Review

Review on Smart Nanocarrier Bilayer Lipid-Coated graphene@MSN Nanocomposites

Ketan B. Patil * and Jayvadan K. Patel

Posted Date: 16 August 2023

doi: 10.20944/preprints202308.1166.v1

Keywords: Mesoporous materials; lipid bilayer; graphene oxide; graphene@MSN nanocomposites

Review

Review on Smart Nanocarrier Bilayer Lipid-Coated graphene@MSN Nanocomposites

Ketan B Patil [1,2,*] and Jayvadan K. Patel [3,4]

[1] Faculty of Pharmacy, Nootan Pharmacy College, Sankalchand Patel University, Visnagar 384315, Gujarat, India
[2] Department of Pharmaceutics, H. R. Patel Institute of Pharmaceutical Education and Research, Shirpur 425405, MH, India
[3] Formulation Scientist, Aavis Pharmaceuticals, Hoschton-30548, Georgia, United States
[4] Professor Emeritus, Sankalchand Patel University, Visnagar
* Correspondence: Ketan.90@rediffmail.com; Tel: +919923414677

Abstract: In the contemporary era, there has been a notable surge in the systematic utilization of therapeutic drugs that exhibit stimulus-responsive drug release patterns in specific target areas. However, challenges such as premature drug release and limited biocompatibility persist. To address these issues, the application of a lipid coating on mesoporous silica nanoparticles (MSNs) has emerged as a promising strategy. This lipid coating not only enhances the stability and biocompatibility of nanocarriers but also facilitates targeted drug delivery to diseased cells while minimizing drug release throughout the body. MSNs, renowned for their unique attributes including high porosity, morphology, and controllable pore size, have been widely recognized as suitable platforms for drug/gene delivery systems. Furthermore, graphene-based nanomaterials such as graphene oxide and reduced graphene oxide have garnered significant interest in the fields of biology and biomedicine. These materials possess exceptional characteristics such as a large surface area, distinct surface properties, high biocompatibility, and pH sensitivity, making them ideal candidates for incorporating drugs, genes, photosensitizers, and other cargo to design innovative drug delivery systems. This study aims to emphasize the ongoing efforts and advancements in enhancing the capacity and versatility of nanocomposites comprising graphene MSN composites for applications in drug delivery.

Keywords: mesoporous materials; lipid bilayer; graphene oxide; graphene@MSN nanocomposites

1. Introduction

Our planet is replete with a vast array of materials that serve as the bedrock of our contemporary society. Among this diverse range of materials, carbon-based substances have garnered significant prominence and assume a vital function in shaping human civilization. Presently, it would be an understatement to suggest that the absence of carbon materials renders life on Earth implausible. Since its inception in 2004, graphene has been acclaimed as an extraordinary breakthrough within the sphere of science and technology, exemplifying unparalleled excellence [1]. The first graphene was extracted from graphite using a technique called micromechanical cleavage. This methodology facilitated the convenient production of graphene crystallites of exceptional quality, subsequently catalyzing extensive experimental endeavors [2]. The hexagonal crystal structure of monolayer graphite, characterized by its simplicity and significance as a carbon-based crystalline allotrope with a C-C bond distance of 0.142 nm, has garnered considerable interest across diverse domains such as sensors, biomedicals, composite materials, and microelectronics [1] Graphene, an atomically thin two-dimensional nanomaterial comprised of carbon, has garnered significant attention and research focus within the realms of scientific investigation and technological advancement. This heightened interest stems from the extraordinary electric, mechanical, and chemical properties exhibited by graphene, setting it apart from conventional materials. The exceptional attributes of graphene have propelled it to the forefront of scientific exploration and have served as a driving force behind its integration into a wide array of technological applications [3].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 August 2023 doi:10.20944/preprints202308.1166.v1

Carbon, the sixth element in the periodic table, possesses an electronic configuration in its ground state of $1s^2 2s^2 2Px^1 2Py^1 2Pz^0$, as depicted in Figure 1b. This electronic configuration is representative of the atomic structure of a carbon atom. For ease of comprehension, Figure 1a illustrates the nucleus of a carbon atom surrounded by six electrons, with four of them occupying the valence shell. These valence electrons can undergo hybridization, resulting in the formation of three distinct types: sp, sp^2, and sp^3. The formation of sp^2 hybrids is demonstrated in Figure 1c, where carbon atoms share sp^2 electrons with their neighboring carbon atoms, leading to the creation of a planar honeycomb lattice known as monolayer graphene. The unit cell of a graphene crystal, depicted by a purple parallelogram in Figure 1d, consists of two carbon atoms, and the unit-cell vectors a_1 and a_2 possess an identical lattice constant of 2.46 Å. The remarkable stability of the planar ring structure arises from electron resonance and delocalization, contributing to its robust nature. When two adjacent carbon atoms in the graphene layer undergo sp^2 hybridization, as shown in Figure 1e, a π bond perpendicular to the planar structure is formed through the overlap of the 2pz orbitals. Simultaneously, an in-plane σ bond is established by the hybridization of the sp^2 orbitals (2s, 2px, and 2py). The resulting covalent σ bond possesses a compact interatomic distance of approximately 1.42 Å, surpassing the strength of sp^3 hybridized carbon-carbon bonds observed in diamonds. Consequently, monolayer graphene exhibits exceptional mechanical properties, including an impressive Young's modulus of 1 TPa and an intrinsic tensile strength of 130.5 GPa. In terms of its electronic structure, monolayer graphene presents a unique feature where the conduction band (band 8) and the valence band coexist without a band gap, owing to the presence of a half-filled π band that enables the mobility of free electrons. Additionally, the π bonds play a crucial role in facilitating weak van der Waals interactions between adjacent graphene layers in bilayer and multilayer graphenes. These interactions contribute to the overall stability and properties of these layered structures. The comprehensive understanding of the atomic structure, hybridization, and bonding in graphene provides valuable insights into its exceptional properties and paves the way for its diverse applications in various fields [4,5].

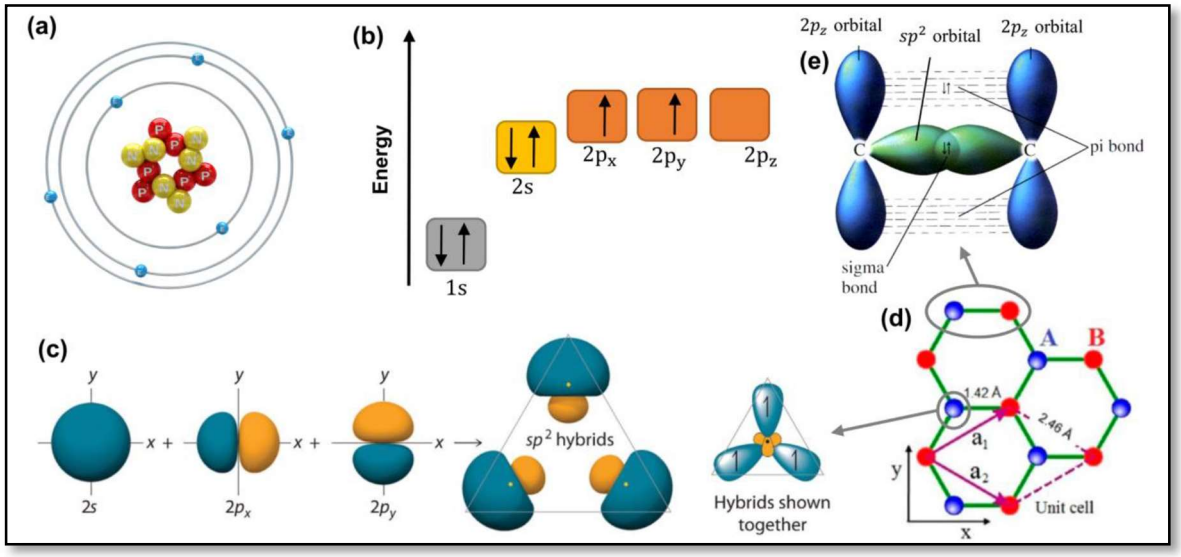

Figure 1. a) A carbon atom's atomic structure. b) levels of energy for the outer electrons of carbon atoms. c) development of sp2 hybrids. d) A and B are carbon atoms from separate sub-lattices in the graphene crystal structure, while a1 and a2 are unit-cell vectors. e) Sp2 hybridization produces the sigma and pi bonds.

