REVISTA BIO CIENCIAS
http://revistabiociencias.uan.edu.mx
https://doi.org/10.15741/revbio.12.e1860
ISSN 2007-3380

Original article /Artículo original

Theoretical Study of Pharmaceutical Dimer and Trimer Formation via DFT Calculations

Estudio Teórico de la formación de Dímeros y Trímeros Farmacéuticos mediante cálculos DFT

Elvir-Padilla, L.G.[1], *Diaz Ponce, A.*[2], *Olvera González, J.E.*[3], *Morales-Palacios, F.G.*[4], *Villanueva-Mejía, F.*[5*]

[1] *TecNM / Instituto Tecnológico de Aguascalientes, Aguascalientes, 20256, Aguascalientes, México*
[2] *CONAHCYT-Centro de Investigaciones en Óptica, Unidad Aguascalientes, Aguascalientes 20200, Mexico.*
[3] *Laboratorio de Iluminación Artificial, Tecnológico Nacional de México Campus Pabellón de Arteaga, Carretera a la Estación de Rincón Km. 1, Pabellón de Arteaga, Aguascalientes 20670, Mexico*
[4] *Instituto de Investigación Químico Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, Ed. B-1, Ciudad Universitaria, Morelia 58030, Michoacán, México*
[5] *TecNM / Instituto Tecnológico de Pabelón de Arteaga, 20670, Pabellón de Arteaga, Aguascalientes, México.*

Please cite this article as/Como citar este artículo: Elvir-Padilla, L.G., Diaz- Ponce, A., Olvera-González, J.E., Morales-Palacios, F.G., Villanueva-Mejía, F. (2025). Theoretical Study of Pharmaceutical Dimer and Trimer Formation via DFT Calculations. *Revista Bio Ciencias*, 12, e1860. https://doi.org/10.15741/revbio.12.e1860

Article Info/Información del artículo
Received/Recibido: December 27th 2024.
Accepted/Aceptado: June 27th 2025.
Available on line/Publicado: August 11th 2025.

ABSTRACT

This study investigates the impact of molecular aggregation on the multicomponent adsorption of pharmaceuticals. Acetaminophen, diclofenac, and naproxen were selected. Density Functional Theory calculations were performed to analyze the thermodynamic feasibility of dimer and trimer formation for both homogenous and heterogeneous combinations. Molecular electrostatic potential and dual descriptor analyses provided insights into the reactive sites and the stability of these aggregates. Results indicate that dimer formation is thermodynamically favorable, particularly for NAP. The calculated interaction energies and distances for dimers and trimers offer a quantitative understanding of the aggregation behavior. This theoretical framework reveals how molecular aggregation influences the competitive adsorption of pharmaceuticals, providing crucial insights into the design of more effective water treatment strategies.

KEY WORDS: Multicomponent adsorption, DFT, pharmaceutical compounds, molecular aggregation.

***Corresponding Author:**

Francisco Villanueva-Mejía. Instituto Tecnológico de Pabellón de Arteaga. TecNM. Carretera a la estación de Rincón de Romos, Km. 1, 20670 Pabellón de Arteaga, Ags. México. Teléfono (443) 2300769. E-mail: francisco.vm@pabellon.tecnm.mx

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ISSN 2007-3380

RESUMEN

Este estudio teórico examina el impacto de la agregación molecular en la adsorción multicomponente de productos farmacéuticos. Se seleccionaron acetaminofeno, diclofenaco y naproxeno. Se realizaron cálculos de Teoría del Funcional de la Densidad para analizar la viabilidad termodinámica de la formación de dímeros y trímeros, tanto homogéneos como heterogéneos. Los análisis del potencial electrostático molecular y el descriptor dual proporcionaron información sobre los sitios reactivos y la estabilidad de estos agregados. Los resultados indican que la formación de dímeros es termodinámicamente favorable, particularmente para naproxeno. Las energías e interacciones calculadas para dímeros y trímeros ofrecen una comprensión cuantitativa del comportamiento de agregados. Este estudio teórico revela cómo la agregación molecular influye en la adsorción competitiva de fármacos, proporcionando información crucial para el diseño de estrategias más efectivas de tratamiento de aguas.

PALABRAS CLAVE: Adsorción, productos farmacéuticos, DFT, agregados moleculares.

