exhibit a characteristic puckered conformation. The Ga–Se and In–Se bond lengths are approximately 2.45 Å and 2.69 Å, respectively. These values suggest moderately strong covalent bonding, which creates a chemically active surface that can interact with drug molecules [43]. MoSe₂ and WTe₂, on the other hand, are transition-metal dichalcogenides (TMDs) that possess the renowned sandwich-like X–M–X structure, where M is Mo or W and X is Se or Te. The employed computational parameters' reliability is confirmed by the optimized bond distances of 2.53 Å for Mo–Se and 2.76 Å for W–Te, which are consistent with previous DFT reports [44].

The optimized geometries of the HU-adsorbed complexes (HU@GaSe, HU@InSe, HU@MoSe₂, and HU@WTe₂) are illustrated in Figure 2. The hydroxyurea molecule maintains its planar configuration without any significant deformation after adsorption, indicating a physisorption interaction dominated by van der Waals forces rather than strong chemisorption. Furthermore, the molecule remains essentially intact. The non-covalent nature of the interaction is further substantiated by the equilibrium adsorption distances between the HU molecule and the substrate surface, which range from 2.8 to 3.4 Å.

HU@MoSe₂ demonstrates the minimum adsorption distance (approximately 2.87 Å) among the examined systems, suggesting a slightly stronger coupling than the other substrates. HU@WTe₂ demonstrates the greatest separation (approximately 3.45 Å), which corresponds to a weaker interaction. The mechanical stability of the complexes is underscored by the minimal distortions in both the HU molecule and the substrate lattices, which suggest that all structures have attained equilibrium geometries that are suitable for additional electronic analysis. In summary, the geometric optimization (Figs. 1 and 2) illustrates that the energetic feasibility of hydroxyurea adsorption on GaSe, InSe, MoSe₂, and WTe₂ surfaces is established without causing structural damage. This provides a solid foundation for the subsequent investigation of the electronic and adsorption characteristics of the aforementioned surfaces.

