SRI VENKATESWARA INTERNSHIP PROGRAM FOR RESEARCH IN ACADEMICS (SRI-VIPRA)

SRI-VIPRA

Project Report of 2024: SVP-2444

"Supramolecular Innovations: Unveiling Their Advantages in Disease Treatment"

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SRIVIPRA PROJECT 2023

Title: Supramolecular Innovations: Unveiling Their Advantages in Disease Treatment

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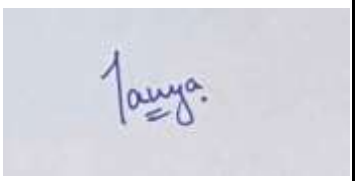
1		Tanya Virmani	1522003	B.Sc. (Hons) Chemistry, Semester 5	
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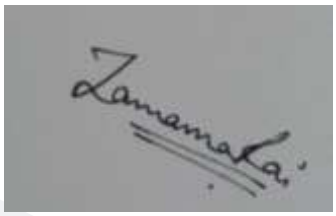
5		Tamanna Rai	1523004	B.Sc. (Hons) Chemistry, Semester 3	
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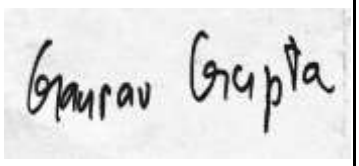
8.		Gaurav Gupta	1523005	B.Sc. (Hons) Chemistry, Semester 3	
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Signature of Mentor

Certificate of Originality

This is to certify that the aforementioned students from Sri Venkateswara College have participated in the summer project SVP-2444 titled "**Supramolecular Innovations: Unveiling Their Advantages in Disease Treatment**" The participants have carried out the research project work under my guidance and supervision from 1st July, 2024 to 30th September 2024. The work carried out is original and carried out in hybrid mode.

Signature of Mentor

Acknowledgements

We wish to extend our deepest gratitude to Sri Venkateswara College, our esteemed principal Prof. V. Ravi , and our project mentor and coordinator Dr. Shefali Shukla for the invaluable opportunity to undertake this research project on - **"Supramolecular Innovations: Unveiling Their Advantages in Disease Treatment**". Dr. Shukla's guidance has been instrumental to the success of this project. This experience has greatly expanded our understanding of supramolecular innovations and will undoubtedly benefit our future endeavours.

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Objectives

The main objective of this project is to inculcate scientific aptitude and research skills in the students by simultaneously providing knowledge and awareness about the role of supramolecular complexes in disease diagnostics and therapeutics covering a number of diseases, especially cancer.

Introduction

Supramolecular Chemistry, a sub-division of nanoscience, is defined as the 'chemistry beyond the molecules' whereas a supramolecule is a distinct system of molecules, termed as host and guest respectively which are held together by non-covalent interactions, especially hydrogen bonds.[1]

The properties of supramolecular complexes which facilitate disease treatment and have biomedical applications are- Self-Assembly and Stimuli Responsiveness. Supramolecular Systems can reversibly undergo self-assembly i.e. from single isolated molecules to formation of complex well-ordered host-guest combined structures. Also, they have the ability to respond to various stimuli- External (Temperature, Light, Ultrasound, Electrical, Magnetic) and Internal (pH, Redox, Enzymes).[2]

The physio-chemical properties and related biological activities of supramolecules ultimately reveals that they have good biocompatibility, low toxicity and can easily cross biological barriers. The competitive host-guest recognition and the complexation instead of chemical reaction at the site having biomarkers like ATP, spermine and bile acids are observed in the supramolecular systems.

Supramolecular Innovations have numerous applications in drug design, development of biomaterials, understanding biological processes and diagnostic imaging which ultimately helps in treating diseases. Creating synthetic molecules which when interact with specific body targets like enzymes, receptors etc. led to formation of novel drugs and when they interact with biological systems and thereby promote regeneration led to development of biomaterials. Designing supramolecules to understand gene expression and protein functions can be a classic example of understanding biological processes. Designing supramolecular structures which when labelled with imaging agents like radioisotopes and fluorescent dyes helped in diagnostic imaging i.e. non-invasive detection of disease markers.[3]

The major significance of supramolecules is seen in the field of chemotherapeutics. These complexes prevent metastasis and angiogenesis and thereby cause cell apoptosis in the cancer theranostics.[4]

Supramolecules contribute to cancer treatment through various approaches, including bioimaging, photodynamic therapy (PDT), drug delivery systems, gene delivery, and combined drug/gene codelivery. Bioimaging provides information regarding disease diagnostics i.e. supramolecular application in this field leads to visualisation of target cells without inducing toxicity and side-effects to the biological systems. Photodynamic Therapy (PDT) is a non-invasive method for cancer treatment that remains non-toxic due to the controlled application of light irradiation. Drug delivery systems ensure effective and accurate drug loading, along with targeted and controlled release at the specific site. It also

enhances the water-solubility of the anti-cancer drugs leading to better chemotherapeutic efficacy. Gene delivery is also carried out using supramolecules nowadays as non-viral gene delivery systems are preferred due to low toxicity and high efficiency. Drug/Gene co-delivery is utilised in treatment of cancer where traditional anti-cancer drugs and therapeutic genes are combined to provide synergistic treatment to enhance therapeutic efficacy and to hamper drug resistance effect.[5]

