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Encapsulation of Naproxen with Meso-Tetradodecyl-Pyrogallol[4]arene: Complexation, Characterization, and Molecular Docking Insights: Enkapsulasi Naproksen dengan Meso-Tetradodecyl-Pyrogallol[4]arene: Pembentukan Kompleks, Karakterisasi, dan Wawasan Docking Molekuler

Essam S. Khudhier, ahes7714@gmail.com (*)
Department of Pharmaceutical Chemistry, College of Pharmacy, Basrah University, Basrah, Iraq

Maan S. AlNuaim , ahes7714@gmail.com
Department of Pharmaceutical Chemistry, College of Pharmacy, Basrah University, Basrah, Iraq

Khulood H. Oudah , ahes7714@gmail.com
Department of Pharmacy, Mazaya University College, Nasiriyah 64001 , Iraq

(*) Corresponding author

Abstract

General Background: Supramolecular encapsulation using macrocyclic hosts has emerged as a strategy to address solubility and stability limitations of poorly water-soluble drugs. **Specific Background:** Naproxen, a widely prescribed nonsteroidal anti-inflammatory drug, exhibits low aqueous solubility and gastrointestinal irritation, prompting investigation of meso-tetradodecyl-pyrogallol[4]arene (C12-Py[4]arene) as a hydrophobic macrocyclic carrier capable of forming inclusion complexes through noncovalent interactions. **Knowledge Gap:** Although pyrogallol[4]arenes possess tunable cavities and self-assembly properties, detailed characterization of naproxen encapsulation combining spectroscopic, morphological, and molecular docking analyses remains limited. **Aims:** This study aimed to encapsulate naproxen within C12-Py[4]arene via mechanochemical grinding, characterize the resulting complex (PYX7), and evaluate binding affinity using molecular docking. **Results:** UV–Vis spectroscopy revealed bathochromic shifts at 318.00 and 332.50 nm, while FTIR analysis showed C=O band shifting from 1725 to 1689 cm^{-1}, confirming hydrogen bonding. SEM demonstrated altered semi-spherical agglomerates with heterogeneous morphology. Docking simulations predicted favorable binding energy (−7.00 kcal/mol), supported by hydrogen bonding and π–π stacking interactions within the hydrophobic cavity. **Novelty:** The integration of solvent-free complexation, spectroscopic validation, SEM imaging, and in silico modeling provides a comprehensive profile of PYX7 formation. **Implications:** These findings identify C12-Py[4]arene as a supramolecular carrier for naproxen and support further evaluation of pyrogallol[4]arene-based systems in NSAID delivery research.

Keywords: Supramolecular Encapsulation, Naproxen, Pyrogallol4arene, Inclusion Complex, Molecular Docking

Key Findings Highlights:

1. Spectral shifts verified noncovalent host–guest interactions.
2. Microscopy demonstrated nano-assembly formation with structural heterogeneity.
3. Computational modeling showed favorable binding energetics and structural complementarity.

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Introduction

Naproxen, a propionic acid analogue, is one of the most frequently prescribed of the NSAIDs, and has been administered for the treatment of pain, inflammation, and arthritis. It acts non-selectively to inhibit cyclooxygenase enzymes (COX-1 and COX-2), resulting in decreased prostaglandin synthesis and ameliorated inflammation. Despite its therapeutic utility, naproxen suffers from serious biopharmaceutical concerns: low aqueous solubility and poor GI tolerability. The solubility of a compound in water of a concentration of 0.016 mg/mL suppresses the solubilization (dissolving) and absorption thereof, and the free carboxyl group in water can potentially lead into ulceration of gastric mucosa after extended use (6). Hence, it is very possible to perform studies targeting its properties in terms of its solubility, stability and bioavailability and that at the local level alleviate some side effects that occur with naproxen. Recently, supramolecular chemistry has become an innovative drug formulation technique that allows for the flexible encapsulation of bioactive molecules with non-covalent moieties on a small scale. Supramolecular hosts form inclusion complexes through the interaction of hydrogen bonding, π–π stacking, and hydrophobic forces that can alter the physicochemical and pharmacokinetic properties of therapeutic agents (4). Numerous families of macrocyclic hosts—cyclodextrins, calixarenes, cucurbiturils, pyrogallol[4]arenes—have been studied well for this purpose. Pyrogallol[4]arenes are found to have attracted more interest because of their excellent structural freedom and multiple phenolic hydroxyl groups within the inner cavities for hydrophobic pores and high host–guest interactions, which is particularly beneficial for poorly soluble pharmaceuticals (1, 5). Pyrogallol[4]arenes are cyclic tetramers whose structural characteristics include the synthesis of pyrogallol and aldehydes by the condensation of the two component groups by acid (3) into a bowl shape macrocycle, self-assembly is achieved by hydrogen bonding and this macrocyclic assembly occurs in solution as well as solid. Changes in meso position facilitate the precise control of cavity size, polarity and assembly characteristics. Specifically, meso-tetradodecyl-pyrogallol[4]arene (C12-Py[4]arene) with long dodecyl chains acts to promote hydrophobic stabilization and spontaneously generate nanocapsules and vesicular aggregates in polar solvents (2, 7). These characteristics are in agreement with the incorporation of hydrophobic and amphiphilic components, such as naproxen, and encapsulation, potentially attenuating GI irritation and improving solubility. C12-Py[4]arene addition of naproxen should confer a variety of therapeutic advantages:

- Non-covalent encapsulating agent (not covalent) with greater water-solubilization capacity.

- Protection of mucosal irritation of acidic groups in the host cavity

- Increased thermal and photostability in a localized microenvironment.

- Water-driven hydrophobic diffusion in the macrocyclic system determines release dynamics. Computational molecular docking studies (CMDs) also serve an important role in disentangling the host-guest interactions, but the atomic level is adopted. These docking simulations may yield insights into binding formats, energy profiles, stabilizers, in particular hydrogen associations and van der Waals dynamics influencing the stabilisation of inclusion complexes (8, 9). Therefore, by combining in silico analysis with their experimental approaches, a complete characterization of the molecular encapsulation process of the supramolecular drug carrier can be formed, and such a characterization will be beneficial for the better planning of the more specific optimization plans. Here, a pathway to complexate naproxen with meso-tetradodecyl-pyrogallol[4]arene (C12-Py[4]arene) to prepare a novel inclusion complex PYX7 was presented. The encapsulation was also performed under solvent-free conditions, following a mechanochemical grinding process to enable host–guest interactions. UV–Vis spectroscopy and FTIR spectroscopy tools were applied to characterize the electronic connections and hydrogen-bonding interaction, followed by scanning electron microscopy (SEM) to study the structure morphology. At the molecular level, binding affinities and conformational stability of naproxen and C12-Py[4]arene as well as the binding behavior of the compounds are also examined by molecular docking studies. It has shown new avenues for using pyrogallol[4]arenes to be used to deliver NSAIDs or other hydrophobic therapeutic compound through super-effective supramolecular nanocarriers.

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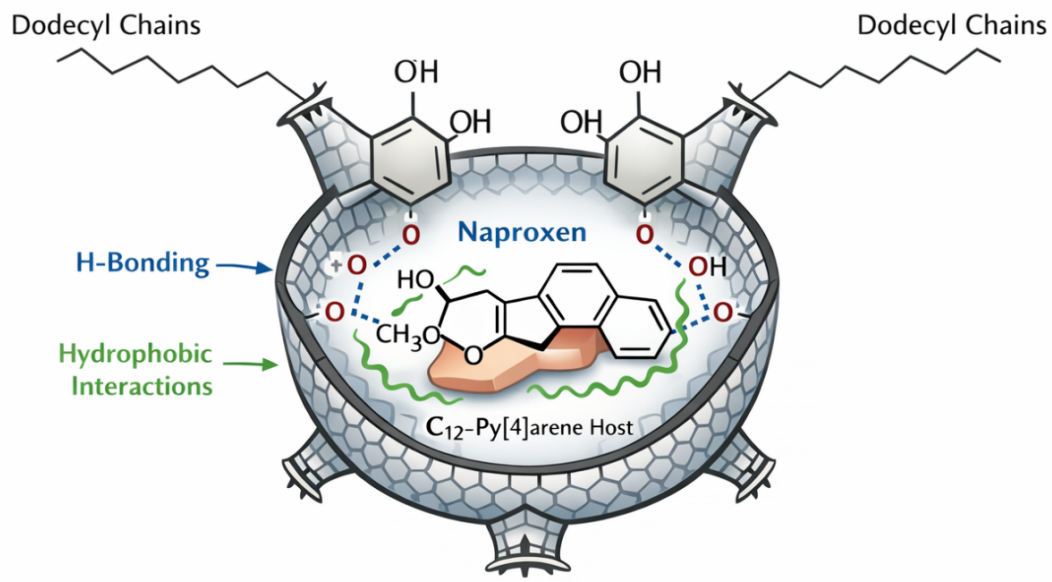

Figure 1: Schematic representation of Naproxen encapsulated within meso-tetradodecyl-pyrogallol[4]arene (C_{12}-Py[4]arene) showing key interactions.