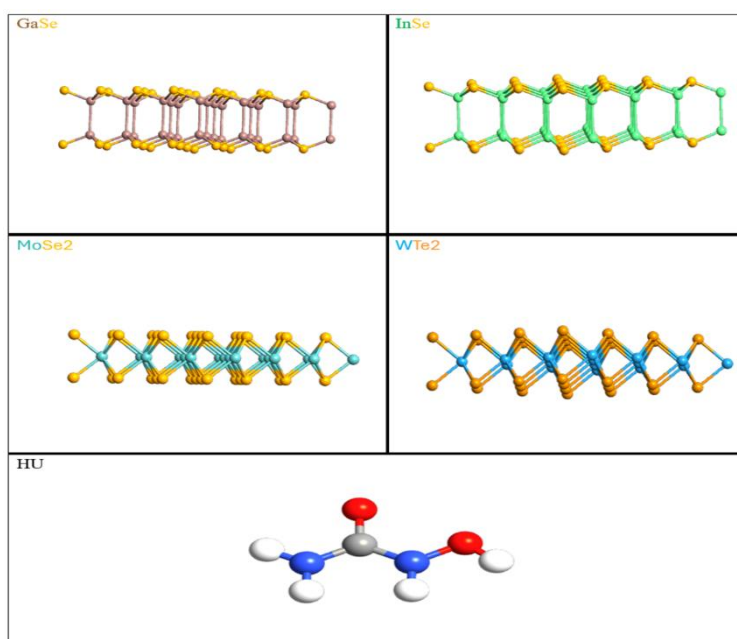


Figure -1 The geometric optimization substrates and drug molecule

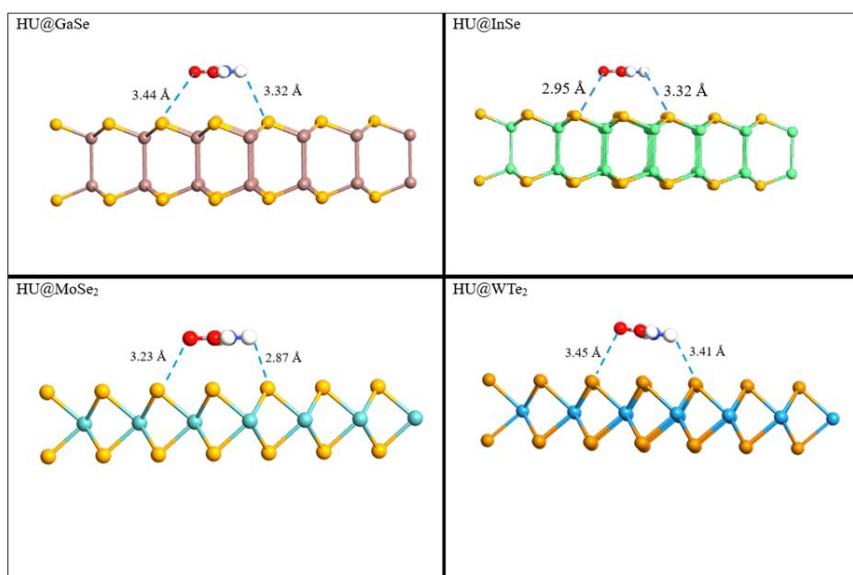


Figure -2 Optimization geometries of HU-complexes

3.2. Electronic Properties

The electronic properties of the pristine substrates and their respective HU-loaded complexes were examined to assess the impact of hydroxyurea adsorption on the band structure, Fermi level location, and work function. The computed values of total energy (E), Fermi level energy (E_{FL}), work function (Φ), highest occupied molecular orbital (E_{HOMO}), lowest unoccupied molecular orbital (E_{LUMO}), and energy gap (E_g) are shown in Table 1.

Figure 3 illustrates that the unaltered monolayers of GaSe, InSe, MoSe₂, and WTe₂ have semiconducting properties, characterized by direct or near-direct band gaps of 2.817 eV, 0.949 eV, 1.457 eV, and 1.049 eV, respectively [45-48]. These results are consistent with previous DFT findings and validate that all substrates exhibit suitable electronic properties for bio-nano applications. The comparatively large band gap of GaSe indicates more intrinsic stability and less charge mobility, whereas the smaller gaps of InSe and WTe₂ signify enhanced electrical conductivity, which may promote charge transfer during adsorption processes.

Significant alterations in the electronic characteristics are seen after hydroxyurea adsorption. The band gap (E_g) marginally diminishes across all systems, as seen in Table 1 and shown in the band structures in Fig. 5. The reduction ratios (ΔE_g %) vary from -0.07 % to -1.08 %, indicating a little decrease of the energy gap and implying that the adsorption process fosters weak electronic interaction between the drug molecule and the substrate surface. Among the examined complexes, HU@GaSe and HU@InSe exhibit the most significant band gap decrease (≈ 1 %), indicating that their π -orbital interactions with HU are more robust than those in HU@MoSe₂ or HU@WTe₂.

The Fermi level (E_{FL}) of each system experiences a little change in post-adsorption, indicating charge redistribution between the HU molecule and the 2D layers. The work function ($\Phi = -E_{FL}$) shows slight fluctuations, ranging from 0.28% to 1.52% (Table 1). This nuanced alteration suggests that hydroxyurea adsorption may affect the electron emission

capacity and surface reactivity of the substrates while little impacting their electronic identity. The slight elevation in Φ observed for HU@WTe₂ indicates improved surface sensitivity, potentially beneficial for drug-sensing or monitoring applications.

The associated density of states (DOS) graphs, shown in Fig. 4, provide further understanding of the electrical interaction process. The DOS spectra of all virgin substrates exhibit distinct energy gaps at the Fermi level, characteristic of semiconducting 2D materials. Following hydroxyurea adsorption, minor extra states appear along the conduction and valence band boundaries, indicating modest orbital hybridization between HU and the substrate. No deep localized states exist inside the gap area, hence reaffirming the physisorption characteristics of binding and the structural integrity of the nanocarriers.

The electronic study (Table 1 and Figs. 3-5) indicates that hydroxyurea adsorption causes modest changes in Fermi energy and a tiny decrease in band gaps, aligning with a non-destructive, weakly interacting adsorption process. The modest electronic perturbations indicate that GaSe, InSe, MoSe₂, and WTe₂ are viable, biocompatible nanocarriers that can maintain their semiconducting properties while hosting therapeutic compounds on their surfaces.