Synthesis and Characterization

- ***Method of Synthesis***

In this section, we explore the non-covalent forces driving supramolecular assembly, crucial for therapeutic applications. Key forces include hydrophobic interactions, hydrogen bonding, host-guest interactions, and electrostatic interactions. To harness these forces for disease treatment, researchers employ synthesis strategies such as molecular self-assembly, supramolecular polymerization, host-guest chemistry, and bioconjugation. Effective synthesis involves tuning molecular structure and properties, incorporating stimuli-responsive elements, targeting moieties, and ensuring biocompatibility and minimal toxicity. By mastering these design principles, researchers can develop innovative supramolecular therapeutics, offering new hope for treating complex diseases by creating therapeutic nanoparticles, dynamic materials for drug delivery, molecular containers for targeted therapy, and integrated biomolecular systems for enhanced efficacy.

(1)Methods of synthesis of supramolecular platinum complexes for cancer therapy

Supramolecular Pt(II) complexes utilize host-guest interactions and self-assembly for their development as anticancer agents and drug delivery systems. These complexes vary from small host-guest arrangements to large metallo-supramolecules and nanoparticles. By integrating the biological properties of platinum compounds with novel supramolecular architectures, these complexes inspire new anticancer strategies that address the challenges associated with conventional Platinum drugs. We will talk about 2 distinct types of supramolecular Pt(II) complexes, categorized by variations in platinum cores and supramolecular structures. These include supramolecular complexes of unconventional Pt(II) metallodrugs and supramolecular complexes of Pt(IV) prodrugs resembling fatty acids.

A. Supramolecular complexes of unconventional Pt(II) metallodrugs:

In recent decades, numerous nonclassical Pt(II) metallodrugs have been developed, featuring mechanisms of action that differ significantly from those of approved drugs. The integration of Pt(II) complexes with supramolecular chemistry offers new insights into bioinorganic chemistry and advances in cancer therapy.For instance, Marek introduced innovative monofunctional Pt(II) compounds featuring an adamantyl moiety, which can form host-guest complexes with cucurbit. Additionally, Che recently utilized intracellular self assembly of organoplatinum(II) complexes for cancer therapy. A compound, which contains a glucose moiety, can self-assemble into nanoparticles approximately 100 nm in size,

entering cancer cells through endocytosis. Importantly, the glycosidic linkage is cleaved by β-glucosidase inside the cells, leading to the formation of 5d, which features a hydroxyl group. Compound 5d subsequently self-assembles into nanofibrils. This development of supramolecular structures results in increased autophagic vacuole formation, lysosomal membrane permeabilization and mitochondrial membrane depolarization, along with notable in vivo efficacy.

B. Supramolecular assemblies of Pt (IV) prodrugs mimicking the structure of fatty acids.

The Pt(IV) prodrug strategy is commonly employed to enhance the therapeutic index and reduce the side effects of Pt-based metallodrugs. Typically, Pt(IV) prodrugs are created through the chemical oxidation of an active square-planar Pt(II) species, which incorporates two "axial" ligands. This transformation results in an octahedral Pt(IV) complex that is more stable and less prone to ligand substitution than its Pt(II) precursor. In the reducing environment of cancer cells, the Pt(IV) center is converted back to Pt(II), releasing the two ligands and regenerating the active square-planar Pt(II) complex.Fatty acid-like Pt(IV) prodrugs (FALPs) represent a category of Pt(IV) prodrugs that have gained significant attention in recent years. Designed to mimic fatty acid structures, FALPs can exploit host-guest interactions with human serum albumin (HSA) for improved drug delivery.

Recent studies indicate that these innovative Pt(IV) prodrugs can be easily integrated into nanoparticles through non-covalent encapsulation or covalent conjugation, owning to their amphiphilic characteristics. The FALP scaffold can also be modified to include oxaliplatin and carboxylate hydrocarbon tails. Most reported FALPs demonstrate superior in vitro potency against a diverse range of cancer types and show promising in vivo efficacy in various mouse models. Overall, FALPs have emerged as a powerful platform with unique mechanisms of action, significant structural diversity, and promising translational potential.[6]