Figure 1.

Aim of Study

Encapsulate naproxen within meso-tetradodecyl-pyrogallol[4]arene (C12-Py[4]arene) to yield a complex (PYX7).

Characterize the resulting complexes using spectroscopic, thermal, and morphological analyses.

Use molecular docking to evaluate binding affinity and stability.

Assess the potential of C12-Py[4]arene as a supramolecular carrier for NSAID delivery.

Materials and Methods

Materials

Host: meso-tetradodecyl-pyrogallol[4]arene

Guest: Naproxen sodium (≥99% purity).

Synthesis of meso-tetradodecyl-pyrogallol [4] arene

A pre-dried round bottom flask (250 mL) containing a magnetic stirrer and fitted to a reflux condenser and dropping funnel is placed in an ice bath under an inert atmosphere. Pyrogallol(11.49gm,91.11mmol), was dissolved in ethanol (100 mL), and a methanesulfonic acid (2mL) solution in ethanol (20mL) was added dropwise to the stirring solution maintaining the temperature at (0 ºC). This is followed by the dropwise addition of a solution of dodecanal(16.8gm,91.14mmol) dissolved in ethanol (25mL) to the reaction mixture . The reaction mixture was removed from an ice bath and heated in an at (100 ºC) under vigorous stirring for24 hours.The mixture was left to stir and monitored by silica gel TLC using a DCM/MeOH (9:1) mixture as the developing solvent, R*f* value (0.6). After the reaction has been completed, the mixture was allowed to cool at room temperature,the mixture was poured into an ice-water to obtain an off-white crystalline solid which was filterated and washed with an ice cold methanol.The solid was collected and dried.The product obtained in (70% yield).

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Complexation Protocol

The encapsulation of naproxen with C12-Py[4]arene using a grinding method involves several key steps aimed at enhancing the solubility and bioavailability of the drug. Here is a detailed procedure based on the principles of drug formulation and encapsulation techniques(11). Accurately weigh the required amounts of naproxen and C12-Py[4]arene based on the desired encapsulation ratio.Place the weighed naproxen and C12-Py[4]arene into the grinding apparatus.Grind the mixture thoroughly using a mortar and pestle or a ball mill. The goal is to achieve a fine powder where the pyrogallol[4]arene effectively coats or interacts with the naproxen particles.Continue grinding for an adequate time (typically 30 minutes to several hours) until you observe a homogeneous mixture with reduced particle size.Analyze the particle size distribution and morphology using techniques like scanning electron microscopy (SEM).This grinding method for encapsulating naproxen with C12-Py[4]arene aims to improve its solubility and bioavailability, which is crucial for its efficacy(12).

Characterization Techniques:

UV–Vis Spectroscopy: measured absorption shifts.

FTIR: examined C=O and O–H stretching interactions.

SEM: visualized morphology and particle size.

Molecular Docking Studies

Docking simulations were conducted using AutoDock Vina. The 3D structure of C12-Py[4]arene was modeled and minimized using Gaussian. Naproxen was docked into its hydrophobic cavity, and binding free energies (ΔG) were computed. Interaction analyses (hydrogen bonding, van der Waals, π–π stacking) were carried out with PyMOL and Discovery Studio.

Results and Discussion

UV–Vis Spectroscopy Measurements

Encapsulation of naproxen with the receptor (PYG3) produced a bathochromic shift in naproxen’s absorption band, due to π−π stacking or hydrogen bonding with the pyrogallol[4]arene,

indicating host–guest interaction. 318.00 nm and 332.50 nm these peaks are indicative of a bathochromic shift (red shift) in comparison to the free naproxen (generally λmax ~270–330 nm). This shift indicates changes in the electronic environment, including the effects of host-guest interactions (e.g., π-π stacking or hydrogen bonding) that lead to stabilization of the excited state. Spectral shifts and new absorbance bands are evidence of successful host-guest interactions. Improvement in stability or solubility for naproxen inside the macrocyclic cavity may be speculated.