2. Graphene oxide (GO)

Graphene oxide (GO) is a material derived from graphene, consisting of individual layers of graphene with oxygen-containing functional groups. It is produced through the oxidation of graphite, where strong oxidizing agents, such as potassium permanganate or sodium nitrate, are used

 doi:10.20944/preprints202308.1166.v1

along with sulfuric acid and nitric acid [6]. The oxidation process introduces defects and functional groups onto the graphene structure, making GO hydrophilic and easily dispersible in solvents such as water. GO exhibits unique properties such as high surface area, good dispersibility, and tunable chemical reactivity. These characteristics make it suitable for various applications, including energy storage, sensing, biomedical devices, and composite materials [7]. GO serves as a precursor for the synthesis of reduced graphene oxide (rGO) through the removal of oxygen-containing groups, allowing the restoration of the sp2 carbon network. With its exceptional properties and versatile nature, GO holds significant potential for advancements in a wide range of technological fields [8].

2.1. Synthesis of graphene oxide (GO)

The synthesis of graphene oxide (GO) commonly involves the oxidation of graphite, followed by exfoliation to obtain individual layers of graphene oxide. The same methods were employed in this study for the synthesis process such as Hummers' method (With Modification) [9], Brodie method , Staudenmaier method [10].

2.2. Unique properties of graphene

Graphene exhibits a range of unique properties that set it apart from other materials. Such as graphene is a single layer of carbon atoms arranged in a hexagonal lattice, resulting in a two-dimensional structure. This ultrathin nature grants it remarkable properties and opens up new avenues for research and applications [11]. Despite its atomic thinness, graphene exhibits exceptional mechanical strength. It has a reported tensile strength of approximately 130 GPa, making it one of the strongest materials known [5,12]. Similarly, graphene possesses excellent electrical conductivity due to its unique band structure. Its delocalized π electrons allow for the efficient transport of charge carriers, making it an ideal material for electronic and optoelectronic devices [12–15]. In addition, graphene demonstrates exceptional thermal conductivity, surpassing most other materials. Its ability to efficiently conduct heat makes it promising for thermal management applications [14,15]. In addition to that, its exceptional electrical and thermal conductivity, graphene is optically transparent. It absorbs only a small fraction of light across a wide range of wavelengths, making it suitable for transparent electrode applications in displays, solar cells, and other optoelectronic devices [16]. In oder to graphene is highly flexible and can be bent or stretched without losing its electronic properties. This flexibility allows for the integration of graphene into various flexible and wearable electronics [17–19]. Further more graphene exhibits excellent chemical stability, enabling its use in diverse environments and making it resistant to degradation under harsh conditions [20]. Moreover, graphene exhibits the quantum Hall effect, which is a phenomenon observed at low temperatures and high magnetic fields. This effect demonstrates the unique behavior of electrons in graphene and has potential applications in quantum computing and metrology [21]. Additionally, graphene has an enormous surface area per unit mass due to its two-dimensional structure. This property makes it useful for applications such as energy storage, catalysis, and gas sensing [22].

2.3. Applications of graphene in various fields

Graphene's high electrical conductivity and transparency make it suitable for developing faster and more efficient electronic devices. It can be used in flexible displays, touchscreens, transistors, and integrated circuits. Graphene-based optoelectronic devices, such as photodetectors and light-emitting diodes (LEDs), are also being explored [23]. Furthermore, graphene has shown promise in energy storage applications. It can be used to enhance the performance of batteries, supercapacitors, and fuel cells. Graphene-based materials enable faster charging, higher capacity, and longer-lasting energy storage devices [24,25]. Likewise, graphene can reinforce and enhance the properties of various materials, making them stronger, lighter, and more durable. Graphene composites find applications in the aerospace, automotive, construction, and sports equipment industries, among others [26]. In addition, graphene's high sensitivity and large surface area make it an excellent material for sensors. It can be used to develop highly sensitive gas sensors, biosensors for detecting

 doi:10.20944/preprints202308.1166.v1

diseases, and environmental sensors for monitoring pollutants [27–29]. Similarly, graphene's unique properties enable efficient water filtration. Graphene membranes can selectively allow water molecules to pass through while blocking other contaminants, leading to improved water purification techniques [30–32]. Then, graphene-based materials have potential applications in biomedical fields, including drug delivery systems, tissue engineering, and bioimaging. Graphene's biocompatibility and ability to interact with cells make it valuable for developing advanced biomedical devices and therapies [33–35]. After that graphene's excellent thermal conductivity makes it useful for thermal management applications. It can be integrated into electronic devices to dissipate heat efficiently and prevent overheating [36–38]. In addition, graphene-based materials are being explored for environmental remediation applications. They can be used for pollutant removal, water purification, and air filtration, contributing to a cleaner and more sustainable environment [39,40]. As well graphene coatings protect against corrosion, wear, and chemical reactions. Graphene-based barrier films offer impermeability to gases and moisture, making them valuable for packaging and preserving sensitive materials [41].

3. Mesoporous silica nanoparticles (MSN)

Porous silicas are highly significant materials due to their extensive applications in catalysis and partition processes. Zeolites, a diverse group of crystalline aluminosilicates, form a substantial family within this category. Upon subjecting an unidentified silicate mineral to heat, peculiar crystals were observed to undergo foaming and bubbling, accompanied by the release of vapor bursts. The renowned Swedish scientist Cronstedt made his discovery in 1756. Despite initially receiving limited attention from the scientific community, zeolite minerals began to garner comprehensive documentation during the mid-19th century. Notably, McBain's investigation of the mineral chabazite revealed its ability to selectively adsorb molecules smaller than 5 Å in diameter, leading him to introduce the term "molecular sieve" [42]. In the 1990s, novel mesoporous materials emerged, sharing similarities with the distinctive properties of MCM-41. The synthesis of these mesoporous materials involved the incorporation of long-chain (C-16) alkyl trimethylammonium cations into the layered silicate kanemite, followed by calcination to eliminate organic species derived from the surfactant. The condensation of the silicate layers resulted in the formation of a three-dimensional structure with microscopic pores. Solid-state spectroscopic analysis of the silicon (Si) content indicated that a significant fraction of the partially condensed silica species $Si(OSi)_3(OH)$ had been transformed into completely condensed silica species $Si(OSi)_4$ during the intercalation and calcination processes, effectively removing the organic components from the sample. The X-ray powder diffraction analysis only displayed a negligible peak at extremely low angles, lacking any meaningful information [43]. The discovery of the M41S family of silicate or aluminosilicate mesoporous molecular sieves can be attributed to the research efforts of Mobil Corporation scientists in 1992. Subsequently, the development and refinement of these molecular sieves were carried out at Mobil Corporation Laboratories. One notable characteristic of the M41S family is their exceptional pore structures, characterized by wide and uniform pore sizes. In this family, three distinct mesophases have been identified including lamellar (MCM-50-Mobil Crystalline Materials), hexagonal (MCM-41), and cubic (MCM-48). The hexagonal mesophase has known as MCM-41 exhibits uniform-sized channels with widths ranging from 15 to 100, depending on the employed templates, auxiliary organic compounds, and the specific reaction applications [44]. Mesoporous materials are characterized by the presence of pores with diameters ranging from 2 to 50 nm. The International Union of Pure and Applied Chemistry (IUPAC) has established a classification system for porous solid materials, categorizing them based on their principal pore diameters [45] such as Microporous (less than 2 nm), Mesoporous (diameter: 2–50 nm), Macroporous (more than 50 nanometers)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 August 2023 doi:10.20944/preprints202308.1166.v1