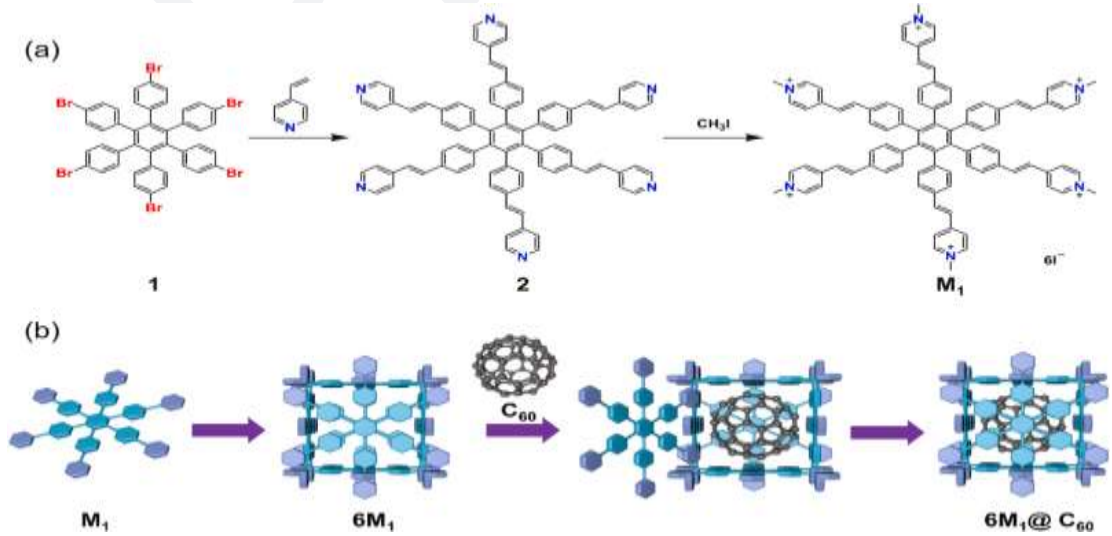
(2) Method of synthesis of Fullerene [60] encapsulated water-soluble supramolecular cage for prevention of oxidative stress-induced myocardial injury:

Acute myocardial infarction (AMI) is the leading cause of death related to cardiovascular disease. When coronary arteries become obstructed, the myocardium can suffer from inadequate oxygen supply, resulting in myocardial necrosis, fibrosis, and ventricular remodeling, which significantly impair heart function. Current antioxidant therapy strategies encompass dietary support, gene therapy, free radical scavengers, polyethylene glycol (PEG) binding, and nanomedicine-based technologies. However, their effectiveness and applications often fall short. Given the limitations of these approaches, identifying a potent and efficient antioxidant is crucial for preventing the onset and progression of diseases, including those linked to acute myocardial infarction.

Fullerenes and their derivatives are often referred to as "free radical sponges" because of their highly electron-deficient structure, which readily interacts with radicals. Furthermore, the antioxidant, antibacterial, antiviral, drug delivery, and tumor therapy activities of fullerenes have been widely recognized in biology and medicine. However, their spherical

and hydrophobic surface often leads to limited water solubility. To enhance the water solubility of C60 for broader biomedical applications, significant efforts have been made. Most strategies involve modifying the chemical structure of C60 by introducing hydrophilic groups. However, such functionalization can compromise some of its properties, particularly its electron-deficient nature. For instance, the opening of double bonds during typical C60 modification can disrupt its overall conjugation. Thus, enhancing the water solubility of C60 while maintaining its original structure continues to be a key objective.

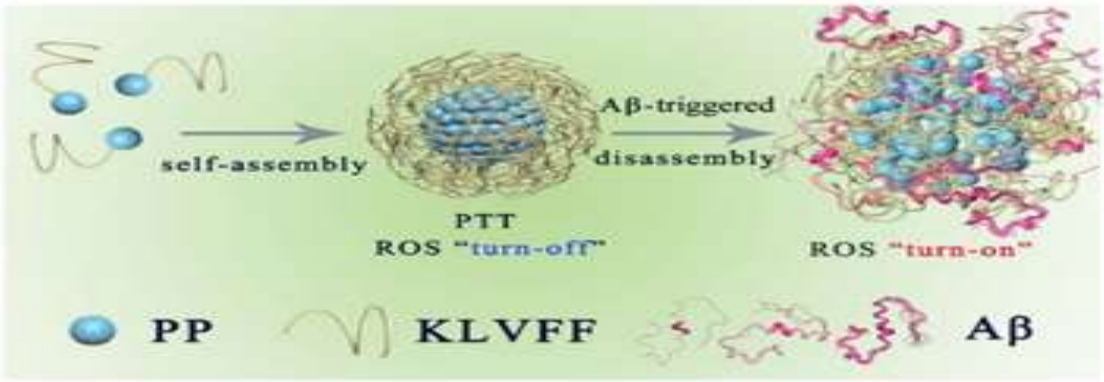
The self-assembly of small water-soluble molecules into complex architectures is proving to be a promising approach. Supramolecular self-assembly, particularly of amphiphilic molecules, has been widely employed to create various nanostructures featuring channels and cavities in aqueous environments, making it an ideal solution for diverse applications.
Inspired by the traditional burr puzzle game, a study designed a hexagram-shaped amphiphile (M1) featuring six hydrophilic vinyl pyridyl groups attached to a hydrophobic hexaphenylbenzene core. The hydrophobic effect was a key factor in the self assembly process. Single-crystal-X-ray diffraction provided clear evidence of cube-like structures formed from six monomers of M1 in pure water through this hydrophobic effect. Furthermore, the cage was capable of encapsulating a C60 molecule within its hydrophobic interior, significantly enhancing the water solubility of C60. The 6M1@60 complex was subsequently tested for its ability to reduce reactive oxygen species (ROS) in cardiomyocytes. Remarkably, 6M1@C60 significantly lowered water- induced intracellular ROS levels, thereby slowing apoptosis and inflammatory responses, resulting in improved cell viability in cardiomyocytes. In a mouse model of myocardial ischemia-reperfusion injury, the application of 6MI@C60 effectively reduced myocardial injury and improved cardiac function. It also decreased ROS levels in myocardial tissue, inhibited myocardial apoptosis, and alleviated myocardial inflammatory responses. This entire process was confirmed through the Akt/Nrf2/HO-1 pathway, underscoring the significance of these findings for the treatment of oxidative stress-related cardiovasculardisease.[7]



(3) Supramolecular self-assembly for targeted photooxygenation of amyloid-β in the treatment of Alzheimer's disease.

