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Metal Species–Encapsulated Mesoporous Silica Nanoparticles: Current Advancements and Latest Breakthroughs — Source link

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Please submit a plain text version of your cover letter here.	Helsinki, 30 May 2019, Dr. Jos Lenders Editor Advanced Functional Materials Re: Manuscript ID- adfm.201902652 Dear Dr. Lenders, I would like to submit the revised manuscript entitled “Metal Species-Encapsulated Mesoporous Silica Nanoparticles: Current Advancements and Latest Breakthroughs” (Manuscript ID- adfm.201902652). No conflict of interest exists in the submission of this manuscript and the final manuscript was approved by all authors for publication. The authors highly appreciate the valuable comments and suggestions from reviewers during the peer-review process. We have carefully revised the manuscript, according to the reviewer’s suggestion. Our replies and explanation point-by-point to each of the reviewers' comments are enclosed, and the changes were marked in the revised manuscript. I hope you our review paper can now be considered for publication in Advanced Functional Materials. Thank you in advanced for your kind consideration! Sincerely, Hélder Santos _____ Hélder A. Santos, Associate Professor (Pharm. Nanotechnol.), Head of Division Head of the Division of Pharmaceutical Chemistry and Technology Head of the Nanomedicines and Biomedical Engineering Group Head of the Preclinical Drug Formulation and Analysis Group

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Abstract:	Despite their advantageous morphological attributes and attractive physicochemical properties, mesoporous silica nanoparticles (MSNs) are merely supported as carriers or vectors for a reason. Incorporating various metal species in the confined nanospaces of MSNs (M-MSNs) significantly enriches their mesoporous architecture and diverse functionalities, bringing exciting potentials to this burgeoning field of research. These incorporated guest species offer enormous benefits to the MSN hosts concerning the reduction of their eventual size and the enhancement of their performance and stability, among other benefits. Substantially, the guest species act through contributing to reduced aggregation, augmented durability, ease of long-term storage, and reduced toxicity, attributes that are of particular interest in diverse fields of biomedicine. In this review, we first aim to discuss the current advancements and latest breakthroughs in the fabrication of M-MSNs, emphasizing the pros and cons, the confinement of the species in the nanospaces and various factors influencing the encapsulation of metal species in MSNs. Further, we provide an emphasis on potential applications of M-MSNs in various fields, including in adsorption, catalysis, photoluminescence, and biomedicine, among others, along with a set of examples. Finally, we summarize the advances in M-MSNs with perspectives.

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Metal Species-Encapsulated Mesoporous Silica Nanoparticles: Current Advancements and Latest Breakthroughs

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Abstract

Despite their advantageous morphological ~~features~~ attributes and attractive physicochemical properties, ~~the~~ mesoporous silica nanoparticles (MSNs) are ~~only~~merely supported as ~~a~~ carriers or ~~a~~ vectors for a reason. Incorporating various metal species in the confined nanospaces of MSNs~~To~~ (M-MSNs) significantly enriches their mesoporous architecture and diverse functionalities~~, these innovative carriers have been impregnated or encapsulated with diverse metal species (M-MSNs) in their confined nanospaces~~, ~~where they have brought~~bringing ~~the~~ exciting potentials to this burgeoning field of research. These incorporated guest species~~s~~ ~~metal species~~ offer ~~numerous~~ enormous benefits to the ~~the mesoporous silica framework~~MSN hosts concerning the reduction ~~in~~ of their eventual size~~,~~ and the enhancement of their performance ~~as well as~~and stability, among other benefits. Substantially, the guest species ~~payback~~ act through ~~the~~ contributi~~on~~ings ~~in~~to ~~terms of~~ ~~The metal species that enclosed in the mesoporous materials gain enormous benefits such as~~ reduced aggregation, augmented ~~stability~~durability, ease of long-term storage, and reduced toxicity, ~~which~~ attributes that are of particular interest in diverse fields of biomedicine~~drive them for processing and application in various fields~~. In this review, we first aim to discuss the current advancements and latest breakthroughs in the fabrication of M-MSNs, emphasizing the pros and cons, the~~ir~~ confinement of the species in the nanospaces and ~~then~~ various factors influencing the encapsulation of ~~diverse~~ metal species ~~incorporation~~ in ~~the~~ MSNs. Further, we provide an emphasis ~~and discussions, focusing~~ on potential applications of M-MSNs in ~~diverse~~ various ~~interdisciplinary~~ fields, including ~~such as~~ in adsorption, catalysis, photoluminescence, and biomedicine, among others, along with a set of examples. Finally, we summarize the advances ~~of~~ in M-MSNs with perspectives ~~of M-MSNs with perspectives~~.

Keywords: mesoporous silica nanoparticles, metal nanoparticles, biomedical field, catalysis, controlled drug ~~release~~ delivery

1. Introduction

With the advent of nanotechnology, most ~~of the~~ technological fields of science and engineering have been fascinatingly advanced ~~for~~ toward the development of various innovative products that have better performances.[1] In the past two decades, ~~the rapid~~tremendous progress ~~of this field~~ has been evidenced by ~~the~~ advancements ~~of~~ in fabricating different inorganic nanosystems with intrinsic functionalities for diverse applications,[2] due to their unique advantages such as ease of synthesis and scalability, cost-effectiveness, and size- and shape-dependent physicochemical properties.[3] Among the various ~~kinds~~ types of inorganic nanomaterials available, mesoporous silica nanoparticles (MSNs), have ~~attracted~~ garnered ~~enormous~~vast interest ~~of~~ from researchers due to their attractive physico-chemical features such as tunable morphology, extensive surface area (~1500 m^2/g) and pore volume, adjustable and uniformly-sized mesopores (2-5 nm), tunable sizes (50-150 nm), shapes (hexagonal, wormhole-like, cubic, and lamellar~~, disordered, and wormhole-like~~) and morphologies (spheres, helical fibers, ~~hollow spheres, fibers, crystals,~~ tubules, ~~helical fibers,~~ gyroids, crystals, and numerous other hierarchical complex ~~structures~~architectures), ease of surface functionalization (both

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interior as well as exterior), unique topology, colloidal and thermal ~~stability~~stabilities, and high dispersity~~, and unique topology (surface and inner porous architectures)~~.[4] The exceptional topology of ~~the~~ surfactant-templated MSNs makes them unique with desirable properties~~,~~ that ~~could~~ can be obtained by controlling the ~~synthesis~~ preparation conditions, ~~involving~~ such as the reaction temperature, pH value, ~~reaction temperature,~~ stirring speed, and ~~and~~ type of silica source, ~~and as well as~~ands well as ~~the~~ surfactant, among others.[4j, 4m, 4n, 5] ~~Moreover, numerous desirable characteristic features such as controllable pore size, tunable particle shapes and sizes, and well suspended stable solution, among others, are essential for their applications.[4j, 5] All t~~These advantages make the MSNs as versatile materials and ideal choice for ~~various applications such as~~ catalysis,[6] adsorption,[7] optical devices,[4j] polymeric fillers,[8] and diverse biomedical applications ~~such as~~including bio-imaging,[4r, 4t, 4u, 9] biocatalysts,[10] biosensing,[11] tissue engineering,[4f] and drug/gene delivery accounting for targeted and controlled release systems.[3d, 4i, 4o-t, 4v, 12]

With these significant advantages and attractive physicochemical properties, it is highly anticipated to harness the desirable and beneficial properties of MSNs through the incorporation of various metals and their respective conjugates for ~~their~~ exploration in ~~the~~ innovative applications with ~~better~~ exceptional performance~~s~~.[13] ~~{Ramanathan, 2018 #504}~~ The encapsulated metal species ~~Various metal species that are encapsulated~~ in the confined nanospaces of MSNs (M-MSNs) not only significantly enrich the mesoporous architecture and functionalities of MSN~~s~~, but also tend to overcome their intrinsic limitations, such as their poor suspension ability and _stability, ~~devoid~~ lack of intriguing properties, ~~difficulties~~ difficulty in long-term storage, and toxicity in ~~the~~ biological fluids to a considerable extent~~, among others~~.[13a] In ~~this framework, the inc~~corporati~~on~~ng ~~of~~ diverse metal species into MSNs offers mutual

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benefits concerning ~~referring to~~ the enhancement of their physicochemical properties resulting in their ~~the~~ wide-spread applicability~~expansion of their applicability in various fields~~. ~~On~~ In ~~the~~ ~~a~~the ~~way~~ process of ~~advancing~~progressing ~~the~~ MSN designs ~~concerning~~regarding ~~the~~ structural and functional attributes ~~with metals~~, researchers ~~currently~~ are predominantly focused on addressing ~~attempt to address the~~ challenges such as the stability, biocompatibility, and biodegradability ~~aspects~~ of the ~~encapsulated metal species as well as MSNs~~M-MSN composites ~~with~~ ~~in regards to~~regarding catalytic and biomedical applications. However, it should be noted that these concerns are predominantly ~~attributed~~connected to various physicochemical properties of the final ~~nano~~composites such as the type of metal used, particle size, ~~the~~ degree of silica condensation, and chemical functionalization. In this context, these advances provide experts from different fields, ~~comprising~~ including but not limited to biology, medicine, chemistry, and~~,~~ engineering, among others, with ~~excellent~~tremendous opportunities for ~~their~~ innovative explorations and ~~also~~ will motivate the advent of new technologies.[14]

Despite ~~the~~ several reports on MSNs for use in drug delivery and other applications by us and other groups,[4f, 4j, 4m, 4o, 4q, 7, 15] the scope of ~~the~~is review covers the current advancements and latest breakthroughs in the fabrication of M-MSNs, emphasizing the pros and cons, the~~ir~~ confinement of the metal species in the nanospaces and ~~then~~ various factors influencing the encapsulation of metal species in MSNs. ~~Herein~~In the further sections, we first discuss the importance of metals and their impact on MSNs, highlighting the benefits, challenges, and desirable properties of M-MSNs. We then discuss the preparation methods for the efficient fabrication of M-MSNs. ~~Following that~~Next, we ~~illustrate~~ emphasize various fabrication strategies for ~~the confinement of~~encapsulating the metal species in the ~~appropriately~~ confined nanospaces of MSNs. Further, w~~W~~e ~~then discuss~~present the crucial factors ~~during synthesis that~~

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affectinfluencing the incorporation of metals in the mesoporous sieves. Next, we present onwe present how these M-MSNs have been utilized in various fields, by choosing somea few selected examples focusing on adsorption, catalysis, photoluminescence, and the biomedical field, highlighting drug delivery, bio-imaging, peptide enrichment, artificial enzymes, and other diverse miscellaneous applications. Finally, we summarize the review with perspectives highlighting the future trends and addressing the limitations of M-MSNs fortheir biomedical applications and the steps that need to be followedrequired steps for their translation from the bench to clinical practice.

2. Impact of metals Metals on MSNs

Despite the successes in utilizing Indeed, MSNs with ordered mesoporous framework have been utilized in various applications due to their desirable characteristics. However, the advantageous morphological features and attractive physicochemical properties of MSNs only support them as a vectors/carriers for a reason. To enrich the mesoporous architecture and functionalities of MSNs, various metal species have beenare incorporated in the confined nanospaces of MSNs, which are of particular in interest in diverse applications. These composites can be used for various applications due to their tunable adaptable physicochemical features and electronic and chemical properties.. These M-MSNs resulting from the synthetic advances that enable better control over their composition, size, and morphology. Various metal species have been incorporated into the mesoporous silica frameworks include, such as aluminium (Al),[16] bismuth (Bi),[17] cerium (Ce),[18] chromium (Cr),[19] cobalt (Co),[20] copper (Cu),[21] gadolinium(Gd),[22] gallium (Ga),[16a, 23] gold (Au),[14, 24] indium (In),[25] iridium (Ir),[26] iron (Fe),[27] manganese (Mn),[28] molybdenum (Mo),[29] nickel (Ni),[18, 30] palladium (Pd),[21b, 24, 26, 31] platinum (Pt),[4n, 14b, 26, 32] rhodium (Rh),[26, 32b] rhuthenium (Ru),[22] silver (Ag),[14b, 28b]

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titanium (Ti),[14c] Zinc (Zn),[33] Zirconium (Zr),[34] and their respective oxides ~~(~~[aluminium oxide (Al_2O_3),[35] cadmium oxide (CdO),[36] cerium oxide (CeO_2),[27c] cobalt(II) oxide/cobaltous oxide (CoO),[20a, 37] cobalt (II,III) oxide (Co_3O_4),[20a, 38] cobalt(III) oxide/ cobaltic oxide (Co_2O_3),[38] chromium(III) oxide (Cr_2O_3),[39] copper~~upric~~ oxide (CuO),[40] ferric oxide (Fe_2O_3),[35, 39, 41] ferrous oxide (Fe_3O_4),[31, 42] indium oxide (In_2O_3),[43] magnesium oxide (MgO),[44] manganese oxide (Mn_3O_4),[26] manganese dioxide (MnO_2),[45] molybdenum dioxide (MoO_2),[46] molybdenum trioxide (MoO_3)[47] nickel oxide (NiO),[30a, 48] palladium oxide (PdO),[16a] titanium dioxide (TiO_2),[28b, 34, 49] vanadium oxide,[50] zinc oxide (ZnO),~~[35, 50]~~),~~ [36, 51]~~], sulphides ~~(~~[cadmium sulphide (CdS), zinc sulphide (ZnS~~))~~[35, 51]~~)~~][36, 52] and selenides ~~(~~[cadmium selenide (CdSe), zinc selenide (ZnSe~~)),~~)]. [36]~~among others.~~[35] ~~On the other hand~~In addition, various combinations of metals have also been encapsulated in the mesoporous materials, including bimetallic systems,[17, 53] metal-immobilized core (metal)-mesoporous silica shell systems[21d]/metal-modified MSNs[18] and others, such as alkali metal ion-~~modification~~ modified~~in~~ ~~M~~ MSNs.[27a] These hybrid materials have gained ~~enormous~~ potential interests in various fields such as adsorption~~bents~~,[35, 37, 42c] catalysis~~sts~~,[14d, 17, 34, 41d, 54] ~~artificial enzymes.~~[14d] drug delivery ~~systems~~,[21a, 27c, 42e] ~~contrast agents~~bioimaging,[42f] ~~photoluminescent~~ photoluminescence~~agents~~,[51b] ~~biosensors~~biosensing,[11] gas ~~sensors~~sensing,[53a] and radioactive metal ~~extractors~~sorption.[42a]

~~In this framework~~Indeed, the incorporated~~se~~ guest ~~molecules, *i.e.*,~~ metal~~lic~~ species~~,~~ offer numerous benefits to the mesoporous frameworks ~~with respect to~~such as ~~the~~ tailoring the size of the MSNs and~~,~~ enhancing their performance~~,~~ as well as their stability attributes.[16b, 55] In fact, the eventual size of the delivery carriers plays a crucial role in biomedical applications ~~concerning~~regarding their long-term circulation in the blood and substantial cellular internalization ~~process and other attributes such as long circulation time in the blood~~. Although

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the control over the self-assembly and degree of silica condensation often result in tailoringhas beenis achieved the sizes of MSNs, it is evident that the conventional hydrothermal process based on the high dilution approach used in the fabrication of MSNs often often results in the pristine particles MSNs with sizeswith size close to greater than 100 nm and even in the some instances, micrometer range due to severe irreversible aggregation yielding in the unstable MSN colloids, which is undesirable of MSNs.[4j] In some instances, the metal species help support the mesoporous support frameworks for in their size confinement to achievceward prepare a stable MSN colloids solution of MSNs in the size range of tens of nanometers. For instance, In one case, the transition metal ions (Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+})-chelating surfactant micelle complexes were used as templates for synthesizing silica-based mesoporous silica materials, which eventually resulted in the a significanta reduction reduced of their final overall diameter of the MSNssize, due to the altered stabilization constant of the the structure--directing surfactant after complexation with the metal species.[56] Moreover, tThese innovative metallic species incorporated M-MSN nanocomposites offer numerous specific advantages in with respect toconcerning the anticipateddiverse applications. For example, in the catalytic field, these fabricated metal species contained in the active sites of mesoporous framework MSNs facilitates the enhancement ofaugmented performance efficiency, in terms of the activity, selectivity, recyclability, lifetime and reusability of MSNs due to superior magnetic, catalytic, optic, (Localized Surface Plasmon Resonance, LSPR), or electronic properties.[16b, 57] In From the biologist's point of view, these impregnated metal species impregnated in the mesoporous frameworkMSNs are also beneficial in for enrichingelevating the applicability of MSNs in terms of drug loading efficiency enhancement, and achieving their substantial triggered release in at the specific sites, such as the endosomal environment (pH-4.5-6.0) of the tumor cells.[21a, 58] In a

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~~few~~some instances, the use of iron ~~-~~oxide species as a core ~~that are incorporated in the core of MSNs~~ enable~~d~~ the targeting ~~ability of MSNs as well as~~and ~~providing~~ provides a better imaging view field in diagnosis.[59] In addition, these metal nanoparticles (~~-~~MNPs) can ~~also~~ be ~~fabricated~~ immobilized as capping agents ~~on~~ over ~~the~~ mesopores ~~surface~~ *via* specific stimuli-responsive ~~linkers~~anchors, ~~which e~~enablinges the responsive release of drug cargo ~~from the mesopores~~.[60] Moreover, the fabrication of M~~-these metal species incorporated mesoporous silica~~MSNs is highly eco-friendly similar to that of conventional MSNs as the fabrication strategies ~~utilized to fabricate them~~ do not usually rely on the use of organic solvents, ~~which as the traces of organic solvent residues in the end product~~ may result in ~~the~~ damage ~~of~~ to body tissues upon their application. In addition to ~~applicability and~~ enriching the functionalities of MSNs, the ~~concomitant~~simultaneous encapsulation of metal species ~~encapsulation~~ in the mesoporous support reduces the number of synthetic steps ~~of a~~in the multi-step preparation process ~~during the formulation design~~ by avoiding ~~the~~ additional surface ~~functionalizations~~functionalization~~'~~ and facilitating the carrier safety concerning the biocompatibility ~~issue~~ and degradation or disordering issues of ~~mesoporous framework~~MSNs ~~during processing~~.[21a, 58, 61]

~~On the other hand~~To this end, the applicability of the~~se guest nanoparticles~~ MNPs ~~has also been~~can also be significantly ~~enriched~~ augmented by depositing ~~them~~ these guest species in the MSN~~high surface area mesoporous silica~~ support. Numerous studies have demonstrated that~~Oftentimes,~~ these ~~metal nanoparticles (~~MNPs~~)~~ have been~~ can be utilized ~~solely~~ in a wide variety of potential applications due to their fascinating physicochemical properties, which are significantly different from those of~~ir~~ bulk matters of ~~the~~ similar compositions.[62] However, ~~it is evident that free~~ MNPs alone tend to aggregate tremendously due to their~~possess~~ high surface ~~energies~~energy ~~and tend to aggregate tremendously~~, resulting in ~~the~~ poor stability, decreased

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~~deprived~~ suspension ability, lack of ~~devoid of~~ intriguing properties, difficulties in long-term storage, and high toxicity imposing health risks, which limit~~ing~~ their processing and ~~application~~ applicability, specifically in biomedicine~~regarding biological applications~~.[13a] Moreover, ~~tMoreover, the~~ potential toxicity may ~~originate~~instigate from the particulate ~~nature~~ matter of MNPs, ~~which display catalytic effects~~ due to their increased surface-to-volume ratio. To overcome these issues, MNPs ~~are~~ have been ~~often~~ encapsulated in the confined void spaces of mesoporous and microporous materials, including silica, zeolites, and activated carbon~~s~~.[32a] Among the various materials available, ~~mesoporous silica materials~~MSNs appear to be an efficient platform for the encapsulation of MNPs because of their well-ordered framework, tunable pores, high surface area, ~~stable~~ stability and thermally robustness, among other properties~~.~~.[58, 61a, 63] Moreover, the advantageous~~se~~ structural characteristics of these inorganic mesoporous shells provide a robust 3D platform that can significantly offer~~ing~~ ~~the~~ protection against the sintering of MNPs by enabling their uniform distribution and confinement ability in the mesopores ~~and the structural characteristics of MSNs enable the uniform distribution of the metallic species due to the effects of host size as well as its confinement ability~~.[38, 64] In particular, the toxicity issues of MNPs ~~could be~~can also be ~~overcome~~ addressed by incorporating them into MSNs to a considerable extent, ~~due to relatively good excellent biocompatibility~~ as the resultant silicic acid species of ~~them~~ MSNs ~~in the physiological fluids~~ are relatively nontoxic and offer excellent biobehavior *in vitro* and *in vivo*. Thereby, ~~this~~ these innovative composites act as excellent candidates by ~~approach~~ circumvent~~s~~ting ~~the~~se issues associated with ~~the~~ MNPs and promote~~s~~ their utilization in diverse biomedical applications.[38, 53d, 58, 61a, 63] ~~In addition~~In regard~~s~~ to the encapsulation of MNPs, MSNs are highly advantageous over ~~others~~ other inorganic supports, ~~during the composite fabrication~~ as they offer an ~~enormous~~ extensive functionalization

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surface in both the exterior (on the surface) and interior (in the mesopore) space, where MNPs can be arranged through ~~the~~ chemical linkage or physically immobilized through ~~the~~ electrostatic interactions, respectively.[6, 61a, 63] However, the immobilization of metals utterly depends on the size and volume of the mesopores~~,~~ and the overall size (if nanoparticulate forms are used) ~~as well as~~and charge of the metals. In addition to the ability ~~of loading encapsulating~~to encapsulate metal species ~~by the~~in the ~~MSN's~~ interior of MSNs ~~surface area~~, the precise ~~as well as~~and selective modification of ~~the~~ MSN surfaces both interior ~~as well as exterior~~ and exterior, is another crucial factor to be considered ~~in~~ for the achievement of ~~the~~ effective designs.[65] In ~~a few~~some instances, this approach allows ~~the~~ effective control over the host (MSN)--guest (metal species) interactions, which ~~drive~~ may influence the delivery kinetics and the stability of the encapsulated metals.[66]

3. Generalized Preparation ~~methods~~ Methods

Hierarchically-ordered MSNs are the highly exceptional materials, whose uniqueness can be predominantly characterized by their ordered mesostructured pores and the disordered arrangement of atoms in the siliceous frameworks.[4j, 4m, 4o, 4q, 32c] The generalized templating method typically ~~depends~~rely on the utilization of cationic surfactants that act as structure-directing templates, which significantly drive the co-condensation of silica precursor in the alkalescent conditions, resulting in the advantageous morphological characteristics, such as the extensive surface area and high porosity.~~The generalized synthesis of MSNs is based on the utilization of cationic surfactants that act as templates and drive the condensation of silica precursor in the basic conditions.[21a, 67]{Narayan, 2018 #503} This templating method has been widely applied in preparing MSNs that possess abundant morphological characteristics such as extensive surface area and pore volumehigh porosity.[20a, 66]~~ However, the convenient self-

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assembly of surfactant- and silica species is ~~typically~~ usually based on the~~ir~~ mutual interactions between them~~,~~. ~~However, i~~It should be noted that~~but~~ the morphology and dimensions of MSNs utterly depend on the reaction kinetics of sol-gel chemistry, water content, and temperature, ~~and~~ as well as the pH value of the reaction ~~-~~medium.[4j, 68] In addition, several other experimental factors~~, play crucial roles in the synthesis of MSNs such as~~ including surfactant-silica interactions, assembly kinetics, silica condensation, nucleation and growth rates, influence the eventual morphology of MSNs. The critical roles of all these factors ~~in the synthesis~~during the fabrication of nano-sized ~~mesostructured silica particles~~MSNs have been ~~clearly~~ explicitly ~~emphasized~~highlighted in a recent compilation by Lin and ~~Mou *et al*~~colleagues.[4j]

Though~~,~~ there ~~has been~~is a commonly used templating method ~~for the synthesis of M-MSNs~~, ~~the~~ tremendous ~~advancements~~ ~~progress~~advancements ~~in the past decade~~ has~~s~~ve been evidenced over the past decade ~~in the past decade has evidenced~~by the development of numerous strategies for the fabrication of noble metal or metal oxide ~~nanoparticles~~species-encapsulated MSNs.[4j, 4o, 4q, 15e] Based on the structural stability and convenient synthesis, various templates such as quaternary ammonium salts ~~surfactants~~ and Pluronic copolymer-based surfactants have been used ~~for synthesizing~~to synthesize the most popular mesoporous products with p6mm hexagonal architectures, namely, the Mobil composition of matter (MCM)~~MCM~~-41, and the Santa Barbara amorphous-type material (SBA)-15, respectively. In general, the quaternary ammonium surfactants are highly suitable ~~in~~for accommodating the metal cations (such as ~~zinc~~ Zn and ~~copper,~~Cu~~, etc.,~~) through ~~the~~ strong electrostatic interactions *via* the ion-templating approach, leading to their substantial deposition in the mesoporous substrates.[16b] while the templates of SBA-15 species can accommodate ~~the~~ MNPs (for example Pt and Rh nanoparticles) directly in the mesopores through encapsulating them in the templates.[32b] Although there exist~~s~~ certain

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differences in the synthetic conditions, including the pH of the reaction medium and templates used, which leadeading to the different morphological attributes and diverse interactions and final pore sizes, both of these templates eventually lead to the generation of ultra-fine, stable metal species, *i.e.*, metal ions as well asand MNPs, that are enclosed in the mesoporous support along withand have sameimilar surface properties. Despite the significant advancements, the incorporationion of metal species in the mesoporous support often relies on the optimization of synthetic conditions by appropriately selecting the surfactant and reaction conditions, accounting tofor sufficient pore sizes and volume as well as the fabrication of organic linkers, which make these composites expensive, and therefore, reducinge their economic feasibility and industrial applicability. the challenge of the incorporation of metals in the mesoporous support relies on demanding synthesis of sufficient pore sizes and volume as well as the fabrication of organic linkers together with the compatibility issues, which may make the syntheses of these composites expensive and therefore reducing their economic feasibility and industrial applicability. MoreoverFurthermore, the poor solubility of the immobilized organic linkers may result in the the poor biodegradability and, leading leads to toxicity issues.[66] HerewithHerein, we pile-uppresent and discuss the most commonly used methods in fabricating the metal/metal oxides in MSNs, including self-assembly/co-condensation, post-grafting, template ion-exchange (TIE) and others, such as supercritical-assisted deposition, highlighting the pros and cons as well as the changes in the reactive reaction conditions.

3.1. Self-assemblyAssembly/coCo-condensation Condensation method

The co-condensation approach, often referred to as a direct hydrothermal method, is the most commonly used synthetic process that involves involving the co-operative self-assembly of the desired metals/metal oxide precursors/MNPs and silica precursors.[49] In a typical surfactant-

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mediated co-condensation of MSNs, the diluted amount of the silica precursor is initially added to the aqueous ammonia containing the micellar structures of the surfactant (cetyl trimethyl ammonium bromide, CTAB) molecules for ~~its~~ initial nucleation and ~~then~~ the desired metal precursor and the concentrated amount of silica are then subsequently added to the ~~initial~~ mixture, resulting in ~~the,~~ ~~resulting in the formation of~~ metal-impregnated ~~mesostructured nanoparticles~~MSNs. Substantial mesostructured porous frameworks can be obtained~~-~~ after the removal of the surfactant ~~removal~~ by either calcination of the silica support at high temperatures (~550 ºC)[63] or various chemical approaches (e.g., extraction of the surfactant using acidic ethanol, or ammonia in ethanol/isopropanol).[4j, 21a, 58, 61a, 69] In addition ~~to ethanol~~, it is worth noting that using isopropanol as a solvent for ammonium nitrate ~~could~~ can effectively extract the surfactant and significantly enhance the ~~eventual~~ final surface area and pore volume of the MSNs, while still maintaining the order of the mesoarchitectures. This process is the most simplest, cost-effective, and most ~~an~~ efficient method of ~~in the~~ preparation ~~of mesoporous supports~~. Moreover, it is highly advantageous ~~in~~ for efficiently incorporating the metal species in the well-ordered siliceous frameworks, ~~of the uniform sized MSNs~~ as this method does not ~~require~~ rely on any ~~sort of~~ optimization in terms of ~~the~~ adjustment of the pore size or volume of the MSNs or the ~~immobilizing~~ immobilization of organic linkers over their surface.[28b] ~~Further~~Moreover, the encapsulated metal species in the siliceous frameworks have no ~~significant~~substantial ~~influence~~effect on the final particle size (~30-200 nm) ~~as well as~~and or pore sizes (~2-10 nm) of the MSNs, resulting ~~in the~~ in homogenous M-MSNs ~~in~~ at the alkalescent pH ~~conditions~~. This approach is highly suitable for specific transition metals, such as ~~copper~~Cu, while ~~the~~ for others, ~~(such as~~for instance, iron) ~~could often~~ it leads~~s~~ to the precipitation ~~to as iron oxide~~ due to ~~highly prone to its~~their oxidation in ammonia ~~water~~solution. However, the incorporation of ~~iron~~Fe

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species in the siliceous frameworks c~~ould~~an be well-achieved using sodium hydroxide as ~~a~~the reaction medium at ~~the~~ similar pH conditions. ~~However, t~~The appropriate order of addition and the type and~~of~~ form of the metal precursor (either metal ions or nanoparticles) also dictate the position occupied ~~position~~ by the metal, as well as its ~~their~~ loading efficiency in the mesoporous support.[28b] In ~~one case~~some instances, the metal precursors (for example, magnesium oxide) were initially dispersed, and then the surfactant molecules along with the silica precursor (tetraethyl orthosilicate, TEOS) were added later, resulting in ~~the~~ encapsulation of the metal precursors in the hollow compartment of the MSNs as core-shell MgO@~~–~~mesoporous silica ($mSiO_2$) spheres (**Figure~~.~~ 1**A),[44] The pre-addition of metal species ~~had has~~ facilitated the enhancement of their loading amounts, and the substantial coating of a hard and porous ~~silica~~ siliceous shell over ~~them~~, the metal species, ~~had has~~ offered ~~the~~ an improvement of their mechanical stability, ~~enriched~~ enriching the chemical ~~property~~ properties and applicability~~tion~~ over those of other crystalline nanoparticles. Despite its significant advantages, this approach is most suitable for incorporating metal oxides of certain elements such as ~~nanoparticles such as~~Mn, Co, and Ni~~, among others magnesium oxide, cobalt oxide, and nickel oxide~~. However, the pre-addition is not safe in ~~a few~~some instances (for example, iron oxide), as it ~~may~~ leads to the separation of metal oxides, ~~it leads to their may result in the separation of metal oxides, leading~~ resulting in~~to~~ ~~their~~ low encapsulation efficiency~~, for example, iron oxide~~.