Introduction

Multicomponent adsorption of organic pollutants is characterized by antagonistic effects, in which molecules of two or more adsorbates compete for active sites on the surface of the adsorbent (Pauletto *et al*., 2021). Identifying and analyzing the impact of this antagonistic adsorption is essential for designing and optimizing water treatment systems, particularly for real fluids (e.g., industrial and groundwater wastewater) that often contain diverse dissolved chemical species. Previous studies have demonstrated that strong competitive adsorption can occur in multicomponent systems containing relevant organic pollutants, such as dyes and pharmaceutical molecules (Manjunath & Kumar, 2018; Martínez-Costa *et al*., 2018; Karami *et al*., 2020; Medina *et al*., 2021; Zango *et al*., 2021; Gęca *et al*., 2022). Additionally, phenomena such as molecular aggregation have been reported in these systems, which can affect the adsorbent performance (Scheufele *et al*., 2016; Soto *et al*., 2022; Vener *et al*., 2022).

The formation of organic molecular aggregates, such as dimers, trimers, and even tetramers, has been reported in aqueous solutions (Scheufele *et al*., 2016; Soto *et al*., 2022). This phenomenon could have a significant impact on the adsorption mechanism, where the molecular properties of the target compounds, such as geometry and reactivity, play an important role (DellaGreca *et al*., 2003; Nematollahi *et al*., 2009; King *et al*., 2011; Kozlowska *et al*., 2018; Minecka *et al*., 2018; Vener *et al*., 2022). Additionally, this phenomenon may be associated with

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the process of multilayer adsorption, which can occur depending on both the surface chemistry of the adsorbent and the molecular properties of the adsorbate (Zango *et al*., 2021; Wang *et al*., 2022). In the case of multicomponent systems where two or more adsorbates are dissolved in the same solution, the formation of molecular aggregates involves interactions between identical molecules (e.g., molecule A – molecule A) and different molecules (e.g., molecule A – molecule B). The formation of these aggregates could significantly affect separation efficiency, thereby amplifying antagonistic adsorption. Therefore, the analysis and understanding of the molecular aggregation of organic compounds and its impact on the multicomponent adsorption process are crucial for intensifying water treatment strategies for relevant emerging contaminants, such as pharmaceuticals.

Pharmaceuticals are considered persistent environmental contaminants that can be toxic to ecosystems and, moreover, exhibit bioaccumulative characteristics (Vargas-Berrones *et al*., 2020; Huang *et al*., 2021; Duarte *et al*., 2022; Wang *et al*., 2022). Despite their impact, these substances are generally not regulated by the Toxic Substances Control Act (Joseph *et al*., 2011; Nghiem *et al*., 2016; Peña-Guzmán *et al*., 2019; Duarte *et al*., 2021; Duarte *et al*., 2022;). The diversity of pharmaceutical compounds consumed globally includes analgesics, antibiotics, hormones, and steroidal and non-steroidal anti-inflammatory drugs (Kyzas *et al*., 2013; Gómez-Canela *et al*., 2019; Mlunguza *et al*., 2019; Gómez-Avilés *et al*., 2021). Among these, diclofenac (DFC), acetaminophen (APAP), and naproxen (NAP) are commonly used for the treatment of diseases in humans and animals. However, water contamination caused by the excretion of non-bioassimilated drugs by humans/animals, in addition to their improper management, has been associated with potential environmental impacts, including the bacterial resistance development (Passerat *et al*., 2011; Kebede *et al*., 2019).

A limited number of studies have reported the multicomponent adsorption of pharmaceuticals, primarily in binary and ternary systems (Nielsen & Bandosz, 2016; Dhiman & Sharma, 2019; Manjunath *et al*., 2020; Gómez-Avilés *et al*., 2021; Pauletto *et al*., 2021; Puga *et al*., 2022). For example, these studies have analyzed the simultaneous removal of trimethoprim, sulfamethoxazole, and carbamazepine using an adsorbent obtained from the pyrolysis of fish waste and sewage sludge (Nielsen & Bandosz, 2016); the binary adsorption of paracetamol, diclofenac, ofloxacin, and ciprofloxacin with zinc oxide nanoparticles (Dhiman & Sharma, 2019); the removal of fluoxetine, venlafaxine, and trazodone in a ternary mixture using biochar in a packed bed column (Puga *et al*., 2022); the binary adsorption of nimesulide and paracetamol on activated carbon (Pauletto *et al*., 2021); the binary and ternary adsorption of tetracycline, metronidazole, and sulfadiazine on activated carbon (Manjunath *et al*., 2020); and the ternary adsorption of tetracycline, diclofenac, and acetaminophen on organo-sepiolite (Gómez-Avilés *et al*., 2021). These studies have concluded that strong antagonistic adsorption can occur in mixtures of different pharmaceuticals. However, the role of molecular aggregation of pharmaceutical molecules has not been thoroughly understood, despite the available evidence of this phenomenon during the adsorption of these organic compounds (Gómez-Avilés *et al*., 2021).