Table 1 - The values of the total energy (E), Fermi level energy (E_{FL}), work function (Φ), E_{HOMO} , E_{LUMO} , and energy gap (E_g) for the structures in (eV) unit

Structure	$E(eV)$	$E_{FL}(eV)$	$\Phi(eV)$	$\Delta\Phi$ (%)	E_{LUMO}	E_{HOMO}	$E_g(eV)$	ΔE_g (%)
GaSe	-14605.848	-5.232	5.232	-	-6.641	-3.824	2.817	-
InSe	-31031.363	-5.235	5.235	-	-5.750	-4.801	0.949	-
MoSe ₂	-19955.450	-5.402	5.402	-	-6.133	-4.676	1.457	-
WTe ₂	-25262.603	-4.136	4.136	-	-4.649	-3.600	1.049	-
HU@GaSe	-16238.763	-5.250	5.250	0.343	-6.645	-3.858	2.787	-1.076
HU@InSe	-32663.990	-5.252	5.252	0.286	-5.757	-4.818	0.939	-1.065
HU@MoSe ₂	-	-5.423	5.423	0.332	-6.154	-4.698	1.456	-0.068
	21588.468							
HU@WTe ₂	-26895.555	-4.206	4.206	1.524	-4.714	-3.665	1.048	-0.095