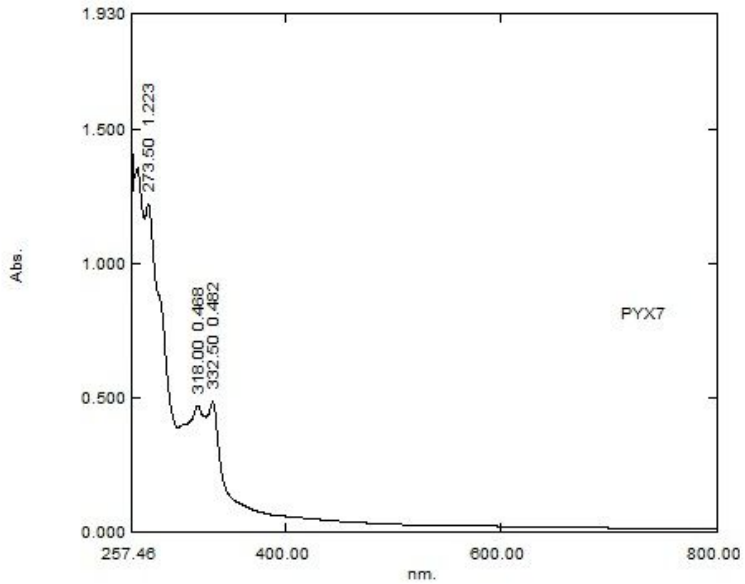

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Figure 2. **Figure 1: UV. spectrum of PYX 7 in DMSO**

FTIR Spectroscopy

Naproxen's C=O stretching band (1725 cm^{-1}) shifted to 1689 cm^{-1} as show in (Figure 2) upon complexation, confirming hydrogen bonding with C12 Py[4]arene hydroxyls.