Alzheimer, a type of dementia, has became one of the concerning disease affecting more than 50 million people worldwide. Since, the aggregation of amyloid-β peptides (Aβ) is responsible for AD pathogenesis, the prevention of Aβ aggregation has been sought as a promising strategy to treat AD. Recently, photo-oxygenation of Aβ has been considered as efficient way to suppress the aggregation in AD. However, currently developed photosensitizers cannot be able to achieve enhanced blood-brain barrier (BBB) permeability and selective photo-oxygenation of Aβ, leading to poor therapeutic effect, serve off targeting toxicity and substandard bioavailability. Herein, a peptide-based porphyrin supramolecular self-assembly (PKNPs) with Aβ-responsive structure transformation was designed for the selective photo-oxygenation of Aβ which has enhanced BBB penetrability and switchable photoactivity and has proven to be effective in inhibiting Aβ aggregation in living organisms.

PKNPs are formed through the self-assembly of a porphyrin derivative photosensitizer (5-(4-carboxyphenyl)-10,15,20-triphenylporphyrin, PP) and the Aβ-targeting peptide KLVFF. Porphyrin is chosen as the photosensitizer due to its exceptional optical and electronic properties, and its hydrophobic nature allows it to serve as a fundamental component in creating supramolecular nanostructures. Studies have shown that, hydrophobic interactions and π-π stacking interactions facilitate porphyrin-peptide conjugate (PP-KLVFF) self-assembly into spherical nanostructured PKNPs and inhibit their fluorescence emissions and ROS generation. Therefore, PKNPs have excellent photothermal effect under illumination, which is helpful to increase their BBB permeability. Notably, PKNPs allow disassembly upon specific interaction with Aβ which leads to smooth transformation from photothermal activity to photodynamic activity. As a result, PKNPs achieve selective photo-oxygenation of Aβ without affecting any non-specific protein such as insulin, bovine serum albumin (BSA). To the best of our knowledge, supramolecular self-assembly is a novel photosensitizer for activable PDT against Aβ.[8]



Scheme 1 Schematic illustration of the self-assembly process and Aβ-triggered disassembly process of PKNPs.

- **Characterization Techniques**

  Characterization techniques are crucial for elucidating the structural and functional attributes of supramolecular nanostructure-based drug delivery systems. These complex systems, designed to improve drug solubility, stability, and targeted delivery, require thorough analysis to understand their intricacies. The following advanced characterization methodologies are typically employed:

1. ***Nuclear Magnetic Resonance (NMR) Spectroscopy:***

   This technique provides detailed information about the molecular environment, including the chemical surroundings and electronic interactions of the nuclei. NMR can reveal how atoms are connected within the molecule, their spatial arrangement, and how they move relative to each other over time. This makes it possible to understand the three-dimensional structure of the supramolecular system, as well as the nature and strength of the interactions between its components.

   Overall, NMR offers a comprehensive view of the molecular architecture and behaviour of supramolecular compounds, making it an indispensable tool for researchers in this field.[9]

2. ***Electron Paramagnetic Resonance (EPR) Spectroscopy:***

   Electron Paramagnetic Resonance (EPR) is a powerful technique used to study systems that contain unpaired electrons, such as free radicals or transition metal complexes. By applying a magnetic field, EPR measures the energy transitions of these unpaired electrons, which provides detailed information about their electronic environment. This technique helps researchers understand the electronic structure, spatial distribution, and dynamic behaviour of the electrons within supramolecular assemblies. As a result, EPR provides crucial information about the interactions and characteristics of these intricate systems on a molecular scale.[9]

3. ***Mass spectrometry and ion mobility spectrometry***

   Mass Spectrometry (MS) serves as a vital method for analysing the molecular weight and composition of supramolecular compounds. By ionizing chemical species and measuring their mass-to-charge ratios, MS provides precise information about the molecular makeup of these compounds.

   In addition to identifying the molecular weight, MS can also reveal the stoichiometry of the supramolecular system, which refers to the ratio of different components within the assembly. This is particularly important for understanding how the individual molecules come together to form the larger supramolecular structure. Furthermore, MS can provide insights into the binding interactions within the system. By analyzing the fragmentation patterns and the presence of specific ion peaks, researchers can deduce how the molecules interact with each other, the strength of these interactions, and the overall stability of the supramolecular assembly.[9]

4. ***Ion Mobility Mass Spectrometry (IM-MS):***

IM-MS is a sophisticated analytical method that combines ion mobility separation with mass spectrometry. This integration enables a more comprehensive analysis of supramolecular complexes. In this process, ions are initially separated based on their movement through a gas while under the effect of an electric field. This separation is influenced by the shape, size, and charge of the ions, allowing researchers to distinguish between different conformations and sizes of the supramolecular complexes. After this separation, the ions are analysed by mass spectrometry, which measures their mass-to-charge ratios.