This study focused on analyzing the impact and role of molecular aggregation of NAP, APAP, and DFC molecules. To this end, calculations based on Density Functional Theory (DFT)

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were performed to analyze atomic interactions and molecular properties of monomers, dimers, and trimers of the evaluated pharmaceutical compounds.

Material and Methods

DFT Calculations for the Analysis of Molecular Aggregation

Molecular calculations, including volumes, dimensions, reactivities, molecular electrostatic potential (MEP), Fukui functions, and the dual descriptor (DD), were applied to the structurally optimized molecules to develop effective strategies to mitigate environmental impacts and reduce pollution associated with these compounds. Initially, the molecules of acetaminophen, diclofenac, and naproxene were modeled using the MOLDEN software as a basis for an *ab initio* conformational analysis, conducted through the Monte Carlo conformation search method implemented in Spartan 16 (Shao *et al*., 2006). This analysis is crucial due to the multiple degrees of freedom present in the chemical structure of these compounds. A maximum limit of 1000 conformers was set for evaluation. Subsequently, the cumulative Boltzmann weights of the conformers were calculated and analyzed in detail. The conformers selected for geometric optimization met a criterion of energy difference below 5 kcal/mol.

The selected molecular structures were optimized using DFT calculations with the Gaussian16 software package (Frisch *et al*., 2016) at the B3LYP theoretical level and the 6-311++G(d,p) basis set. Once the molecular structures of the three pharmaceutical compounds were optimized and characterized, their reactivity properties were calculated. For this purpose, two main reactivity descriptors were determined, covering both covalent and non-covalent interactions. The covalent descriptor, represented by the MEP, provides information on the response of the electron density to the approach of a unit positive charge. This descriptor was visualized using a color scheme, where regions of higher negative density were represented in red and regions of positive density in blue, facilitating the analysis of the electronic and reactive properties of the studied molecules, Equation 1. This descriptor is defined as follows:

$$V(r) = \sum_{A} \frac{Z_A R_A}{|R_A - r|} - \int \frac{\rho(r')}{|r' - r|} dr' \qquad (1)$$

Where Z_A is the atomic number of nucleus A, $R_A$is the position of nucleus A, $|R_A - r|$is the distance from the point r, and $\rho(r')$ is the electron density at each volume element. These reactivity descriptors were calculated in an aqueous medium using polarized continuum models (PCM) (Cossi *et al*., 1996; Giles *et al*., 1960). On the other hand, the Fukui functions correspond to the description of non-covalent reactivity, defined as a finite difference approximation:

$$f(r)^{+}_{v,N} = \rho(r)_{v,N+1} - \rho(r)_{v,N} \qquad (2)$$

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$$f(r)^{-}_{v,N} = \rho(r)_{v,N} - \rho(r)_{v,N-1} \quad (3)$$

Where $\rho(r)_{v,N}$, $\rho(r)_{v,N-1,}$ and $\rho(r)_{v,N+1}$ are the electron densities of the system N, N^{-1}, and N^{+1} electrons, respectively, all corresponding to the ground-state geometry of the N-electron system. The function related to the change in density $f(r)$ is a response to changes in the number of electrons N according to Maxwell's relation. Equation 2 evaluated a nucleophilic attack, representing the response of the pharmaceutical compound to stabilize an incoming charge, and Equation 3 evaluated an electrophilic attack, representing the response of the pharmaceutical compound to stabilize an outgoing charge. In this way, $f+(r)$ and $f-(r)$ of the Fukui functions are useful non-covalent chemical descriptors for the three pharmaceutical compounds.

Once the Fukui functions were calculated, the Dual Descriptor (DD) (Morell *et al*., 2005) of the three pharmaceutical compounds was determined. The DD is another non-covalent descriptor and describes the difference between $f+(r)$ and $f-(r)$. Both reactivity descriptors, along with the geometric representation, were visualized using the VESTA software (Visualization for Electronic and Structural Analysis) (Momma & Izumi, 2011).