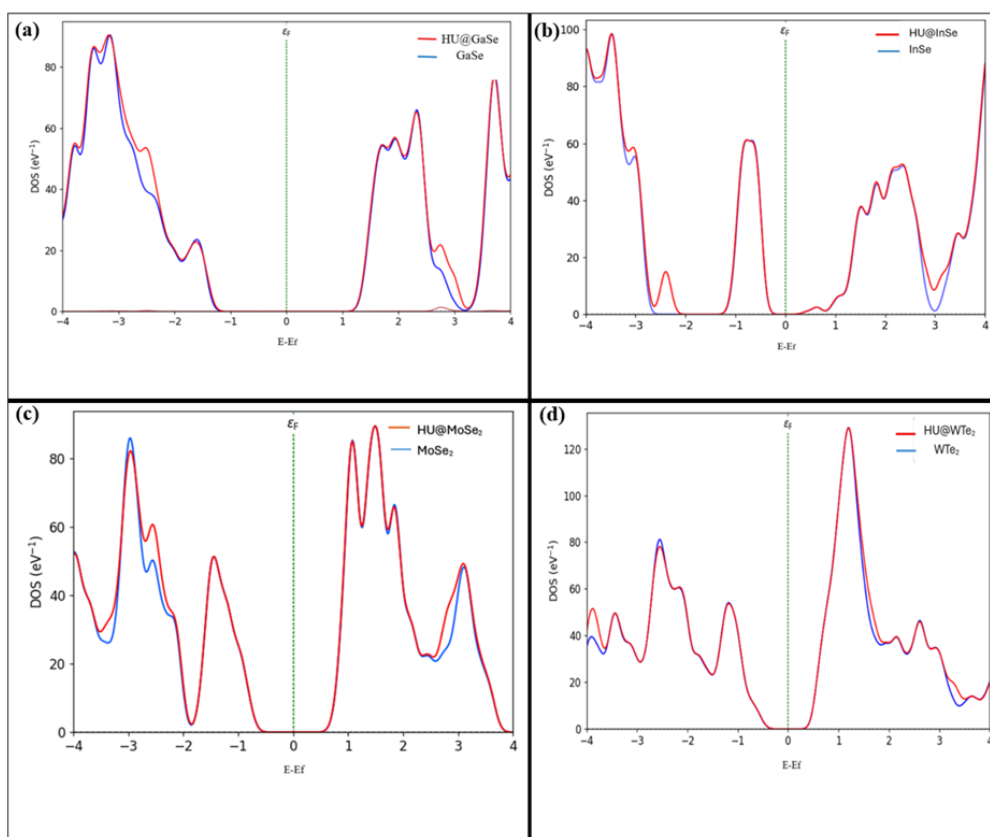


Figure -3 The DOS of (a) GaSe, (b) InSe, (c) MoSe₂, and (d) WTe₂ structures

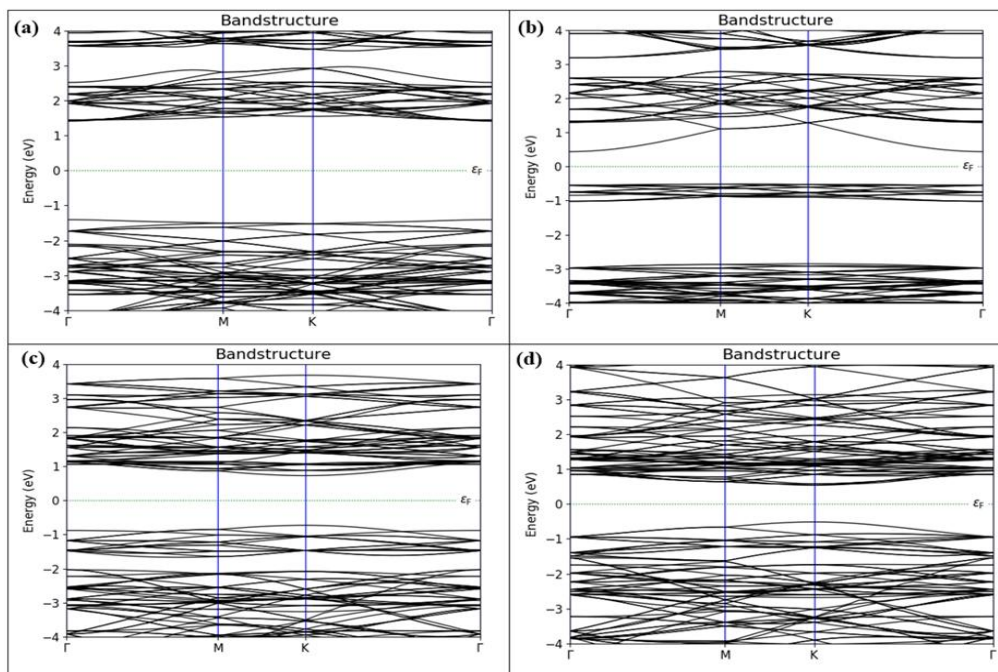


Figure -4 The band structure of (a) GaSe, (b) InSe, (c) MoSe₂, and (d) WTe₂ structures

3.3. Density of States and Band Structure

To enhance comprehension of how hydroxyurea adsorption alters the electronic distribution of the analyzed systems, the density of states (DOS) and band structure profiles were systematically compared (Figs. 3-5). The observed alterations directly indicate the intensity of orbital hybridization and charge transfer between the drug molecule and each substrate. In all HU-complexes, the overall band structure of the host monolayers is preserved, indicating that adsorption does not alter the inherent lattice or electronic symmetry. Nonetheless, minor supplementary electronic states emerge at the Fermi level, which marginally reduces the band gap and increases surface sensitivity. These characteristics are most pronounced in HU@GaSe and HU@InSe, where shallow impurity levels appear at the conduction band minimum, indicating weak π - π^* interaction between the oxygen/nitrogen lone pairs of HU and the p-orbitals of Se atoms.

The density of states (DOS) patterns for HU@MoSe₂ and HU@WTe₂ exhibit little intensity redistribution around the valence-band edge, indicating restricted charge delocalization from HU to the metal d-states. This nuanced overlap elucidates the minor decrease in their band gaps previously observed and corroborates a physisorption-dominated interaction, which maintains semiconducting properties while marginally enhancing electronic conductivity.

From a practical standpoint, these little DOS adjustments are beneficial. The substrates function as stable, reversible drug hosts, enabling electronic responsiveness appropriate for regulated release or sensing without experiencing a metallic transition. The enduring presence of a limited band gap in all complexes guarantees that their electrical properties are both predictable and adjustable for biological applications.