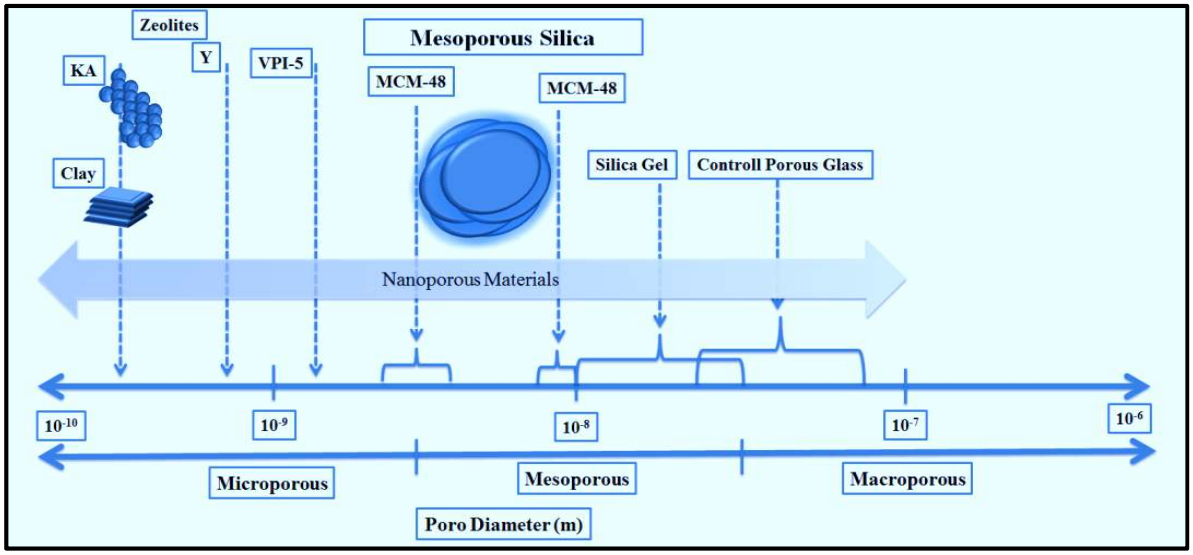

Figure 2. a) Classification of porous materials.

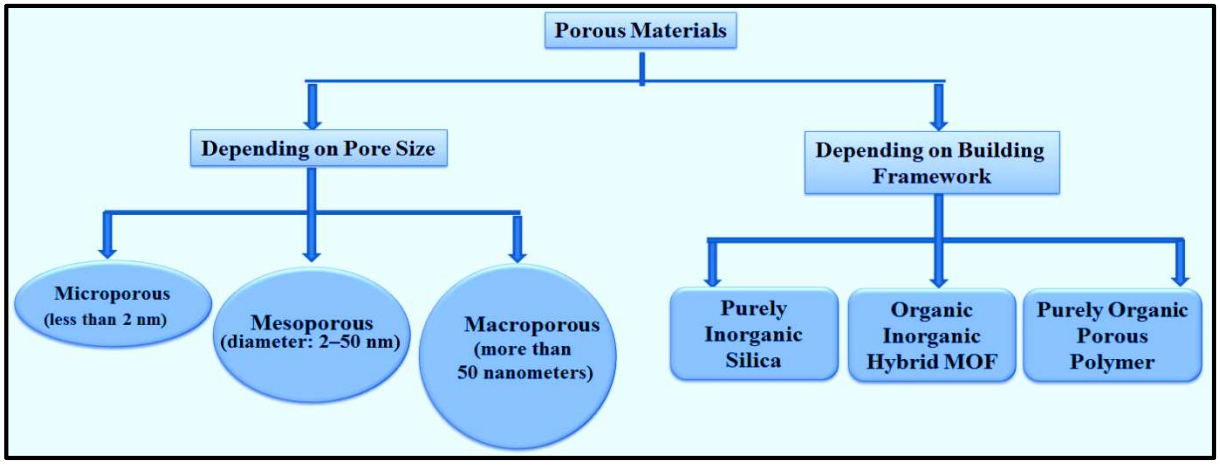

Figure 2. b) Schematic diagram of the nanoscale distribution of some porous materials.

3.1. Synthesis methods of MSN

Mesoporous silica nanoparticles (MSN) can be synthesized using various methods, including template-assisted synthesis [46], sol-gel methods, and hard template methods [47].

3.2. Properties of MSN

MSN exhibits a high surface area due to its mesoporous structure, which provides a large number of accessible surface sites for interactions with other substances. This property is beneficial for various applications such as adsorption, catalysis, and drug delivery [48]. Furthermore, MSN offers the advantage of controllable pore sizes ranging from a few to several tens of nanometers. The uniform pore size distribution allows for precise control over the size exclusion of molecules, making them ideal for molecular sieving and size-selective adsorption [49]. Likewise, MSN has a significant pore volume that allows for the loading and release of various substances, such as drugs or catalysts. The large pore volume also contributes to their high adsorption capacity [50]. Moreover, the surface of MSN can be modified or functionalized with various functional groups, such as amino, carboxyl, or hydroxyl groups. This tunability of surface chemistry enables the attachment of specific molecules, biomolecules, or targeting ligands, making MSN suitable for targeted drug delivery and controlled release [51]. Then, silica, the main constituent of MSN, is generally considered biocompatible and nontoxic. This property makes MSN attractive for biomedical applications, including drug delivery,

 doi:10.20944/preprints202308.1166.v1

imaging, and tissue engineering [52]. In addition, MSN exhibits excellent thermal and chemical stability, allowing them to withstand harsh reaction conditions and maintain their structural integrity. This stability is crucial for applications in catalysis and high-temperature processes [53]. Besides, MSN can be synthesized with different shapes, including spheres, rods, and fibers, providing versatility in their applications. Additionally, the presence of a mesoporous structure allows for the incorporation of various functional materials, such as metals, polymers, or nanoparticles, further expanding their potential applications [54].

3.4. Applications of MSN

MSN has been extensively studied as drug delivery carriers due to their large surface area and tunable pore size. They can efficiently encapsulate and protect drugs, enabling controlled release and targeted delivery to specific cells or tissues. MSN can enhance drug stability, improve therapeutic efficacy, and minimize side effects [55]. Similarly, MSN can be functionalized with imaging agents, such as fluorescent dyes, quantum dots, or magnetic nanoparticles, to enable enhanced imaging capabilities. The high surface area of MSN allows for the loading of imaging probes, enabling precise visualization of tissues, cells, or biomarkers for diagnostic purposes [56]. Furthermore, MSN can be engineered to have combined diagnostic and therapeutic functions, enabling theranostic applications. By integrating imaging agents and therapeutic molecules within MSN, simultaneous diagnosis and treatment can be achieved, leading to personalized medicine approaches [57]. As well MSN-based biosensors have been developed for the detection of various analytes, including biomarkers, proteins, nucleic acids, and pathogens. The mesoporous structure of MSN provides a suitable environment for biomolecular interactions, leading to sensitive and selective detection with potential applications in disease diagnosis and monitoring [56]. Additionally, MSN can serve as efficient carriers for nucleic acid delivery, including plasmid DNA, siRNA, and miRNA. The large surface area and pore volume of MSN allow for high loading capacity and protection of nucleic acids. MSN can protect the payload from degradation and facilitate controlled release, enabling effective gene therapy [58]. Then, MSN has been explored for tissue engineering applications, acting as scaffolds for cell growth and tissue regeneration. The porous structure of MSN provides a favorable environment for cell adhesion, proliferation, and differentiation. MSN can be functionalized with bioactive molecules to enhance cellular interactions and promote tissue regeneration [59,60]. Moreover, MSN can be utilized for antimicrobial purposes by loading antibacterial agents or releasing antimicrobial compounds. The large surface area of MSN allows for high drug loading, providing sustained release of antimicrobial agents to combat bacterial infections and prevent biofilm formation [61]. In the same vein, MSN can be employed as a carrier for vaccine delivery, enabling controlled release and targeted immune response. MSN can encapsulate vaccine antigens, protect them from degradation, and enhance their presentation to immune cells, leading to improved vaccine efficacy [62].