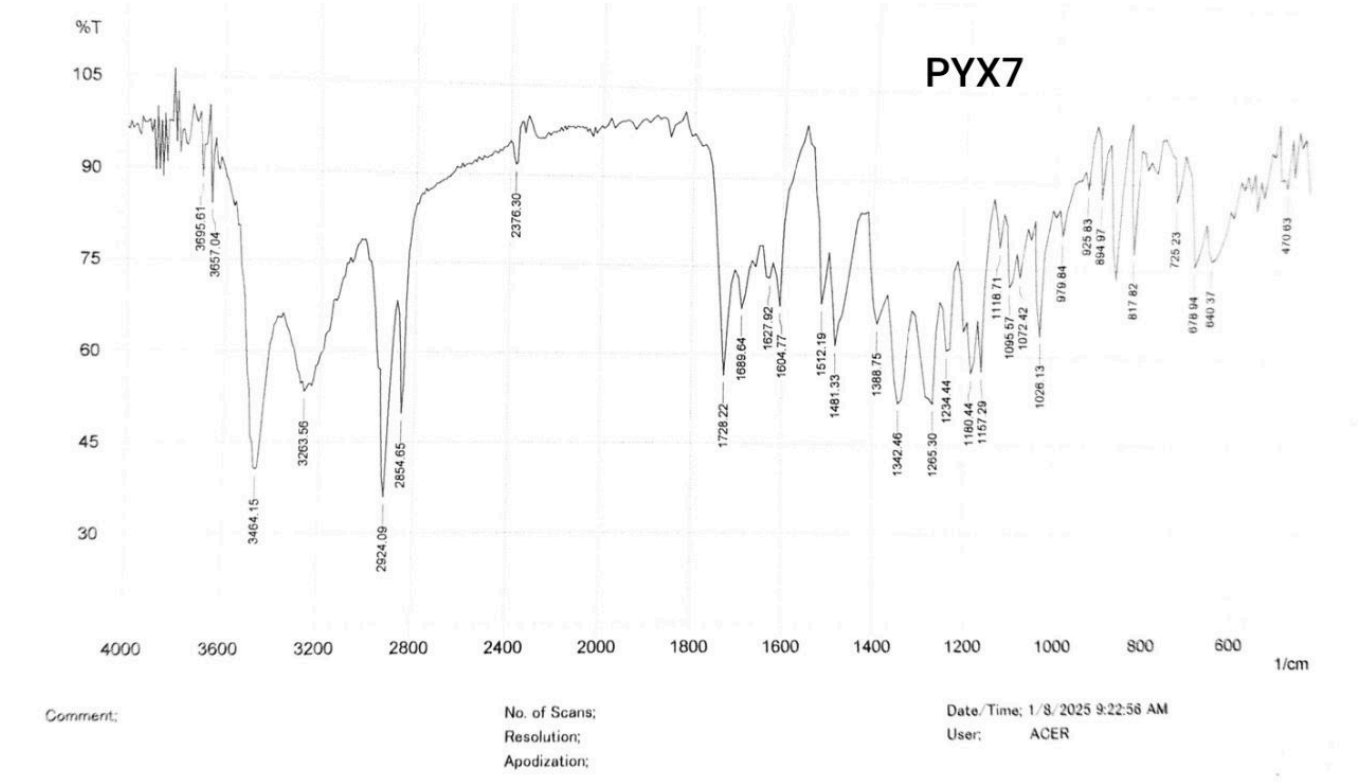

Figure 3.

Morphological Analysis

SEM revealed spherical nano-assemblies, well-suited for drug delivery applications. PYX7, however, shows bigger and Irregular, semi- spherical agglomerates composed of smaller fused plate-like particles that are produced by the disruption of the structure. This indicates that the drug disrupts the intracellular morphology in the native state and potentially disrupts intermolecular interactions or self-assembly. The alteration of mapping PYX7 deposited with naproxen is a result of the addition of naproxen to the surface and the composition heterogeneity. This heterogeneity may be due to phase separation, non-uniform distribution of the drug, and partial recrystallization, which resulted from a high increase in surface roughness, as can be seen in the SEM images.PYX7, with its unique morphology and characteristic surface properties, has promising pharmaceutical potential, in particular drug delivery systems.

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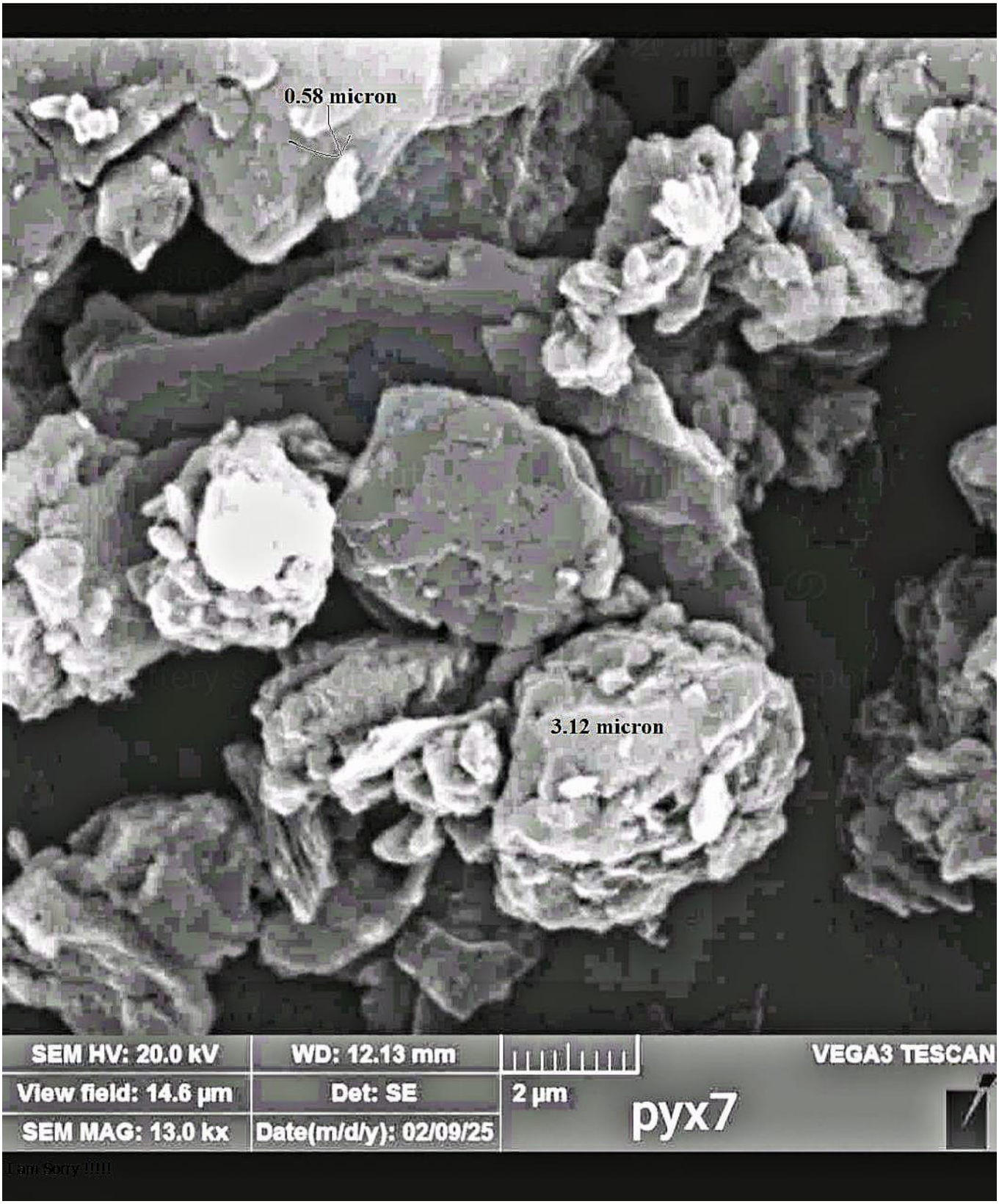