Numerous interesting studies have ~~also been~~ reported the synthesis of M-MSNs ~~by~~ using the co-condensation method with slight modifications. The modified conditions included ~~change~~ changing the~~of~~ solvent (ethanol), reaction conditions (base or acidic), and surfactant template or structure-~~–~~directing agent (N-hexadecyl ethylenediamine triacetate, HED3A), the addition of stabilizers or encapsulating agents (*e.g.,* polyethylene oxide (PEO)[48b] and polyethyleneimine

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(PEI)[21b]), and the use of long-term hydrothermal treatments or a drying time ~~for~~of ~~(~~ 7 days~~)~~, which significantly enhanced the physicochemical attributes, mechanical stability and ~~loading~~ encapsulation efficiency of the metal species in the ~~the mesoporous support~~MSNs.[20b, 28b, 38, 48a, 53a] ~~In a way,~~ Niu and co-workers[48a] ~~-~~fabricated ~~the~~ metal oxide-encapsulated MSNs using an anionic surfactant template, *i.e.,* ~~N-hexadecyl-ethylenediamine-triacetate (~~HED3A~~)~~ in sodium hydroxide, which acted as a structure-directing agent ~~as well as~~and a ~~metal-~~metal-chelating agent. ~~In addition, t~~The positively charged metal species ~~could~~were ~~-metals were~~ efficiently bound to the anionic surfactant through strong electrostatic interactions~~,~~. These interactions facilitated a ~~resulting in their~~ high loading efficacy of metal species due to the coordination effect and significantly ~~enabled~~ enabling ~~the~~ self-assembly in the concentrated solutions to form regular architectures by placing ~~them~~ the metal species in ~~the~~ mesopores. In ~~F~~further studies~~more~~, this approach has been extensively utilized by the group in synthesizing ~~the diversiform diverse~~various metal species-encapsulated mesoporous silica composites, such as oxides of Ni, and Co ~~nickel oxide, cobalt oxide~~, and zinc ferrite.[38, 48a, 53a]

In the past decade, ~~the~~ considerable interest has been gained by the researchers in ~~the~~ immobiliz~~ation~~ing the ~~of~~ metal species using the self-assembly approach, predominantly focusing on the improvement of various physicochemical attributes and ~~loading~~ encapsulation efficiency of the ~~nanocomposites~~MSNs. However, the stabilization of the highly dispersed metals or metal oxides in the ordered mesoporous channels is challenging as they eventually result in the formation of ~~lumps~~severe aggregates~~,~~ ~~that~~ and ~~block~~block the pores, which limit~~ing~~ their applicability in the catalytic ~~several~~ applications ~~such as catalysis,~~. However, these consequences ~~which~~ depend~~s~~ on the mass transfer of reactants and products.[48b] In an attempt to improve the stabilization of metal species and their loading ~~amount~~efficiency~~s~~ in ~~the~~ MSNs *via*

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co-condensation method, Yi ~~et a~~and colleagues~~l.~~[48b] utilized~~sed the~~ PEO polymer for the encapsulation of metals, in which the interactions between the templating agent and metal resulted in the crown ~~-~~ether type ~~confirmation~~ conformation (Figure~~.~~ 1B). These capsules (metal in combination with PEO) were distributed thoroughly between the template and silica *via* effective protonation of a polymer, due to the hydrophilic characteristics of ethylene oxide ~~under~~ at the acidic ~~conditions~~pH. Further, the hyperbranched ~~polyethyleneimine (~~PEI~~)~~-metal complexes were synthesized in the aqueous solutions, and ~~then~~ they were then introduced into the reaction medium for the ease of adsorption of metals onto the frameworks, resulting in their ~~improving~~ improved encapsulation ~~their loading~~ efficiency~~y and ease of adsorption of metals in the framework~~.[21b] However, the molar ratio of the stabilizer to the surfactant template played a ~~crucial~~key role in the metal loading ~~process~~procedure as the higher ratio of these components resulted in the collapse of the critical micelle concentration (CMC) of the templating agent~~.~~. T~~t~~herefor~~use~~, it is a prerequisite to ~~optimize~~ optimi~~nge~~ the CMC of the template in the self-assembly process. In some cases, ~~the~~ transition metal-chelating surfactant micelles (Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} to Pluronic P123) ~~are~~ can also be utilized as surfactant templates to improve~~for improving~~ the loading efficiency of metals in the MSNs, ~~as well as~~and ~~achieving~~ achieve ~~a~~ better control over the size of MSNs.[56] ~~Although~~ Though this hydrothermal process ~~has been~~is widely applied, the applicability is limited ~~in a few instances~~ as the preparation conditions, in some instances, are stringently dependent on the ~~kinds~~ types of metals used.[16b]

3.2. Post-~~grafting~~ Grafting ~~method~~

The post-grafting approach is another ~~widely used~~ synthetic process widely used to load metals ~~onto~~ into MSNs~~,~~ due to their abundant functionalization surface (both interior ~~as well as~~and exterior), facilitating the immobilization of various organic linkers such as

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organosilanes.[4p] However, the immobilization of any desired metal ~~happens to be~~is favorable based on its interaction with the surface hydroxyl groups (-Si-O-H) of MSNs~~,~~. However, ~~but~~ in some instances, it may lead~~s~~ to the formation of irreversible covalent linkages with the immobilized metal species (-Si-O-M (Metal)), resulting in ~~the de~~~~prived~~creased performance. The i~~The I~~mm~~immo~~obiliz~~ation~~ation of metal species can generally be ~~approach generally involves~~ performed by ~~the~~ dissol~~ution~~ving ~~of~~ the metals/metal oxides/other metal precursors in the organic solvent/water and subsequently ~~immobilized~~ conjugating them onto the pre-synthesized ~~mesoporous silica support~~MSNs under nitrogen,[17] or vacuum.[35] ~~The~~ This ~~post grafting method~~approach is highly advantageous over others as it results in no chances of aggregation of the immobilized MNPs upon thermal treatment and subsequently, preserves the efficacy of the immobilized~~the~~ metal species. More often, various organosilanes such as 3-aminopropyl-trimethoxysilane (APTMS)[42c] or 3-aminopropyl-triethoxysilane (APTES)[14d] are functionalized onto ~~the~~ MSN~~'s~~ surface~~s~~ ~~for~~ to immobilize~~ing~~ various metals of interest~~, to overcome the difficulties in immobilizing such tiny nanoparticles on an inert support.~~[53f, 63] In addition to ~~immobilization of~~ simple organosilane ~~linkers~~anchors, it is ~~also~~ feasible to immobilize ~~the~~ metal species ~~over~~ through ~~the~~ bulk organic molecules, such as dendrimer~~s species,~~[32b] ~~and the subsequently reduced MNP complexes of dendrimers are further immobilized over the MSN support. This strategy is highly advantageous as it can generate ultra-fine nanoparticles which have a substantial fraction of the atoms in bulk due to distinct functional groups and structure of dendrimers.~~[31b] ~~In~~ one case, Somorjai ~~et al~~and colleagues~~,~~[32b] immobilized ~~the~~ Pt and Rh nanoparticles through a dendrimer-templated strategy, in which ~~the~~ MNPs~~nanoparticles~~ of ~1 nm size were ~~synthesized~~ fabricated in the interior of a ~~fourth generation~~ polyaminoamide (PAMAM, fourth-generation) dendrimer (**Figure~~.~~ 2**A), and further, these ~~nanoparticles~~ MNPs-immobilized

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ligands ~~are~~ were loaded into ~~the mesoporous support~~MSNs. This dendrimer-templating strategy ~~had~~ has not only offered ~~the~~ internal cavities for nanoparticle growth upon reduction but also provided a shell, which ~~that~~ prevented ~~their~~ aggregation ~~for the~~and resulted in ~~the~~ enhanced catalytic applications. This strategy is highly advantageous, as it can generate ultra-fine nanoparticles, which ~~have~~contain a substantial fraction of the atoms in bulk due to the distinct functional groups and structure of the dendrimers. Similarly, various o~~Other~~ ~~O~~ther ligands for the ~~metal~~ immobilization of metal species ~~functionalization strategies for metal immobilization~~ include sulfonic acid, and cyclam, among others~~, among others~~.[41b, 70] Although the immobilization is successful in encapsulating metal species, ~~However, Though the approach of utilizing various organic linkers offers several advantages in immobilizing metals over the MSNs, it should be noted that~~ the selection of the organic linker and subsequent miscibility in appropriate organic solvent play~~s~~ a crucial role as the low solubility of the organic linker may ~~lead~~ result in ~~the to~~ altered surface chemistry, and physicochemical attributes of the M-MSNs, leading to ~~of the eventual formulation such as~~ poor suspension ability ~~and~~, solubility issues, and reduced degradability, which limit their applicability in diverse applications~~biomedicine may lead to toxicity issues in biomedical applications~~.[14d]

In addition to the various above-mentioned post-grafting ~~methods~~strategies ~~of utilizing the organic linkers to immobilize diverse metal species over the mesoporous support~~, it is ~~also~~ possible to directly graft the metals ~~on the mesoporous support~~into MSNs without using any anchoring molecules. This strategy ~~could~~ can overcome the ~~above mentioned~~said limitations of solubility as well as the biodegradability issues of organic linkers. The direct immobilization approach is advantageous over ~~the other~~ organic anchors~~,~~ based post-grafting strategies ~~as the fabrication of M-MSNs is processed at~~in terms of reduced synthetic steps. ~~In a way,~~ Zhu and

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colleagues ~~*et al.*~~[51b] proposed a solvent ~~as well as~~and ~~a~~ ligand-free method for the effective immobilization of metals. The metal oxide (herein ZnO) was immobilized by direct~~ly~~ grinding with the prepared pristine SBA-15 material, in which the ~~desired~~ metal oxide ~~content~~ was occluded with the template~~.~~. This strategy enabled the doping of ~~, enabling the loading of large~~ high amounts of metals in the mesoporous channels, resulting in the considerable microporosity in the eventual composites.~~,~~ It was concluded that the mesophase depending on the molecular geometry of the surfactant could be conveniently tailored to different dimensions by utilizing various doped metal~~changing the doping the metal~~ ions in the templates. Similarly, ~~the~~ metal oxides can also be immobilized in ~~the~~ mesoporous materials by applying ~~the~~ a static vacuum maintained at 110 °C.[18] In an attempt to graft various MNPs ~~over~~ into the interior ~~surface~~ of hollow ~~mesoporous silica~~MSNs (HMSNs), Lee and coworkers ~~*et al.*~~[26] fabricated ~~the~~ metal nanocrystals in the void spaces of ~~hollow H~~silica ~~nanoparticles~~MSNs that were pre-functionalized with the Mn_3O_4 surface by a galvanic replacement reaction without the use of any additional reducing agents ~~and~~ or organic linkers. The removal of ~~a~~ part of the inner Mn_3O_4 surface ~~has~~d created a layer of the interior metal surface along with ~~the enormous~~ large void spaces for the efficient deposition of MNPs. ~~The h~~High ~~density~~ densities of the ultrafine noble metals and their alloys were effectively deposited on ~~an~~ the interior metal surface enclosed by a selective mesoporous shell for catalytic applications (Figure~~.~~ 2B)**.** These hollow architectures are highly advantageous over ~~the~~ core-shell structures with a single large core in efficiently depositing the MNPs and in their catalytic performance ~~applications in terms of~~concerning activity, recyclability, and selectivity ~~and catalytic applicability~~. Despite the success in the immobilization of various metals on the mesoporous support, ~~there exist~~this approach faces ~~certain some problems such as~~ the stability issues, including the preservation of metal species ~~as~~

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~~well as~~and loading efficiency of the metal constructs,~~ that which~~ predominantly depend~~s~~ on the possible interactions between the grafted molecules and have remained ambiguous.[16b] Therefore, it is essentially required to address these ~~limitations~~issues, ensuring the efficient loading of the metal species. Moreover, these limitations ~~of post-grafting~~ also restricted ~~its~~the utilization of this strategy ~~over~~compared to other approaches such as ion-exchange and chemical vapor deposition.

3.3. ~~Template ion-exchange (~~TIE~~)~~ ~~method~~

The ~~template ion-exchange~~TIE ~~(TIE)~~ method works on ~~the~~ a principle similar to that of the post-synthetic grafting method, but it differs in utilizing no auxiliary immobilization of organic linkers for the uniform deposition of metal species. ~~In this context, t~~The TIE strategy is often favorable for use to incorporate metal~~lic~~ cations ~~over the~~into ~~mesoporous silica materials~~MSNs by ~~an an~~the ion-exchange process in two ways.[20a] ~~More often, it is carried out in two ways, o~~One method~~of them~~ is by exchanging the acid positions as with solids of Al-MCM-41, which is not very strong compared to other mesoporous supports such as zeolites. ~~The~~ Another ~~way~~method of exchange ~~happens to be favorable~~is ~~other way is~~ by ~~exchanging~~switching the surfactant template cations~~,~~. The latter approach is~~which is~~ comparatively ~~strong~~ more feasible and stable ~~over~~ than the ~~other~~ former method.[16b, 20a, 27b] In a typical TIE method, the mechanism lying behind the immobilization of the metal ions ~~onto the mesoporous support~~in the MSNs is ~~that~~ the exchange of structure-directing template ions in the mesoporous silica (MCM-41) support with the metal ions.[27b] This process generally happens ~~in a sequential wa~~sequentially through an intriguing series of steps. Initially, the template ion and a proton in the

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media ~~are~~ replaced ~~with~~ each other, and ~~then~~ the proton is then subsequently switched with the desired metal ions. Further~~more~~, the remaining surfactant template molecules can be removed by calcination procedures, resulting in the desired ~~metal-impregnated mesoporous materials~~M-MSNs. This process is a convenient and generalized preparation method that is often favorable ~~to~~ for the exchange or ~~the uniform~~ introduction of various metal~~lic~~ cations (Mn, Al, Ti, Cr, Zn, and Zr) uniformly ~~on~~ into ~~mesoporous materials~~MSNs ~~(Mn, Al, Ti, Cr, Zn, and Zr, *etc.*)~~ at a high dispersion rate in ~~the~~an aqueous ~~solutions~~environment. ~~But, t~~The minor disadvantage of this process is that~~, in some instances, it results in~~ the fine-sized particles of various metal species (Fe, Co, Ni, Cu, Ga, Pd, and Pt)~~, over the MSN surface, which may~~ lead to aggregation ~~and subsequently poor efficiency~~ of the MNPs over the MSN surface.[16b] Moreover, ~~it is~~this approach is ~~only~~ highly suitable ~~to operate the~~for ~~the~~ host species, such as MCM-41, that are fabricated using ~~with~~ ionic templates, which is ~~that have been employed for MCM-41 materials, which are~~ appropriate for predominantly exchanging ~~only~~ the metal cations. However, this strategy yields stable, discrete, and homogenous ~~MNPs encapsulated mesoporous silica architectures~~M-MSNs with notable performance efficiency.[16b, 27b]

3.4. Supercritical CO_2 (SC-CO_2)-~~assisted~~ Assisted ~~deposition~~Deposition

The SC-CO_2-assisted deposition approach is ~~another the~~an advanced strategy ~~of operation~~ for immobilizing metal species in MSNs ~~immobilization~~. The supercritical fluid (SCF) technology is perhaps the ~~most~~utmost efficient high-pressure technique that has been commercially used in various applications due to its environmentally benign nature and economically promising character.[71] This technology takes ~~the~~ advantage of ~~the~~ benign solvents, *i.e.,* CO_2 and water, ~~that offer a considerable interest in the~~can be used for ~~the~~ deposition of various guest molecules, ~~including the MNPs, over various inorganic porous supports because of such~~due to the attractive

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properties ~~as~~ of being non-toxic, non-flammable, non-reactive, non-polluting, and cost-effective.[71a] The benign solvents operated at high pressures and optimal temperatures can be used for the convenient deposition of various guest molecules, including MNPs, over various inorganic porous supports. Other advantages of this strategy include rapid diffusion and a high degree of deposition of metals into the mesoporous supports, ~~due to~~owing to the gas-like diffusivity and viscosity of high-pressure SC-CO_2 ~~and~~ along with ~~easier~~ high scalability of M-MSNs preparation. In addition, the liquid-like density of ~~it~~ SC-CO_2 enables the dissolution of a wide-variety of metal species, facilitating ~~the~~ changes in the size and porosity of the nanoparticles and also enable better control over the morphology of the substrates. ~~Moreover, the by altering slight changes in~~ the critical conditions, *i.e.*, the operation~~n~~g pressure and temperature ~~of the high pressure operations may facilitate the changes in the size and porosity of the nanoparticles and also enable better control over the morphology of the substrates~~. Notably, the time of operation is comparatively quicker over the above-mentioned approaches, as the high-pressure conditions drive the deposition onto the inert support. [19a] ~~In one case,~~ Aspromonte and co-workers successfully deposited~~fabricated cobalt oxide~~metal oxide ~~s~~ nanoparticles of Co (CoO and Co_3O_4) ~~nanoparticles~~ over ~~the~~ a mesoporous silica substrate using the SC-CO_2-assisted reactive deposition method.[20a] During the batch operation of the deposition process, an appropriate SC-CO_2 soluble organometallic precursor was ~~opted~~ used and pumped onto a packed substrate ~~at the~~under optimized conditions of pressure and temperature (70 °C and 110 bar) for 3 h, resulting in the efficient deposition of metal species into the MSNs.[20a] ~~However,~~Even though the high pressure of ~~these~~is benign solvent drive the movement of the molecules for their effective deposition onto ~~an~~ inert support like MSNs, the chances of aggregation of the metal species ~~as well as~~and the overall composites are high, which is undesirable for biomedical

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applications of such composites ~~by using this approach~~. Although ~~the~~ this approach resulted in the successful immobilization of ~~-~~ metal Co ~~metal species~~ ~~cobalt~~ over the mesoporous support, ~~the~~ in-depth ~~deep~~ analyses ~~on~~ of the optimization of critical parameters for ~~operating~~ many kinds of metal precursors and the effect of the high-pressure conditions ~~over~~ on ~~the mesoporous framework~~ mesoporous silicas, which result ~~ing~~ in the morphological changes, ~~yet~~ remain to be explored.

In addition ~~to various techniques mentioned above~~, a considerable amount of work involving the ~~encapsulating~~ encapsulation of the metal species ~~on~~ in inert supports, ~~like~~ such as silica has ~~also~~ been ~~done~~ well documented ~~by~~ using the incipient wetness impregnation approach.[72] This strategy is one of the most common methods utilized to encapsulate ~~the~~ metal species ~~s~~ in ~~the~~ micro- and mesoporous materials as it allows the efficient encapsulation of metals in high amounts and is also suitable for ~~with~~ many precursors. However, the applicability of this approach is limited due to the low dispersion efficiency of metals because the interactions between the guest and host molecules often rely on ~~the~~ weak physical interactions during the encapsulation process.[20a] ~~Amongst~~ Overall ~~the discussed approaches~~, the self-assembly/~~encapsulation of metal species through~~ co-condensation approach ~~or self-assembly seems~~ is the most applied fabrication approach due to its high ~~ly~~ ~~feasible~~ feasibility for use ~~for~~ in encapsulating a significant number of metal species ~~metal species~~ with homogenous dispersion ~~as well as no significant aggregation~~. ~~and suitable for significant number of metal species.~~ However, the pore sizes c~~ould~~an be altered depending on the position of encapsulation, ~~where~~ on which the metals in the ~~the~~ siliceous frameworks have no significant influence, while ~~the~~ MNPs in the pores resulting ~~ing~~ in ~~the~~ reduced pore sizes. ~~M~~Moreover, ~~t~~The most common disadvantage of ~~all~~ the ~~se~~ above-mentioned approaches based on hydrolysis, *i.e.*, covalent post-grafting,

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chemical decomposition, complexation, and ion-~~-~~exchange is that the absorption or doping of metal ions onto the silica supports tend to be uncontrolled, leading to ~~the~~ an increase in the size of the eventual composites, *i.e.,* large-sized particles are obtained by the external growth of inorganic precursors over the mesoporous silica surface. However, it should be noted that the selection of a fabrication approach explicitly depends on the M-MSNs requirements and their suitability for applications.

4. Metals in the ~~confined~~ Confined ~~nanospaces~~Nanospaces

~~The~~ Convenient arrangement of different viable forms of the metal species, *i.e.*, metal ions/metal oxides/MNPs, in the~~-confined~~ nanospaces of ~~mesoporous silica materials~~MSNs is systematically discussed ~~in this section~~here-under. Oftentimes~~Herewith~~, the metals ~~can be~~are likely arranged by depositing at various positions of the ~~the mesoporous silica architectures~~ MSNs, such as ~~the~~ core,[32a] dispersed,[14c] or immobilized/grafted *via* functionalization in the mesopores,[38, 45, 48a, 53a, 73] o~~n~~ver the surface,[17] in the siliceous frameworks,[21a, 58, 61a] and as capping agents/gatekeepers (**Fig~~.~~ure 3**).[15f, 27c, 60a, 74] In addition, the extensive ~~available~~ surface area and functionalization surface of ~~a mesoporous substrate~~MSNs facilitate the ~~possibility of~~arrangement of different ~~arranging diverse metal~~metal species~~s~~, species ~~at its~~ multiple positions.[20a, 21d, 61a] ~~Moreover, the Janus-type smart nanoarchitectures are also fabricated by encapsulating the MNPs either directly on the surface or incorporating them into the core of asymmetrically grown silica construct.[75]~~ The possible combinations ~~of metals at multiple positions~~ include metals/metal oxide nanoparticles-deposited core (metal)-mesoporous shell and

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MNPs-immobilized metal-impregnated MSNs, among others.[20a, 21d, 28b, 61a] In some cases, the immobilized metal ions in the mesopores ~~of MSNs are~~ can be subsequently ~~reduced~~ transformed to their corresponding MNPs ~~to augment by providing the specific conditions for the enhancement of~~ their physicochemical properties and performance efficiency ~~as the nanoparticulate forms tend to possess~~ due to the high surface energy and other morphological ~~as well as~~ and physico-chemical attributes of nanoparticulate forms over the~~ir~~ counterparts~~such as light absorption ability and others~~.[73] However, t~~T~~his ~~kind~~ type of transformation is predominantly optional based ~~arrangement of metals in the mesoporous substrate predominantly depends~~ on the ~~critical~~ requirements for application~~application of MSNs~~. Moreover, the Janus-type smart nanoarchitectures can also be fabricated by encapsulating the MNPs either directly on the surface or by incorporating them into the asymmetrically grown silica core.[75] Herewith, we provide ~~an~~ a comprehensive overview of the possible combinations of ~~metal encapsulated onto MSNs~~M-MSNs ~~including core-shell type architectures, metals in the mesopores, impregnated in the siliceous framework, as capping agents/gatekeepers, metals at multiple positions and Janus-type architectures~~ (Figure~~.~~ 3).

4.1. Hierarchical ~~Core~~Core-~~shell~~ Shell ~~type hierarchical a~~Architectures

In the past decade, several hierarchical architectures based on MSNs have been synthesized through ~~the~~ modifications ~~of in~~of the Stober process for diverse applications.[4j] Further~~more~~, it is also increasingly recognized that the ~~fabrication of~~ mesoporous silica shell coating ~~coating~~ over the solid silica spheres or ~~other~~ diverse metal/metal oxide nanoclusters often facilitates the ~~enhancement~~ improvement ~~of their~~of their stability at high processing temperatures, ~~and~~ and is of ~~could be of~~ particular interest in catalytic ~~as well as~~and diverse biomedical applications.[14e, 21d, 28b, 31-32, 32c, 76] ~~More often~~Often~~times~~, the core-shell architectures are conveniently synthesized

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using a ~~single~~ single-step procedure, without the requirement of additional anchoring of organic ~~anchors or specific~~ ligands for fabricating the porous silica shells over the metal species, while the deposited negatively-charged silica relyies on ~~is often facilitated by the~~ electrostatic interactions ~~between the silica and~~with the positively-charged ~~the~~ core metals.[32a, 76c] In some instances of using silica species as the core, the pore-directing surfactant templates are coated over the solid silica ~~spheres~~ cores for the efficient deposition of silica and the convenient generation ~~convenient fabrication of core-shell nanostructures as well as the efficient generation~~ of mesopores, as both~~because~~ the core~~, as well as~~ and the shell, possess a similar ~~surface~~ charge. However, it should be noted that the operating conditions during fabrication should be optimized to generate ~~the~~ core-shell ~~structures~~ architectures with different shapes (~~such as~~ spheres, cubes, ~~rods,~~ and rods, ~~cubes,~~ among ~~and~~ others.[14e, 14f, 28b, 32a, 32c, 68, 77] ~~The fabrication of these M-MSNs core-shell architectures offers numerous advantages over other traditional approaches such as organic surfactant coating methods.~~ Unlike the~~se~~ conventional organic polymer or surfactant coating approaches ~~over~~used for MNPs, the silica shell ~~over~~ coating of the MNP cores ~~silica shell~~ offers numerous benefits to the metals, such as increasing the thermal stability, avoiding ~~the~~ undesired aggregation and premature leakage, and providing robust protection against ~~the~~ nanoparticle sintering, among other effects.[28b, 64]

~~The~~ ~~H~~hierarchical ~~se~~ core-shell ~~structures~~ architectures are generally fabricated by ~~depositing~~ generating ~~the~~ a mesostructured silica shell over the ~~core~~ MNP~~s~~ core~~, that covered~~mediated by the ~~with~~ CTAB molecules *via* the ~~base-catalyzed~~ hydrolysis of TEOS and ~~subsequent~~successive co-condensation of silica over the surfactant (CTAB) molecules in the alkalescent environment.[14e] ~~Herein,~~T~~he~~ the versatile CTAB template ~~that~~ deposited over ~~the~~ MNPs acts not only as a ~~structure~~ structure-directing molecule but also as a ~~stabilizing agent~~ er, offering

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~~significant~~substantial protection to the MNPs from ~~oxidizing~~ oxidation ~~them~~ in the aqueous phase. ~~In addition~~Additionally ~~to CTAB~~, ~~in some cases,~~ various shielding agents ~~are~~ can also be utilized ~~for~~ to protect~~ing~~ the ~~surface of~~ MNP surface~~s~~ before depositing the ~~mesoporous~~ silica shell to safeguard ~~their~~ the unique properties of metal species.[32a] ~~For the first time~~ , Lin and colleagues ~~*et al.*~~[32a] fabricated Pt/poly(vinyl pyrrolidone)(PVP)@MCM-41 core-shell architectures for the first time by using the ~~a~~ liquid-phase self-assembly method to ~~enhancing~~ enhance the lifetime and reusability of the encapsulated Pt nanoparticles (**Figure~~.~~ 4**A and B). Initially, the Pt nanospheres were synthesized using a protective agent PVP under a solvothermal process~~. Further, these nanoparticles~~ , and they were ~~which were was~~ then coated with the silica precursor using the CTAB template ~~in the~~ under alkaline conditions. The PVP~~,~~ and ~~as well as~~ CTAB in the ~~the~~ MSN ~~sample~~s ~~s,~~ were ~~eventually~~ finally removed by calcination ~~for~~ to allow~~ing~~ the Pt nanoparticles to exhibit~~ing~~ ~~the~~ efficient catalytic properties ~~of Pt nanoparticles~~. The ~~Fabrication of m~~mesoporous silica shell coating over the Pt nanoparticles significantly protected their extensive surface area for a more extended period ~~of time~~ at the ~~catalyst's~~ operating temperature of the catalyst, ~~which could~~ could facilitate ~~their~~its ~~be used as~~ reusability~~le catalysts~~.[78] In this vein, tremendous efforts ~~in~~ over the past decade have been dedicated to the development of various core-shell architectures using various metal species for diverse applications. However, ~~in most of the instances, it is evident that~~ the lack of control over the surface morphology, textural properties including the pore size and orientation, and ~~the~~ regular shell thickness of the composites, has~~.~~ often limited their ~~efficient applicability~~use in ~~diverse~~ various applications. In an attempt to address these limitations, Kim ~~et al~~and colleagues~~.~~[28b] fabricated ~~the~~ metal/metal oxide and MSN-based ~~metal/metal oxide~~ core-~~mesoporous silica~~ shell nanohybrids using the wet chemical approach for various applications. ~~These s~~Spherical ~~core-~~

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~~shell~~ architectures with different core materials (SiO_2, TiO_2, Ag, and ZnO) and ~~the~~ silica shell thicknesses ~~of mesoporous silica~~ ranging from 20 to 50 nm (Figure~~.~~ 4E) were prepared. In addition, ~~the~~ vertically-aligned shells of mesoporous silica were deposited over the spherical silica core nanoparticles through a three-step approach: i) synthesis of a silica core; ii) deposition of the organic-inorganic composite layer over the core, and iii) removal of the surfactant through ~~the~~ a calcination procedure (Figure~~.~~ 4D).[28b] Moreover, the functionalities and reusability of the core (SiO_2)@mSiO_2 shell architectures were explored by incorporating various metal ions, such as Ag, Mn, and Ti, into the porous mesoporous silica framework. However, ~~it should be noted that~~ the homogeneity of the mesoporous silica shells and the eventual morphological attributes of the composites utterly depended on the dispersion ability of the core particles and also their stability in the corresponding pH value. It was concluded that this strategy could be extended to fabricate spherical architectures with more homogeneity for diverse promising applications, specifically mentioning the degradation of dyes. ~~In addition~~~~Following that~~Since then, several groups have reported ~~the a similar~~ similar types of ~~core shell~~ architectures using various metal species as cores for diverse applications, including the adsorption of heavy metals, catalysis, drug delivery, and imaging, among ~~and~~ others ~~(Fig. 4 F and G)~~.[14e, 31-32, 32c, 42e, 42f, 76a, 76b, 79]

In addition to ~~some~~ specific MNPs-encapsulated core-shell strategies ~~in MSNs~~, it is highly ~~also possible~~feasible to encapsulate diverse metal species in the cores of ~~mesoporous silica~~MSNs ~~cores~~. The synthetic advances of bimetallic species incorporation have opened some new paradigms by offering advantages over traditional colloidal ~~synthe~~preparation~~sis~~ processes.[64] In a generalized ~~colloidal~~ synthesis ~~of bimetallic species~~, organic surfactants ~~are~~ can be covered over the MNPs to protect the bimetallic species. However, they tend to aggregate ~~during the~~under harsh conditions and ~~amass~~accumulate with the reactants ~~and~~, thus resulting in ~~the~~ poor

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performance efficiency. Moreover, the conventional encapsulationfabrication of bimetallic species directlystraightdirectly in the mesoporous shell through the conventional way of encapsulation also suffers from a significant limitation of profoundly challenging in the removal of the organic surfactants. Inspired by the fact that reliesiance on the structural similarities between the MNPs MNPs capped with organic surfactants and the inorganic shells in possessingfor producing the functionalized surfaces, Pei and coworkersat al.[64] synthesized the bimetallic species-incorporated mesoporous silica shells using the a novel seeded growth approach to addressing the critical issues associated with the conventional coating strategies, including such as the removal of the organic surfactant bound to the bimetallic shells. Furthermore, motivated by the various significant considerations of the available core-shell approaches strategies available, the authors initially synthesized the $Pt(M_1)@mSiO_2$ core-shell nanoparticles, and then the secondary metals (M_2 - Pd, Rh, Ni, or Cu) were introduced into the $Pt(M_1)@mSiO_2$ for the seeded growth, which eventually resulted in the bimetallic core-shell nanoparticles ($M_1M_2@mSiO_2$) throughin four different ways methods by substantial annealing and etching of the metals (**Figure 5**). However, the critical optimization of the metal species ratio and the interactions between the metals played a vital roles in achieving the loading efficiency and desired size of the composites. It was concluded that through the aid of from the mesoporous silica layer over the bimetallic species in acting as an inorganic capping agent and stabilizer as well as capping shell, this approach had has significantly provided tunability in of the bimetallic structure and composition, promoting the stability and eventual size of the composites. Further advancements in of this strategy could can lead to the design of enormous diverse intermetallic nanoarchitectures for diverse various applications.[64]

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4.2. Immobilized in the mesoporesMesopores