4. Bilayer Lipid Coated graphene@MSN nanocomposites

Bilayer lipid-coated graphene MSN composite structures possess unique properties that make them attractive for various applications in biomedicine. Here are some key properties of bilayer lipid-coated graphene MSN composite: high surface area, biocompatibility [30], controlled release [63], stability and protection, targeted delivery [63], versatility, and multimodal imaging [64]. In 2022 Deshmukh *et al.* investigated a hybrid multifunctional lipid-coated graphene oxide mesoporous silica nanocomposite (GO-MSN) that has been developed for the controlled delivery of rizatriptan benzoate (RiB). By incorporating a lipid coating, the fabricated carrier achieves an extended circulation time, enhancing the targeted delivery of RiB. The fabrication process involved a modified Hummers method to obtain a uniform sheet of GO, followed by a sol-gel approach to synthesize mesoporous silica, forming the nanocomposite. In vitro, release studies demonstrated that RiB release from RiB-GO-MSN and lipid-decorated GO-MSN was 70.74% and 63.45%, respectively. The lipid coating effectively delayed the release of RiB by approximately 8 hours. The entrapment efficiency of RiB-MSN and GO-MSN was measured at 48.17% and 62.29%, respectively. The presence of GO

 doi:10.20944/preprints202308.1166.v1

facilitated an increased entrapment of RiB, as RiB molecules could be trapped within the inter and intra spacing of GO. This study highlights the effectiveness of the simple methodology employed in the synthesis of GO-MSN, enabling efficient delivery of RiB to the brain for the management of migraine [63]. Likewise, Wei *et al*., and his colleagues have prepared a sandwich-like structure of mesoporous silica/graphene nanocomposites (MSGs), where mesoporous silica is assembled within the interlayer space of graphite oxide (GO) using intercalated surfactants as a template. This templated synthesis method involves the utilization of intercalated ammonium cation surfactants and neutral amines as co-surfactants to guide the hydrolysis and condensation of inorganic precursors (such as tetraethoxysilane, TEOS) within the GO galleries. The confinement effects provided by the GO galleries result in a compact arrangement of the mesoporous silica framework, sandwiched between the adjacent graphene sheets. A single line of aligned mesopores parallel to the GO galleries is observed. The pore sizes of the MSGs vary from 1.2 to 2.1 nm, depending on the chain length of the intercalated surfactants. Our templated method for synthesizing graphene-based nanocomposites offers the potential for a wide range of porous graphene-based nanocomposites with distinct morphologies and properties [65]. Furthermore, in Fonseca *et al*., 2018 a pioneering nanocomposite based on graphene oxide (GO) and mesoporous amino silica nanoparticles (H2N-MSNs) has been developed, aiming to investigate its biological interaction with red blood cells (RBCs) and human blood plasma, thereby exploring nano-bio interactions. Both silica nanoparticles and various graphene oxide-based materials have been individually recognized for their propensity for hemolysis and strong interaction with human plasma proteins. In this study, the GO-MSN interaction was thoroughly examined to understand its potential in mitigating the reported effects. The synthesis involved covalently attaching H2N-MSNs onto the GO surface through an amidation reaction. GO-MSN nanocomposites were obtained by varying the mass of H2N-MSNs, and their comprehensive characterization was carried out using FTIR, NMR, XRD, TGA, zeta potential, and TEM techniques. The characterization results not only confirmed the successful formation of nanocomposites but also indicated predominantly covalent bond attachment through amine-epoxy reactions. Additionally, an unexpected reduction reaction of GO by H2N-MSNs was observed, for which a proposed mechanism was put forward. Furthermore, biological assays demonstrated a significant decrease in hemolysis (RBC lysis) and a notable reduction in the interaction with human plasma proteins (protein corona formation). These significant findings contribute towards achieving in vivo biocompatibility and enhancing our understanding of nanobiointeractions. Ultimately, this research paves the way for potential applications of GO-MSN nanocomposites in nanomedicine, particularly as a drug delivery system [64]. Besides Liu *et al.,* In this investigation successfully synthesized a multifunctional drug carrier, namely polydopamine doped mesoporous silica-coated reduced graphene oxide (rGO/MSN/PDA), by introducing dopamine hydrochloride into the oil-water biphasic reaction system. This nanocarrier exhibits a synergistic effect by combining chemotherapy and photothermal therapy for effective anticancer treatment. Compared to mesoporous silica-coated graphene oxide (GO/MSN), rGO/MSN/PDA demonstrates nearly twice the photothermal conversion efficiency, owing to the reduction of GO and the incorporation of PDA. Additionally, rGO/MSN/PDA exhibits a pH-responsive release profile for the anticancer drug DOX, indicating a higher release in tumor cells. In vitro cell experiments further confirm the improved biocompatibility of rGO/MSN/PDA compared to GO/MSN, highlighting its potential as a promising tool for enhancing the therapeutic efficacy against hepatocellular carcinoma cells through synergistic chemo-photothermal therapy. Since devised nanocomposites open a new path for cancer management [66]. Moreover, Dalagan and Enriquez, 2014 investigation shows that a hydrothermal method was employed to synthesize silica-graphene oxide composites, enabling simultaneous functionalization and reduction of graphene oxide (GO) in the presence of mesoporous silica. Two types of silica, mesoporous synthetic silica (MSU-F) synthesized via the sol-gel method, and mesoporous mineral silica (meso-celite) obtained from pseudomorphic synthesis, were utilized in this study. Analysis of the infrared spectra of the composites revealed the disappearance of the carboxyl peak at 1735 cm-1, indicating the reduction of the -COOH group. Furthermore, an increase in the intensity of the band at 1385 cm–1 was observed, which can be attributed to the vibration of the Si-O-C=O moiety formed through the reaction between

the -COOH group of GO and the silanol (Si-OH) of silica. Raman spectral analysis indicated a reduction in the intensity ratio of the D to G bands, suggesting the successful reduction of GO into graphene sheets. TEM images showcased the coupling of silica onto the GO surface, demonstrating a dense loading of silica on the planar structure of GO [67]. Later, in 2018, Liu *et al*., Investigated a novel antibacterial material, namely silver-decorated sandwich-like mesoporous silica/reduced graphene oxide nanosheets (rGO/MSN/Ag), that was successfully synthesized using a simple method. The reduction of rGO and Ag nanoparticles occurred within the reaction system without the need for additional reductants. The modified silver nanoparticles in the rGO/MSN/Ag composite contributed to its enhanced photothermal conversion capacity. Remarkably, the nanosheets exhibited excellent antibacterial activities against P.putida, E.coli, and Rhodococcus, even at relatively low dosages, as confirmed by the minimum inhibitory concentration (MIC) test. Furthermore, when exposed to 808 nm laser irradiation, the antibacterial effect of the nanosheets on E.coli at high concentrations was significantly enhanced due to the induced photothermal effect of near-infrared light. Cytotoxicity evaluation using hepatocyte LO2 cells demonstrated that the rGO/MSN/Ag nanosheets exhibited low toxicity and no detectable cytotoxicity at the antimicrobial dose. Considering their cost-effectiveness and potent antibacterial activity, the prepared rGO/MSN/Ag nanosheets hold great promise as valuable antibacterial agents for various applications [68].

4.1. Fabrication of GO@MSN nanocomposites

It involves the integration of graphene oxide (GO) with mesoporous silica nanoparticles (MSN). Step-I -Synthesis of Graphene Oxide (GO): Graphene oxide can be synthesized from graphite using the modified Hummers' method or the modified Brodie's method. In the modified Hummers' method, graphite is oxidized using a mixture of concentrated sulfuric acid, potassium permanganate, and sodium nitrate. The resulting graphite oxide is then exfoliated to obtain graphene oxide sheets with oxygen-containing functional groups [64]. Step-II -Synthesis of Mesoporous Silica Nanoparticles (MSN): Mesoporous silica nanoparticles can be synthesized using a sol-gel method. Typically, a silica precursor such as tetraethyl orthosilicate (TEOS) is mixed with a structure-directing agent (surfactant) and a catalyst. The mixture is then hydrolyzed and condensed to form silica nanoparticles with well-defined mesoporous structures [69]. Step-III Preparation GO@MSN nanocomposites: To prepare the GO@MSN nanocomposites, different ratios of GO and silica are being reacted. The process involves adding one mL of concentrated H2SO4 to the mixture of GO and silica. Then reflux the solution at 100 °C for 24 hours Filter the GO-silica mixture. Later wash the filtered GO-silica with distilled water. Furthermore, dry the GO-silica at room temperature [67].