The results of the computational chemistry calculations allowed for the analysis of the thermodynamic feasibility of the formation of molecular aggregates of the evaluated pharmaceuticals. In this analysis, the presence of dimers and trimers generated from the aggregation of these organic molecules dissolved in the aqueous solution was assumed. Preliminary calculations indicated that the formation of these aggregates was thermodynamically feasible. These molecular aggregates corresponded to interactions between the same pharmaceutical compound (e.g., A - A) and different pharmaceutical molecules (e.g., A – B). Molecular aggregates containing the same pharmaceutical molecule were termed homogeneous dimers or trimers, while those composed of different pharmaceutical molecules were termed heterogeneous dimers or trimers. Multiple initial configurations were analyzed to maximize attraction/repulsion interactions, with the most thermodynamically stable molecular structures selected based on interaction energies and separation distances.

The interaction energy (E_{int},kcal/mol), Equation 4, to evaluate the stability of pharmaceutical dimers $(n_{monomero} = 2)$and trimers ($n_{monomero} = 3$) was calculated using the following expression (Rodríguez-Ropero *et al*., 2008; Villanueva-Mejía *et al*., 2019):

$$E_{int} = E_{complejo} - \sum_{i=1}^{n_{monomero}} E_{monomero,i} \quad (4)$$

Where $E_{complejo}$ is the calculated energy of the dimer or trimer, and $E_{monomero,i}$ is the calculated energy of the pharmaceutical monomer i included in this molecular aggregate. The molecular volumes of the pharmaceuticals and their aggregates were also estimated using the Connolly surface approximation.

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Results and Discussion

Figure 1 and Table 1 show the representation of the optimized molecules of the tested pharmaceuticals, including their MEP, DD, and molecular dimensions. The analysis of the Boltzmann distribution indicated that the frequencies of the most stable and abundant monomers of APAP, DFC, and NAP were 64.5 %, 79.2 %, and 69. 8%, respectively. The calculated molecular volumes were: 251 Å³ for DFC > 219 Å³ for NAP > 140 Å³ for APAP.

It was identified that the APAP molecule has two proton-attracting regions, corresponding to the oxygen atoms of the hydroxyl group in the para position and the oxygen of the acetyl group. On the other hand, the positively charged region was located at the hydrogen atoms of the hydroxyl group and the secondary amine (see the MEP in Figure 1). In the case of the DFC molecule, the proton-attracting region corresponded to the oxygen atoms of the carbonyl group of the –COOH group, and the repulsion region was identified at the hydrogen atom of the OH group in the same –COOH group. The oxygen atoms of the –COOH and ether (-O-) groups were the proton-attracting regions of the NAP molecules, while the repulsion region was found at the hydrogen atom of the OH group in the –COOH group. The DD results are also presented in Figure 1, indicating the regions of electrophilic attacks (yellow) and nucleophilic attacks (blue) for these pharmaceutical molecules.

The results of the DFT calculations for a set of dimers and trimers that could form through the aggregation of pharmaceutical molecules in aqueous solution are reported in Figures 2 and 3, and in Table 2. The calculated molecular volumes for the homogeneous dimers were: 503 Å³ for DFC+DFC > 437 Å³ for NAP+NAP > 287 Å³ for APAP+APAP. These dimers were obtained from the interaction of oxygenated functional groups, showing interaction distances between 1.59 and 1.78 Å. For example, the APAP molecules interacted to form the APAP+APAP dimer through the hydrogen atom of the hydroxyl group and the oxygen atom located in the acetyl group, showing an estimated separation distance of 1.74 Å.

On the other hand, the heterogeneous dimers obtained from the interaction of different pharmaceutical molecules were also associated with oxygen-containing functional groups (e.g., the hydroxyl group of the NAP molecule and the acetyl group of the APAP molecule to generate the NAP+APAP aggregate). The estimated molecular volumes of these heterogeneous dimers were: 473 Å³ for DFC+NAP > 393 Å³ for DFC+APAP > 373 Å³ for NAP+APAP, while the separation distances ranged between 1.59 and 1.79 Å.

In the case of homogeneous pharmaceutical trimers, the calculated molecular volumes were: 753 Å³ for DFC+DFC+DFC > 690 Å³ for NAP+NAP+NAP > 430 Å³ for APAP+APAP+APAP, respectively. The interaction distances in these molecular aggregates ranged between 1.53 and 1.85 Å, where the hydroxyl, acetyl, and carboxyl functional groups of the pharmaceutical compounds were involved in forming the trimers.