Well-ordered mesoporous architectures of ~~MSNs~~ silica have attracted the enormous interest ~~from researchers~~ over other inorganic nanomaterials as they can ~~be able to~~ encapsulate and carry various substrates ranging from ~~tiny~~ small-sized ~~molecules like small molecule~~ therapeutic~~s~~ molecules to biomacromolecules, such as enzymes in their porous gallery. However, the incorporation of these species often relies on the pore size and~~s well as~~ volume and the specific interactions between the host and guest molecules ~~that~~, which play ~~a~~ significant role~~s~~ in determining their loading efficiency.[4m] Based on these considerations, several groups have reported the immobilization of metal~~lic~~ species in the mesopore~~s~~ channels for diverse applications, which ~~are~~ is of particular interest in ~~the catalytic~~ catalysis and biomedicine~~al field~~.[14c, 30a] However, it should be noted that the direct immobilization of MNPs is often ~~difficult~~ challenging, as the~~ir~~ ~~size and~~mesopore ~~pore~~ size should be larger compared to the MNP size, allowing ~~of the MSNs play a crucial role in~~ the~~ir~~ access and effective deposition of MNPs in the porous gallery of MSNs. To address this size-related issue ~~More often, due to size related concerns~~, the ionic forms of noble metals are initially inserted into the pores, such that the deposited ions can be then reduced to ~~its~~ the corresponding nanoparticulate form within the pores of ~~the mesoporous silica structures~~MSNs.[30a] The fabrication of MNPs inside the porous architectures of MSNs is highly beneficial, as they ~~are~~ can be easily engineered to provid~~inge~~ increased surface area~~, and increase the surface area of the eventual composite~~, in which the shape-selective behavior of MNPs and other attractive physicochemical properties of MSNs can be pooled ~~for~~ to ~~the~~ achiev~~inge~~ the ~~the~~ exceptional performance of the MNPs.[14c]

In general, t~~T~~he convenient fabrication of MNPs in ~~the~~ mesopores is ~~generally performed~~achieved ~~by~~ using various ~~ways~~ strategies such as the chemical vapor deposition (CVD) method, ~~and~~ chelating template-assisted ~~fabrication~~ approach, and nanocasting strategy~~.~~

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~~among others.~~[14c, 38, 45, 48a, 53a] In the CVD method, the metal ions are initially conjugated ~~to~~ onto the surface, *i.e.,* both interior, ~~as well as~~and the exterior, of the mesoporous silica support, and ~~then~~ the metal~~lic~~ substrates are then chemically ~~decomposed~~ transformed to their respective MNPs.[14c] However, ~~it~~ this approach suffers from a minor disadvantage, *i.e.,* the yield of metal deposition in the pores is low. Another ~~way~~ method of metal immobilization in the mesoporous support is the chelating template-assisted fabrication of MNPs.[38, 48a, 53a] This generalized synthesis corresponds to the fabrication of hydrophobic templates as metal ion carriers by combining the functions of pore formation and ~~mesoporous silica~~ structure direction, ~~on~~ facilitating the efficient deposition of metal precursors in the mesopores by evenly distributing them after calcination. Moreover, the incorporation of metal species *via* this process also favors the mesophase transformation. An intriguing series of studies based on the fabrication of ~~cobalt oxide~~diversiform metal oxides of Co/mesoporous silica composites ~~has been~~~~were~~was reported using this method by Niu *et al.*[38] Initially, the structure directing surfactant molecules were chelated with the metal oxide in the solution, and then the co-condensation of silica over the surfactant eventually led to the confinement of various metal oxide ~~nanoparticulate forms~~ forms of Co ~~cobalt oxide nanoparticles~~(Co(III) and Co(II)) in the mesopores. ~~On the other hand, various d~~Different organosilanes ~~are~~ were also immobilized in the ~~intrachannel surface of mesopores~~ mesoporous channels to increase ~~its~~ the hydrophilicity, ~~which~~ enable~~s~~ling the ~~ease~~ easy ~~of~~ penetration of metal precursors. Moreover, this modification ~~enhances~~ enhanced the surface reactivity and subsequently ~~augments~~ augmented the immobilization of metal~~lic~~ species in the mesopores through ~~the~~ electrostatic interactions.[53f]

4.3. Impregnated in the ~~framework~~ Frameworks

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Undoubtedly, MSNs with attractive properties are of great interest ~~in~~ for diverse applications as a carrier due to their low density and high colloidal, thermal, ~~as well as~~and mechanical ~~stability~~stabilities.[61b, 80] However, the essentially amorphous silica in the channel wall of MSNs ~~that~~ imparted by the neutral character of pure silica limits its applicability in some applications, such as in catalysis and adsorption, among others.[20a] In recent times, much attention has been given to~~ained in~~ altering the siliceous frameworks ~~of MSNs~~ by incorporating ~~diverse~~various metals, which offers ~~the~~ desired properties ~~on~~~~into~~ these mesostructured architectures ~~of silica~~. In ~~the past two decades~~recent times, a great deal of effort~~s~~ has been ~~put forward~~made regarding ~~in~~ the advancement of MSNs ~~as a carrier~~ involving the impregnation of active metal species onto their silica walls, owing to their enormous potential for use in diverse applications.[21a, 58, 61a, 81] Aluminum was ~~at first~~ incorporated into the silica wall for the first time through a simplified co-condensation method, by dispersing the Al ~~atoms~~ homogeneously in the ~~silica~~ siliceous matrix.[81] The ~~incorporation~~integration of alumina species in the silica wall has ~~ha~~offered ~~d added~~ ~~the~~specific advantages to the MSNs, such as ~~improved~~ improving the chemical functionality of alumina to MSNs, their surface acidity, and their performance in catalysis. However, the impregnated metal species in the pore walls of the silica significantly ~~had~~ reduced the concentration of silanol groups available to adsorb the required amount of alumina in the pores. For instance, this could be addressed by ~~this was solved by~~ the presence of hydroxyl groups of the first layer of grafted alumina, which would~~, which~~ stabilize~~d~~ the additional alumna layers demonstrating ~~the~~ excessive loading of alumina in the stable MSNs. Nevertheless, ~~a~~ critical care should be taken in optimizing the reaction conditions~~,~~ concerning the ~~reactants ratio~~atio of the reactants of metal species ~~as well as~~~~and~~to silica as ~~the~~ higher amounts of metal may lead to the separation of individual metal oxide nanoparticles and the distortion of the siliceous frameworks

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and, resulting results in the separation of individual metal oxide nanoparticles and disordered siliceous framework in the irregular shapes.[20a] Another important critical feature to be considered during thewhile impregnation impregnatingof metal species in the silica walls is that the mesoporous support material should possess wide pores and a large pore volume to overcome circumvention of substantial narrowing of pores that, which subsequently influences the grafting of other guest species. In a wayFor instance, other metals such asvarious transition metals such as cobaltCo, ironFe, copperCu, and nickel Ni were can bealso impregnated in the silica walls of MCM-41 molecular sieves for various diverse applications.[21a, 58, 61a, 82]

As mentioned earlier, the unique siliceous frameworks and pore channels of mesoporous silica materialsMSNs aid them as a carrier for delivering various active therapeutic moieties or other agents for biomedical applications. However, preceding reports indicated that the loading of active moieties generally relies on the affinities between the host and guest molecules, which are significantly accomplished through the weak interactions between them, resulting in their low loading efficiency due to the physical adsorption in the pores and their simultaneous exchange with the surrounding ions during the loading process.[4o, 83] In this context,In one case, the siliceous frameworks of the traditional mesoporous silica frameworkMSNs for drug delivery was were modified doped using with the divalent metal, Cu, for their use in drug delivery, which substantially enhanced thefor the enhancement of loading efficiency of the drugs through establishing the coordination interactions.[21a] In addition, tThese coordination interactions between the metal and the guest molecules also acted as a responsive switch for their efficient release, specifically in the acidic microenvironment of tumors (**Figure. 6**).[58] Moreover, the positive charge imparted by the impregnated transition metals to MSNs the siliceous framework improved the cellular internalization efficiency by enhancing the interactions with the negatively

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negatively-charged biological membranes ~~for drug delivery application~~.[21a] The structural characteristics of the metal in the mesoporous architecture were systematically explored by the electron spin resonance (ESR) studies, demonstrating that the Cu species were axially impregnated in the framework with the siloxyl groups of MSNs. In addition, these results suggested that the Cu in the siliceous frameworks ~~had~~ displayed a distorted square pyramidal octahedral coordination ~~in the siliceous framework~~ due to the Jahn-Teller effect. ~~Furthermore, the~~ *In vitro* ~~metal~~ release ~~studies~~ experiments of metal in combination with the ESR measurements confirmed that the Cu(II) species in the framework were merely stable with no significant changes in the g values. In addition to effective loading as well as delivery of drugs, it is ~~also~~ fascinating that the loaded transition metals in the silica walls, for instance, Cu and Fe, assisted the delivered drugs in enhancing their therapeutic efficiency through synergistic effects by participating in the ~~augmentation of~~generation of reactive oxygen species (ROS) levels through a Fenton-like reaction.[21a, 58]

4.4. Capping ~~agents~~Agents/~~gatekeepers~~Gatekeepers

In recent times, MSNs-based intelligent delivery vehicles have garnered enormous attention ~~from researchers~~ for biomedical applications due to their low toxicity, site-specific delivery, efficient biodistribution, and ~~bioavailability~~ enhancement of the bioavailability of drugs and their therapeutic efficacy.[69] ~~Further~~In this vein~~more~~, ~~the~~ tremendous progress has been evidenced by ~~the~~ advancements of these vehicles achieved by appropriately fabricating the ~~surfaces of~~ MSN surface~~s~~ to enhance their delivery efficiency. One ~~of~~ such modification~~s~~ includes ~~the~~ engineering of the mesopore surface by immobilizing ~~the~~ capping agents, which substantially avoids the premature leakage of the encapsulated therapeutic cargo. In this framework, there has been enormous interest in the development of gate-like elements ~~that~~, which can be ~~have been~~

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controlled photochemically, ionically, and electrochemically for drug delivery applications.[74c] In addition to safeguarding the therapeutic guests ~~the protection of drug cargo~~, these responsive metallic caps act as switches/nanovalves ~~and~~ in triggering the release of drugs specifically at the desired site, which ~~are~~is of particular interest in biomedicine. Another advantage of these metallic caps on the surface of the mesopores is that they facilitate ~~the~~ a high loading efficiency of drugs into the mesopores.[84] Various metal species used ~~act~~ as capping agents ~~include~~ (iron oxide, ~~cerium oxide~~CeO_2, CdS~~cadmium sulphide~~, and ~~gold~~ Au and ~~silver~~ Ag nanoparticles)~~,~~ ~~among others, that~~ have been engineered *via* tethering molecular or supramolecular gating groups, including ~~the~~ acid-labile, light-sensitive, molecularly-responsive linkers, which respond to a specific trigger~~, and~~, allowing~~s~~ the ~~specific~~ release of guest molecules from the ~~the~~ mesopores.[15f, 27c, 60, 74, 84-85] ~~Moreover, these nanoparticle-capped MSNs have been utilized for various applications, which are of particular interest in biomedical and catalytic fields.[60b, 84, 86]~~ In one case, Lin *et al*.[60b] developed a controlled drug release system based on ~~gold~~Au-capped MSNs for the photo-induced intracellular release of paclitaxel (**Figure~~.~~ 7**A). Initially, the surface of the Au~~gold~~ nanoparticles was functionalized with a photosensitive linker (thioundecyl-tetraethyleneglycolester-*o*nitrobenzylethyldimethyl ammonium bromide, TUNA) and they were capped ~~them~~ onto the negatively-~~ ~~charged MSNs. Upon irradiation, the photolabile linker was dismantled and subsequently released the guest molecules by uncapping the mesopore. ~~This~~ These ~~triggered~~ triggered-release characteristics of the metal caps facilitated a "zero premature release" ~~feature~~ featur~~ing~~e for~~of~~ a highly toxic drug~~ cargo,~~; ~~and~~ however, the drug-loaded containers were extremely biocompatible in the absence of light irradiation. ~~Moreover~~~~Following~~ ~~that~~Afterward, ~~they~~ the researchers developed various nanoparticles such as iron oxide, and ~~cadmium sulfide~~CdS, for use as metallic caps on MSNs for the controlled delivery of

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neurotransmitters and other drug molecules for ~~various biomedical~~diverse applications in medicine.[60a, 85d] Similarly, various ~~external stimuli based gold Au capping models~~gatekeepers ~~that~~ responding to different external stimuli have also been proposed, such as pH-responsive ~~gold~~Au-capped MSNs achieved through an acid labile linker, ((3,9-bis(3-aminopropyl)-2,4,8,10-tetraoxaspiro[5.5]undecane))[86] ~~through~~ with which the release of drug cargo from the mesopores ~~is~~ can be attained only ~~at the~~in low pH environments (Figure~~.~~ 7B). ~~Together, t~~The use of these intelligent supramolecular functional structures as effective capping models substantially facilitates the release of guest molecules at the desired site.

Despite the success in the generation of effective capping models ~~as~~ for smart drug delivery~~supramolecular functional structures over mesopores in driving the release of guest molecules appropriately to the desired site~~, ~~there exists certain~~ these innovative constructs suffer from limitations ~~for~~ of their potential utility in ~~the~~ advanced applications such as a lack of reversibility~~ and~~, operational flaws in the physiological environments and the appropriate use of a unique stimulus for the release of ~~a~~ specific ~~drug release of~~ drugs.[74c] Motivated by these considerations, there has been ~~an~~ increasing interest in the development of multi-responsive molecules for ~~metal~~ capping metals over MSNs, such that the ~~gate~~ gate-~~holding~~ anchoring linkers respond to multiple ~~external~~ stimuli ~~and they~~, ~~display~~exhibiting the release of therapeutic cargo in ~~the aqueous~~ physiological environments. For instance, a~~A~~n innovative nanoscopic molecular movable gate-like switch based on ~~the~~ a reversible borester link ~~that~~ was fabricated ~~responds~~ to ~~combinatorial~~ respond to simple external stimuli such as near-infrared (NIR)-light and pH for the prompt delivery of drug cargo ~~from the mesopores~~.[74c] Further, ~~the as~~ a ~~proof~~ proof-~~of~~-of-concept relevant to the gating effect in water was investigated. In addition to the irreversibility of immobilized gatekeepers, another significant limitation of smart nanocontainers

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that should be taken into account ~~during the fabrication of effective capping agents~~ is the adsorption of loaded molecules onto the metallic cap surfaces, which may result in ~~the~~ reduced performance~~. Moreover, it may~~ and influence their stability during application. In an attempt to clarify these ~~critical~~ issues, Fu ~~et al~~and colleagues~~,~~[87] developed ~~the~~ innovative ~~Redox~~redox-triggered smart nanocarriers based on installing ~~these~~ supramolecular switches, *i.e.,* mono-functionalized β-cyclodextrin with ~~the~~a ferrocene moiety (Fc-β-CD), over the surface of ~~the~~ MSNs~~,~~. The switching approach ~~which undergoes~~ exhibited a reversible transition from the self-complexation to self-dissociation in the presence of redox stimuli ~~from self-complexation to self-dissociation for~~to ~~regulating~~ regulate the ~~entrapped~~ encapsulated organic corrosion inhibitors~~,~~ ~~that~~ rendering ~~a reliable~~consistent and ~~long lasting~~ incessant protection of ~~aluminium~~ Al alloys with excellent anti-corrosion performance (**Figure~~.~~ 8**). Al~~T~~though~~,~~ the bi-layered nanocomposite Ce(IV)-doped zirconium oxide (ZrO_2)~~-~~ SiO_2 sol-gel coating ~~had~~ has exhibited ~~the~~ satisfactory, self-healing functionality, the release ~~as well as~~and encapsulation of the guest cargo (*p*-coumaric acid (CA)) in the mesopores utterly depended on the redox potential of the environment.

4.5. Metals at ~~multiple~~ Multiple ~~positions~~Positions

It is increasingly recognized that ~~the~~ metal species~~,~~ in combination with ~~the~~a mesoporous support~~,~~ offer enormous advantages ~~for~~ due to their utility in diverse applications. In addition, tremendous progress has been evidenced by ~~the~~ advancements in the generation of diverse composites of M-MSNs. One ~~of~~ such advancement~~s~~ is the combination of two or more metal~~lic~~ species in the ~~the single~~a support, offering numerous additional advantages such as one ~~of them~~species ~~metals~~ augment~~s~~ing the loading efficiency of the other metal and ~~synergizes~~ synergi~~ng~~ed ~~the~~ beneficial properties for ~~the~~ improve~~ment~~ed therapeutic benefits ~~of the functionalities, among others~~.[20a, 21d] In this context, various combinations of metals ~~in a system~~

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have been reported such as metal/metal oxide in the pores ~~as well as~~and in the silica wall,[20a] metal grafted over the surface ~~as well as~~and impregnated into the framework,[61a] metal as the core ~~as well as~~and in the mesopores of MSNs,[21d] and metal as a cap over the mesopore ~~as well as~~and in the core of MSNs~~, among others~~.[85e] ~~In an example from~~ Boix and colleagues ~~*et al.*~~[20a] ~~the~~ dispersed metal oxide nanoparticles of Co (~~-~~CoO and Co_3O_4) ~~cobalt oxide nanoparticles~~ in Al-MCM-41 ~~by~~ using the SC-CO_2 reactive deposition method. ~~They~~They demonstrated that ~~has~~d ~~shown~~ significantly higher amounts of ~~cobalt~~ Co deposition in Al-MCM-41 were observed compared to that ~~of~~ in the Al-free support, indicating ~~that~~ ~~that~~ the Al in the mesoporous support ~~had~~ enhanced the incorporation of ~~metal cobalt~~ Co species ~~in the mesoporous support~~. In addition to the loading efficiency of metal species, ~~it is evident that the~~ multiple species can significantly enrich the functionalities of MSNs over the effect from a single metal-supported ~~mesoporous support~~MSNs. ~~In one case,~~ Deng and coworkers ~~*et al.*~~[21d] synthesized ~~the copper~~ Cu metal-immobilized magnetic MSNs with the ~~a~~mesoporous silica shell over a magnetite core ~~and mesoporous silica shell~~ for peptide enrichment application. MSNs with perpendicularly~~-~~ aligned mesoporous channels over the iron oxide core were fabricated by a ~~surfactant~~ surfactant-templating method and the interior mesopore surface ~~of mesopores~~ was further modified with ~~the copper~~ Cu ions *via* a surface-grafted carboxyl group-containing spacer for ~~their~~ efficient chelation ~~in the mesopores~~. These intelligent carriers, combined with the attractive properties of iron oxide ~~in the core~~, their tunable porosity, and the specific affinity of ~~copper~~ Cu ions towards peptides, significantly enhanced the peptide enrichment ~~process~~. ~~In another study~~Similarly, Zhang and colleagues ~~*et al.*~~[85e] developed ~~the~~ a multifunctional theranostic platform based on MSNs by incorporating multiple metal~~lic~~ species such as ~~silver~~ Ag nanoparticles (Ag-NPs~~SNPs~~)

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and ~~gold~~ Au nanorods (~~GNRs~~Au-NRs) at different locations of the mesoporous support for synergistic ~~enhancement of the~~ cancer ~~therapeutics~~ therapy (**Figure~~.~~ 9**).

~~W~~While~~n~~ focusing on the augmentation of functionalities of the carrier through synergistic efficacy, it is highly required to address the compatibility and toxicity issues concerning the ~~incorporation of~~ multiple metal species in the inert support for biomedical applications. In an attempt to address these critical issues, recently, ~~our group~~we ~~had~~ designed ~~the~~ smart nanocontainers based on multiple metals-grafted MSNs for the exploration of new antibacterial modalities to combat ~~the~~ antibiotic resistance only in the presence of light.[61a] ~~On the other hand,~~ ~~t~~The ~~silver~~ Ag ions were reduced to Ag-NPs ~~silver nanoparticles (SNPs)~~ over the surface of the MSNs, and ~~which~~ ~~had~~ facilitated the specific release of ~~silver~~ Ag ions ~~and~~ toward efficient~~ly~~ ablation of~~ed~~ the gram-negative bacterial strains *via* membrane damage, indicating that the ~~silver~~ Ag nanoparticles on the surface of the MSNs ~~had~~ expanded the phototherapeutic spectrum of curcumin. ~~Thus~~Therefore, these ~~decorated~~ metal species ~~over~~ decorating the MSN surface not only ~~facilitates~~ facilitated ~~the~~ synergistic efficacy but also ~~promotes~~ promoted the therapeutic benefits ~~to~~ of the existing treatment modalities. Very recently, we designed MSNs-based dual-metal (Cu and Fe) doped, biodegradable Janus-type ~~(sphero-ellipsoid)~~ nanoreactors for ~~chemodynamic~~cancer therapy. Interestingly, the convenient doping of~~arrangement of~~ two ~~different~~ transition metals in the silica~~c~~eous frameworks~~ walls~~ resulted in the altered shapes (sphero-ellipsoid), attributing to the~~ir~~ positive charge and convenient distribution of metal species in the intrinsic siliceous frameworks. The coordination interactions with the guest species specifically facilitated their release in the acidic microenvironment of cancer and further augmented the anticancer efficacy ~~along with~~through the generation of cytotoxic ROS through Fenton-like chemistry based chemodynamic therapy. Although it is quite impressive in enriching

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the functionalities by using multiple metal species, which, however, require in-depth investigations to ensure their safety and performance attributes.

4.6. Janus-type ~~architectures~~Architectures

~~The a~~Asymmetric nanostructures, based on various hybrid compositions often referred to as Janus architectures, have attracted ~~the~~ immense interest from researchers in ~~diversified~~ diverse fields of science due to their high surface area, better performance, and high stability~~, among others~~.[75a, 75b, 88] ~~Moreover, t~~The M-MSNs ~~based with this kind of~~ asymmetric architectures have emerged very recently~~,~~ to address ~~the~~ a significant limitation of the lack of enough room for loading ~~the~~ guest molecules, associated with ~~the~~ conventional Janus particles (dense polymers and silica)~~., *i.e.,* based on solid or dense polymers and silica, *i.e.,* the lack of enough room for loading the guest molecules such as therapeutic and contrast agents~~.[75a, 89] ~~On the other hand~~~~Moreover~~In this context, ~~the~~ conventional MSN carriers~~, as well as~~and hollow ~~-~~structured nanocarriers ~~and others~~ with symmetric geometry~~,~~ are among them as they face~~also facilitate provide limited space and~~ difficulty in loading multiple therapeutic agents for synergistic efficacy due to the limited space. Thus, developing a versatile design with multiple compartments for the independent storage of multiple therapeutic agents ~~is~~ has become a ~~highly~~ highly anticipated task~~desired~~. ~~Recently, t~~~~The r~~emarkable progress ~~in the past couple of years~~ has been evidenced by the development of numerous designs of asymmetric Janus-type architectures, which are of particular interest in various fields~~ including biomedicine and catalysis~~.[75a] These innovative carriers~~y~~ ~~facilitate~~can be used for the co-delivery ~~efficacy~~ of multiple drugs by ~~avoiding~~circumventing their compatibility issues with drugs possessing different physiochemical properties. Moreover, there ~~is area chances~~is ~~the~~a possibility ~~to develop a~~for such a delivery system that can efficiently deliver different agents at different desired sites.

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~~In addition, i~~It should be noted that ~~the~~ fine tuning of the surface tension and lattice ~~mismatch~~disparity ~~between~~amid the silica and the core particles resulting in Janus architectures is often ~~difficult~~challenging due to ~~the~~ the amorphous nature and isotropic properties of silica. However, this ~~could~~ can be achieved ~~better~~ *via* a liquid/solution-phase synthesis route, which results in the fabrication of inorganic crystals. In addition, the chemical composition and crystal structures play a crucial role in the formation of Janus architectures. In this context, several upconversion nanoparticles (UCNPs) have been utilized in the synthesis of MSNs-based Janus-type architectures as optical probes for ~~biomedicine~~ biomedical applications~~,~~ because of their efficiency in emitting ~~the~~ high energy photons upon excitation by low~~-~~energy radiation.[90] For ~~example~~instance, Zhao and colleagues ~~*et al.*~~[75a] reported ~~the complex and multifunctional~~ versatile dual-compartment Janus~~-~~MSNs achieved for the first time utilizing ~~the~~ UCNPs (NaGdF4:Yb,Tm@NaGdF4) ~~by~~ through a novel anisotropic island nucleation and growth method, ~~with the~~producing ordered mesostructures (**Figure~~.~~ 10**). Initially, the UCNP core was coated with silica and then with mesoporous silica *via* the Stober method. Further, ~~the~~ heterogeneous nucleation followed by the anisotropic growth of MSNs~~, which~~ significantly resulted in ~~the~~ Janus architectures yielding ~~the~~ dual-independent mesophases for the loading ~~the~~ of dual guests ~~in them~~, respectively. The ~~utilization~~use of two different silica precursors ~~both~~, TEOS and ~~another~~ organosilane [bis(triethoxysilyl)ethane, BTEE], ~~resulted~~ensued in ~~the~~ anisotropic polymerization ~~on~~ over the core-shell ~~surface of the core-shell~~ due to their ~~distinct~~different chemical ~~structures~~ functionalities and optimizing the ~~synthetic~~ reaction conditions for the formation of a single crystal cubic mesophase domain.[75a] Further modifications were made by immobilizing various functional groups over MSNs for the responsive release of guest molecules, which could find

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~~their ways~~applications in ~~diverse~~ biomedic~~al applications~~ine~~biomedicine toward drug delivery, and imaging, among and others~~.

In addition to the generation of Janus-type structures *via* chemical-based synthetic approaches, there has been increasing interest in the past decade for their generation by various other approaches, such as vacuum sputtering, and electron beam evaporation ~~and vacuum sputtering, among others~~.[75b, 75c] Unlike the asymmetric Janus composites containing a multicompartment mesoporous silica model ~~that~~ as described above, researchers have developed the direct and ~~irregular~~uneven deposition of the metal species (Pt and Au) as layers on~~ver~~ the surface of ~~mesoporous silica~~MSN ~~surface~~ (**Figure~~.~~ 11**). These hemispherical thin metallic films of ~~around~~ approximately 2-10 nm in thickness showcase different faces on each side of the MSNs, which act as nanomotors for catalysis and therapeutic cargo delivery.[75b] In addition, the irregular deposition of Pt islands over the MSN surface exhibited ~~the~~ a ~~better~~~~improved~~better catalytic performance ~~than~~ over that of the regular, smooth surface ~~,~~ due to their high surface area. Moreover, the light-driven thermal gradients due to the hemispherical ~~gold~~ Au shells across the Janus nanoparticles drove these nanomotors at an ultrafast speed *via* self-thermophoresis for potential cargo transportation in a bio-friendly manner ~~for~~ through photothermal effects.[75c] Despite their success and high sophisticated performance, ~~The major disadvantage of these approaches regarding their applicability as a drug carrier is that~~ these approaches are not suitable as ~~a~~ drug carriers ~~to load~~in delivering ~~the~~ sensitive therapeutic molecules such as proteins. Moreover, they may ~~face~~ cause the damage of loaded drug molecules during the coating process, and the safe conveyance of drug cargo remained unclear, ~~is also highly challenging~~ as these motors rotate at ~~a~~ high speed in the physiological fluids. We believe that integrating various other approaches, such as immobilizing gatekeepers or ~~other~~ additional supramolecular

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functionalization to establish the host-guest chemistry, will be more effective in the advancement of these innovative designs. Though the advancements of nanocarriers are highly innovative ~~and nanocarriers~~ with the augmented efficacy, ~~the~~ fundamental studies relevant to the critical parameters during biomedical applications such as ~~the~~ biosafety issues ~~and~~, therapeutic cargo delivery to the target locations, and the drug loading efficiency, need to be optimized ~~parameters optimization yet remained to be explored.~~.

5. Factors ~~influencing~~ Influencing ~~the~~ M-MSNs ~~formation~~Formation

Since their invention, ~~much~~considerable research efforts ~~has~~ ha~~vs~~ve~~e~~ been dedicated to the development of MSNs with different shapes, morphologies, and topologies. Typically, the formation of ~~the~~a well-ordered siliceous mesoporous framework is based on the interactions between the structure-directing surfactant template and the silica precursor, *i.e.*, TEOS/tetramethyl orthosilicate (TMOS), and their assembly utterly depends on the kinetics of sol-gel chemistry.[4j, 4m, 4s] In this context, it is possible to tailor the size and morphology of the MSNs, resulting in the desired physicochemical attributes~~,~~ that are appropriate for ~~which are of particular interest in~~ diverse applications.[4m] It is noteworthy that De Cola and coworkers recently fabricated MSNs with di~~verse~~stinct morpholog~~y~~ies ranging from hexagonal platelets to twisted rods at a controlled aspect ratio~~s~~ by using bile acids as co-surfactants, indicating that the shapes were significantly controlled due to the specific interactions between the CTAB and bile acids.[68] These diverse shapes could be appropriately suitable for different applications, such as attractive templates for separation operations, indicating that this cost-effective strategy paves a convenient means for morphology modulation of MSNs. To this end, M-MSNs are generally fabricated in a ~~way~~ manner similar to the procedure followed for conventional MSNs. However,

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~~it should be noted that~~ the convenient impregnation of metals in MSNs depends on various factors, such as the charge and pH value of the medium and the incubation time for processing.

In ~~general~~deed, the charge of silica species varies with the pH value of the reaction medium, which influences the hydrolysis of silane and the subsequent formation of the siloxane bond.[4j, 4m, 4o, 4q, 4s, 69] However, it ~~is~~ has been determined that ~~the~~ a pH value of the medium at around ~9.0 favorably results in ~~the~~ a well-ordered and stable siliceous mesoporous framework due to the robust interactions between surfactant template and the silicates.[4j] ~~In a way, e~~Ethanolic solutions of metal salts such as copper nitrate or others such as iron nitrate can be added for ~~their~~ co-condensation along with the silica precursor *via* a modified Stober process, which results in the impregnation of metals into the siliceous frameworks. ~~Nevertheless~~However, this method is highly suitable for use to immobilize specific~~the only limited~~ metal species~~s~~ ~~that~~ possessing ~~with~~ stable oxidation states in MSNs such as ~~copper,~~Cu, Fe ~~iron,~~, and Cr ~~chromium, among others~~in ~~MSNs~~.[13b, 59c, 91] ~~{Liu, 2019 #436}~~ On the other hand, the pH value of the reaction medium also plays a vital role in ~~the~~ effective metal encapsulation. In some instances, ~~the~~a ~~the~~ change in the pH value of the reaction medium ~~value of the reaction medium~~ may result in the precipitation of metal ions, and the pH is also a dominant factor ~~that~~ influencing the final particle size. Moreover, ~~the pH value of the reaction medium also~~it significantly influences the applicability of the switching mode of metals in the MSN host, *i.e.,* the formation of the coordination linkage between the metal in the silica walls ~~frameworks of MSNs~~ and the guest moieties. In this context, the most favorable pH value of the synthesis medium for ~~the formation of~~establishing these coordination interactions is approximately 6.0, at which ~~significantly enhances~~ the loading of guest molecules can also be augmented.[21a] Another advantage of these coordination interactions ~~with respect to~~concerning biomedical applications is that they are highly stable in ~~the~~

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physiological fluids but are sensitive to the acidic endosomal environment of ~~the~~ tumor cells and other infection sites, resulting in ~~the~~ enhanced release of the therapeutic cargo at the diseased sites by concomitantly avoiding premature leakage.[4s, 21a, 58, 61a, 63]

Another critical factor that plays a ~~dynamic~~n active role in the formation of M-MSNs is the incubation time for the formation of resultant nanocomposites. ~~In general, t~~The required time ~~required~~ for the hydrothermal aging of nanocomposites ~~according to the~~based on a modified Stober process ~~after the final injection of silica~~ is around 16-20 h ~~ours~~ after the final injection of silica. Although other modified approaches ~~have attracted attention~~ reduced ~~for the~~is hydrothermal time ~~synthesis~~ of MSNs ~~in a quicker way~~ by just stirring for a while ~~a couple of hours~~ with no additional hydrothermal treatment, it ~~has~~ is rarely ~~been~~ applied in the synthesis ~~of~~ due to the resultant non-uniform-sized M-MSNs.[4j] However, the Stober method has been widely investigated ~~widely~~ for the development of MSNs with different sizes and the advancement of carriers. Based on the Stober-like process, it is possible to generate M-MSNs at altered incubation times. However, with the increase of time, the effects would be more confined to the mesoporous silica shell rather than the metal species. ~~In one case,~~ Matsuura and colleagues ~~*et al.*~~[14e] synthesized the metal-encapsulated core-shell nanoparticles, in which they found that the mesoporous silica shell was coated ~~over~~ on the surface of Au-NRs ~~GNRs~~ within ~~an hour~~1 h of final injection of the silica precursor (**Figure. 12**). ~~However, t~~The silica coating was partially detached, ~~resulting~~ resulted in the core-shell MSN architectures with ~~incomplete polymerization and substantially, the~~ poor mechanical stability ~~of~~ due to the ~~the core-shell architecture~~incomplete polymerization. Further~~more~~, the experiments were continued by extending the reaction time to 10 h~~ours~~ and subsequently, 500 h~~ours~~. ~~,~~ The~~se~~ delay~~ed~~ in incubation periods resulted in the ~~demonstrating that these~~ samples ~~resulted in the formation of~~with a ~~more~~ highly porous stable

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silica coating shell ~~of mesoporous silica~~ with a ~~highly porous shell and a~~ thickness of ~15 nm, ~~which~~ facilitate~~s~~ing the interaction of ~~the~~ encapsulated metal species with the surrounding environment. In addition, the dissolution of the metal core by acid etching can ~~possibly~~ generate the ~~hollow~~ H~~type~~ MSNs for the encapsulation of bulk molecules and their substantial controlled release during delivery applications.[14e] Other miscellaneous factors such as the amount of TEOS, reaction temperature, water content, among others, which have no significant influence on the formation or altering the metal encapsulation in MSNs.[4j] However, they may play vital ~~a crucial~~ roles in the formation of silica frameworks similar to ~~that of~~ the time factor.