The analyses of the density of states (DOS) and band structure (Figs. 3-5) indicate that hydroxyurea adsorption generates shallow hybrid states and slight bandgap narrowing—phenomena that enhance the weak, reversible characteristics of adsorption while maintaining the advantageous semiconducting structure of GaSe, InSe, MoSe₂, and WTe₂.

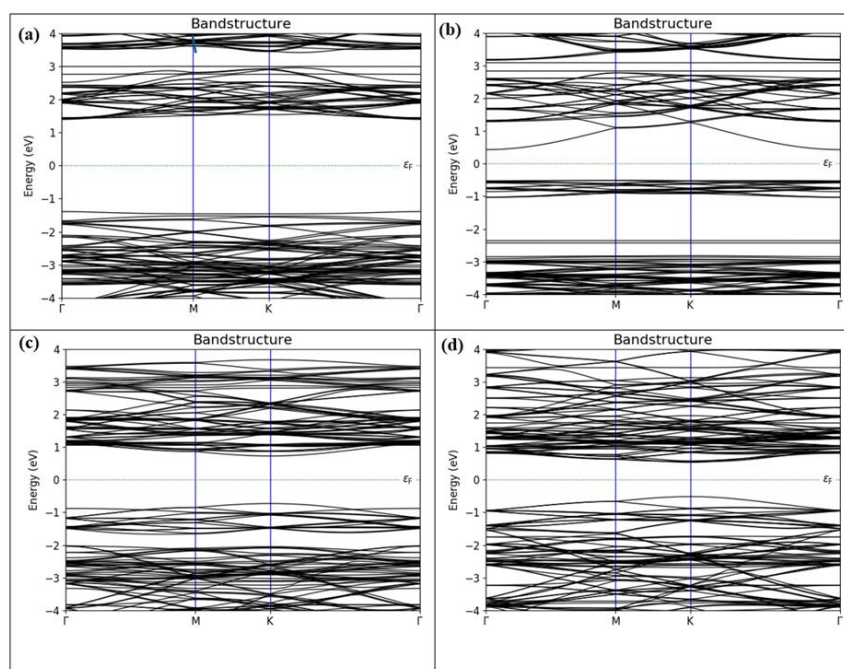


Figure -5 The band structure of (a) HU@GaSe, (b) HU@InSe, (c) HU@MoSe₂, and (d) HU@WTe₂ structure

3.4. Adsorption Energy and Recovery Time

The adsorption strength between hydroxyurea and each substrate was quantitatively evaluated using the computed adsorption energy (E_{ads}), charge transfer (CT), and recovery time (τ), as detailed in Table 2 and shown in Fig. 6. All complexes exhibit negative adsorption energies, indicating that the adsorption of hydroxyurea on the surfaces of GaSe, InSe, MoSe₂, and WTe₂ is thermodynamically advantageous. Among these, HU@MoSe₂ demonstrates the greatest negative value (-1.196 eV), followed closely by HU@WTe₂ (-1.130 eV) and HU@GaSe (-1.093 eV), but HU@InSe has the lowest interaction (-0.805 eV). This sequence indicates that the adsorption affinity adheres to the following hierarchy: HU@MoSe₂ > HU@WTe₂ > HU@GaSe > HU@InSe.

The pronounced adsorption on MoSe₂ is due to the elevated polarizability of Se atoms and the considerable electronegativity disparity between Mo and Se, facilitating dipole-dipole interactions with the polar N–H and C=O groups of hydroxyurea. In contrast, the decreased adsorption strength on InSe signifies a less electronic overlap, resulting in facilitated desorption—a characteristic that may be advantageous for rapid drug release.

As presented in Table 2, the calculated deformation-energy values indicate that the adsorption of hydroxyurea on the monolayers under investigation is accompanied by structural rearrangement in both the drug molecule and the substrate. The extent of geometric modification is contingent upon the nature of the surface, as evidenced by the variation in these values among the studied complexes. This reflects varying degrees of structural adaptation at the time of complex formation.