The calculated molecular volumes of the heterogeneous trimers obtained from the aggregation

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of different pharmaceutical molecules were: DFC+NAP+DFC (752 Å³) > NAP+NAP+DFC (723 Å³) > DFC+DFC+APAP (653 Å³) > APAP+DFC+NAP (621 Å³) > NAP+NAP+APAP (601 Å³) > APAP+APAP+DFC (542 Å³) > NAP+NAP+APAP (518 Å³). The molecular interaction distances between oxygenated functionalities in these trimers ranged between 1.51 and 1.86 Å.

In general, the MEPs of the pharmaceutical trimers showed an attractive zone and a repulsive zone, as observed in Figure 3. The DD results also indicated the presence of zones for nucleophilic and electrophilic attacks depending on the type of trimer formed by these pharmaceutical compounds.

Based on the calculated interaction energies, the thermodynamic stability of the dimers is expected to follow the trend: NAP+NAP > DFC+NAP > DFC+DFC > APAP+NAP > APAP+DFC > APAP+APAP (see Table 2). In general, the calculated E_{int} values indicated that the formation of all these dimers is thermodynamically feasible, with NAP-based dimers being the most energetically favorable.

For homogeneous and heterogeneous trimers, the stability of these aggregates corresponded to: NAP+NAP+NAP > APAP+DFC+NAP > DFC+DFC+DFC > DFC+DFC+NAP > NAP+NAP+DFC > APAP+APAP+APAP > APAP+NAP+APAP > APAP+DFC+APAP > NAP+NAP+APAP > DFC+DFC+APAP. Notably, the trimer NAP+NAP+NAP was the most thermodynamically stable structure. These DFT results demonstrated that dimers are expected to be the most predominant aggregates in multicomponent solutions of these pharmaceuticals.

While experimental studies have characterized the interactions of diclofenac or acetaminophen with aspirin (Catella-Lawson *et al*., 2001; Schuijt *et al*., 2009), the self-association of these drugs (formation of dimers/trimers) remains experimentally unexplored. From a computational perspective, although molecular docking studies of individual non steroidal anti-inflammatory drugs with protein residues exist (Deb *et al*., 2017; Dwivedi *et al*., 2015), a critical gap persists: no systematic modeling of intermolecular drug-drug interactions has been performed to evaluate their self-aggregation potential. This omission is particularly significant, as pharmaceutical aggregate formation could alter key physicochemical properties, such as solubility, bioavailability, and release profiles, with direct implications for application efficacy.

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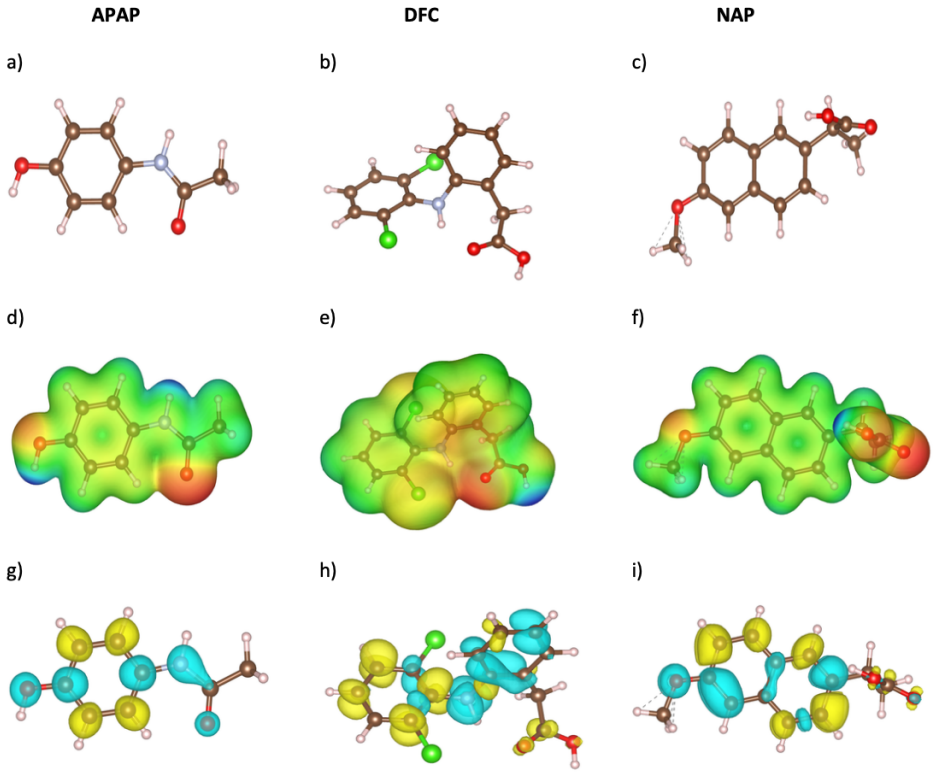