4.2. Characterization of GO@MSN nanocomposites

The characterization of GO@MSN nanocomposites involves analyzing various properties and parameters to understand their structure, morphology, and behavior. Some common characterization techniques used for GO@MSN nanocomposites such as SEM are used to observe the surface morphology and structure of the nanocomposites. It provides high-resolution images that help assess the distribution of GO within the MSN matrix and examine the overall composite morphology [63]. Similarly, TEM is employed to study the internal structure and arrangement of GO and MSN in nanocomposites. It provides detailed information about the size, shape, and distribution of nanoparticles and the interaction between GO and MSN at the nanoscale [64]. Likewise, XRD is utilized to determine the crystalline structure of the nanocomposites. It helps identify the presence of GO and MSN, evaluate their degree of crystallinity, and assess potential changes in the crystalline structures due to the incorporation of GO [64,67]. Later, FTIR analysis is used to identify the functional groups present in the nanocomposites. It helps confirm the successful integration of GO and MSN by detecting characteristic absorption peaks corresponding to oxygen-containing groups on GO and silica groups on MSN [67]. Furthermore, In Fonseca TGA is employed to analyze the thermal stability and weight loss behavior of the nanocomposites [70]. It helps determine the content of GO and MSN, assess their thermal properties, and evaluate the effectiveness of the integration process. Additionally, Brunauer-Emmett-Teller (BET) analysis is used to measure the specific surface

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 August 2023 doi:10.20944/preprints202308.1166.v1

area and porosity of the nanocomposites [71]. It helps assess the impact of GO integration on the surface properties and porosity of MSN. In addition, DLS is utilized to determine the particle size distribution and stability of the nanocomposites in a liquid suspension [72]. It provides information about the hydrodynamic size and polydispersity of the nanoparticles, indicating their stability and potential aggregation behavior. In addition, zeta potential measurement is performed to evaluate the surface charge and stability of the nanocomposites. It helps assess the electrostatic interactions between GO and MSN and provides insights into their colloidal stability [64].

Table 1. Synthesis of GO@MSN nanocomposites.

GO Synthesis Method	MSN Synthesis Method	GO@MSN nanocomposites Method	Drug Delivery	Drugs/Cargo	Outcome	Ref
Modified Hummers method	Sol-gel approach	-	Controlled Drug Delivery	Rizatriptan Benzoate	To effectively treat migraines, GO-MSN can transfer Rizatriptan Benzoate to the brain.	[63]
Modified Hummers method	Sol-gel method & Kim and Pinnavaia	Hydrothermal method	-	-	The supercapacitor, sensor, or a catalyst support	[67]
Modified Hummers method	Modified Stober method	-	-	Red blood cells and Human plasma proteins	Decreased hemolysis, Significantly reduced human blood plasma protein interaction with nanocomposites	[64]
Modified Hummers method	Sol-gel method	Gallery templated method	-	-	A broad range of porous graphene-based nanocomposites	[65]
Modified Hummers method	-	Oil-water biphase stratification approach	-	Silver nitrate	Excellent antibacterial effect against *Rhodococuss*, *E.coli*, and *P.putida* with low cytotoxicity	[68]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 August 2023 doi:10.20944/preprints202308.1166.v1

Modified Hummers method	-	Oil-water biphase stratification approach	-	Polydopamine & doxorubicin hydrochloride	To enhance the anticancer impact, use chemo-photothermal treatment.	[66]

4.3. Miscellaneous application of GO@MSN nanocomposites

GO@MSN nanocomposites have shown great potential for various applications due to the unique combination of graphene oxide (GO) and mesoporous silica nanoparticles (MSN). Here are some notable applications of GO@MSN nanocomposites such as the high surface area and porosity of MSN allow for efficient loading and controlled release of therapeutic agents. The incorporation of GO further enhances drug loading capacity and provides additional functionalities such as pH-responsive drug release and targeted delivery [63,64]. Furthermore, the optical properties of GO enable it to act as a contrast agent in imaging techniques such as fluorescence imaging and photoacoustic imaging. The integration of MSN with GO allows for improved stability, biocompatibility, and enhanced imaging performance for diagnostic applications and the unique structure and chemical properties of GO@MSN nanocomposites make them excellent catalysts for various chemical reactions. The large surface area of MSN supports high catalytic activity, while the presence of GO enhances the stability and selectivity of the catalysts [67]. Likewise, GO@MSN nanocomposites have been utilized in the development of sensors for detecting various analytes. The high surface area and surface functionalization of GO@MSN enables sensitive and selective detection of target molecules, making them suitable for applications in environmental monitoring, food safety, and biomedical diagnostics [65]. Moreover, GO@MSN nanocomposites have been explored for energy-related applications such as supercapacitors and lithium-ion batteries. The high conductivity of GO facilitates efficient charge transport, while the mesoporous structure of MSN provides a high surface area for enhanced energy storage and conversion performance [73].

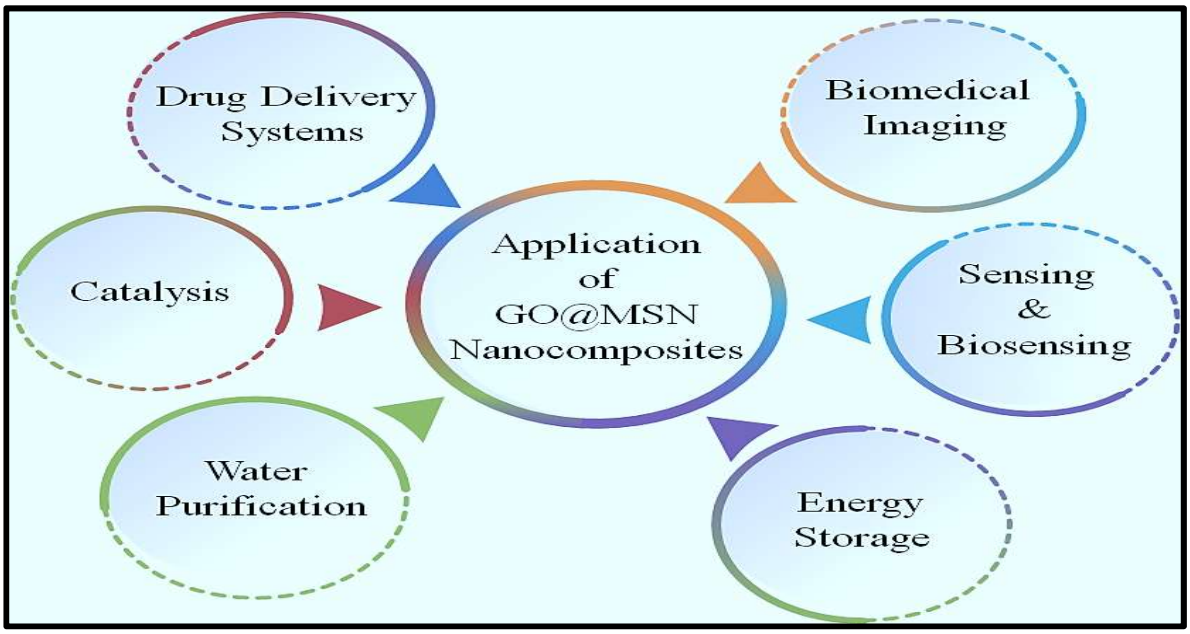

Figure 3. Application of GO@MSN nanocomposites.