By combining these two techniques, IM-MS provides comprehensive information about the shape, size, and mass of the supramolecular complexes. This dual approach enables researchers to gain deeper insights into the structural characteristics and conformational diversity of these complex systems, which is essential for understanding their behaviour and interactions.[9]

5. ***Small-Angle Neutron Scattering (SANS) and Small-Angle X-ray Scattering (SAXS):***

These are powerful techniques used to analyse the structural properties of supramolecular assemblies in solution. These methods involve measuring the scattering of neutrons or X-rays at small angles, which provides information about the organization of materials on a nanometre to micrometre scale.[9]

6. ***Cryogenic Transmission Electron Microscopy (Cryo-TEM):***

Cryo-TEM is a powerful imaging technique that captures high-resolution images of supramolecular structures while preserving their native state. By rapidly freezing the samples, Cryo-TEM prevents the formation of ice crystals that could damage the delicate structures. This method allows researchers to visualize the morphology and arrangement of supramolecular assemblies with exceptional clarity. The images obtained from Cryo-TEM reveal detailed information about the size, shape, and organization of the components within these complex systems, providing valuable insights into their structural properties and interactions.[9]

7. ***Isothermal Titration Calorimetry (ITC):***

ITC is a intricate technique used to measure the heat changes that occur during binding interactions between molecules. By precisely monitoring these heat changes, ITC provides valuable thermodynamic data, including binding constants, enthalpy changes (ΔH), and entropy changes (ΔS).

Binding constants reflect the strength of the interaction between molecules. Enthalpy changes measure the heat absorbed or released during the binding process, reflecting the energy changes associated with the interaction. Entropy changes provide insights into the disorder or randomness introduced during the binding process.[10]

8. ***X-ray Crystallography:***

It is a technique used to determine the three-dimensional structure of crystalline supramolecular compounds. By directing X-rays at a crystal, the technique measures the diffraction patterns produced as the X-rays interact with the crystal lattice. These patterns

are then analysed to reveal detailed atomic-level information about the arrangement of atoms within the compound. This method provides precise insights into the molecular geometry, bond lengths, and angles, allowing researchers to understand the exact structure and spatial organization of the supramolecular assembly. This detailed structural information is crucial for elucidating the properties and functions of these complex systems.[9]

9. Single Molecule Spectroscopy:

This technique facilitates the examination of individual supramolecular complexes. This method yields detailed insights into their interactions and behaviour at the single-molecule level, offering a precise understanding of the dynamic processes and molecular mechanisms within these complex systems.[9]

10. Light Scattering:

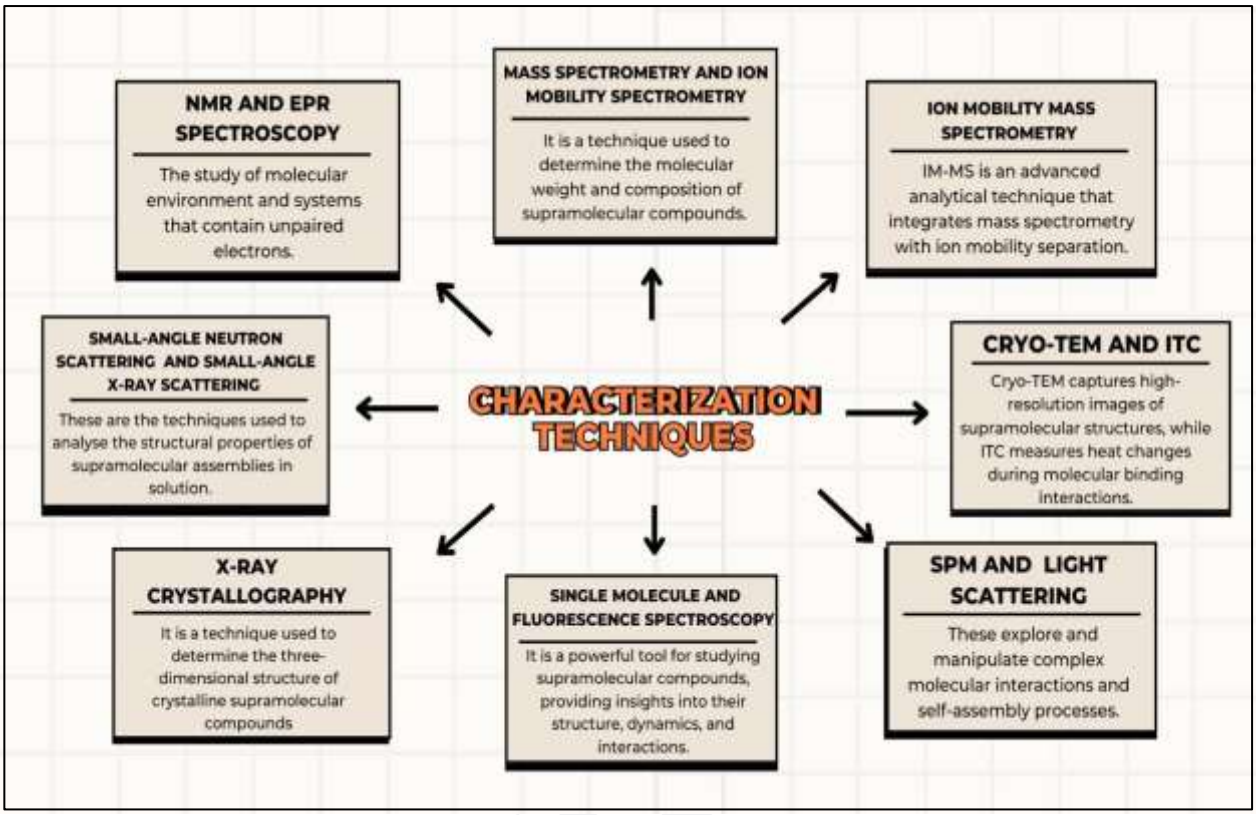
Light Scattering encompasses techniques like Dynamic Light Scattering (DLS) and Static Light Scattering (SLS), which are employed to analyse the size distribution and molecular weight of nanoparticles and supramolecular complexes. DLS measures the fluctuations in light intensity caused by the Brownian motion of particles in a solution, providing information about their hydrodynamic size and distribution. SLS, on the other hand, measures the intensity of scattered light at different angles to determine the molecular weight and overall size of the particles. Together, these techniques offer valuable insights into the physical characteristics of supramolecular assemblies.[9]