6. Interesting ~~properties~~ Attributes

Compared with ~~the~~ conventional MSNs that possess~~ing the~~ a pure siloxane compositions throughout, the introduction of diverse metal species into the mesopores or ~~on~~ in the silica walls ~~could~~ can significantly influence and enrich the ~~respective~~corresponding physicochemical properties and biocompatible attributes of the resultant M-MSNs architectures. ~~Herewith~~In this section, we discuss the intrinsic and acquired fundamental ~~properties~~ attributes of MSNs that are usually altered after the incorporation of metal species, such as the stability, suspendability, encapsulation and release of drugs ~~loading~~, ~~efficiency and its release effect,~~ degradability, and biosafety~~, biocompatibility and other attractive properties that are usually altered after the incorporation of metal species~~. ~~In addition~~Moreover, ~~we also give an overview of~~ various other properties such as the magnetic and luminescent properties (explicitly discussed under the photoluminescence sub-section of the applications section)~~,~~ of MNPs can also be altered after when the~~y~~ metal species are encapsulated into the MSNs ~~among others~~.

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6.1. Stability

It is an important prerequisite to ~~preserve~~ consider the stability attributes of such composites~~a nanoparticulate system~~ during pharmaceutical formulation~~the development of composites for diverse applications~~.[32c, 42a, 92] More often, the colloidal stability of the ~~nanoparticles~~ nanoparticulate forms ~~in any pharmaceutical formulation~~ utterly depends on their structural stability, which is predominantly determined by the interaction between themselves and with the surrounding molecules in the environment. ~~The~~ Nanoformulations with poor stability often ~~times~~ result in ~~the~~ undesired serious problems that are associated with ~~the~~ storage and administration approaches. The attractive physicochemical properties of the nanocarriers play a major role in their structural stability ~~as well as~~and the consistency of other attributes, such as colloidal, thermal, and hydrothermal stabilities.[15b, 93] MSNs are one such species of inorganic nanocomposites with optimized colloidal and thermal stabilities, and~~, which~~ are of particular interest for their applicability in various biomedical applications and other fields due to their robust siliceous framework and exceptional electronic architecture.[4q] ~~On the other hand,~~Moreover, the encapsulation of metals such as iron in the form of iron oxide~~,~~ ~~or~~ and ~~platinum~~Pt~~,~~, in the MSNs enriches their stability due ~~owing~~ to their exceptional chemical stability ~~of the metals~~. However, ~~the~~ significant thermal stability is often ~~favored~~ contributed by ~~the~~ transition metals. In this context, these M-MSNs nanocomposites can be predominantly utilized as catalysts for ~~high~~ high-temperature (>500°C) reactions ~~owing~~ due to their significant thermostability. It is evident from preceding reports that ~~they have shown~~ no fundamental change was observed in their structures even after several reaction cycles ~~was observed~~.[4j, 32c, 92a, 94] ~~On the other hand~~In addition, the incorporated ~~transition~~ metal~~s~~ species ~~that are incorporated~~ into the

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siliceous framework ~~also~~ greatly contributed ~~in~~to ~~improved~~ improving the hydrothermal stability of the MSNs, due to highly stable Si-O-M linkages (M=Al) ~~in~~ on the mesoporous silica ~~framework~~surfaces ~~as well as~~and ~~large amount of~~high mesoporosity ~~mesopores~~.[95] In ~~a~~one case, Al-containing mesoporous silica species were more hydrothermally stable compared to ~~those of~~ the counter pristine silica species.[95] ~~-~~However, it should be noted that the stability of the M-MSNs ~~utterly~~ predominantly depends on the raw material of silica and the degree of oligomerization of the silicate ions in them.[16b] For instance, aluminum was incorporated into ~~the~~ mesoporous ethane-~~-~~silica frameworks based on 1,2-bis(trimethoxysilyl)ethane, in which ~~the high hydrothermal stability was facilitated by ethane-bridged siliceous frameworks~~ethane-bridged siliceous frameworks facilitated ~~the~~ high hydrothermal stability.[96] ~~It~~ The stability of the overall construct also depends on the critical ratio of metal to silica content during the synthesis, ~~where~~ as ~~the~~ high amounts of metal deposition in the MSNs may significantly influence the stability of the composites.

6.2. Magnetic ~~properties~~Properties

In the past decade, ~~vast~~ much research has been dedicated to the development of magnetic nanoparticles (*i.e.,* iron-based nanoconjugates) by integrating ~~the~~ a ~~wide~~ wide-range of fields due to their attractive physicochemical properties such as their intrinsic paramagnetic ~~property~~properties, innocuous nature, and highly reactive surface~~, among others~~.[59d, 97] In addition, the rapid developments ~~in the past decade~~ has~~s~~ve ~~been~~ evidenced ~~by~~ the advancements of magnetic nanoparticles (iron oxide)-encapsulated MSN nanohybrids in the preparation of

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targeted drug delivery systems by adding the advantage of magnetic properties to these highly ~~efficient nanocarriers~~porous mesostructures.[97b] Due to the distinct topological and morphological features of MSNs, ~~the~~ iron-based nanoconjugates can be encapsulated into MSNs at various ~~possible~~ locations, such as incorporated into the core, or pores, or impregnation into the siliceous frameworks.[59b, 98] In this ~~framework~~context, the typical pore size of MSNs can be adjusted to the desired diameter suitable for the incorporation of iron-based species by using ~~the~~ pore swelling agents, such as trimethylbenzene or n-octane, ~~f~~facilitating~~or~~ the~~ir~~ homogeneous distribution of the MNPs in the ~~the mesopores~~MSNs.[98] Further advancements have been made in increasing the magnetite content in various mesoporous silica materials, such as the temperature programmed reduction (TPR) of iron oxide method for the substantial enhancement of magnetization effects.[99] These superparamagnetic iron-oxide-based MSN nanocomposites could ~~be~~ effectively be internalize~~dd~~ into human cell lines ~~facilitated by~~ due to the positive charge ~~that~~ contributed by ~~iron~~Fe species, ~~enabl~~indicating ~~their~~ wide-spread potential in the fields of biotechnology and medicine.~~These nanocomposites exhibiting superparamagnetic properties with enhanced cellular internalization into human cell lines (mesenchymal stem cells and human bone cells) enable their wide spread potential in the fields of biotechnology and medicine.~~[59b]

6.3. Drug ~~loading~~ Encapsulation and ~~release~~Release

The optimum ~~drug~~ loading efficiency of drugs in the carriers and ~~its~~ their ~~efficient~~ substantial delivery at the target site are the ~~important~~ predominant features of a pharmaceutical formulation ~~in medicine. These features~~, which should be explicitly addressed during the design of a delivery vehicle for achieving ~~efficient~~ effective therapy~~nostics~~.[4q, 100] Nanoparticles gained enormous importance in the drug delivery application due to their high surface-to-volume ratio

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for accommodating various therapeutics (drugs/genes/peptides ~~as well as~~and contrast agents) and abundant surface chemistry for immobilizing targeting agents to influence their ~~biobehaviour~~biobehavior. Indeed, MSNs are ~~the~~ one ~~of~~ such versatile ~~drug carriers~~nanocarriers, which can accommodate various therapeutic guests and ~~in some instances~~easey to ~~of co~~immobilize~~peupled~~~~ing~~ with the targeting ligands owing to their exceptional morphological attributes, physicochemical properties, and biological acceptance.[4o, 4q] Since, the major focus of the review is on the influence of metal species on drug delivery, this section is predominantly focused on emphasizing the aspects of drug loading and controlled release of therapeutic molecules.

~~Despite their significant advantages as delivery vehicles, the drug loading efficiency of MSNs still remained an unresolved issue as in most of the cases the yields were poor. It is a critical parameter that should be addressed to facilitate their applicability in clinics.~~ Owing to ~~its~~their ~~porous~~ morphology~~v~~ical attributes, ~~the~~ MSNs ~~are able to~~can significantly enhance the solubility of hydrophobic drugs, which predominantly depends~~ent~~ on ~~the~~ hydrophobic interactions.[4o] However, the drug encapsulation efficiency of~~in~~ MSNs usually depends on the affinity between the host silica framework and the guest drug molecules, ~~where~~in which the therapeutic moieties are loosely bound ~~with~~to the non-functionalized silica matrices through weak physical interactions. These interactions may ~~be~~ not be enough to ensure the loading capacity and facilitate the rapid release of the drugs before reaching the target site.[69] ~~In fact, t~~The loading of guest molecules *via* these ~~consequences~~interactions in the mesopores depends on the properties, polarity, circulation half-life, and degradation rate of the cargo. ~~More often~~Often~~times~~, the interactions of the guest molecules with the host matrix *via* diffusion kinetics substantially govern the release of the drugs. With this in mind, several advancements have been made in

modifying the surfaces through immobilizing functional groups for the sustained release of drugs, which ~~could offer~~can ~~the resistance~~~~confront~~facilitate the ~~in the~~ delivery of drugs. Moreover, ~~the~~ meso~~overloaded~~ pores overloaded with drugs may also experience ~~the~~a reduction ~~in~~of the release rate due to ~~the~~ obstruction by solvent molecules in the environment, resulting in ~~the~~ ~~sustained~~delayed release of the drugs.[3d]

~~In general, the drug encapsulation efficiency in MSNs usually depends on the affinity between the host silica framework and the guest drug molecules, where the therapeutic moieties are loosely bound with the non-functionalized silica matrices through weak physical interactions, which may be not enough to ensure the loading capacity. On the other hand, these interactions oftentimes result in the rapid release of the drugs before reaching the target site.[64] In fact, the loading of guest molecules *via* these consequences in the mesopores depend on the properties, polarity, circulation half-life and degradation rate of the cargo. More often, the interactions of the guest molecules with the host matrix *via* diffusion kinetics govern the release of the drugs.~~ In ~~a few instances~~specific instances ~~likeof~~ such as the deliver~~ying~~y of ~~of~~ anticancer drugs, various auxiliary chemical functionalization approaches have been proposed for encapsulating amphiphilic and hydrophilic drugs that are delivered in a controlled fashion through the covalent~~ly~~ binding (stable as well as labile bonds) of drugs~~-~~, for example, hydrazone bonds~~,~~ with the host matrices *via* multi-step functionalization. These labile linkages specifically ~~through a stable as well as labile bonds in respo~~respond~~nse~~ to external and biological stimuli at the desired site~~,~~ ~~for example, hydrazone bond formation *via* multi-step functionalization~~ for the delivery of drugs, such as delivery through a pH-responsive linkage specifically in the tumor microenvironment.[63, 101] In addition to the conjugation of therapeutic species through ~~a~~ chemical linkages, it is also feasible to fabricate various gatekeeping agents to restrict the premature

release of drugs.[79b, 85e] These attributes of MSNs contributed by a~~bundant~~ppropriate surface chemistry has made them smart nanocarriers through the~~se~~ outfitted linkages that respond to specific external (magnetic, temperature, ultrasound, and light) or biological (molecules, such as enzymes and redox products, and pH values) stimuli.[15f, 102] In this context, the multi-step functionalization of drug carriers often leads to the instability and ~~tailored~~ tailoring of ~~mesoporous silica frameworks~~MSNs due to long-term exposure to organic solvents and mechanical abrasion ~~while~~ during the loading of drug molecules.[91]

~~In regard to~~~~Regarding~~For ~~the~~~~facilitate~~ responsive delivery and t~~T~~o overcome the~~se~~ limitations of conventional multi-step funcationalizations, ~~the~~ transition metals ~~were~~ can be incorporated into the silica frameworks through a one-step condensation approach, which results~~ed~~ in the formation of stable and robust coordination interactions with the guest molecules.[21a, 58] These transition metal-encapsulated MSNs offer numerous advantageous over traditional carriers such as enhancement of the loading efficiency of drugs through ~~the~~ strong coordination interactions and concomitantly ~~overcome~~ overcoming the disadvantage of the fast releasing effect during the drug loading process. Another advantage is that these coordination interactions facilitate the responsive release of drugs owing to their sensitivity to the endosomal acidic environment, precisely at ~~the~~ infection sites or tumor environments, avoiding ~~the~~ premature leakage of the drugs in ~~the~~ physiological fluids.[58] In addition, these transition metal species, specifically ~~Fe iron~~ Fe and ~~copper~~Cu~~and Cu~~, enhance the therapeutic efficiency of drugs by participating catalytically in ~~the~~ molecular pathways such as the generation of toxic free radicals ~~generation~~through Fenton- a~~nd~~s well as Fenton-like ~~reactions~~chemistries.[103] This strategy has emerged as one of such advanced possible treatment choices in treating cancer~~ cells~~. Typically, ~~the~~ ROS are produced by metabolic activation~~-~~mediated catalysis in the normal aerobic

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environment, resulting in the conversion ~~to~~of molecular oxygen to deadly hydroxyl ions through superoxide and hydrogen peroxide (H_2O_2). Owing to the higher availability of non-radical H_2O_2, and the ease of ~~its~~their diffusion through membranes, these species can be used as efficient targets to ablate tumors through converting them to toxic free radicals in the presence of ~~iron~~Fe (Fe_2O_3, $MnFe_2O_4$) and ~~copper~~Cu, according to Fenton and Fenton-like ~~reactions~~chemistries, respectively.[103-104] Despite their beneficial effects in ablating tumors, this ROS science still faces specific limitations, such as low stability, high aggregation over the surface, and specific selectivity. To address these limitations, ultra-high throughput techniques, such as ultrasound- and light-induced approaches have also been developed for the generation of ROS, which, however, still limit their applicability due to low penetration depth and limited localization of irradiated light, respectively. ~~On the other hand~~Moreover, chemotherapy, in combination with ~~the~~ Fenton agents for chemodynamic therapy, has resulted in the efficient ablation of tumors. Although the contribution of Fenton-based chemistry in various advanced therapeutics, such as photothermal therapy (PTT), and photodynamic therapy (PDT) ~~and photothermal therapy (PTT) photodynamic and photothermal therapy,~~ is significant, ~~however,~~ the problems associated with such therapies ~~yet~~ ~~still~~ remain~~ed~~ ~~to~~ unresolved.[103a]

~~Furthermore~~In addition to direct encapsulation of metal species in the frameworks, it is feasible to accommodate the transition metals through immobilizing the organic groups ~~are immobilized~~ in MSNs ~~to accommodate the transition metals~~, which ~~are~~ can be ~~subsequently~~ utilized for ~~loading~~ immobilizing various~~the~~ guest molecules, resulting in the "host-metal-guest" architectures.[105] The dissociation of either of the coordination links between ~~the~~ metal-guest or host-metal, in response to pH ~~variations~~or other stimuli, results in the release of ~~the respective~~ guest molecule complexes ~~under the specific pH conditions~~. However, it should be noted that

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appropriate selection of functional groups ~~as well as~~and the transition metal species plays~~s~~ ~~a~~ decisive roles in the delivery of guest molecules at the desired microenvironment.[105a]

6.4. Suspension a~~da~~bility

Suspendability is another essential physical attribute to be considered ~~in regard to~~regarding the formulation of pharmaceutical nano delivery vehicles for biomedical applications to avoid ~~the~~ non-uniformity in the dosage of therapeutic agents during administration~~,~~ and to ensure that the nanoformulation does not impose any health risks.[21a, 106] Indeed, MSNs are uniformly suspended due to their appropriate surface charge, ultra-fine size, and ~~its~~ ~~their~~ exceptional electronic architecture. Critical care concerning the aggregation of nanoparticles is taken into account in addition to their growth during ~~the~~ synthesis to avoid its effect on the final size distribution and maintain a stable suspension of uniform MSNs.[4j] More often, the high dilution method is ~~applied~~ utilized to preserve the stable colloidal solution of MSNs, which yields products in the arbitrary size range (30-200 nm) ~~of several tens to hundreds of nanometers~~. ~~In addition, s~~Several other approaches, such as utilization of the binary surfactant mixture, triblock polymers, triethanolamine (TEA), polyethylene glycol (PEG), ~~triethanolamine (TEA),~~ and amino acid residues (poly-L-lysine, PLL), have also been ~~utilized~~ used to ~~reducing~~ reduce ~~the~~ aggregation by preventing the direct contact of silanol groups.[107] Alt~~T~~hough the tiny size of the nanoparticles facilitates their significant suspension ability, in some instances, the differences in surface charge ~~differs with respect to~~concerning organic solvents ~~and~~ may result in ~~the~~ critical aggregation and subsequent deposition of the nanoparticles. To this end, the incorporation of metals may not have a significant influence on the overall suspendability of MSNs. However, there exist different views ~~with respect to~~concerning the suspendability of M-MSNs. From the MNPs point of view, ~~the~~ coating ~~of~~ with a thermostable~~,~~ and ~~biocompatible~~ robust mesoporous

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silica shell can reduce the undesired clustering and ~~severe~~ aggregation of ~~them~~ MNPs, due to its well-ordered morphology and surface chemistry, resulting in ~~the~~ enhanced applicability ~~due to the high surface area~~. On the other ~~hand~~~~side~~hand, ~~the~~ MSNs, when loaded with ~~the~~~~se~~ transition metals-based MNPs~~-~~, may have chances of slight aggregation yielding larger-sized MNPs on the surface of the ~~mesoporous support~~MSNs due to enhanced density. However, avoiding the aggregation of MNPs during immobilization on~~to~~ heterogeneous supports, such as ~~like~~ mesoporous silica, will ~~bring~~ lead to several practical benefits for their utility in diverse applications. ~~Moreover~~However, the metal~~lic~~ species ~~that are~~ incorporated either in the frameworks or in the pores of MSNs have no significant influence on the suspendability feature of MSNs, as the interactions between the incorporated metal species are negligible, ~~and subsequently~~ resulting in ~~their~~ exceptional suspendability~~Indeed, the encapsulation of diverse transition metal species enhance the charge densities over the silica support which not only play a crucial role in the dose uniformity but also subsequent cellular internalization process.~~[21a] ~~However~~Nevertheless, the encapsulation of diverse transition metal species in the mesoporous containers might influence the suspendability of the eventual final constructs due to altered densities and charge differences over the silica contributed by multiple heavy metal species, for instance, achieved by placing one of the metal species in the pores or over the surface and another in the core of MSNs.[61a, 85e] These consequences ~~could~~may lead to altered dose uniformity in comparison to that from pristine MSNs or single metal-~~containing~~enclosed MSNs.~~Moreover, the metallic species that are incorporated either in the framework or in the pores of MSNs have no significant influence on the suspendability feature of MSNs because the interactions between the incorporated MNPs are negligible, and subsequently resulting in their exceptional suspendability.~~

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6.5. ~~Biocompatibility and safety~~Biosafety

In addition to ~~the~~ therapeutic efficiency, ~~the~~ biocompatibility evaluation of biomedical formulations is an essential attribute, which plays a crucial role in ~~that needs to be addressed to~~ translating~~e~~ these products from the bench to clinic~~als practice~~.[4b, 4q] ~~In general, the~~ ~~b~~Biocompatibility is often considered for the evaluation of materials intended for biological applications, such that they elucidate the facts ~~of any chances of~~ inducing or provoking adverse biological responses at various levels including molecular, tissue and organ levels in the body.[108] ~~As it~~It is evident from the tremendous progress that the nanoparticles are future medical devices for various biomedical applications, including but not limited to drug delivery, gene transfection systems, tissue engineering, and invasive sensors~~, among others~~. Thus, it is an essential prerequisite for exploring the~~ir~~ biocompatibility of such nanoformulations.[4o, 109] ~~Above all~~Together, it is exceptionally crucial to assess the biocompatibility of nanocontainers for drug delivery to ensuring their reliable drug delivery and minimize the adverse effects or no effect on the healthy tissues. Due to concerns over the risks of nanomaterial in biological applications, there has been a dramatic increase in the research that predominantly focused on human safety for clinical applications.[4q, 110] Moreover, it is not astonishing that the biocompatibility assessment of the engineered nanoparticles intended for biomedical applications has been extended from the preliminary investigations at the laboratory scale to the industrial scale.[111] Although the engineered nanoparticles are biocompatible or intrinsically nontoxic, it does not ~~necessarily~~inevitably ~~mean~~ represent that they are ~~nontoxic~~ safe, since the potential toxicity of any material originates from their particulate nature concerning the ~~surface~~ surface-~~to~~-to-volume ratio of exposure or reachable atoms~~,~~ and catalytic functionalities imposed by the surface atoms causing the generation of toxic radicals.

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MSNs are ~~well known~~~~eminent~~well-known for their ~~excellent~~ biocompatibility due to the extensive functional hydroxyl groups in the siliceous matrices, which exceptionally dissolve ~~under~~ in physiological fluids, resulting in ~~the~~ non-toxic silicic acid species. Further advancements have been made by the grafting of polymeric substrates or organic ligands that enhance the cytocompatibility of MSNs ~~carriers~~.[4j, 4o, 4q] These approaches have been under exploration because, in some instances, ~~the~~ non-functionalized MSNs have exhibited ~~themselves~~ systemic toxicity but not from any resultant degradation products or contaminants, suggesting that the surface modification of mesoporous silicates could reduce the toxicity during their biomedical application.[112] ~~In a way, a~~A considerable amount of efforts ~~have~~ has been dedicated by ~~the~~ researchers ~~for~~ toward the surface functionalization of MSNs to increase the hydrophilic functionalities for their biocompatibility enhancement both *in vitro* ~~as well as~~and *in vivo*.[69]

Similarly, the metal ~~species~~ species-encapsulated ~~in~~ MSNs have also shown no significant influence on the cytocompatibility in some cell lines. Along this line, numerous studies have been performed to explore the safety attributes of M-MSNs in various cell lines. For example, mesoporous silica-capped with iron oxide nanoparticles ~~exhibited~~presented ~~exceptional~~ excellent biocompatibility in HeLa cells *in vitro*.[85d] Further~~more~~, the biocompatibility and efficiency of the intracellular delivery of ~~the~~ iron oxide-MSN hybrids in human cervical cancer cells have also offered ~~a~~ promising potential in exploring ~~the~~ inter- and intracellular chemical as well as neurochemical communications *in vitro*.[85d] ~~However, it should be noted that there exists a relationship between the chemical stability and the cytotoxicity of nanoparticles.~~ In addition to iron oxide, several other transition metals, ~~as well as~~and precious metal species–encapsulated ~~in~~ MSNs have ~~also~~ been subjected to biocompatibility evaluations in various cell lines *in vitro* ~~as well as~~and in animal models *in vi~~t~~vo*. In ~~a~~one case, Shen and colleagues demonstrated the safety

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of intravenously administered GNRs-encapsulated MSNs, which resulted in lower systematic toxicities in Balb/c mice.[113] In another case, Li and colleagues demonstrated that ~~the gold~~Au-coated iron ~~-~~oxide species exhibited excellent compatibility in HeLa cells, and no significant damages were observed in ~~the~~ Balb/c mice ~~to~~after an administered high dosage of M-MSN composites.[114] In addition, Zhang and coworkers stated that ~~the~~ Ru/Gd-co-doped into ~~the~~ Al-MSNs for dual-imaging modalities ~~have shown~~possessed ~~exceptional~~excellent biocompatibility with the HepG-2 cell line ~~as well as~~and substantial safety in ~~the~~ Balb/c mice as an animal model. However, it should be noted that there exists a relationship between the chemical stability and the cytotoxicity of nanoparticles. In this vein, p~~P~~receding reports have indicated that ~~the chemically~~ chemically- stable MNPs have no significant influence on the cellular toxicity, while ~~the~~ nanoparticles that are transformable, such as those that are oxidized, reduced or dissolved, in physiological fluids exhibit ~~the~~ cytotoxicity and even genotoxicity *in vitro*.[115] In another study, the ~~incorporation~~ encapsulation of iron oxide~~-~~ in the ~~mesoporous~~ MSN frameworks at the silica-to-Fe ~~the a~~ ratio of 1:1, ~~silica to iron Fe has~~ exhibited significant biocompatibility *in vivo*.[59c] ~~More importantly~~Notably, they were well-tolerated by the biological system *in vivo,* and ~~the~~ moderate inflammatory responses were ~~had~~ elicited in the beginning after administration~~,~~ but ~~were~~ diminished with time, demonstrating that they could be safely used for short-term treatments.[59c] However, the appearance of ~~iron~~Fe-laden macrophages after 8 weeks indicated ~~the~~ a potential hemosiderosis-like condition that ~~needs~~ needed to be further investigated to understand their long-term safety.[59c] Nevertheless, the biosafety considerations ~~with respect to~~concerning long-term treatment ~~of~~ with these innovative composites yet remained to be explored. ~~In a way~~T~~ogether, t~~he biosafety evaluations ~~*in vivo*~~ of MSNs *in vivo* have also revealed that the bio-behaviors of MSNs are significantly dependent on ~~their~~ various factors, such as the

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preparation procedures, particle size, surface chemistries, geometries, and dosage, as well as on the dosing parameters and administration routes.[15h]

6.6. Degradability

~~In regard to~~Concerning biomedical applications, another critical consideration is that the administered nanoparticles should be eliminated after ~~successfully~~ delivering the therapeutic cargo successfully. Often~~times~~, t~~T~~he nanocarriers are ~~possibly perhaps~~ eliminated as such or in its particulate form after degradation in the physiological microenvironment. In a way, t~~In a way or the other, t~~his key attribute is related to ~~the~~ the ~~the~~ biocompatibility of the particles and is also an important ~~feature~~ characteristic to be considered for the utilization of nanoformulations in biomedical applications, as it is one of the critical issues to be considered for clinical translation.[4q, 116] In this context, the delivered nanoparticles ~~should~~ought to possess ~~the~~ ~~ability of~~ degradation ability when administered *in vivo* ~~so~~ so that they can be ~~easily~~certainly ~~excreted~~ eliminated from the body ~~as it is one of the critical issues to be resolved in their clinical translation~~. Otherwise, the long-term accumulation of nanoparticles in the body may poses ~~to~~ severe and unpredictable toxicity risks. Unlike ~~the~~ polymeric carriers, inorganic materials-based nanoparticles are ~~in one way~~ advantageous as they are highly stable in ~~the~~ physiological fluids due to their structural integrity.[116] However, in another way, the poor biodegradability is a ~~major~~ significant challenge, ~~problem that is being faced by them and~~ leading to severe biosafety concerns *in vivo*. Thus, there is an urgent requirement for the development of biodegradable inorganic nanocomposites or for incorporating ~~certain~~ specific stimuli-responsive units in their

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frameworks, which make them degradable for excellent biocompatibility and ~~a~~ better therapeutic outcome.[116-117] ~~Alike~~Similar to other inorganic nanocarriers, MSNs also face the drawback of slow biodegradation, which often takes several weeks to months owing to their~~ir~~ high thermal, mechanical~~chemical~~, and chemical ~~mechanical~~ stabilities.[59a] To a considerable extent, there has~~ve~~ been certain modifications ~~in~~of the siliceous frameworks achieved by introducing specific labile components such as disulfide- bridged silsesquioxane, and other organic groups, such as through peptide-dop~~ed~~ing, which facilit~~iat~~esd the ~~safer frameworks by~~ degradi~~ng~~ation of these inert frameworks in the respective stimuli and ~~their~~ substantial *in vivo* clearance.[118] Although these innovative organosilicas displayed time- dependent biodegradation behavior in various bio-mimicking environments, the ~~however~~examination of the critical degradation behavior and characterization of the resultant end products have not yet been ~~complete~~thoroughly explored, ~~which~~requiring ~~demand accurat~~precise mechanisms related to ~~redox R~~redox-triggered and hydrolysis- induced degradation.[118a, 118b] In another case, De Cola and coworkers demonstrated the finely controlled degradation of MSNs by incorporating the stimuli-responsive imine groups, which resulted in ~~the~~a faster degradation rate in both acidic ~~as well as~~and neutral environments.[119] ~~However~~In conclusion,~~,~~ the degradation rate of MSNs depends on the functionalization, the degree of silica condensation and particle size, ~~as well as~~and the pore morphology.