 doi:10.20944/preprints202308.1166.v1

5. Challenges and limitations

Bilayer lipid-coated graphene@MSN nanocomposites possess numerous advantages for biomedical applications, but they also face certain challenges and limitations that need to be addressed. Both the bilayer lipid coating and the mesoporous silica nanoparticles can be susceptible to degradation over time. Ensuring the stability of the coating and preventing the degradation of the nanoparticles is crucial for maintaining the desired properties and functionalities of the material [74,75]. In addition, achieving a uniform and complete coating of bilayer lipids on the graphene surface and achieving high loading efficiency of therapeutic agents within mesoporous silica nanoparticles can be challenging [76]. In addition, uniformity in coating and optimal loading efficiency is important to ensure consistent performance and controlled release of therapeutic agents [77]. Thus, the biocompatibility and potential toxicity of bilayer lipid-coated graphene@MSN nanocomposites require thorough investigation. It is essential to assess their interactions with biological systems, including potential inflammatory responses, cytotoxicity, and long-term biocompatibility to ensure their safe use in biomedical applications [55,78]. Achieving precise control over the release kinetics of encapsulated drugs from mesoporous silica nanoparticles can be challenging. Fine-tuning the release profile, such as sustained or triggered release, requires careful optimization of factors such as pore size, surface modifications, and drug properties [79]. Similarly, understanding the clearance pathways and biodistribution of bilayer lipid-coated graphene@MSN nanocomposites is crucial for their safe application. Studying their fate in vivo, including their potential accumulation in organs or tissues, is important to assess their biocompatibility and minimize potential adverse effects [80,81]. Scaling up the production of bilayer lipid-coated grapheme [82] and MSN while maintaining consistent quality and performance can be challenging. The synthesis methods and coating techniques may require optimization to enable large-scale manufacturing, which can add complexity and increase costs [83]. Moreover, the regulatory approval process for novel biomedical materials can be rigorous and time-consuming. Bilayer lipid-coated grapheme [84] and MSN need to undergo comprehensive testing and evaluation to meet regulatory standards for safety, efficacy, and quality before their clinical translation [56]. The production and functionalization processes of bilayer lipid-coated grapheme [33] and MSN can be complex and costly. Developing cost-effective synthesis methods and optimizing manufacturing processes are important for their wider accessibility and commercial viability [85].

7. Current research

Current research on bilayer lipid-coated graphene@MSN nanocomposites is focused on expanding their applications in various biomedical fields and addressing the existing challenges. Such as researchers are exploring the potential of bilayer lipid-coated graphene@MSN nanocomposites for targeted drug delivery [86]. Efforts are being made to improve the targeting efficiency by incorporating ligands or antibodies on the surface of the nanoparticles, enabling specific recognition and uptake by target cells or tissues [87]. In the same manner, the use of bilayer lipid-coated graphene@MSN nanocomposites for combination therapies is being investigated. By encapsulating multiple therapeutic agents within the mesoporous silica nanoparticles, it is possible to deliver synergistic drug combinations or co-deliver drugs and nucleic acids for enhanced therapeutic efficacy [63]. Furthermore, bilayer lipid-coated graphene@MSN nanocomposites offer unique properties for imaging and diagnosis. Ongoing research aims to enhance their imaging capabilities by incorporating contrast agents or imaging probes within the nanoparticles. Additionally, efforts are being made to develop multifunctional systems that can simultaneously deliver therapeutics and provide imaging capabilities [33]. Later, Researchers are exploring the potential of bilayer lipid-coated graphene@MSN nanocomposites in regenerative medicine applications. These nanoparticles can be utilized for controlled release of growth factors, stem cell encapsulation, or as scaffolds for tissue engineering, promoting tissue regeneration and wound healing [88,89]. Moreover, The development of bilayer lipid-coated graphene@MSN nanocomposites for bioimaging and biosensing applications is an active area of research. Their unique optical and electrical properties enable sensitive detection of biomarkers, leading to advancements in early

 doi:10.20944/preprints202308.1166.v1

disease diagnosis and monitoring of treatment responses [55]. Then, integrating therapeutic and diagnostic capabilities into a single system, known as nano theranostics, is a promising research direction. Bilayer lipid-coated graphene@MSN nanocomposites can be engineered to combine imaging, therapeutic delivery, and monitoring functionalities, enabling personalized medicine approaches and real-time treatment evaluation [90,91]. Further investigations are being conducted to evaluate the long-term biocompatibility and safety profiles of bilayer lipid-coated graphene and MSN. This includes in-depth studies on their interactions with biological systems, potential toxicity, immunological responses, and clearance pathways to ensure their safe use in clinical settings [55].

8. Future perspectives

The future perspectives for bilayer lipid-coated graphene@MSN nanocomposites are highly promising and hold great potential for advancements in various fields. The combination of graphene@MSN nanocomposites with a bilayer lipid coating opens up exciting opportunities for innovative biomedical applications. Moving forward, several areas of focus can be identified. First, further research is needed to optimize and tailor the properties of these nanomaterials to meet specific application requirements. This includes fine-tuning the composition, size, and surface characteristics to enhance their stability, biocompatibility and targeted delivery capabilities. Additionally, exploring novel synthesis methods and functionalization techniques can offer new avenues for improved performance and versatility. Second, the development of multifunctional systems that integrate Bilayer Lipid Coated graphene@MSN nanocomposites with other functional components, such as targeting ligands, imaging agents, or therapeutic payloads, is a promising direction. These advanced nanoplatforms can enable synergistic effects and enhanced therapeutic outcomes, as well as provide real-time monitoring and imaging capabilities for diagnostics and therapeutics. Furthermore, the translation of bilayer lipid-coated graphene@MSN nanocomposites into clinical applications requires a comprehensive evaluation of their safety, biocompatibility, and long-term effects. Continued research efforts should focus on rigorous toxicity studies, in vivo assessments, and long-term monitoring to ensure their reliability and minimize potential risks. In terms of manufacturing and scalability, future perspectives lie in developing scalable and cost-effective production methods that maintain the desired properties and functionalities of these nanomaterials. This will be crucial for their practical implementation in clinical settings and widespread adoption. Collaboration among researchers, clinicians, industry partners, and regulatory bodies is essential to accelerate the translation of bilayer lipid-coated graphene@MSN nanocomposites from the laboratory to real-world applications. Establishing standardized protocols, guidelines, and regulations will ensure the safe and ethical use of these nanomaterials while promoting their rapid integration into healthcare practices.

9. Conclusion

The review on bilayer lipid-coated graphene@MSN nanocomposites underscores the significant potential of these nanomaterials in various biomedical applications. The combination of graphene@MSN nanocomposites with a bilayer lipid coating offers unique properties and advantages for drug delivery, imaging, tissue engineering, and regenerative medicine. The synthesis methods discussed, including template-assisted synthesis, sol-gel methods, hard template methods, and electrostatic adsorption, provide versatile approaches to fabricating these nanomaterials with precise control over their structure and properties. This enables tailored designs for specific biomedical applications, allowing for enhanced therapeutic efficacy, targeted delivery, and imaging capabilities. The properties of bilayer lipid-coated graphene and MSN, such as high surface area, tunable pore sizes, biocompatibility, and controlled release, make them attractive for various biomedical applications. Their ability to encapsulate and deliver therapeutic agents, provide sustained release, and interact with biological systems holds great promise for improving healthcare outcomes. While these nanomaterials exhibit significant advantages, some challenges and limitations need to be addressed. Stability, scalability, biocompatibility, and long-term safety considerations are areas that require further research and development efforts. Rigorous evaluation of their toxicity

profiles, in vivo behavior, and long-term effects are crucial for their successful translation into clinical applications. Future research directions and perspectives for bilayer lipid-coated graphene@MSN nanocomposites encompass advanced drug delivery systems, theranostic applications, tissue engineering, regenerative medicine, biocompatibility evaluation, scale-up manufacturing, and clinical translation. Continued collaborations between researchers, clinicians, and regulatory bodies are necessary to drive innovation, ensure safety, and facilitate the practical implementation of these nanomaterials in healthcare settings. In summary, bilayer lipid-coated graphene@MSN nanocomposites represent promising nanomaterial platforms with the potential to revolutionize biomedical applications. In this line, the proposed review article of an open new avenue for technological advancements, and graphene-based mesoporous drug delivery field of biomedical sciences.