11. Scanning Probe Microscopy (SPM):

Scanning Probe Microscopy (SPM) encompasses techniques such as Atomic Force Microscopy (AFM) and Scanning Tunnelling Microscopy (STM). AFM uses a sharp tip to scan the surface of a sample, producing high-resolution images that reveal the surface topography, including height, roughness, and mechanical properties. STM, on the other hand, measures the tunnelling current between a conductive tip and the sample surface, providing detailed information about the electronic properties and atomic structure. Together, these techniques offer comprehensive insights into the physical and electronic characteristics of supramolecular structures at the nanoscale.[10]

12. Fluorescence spectroscopy

Fluorescence spectroscopy is a powerful tool for studying supramolecular compounds, providing insights into their structure, dynamics, and interactions. It offers high sensitivity and selectivity, enabling real-time monitoring and spatial resolution, and is used to study various supramolecular systems, including dendrimers, micelles, and metal-organic frameworks.[10]



The careful application of advanced characterization techniques enables researchers to gain a thorough and nuanced understanding of the physical, chemical, and biological properties of supramolecular compounds. The optimization of these compounds unlocks their potential for groundbreaking therapeutic applications.

Application of Supramolecular Innovations in Disease Treatment

Supramolecular chemistry, the science of non-covalent interactions, has revolutionized disease treatment with advanced materials and systems that exhibit unique responsiveness, biocompatibility, and modular functionality. By leveraging host-guest interactions, molecular self-assembly, and responsive polymers, supramolecular innovations offer highly promising platforms for drug delivery, cancer therapy, gene therapy, and diagnostics. The following sections outline key applications, as informed by recent literature. The field of supramolecular chemistry offers promising advancements for disease treatment through innovative materials and mechanisms. By harnessing the unique interactions between molecules, supramolecular innovations are enhancing the efficacy and specificity of therapeutic interventions.[11]

1) *Supramolecular Hydrogels in Biomedical Applications*

One significant advancement is the development of supramolecular hydrogels based on phenylalanine (Phe) dipeptides. These hydrogels demonstrate exceptional abilities to form nanofibers and construct networks that can encapsulate drugs, thereby creating effective delivery systems. Their applications span a range of biomedical areas, including wound healing, cancer therapy, and eye protection. The ability to design and control these hydrogels at the molecular level allows for tailored therapeutic solutions and improved clinical outcomes.[11]

2) ***Artificial Ion Channels and Their Biomedical Impact***

Supramolecular macrocyclic artificial ion channels (AICs) represent another innovative application. Inspired by biological ion channels, these macrocyclic structures, such as cyclodextrins and crown ethers, are designed to mimic the natural transport functions of ion channels. They offer advantages like biocompatibility and precise structural control. The potential biomedical applications of AICs include antibacterial treatments, anticancer therapies, biosensing, and managing channelopathies. This technology exemplifies how supramolecular principles can be used to address complex medical challenges.[12]

3) ***Supramolecular Interactions in Drug Delivery Systems***

The role of supramolecular interactions in drug delivery systems (DDSs) is crucial yet often underutilized. Supramolecular interactions enhance various aspects of DDS performance, including biocompatibility, drug loading capacity, stability, targeting, and controlled release. Despite the known benefits, these interactions are frequently overlooked in the design of DDSs. This discussion highlights the importance of integrating supramolecular interactions into DDS development to improve therapeutic efficacy and address clinical needs more effectively.[12]