Although numerous reports have demonstrated the critical mechanisms and pathways for drug delivery *in vitro*, investigations of the therapeutic benefits of M-MSNs at the molecular level~~s~~ and their degradation behavior *in vivo* are still in infancy.[4h] In ~~this context~~recent times, a ~~some~~ few studies have~~reports in the past few years have~~ demonstrated the degradation behavior of metal ions-doped MSNs *in vitro*. However, ~~the~~ critical investigations relevant to fundamental

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studies on the degradability of M-MSNs and their behavior *in vivo* ~~yet~~ remain~~ed~~ to be explored. ~~It is evident that~~Some insights suggest ~~account~~ that the degradation behavior of ~~the~~ M-MSNs critically depends on the position of metal deposition, in which the metals in the core and that are deposited in the mesopores unconditionally follow the degradation behaviors of ~~the~~ traditional MSNs. In some cases, the metal ions impregnated into the silica wall alter the degradation ~~ability~~ behavior of the composite due to decreased silica species in the wall and substantial formation of Si-O-M species throughout the framework~~,~~. These ~~*i.e.,*~~ coordination interactions with metals ~~facilitating~~ facilitate ~~the~~ stimuli-responsive degradation, meaning that these structures ~~should be~~are degraded when they reach the target site into small and non-toxic building units, which can be conveniently ~~cleared~~ excreted~~out of the body~~, ensuring no accumulation-induced biosafety risk. ~~In one case,~~ Shi and colleagues ~~*et al.*~~[120] developed ~~manganese~~Mn-doped ~~hollow~~ HMSNs (Mn-HMSNs) *via* a "metal ion-doping" strategy, which exhibit~~ing~~ed ~~that had has shown~~ the tumor-sensitive biodegradation ~~property~~properties, in which the enhanced transition metal-doping within the framework promoted the disintegration and biodegradation of the ~~hollow~~ HMSNs ~~(HMSNs)~~, and further significantly accelerated the dissociation of Si-O-Si moieties of the silica wall. ~~Moreover, t~~The rapid degradation ability of Mn-HMSNs in the slightly acidic and reducing microenvironment~~environment that~~ , mimicking that of ~~the~~ tumors ~~microenvironment had~~ resulted in the enhancement of the drug release~~,~~ , demonstrating ~~the~~ on-demand biodegradation and subsequent ~~release~~ delivery of the drugs ~~from the inorganic nanomaterials~~.[120] In another study, they synthesized the ~~iron~~ Fe ions-encapsulated HMSNs using the simple chemical reaction, and ~~then~~ their degradation behavior was then ~~comprehensively~~systematically evaluated ~~both~~ in the simulated body fluids ~~at the intracellular level~~. Interestingly, t~~T~~hese innovative constructs ~~had exhibited~~showed a specific coordination-accelerated biodegradation

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behavior at different time intervals (**Figure. ~~13B~~13A**).[121] In addition to the physiological pH stimuli, it is ~~also possible~~feasible to fabricate M-MSNs~~, which~~ that respond to other physiological stimuli, such as through molecular (protein) responsiveness and magnetic responsiveness, ~~and~~ to allow rapid biodegradation of the carrier. Khashab and colleagues ~~*et al.*~~[59a] synthesized the iron oxide-containing biodegradable MSNs for drug delivery applications. ~~They demonstrated that t~~These ~~mesoporous silica materials~~MSNs significantly ~~had~~ exhibited ~~the~~ protein-mediated biodegradability (in only 3 days), and the mechanism was proposed ~~with~~ by ~~the evaluation~~evaluating ~~of~~ this behavior in various media mimicking ~~the~~ physiological fluids and in deionized water with or without transferrin proteins (Figure. ~~13A~~13B). With these characteristics, these nanocomposites ~~would have~~possess~~ed~~ ~~a~~ great potential for use in the next generation of biomedical applications for the delivery of large therapeutic cargos under acidic pH or magnetic stimuli. Though the studies gave some basic insight~~s on~~ into the biodegradation behavior *in vitro* in the presence of biological stimuli, the critical evaluation of their behavior *in vivo* and substantial elimination from the body is ~~yet remained to be explored~~still in infancy. However, we anticipate that ~~the~~ other factors concerning the ~~movement~~ infiltration of the building units of the carrier after degradation and overcoming critical physiological interventions as well as robust metabolic barriers, ~~play~~ should also be considered as they play a crucial role in the~~ir~~ elimination of M-MSNs.

7. Potential ~~applications~~ Applications

Since ever their inception in the early ~~90's~~'90s, MSNs ~~have~~ have attracted the enormous attention from researchers in a ~~wide~~ wide variety of applications due to their aforementioned attractive properties.[4o-q, 15f, 21c, 33, 79a, 122] Moreover, the remarkable progress in recent past has evidenced ~~the~~ significant advancements in designing MSNs for diverse applications, and their

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progress has been summarized in some reviews.[1a, 4j, 4m, 4o, 4q, 15f, 21c] These reviews gave a precise emphasis on selected recent developments in this exciting and rapidly expanding field. However, the advances of MSNs concerning the encapsulation of metals ~~association in it~~ and the benefits offered by ~~them~~ these innovative composites as well as their potential applications have not discussed yet. Herewith, we ~~discuss~~ emphasize the utilization of M-MSNs in various fields, which are categorized into the following sections, namely the adsorption, biomedicine focusing drug delivery, bio-imaging, peptide enrichment, ~~DNA~~nucleic acid (deoxyribose nucleic acid~~,~~ DNA) detection, and artificial enzymes, catalysis, photoluminescence, and other applications, focusing semiconductors, lithium storage, gas sensing, and Uranium extraction.

7.1. Adsorption

Recently, t~~In recent times, t~~he contamination of water with heavy metal ions and toxic organics has become a significant health concern due to increased industrial growth, agricultural waste, and other natural processes.[31, 35, 123] These ~~consequences~~ adulterations often result in severe illnesses, such as cancer, nausea, mutation, organ malformation, coma, and mental retardation, among others.[44] Along this line, ~~the~~ common pollutants include heavy metal ions (~~lead~~Pb, ~~chromium~~Cr, ~~arsenic~~Arsenic (As)), toxic organics (methylene blue), and gases (sulfur dioxide), among others.[30b, 42c] Numerous approaches have been applied ~~to~~ for the removal of toxic pollutants such as adsorption, membrane filtration, ion-exchange techniques, electrochemical treatment, and precipitation, among others.[42c, 44] Among all the available strategies ~~that are available~~ for toxic substances removal, the adsorption process has gained enormous attention due to its easy operation, stability, cost-effectiveness, and high-performance efficiency.[31, 35, 37, 124] Thus, there is an increase in the demand for the development of effective adsorbents for the elimination of toxic agents from water.[42c] In this framework, ~~much~~

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~~research~~enormous effort~~s~~ ha~~ve~~s ~~has~~ been dedicated to the advancement of various adsorbents for the removal of heavy metals. Currently~~, the~~ available adsorbents include zeolites, activated carbon, carbon nanotubes, metal-organic frameworks (MOFs), lignocellulose substrates, dead fungal biomass, charcoal, and low-cost materials from paper waste, among others.[31, 42c] Some of these adsorbents, specifically zeolites~~,~~ and ~~metal-organic frameworks (~~MOFs,~~)~~ are highly stable ~~and~~due to possessing uniform pores, which result in the strong binding to ~~the~~ toxic substances.[123] However, ~~the~~ general stability against aqueous environments and production costs still remain~~ed as~~ serious concerns. ~~On the other hand~~Alternatively, ~~the~~ activated carbon-based materials are advantageous ~~among~~over zeolites and MOFs, in terms of potentially sustainable synthesis along with potential shaping into well-ordered architectures, low cost, and high thermal ~~as well as~~and chemical stability. ~~{Oschatz, 2018 #512}~~Nonetheless, the less~~-~~polar~~ity~~ attribute provides weak affinity toward~~s~~ some toxic gases such as CO_2~~,~~ compared to those of MOFs and zeolites.[123] Despite their efficiency in adsorbing toxic substances, including ~~the~~ gases ~~by other notable adsorbents~~, most of these adsorbents ~~adsorbents~~ suffer from ~~their~~ specific ~~own~~ ~~disadvantages~~ limitations, such as selectivity, inherently low adsorption capacity, ~~and~~ thermal instability, and expensiveness~~, among others~~.[31]

To this end, MSNs have been more promising as adsorbents over ~~others~~other substances, due to their attractive properties such as ~~,~~high surface area, tunable porosity with a narrow size distribution, low toxicity, and well-defined surface properties~~, among others~~.[4j] ~~{Shieh, 2013 #518}{Walcarius, 2010 #519}~~

Further advancements have been made in modifying MSNs such as through surface modifications with organic functional groups or by impregnating various metals/metal oxides for the improvement of their adsorption capacity, which ~~would be~~becomes significantly higher than

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~~that~~ those of ~~the~~ conventional MSNs and other adsorbents.[31, 35, 37, 124] ~~Surface functionalization of MSNs with organic groups predominantly adsorb the heavy metal ions through the electrostatic interactions.~~ Various functional groups have been immobilized to exhibit highly selective adsorption capacity, such as amine- or thiol groups-immobilized MSNs for the selective adsorption of ~~copper~~ Cu(II) and mercury (~~mercury~~Hg(II)) through recognizing specific functionalities.[125] The s~~S~~urface functionalization of MSNs with organic groups predominantly adsorb ~~the~~ heavy metal ions through ~~the~~ electrostatic interactions. However, the anticipated adsorption efficiency of ~~adsorption of~~ metal ions is highly challenging, ~~not up to the anticipated levels~~as ~~there are certain instances~~there are certain ~~instances~~findings stating that ~~the~~ extensive functionalization would lead to ~~the~~ reduced adsorption of heavy metals.[126] Alternatively, the metal species~~s~~ such as iron oxide and others~~, that are~~ encapsulated in the MSNs result in the efficient removal of toxic substituents through ~~the~~ adsorption phenomena by combining the attractive properties of the metals (magnetic behavior in the case of ~~iron~~Fe) ~~along~~ with the features of the MSNs, such as their vast surface area and enormous porosity. M~~The m~~agnetic ~~core~~ core-containing MSNs are highly advantageous for use as adsorbents over other materials ~~because~~ as they can be easily separated and recycled by applying ~~the~~ a magnetic field.[127] The adsorption ~~phenomena~~ phenomenon ~~through~~ exhibited by the M-MSNs is highly convenient, ~~over others~~ as it is facilitated by providing a couple of driving forces for the transfer of heavy metal species onto the support. The ~~pre~~dominant driving force is the concentration gradient that drives the molecules from the surrounding medium toward~~s~~ the solid porous support, which is similar to the case for other adsorbents. ~~While it~~It differs in ~~the case of~~ the second driving force, which is ~~that~~ facilitated by the interactions between the encapsulated metal species in the MSNs, and subsequently, the high surface area and enhanced mass transfer ~~enabled by~~of the MSNs

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retain and accommodate the guest molecules efficiently. However, it should be noted that the adsorption efficiency of these innovative composites utterly depends on ~~the~~ two predominant attributes concerning M-MSNs. One ~~of them~~ is the loading efficiency of metals, and the ~~an~~other is the pore size of the mesoporous support ~~facilitating~~ facilitates the easy adsorption of metal species.[44] Enhanced metal amounts in the mesoporous framework significantly augment the heavy metal adsorption through increased interactions ~~either~~ by either physical or electrostatic interactions. Further, the adsorption of heavy metal adsorbates into the pores of MSNs significantly requires a large ~~the appropriate~~ enough ~~pore space~~size to facilitate~~ing~~ their entry of guest molecules during the adsorption process.[44] However, i~~I~~t should be noted that the pore size of the M-MSNs must be ~~higher compared to~~larger than the heavy metal guest ~~adsorbate~~adsorbates ~~heavy metal guest species~~, which ~~only could~~ leads to their efficient adsorption into the mesopores. ~~However~~Nevertheless, in some instances, ~~like~~ the adsorption of toxic gases does~~es~~ not ~~really~~certainly depend on the pore size of the MSNs, ~~which~~ as they can be conveniently removed by even MSNs ~~even~~ with ~~the~~ small particle ~~as well as~~and pore sizes.[128] Other factors such as the location of metal deposition in the MSNs and the form of the metals used also play ~~a~~ substantial roles in the efficient adsorption ~~of unwanted substances~~process. In addition to Fe in the form of iron oxide~~iron~~, there has been increasing interest in the application of other metal oxide species in MSNs such as MgO, which facilitates selective adsorption at low cost. In an attempt to address this issue, Yu and coworkers ~~*et al.*~~[44] fabricated core-shell structured MgO@mSiO$_2$ by a programmed method for the adsorption of the organic toxin methylene blue and lead ions (**Figure~~.~~ 14**). These core-shell nanostructures with excellent structural and mechanical stability exhibited significant removal capabilities ~~of~~ for unwanted toxins, greater by 6-fold compared to that of the MgO core itself due to the high surface area and

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enhanced mass transfer rates provided by the mesoporous support. In addition, the mesoporous silica coating over MgO ~~had~~ provided a durable porous shell over the metal oxides to ~~improving~~ improve its mechanical stability. Moreover, various other metals/metal oxides, such as aluminum oxide (Al_2O_3), CeO_2~~cerium oxide~~, ~~copper oxide~~CuO, lithium chloride (LiCl), and iron oxide, have also been incorporated into MSNs for the effective adsorption of toxic pollutants (**Table 1**).

7.2. Biomedical ~~applications~~ Applications

The integration of nanotechnology with medicine has become a new exciting direction, which has garnered enormous attention of researchers ~~in~~ to design~~ing~~ ~~the~~ various innovative methods and functional biomaterials for various applications, such as delivery of therapeutic cargo into the targeted cells or tissues using safe and trackable routes, bio-imaging, nucleic acid detection, and peptide enrichment, among others.[89] Nanomedicine ~~that~~ using ~~the~~ drug delivery vehicles scaled- down to the nanometer range has become an emerging alternative to most of the conventional therapeutic agents ~~in~~ for addressing ~~the~~ biopharmaceutical issues by improving ~~their~~ pharmacokinetic behaviors, such as enhancement of the solubility ~~as well as~~and intestinal permeability ~~enhancement~~ of drugs with poor bioavailability, ~~targeted~~ targeting, ~~as well as~~ controlled delivery, and protection from ~~the~~ harsh environments, among others.[3d, 106] In addition, these ~~unique~~versatile nanoparticulate systems possess high surface-to-volume ratios and a~~mple~~bundant surface chemistry, facilitating the encapsulation of various therapeutic guest molecules ~~such as drugs/genes/peptides and contrast agents for diagnosis~~ and surface modifications for immobilize~~ing~~ targeting ligands ~~for~~to improv~~ing~~e their ~~bioavailability~~bio-behavior, respectively. ~~are multifunctional as they provide enough room for accommodating not only therapeutic agents but also diagnostic agents as well as targeting moieties for tracing the carrier and direct it to the desired site, respectively.~~[3d]~~[3d]~~ In this regard, ~~the~~ smart nanosystems

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that can respond to specific stimuli from either ~~the~~ internal sources, such as the pH, ~~,~~ ; temperature ~~,~~ ; ~~and~~ specific biomolecules, for example, ~~like~~ enzymes ~~,~~ ; and redox activities or ~~an~~ from an external source, such as light, electromagnetic fields, ultrasound and mechanical sources, ~~,~~ have been designed for precise control over ~~the~~ delivery and other biomedical applications.[61b, 80] These versatile nanocarriers have opened ~~up~~ new horizons for safe and effective delivery of various therapeutic agents.[58, 129] MSNs are one ~~of~~ such ~~kinds~~material ~~that~~ with a high ~~-~~performance efficiency due to their attractive characteristics such as a flexible surface for the functionalization/immobilization of targeting ligands, high surface area and tunable porosity for loading therapeutic cargo/imaging agents, biocompatibility, and biodegradability, among others.[61b, 80, 109, 130] These unique nanostructures ~~that~~ functionalized with various organic groups have been utilized for controlled drug release, biosensing, and molecular recognition.[3a, 3c, 15f, 28b] In a way, ~~metals incorporated into~~M ~~-~~MSNs have further enriched their functionalities ~~concerning~~ for better drug loading and release effects, facilitating the solubility enhancement of poorly soluble drugs ~~,~~ and enhanced loading efficiency through metal affinity interactions with the drugs. ~~Moreover, the metal affinity with the guest molecules~~ ~~In~~ In addition to drug delivery, they can enrich the functionalities of MSNs in other applications such as efficient peptide adsorption ~~,~~ and can augment the imaging view field of contrast agents, among other abilities.[58, 80, 130]

7.2.1. Drug ~~delivery~~ Delivery

Drug delivery usually relies on various pharmaceutical carriers that actively transport the active pharmaceutical agents to achieve desired therapeutic effects as ~~the~~ drugs often suffer from critical limitations ~~associated with~~such as solubility and diffusion.[71a] ~~Furthermore,~~ Tthese carriers help to protect the sensitive drugs from degradation in ~~from~~ the harsh

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microenvironments ~~in~~ of the body ~~from degradation and uneven distribution~~. ~~It is evident that the mesoporous silica~~MSNs-based nanocarriers are highly suitable as drug carriers ~~because of~~owing to their well-known physicochemical characteristics, ~~such as~~ biocompatibility, optimum drug loading efficiency, biodegradability, and enhancement of aqueous solubility ~~as well as~~and subsequently bioavailability.[3a, 3c, 4a, 26, 74a, 75a, 79b, 114, 131] In the field of drug delivery, the tremendous advancements of MSNs in the past two decades ~~has~~ have been evidenced by ~~the~~ great progress in the development of numerous innovative formulations concerning the improvement of ~~the~~ drug loading ~~efficiency~~ efficiencies ~~in the porous architectures as well as~~and ~~its~~ release at the desired sites, and the research is being continued.[15f, 28b] In ~~their~~ these innovative ~~research~~ studies, various advances in the morphology~~,~~ and size-controlled synthesis of MSNs and their surface functionalization ~~that~~ have made them suitable for drug loading, and delivery *via* efficient internalization into various tissues for effective therapeutic outcomes ~~have~~ has been well documented.~~[1a, 4j, 4m, 4o, 4p, 75b, 89, 131a, 131b, 132]~~ Although ~~the~~ progress relevant to the fabrication of gate-keeping materials on the surface for smart delivery has been achieved, ~~however~~ there are several challenges that still remain ~~several challenges~~ to be addressed, as most of the designs are still in infancy ~~at~~in the preclinical stage and need in-depth investigations requiring ~~urge~~important breakthroughs for the construction of targeted drug delivery systems.[1a, 4j, 4m, 4o, 4p, 75b, 89, 131a, 131b, 132]

Indeed, ~~For an optimal nanocarrier like MSNs,~~ a high drug ~~loading~~ encapsulation efficiency is not only an~~n essential~~ ~~necessary~~essential condition to ~~promise~~ provide an effective therapeutic outcome for an optimal nanocarrier like MSNs, but ~~also an the~~an on-demand responsive release of ~~drugs~~ therapeutic guests is also ~~requ~~a ~~ired~~prerequisite to precisely control ~~its it~~the~~s~~ profiling regarding the duration, timing, and magnitude.[66] In recent years, remarkable effort~~s~~ has ~~have~~

been dedicated by researchers toward fabricating the molecular and supramolecular switches in MSNs for the efficient delivery of many therapeutic agents such as drugs, proteins, vaccines, and other biomolecules.[3a, 3c, 4a, 15f, 26, 28b, 74a, 75a, 79b, 114, 131] Among ~~them~~these approaches, ~~the~~ metal-~~based~~ species have also been incorporated into the MSNs, which have shown ~~an~~ exceptional potential ~~toward~~for use in~~s~~ the construction of functional nanodevices with unique structural and functional attributes.[89, 133] In this context, these metal-based nanoswitches possess ~~an abilit~~abilities~~y~~ such that they respond to various stimuli in the microenvironment, including the biological triggers ~~such as~~(~~-~~temperature change, the pH value of the surrounding environment, ~~temperature change,~~ ~~sensitive to~~ and specific biomolecules~~,~~), and applied external triggers~~,~~ ~~such as applied~~ (magnetic field or light irradiation)~~,~~ for the controlled release of the therapeutic cargo. There exist several reports in the literature based on ~~the~~ acid~~–~~-labile metallic ~~switches~~ gatekeepers over MSNs for the efficient delivery of therapeutic molecules to~~ward~~ treat~~s~~ various diseases ~~like~~ such as cancer, among others.[27c, 42e, 63, 74c, 86, 129a] For example, the tethering of acid-labile ~~tethering~~ molecular groups such as (3,9-bis(3-aminopropyl)-2,4,8,10-tetraoxaspiro[5.5]undecane)[86] anchoring ~~the~~ gold nanoparticles (Au-NPs) over MSNs allows the specific release of guest species from the mesopores only ~~at the~~in low pH environments, facilitating ~~the~~ on-demand release ~~at the~~in tumor environments~~,~~ by avoiding ~~the~~ premature leakage in the physiological environment.[15f, 27c, 60, 74, 84-85] Another such example is based on the impregnation of ~~the~~ transition metals (~~copper and iron~~Cu and Fe) in the siliceous frameworks, which offer the coordination interactions to the loaded guest molecules, resulting in the ~~augmented~~enhanced loading efficiency and facilitating ~~the~~ release in ~~the~~ acidic environments through protonation of the guest species.[58, 91, 104] However, this approach could be efficiently utilized for therapeutic guests with amine functional groups (See Sections 4.4 and 6.4 for details).

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In some instances, ~~it is also evident that~~ the encapsulated transitional metals not only support the carrier in augmenting the ~~-~~drug ~~enhancing~~ loading ~~as well as~~and its ~~the~~ release efficiency but also ~~support~~ extend ~~in~~ the support in therapy ~~treatment approach~~ by participating in the molecular pathways and enhancinge the therapeutic outcome through synergism.[133] A few transition metals of ~~its~~ these kinds, such as, ~~iron and copper~~Fe and Cu, have been utilized to achieve these actions as the electronic architecture of these metals facilitates ~~them in~~to ~~participating~~ participate in the redox chemistry and to catalyze the generation of highly toxic ROS (explicitly discussed in the Section 6.4~~, Drug loading and release~~), which can devastate the cancer cells. It should be noted that these trace elements do not significantly affect the normal physiological processes as they ~~These essential trace elements~~ are the fundamental parts of many important enzymes in vital biological processes ~~in the body, which do not significantly affect the normal physiological processes~~. For example, ~~Kankala and Lee et al.~~we [21a, 61a] designed the copper-impregnated mesoporous silica frameworks for the efficient delivery of therapeutic molecules against cancer and bacteria.[21a, 61a] Herein, the metallic ~~switch~~species (Cu) ~~, i.e., copper, that was~~ impregnated in the ~~mesoporous silica~~MSN frameworks ~~had~~ played multiple roles such as the enhancement of drug loading ~~as well as~~and ~~its~~ release in ~~the~~ acidic environment, specifically in ~~the~~ tumors (pH-responsive release), and further enhanced the levels of ROS by participating in the Fenton-like reaction, resulting in the conversion of intracellular ~~hydrogen peroxide~~H_2O_2 levels, which were often higher in the ~~cancer~~ tumor cells compared to normal cells.[58] In addition, these nanocarriers played a ~~crucial~~critical role in the ablation of cancer ~~cells~~ by overcoming multi-drug resistance (MDR) through synergism (**Figure~~.~~ 15**).[58] In another study, ~~they~~ we immobilized ~~silver~~Ag-indole-3-acetic acid hydrazide complexes through the pH-sensitive hydrazone bond over the mesoporous material (IBN-4) for the efficient killing of

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malignant bacteria.[63] ~~However~~Interestingly, ~~it should be noted that, in any case,~~ the releasing and loading profiles were ~~observed~~distinguished depending on the type of metal species ~~as well as~~and drugs used involving the nature of the host-guest interactions and the kinetics degradation of the material ~~kinetics degradation~~, inferring that . ~~Thus,~~ the selection of metal species significantly plays a crucial role during the nanocarrier design ~~of nanocarriers~~. Moreover, ~~the nanocarriers should be designed for a particular disease by~~ critical~~ly~~ ~~optimizing~~ optimization of the metal species concerning the host-guest interactions should be taken into account for better drug loading and release efficiency for ~~a~~ better therapeutic outcome. It should be noted that~~T~~ these~~se~~ metal species with the catalytic ability for free radical generation are highly suitable for specific pathological conditions~~only some diseases~~ relevant to apoptosis, such as cancer~~, but not for certain conditions like tissue regeneration and others~~.[58, 63]

Assembling different types of functional nanomaterials (multiple metal species) into a single construct often results in customized nanocomposites that can provide unique properties when put together for biomedical applications. Moreover, these nanocomposites offer numerous benefits that are derived from each of the ~~nanoparticels~~nanoparticles in the design synergistically over those of the individual components.[114] ~~Accordingly,~~ Yeh and coworkers ~~*et al.*~~[114] synthesized versatile drug carriers based on the mesoporous silica shell coated over the iron oxide-encapsulated ~~gold~~ Au ~~as a~~ core, which offered enormous benefits in therapeutic applications. Initially, ~~the~~ truncated octahedral iron oxide nanoparticles were coated with ~~gold~~ Au through the polymer-mediated synthesis *via* post-grafting and substantially yielded the ~~gold~~ Au trisoctahedral nanoshells, which provided the integration of magnetic property with the plasmonic functions of ~~gold~~ Au and resulted in the NIR-responsive nanomaterials (**Figure~~.~~ 16**). Further~~more~~, the mesoporous silica coating on the ~~gold~~ Au surface ~~yielded~~ resulted the multi-

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modal core-shell nanocarriers with the combination of on-demand release, magnetic resonance imaging (MRI)-monitored magnetic targeting of the tumor, and NIR-assisted photothermal therapy. The ~~beneficial~~advantageous~~beneficial~~ effects ~~that were~~ offered by the metal species in the MSNs, such as various characteristics such as pH-, ultrasound-, thermos- or magnetically-responsiveness could ~~efficiently~~ act toward efficient cancer theranostics.[42e, 85e, 113] Therefore, the production of ~~multiple~~ various metal species-encapsulated MSNs ~~could~~ can potentially allow high encapsulation and release efficiencies of therapeutic guests ~~drug loading as well as its releasing efficiency~~ ~~in the mesoporous supports~~ and their targeting ability, leading to a better therapeutic outcome. Despite the advancements and success in achieving a better therapeutic outcome by incorporating multiple metal species, it is ~~highly required~~essential ~~to consider~~ to address the critical considerations of nanoformulations such as biocompatibility and their elimination rates for not imposing any health risks.

7.2.2. Bio-imaging

Bio-imaging is a process that allows the visualization of biological architectures and their functional analysis by ~~captivating~~using the benefits of high~~ly~~ contrast agents.[9, 71a, 134] More often, ~~the~~ inorganic nanostructures are preferred over organic molecules~~,~~ due to their stable structural architecture and long biological half-lives.[4i, 4u, 71a, 135] Among them, ~~the~~ paramagnetic species are ~~the~~ highly effective contrast agents, which ~~have been utilized~~are of particular interest for various applications, such as drug delivery, catalysis, and tissue-specific targeting. However, the~~ir application~~ applicability of contrast agents~~-~~ is limited due to their low uptake efficiency and cytotoxicity.[42d, 85f, 136] To overcome these limitations, ~~these~~ superparamagnetic species, such as ~~like~~ iron oxide and others~~,~~ can be integrated with ~~mesoporous silica~~MSNs, yielding ~~the~~ versatile, uniform~~ly~~ ~~-~~sized nanocomposites for simultaneous bio-imaging and drug delivery, owing to their

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highly accessible pore volume~~, as well as~~, large surface area and high colloidal stability in ~~the~~ physiological fluids, as well as being~~nd~~ small enough to possess a long retention time in the blood. ~~Incorporation~~ The incorporation of these superparamagnetic species into MSNs offers numerous advantages, such as ~~they can be used for~~ responsive delivery, enhance ~~their~~d cellular uptake, and reduce~~d the~~ toxicity.[85f] In addition, these magnetic substances can ~~enhance~~increase the temperature in~~side~~ the interior of tumor cells for ~~magnetic resonance imaging (~~MRI~~)~~-guided magnetic hyperthermia therapy.[59d]

Despite the success in the fabrication of iron oxide-MSN composites and their efficacy testing *in vitro*, the *in vivo* efficiency of these materials ~~remained~~ remains unclear due to their size and aggregation.[137] Moreover, ~~it is evident that the~~ uniformity ~~in~~ of the sizes of the iron oxide species as cores ~~as well as~~and the thickness of the mesoporous shell ~~was~~ is highly challenging ~~to maintain~~, which has ~~might~~ also limited their applicability *in vivo*. In an attempt to ~~elucidate~~ address the ~~in vivo se facts~~issues~~effects of these hybrid nanocomposites based on magnetic species coupled with MSNs~~, Hyeon and colleagues ~~*et al.*~~[42f] ~~prepared~~ fabricated discrete, monodispersed and uniformly- sized core-shell MSNs by incorporating ~~by using~~ Fe_3O_4 nanocrystals in the core for simultaneous fluorescence imaging, MRI, and drug delivery. The potential imaging *in vivo* elucidated that the intravenously injected nanoparticles were preferentially accumulated at the tumor sites through the enhanced permeation and retention effect (EPR) and were retained for more than 24 h~~ours~~ (**Figure~~.~~ 17**A-C). Further~~more~~, the fluorescence imaging of excised organs of mice and tumors resulted in the significant deposition of the nanoparticles in tumors through the EPR effect (Figure~~.~~ 17D). In addition, the immunostaining of sectioned tumor tissues ~~had~~ shown that the CD31-positive vasculatures and

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~~the~~ accumulated nanoparticles were observed through the rhodamine B isothiocyanate (RITC) filter (~~Fig~~Figure~~.~~ 17E, middle image).

Considering the ~~facts~~ issues about the dreadful threats like cancer, the combination therapeutics have attracted significant attention from researchers in generating versatile platforms by integrating multiple imaging and therapeutic modalities ~~in a single platform~~. Along this line, the imaging-guided combinatorial ~~therapeutics~~ therapeutic strategies ~~attained~~achieved by integrating the two dimensional (-2D) and three dimensional (-3D) platforms show enormous ~~promise~~ potential in diverse areas of biomedicine. Similarly, a new type of 2D nanomaterials transition metal dichalcogenides (TMDCs) were introduced to acquire additional functionalities such as drug loading, strong NIR absorbance for PTT~~PTT~~ ablation, and X-ray computed tomography (CT) imaging, and stimuli-responsive drug delivery~~, among others~~. Liu and colleagues~~*et al.*~~[42d] designed iron oxide composites based on ~~a using a two dimensional~~2D ~~platform based on~~ TMDC~~s~~ platform. ~~Su for the decoration of iron oxide *via* self-assembly and su~~bsequently, these composites were coated with a layer of mesoporous silica for ~~for~~ loading ~~the with~~ doxorubicin (~~–~~DOX), onto which PEG was ~~attached~~ immobilized (WS2-IO@MS-PEG) (**Figure~~.~~ 18**A). This versatile platform possessed interesting properties including superparamagnetism, NIR light, and X-ray absorbance, pH-sensitive therapeutic cargo release. In addition, the administered nanocomposites were efficiently ~~observed~~detected in the tumor tissues *via* multi-modal imaging, *i.e.,* X-ray ~~computed tomography (~~CT~~),~~ fluorescence, and ~~magnetic resonance (MR) imaging~~MRI studies (Figure~~.~~ 18B-F). ~~In this context, t~~Though the ~~the~~ mesoporous silica shell surrounding the iron oxide core ~~conveys~~ was able to release DOX in a controlled fashion~~drugs~~, the responsive delivery by TMDCs further enhanced the release of ~~encapsulated drugs~~DOX at the ~~triggered~~ target site. Herein, ~~the~~ TMDCs possessed not only

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similar characteristics to ~~its~~ their sister material graphene but also with the different elementary compositions, which could ~~be helpful in tuning~~help in tuning the auxiliary functionalities. However, in-depth investigations are required to explore the~~there is still a long way to go in~~ engineering ~~the~~ of TMDC-based hybrid composites for theranostic platforms and ~~investigating~~elucidate the fundamental studies concerning their compatibility ~~as well as~~and degradation behavior *in vivo*.