Acknowledgments: The author expresses gratitude to the HRPIPER, Shirpur for the provision of essential infrastructure and resources.

References

1. Tiwari, S.K., et al., *Graphene research and their outputs: Status and prospect.* 2020. **5**(1): p. 10-29.
2. Choi, W., et al., *Synthesis of graphene and its applications: a review.* 2010. **35**(1): p. 52-71.
3. Zobir, S.A.M., S.A. Rashid, and T. Tan, *Recent development on the synthesis techniques and properties of graphene derivatives*, in *Synthesis, Technology and Applications of Carbon Nanomaterials*. 2019, Elsevier. p. 77-107.
4. Yang, G., et al., *Structure of graphene and its disorders: a review.* 2018. **19**(1): p. 613-648.
5. Lee, C., et al., *Measurement of the elastic properties and intrinsic strength of monolayer graphene.* 2008. **321**(5887): p. 385-388.
6. Razaq, A., et al., *Review on graphene-, graphene oxide-, reduced graphene oxide-based flexible composites: From fabrication to applications.* 2022. **15**(3): p. 1012.
7. Brisebois, P. and M.J.J.o.M.C.C. Siaj, *Harvesting graphene oxide–years 1859 to 2019: a review of its structure, synthesis, properties and exfoliation.* 2020. **8**(5): p. 1517-1547.
8. Dideikin, A.T. and A.Y.J.F.i.P. Vul', *Graphene oxide and derivatives: the place in graphene family.* 2019. **6**: p. 149.
9. Zaaba, N., et al., *Synthesis of graphene oxide using modified hummers method: solvent influence.* 2017. **184**: p. 469-477.
10. Feicht, P., et al., *Brodie's or Hummers' method: oxidation conditions determine the structure of graphene oxide.* 2019. **25**(38): p. 8955-8959.
11. Gadipelli, S. and Z.X.J.P.i.M.S. Guo, *Graphene-based materials: Synthesis and gas sorption, storage and separation.* 2015. **69**: p. 1-60.
12. Smith, A.T., et al., *Synthesis, properties, and applications of graphene oxide/reduced graphene oxide and their nanocomposites.* 2019. **1**(1): p. 31-47.
13. Kuilla, T., et al., *Recent advances in graphene based polymer composites.* 2010. **35**(11): p. 1350-1375.
14. Rhee, K.Y.J.N., *Electronic and thermal properties of graphene*. 2020, MDPI. p. 926.
15. Sang, M., et al., *Electronic and thermal properties of graphene and recent advances in graphene based electronics applications.* 2019. **9**(3): p. 374.
16. Woo, Y.S.J.M., *Transparent conductive electrodes based on graphene-related materials.* 2018. **10**(1): p. 13.
17. Uz, M., et al., *Fabrication of high-resolution graphene-based flexible electronics via polymer casting.* 2019. **9**(1): p. 1-11.
18. Jang, H., et al., *Graphene-based flexible and stretchable electronics.* 2016. **28**(22): p. 4184-4202.
19. Lee, S.-M., J.-H. Kim, and J.-H.J.M.T. Ahn, *Graphene as a flexible electronic material: mechanical limitations by defect formation and efforts to overcome.* 2015. **18**(6): p. 336-344.
20. Im, M.J., et al., *High uniformity and stability of graphene transparent conducting electrodes by dual-side doping.* 2022. **605**: p. 154569.
21. Wang, Y., et al., *Quantum Hall phase in graphene engineered by interfacial charge coupling.* 2022. **17**(12): p. 1272-1279.
22. Priyadarsini, S., et al., *Graphene and graphene oxide as nanomaterials for medicine and biology application.* 2018. **8**: p. 123-137.
23. Mondal, H.S., et al., *Optoelectronics based dynamic advancement of graphene: Characteristics and applications.* 2018. **8**(4): p. 171.
24. Miller, E.E., Y. Hua, and F.H.J.J.o.E.S. Tezel, *Materials for energy storage: Review of electrode materials and methods of increasing capacitance for supercapacitors.* 2018. **20**: p. 30-40.
25. Xiang, Y., et al., *Advances in the applications of graphene-based nanocomposites in clean energy materials.* 2021. **11**(1): p. 47.

26. Valorosi, F., et al., *Graphene and related materials in hierarchical fiber composites: Production techniques and key industrial benefits.* 2020. **185**: p. 107848.
27. Khort, A., et al., *High-performance selective NO2 gas sensor based on In2O3–graphene–Cu nanocomposites.* 2023. **13**(1): p. 7834.
28. Huang, H., et al., *Graphene-based sensors for human health monitoring.* 2019: p. 399.
29. Kulakova, I. and G.J.M.U.C.B. Lisichkin, *Biosensors Based on Graphene Nanomaterials.* 2022. **77**(6): p. 307-321.
30. Homaeigohar, S. and M.J.N.A.M. Elbahri, *Graphene membranes for water desalination.* 2017. **9**(8): p. e427-e427.
31. Aghigh, A., et al., *Recent advances in utilization of graphene for filtration and desalination of water: a review.* 2015. **365**: p. 389-397.
32. Huang, L., et al., *Graphene-based membranes for molecular separation.* 2015. **6**(14): p. 2806-2815.
33. Li, J., et al., *Promising graphene-based nanomaterials and their biomedical applications and potential risks: A comprehensive review.* 2021. **7**(12): p. 5363-5396.
34. Dasari Shareena, T.P., et al., *A review on graphene-based nanomaterials in biomedical applications and risks in environment and health.* 2018. **10**: p. 1-34.
35. Priya Swetha, P.D., et al., *Graphene and graphene-based materials in biomedical science.* 2018. **35**(8): p. 1800105.
36. Fu, Y., et al., *Graphene related materials for thermal management.* 2020. **7**(1): p. 012001.
37. Lin, H., et al., *Recent advances in thermal conductivity and thermal applications of graphene and its derivatives nanofluids.* 2022: p. 119176.
38. Renteria, J.D., D.L. Nika, and A.A.J.A.s. Balandin, *Graphene thermal properties: applications in thermal management and energy storage.* 2014. **4**(4): p. 525-547.
39. Hirani, R.A.K., et al., *Wastewater remediation technologies using macroscopic graphene-based materials: A perspective.* 2021. **3**: p. 688552.
40. Wang, Y., et al., *Environmental remediation applications of carbon nanotubes and graphene oxide: Adsorption and catalysis.* 2019. **9**(3): p. 439.
41. Ollik, K. and M.J.C. Lieder, *Review of the application of graphene-based coatings as anticorrosion layers.* 2020. **10**(9): p. 883.
42. McBain, J.W., *The sorption of gases and vapours by solids*. 1932: G. Routledge.
43. Yanagisawa, T., et al., *The preparation of alkyltrimethylammonium–kanemite complexes and their conversion to microporous materials.* 1990. **63**(4): p. 988-992.
44. ALOthman, Z.A.J.M., *A review: fundamental aspects of silicate mesoporous materials.* 2012. **5**(12): p. 2874-2902.
45. Zhao, X.S., et al., *Advances in mesoporous molecular sieve MCM-41.* 1996. **35**(7): p. 2075-2090.
46. Chen, Z., et al., *A non-surfactant self-templating strategy for mesoporous silica nanospheres: beyond the Stöber method.* 2020. **12**(6): p. 3657-3662.
47. Ghimire, P.P., M.J.J.o.C. Jaroniec, and I. Science, *Renaissance of Stöber method for synthesis of colloidal particles: New developments and opportunities.* 2021. **584**: p. 838-865.
48. Rizzi, F., et al., *High surface area mesoporous silica nanoparticles with tunable size in the sub-micrometer regime: Insights on the size and porosity control mechanisms.* 2021. **26**(14): p. 4247.
49. Niroumand, U., et al., *The Effect of Size, Morphology and Surface Properties of Mesoporous Silica Nanoparticles on Pharmacokinetic Aspects and Potential Toxicity Concerns.* **10**: p. 237.
50. Niedermayer, S., et al., *Multifunctional polymer-capped mesoporous silica nanoparticles for pH-responsive targeted drug delivery.* 2015. **7**(17): p. 7953-7964.
51. Kolimi, P., et al., *A systemic review on development of mesoporous nanoparticles as a vehicle for transdermal drug delivery.* 2023. **7**(1): p. 70-89.
52. Mohamed, F., et al., *Biocompatible Supramolecular Mesoporous Silica Nanoparticles as the Next-Generation Drug Delivery System.* 2022. **13**: p. 1826.
53. Mitran, R.-A., et al., *Thermal stability enhancement of mesoporous SBA-15 silica through nanoconfinement of ceria nanoparticles.* 2020. **306**: p. 110484.
54. Selvarajan, V., S. Obuobi, and P.L.R.J.F.i.c. Ee, *Silica nanoparticles—a versatile tool for the treatment of bacterial infections.* 2020. **8**: p. 602.
55. Zhang, C., et al., *Applications and biocompatibility of mesoporous silica nanocarriers in the field of medicine.* 2022. **13**: p. 104.
56. Ahmed, H., et al., *Biomedical applications of mesoporous silica nanoparticles as a drug delivery carrier.* 2022: p. 103729.
57. Živojević, K., et al., *Advanced mesoporous silica nanocarriers in cancer theranostics and gene editing applications.* 2021. **337**: p. 193-211.
58. Carvalho, A.M., R.A. Cordeiro, and H.J.P. Faneca, *Silica-based gene delivery systems: From design to therapeutic applications.* 2020. **12**(7): p. 649.
59. Chen, L., et al., *Mesoporous silica nanoparticles for tissue-engineering applications.* 2019. **11**(6): p. e1573.
60. Ghosh, S. and T.J.J.F.i.M. Webster, *Mesoporous silica based nanostructures for bone tissue regeneration.* 2021. **8**: p. 692309.