Figure 1. a), b), and c) correspond to the schematic representation, d), e), and f) is the molecular electrostatic potential (MEP on $\rho(r) = 0.015$ a.u.) and g), h), and i) represents the dual descriptor (DD) of tested pharmaceuticals. Columns are APAP, DFC, and NAP molecules.

Source: Own elaboration, visualized on VESTA.

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Pharmaceutical Aggregation	Schematic representation of the molecule	MEP	DD
APAP+APAP	a)	b)	c)
NAP+NAP	d)	e)	f)
DFC+DFC	g)	h)	i)
APAP+NAP	j)	k)	l)
APAP+DFC	m)	n)	o)
DFC+NAP	p)	q)	r)

Figure 2. Schematical representation, molecular electrostatic potential (MEP on $\rho(r) =$ 0.0013 a.u.) and dual descriptor (DD) of more stable dimer of tested pharmaceuticals.

Source: Own elaboration, visualized on VESTA.

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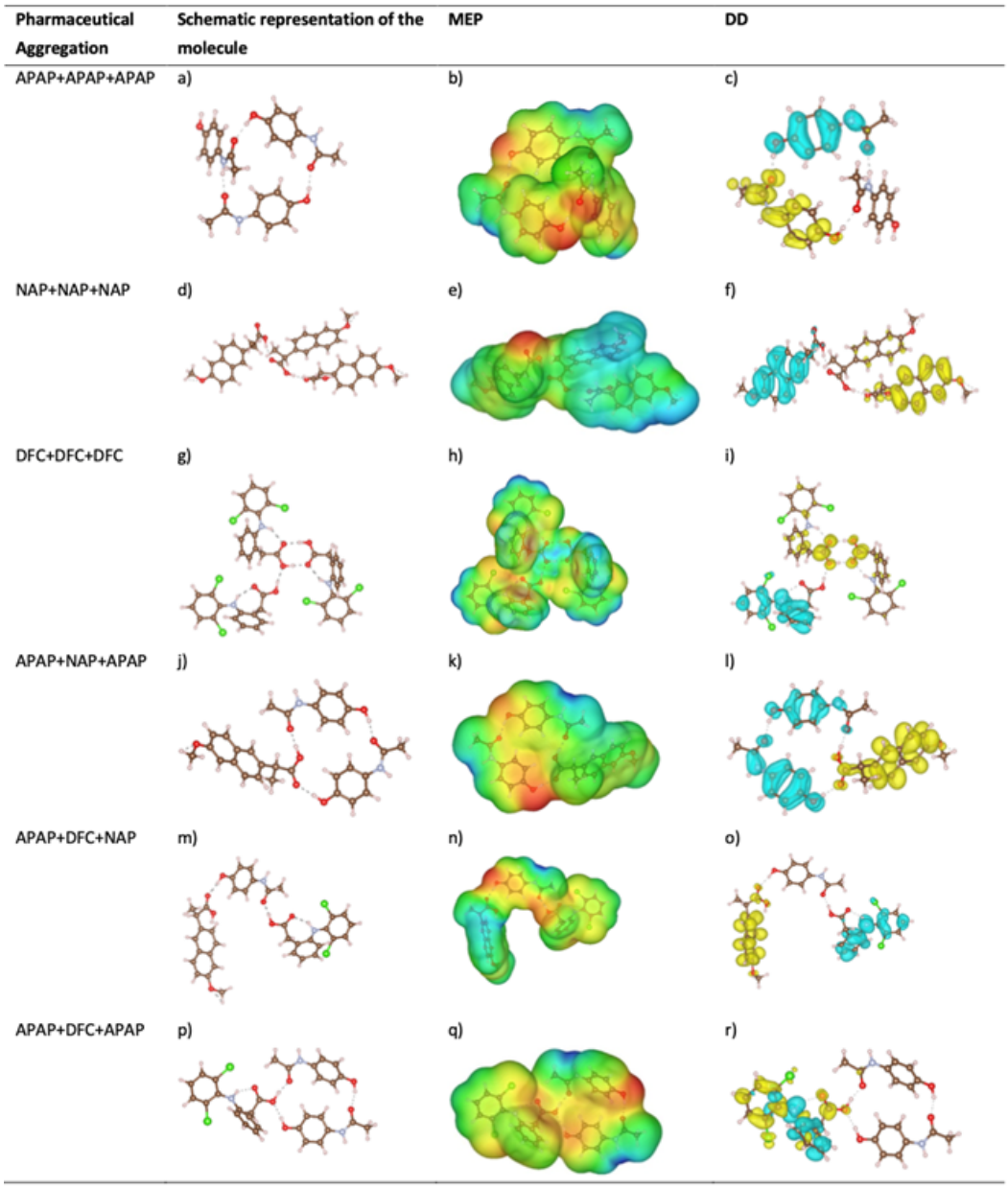