4) Cyclodextrin-Based Supramolecular Systems for Gene Therapy

Cyclodextrin-based molecules have garnered considerable interest due to their biocompatibility, inclusion capability, and versatility in functionalization. Cyclodextrin-based supramolecular structures, such as hydrogels and nanoplatforms, have demonstrated remarkable potential in applications like gene therapy, chemotherapy, antimicrobial drug delivery, and metal extraction. The ability of these molecules to form host-guest complexes allows for precise control over drug release, enhancing the effectiveness and reducing the side effects of therapeutic agents. Notably, cyclodextrin-based sustained gene release systems have shown efficacy in extending the therapeutic duration of gene treatments, improving gene transfection efficiency, and minimizing the need for repeated administrations.[13]

5) ***Supramolecular Peptide Hydrogels for Localized Drug Delivery***

Traditional drugs often suffer from poor permeability and low solubility, limiting their therapeutic efficiency. Supramolecular chemistry has introduced macrocyclic molecules, such as crown ethers, calixarenes, and cucurbiturils, as excellent candidates for biopharmaceutical carriers. These molecules are employed to encapsulate drugs, leveraging host-guest interactions to improve bioavailability and provide reversible and adjustable drug release mechanisms. Such innovations have a profound impact on drug delivery systems, offering a more controlled release, particularly in cancer therapy and other chronic diseases.[14]

6) ***Peptide Nano-Assemblies in Cancer Diagnosis and Therapy***

Peptide-based supramolecular nano-assemblies hold significant promise in both cancer diagnosis and treatment. With their inherent biocompatibility and biodegradability, these assemblies can be tailored for specific therapeutic and diagnostic purposes. In cancer diagnosis, they are used for biosensing and optical or magnetic imaging, offering high specificity for cancer cell biomarkers. In therapy, they have been combined with other nanomaterials to enhance the efficacy of photothermal, chemo, and combined therapies. The flexibility in designing peptide structures allows for the creation of multifunctional platforms with enhanced targeting capabilities and high therapeutic potential.[15]

7) Supramolecular Biomaterials in Cancer Immunotherapy

Supramolecular biomaterials are making strides in cancer immunotherapy by modulating key interactions within the immune system. These materials act as delivery platforms for immunotherapeutic agents, enhancing antigen presentation, activating T lymphocytes, and elimination artforms, they offer a promising approach to improving the efficacy of cancer immunotherapy.[16]

8) ***Advances in Supramolecular Polymers for Drug Delivery and Tissue Engineering***

Supramolecular polymers represent an evolving area in biomedical engineering, particularly for drug delivery and tissue engineering. Their dynamic assembly properties allow them to adapt to a variety of environments, making them ideal for responsive drug delivery systems that can be fine-tuned based on external stimuli such as pH, temperature, or light. Furthermore, they serve as scaffolds for tissue regeneration, providing both structural support and controlled release of bioactive molecules. The integration of supramolecular polymers with nanotechnology further enhances their versatility and efficacy in biomedical applications.[17]

9) ***Supramolecular Peptide Hydrogels for Cancer Therapy***

Supramolecular peptide hydrogels are proving to be effective carriers for cancer drugs. Their ability to self-assemble into nanostructures enables precise delivery of anticancer agents directly to tumour sites. These hydrogels are multifunctional, providing localized therapy and inducing systemic immune responses that prevent tumour recurrence. Furthermore, their injectability and response to biological stimuli make them highly adaptable for various clinical settings, from chemotherapy to immune therapy.[18]

10) ***Supramolecular Nanotheranosticsin Cancer Treatment***

*S*upramolecular innovations are significantly advancing disease treatment by enhancing drug delivery, biomaterials, and diagnostics. Supramolecular chemistry harnesses non-covalent interactions to design sophisticated drug delivery systems, such as hydrogels and nanocarriers, that improve drug stability and targeted release. Macrocyclic compounds are utilized to create artificial ion channels, facilitating precise drug delivery and cellular uptake. Supramolecular nanotheranostics integrate diagnostic and therapeutic capabilities within nanoscale systems, allowing for precise imaging and targeted treatment. These advancements promise more effective, personalized therapies and improved patient outcomes. g tumour-associated macrophages (TAMs). The modular nature of supramolecular biomaterials allows them to be tailored for specific immune-modulating activities, which helps in overcoming the immune resistance seen in many cancers. As versatile and highly effective.[19]

11) ***Stimuli-Responsive Supramolecular Polymers in Biomedical***

Stimuli-responsive supramolecular polymers, formed through non-covalent interactions such as hydrogen bonding, metal-ligand coordination, π-stacking, and host–guest interactions, exhibit dynamic self-assembly capabilities. These polymers respond to various external stimuli (e.g., temperature, light, ultrasound, and magnetic fields) or environmental changes (e.g., pH, redox potential, enzyme activity), making them ideal for biomedical applications. Their versatility has driven the development of smart, water-soluble supramolecular assemblies that mimic natural biological systems.