The Mulliken charge transfer study (Table 2) indicates minor negative charge transfer values (-0.019 e to -0.059 e), suggesting that electrons are transported from hydroxyurea to the substrate across all systems. This little electron donation facilitates a physisorption process mostly governed by electrostatic and van der Waals interactions, as opposed to covalent bonding. The extent of charge transfer is greatest in HU@MoSe₂, which corresponds with its elevated E_{ads} value and enhanced binding affinity.

The recovery period (τ), calculated by transition-state theory, ranges from 3.3×10^1 s for HU@InSe to 1.2×10^8 s for HU@MoSe₂. The exponential correlation between τ and E_{ads} (depicted in Fig. 6) indicates that enhanced adsorption is associated with prolonged desorption durations. Thus, HU@MoSe₂, characterized by its elevated E_{ads} and extended τ , is appropriate for prolonged drug administration, whereas HU@InSe and HU@GaSe, demonstrating shorter recovery durations, are more suited for rapid-release or sensing applications. The adsorption and kinetic studies (Table 2 and Fig. 6) demonstrate that all examined substrates provide stable and reversible binding sites for hydroxyurea. The adjustable desorption durations among the four materials provide versatility in the construction of nanocarriers for either sustained therapeutic release or rapid-response biological sensors.

3.5. Modulation of Work Function

To clarify the impact of hydroxyurea adsorption on surface reactivity, the work function (Φ) variation was assessed for all complexes. The work function is a crucial indicator of a material's capacity to donate or take electrons, and even little variations in Φ indicate quantifiable alterations in its surface potential and electrical responsiveness. Table 1 indicates that the pure substrates have Φ values from 4.136 eV (WTe₂) to 5.402 eV (MoSe₂). Post-adsorption, minor but notable alterations are detected: HU@GaSe rises to 5.250 eV

(+0.34%), HU@InSe to 5.252 eV (+0.29%), HU@MoSe₂ to 5.423 eV (+0.33%), and HU@WTe₂ to 4.206 eV (+1.52%). The minor positive changes suggest an enhancement in surface electron-withdrawal capacity, attributed to the adsorption of the electron-donating HU molecule. The impact is especially significant for HU@WTe₂, whose greater $\Delta\Phi$ indicates increased charge sensitivity, making this substrate advantageous for electrochemical or biosensing applications. The slight increases in GaSe, InSe, and MoSe₂ indicate that their surfaces maintain electronic stability while exhibiting minor boosts in reactivity appropriate for regulated molecule adsorption and desorption. The work function findings indicate that hydroxyurea adsorption may delicately alter the electronic environment of the 2D materials while preserving their inherent semiconducting properties. The tunability of Φ enhances the capability of these substrates as multifunctional platforms for drug administration and bioelectronic sensing.

Table 2- The deformation energy (E_{def}) adsorption energy (E_{Ads}), and Mulliken CT, and the recovery time (τ) for all complex structures.

Structures	E_{def} (eV)	E_{Ads} (eV)	CT(eV)	τ (s)
HU@GaSe	2.009	-1.093	-0.019	2.3×10^6
HU@InSe	2.2821	-0.805	-0.047	3.3×10^1
HU@MoSe ₂	4.9361	-1.196	-0.059	1.2×10^8
HU@WTe ₂	1.6733	-1.130	-0.005	9.6×10^6