Figure 3. Schematic representation, molecular electrostatic potential (MEP on $\rho(r) =$ 0.0013 a.u.) and dual descriptor (DD) of more stable trimer of tested pharmaceuticals.

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Continuation

Pharmaceutical Aggregation	Schematic representation of the molecule	MEP	DD
NAP+NAP+APAP	s)	t)	u)
NAP+NAP+DFC	v)	w)	x)
DFC+DFC+APAP	y)	z)	aa)
DFC+NAP+DFC	ab)	ac)	ad)

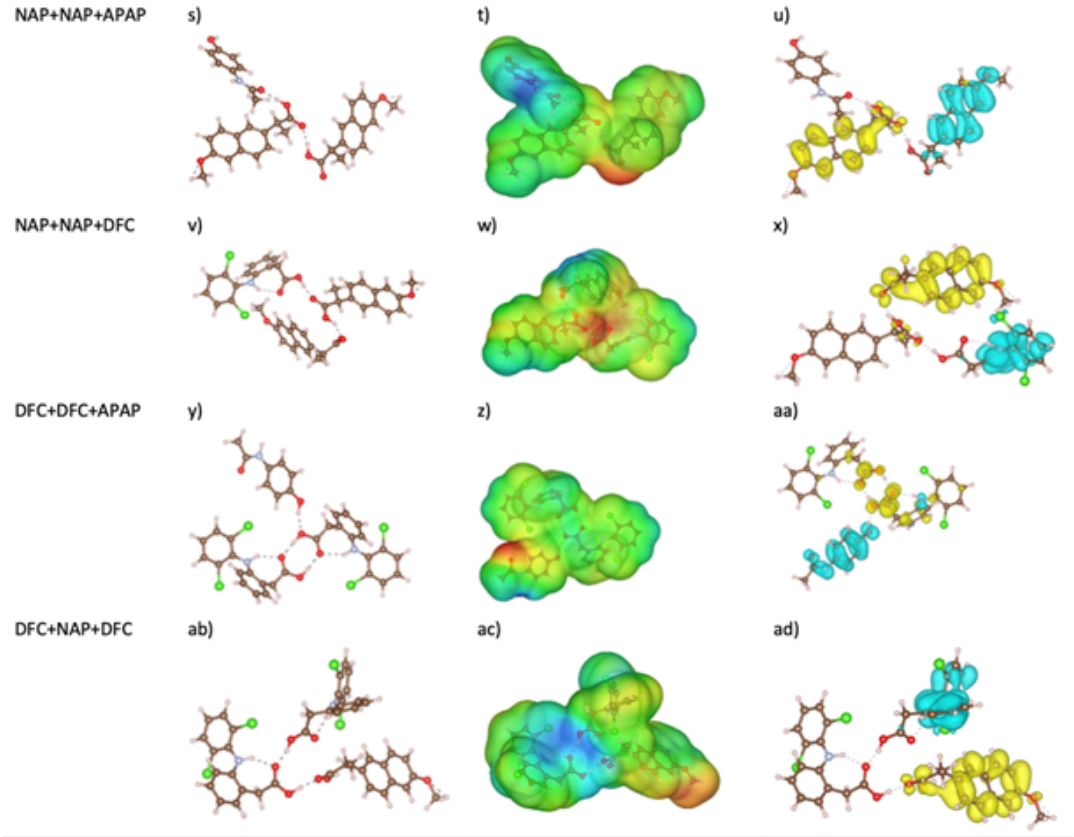

Figure 3. Schematic representation, molecular electrostatic potential (MEP on $\rho(r) =$ 0.0013 a.u.) and dual descriptor (DD) of more stable trimer of tested pharmaceuticals.