Figure 4. **Figure 3: SEM Photograph of PYX7**

Docking Studies

Docking predicted binding energies of –7.0 kcal/mol, supporting stable inclusion. Naproxen's carboxyl group formed

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hydrogen bonds with Py[4]arene hydroxyls, while aromatic regions engaged in π–π stacking. Long alkyl chains contributed additional hydrophobic stabilization.

COMP.	Binding energy	Ligand efficiency	Dissociation constant (nM)	Vdw hb_desolv_energy	H-bonds	Distance of H-bonding	Energy of H-bonding
PYX7	-7.00	-0.41	7.42	-8.19	1	1.994	-0.209

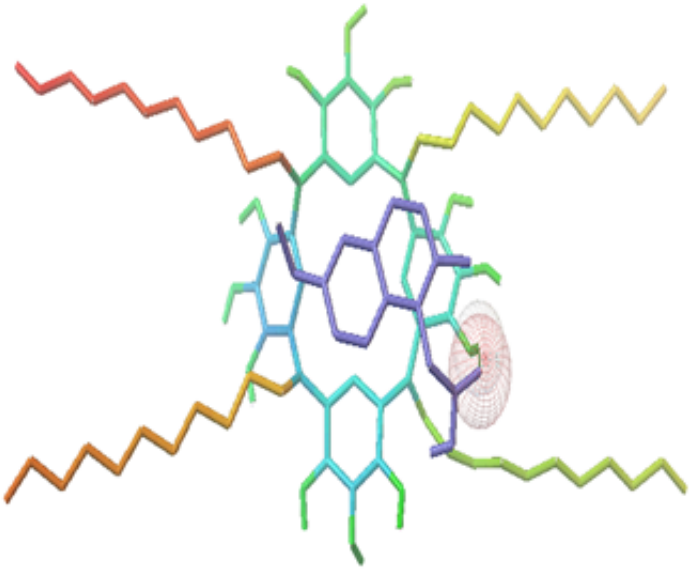

Figure 5. **Figure 4: Molecular Docking of PYX7**

The findings confirm the successful encapsulation of Naproxen within C12-Py[4]arene. Spectroscopic and SEM analyses highlighted noncovalent interactions, including hydrogen bonding and hydrophobic effects, as the primary stabilizing forces. Computational docking validated these observations, demonstrating favorable energetics and structural complementarity.

When compared with alternative carriers such as cyclodextrins and cucurbiturils, pyrogallol[4]arenes exhibit enhanced hydrophobic tunability and self-assembly characteristics (5). The present study broadens their application to NSAID delivery, providing a pathway to improve solubility and minimize gastrointestinal side effects.

Conclusion

Meso-tetradodecyl-pyrogallol[4]arene effectively encapsulates Naproxen, as demonstrated by spectroscopic, thermal, and docking analyses. These results identify C12-Py[4]arene as a promising supramolecular carrier capable of improving the delivery of hydrophobic drugs like naproxen. Future studies should include in vitro release profiling and in vivo pharmacokinetic evaluation to establish clinical translation potential.

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