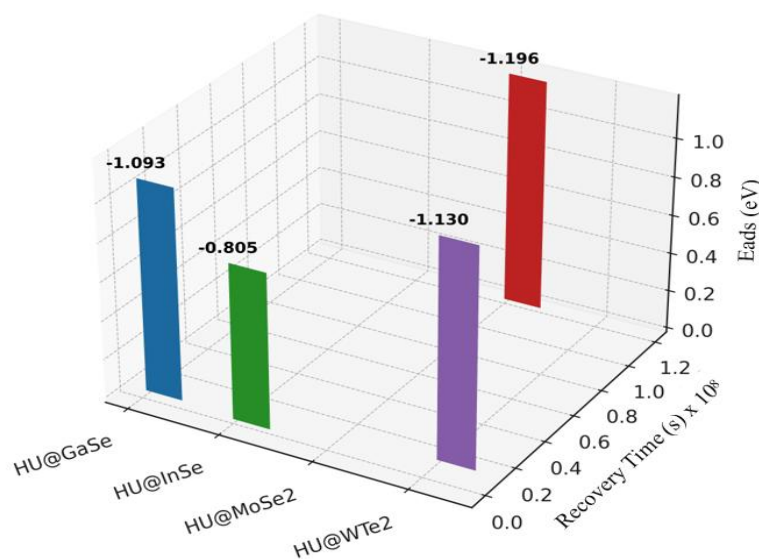


Figure -6 The relationship between adsorption energy and recovery time

3.6. Global Reactivity Indices

Several global reactivity descriptors were computed using Koopmans' theorem and density functional theory (DFT) parameters to enhance comprehension of the impact of hydroxyurea adsorption on the chemical stability and reactivity of the investigated systems, as presented in Table 3. These consist of the ionization potential (IP), electron affinity (EA), chemical hardness (η), softness (S), chemical potential (μ), and electrophilicity index (ω). Collectively, these quantities give a quantitative assessment of the propensity of each system

to donate or receive charge, resist deformation, and engage in electron transfer during adsorption or desorption.

The IP and EA values of the pristine substrates demonstrate that GaSe and MoSe₂ have relatively higher ionization potentials (6.641 eV and 6.133 eV), which suggests that they have a lower reactivity and inherent stability in comparison to InSe (5.750 eV) and WTe₂ (4.649 eV). Consequently, GaSe and MoSe₂ have harder hardness values ($\eta = 1.409$ eV and 0.729 eV), which indicates that they are less susceptible to electronic perturbations. In contrast, InSe and WTe₂ exhibit a higher polarizability and a gentler character, which suggests a more straightforward electronic response to external stimuli, despite their lesser η values of 0.475 eV and 0.525 eV, respectively. All complexes exhibit only minor variations in their reactivity parameters upon hydroxyurea adsorption, which is indicative of the interaction's non-destructive, physisorptive nature. The electron-donor or electron-acceptor capabilities of the substrates are maintained, as evidenced by the proximity of the IP and EA values of the HU@GaSe, HU@InSe, HU@MoSe₂, and HU@WTe₂ complexes to their pristine forms. In each instance, the hardness (η) experiences a slight decrease, which is accompanied by a slight increase in softness (S). This increase is indicative of the slight narrowing of the energy gap, as previously elaborated in Section 3.2.

After adsorption, the chemical potential (μ) and electrophilicity index (ω) demonstrate slight increases. HU@MoSe₂, for example, exhibits $\mu = 5.426$ eV and $\omega = 20.222$, in contrast to $\mu = 5.404$ eV and $\omega = 20.043$ in the unadulterated MoSe₂ compound. These increments corroborate that the hydroxyurea molecule introduces a modest polarization effect, which improves the substrate's ability to attract electron density without compromising overall electronic stability. Likewise, HU@InSe exhibits nearly identical μ and ω values before and after adsorption (approximately 5.28 eV and 29 eV), which further supports the notion of a weak, reversible interaction. The sequence of electrophilicity (ω) values for the HU-adsorbed systems is as follows from a comparative perspective: HU@InSe > HU@MoSe₂ > HU@WTe₂ > HU@GaSe.

This trend is consistent with the relative charge-transfer magnitudes of the surfaces, as reported in Table 2. It suggests that InSe and MoSe₂ surfaces have slightly larger propensities to receive electron density from hydroxyurea, which may strengthen drug–surface coupling during adsorption. Generally, the global reactivity analysis (Table 3) confirms that the electronic reactivity descriptors of GaSe, InSe, MoSe₂, and WTe₂ are only slightly altered by hydroxyurea adsorption. All complexes maintain balanced hardness–softness characteristics, which guarantee structural stability and reversible adsorption dynamics. These results further verify the reliability, low-toxicity, and electronically tunable nanocarrier properties of these 2D materials for the delivery of hydroxyurea.

Table 3- Global reactivity indices.