Source: Own elaboration, visualized on VESTA.

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Table 1. Molecular dimension of the optimized pharmaceuticals (Å). Data highlights of the molecular size, providing insights into the geometric configuration of these compounds post-optimization.

Pharmaceutical compound	Dimensions (Å)		
	X	Y	Z
APAP	8.5603	8.5603	1.7631
DFC	7.9147	9.5821	5.3785
NAP	10.2684	6.0658	4.5883

Source: Own elaboration.

Table 2. Interaction energies and separation distance of the three molecular pharmaceutical compound complexes. Interaction energies provide stability and binding affinity between the compounds, while separation distances hightlight the spatial arrangement of the molecules within each complex.

Pharmaceutical aggregation	**Interaction energy, kcal/mol**	**Distance, (Å)**
APAP+APAP	-136.309	1.737
DFC+DFC	-212.634	1.592
NAP+NAP	-242.769	1.780
APAP+DFC	-173.989	1.598
DFC+NAP	-225.694	1.637
APAP+NAP	-193.326	1.793
APAP+APAP+APAP	-99.602	1.702
DFC+DFC+DFC	-117.528	1.732
NAP+NAP+NAP	-147.132	1.643
APAP+DFC+APAP	-77.048	1.764
APAP+NAP+DFC	-126.150	1.813
APAP+NAP+APAP	-78.988	1.608
DFC+NAP+DFC	-108.782	1.640
NAP+NAP+APAP	-75.671	1.591
DFC+DFC+APAP	-68.842	1.859
NAP+NAP+DFC	-107.025	1.638

Source: Own elaboration.

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ISSN 2007-3380

Conclusions

This study employed DFT calculations to investigate the formation and stability of dimers and trimers of three pharmaceutical compounds: APAP, DFC, and NAP. Our findings reveal relevant insights into the intermolecular interactions and molecular aggregation behavior within this class of pharmaceuticals.

The DFT calculations predict a diverse range of dimer formations with varying interaction energies. The observed differences in interaction energies likely reflect the influence of specific intermolecular forces, such as hydrogen bonding and van der Waals interactions, which are unique to each molecular pair (APAP-APAP, APAP-DFC, APAP-NAP, DFC-DFC, DFC-NAP, NAP-NAP). These variations highlight the complexity of intermolecular interactions. The most energetically favorable dimers are consistent with the observed electrostatic potential mapping, indicating the key role of electrostatic interactions in the process.

The analysis of trimer formations further clarifies the aggregation trends of these pharmaceuticals. The stability of the trimers reflects the cumulative effects of intermolecular interactions among the constituent dimers. The most stable trimer configuration identifies the strongest cooperative interactions occurring within the system. Future research should explore the relationship between these aggregation patterns and potential pharmaceutical properties, such as solubility and bioavailability.

The electrostatic potential maps and dual descriptor analysis provide a detailed understanding of the electrostatic characteristics of the molecules and their contributions to favorable dimer and trimer formations. This suggests that tailored molecular design approaches focusing on electrostatic interactions could potentially control aggregation behavior.

The observed aggregation patterns could have significant implications for the formulation and administration of these pharmaceutical compounds. Understanding the intermolecular interactions responsible for aggregation may be crucial for improving the solubility, stability, and bioavailability of these drugs.

Author Contributions

Conceptualization: L.G.E.P., F.V.M.; Methodology: L.G.E.P., F.G.M.P., F.V.M.; Software: L.G.E.P., F.G.M.P., A.D.P.; Validation: L.G.E.P., F.G.M.P., A.D.P.; Formal analysis: A.D.P., J.E.O.G.; Data curation: A.D.P., F.G.M.P., J.E.O.G.; Writing - original draft: L.G.E.P., F.G.M.P., J.E.O.G.; Writing - review & editing: A.D.P., F.V.M.; Project administration: L.G.E.P., F.V.M.

All authors have read and approved the final manuscript.

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ISSN 2007-3380

Acknowledgments

F.V.M. acknowledges the National Supercomputing Center at the Potosino Institute of Scientific and Technological Research for providing computational resources (Project No. TKII-E-0524-I-230524-42/PR-62) used in this research.

Conflict of Interest

The authors declare no conflict of interest.

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