The primary focus of recent research has been on the design of stimuli-responsive supramolecular systems for controlled drug delivery and diagnostics. These polymers, incorporating hydrophobic cores or macrocyclic hosts like cyclodextrins, can regulate the transport and release of therapeutic agents in response to specific triggers, ensuring precise control over drug release mechanisms. This ability to respond to environmental stimuli makes them valuable for preventing, diagnosing, and treating a range of human diseases, particularly through localized and controlled therapeutic delivery.

Supramolecular innovations have brought transformative advances in disease treatment, spanning gene therapy, cancer diagnosis, drug delivery, and immunotherapy. From cyclodextrin-based sustained release systems to peptide nano-assemblies and supramolecular biomaterials, these materials have introduced new methods to improve therapeutic efficacy, reduce side effects, and enable more targeted treatments. As research progresses, supramolecular systems are expected to play a more significant role in the treatment of various diseases, potentially leading to breakthroughs in personalized medicine, tissue engineering, and long-term disease management.

The development of supramolecular polymers, hydrogels, and nanotheranostics showcases the vast potential of supramolecular chemistry in advancing biomedical sciences. Future research will likely focus on enhancing the stability and scalability of these systems, developing stimulus-responsive systems for on-demand therapeutics, and expanding their applications beyond cancer to other chronic and genetic diseases.[20]

12) Drug Design

Drug design is among the most significant applications of supramolecular chemistry. Supramolecular chemists design and synthesize molecules that can bind to specific body targets (enzymes, receptors, or other disease related proteins) with high specificity and affinity, creating novel drugs with enhanced efficacy and fewer side effects. This approach provides unparalleled molecular precision, optimized drug incorporation, and smart delivery technologies that react to changing physiological conditions.[21]

13) Diagnostic Imaging

Supramolecular chemistry also has the potential to be applied in diagnostic imaging. Disease-related biomolecules (such as proteins and nucleic acid) can be targeted by designing supramolecular structures. Labelling these structures with imaging agents, such as fluorescent dyes or radioisotopes, enables non-invasive detection of disease markers. For instance, aptamers are short sequences of DNA or RNA that can tightly and specifically bind to particular targets. By conjugating aptamers with imaging agents, researchers can construct targeted imaging probes.[22]

14) Supramolecular devices to improve the treatment of brain diseases

Supramolecular devices are revolutionizing brain disease treatment by enhancing central nervous system (CNS) drug delivery, a major focus of pharmaceutical research hindered by the blood-brain barrier (BBB) that limits access to 98% of small-molecule drugs and nearly all high molecular weight compounds. Innovative solutions include liposomes, niosomes, cyclodextrins,

and nanogels that facilitate physiological BBB crossing, reducing systemic drug levels and side effects. Combining macromolecular and lipidic materials with native/biological molecules has advanced supramolecular devices, demonstrating encouraging results in treating brain tumors and cerebral diseases. These devices effectively cross the BBB non-invasively, enhancing biopharmaceutical parameters and enabling targeted therapeutic action through active and passive targeting strategies, which provide clinical benefits including reduced drug dosage, minimized side effects, enhanced cerebral distribution, and improved patient compliance. Furthermore, coating supramolecular carriers with PEG moieties prolongs blood circulation and promotes CNS penetration through BBB interaction, making supramolecular devices a promising tool for CNS drug delivery and improved treatment options for brain diseases.[23]

Conclusion and Future Scope

In conclusion, supramolecular innovation is poised to revolutionize disease treatment by harnessing the power of non-covalent interactions and self-assembly. By crafting precision-tailored materials and nano systems, researchers can bypass traditional therapeutic limitations, targeting diseases at the molecular level. As this field continues to evolve, the synergy of supramolecular chemistry, nanotechnology, and biomedicine will yield transformative breakthroughs, enabling personalized medicine, enhanced diagnostic accuracy, and more effective treatments. With its vast potential to reshape the disease treatment landscape, supramolecular innovation embodies a beacon of hope for improved human health and quality of life.

The future of supramolecular innovation holds immense potential for revolutionizing disease treatment, leveraging adaptive and responsive materials that adjust properties in real-time to optimize therapeutic outcomes. Advances in supramolecular chemistry may yield artificial molecular machines and nanodevices capable of targeted tasks, such as molecular transport, information processing, and mechanical work, enabling precise drug delivery and diagnostic applications. Integrating artificial intelligence and machine learning will accelerate discovery, enabling data-driven design of supramolecular systems for personalized medicine. Smart supramolecular nanocarriers will facilitate targeted imaging, responsive therapeutics, and controlled release, while sustainable, bio-based materials will reduce environmental impact. Breakthroughs in supramolecular electronics will enable advanced nanoelectronics and molecular-scale devices, transforming information processing and storage. Furthermore, supramolecular materials will contribute to sustainable energy technologies, including energy storage, conversion, and harvesting. As researchers address predictability, stability, and scalability challenges, interdisciplinary collaboration will drive supramolecular chemistry's transformative impact on complex scientific and technological problems, yielding novel materials with diverse applications in medicine, energy, and electronics, ultimately shaping a sustainable and healthier future.[24]

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