61. Abbasi, M., et al., *An intriguing approach toward antibacterial activity of green synthesized Rutin-templated mesoporous silica nanoparticles decorated with nanosilver.* 2023. **13**(1): p. 5987.
62. Montalvo-Quirós, S., et al., *Mesoporous silica nanoparticles as a potential platform for vaccine development against tuberculosis.* 2020. **12**(12): p. 1218.
63. Deshmukh, P.K., et al., *One step synthesis approach of mesoporous silica packed with graphene oxide nanosheet: Characterisation and drug release aspects.* 2022. **37**(11): p. 1677-1690.
64. Fonseca, L.C., et al., *Nanocomposites based on graphene oxide and mesoporous silica nanoparticles: Preparation, characterization and nanobiointeractions with red blood cells and human plasma proteins.* 2018. **437**: p. 110-121.
65. Wei, L., et al., *Porous sandwich-like silica/graphene nanocomposites obtained via templating of porous silica with CTAB in the gallery region of graphene oxide.* 2017. **241**: p. 58-65.
66. Liu, R., et al., *Polydopamine doped reduced graphene oxide/mesoporous silica nanosheets for chemo-photothermal and enhanced photothermal therapy.* 2019. **96**: p. 138-145.
67. Dalagan, J.Q. and E.P.J.B.o.M.S. Enriquez, *One-step synthesis of mesoporous silica–graphene composites by simultaneous hydrothermal coupling and reduction of graphene oxide.* 2014. **37**: p. 589-595.
68. Liu, R., et al., *Enhanced antibacterial activity of silver-decorated sandwich-like mesoporous silica/reduced graphene oxide nanosheets through photothermal effect.* 2018. **29**(10): p. 105704.
69. Narayan, R., et al., *Mesoporous silica nanoparticles: A comprehensive review on synthesis and recent advances.* 2018. **10**(3): p. 118.
70. Mukheem, A., et al., *Fabrication and characterization of an electrospun PHA/graphene silver nanocomposite scaffold for antibacterial applications.* 2018. **11**(9): p. 1673.
71. Sinha, P., et al., *Surface area determination of porous materials using the Brunauer–Emmett–Teller (BET) method: limitations and improvements.* 2019. **123**(33): p. 20195-20209.
72. Jia, Z., et al., *Dynamic Light Scattering: A Powerful Tool for In Situ Nanoparticle Sizing.* 2023. **7**(1): p. 15.
73. Mahmood, N., et al., *Graphene-based nanocomposites for energy storage and conversion in lithium batteries, supercapacitors and fuel cells.* 2014. **2**(1): p. 15-32.
74. Moghaddam, S.P.H., R. Mohammadpour, and H.J.J.o.C.R. Ghandehari, *In vitro and in vivo evaluation of degradation, toxicity, biodistribution, and clearance of silica nanoparticles as a function of size, porosity, density, and composition.* 2019. **311**: p. 1-15.
75. Seré, S., et al., *Altering the biodegradation of mesoporous silica nanoparticles by means of experimental parameters and surface functionalization.* 2018. **2018**.
76. Wang, Y., et al., *Multifunctional mesoporous silica-coated graphene nanosheet used for chemo-photothermal synergistic targeted therapy of glioma.* 2013. **135**(12): p. 4799-4804.
77. Okamoto, Y., et al. *Fabrication of supported lipid bilayer on graphene oxide*. in *Journal of Physics: Conference Series*. 2012. IOP Publishing.
78. Gurunathan, S. and J.-H.J.I.j.o.n. Kim, *Synthesis, toxicity, biocompatibility, and biomedical applications of graphene and graphene-related materials.* 2016. **11**: p. 1927.
79. Kwon, S., et al., *Silica-based mesoporous nanoparticles for controlled drug delivery.* 2013. **4**: p. 2041731413503357.
80. Yang, K., et al., *In vivo pharmacokinetics, long-term biodistribution, and toxicology of PEGylated graphene in mice.* 2011. **5**(1): p. 516-522.
81. Huang, X., et al., *The shape effect of mesoporous silica nanoparticles on biodistribution, clearance, and biocompatibility in vivo.* 2011. **5**(7): p. 5390-5399.
82. Passaretti, P.J.F.i.M.B., *Graphene oxide and biomolecules for the production of functional 3D graphene-based materials.* 2022. **9**: p. 774097.
83. Tene, T., et al., *Toward large-scale production of oxidized graphene.* 2020. **10**(2): p. 279.
84. Loh, J.S., et al., *Do lipid-based nanoparticles hold promise for advancing the clinical translation of anticancer alkaloids?* 2021. **13**(21): p. 5346.
85. Dumontel, B., et al., *Natural Biopolymers as Smart Coating Materials of Mesoporous Silica Nanoparticles for Drug Delivery.* 2023. **15**(2): p. 447.
86. Rahmatolahzadeh, R., et al., *Aspartic acid functionalized PEGylated MSN@ GO hybrid as an effective and sustainable nano-system for in-vitro drug delivery.* 2018. **63**(2): p. 257-264.
87. Castillo, R.R., et al., *Advances in mesoporous silica nanoparticles for targeted stimuli-responsive drug delivery: an update.* 2019. **16**(4): p. 415-439.
88. Maleki, M., et al., *Graphene oxide: a promising material for regenerative medicine and tissue engineering.* 2020. **11**(1): p. 182-200.
89. Bansal, K.K., et al., *Therapeutic potential of polymer-coated mesoporous silica nanoparticles.* 2019. **10**(1): p. 289.

 doi:10.20944/preprints202308.1166.v1

90. Li, X., et al., *Thermosensitive lipid bilayer-coated mesoporous carbon nanoparticles for synergistic thermochemotherapy of tumor*. 2018. **10**(23): p. 19386-19397.
91. Dennahy, I.S., et al., *Nanotheranostics for image-guided cancer treatment*. 2022. **14**(5): p. 917.