Due to their advantageous characteristics and acceptable biocompatibility *in vitro*, a ~~numerous~~ handful of studies have been performed to explore the applicability of M-MSNs *in vivo* (**Table 2**).[14f, 22, 42d, 42f, 85f, 113-114, 138] ~~[21]~~ ~~With~~In ~~regard to~~ these studies, it ~~is wa~~is evident that ~~the~~ only a few ~~of such specific~~ metal ~~species~~ species (~~such as~~ iron oxide and ~~gold~~ Au) ~~species that~~ encapsulated in the ~~mesoporous silica nanocontainers~~MSNs ~~were~~ have been tested ~~toward~~for~~s~~ biomedical applications, such as drug delivery and multi-modal bioimaging *in vivo* ~~so far~~to date (Table 2).[85f, 114] The ~~The *ii*~~*in vivo* performance of these M-MSNs in biomedicine ~~towards biomedical applications~~ ~~i~~was remarkable ~~in *in vivo*~~ compared to that of ~~the~~ naked MSNs as the transition metals ~~had~~ significantly ~~augmented~~ contributed ~~their~~~~the~~ functional attributes, ~~due to their~~such as superior magnetic, catalytic, optic (~~S~~surface ~~P~~plasmon ~~R~~resonance, SPR), or electronic properties.[21a, 42d, 58, 114] ~~It is was evident that~~Notably, the characteristics ~~purposes commitments~~ of MSNs ~~are~~ can be maximized by using~~due to~~ metal species ~~with respect to~~~~concerning~~appropriate for ~~the~~ the application ~~due to metal species~~, ~~which resulted in~~such as ~~augmented~~ drug loading~~,~~; achieving synergistic therapeutic effects, including such as chemo-/~~as well as~~ photothermal efficacy~~,~~; and facilitating multi-modal imaging and targeting within a single composite.[42d, 113-114] However, these studies are merely the experimental approaches in the preclinical stage~~,~~; ~~which,~~ however, ~~demand more~~ in-depth investigations are needed ~~studies~~

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~~are required~~ to fully understand the efficiency of M-MSNs *in vivo* and could ~~be possible to~~ extend their applicability ~~in~~ to clinical trials. ~~-~~Very recently, a study has reported the clinical applicability of MNPs~~,~~ based on a silica-Au nanoparticles-dispersed on-artery patch for cardiac tissue engineering applications.[4b] It was concluded that there were no significant toxic effects or serious clinical complications in the group of patients during the clinical intervention.[139] Although ~~it is not in~~the study is not within the scope of the M-MSNs, it is noteworthy to discuss these facts, which w~~ould~~ill help in giving ~~the readers in giving~~ better insight to the reader~~s~~s. ~~Moreover, i~~It should be noted that the history of the approval of nanoformulations by the United States Food and Drug Administration (US-FDA) elucidates the fact that the difference between ~~the~~ great effort~~s~~ ~~as well as~~and investments ~~toward~~in~~s~~ theranostic nanoformulations and their approval ~~by United States Food and Drug administration (US FDA)~~ is significantly ~~very~~ high due to numerous issues from a scientific point of view,~~s~~ such as achieving sufficient loading and carrying capacities~~y~~, ~~achieving~~ controlled delivery after overcoming numerous biological barriers, ~~sufficient loading and carrying capacity,~~ efficient delivery at the target site, and controlled biodegradation, as well as addressing the excretion and toxicity issues of the resultant byproducts~~ and scale up problems~~. In addition to these issues, several other practical ~~issues~~problems include reproducibility, controlled fabrication, and scale-up, among others. These critical problems associated with the currently available fabrication and characterization approaches ~~of~~for M-MSNs are far ~~away~~ from ~~their~~ practical applications.[5] However, ~~Recently steps have been taken towards the clinical applicability of metal nanoparticles~~MNPs ~~such as a silica gold nanoparticles dispersed on artery patch for cardiac tissue engineering application.[4b] It was concluded that there were no significant toxic effects or serious clinical complications in the group of patients during the clinical intervention.[138] To this end, though naked MSNs have~~

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~~exhibited excellent characteristics *in vivo* concerning the biocompatibility, degradation as well as bio-distribution and low toxicity, so far there is only one clinical trial was performed due to several challenges and essential hurdles ranging from the scale-up of quality MSNs to acceptable biological performances concerning the detailed bio-behavior.~~[5] ~~B~~based on these considerations that have created hope in the advancement of these innovative constructs, we believe that for metal species-encapsulated MSNs, ~~with in~~ in-depth analysis ~~on~~ of the evaluation of the toxicity and other biocompatibility attributes ~~will~~ should be certainly ~~be~~ explored ~~in clinical trials as they make~~to make a significant difference with regard to MSNs ~~on~~ for ~~their~~ biomedical applications.

7.2.3. DNA ~~d~~Detection

Nucleic acid detection is one of the fundamental studies in the biological and biomedical fields, which plays a crucial role in gene~~tic~~ therapy~~,~~ and clinical diagnostics.[140] Choosing a safe and cost-effective method for DNA detection is exceptionally decisive in the field of clinical diagnostics. Currently, various traditional methods such as polymerase chain reaction (PCR), DNA sequencing, and others, have been widely used for DNA detection.[141] However, they possess several disadvantages, such as time-~~consuming~~consumption, and ~~the~~ complexity ~~in~~ of labeling, among others.[141] In addition, much research in the past decade has witnessed ~~the~~ exceptional advancements in the development of various ultrasensitive bioassay procedures based on inorganic ~~based~~ materials ~~–~~that ~~have~~yield ~~–~~better performance owing to their ~~by utilizing the advantages of~~ intrinsic properties ~~of inorganic based materials~~.[140, 142] Along this line, ~~the~~ DNA detection is highly~~was~~ favorable *via* the loading of various dyes ~~in the mesoporous silica architectures~~into MSNs, such as Rhodamine B. However, the applicability of these composites is limited due to the restricted entrapment of ~~amount of~~ dye ~~was trapped in MSNs~~. Moreover, the appropriate location ~~of adsorption of~~for nucleic acids adsorption onto MSNs ~~as~~

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~~well as~~and critical mechanisms ~~involved~~ involving ~~in~~ the adsorption remain~~ed~~ unclear. To this end, M-MSNs have been utilized in recent years for the effective detection of DNA and other nucleic acids. With the added advantages of MSNs, ~~the various metallic species,~~ Pt nanoparticles-based MSNs ~~metal species (such as Pt nanoparticles) incorporated in the silica constructs~~MSNs improve the affinity of nucleic acid detection due to their electronic architecture, imposing ~~the~~ electrostatic interactions and catalytic signal amplification ~~by~~ from the transition metal~~s~~. ~~For example,~~ Wang and colleagues ~~*et al.*~~[141] designed ~~the~~ gated MSNs combined with the catalytic amplification of Pt nanoparticles, which acted as a smart reporter for the label-free detection of DNA. Initially, the MSNs-based core-shell nanoparticles (Pt@mSiO$_2$) were synthesized, and ~~then the~~ single-stranded DNA probes were then fabricated over the surface of the Pt@mSiO$_2$ through ~~the~~ electrostatic interactions. ~~The Pt nanoparticles have been known to possess intrinsic peroxidase-like activity, and~~ Moreover, t~~h~~e DNA coated over the surface prevented the catalysis of tetramethylbenzidine (TMB), the peroxidase substrate of Pt nanoparticles, as ~~the~~ Pt nanoparticles ~~were~~are known for ~~the~~ intrinsic peroxidase-like activity. ~~Moreover,~~I ~~i~~n the presence of complementary DNA for detection, the ~~surface~~ surface-attached DNA was hybridized, and the Pt nanoparticles were available for the catalysis of TMB, demonstrating the efficient detection of available DNA in the solution. The authors ~~claimed~~ validated that this method of DNA detection was highly advantageous over others as it was simpler~~,~~; label-free, *i.e.*, no requirement~~s~~ of labeling the ssDNA~~,~~; and self-signal amplifying in detection. ~~But~~ Nevertheless, t~~t~~his system ~~had~~ possessed similar sensitivity ~~compared~~ to that of the DNA detection system ~~that used~~ using fluorescence resonance energy transfer (FRET). ~~Therefore, further improvements concerning the sensitivity are still required to be progressed for efficient DNA detection.~~

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7.2.4. Peptide ~~e~~Enrichment

Another important biomedical application of M-MSNs is in ~~the~~ peptide enrichment ~~with high safety and sensitivity~~. In proteome research, many endogenous peptides ~~were~~ are known to contain potential biomarkers for recording their pathophysiological state in the body ~~toward~~, which can provide disease-specific diagnostic information.[21d] However, the separation and characterization of these endogenous peptides are ~~really~~ highly challenging due to the complexity and ~~a~~ wide range of biological samples. Therefore, it is necessar~~il~~y ~~important~~ to separate and selectively enrich these endogenous peptides before peptide analysis.[143] Enormous efforts has ~~have been dedicated~~ ~~In a way, much research has been dedicated~~ ~~in~~ to the development of various methodologies ~~toward the~~for qualitative as well as quantitative investigations of endogenous peptides in biological samples, which can achieve ~~more~~ higher clinical sensitivity and specificity ~~over~~ compared to those of various commonly used biomarkers.[144] However, ~~they~~ the methods still face certain limitations, such as selectivity~~,~~ and low efficiency ~~in~~ of the extraction, among others. To overcome these limitations, researchers have applied MSNs for peptidome research due to their high surface area~~,~~ and uniform~~l~~y~~-~~ sized pores, which allow the efficient capturing of ~~low~~ low molecular weight peptides from ~~the~~ biological s~~p~~ecimens~~amples~~, while substantially excluding ~~the~~ large-sized proteins based on the size-exclusion mechanism.[144b] These mesostructured porous ~~More often, these mesostructured porous~~ architectures ~~of silica~~ ensure the selectivity of peptide enrichment~~, by the exclusion of large proteins that are adsorbed on the surface, which is~~ and are highly advantageous over other particles with ~~the~~ larger surface areas, such as multi-walled carbon nanotubes (MWCNTs). The retaining of peptides in the mesopores ~~are~~ is often favorable ~~by~~ due to weak hydrophobic interactions between the peptides and siloxane moieties in the interior pores ~~wall.~~, which has

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substantially limited their applicability~~However, the efficiency of peptide enrichment is limited due to these weak interactions~~. To this end, various meta~~Metal~~ species (for instance, iron oxide, and ~~copper~~Cu) have been enclosed in the MSNs to ~~hold~~ offer significantly attractive features over the direct analysis of proteins in biological samples~~,~~ due to the combination ~~by combining~~ of ~~with~~ the uniformly distributed porous characteristics (~2-5 nm) of MSNs and solid-phase extraction by enclosed iron ~~-~~oxide species, along with superparamagnetic properties, which makes t~~which and acts~~enable them ~~as~~ strong candidates for use ~~for~~ in ~~the diverse applications including~~ peptide enrichment applications. Moreover, these innovative constructs offer specific advantages, such as specificity, selectivity, and ~~convenience as well as~~ performance efficiency, ~~in enrichment in comparison to~~compared to various currently available approaches. ~~In this framework~~ ~~It is evident that high-throughput screening is required for peptide enrichment, where the combinatorial efficacy of porous architectures of MSNs and solid-phase extraction by enclosed iron oxide species along with superparamagnetic properties make them promising and enhance their peptide enrichment applicability. To enhance their peptide enrichment specificity,~~ Deng and colleagues ~~*et al.*~~[143] designed ~~the~~ iron oxide-based MSNs with ~~the~~ a hydrophobic surface for the fast and selective enrichment of hydrophobic endogenous peptides in rat brain extract. Since most ~~of the~~ endogenous peptides are hydrophilic in nature, they ~~further~~then extended the~~ir~~ initial design by immobilizing ~~copper~~ Cu ions into the mesopores of magnetic core-shell nanocomposites (**Figure~~.~~ 19**).[21d] Further~~more~~, the mass analysis of proteins in human serum and urine after treatment indicated that numerous peptides were successfully enriched and separated with the help of multiple metal~~lic~~ species in ~~the~~ MSNs.

7.2.5. Artificial ~~e~~Enzymes

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Natural enzymes, often referred to as biocatalysts, in living organisms, are incredibly active and can ~~able to~~ accelerate the rate of reaction ~~at a higher rate~~ for some ~~a few of the~~ specific substrates in ~~the~~ biological processes.[145] However, artificial enzymes have ~~became~~ become highly desirable, as ~~the~~ natural enzymes face certain limitations in practical applications such as high sensitivity to environmental conditions, instability, ~~the~~ difficult~~ies~~y in recovery and recycling, expensiveness, and low operational stability, among others.[14d] To this end, ~~the~~ nanomaterials ~~–~~ based artificial enzymes, ~~are~~ often known as nanozymes, ~~which possess~~ offer several advantages, such as high stability, ~~-~~against harsh conditions, for example, ~~like~~ extreme pH values~~,~~ ~~–~~ ~~;~~ cost-effectiveness~~;~~ and easily tunable architectures. Various catalytically active inorganic nanomaterials have ~~currently~~ been used as nanozymes, such as graphene oxide, carbon nanotubes, ~~gold~~ Au nanoclusters, magnetic nanoparticles, M-MSNs, and nanoceria, among others.[145-146] Despite the success in ~~the~~ fabricati~~on~~ng ~~of~~ organized artificial functional systems, ~~it is profoundly challenging in~~ the development of ~~the~~ synthetic building blocks for assembling an enzyme-mimetic catalytic cascade is profoundly challenging. ~~In this framework~~Along this line, ~~gold~~ Au nanoclusters with different surface modifications have been fabricated to exhibit glucose oxidase- or peroxidase-like activities.[146c] However, the potential enzyme-mimicking behavior of these nanoclusters is limited and is highly dependent on the surface properties. Moreover, the stability attributes concerning aggregation and distribution have remained ~~as~~ highly challenging tasks, which may also cause a severe decline in their performance.

It is more convincing that ~~the~~ metal-incorporated MSNs are highly suitable to act as solid supports for these artificial catalysts owing to their inert nature and attractive physicochemical properties. With the added advantages of MSNs concerning ~~the~~ catalytic, optical, and electronic properties ~~and~~ to resemble the complexity and functional attributes of the natural enzymatic

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process, Qu and coworkers ~~*et al.*~~[14d] designed a self-activated, enzyme-mimetic ~~simulated~~ catalytic cascade ~~system~~ based on ~~the~~ expanded MSNs encapsulated with ~~the gold~~ Au-NPs~~nanoparticles~~ (EMSN-Au-NPs~~),~~). These nanoreactors were ~~which mimicked~~simulated as ~~as~~ both ~~the~~ peroxidase- and glucose oxidase ~~and peroxidase~~-like nanozymes ~~artificial enzymes~~ with exceptional stability. Herein, these robust nanozymes were self-organized without the ~~support~~sustenance of natural enzymes in performing the oxidation ~~of~~ glucose ~~as well as~~and the activation of peroxidase-like ~~activity~~efficacy by the gluconic acid. Initially, the EMSN-AuNPs catalytically oxidized the glucose molecules, yielding ~~to yield~~ the gluconic acid in phosphate-buffered saline (~~-~~PBS) and further the peroxidase-like activity of the MSNs was activated by gluconic acid at a reduced pH ~~by gluconic acid~~. Despite the significant benefits of M-MSNs as nanozymes, there is still a long way to go in their advancements ~~for~~ in terms of providing ~~the~~ mechanistic insights~~,~~ and scalability before they enter ~~the~~ clinics.

7.3. Catalysis

Knowledge of, understanding, and achieving control over the critical factors ~~that~~ influencing ~~the~~ reaction selectivity ~~is an~~are important prerequisites ~~of~~ for catalysis and ~~then~~ implementing ~~them~~ composite materials ~~then~~ to prepare an efficient and selective catalyst, ~~for~~ resulting in the formation of the desired product.[14c, 32c] ~~In the past few decades~~Over the decades, ~~the~~ transitional metals-based catalysts have attracted increasing attention ~~due~~ owing to their intrinsic physicochemical features, ~~and~~to their ~~-~~ significant catalytic performances, and ~~low cost~~cost-effective nature.[10, 14d, 21c, 54b, 82] In particular, these composites ~~show~~ can exhibit interesting optical, magnetic and electronic properties due to their quantum confinement, ~~which would~~ facilitate~~e~~ing the aggregation of metal ions into nanoparticulate forms ~~that~~, which ~~are~~ is a highly

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~~comparatively~~ efficient process compared to the~~ir~~ose of their counterparts.[4m, 94c, 147] Recent advances in the preparation methods of MNPs have enabled ~~the~~ researchers to achieve ~~the~~ precise control over their size, shape, and composition, ~~that~~ facilitating their utilization as model catalysts.[32c] ~~In addition, a~~A suitable carrier ~~of the catalyst~~ is another crucial factor to be considered for enhancing the~~ir catalytic~~ performance and recyclability of catalysts. In the past decade, MSNs have garnered enormous interest ~~from researchers~~ in the catalysis field due to their aforementioned attractive properties as well as compositional and structural diversities.[95a] Moreover, the high porosity and oriented tiny channels of MSNs act as ~~the~~ ideal solid supports for ~~the~~ accessible active sites in catalysis applications.

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Further advancements have been made to enhance their utility concerning the immobilization of multiple organic functional groups, metals or metal oxide species over the surface silanol groups.[4j] ~~In addition, t~~The narrow distribution of pore channels facilitates the growth of the MNPs such that they ~~get~~ are confined to within that size range. During this confinement, it ~~would be~~is possible to ~~produce~~ generate ~~the a quantized~~ variable quantities~~y~~ of active sites for catalysis.[48c] Moreover, the incorporation of metals ~~or~~/metal oxides into ~~the mesoporous silica support~~MSNs prevents their agglomeration~~,~~ and surface fouling, without affecting the catalytic activity and selectivity.[14c, 48b] With the added advantages of MSNs concerning the physicochemical attributes, these ~~heterogenous~~heterogeneous ~~ones~~ carriers are, in a way, a "green and sustainable approach" as they offer excellent colloidal stability, recyclability ~~as well as~~and recovery, poor degradability and reduce waste production. Moreover, these strong bases are environmentally benign and economically promising in catalyzing various reactions ~~at~~ under mild operating conditions. Various metals ~~like~~, such as ~~gold~~ Au and Ag,~~silver~~[14c] and metal oxides, such as ~~nickel oxide~~NiO,[45b] ~~titanium dioxide~~TiO_2, iron oxide, and ~~cobalt oxide~~diverse

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oxide forms of Co~~,~~ ~~that~~ encapsulated in MSNs have been utilized for efficient catalytic applications.[14c, 34, 48b] ~~Herewith~~Herein, we aim to give a brief emphasis on various reactions catalyzed by metal ~~species~~ species-encapsulated mesoporous silica materials. Broadly speaking, various types of reactions have been predominantly catalyzed by these innovative nanocomposites, ~~such as~~including redox reactions, such as~~including~~ oxidation, ammoxidation, epoxidation, nitridation, dehydrogenation and hydrogenation~~,~~; and metathesis (ethene to propene (ETP) conversion~~),~~—); hydrodesulfurization~~,~~—; isomerization~~,~~—; esterification and other miscellaneous reactions, ~~like~~ such as condensation and annulation reactions (**Figure~~.~~ 20**).[16a, 53f, 54c, 57, 80, 147-148]

As illustrated in **Table 3**, various metals or metal oxides ~~that occupied~~encapsulated at various positions of MSNs act as efficient catalysts.

~~More often~~Oftentimes, the catalytic performance of the M-MSNs composites utterly depends on the type of metal/ metal oxide used and the confinement strategy through which the ~~of~~ metals were loaded into the~~to the mesoporous support~~ MSNs. In general, various criteria concerning the metal species need to be considered ~~before~~ prior to the incorporation of the metals into the support. For instance, allylic C–H bond oxidation ~~have~~ has been studied ~~by~~ using different transition metals such as ~~chromium~~Cr,[149] ~~cobalt~~Co,[150] ~~manganese~~Mn,[151] and ~~copper~~Cu,[152] ~~However, a~~Among ~~them~~them, ~~copper~~ Cu ~~metal~~ grafted into the mesoporous silica *via* APTMS ~~has~~ resulted in ~~the~~ high catalytic efficiency due to its attractive properties, such as high yield, cost-effectiveness, and recyclability, as well as its recovery ability.[152] Another important factor that significantly influences the catalytic efficiency of M-MSNs is the confinement approach. In some instances, the metal species in their nanoparticulate forms loaded into the MSNs rely on the weak interactions between the support and metal. For example, ~~the~~ Au nanoclusters tend to show

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weak interactions with silica and carbon-based materials, while they ~~hold~~ show strong interactions with various supports, such as TiO_2 and hydroxyapatite (HAP)~~, while they hold weak interactions with silica and carbon-based materials~~.[153] ~~More often, the loaded metal species either free or nanoparticulate forms in the MSNs often rely on the weak hydrophobic interactions between support and metal.~~ ~~In some cases, t~~It should be noted that the metals species tend to migrate out of the pores during calcination at high temperatures, which ~~and~~ results in the formation of bulk aggregates, ~~which~~ is almost inevitable and ~~would~~ may result in ~~their~~ poor performance efficiency.[48c] S~~S~~everal approaches have been proposed to improve the metal loading amounts by creating ~~forceful~~ dynamic interactions with the ~~the~~ solid supports. One ~~amongst them~~approach is a~~A~~ templating method that typically utilizes the integration of metal species with the surfactant ~~has been proposed~~, which ~~would~~ can be safe during ~~the~~ calcination. Briefly, Fu ~~et al.~~and colleagues[48c] fabricated ~~tIn this context, the~~ metal oxide species, such as NiO, using a direct template assembl~~ing~~y route ~~by~~through ~~were~~ ~~anchored~~ anchoring *in situ* into the channels of mesoporous silica ~~by a direct template assembling route~~.[48c] The well-distributed NiO in the mesoporous silica was applied ~~in~~ for the epoxidation of styrene with *tert*-butyl hydroperoxide. Further~~more~~, the catalytic activity of this novel material was enhanced by increasing the loading amount~~s~~ of Ni in the mesoporous silica.[48c] Similarly, isolated lithium sites ~~can be~~were anchored on the silica wall by the reaction between the metal alkoxide and silanol groups, resulting in ~~the~~ stable grafted samples for heterogeneous transesterification reactions, which would be very difficult to achieve by conventional methods.[154] ~~In this context, n~~Numerous reports have demonstrated ~~the~~ redox reactions using ~~various~~ diverse metal species ~~in MSNs~~ such as ~~molybdenum oxide~~MoO_3, ~~palladium oxide~~PdO, ~~magnesium oxide~~MgO, ~~boron~~B, ~~aluminium~~Al, ~~ruthenium~~Ru, ~~gallium~~Ga, vanadium (V) and others~~,~~ for ~~the~~ applications focusing

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on dehydrogenation, the hydrogenation of phenols and carbon dioxide, the oxidation of methanol, catalytic epoxidation reactions and others.[16a, 53f, 54c, 57, 80, 147-148]

In addition to transition metals, there has been increasing interest in the generation of alkali metal salts-supported mesoporous solids for increasing the basicity of the highly active sites over the support. Several studies have been dedicated to improveinging the base strength by using various metal oxides, such as cesium and potassium oxides, methylation approach over nitrogen doped mesoporous silica.[154] However, the eventual constructs have shown weak basicity and poor mesostructures. In an attempt to catalyze the heterogeneous trans-esterification reactions, while improving the basicity of the active site of the solid support, Sun et alandand coworkers,[154] fabricated the heterogeneous silica support by anchoring the lithium metal ions onto the silanol group of mesoporous silica *via* an approach based on the molecular precursor approach through the reaction of lithium *tert*-butoxide (LBT) at room temperature resulting in the strong basic site on the silica surface. This approach has shown an excellent catalytic activity in the synthesis of dimethyl carbonate (DMC) from ethylene carbonate and methanol *via* trans-esterification. Among various alkali and alkaline metals as well as metal oxides available, the Li-based synthesis of DMC is higher comparatively compared to that those of the known promising metal species, such as, CaO and Al_2O_3 due to the high loading efficiency of Lithiumlithium, as it was by grafted grafting them onto the silanol groups,. However, the loading efficiency eventually which would depend relylies on the number of silanol groups in the host matrix. On the other hand,Moreover, the alkali metals also supported the catalytic ability of transition metals that encapsulated in the mesoporous solid silicas support through significantly influencing the catalytic behaviors *via* electronic effect and improving the basicity. Wang et alandand colleagues,[155] demonstrated that the alkali metals had increased the dispersion of the transition metal species and also altered the configuration of iron arrangement in the

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support leading to ~~the~~ stabilization of Fe metal~~iron~~, which was accountable for the epoxidation of propylene. Other miscellaneous reactions catalyzed by the M-MSN composites include knoevenagel condensation reaction[54b] and Friedländer annulation reaction ~~by M-MSNs~~, among others.[41d] These eco-friendly and potential reusable heterogeneous catalysts based on M-MSNs ~~were~~ are highly efficient. However, the process and ~~the~~ yield of the end product utterly depend on the surface grafting of various groups for appropriate basicity.[41d]

7.4. Photoluminescence

Indeed, ~~the~~ metal oxides on the nanoscale range (~2~~,~~3~~10 nm) with quantum confinement properties are the promising candidates for optical purposes, such as diagnostic, photocatalytic, and photovoltaic sensing~~,~~ and ~~therapeutic~~ theranostic applications.[51b] These nano-sized structures exhibit enormous luminescence ~~property~~ properties compared to ~~that~~ those of ~~their~~ the corresponding bulk matter~~s~~ due to the high ~~surface~~ surface-to-volume ratio~~,~~ and significant electronic, magnetic, and optical~~, electronic, and magnetic~~ properties~~, among others~~. However, ~~the~~ control over the configuration and the determination of functional attributes of these materials ~~has~~ have become highly ~~difficult~~ challenging in recent years. In addition, the metal oxide nanoparticles ~~lose~~fail to exhibit ~~their~~ luminescence efficiency ~~due to~~in some instances of severe aggregation, which is undesirable. This can be~~o overcome these limitations,~~ addressed by dispersing the photoactive nanostructures ~~are dispersed~~ into the porous supports, such as ~~like silica matrix~~MSNs, to hinder the particle-particle interactions and facilitate ~~the~~ excellent suspension ~~ability~~abilities.[51b] Moreover~~In addition~~, MSNs are highly suitable as a carrier for depositing such~~these~~ photoluminescent materials ~~because of~~due to their morphological attributes such as high surface area~~,~~ and tunable porosity, ~~that~~which~~,~~ facilitates efficiently~~transparency in significantly~~ exploring the optical ~~properties~~ and ~~their intrinsic~~ aforementioned attractive

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intrinsic properties ~~such as high surface area, tunable porosity, and others~~. ~~Moreover, these solid host matrices act as effective support in hindering the particle-particle interactions.~~ The sizes of photoluminescent semi-conductive particles should be such that they are within the range of the size of the narrow pore channels of ~~mesoporous solid~~MSNs ~~support~~, which can result in the band gap ~~enhancement~~enrichment ~~of the band gap~~ of ~~the~~ semiconductors. However, the loading of semiconductive ~~zinc oxide~~ZnO nanoparticles into the silica channels has remained ~~as~~ a problem, as it often results in ~~the~~ aggregation on the external surface of the silica. ~~In one case,~~ Niu and colleagues ~~*et al.*~~[51a] fabricated ~~zinc oxide~~ZnO in MSNs *via* a chelating-template strategy. Initially, the zinc ions were captured by ~~N-hexadecylethylenediamine triacetate (~~HED3A~~)~~, a triprotic surfactant that then directed the mesophase formation, enabling the encapsulation of ~~zinc oxide~~ZnO species inside the mesoporous ~~silie~~siliceous~~a~~ matrix during the calcination procedure. However, the photoluminescent properties of the encapsulated ~~zinc oxide~~ZnO ~~had~~ exhibited ~~a~~ size-dependent light emission and quantum confinement effects ~~of metal oxides~~. Further, ~~this~~ the authors demonstrated that the simple approach ~~can~~ could be extended to ~~various~~ different kinds of metal oxides with host-guest interactions for achieving good dispersibility and superior performance.

Indeed, n~~In general, the n~~anoparticles-related delivery systems are now facing a ~~a few~~few specific ~~critical~~ challenges ~~that have should to be explicitly addressed for exploring demonstrating their efficient delivery~~, such as the lack of ~~ability~~capability to target specific cell types ~~tissues and cell types~~ and ~~escape from the~~ reticuloendothelial system (RES) escape~~uptake~~, which ~~are~~is~~are~~ required to be addressed.[156] To ~~elucidate~~addresse these ~~facts~~issues, various kinds of luminescent nanoparticles have been utilized, namely dye- doped nanocontainers, semiconductor nanoparticles, and MNPs, which are of particular interest in bioanalysis, drug

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delivery, and diagnosis. Recently, M-MSNs have ~~-~~emerged~~volved~~ as a new hybrid platform for luminescent bio-labeling for diverse biomedical applications. In this framework, the concept of encapsulating ~~-~~europium ions (Eu^{3+}-)~~-complexes encapsulation~~ in the mesoporous support has been proposed for cellular labeling, using light excitation (355-365 nm).[157] This was achieved by grafting the transition metal complexes onto the silica wall surface *via* a bi-functional ligand, which was grafted onto the silica wall on one side and chelated with ~~the~~ metal on the other side. In addition,~~ the other way was proposed by impregnating~~ encapsulation of ~~-~~the Eu^{3+} complexes into the MSNs ~~with the Eu^{3+} complexes~~ and then coated ~~elaborated~~ with a silica shell ~~coating, which would~~ achieved ~~a~~ better results in avoiding the premature leakage of the dye.[157] Although the Eu^{3+}-complexed~~s~~-encapsulated MSNs ~~composites~~ have shown significant ~~encapsulation~~loading efficiency of dyes for luminescent bio-labeling, the utilization of UV-light is sub-optimal for cellular labe~~l~~ling applications.

7.5. Miscellaneous

In addition to various applications including catalysis, biomedicine, and photoluminescence, these metal-encapsulated MSNs have been used in various other applications such as lithium storage, gas sensing, and metal extraction. In this section, we provide a brief synopsis of these aspects.

~~In~~ From the synthesis point of view, mesoporous silica-based materials such as SBA-type ~~silica composites~~materials ~~have~~ can be~~been~~ used as hard templates for synthesizing the mesoporous metal oxides (mMOs).[158] These mMOs have been processed by infiltrating the metal ions onto the ~~mesoporous silica~~MSNs~~ support~~. It should be noted that although there ~~exists~~exist certain similarities in the mesostructures and morphologies between mMOs and mesoporous silica materials, however, the textural properties (surface area and pore volume) are

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comparatively lower in mMOs, in the range of 84-121 m^2/g and 0.22-~~–~~0.35 cm^3/g, respectively.[158] Moreover, these constructs exhibit better hydrothermal and chemical stabilities over pure ~~mesoporous silica materials~~MSNs. ~~-~~In a way, graphene-encapsulated mMOs of tin (~~tin~~ Sn) and ~~manganese~~ Mn were synthesized using the silica support for stabilization and better performances ~~as~~ of lithium-ion batteries as they were potential anode materials.[159]

~~On the other hand, T~~the customized metal species, such as metal, metal oxides, and semiconductors can readily put together within the ~~mesoporous silica~~siliceous frameworks mediated by versatile surfactant ~~that acts~~ as capping agents.[4j] ~~In this context, t~~These metal species embedded in the MSNs act as hard templates, which can be removed by acid etching for the generation of ~~hollow~~ HMSNs. These innovative carriers are highly~~, which are highly~~ appropriate for delivering the macromolecules such as therapeutic proteins, ~~because~~ as the ~~inner hollow~~hollow inner space facilitates their efficient encapsulation.[14e]

Another application of ~~–~~M-MSNs, specifically semiconducting metal oxides-encapsulated composites is gas sensing~~, –~~. Owing to the~~which has been extensively investigated using semiconducting metal oxides due to the~~ advantages of metal oxides, such as ~~ir~~ ultra-sensitivity, stability, and long lifespan, these composites have garnered considerable interest in sensing applications~~, and low cost~~.[53a] More often, ferrites have been utilized for gas detection ~~as they display~~due to their characteristic responses toward~~s~~ redox gas species, high thermal, and chemical ~~stability~~stabilities. In one case~~a way~~, spinel zinc ferrite nanoparticles encapsulated into the mesoporous silica support *via* host-guest chemistry have ~~had~~ exhibited higher sensitivity, a lower detection limit, and a quicker response toward~~s~~ gas sensing.[53a]

Another important application of ~~these metallic species in~~ M-~~M~~MSNs is the degradation of organic dyes during wastewater treatment.[53c] *In situ* growth of iron oxide and ~~iron~~Fe metal-

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containing bimetallic systems in MSNs ~~have been found~~can be effectively used ~~effective a~~as a heterogeneous Photo-Fenton catalyst for the degradation of mixed dyes due to the rapid execution, cost-effectiveness, and eco-friendly nature.[53c] ~~This process of degradation of organic dyes and mixed dyes is very rapid, low cost and eco-friendly.~~

Metals incorporated in the mesoporous silica substrates can ~~also~~ be used for the efficient extraction of radioactive metals.[42a] These carriers are potentially more advantageous over others due to their high surface area, and an effective adsorption efficiency in the presence of transition metals~~, among others~~. Functionalized iron oxide-encapsulated MSN composites ~~were~~ have been used for efficient and convenient uptake of uranium from aqueous solutions. In addition, the pH of the medium play~~ed~~ a crucial role in the ~~extraction~~ sorption of radioactive metals~~process~~, in which~~,~~ nearly neutral pH ~~had~~ significantly ~~favored~~ enhance~~d~~s the uranium extraction.