Structure	IP(eV)	EA(eV)	S(eV)	H(eV)	μ (eV)	ω (eV)
GaSe	6.641	3.824	0.355	1.409	5.232	9.718
InSe	5.750	4.801	1.054	0.475	5.275	29.322
MoSe ₂	6.133	4.676	0.686	0.729	5.404	20.043
WTe ₂	4.649	3.600	0.953	0.525	4.125	16.215
HU@GaSe	6.645	3.858	0.359	1.393	5.251	9.895
HU@InSe	5.757	4.818	1.065	0.469	5.288	29.786
HU@MoSe ₂	6.154	4.698	0.687	0.728	5.426	20.222
HU@WTe ₂	4.714	3.665	0.954	0.524	4.189	16.739

3.7. General implications

Valuable insights into the potential of GaSe, InSe, MoSe₂, and WTe₂ monolayers as nanocarriers for the controlled delivery of hydroxyurea (HU) are provided by the comprehensive evaluation of structural, electronic, and adsorption characteristics. The thermodynamically stable adsorption, minimal structural deformation, and reversible electronic modulation of all examined systems are indicative of physisorption-dominated interactions.

MoSe₂ is the most promising candidate among the examined materials, as it possesses the longest recovery time (approximately 1.2×10^8 s), the greatest charge transfer amplitude (-1.196 eV), and the strongest adsorption energy (-1.196 eV). The properties of HU@MoSe₂ indicate that it is capable of efficiently retaining the drug for extended periods, rendering it suitable for localized and sustained drug delivery applications. In contrast, InSe demonstrates the shortest desorption time and the weakest binding (-0.805 eV), suggesting that it has the potential for biosensing or fast-release applications. GaSe and WTe₂ are in intermediate positions, providing a balanced adsorption-desorption behavior that is appropriate for hybrid therapeutic-diagnostic ("theragnostic") platforms.

The minor upward shifts in work function and the modest narrowing of energy gaps observed across all complexes indicate that surface reactivity has been enhanced while maintaining semiconducting integrity. This tunability guarantees that the electronic transport and sensing properties can be precisely adjusted without compromising material stability or biocompatibility. The non-toxic and reversible nature of adsorption, which is essential for biomedical deployment, is further confirmed by the absence of deep trap states or band-structure disruption.

In conclusion, the combined results (Figs. 1-6; Tables 1-3) emphasize that 2D chalcogenide monolayers, particularly MoSe₂ and GaSe, provide a flexible foundation for the development of next-generation nanocarriers that are capable of delivering hydroxyurea in a controlled, efficient, and safe manner. Their balanced adsorption energies, predictable charge-transfer behavior, and stable electronic response render them as promising materials for future experimental validation and integration into multifunctional drug-delivery and sensing systems.

4. Conclusion

This study provides a thorough density-functional-theory analysis of the interaction between the anticancer drug hydroxyurea (HU) and four two-dimensional monolayers—GaSe, InSe, MoSe₂, and WTe₂ in order to assess their functionality as nanocarriers for controlled drug delivery. The results indicate that all of the materials under investigation form thermodynamically stable and reversible complexes with hydroxyurea, all while preserving their semiconducting properties and structural integrity. Physisorption, which is characterized by feeble van der Waals forces and minor charge transfer between the substance and the substrate, dominates the adsorption process. MoSe₂ demonstrates the most stable adsorption behavior and the strongest affinity toward hydroxyurea among the examined systems, suggesting its potential for long-term and sustained delivery. In contrast, InSe exhibits the weakest binding and the quickest desorption response, rendering it a viable candidate for biosensing or rapid drug release. GaSe and WTe₂ exhibit intermediate performance, providing balanced adsorption-desorption characteristics that could support dual therapeutic and sensing functionalities. The intrinsic stability and biocompatibility of the

2D substrates are maintained by the subtle modifications in band structure and surface potential that hydroxyurea adsorption induces, as confirmed by electronic analysis. The tunability of the materials is improved by these minor electronic adjustments, which enable responsive control over drug release and detection processes. In conclusion, the investigation identifies MoSe₂ and GaSe as platforms that are particularly promising for the development of nanocarriers that are safe, efficient, and electronically adaptable for the delivery of hydroxyurea. These insights can be used as a theoretical foundation for the rational engineering of multifunctional nanomaterials in targeted drug delivery and bio-sensing applications, as well as for imminent experimental investigations.

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