8. Conclusions and ~~future~~ Future ~~trends~~ Trends

In summary, this review has emphasized and discussed various approaches involved in the arrangement of diverse metal~~lic~~ species in the confined nanospaces of a ~~the~~ mesoporous silica support for ~~the~~ applications focusing on adsorption, catalysis, photoluminescence, and biomedicine, among others. ~~For instance, t~~These encapsulated metal~~lic~~ species have significantly contributed ~~in~~to enriching ~~ed~~ the functionalities of conventional MSNs by augmenting their optical, electronic, and chemical properties~~,~~ towards the advancement of their applications ~~which significantly extended their applicability~~. In addition, we also gave an overview of the factors influencing the ~~metal~~ incorporation of diverse metal species in MSNs and summarized the properties of nanocomposites concerning their applications in the catalytic and biomedical fields.

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Currently, most of these M-MSNs materials and investigations relevan~~cet~~ to fabrication and applications are indeed in their infant stage. The critical aspects relevant to the fabrication of M-MSNs include controlled and reproducible synthesis and scale-up~~, controlled and reproducible synthesis~~. It should be noted that the currently available fabrication and characterization strategies of M-NSNs are far ~~away~~ from any ~~medicinal~~therapeutic applications, requiring in-depth investigations and innovative breakthroughs toward their applicability. Despite the successful fabrication of diverse metal~~lic~~ species on ~~the~~ mesoporous solid supports through various hybridization procedures including the hydrothermal syntheses~~ that have widely been studied~~, there is no generalized preparation method~~ currently~~, as the preparation conditions of the currently available methods are ~~certainly~~ specifically dependent on the kinds of metal ions used. Moreover, the reported methods that are ~~efficiently~~ ~~work~~ reliant on~~on~~ ~~the post~~ post-modifications ~~by means of~~through grafting and ~~ion~~ ion-exchange onto ~~the~~ silanol groups often result~~ed~~ in ~~the~~ unstable composites~~,~~ and ~~poor~~de~~prived~~creased loading efficiency~~ies~~ of the metal ~~ions~~species ~~loading efficiency~~the loading amount of metal ions is small. ~~In addition,~~Thus, it is ~~also~~ challenging to control the doping of metals ~~by~~ through the available incorporation methods. a~~ As~~s most of the ~~method~~processes that are based on a high dilution method result in ~~the~~ low ~~quantity~~ yields. These challenges eventually affect the scale-up of the ~~Other challenges relevant to~~ M-MSNs ~~include their scaling up, as most of the methods that based on high dilution method result in the low quantity yields~~. Exploring these approaches ~~to the~~ for practical applications including~~in~~ synthesizing bulk quantities, is profoundly challenging ~~concerning~~ in terms of ~~the reproducibility~~reproducible fabrication with~~,~~ uniformity in size~~s~~, loading efficiency of metal/metal oxides or MNPs and their collection. To fulfill these ~~conditions~~limitations, ~~it is required to~~ the development of various cheap sources of organic templates, silica, ~~metal precursors~~ and

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metal precursors ~~organic templates~~ for pore formation is required~~,~~ to reduce the synthetic steps, shorten the time of processing, avoid the requirement of highly alkaline ~~and base~~ conditions and facilitate ~~to carry out under~~ safe conditions ~~to~~ ~~and~~for their ~~explore~~ exploration ~~them~~ for industrial applications. In regard~~s~~ to their applicability ~~to various other fields~~in ~~such as~~ adsorption, catalysis, and photoluminescence, despite the success in the confinement of metal species and the advancement ~~in~~ of their applications, it is highly required to produce ~~the~~ a simple method by which to generate ~~great~~ excellent particle dispersion with superior catalytic, electronic, magnetic, ~~catalytic, optic, or~~ and/or optic ~~electronic~~ properties. Further~~more~~, the mesoporous silica coating over metal substrates ~~would ha~~v~~s~~e the ~~a good great~~abundant potential for use ~~of~~ in the adsorption of toxic substances ~~adsorption,~~ H~~-h~~owever, avoiding the collapse of the mesoporous framework would improve ~~the~~its~~ir~~ performance. Moreover, detailed investigations ~~on~~ of the catalytic properties of these ~~metal species encapsulated MSNs~~M-MSNs are necessary to address various attributes of the metal confinement and hydrophobicity. Together, the available literature suggests that the status of currently available fabrication and characterization techniques are significantly far ~~away~~ from the representative applications of these constructs.

Although extensive research in the past two decades achieved by significantly transforming these innovative M-MSN products from *in vitro* to *in vivo* evaluations ~~,~~and focusing the on biomedical applications has been performed.~~Though the tremendous progress~~numerous ~~investigations~~ ~~in the synthesis, as well as applications of mesoporous silica materials and their advancements in encapsulating various metallic species in the past two decades have been achieved~~performed~~,~~ the safety and toxicity concerns of these innovative M-MSNs remain~~ed~~ ~~as~~ significant challenges, which has limited their potential applicability concerning ~~the in concern to various~~ biomedical applications. Though the biocompatibility of these M-MSNs is ~~successful~~

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acceptable to some extent at the cellular level, it is evident that the toxicity of the nanoparticles significantly ~~varies~~ varie~~d~~s among different cell lines, ~~which~~ requiring~~es~~ in-depth investigations. Moreover, it should be noted that some of the metals exhibit enormous toxicity just above ~~its~~ the background concentration that ~~being~~is present in the environment. Although the mechanisms of toxicity of certain metal species such as Cd, and Cr, among others, remaine~~d~~ unclear, the potential impact of such toxic metals in ~~larger~~more significant amounts poses risks of~~to~~ severe health disorders, instigated by chronic and acute metal toxicity~~,~~ with symptoms, such as lower energy levels, osteoporosis, immunodeficiency, and damage to the functions of major organs, *i.e.*, the brain, liver, lungs and kidneys. Other potential toxicities based on the long term-exposure to excess concentrations of heavy metals include neurodegeneration, multiple sclerosis, and estrogen-related disorders in females such as endometriosis, breast tumors, and premature delivery, ~~as well as~~and severe hypotrophy conditions. These consequences strictly demand ~~for~~ in-depth analyses ~~on~~for establishing the mechanisms o~~n~~f metal-induced toxicity~~,~~ at epigenetic, genetic, and biochemical stages ~~However, it is necessary to evaluate the biocompatibility of such devices~~ in ~~the~~ animal models, followed by ~~and then~~ explor~~e~~ation ~~the same~~ in ~~the~~ clinical studies.

Furthermore, these designs suffer from ~~certain~~ specific uncontrolled biodegradability issues, leading to ~~the~~ long-term accumulation-induced biosafety risk. More often, ~~the~~ siliceous frameworks are ~~often~~ excreted *in vivo* through delayed ~~urine~~renal excretion ~~through~~ ~~by~~in urine instead of through ~~compared to the~~ hepatic digestion, *i.e.*, through feces, ~~which~~but this is, however, significantly dependent on the final size of the MSNs and on surface modifications,~~s~~ such as PEGylation. Similarly, ~~the~~ renal excretion of M-MSNs could also be ~~be happened to be~~ favorable through renal excretion, as the metal species are in tra~~n~~ce amounts compared to the silica in M-MSNs. However, the eventual compatibility and clearance of M-MSNs are strictly

dependent on the biodistribution and ~~the~~ clearance of the respective metal species, in addition to the physicochemical properties, and surface cha~~a~~rge, which affect~~ing~~ the clearance routes and~~s~~ ~~well as~~ rates. However, it should be noted that the available quantification methods based on the fluorescence intensity suffer from certain limitations of quenching and interference ~~of~~ from the background signals of silica, demanding more accurate estimation approaches for reliable information to establish the biodistribution, degradation and substantial clearance of M-MSNs. Some of the m~~. . .~~

~~M~~etal species ~~such as~~ (Mg, and Ca, and a ~~some~~few transition metals~~-~~, Fe and Cu) ~~that are~~ present in trace amounts in the body ~~such as Fe and Cu~~ are highly biocompatible compared to other first-transition-row divalent metals such as Co~~)~~ and Ni~~)~~ and Zn, and c~~ould~~an be eliminated~~xcreted~~ ~~well~~ through renal excretion. We anticipate that the utilization of such highly ~~efficient~~safe transition metals in trace amounts~~,~~ and ~~deprived~~ the decreased usage of ~~multiple~~various toxic metals can overcome these degradability and compatibility issues to a considerable extent. Several methodologies, such as polymeric coatings, ~~and others~~ have been explored~~.~~; ~~which,~~ however, they still require ~~in depth~~detailed investigations to explore their compatibility attributes.

Moreover, ~~We anticipate that~~ there is also ~~a~~ the possibility of ~~also~~ combating these aspects by ~~using~~ utilizing ~~the~~ biocompatible building blocks and biodegradable linkages, such as organosilica components in the M-MSN frameworks, allowing their decomposition and renal excretion, ~~as well as~~and by utilizing the metal species, for example, essential trace elements in the body that are highly compatible ~~and are acting as essential trace elements in the body,~~ . ~~In addition, the utilization of minor quantities of high efficeient metals and deprived usage of multiple toxic metals can also combat these degradability and compatibility issues.~~ M-MSNs

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may be ~~go ahead~~advanced in terms of fabricating ~~the~~ biocompatible as well as biodegradable composites, which would create an enormous scope ~~concerning~~ of their future clinical applications. These strategies may open a new paradigm in the healthcare field to produce biodegradable composites with better performances. Moreover, there is a critical need to conduct more systematic investigations and thorough documentation of their toxicity issues, which will provide ~~a~~ better references for the proper interpretation of results obtained ~~results~~ in the future. ~~However~~In addition, some of the critical ~~issues~~ problems associated with M-MSNs ~~are yet~~ remain~~ed~~ to be addressed, such as their better *in vivo* tracking ~~to~~ for understanding the blood circulation, clearance fate, and other metabolic attributes~~,~~; the proper confinement of metals in the confined nanospaces; and the achievement of surface functionality with optimum stability and targeting ability.

~~Although the degradability is a safety~~ In addition to safety and compatibility issues~~concern that needs to be addressed~~, ~~there is a~~ critical care should be taken regarding the~~requirement concerning the~~ structural stability of the M-MSNs, which significantly ~~nanoparticles~~influenc~~ing~~es their~~ir~~ biobehavior ~~during~~ ~~the~~ drug delivery applications, meaning that the structural intactness of the carrier should be maintained to prevent the leaching of guest molecules before reaching the target site. The carrier should be then degraded into small biocompatible blocks for their easy clearance from the body, ensuring no systemic adverse effects. Thus, it~~It~~ is ~~highly~~ required to maintain a critical balance ~~in~~between the safety and stability of M-MSNs. These effects are often dependent on the ~~kind~~ type of metal used, eventual particle size, surface functionalization, pore morphology, and degree of silica condensation. The i~~I~~ncorporation of functional groups that are stimuli-responsive would help them in the degradation of the M-MSN framework after performing their therapeutic duties and facilitate

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their excretion without any systemic toxicity. In addition, despite the significant benefits of M-MSNs as nanozymes, drug delivery systems, DNA detection~~,~~ ~~and~~ ~~imageable~~ imaging agents, several issues, such as providing the mechanistic insights, sensitivity, and scalability, are~~there is~~ still ~~a long way to go in their~~in infancy, requiring detailed investigations~~ developments for providing the mechanistic insights, sensitivity, and scalability~~. Thus it is required to develop specific, ~~standardized~~consistent ~~methods~~approaches to ~~assess~~evaluate the biological ~~impacts~~effects of M-MSNs before they enter the clinics. Furthermore, the bulk manufacturing of these innovative designs poses ~~to~~ several challenges ~~that need to be addressed~~ for promoting their scale-up and batch-to-batch reproducibility, which are predominant features to~~to~~ translate them from the bench to clinical practice. Moreover, the~~studies~~ investigations on the potential hazards of M-MSNs will be useful in ~~establishing~~creating guidelines for their utilization. We anticipate that the innovative advancements pertaining to ~~the~~ M-MSNs will ~~certain~~undoubtedly continue to emerge ~~in near future~~in the near future.

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Conflict of interest

The authors declare that this article content has no conflict of interest.

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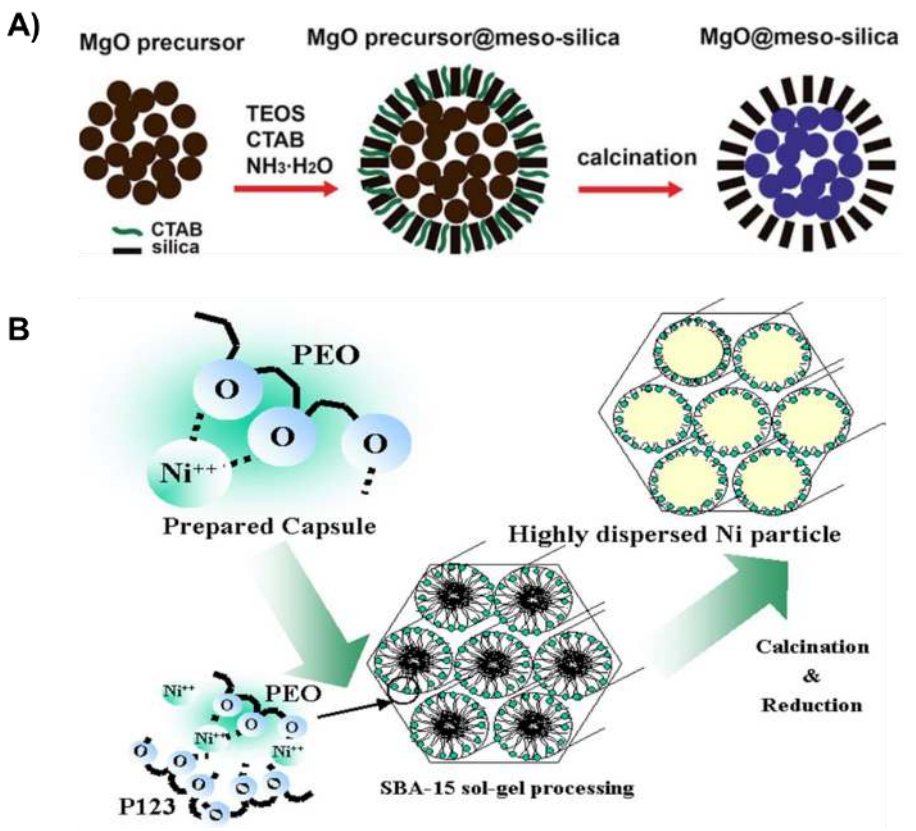

Figure 1. (A) Schematic representation of the preparation of MgO@mSiO$_2$ spheres. Reproduced from Ref. [44] with permission from the Royal Society of Chemistry. B) Encapsulation route *via* ~~polyethylene oxide (~~PEO~~)~~ for the dispersion of NiO onto mesostructured silica. Reproduced from Ref. [48b] with permission from Elsevier.

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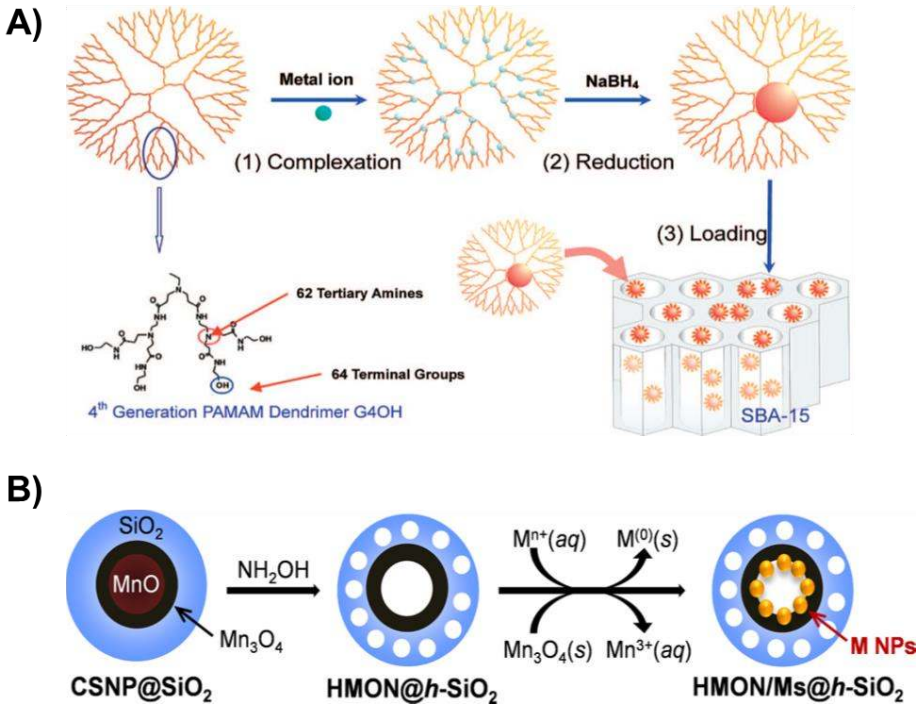

Figure 2. Immobilization of MNPs on MSNs via post-grafting method. A) Synthesis of dendrimer-encapsulated MNPs and the subsequent immobilization of the nanoparticle on mesoporous support. Reproduced from Ref. [32b] with permission from the American Chemical Society. B) Schematic representation illustrating the functionalization of the interior surface of HMSNs and the subsequent immobilization of MNPs. Reproduced from Ref. [26] with permission from the American Chemical Society.

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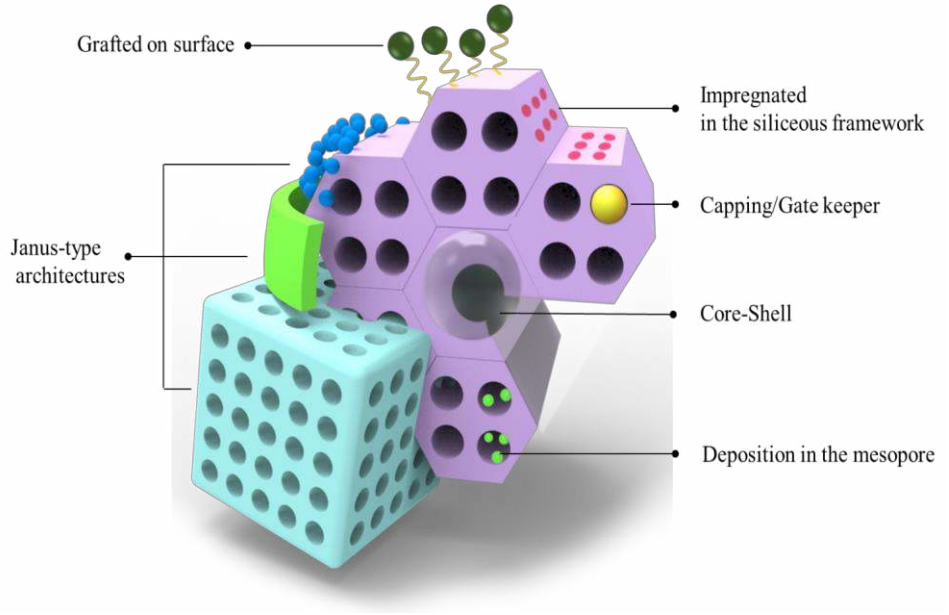

Figure 3. Schematic illustration representing the possible location for the confinement of metal species in MSNs.

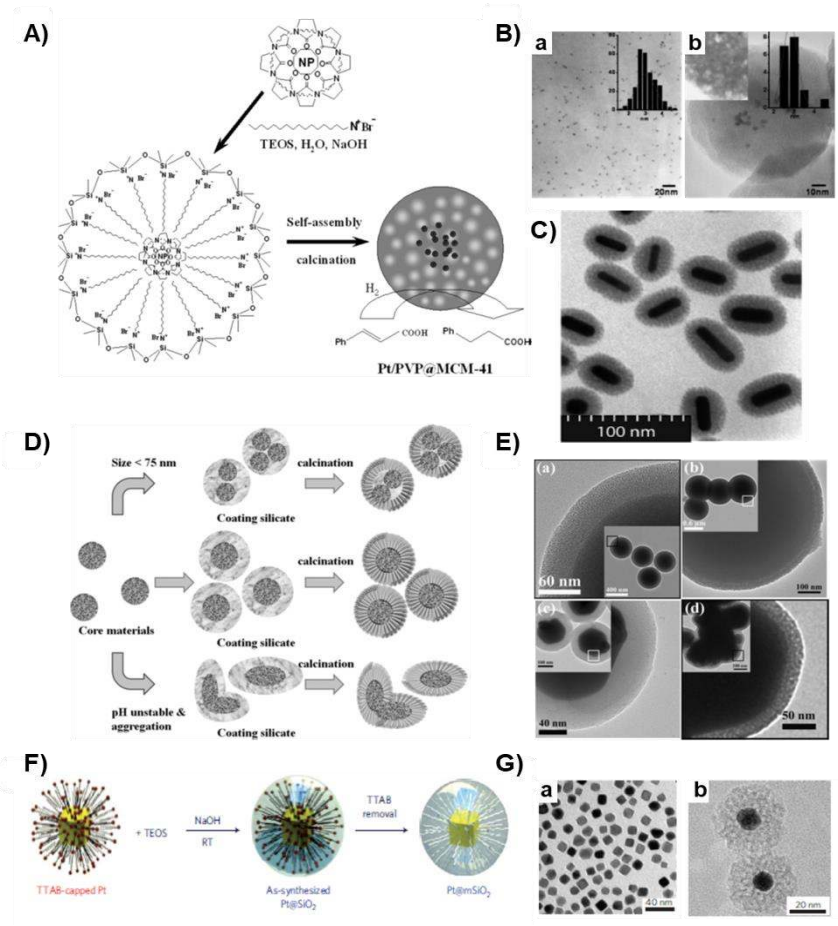

Figure 4. Core-shell architectures of M-MSNs. A) Schematic representation illustrating the preparation of Pt@mSiO$_2$ and their respective B) TEM images (a) Pt nanoparticles (b) core-shell nanospheres. Reproduced from Ref. [32a] with permission from the John Wiley and Sons. C) TEM images of AuNRs@mSiO$_2$. Reproduced from Ref. [14e] with permission from the American Chemical Society. D) Schematic representation of the metal oxide-coated MSNs and their respective E) TEM images illustrating the typical low and high-resolution view of (a)

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SiO_2@mSiO_2, (b) TiO_2@mSiO_2, (c) Ag@mSiO_2, and (d) ZnO@mSiO_2. Reproduced from Ref. [28b] with permission from ~~the~~ John Wiley and Sons. F) Schematic representation illustrating the synthesis of Pt@mSiO_2 nanoparticles, and G) the TEM images of Pt nanocubes and Pt@mSiO_2. Reproduced from Ref. [32c] with permission from the Nature Publishing Group.

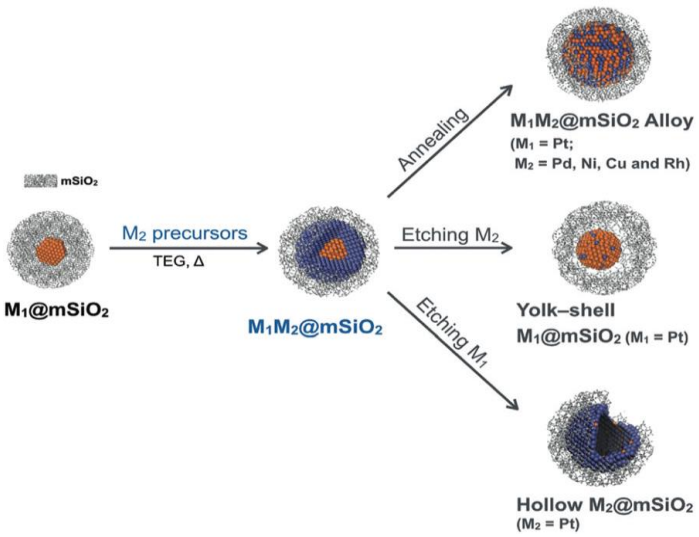

Figure ~~.~~ 5. Schematic representation illustrating the seeded growth of bimetallic M_1M_2@mSiO_2 nanoparticles from M_1@mSiO_2 seeds and their derived nanostructures. Reproduced from Ref. [64] with permission from the Royal Society of Chemistry.

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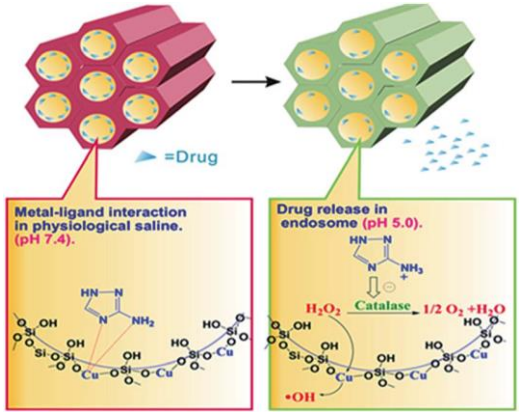

Figure 6. Schematic representation illustrating the copper-impregnated mesoporous silica framework and the mechanistic illustration of pH-responsive delivery in the tumor environment. Reproduced from Ref. [21a] with permission from the Royal Society of Chemistry.

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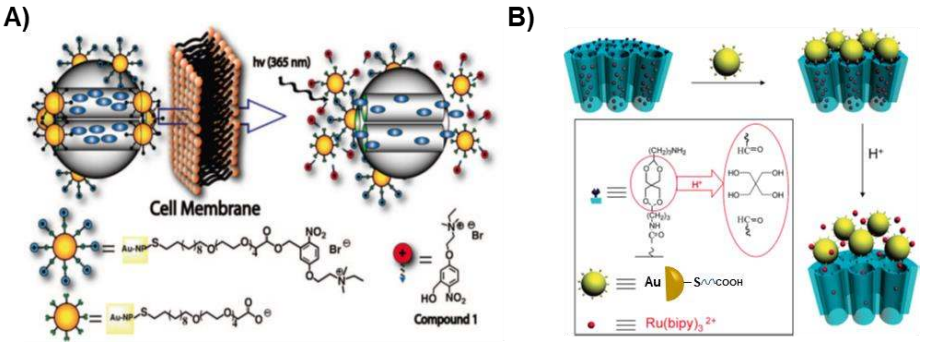

Figure 7. Schematic illustrations of the A) photoinduced[60b] as well as B) pH-responsive[86] delivery of drugs from ~~gold nanoparticles~~Au-NPs-capped MSNs. Reproduced from Refs. [60b, 86] with permission from the American Chemical Society.

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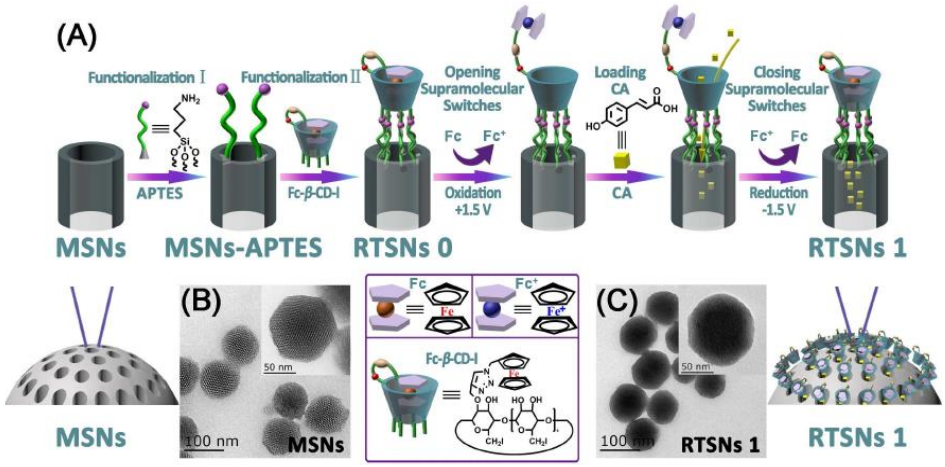

Figure 8. A) Schematic representation of the preparation of Redox-triggered smart nanocarriers (RTSN) showing the sequential steps of functionalization process and potential-driven loading as well as unloading of drug cargo. TEM images of B) MSNs and C) RTSNs. Reproduced from Ref. [87] with permission from the Royal Society of Chemistry.

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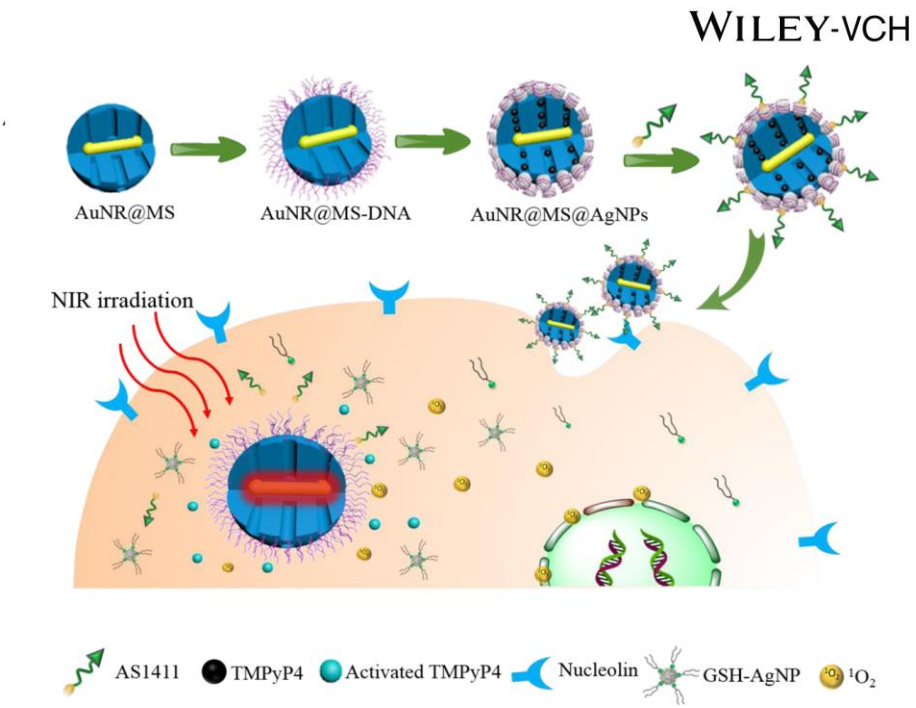

Figure 9. Schematic representation of Ag-NPs gated, mesoporous silica-coated Au-NRs as a new low premature release and multifunctional cancer theranostic platform. Reproduced from Ref. [85e] with permission from the American Chemical Society.

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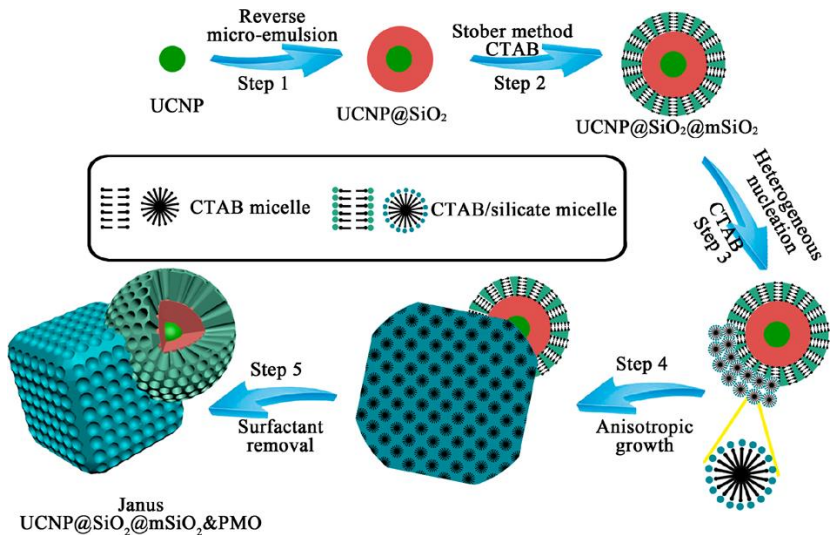

Figure 10. Synthetic procedure for the dual-compartment Janus MSNs, UCNP@SiO_2@ $mSiO_2$&PMO by the anisotropic island nucleation and growth method (UCNP = NaGdF4:Yb,Tm@NaGdF4, $mSiO_2$ = mesoporous silica shell, PMO = periodic mesoporous organosilica). Reproduced from Ref. [75a] with permission from the American Chemical Society.

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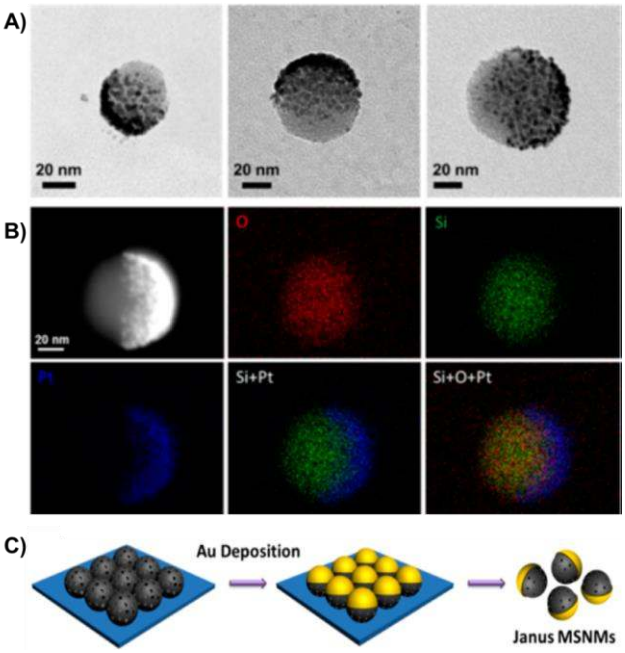

Figure 11. A) Characterization of Janus MSNs with different sizes coated with Pt (2 nm) installed by electron beam deposition. B) STEM-HAADF image and element mapping of Janus MSNs. Reproduced from Ref. [75b] with permission from the American Chemical Society. C) Schematic illustration of ~~gold~~ Au nanosphere-coated Janus MSNs by vacuum sputtering. Reproduced from Ref. [75c] with permission from the American Chemical Society.

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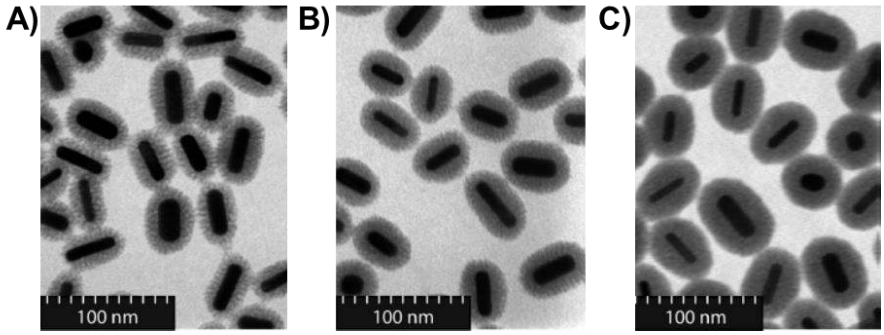

Figure~~.~~ 12. TEM images of mesoporous silica-coated Au-NRs ~~GNRs~~ after (A) 1 h, (B) 10 h, and (C) 500 h. Reproduced from Ref. [14e] with permission from the American Chemical Society.

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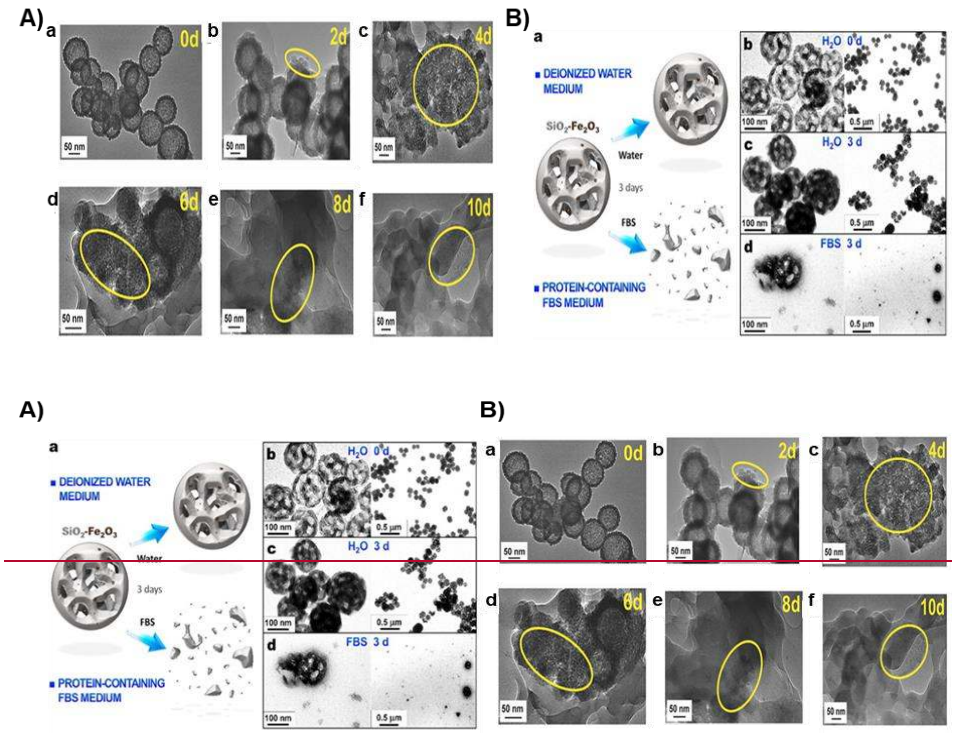

Figure 13. A) TEM images of Fe-HMSNs after the biodegradation in FBS for a) 0, b) 2, c) 4, d) 6, e) 8, and f) 10 days. Reproduced from Ref. [121] with permission from the John Wiley and Sons. AB) (a) Schematic representation of the degradability of large-pore silica-iron oxide nanoparticles in water and in FBS. Biodegradation of Fe-HMSNs, TEM images of the nanovectors before (b) and after three days of dispersion in water (c) or in FBS (d). Reproduced from Ref. [59a] with permission from Elsevier. B) TEM images of Fe-HMSNs after the biodegradation in FBS for a) 0, b) 2, c) 4, d) 6, e) 8, and f) 10 days. Reproduced from Ref. [119] with permission from the John Wiley and Sons.

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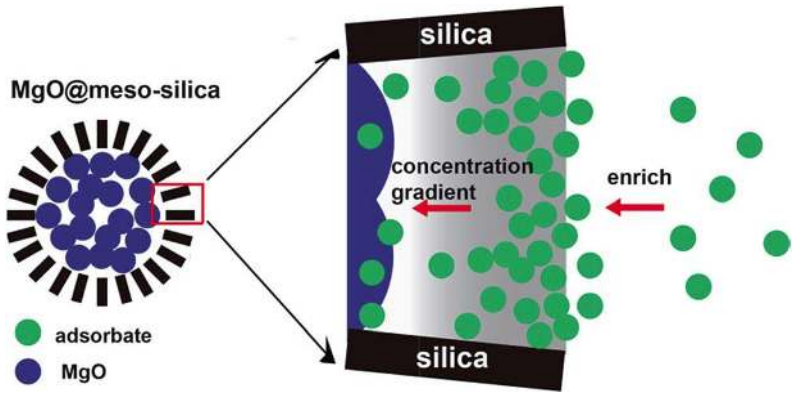

Figure 14. Schematic representation of the adsorption mechanism of the core-shell MgO@mSiO$_2$. Reproduced from Ref. [44] with permission from the Royal Society of Chemistry.

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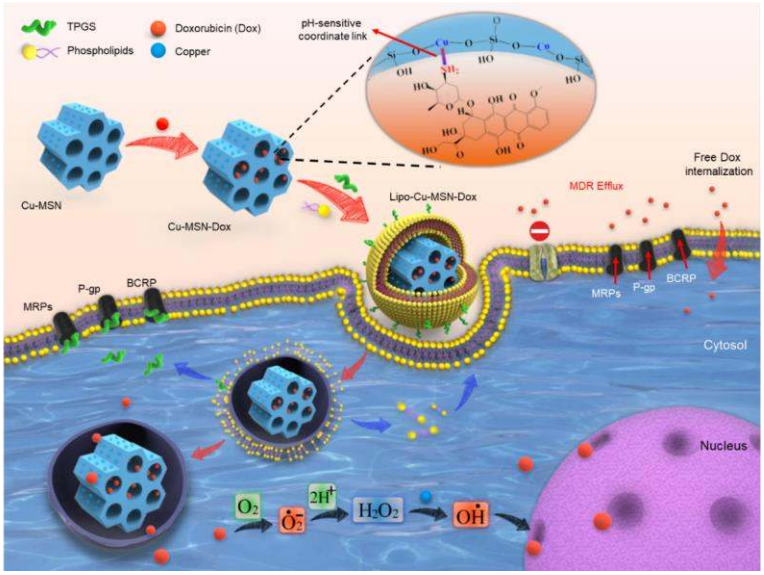

Figure 15. Schematic illustration of synthesis and cell internalization of designed hierarchical nanoformulation elucidating the delivery of doxorubicin (DOX) and plausible mechanism of surpassing MDR. Reproduced from Ref. [58] with permission from the American Chemical Society.

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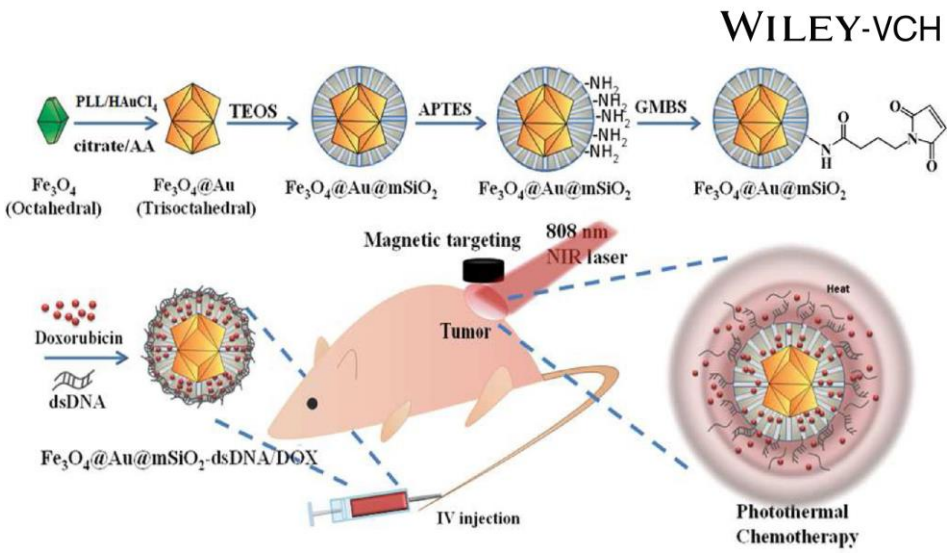

Figure 16. Schematic illustration of the synthesis process of Fe_3O_4@Au@$mSiO_2$-dsDNA/DOX nanoparticles for therapy combining chemotherapy and photothermal treatment of cancer cells in vivo in a magnetic targeting manner. Reproduced from Ref. [114] with permission from the American Chemical Society.

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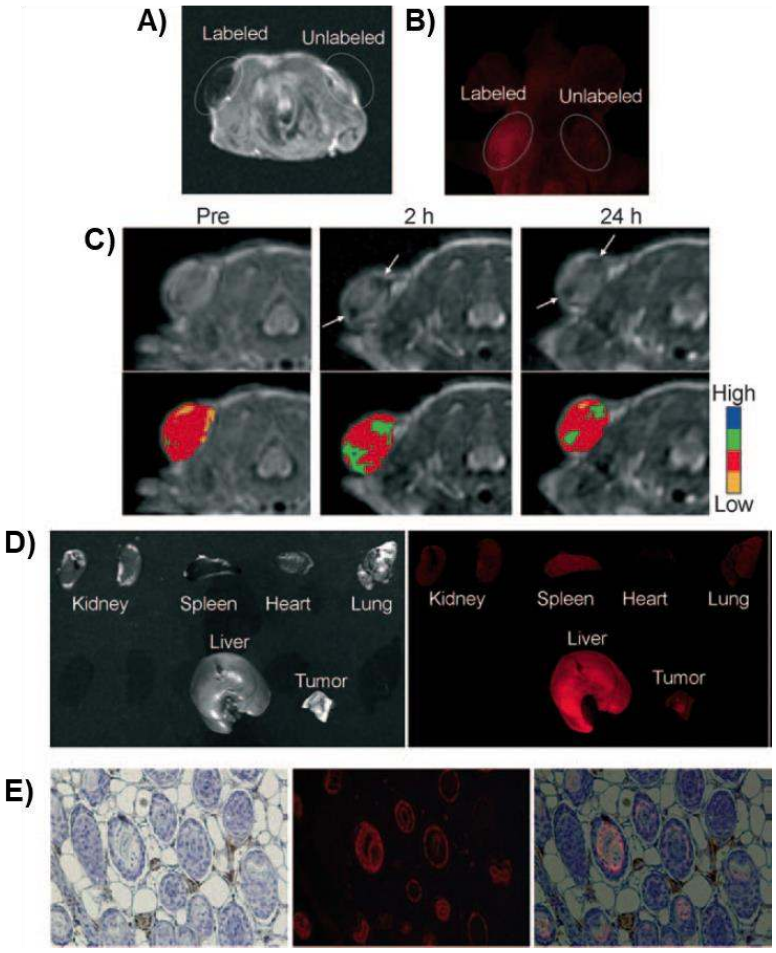

Figure 17. In vivo multimodal imaging using Fe_3O_4@$mSiO_2$. a) In vivo T2-weighted MR and b) fluorescence images of subcutaneously injected MCF-7 cells labeled with Fe_3O_4@$mSiO_2$(R) (10 mg Fe mL^{-1}) and control MCF-7 cells without labeling into each dorsal shoulder of a nude mouse. c) In vivo T2-weighted MR images (upper row) and color maps (lower row) of T2-weighted MR images of a tumor before and after the Fe_3O_4@$mSiO_2$(R) (5 mg Fe kg^{-1}) was intravenously injected into the tail vein of a nude mouse implanted with MCF-7 cells. A decrease of signal

intensity on T2-weighted MR images was detected at the tumor site (arrows). d) Photographic image and corresponding fluorescence image of several organs and the xenograft tumor 24 h after intravenous injection. e) Immunostaining of vasculature (brown) with anti-CD31 antibody and counterstaining of the nucleus with hematoxeylin (blue; left), a fluorescence image of the Fe_3O_4@mSiO_2(R) (middle), and a merged image (right) in the sectioned tumor. The images and paraffin section of the tumor were taken after sacrifice 24 h after injection of the nanoparticles. Reproduced from Ref. [42f] with permission from ~~the~~ John Wiley and Sons.

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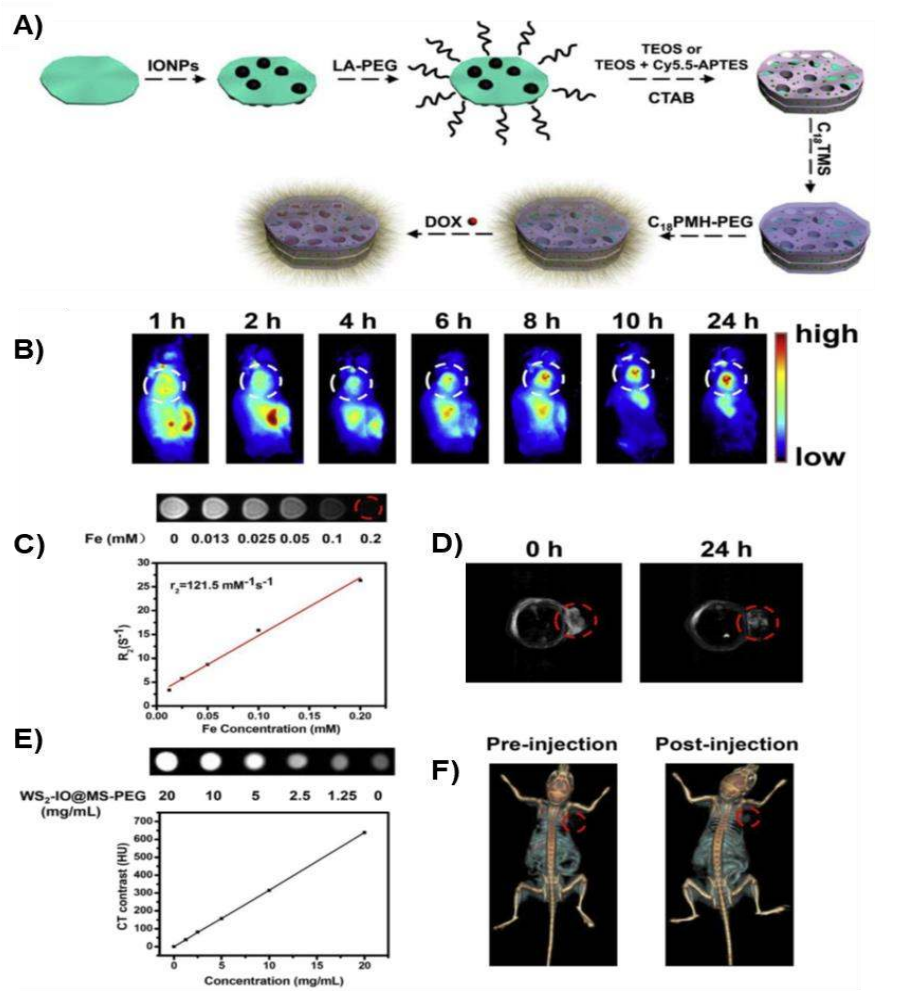

Figure 18. Synthesis, characterization, and multi-modal imaging in vivo of WS2-IO@MS-PEG. (A) A procedure showing the fabrication of WS2-IO@MS-PEG/DOX theranostic nanoparticles. (B) In vivo fluorescence imaging of 4T1 tumor-bearing mice taken at different time points after intravenous injection of Cy5.5-labelled WS2-IO@MS-PEG (highlighted by dashed circles). (C) T2-weighted MR images of WS2-IO@MS-PEG solutions recorded using a 3T MR scanner

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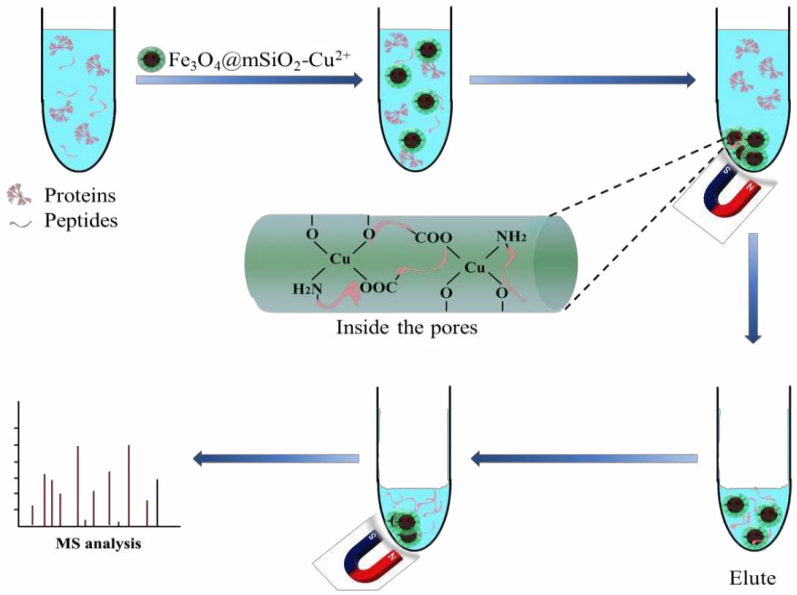
revealed a concentration-dependent darkening effect. (D) In vivo T2-weighted MR images of a mouse taken before (left) and after 24 h of injection (right). Obvious darkening effect showed up in a tumor after intravenous injection with WS2- IO@MS-PEG. (E) CT images and Hounsfield unit (HU) values of WS2-IO@MS-PEG solutions with different concentrations. (F) CT images of mice before and after 24 h of intravenous injection with WS2-IO@MSPEG (2 mg/mL, 200 mL). The CT contrast was ~~obviously~~ enhanced in the tumor area (highlighted by the dashed circles). Reproduced from Ref. [42d] with permission from Elsevier.



Figure~~.~~ 19. Schematic representation illustrating the fast and efficient approach of selective peptide enrichment process using Fe_3O_4@mSiO_2-Cu^{2+} core-shell containers and subsequent

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matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI–TOF MS) analysis. Reproduced from Ref. [21d] with permission from ~~the~~ John Wiley and Sons.

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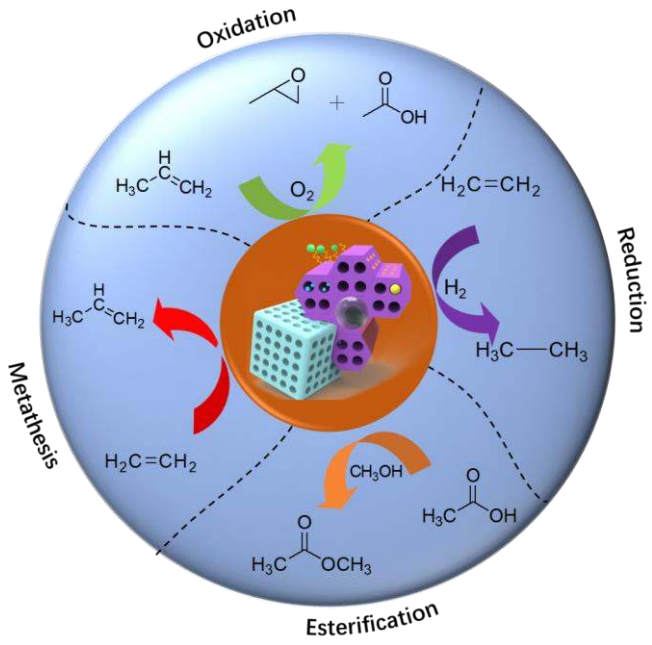

Figure 20. Schematic illustration representing the generalized reactions that have been catalyzed by M-MSNs highlighting the substrates and products.

Table 1. Diverse ~~M~~metal species in MSNs as effective sorbents

Metal	Type of MSNs	Location	Particle size (nm)	MNP size (nm)	Pore size (nm)	Adsorbate	Reference
~~Aluminum oxide~~Al_2O_3	SBA-15	~~On s~~Surface	>250	-	5.30	~~Arsenic~~ As ions from water	[35]
~~Cerium oxide~~CeO_2	MCM-41	~~In m~~Mesopore	~50-200	-	2.0-2.2	Sulphur dioxide from gas	[128]
~~Copper oxide~~CuO	MCM-41	M~~In m~~esopore	~50-200	-	2.0-2.1	Sulphur dioxide from gas	[128]
~~Lithium chloride~~LiCl	MCM-41	M~~In m~~esopore	~50-200	-	1.9-2.1	Sulfur dioxide from	[128]

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Fe_2O_3 Iron oxide	SBA-15	On sSurface	>250	-	5.27	Arsenic As ions from water	[35]
Magnesium oxideMgO	MCM-41	CIn core	~250	15	-	Lead Pb ions and methylene blue from water	[44]

Abbreviations: Al_2O_3-Aluminum oxide; As-Arsenic; CeO_2-Cerium oxide; CuO-Copper oxide; Fe_2O_3-Ferrous oxide; LiCl-Lithium chloride; MCM--Mobil Composition of Matter; MgO-Magnesium oxide; MNPs-Metal nanoparticles; MSNs-Mesoporous silica nanoparticles; Pb-Lead; MNP Metal nanoparticles; SBA--Santa Barbara Amorphous-type material, CeO_2 Cerium oxide, Pb Lead, CuO copper oxide, LiCl Lithium chloride, MgO Magnesium oxide, Al_2O_3 Aluminum oxide Fe_2O_3 ferrous oxide

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Table 2. Examples showing various ~~metallic species on~~M~~-~~MSNs for preclinical studies toward~~s~~ biomedical applications.

Metal species	Position	MNP size (nm)	Particle size (nm)	Pore size (nm)	Animal model	Cell type	Dose	Purpose of delivery	Refer
Au-NRs	Au-NR-caps	30 (l)	~200	5.36	Balb/c mice	4T1 murine breast	112 mg mL^{-1}	Multimodal imaging	[13]
	Core-shell	51 × 13 (l × d)	119~144	2.9	Balb/c mice	A549	25 mg kg^{-1}	Chemo-photothermal therapeutics	[11]
		40 × 10 (l × d)	60~~x*~~30	-	Balb mice	Ehrlich ascites	1.7 mg DOX kg^{-1}		[14]
Au-NRs/ iron oxide	Au-NRs-caps, ~~iron~~Iron -oxide-Core	40 × 15 (l × d)	300 × 180	~2.6	SD mice	Walker 256	1.4 mg mL^{-1}	Multimodal imaging	[85]
~~Gold~~Au/iron oxide	~~Gold~~ Au-coated iron oxide -core	~100	162	~3	Balb/c	HeLa	6.5×10^4 ppm Au kg^{-1}	Multi-functional theranostic platforms	[11]
Iron oxide	Core-shell	15-22	100	2.6	Balb/c mice	MCF-7	5 mg of Fe kg^{-1}	Multimodal imaging	[42]
		~10-20 nm	80	2.5		4T1 murine breast	8.4 mg kg^{-1}	Imaging-guided-cancer therapy	[42]
Ru/Gd-Al	Gd^{3+}-Al^{3+} co-doped and $Ru(bpy)_3^{2+}$	-	60	2.8	Balb/c mice	HepG-2	8.25 mL kg^{-1}	Multimodal imaging	[22]

Abbreviations: Al-Aluminum; Au-Gold; Au-NRs-~~gold~~ Gold nanorods; d-~~diameter~~Diameter; DOX-Doxorubicin; Gd-Gadolinium; l-~~length~~Length; MNPs-Metal nanoparticles; Ru- Rhuthenium; SD- Sprague Dawley.

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Table 3. Examples showing various ~~metallic species encapsulated in MSNs~~M-MSNs for catalytic applications.

Metal/Metal oxide	Material	Particle size (nm)	MNP size (nm)	Pore size (nm)	Type of reaction	Outcome	Reference
~~Copper~~Cu	Al-MSN	80	-	~2.6	Oxidation	Conversion of toluene to benzyl alcohol and then to benzaldehyde.	[160]
	MCM-41	50 -500	-	3.19	Oxidation	Conversion of ammonia to dinitrogen	[161]
~~Copper oxide~~CuO	SBA-15	>500	-	-	Oxidation	Allylic oxidation of cyclic olefins	[152]
~~Gold~~Au	SBA-15	-	0.8	8	Oxidation	Conversion of benzyl alcohol to benzaldehyde, benzoic acid, and benzyl benzoate	[162]
~~Iron~~Fe	MCM-41	50- 500	-	3.42	Oxidation	Conversion of ammonia to dinitrogen	[161]
	MCM-41	-	-	2.5~3.5	Oxidation	Conversion of propylene to propylene oxide	[163]
Iron oxide	SBA-15	-	-	5.3~6.0	Epoxidation	Conversion of propylene to propylene oxide	[155]
M~~a~~n~~ganese~~	MCM-41	50- 500	-	3.48	Oxidation	Conversion of ammonia to dinitrogen	[161]

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	MCM-41	-	-	2.2	Epoxidation	Conversion of stilbene to trans-stilbene oxide	[16b]
~~MoO_3 Molybdenum trioxide~~	SBA-15	50	~5.9	6.0~7.9	Metathesis	Conversion of 1-butene and ethene to propene	[47]
~~Nickel~~Ni	MCM-41	-	-	2.0	Metathesis	Conversion of ethene to propene	[164]
Ni~~ckel Oxide Nickel oxide~~	SBA-15	50	4.1~12.5	6.6~7.5	-	Hydro-dechlorination of chlorobenzene to benzene	[48b]
	HMS	<500	2~5	1.7~3.3	Epoxidation	Conversion of styrene to 2-Phenyloxirane	[48c]
~~Palladium~~Pd	MCM-41	-	-	2.3	Sonogashira reaction	Conversion of aryl and heteroaryl halides to terminal alkynes	[165]
	MCM-41	70–120	-	2.5	Kumada–Corriu reaction	Cross-coupling of aryl iodides or bromides with Grignard reagents to their corresponding biaryls (C-C bond)	[166]
	MCM-41	-	-	2.3	Coupling reaction	Coupling of acyl chlorides and terminal alkynes resulted in ynones	[167]
	MCM-41	~50	-	2.5	Heck reaction	Aryl halides and acrylate	[168]

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						to form substituted alkene	
	MCM-41	-	-	2.3	Cross-coupling	Coupling of acyl chlorides with triarylbismuths resulted in diaryl and alkyl aryl ketones	[169]
~~Vanadium~~V	MCM-41	-	-	2.3~2.7	Oxidative dehydrogenation	Conversion of propane to propene	[57]
Vanadium oxide	MCM-41	-	-	~2	Hydroxylation	Conversion of benzene to phenol	[50]
Z~~ir~~~~conium~~	MCM-41	-	-	2.07~2.17	Isomerization	n-Pentane isomerization	[170]
	MCM-41	~50	6.4	2.1	Isomerization	Butane isomerization	[171]
~~Copper-iron~~ ~~(~~Cu-Fe~~)~~	MCM-41	50-500	-	3.43	Oxidation	Conversion of ammonia to dinitrogen	[161]
~~Copper-Manganese~~ ~~(~~Cu-Mn~~)~~	MCM-41	50-500	-	3.38	Oxidation	Oxidation of ammonia to dinitrogen	[161]
~~Gold-Copper~~ ~~(~~Au-Cu~~)~~	SBA-15	-	~3	7.0	Oxidation	Oxidation of CO	[172]
~~Gold-Indium~~ ~~(~~Au-In~~)~~	SBA-15	-	~2	7.8~8.1	Hydrogenation	Hydrogenation of crotonaldehyde to crotyl alcohol	[173]
~~Gold-Silver~~ ~~(~~Au-Ag~~)~~	MCM-41	~50	3.7	2.3	Oxidation	Oxidation of CO	[174]

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~~Manganese Iron (~~Mn-Fe~~)~~	MCM-41	50-500	-	3.4	Oxidation	Conversion of ammonia to dinitrogen	[161]
~~Silver Copper (~~Ag-Cu~~)~~	SBA-15	~100	17~58	5.3~5.8	Oxidation	Conversion of methanol to CO_2	[53f]

Abbreviations: Al- Aluminium; APTMS – Aminopropyltrimethoxysilane; Ag-Cu - Silver-Copper; Au –Gold; Au-Ag - Gold-Silver; Au-Cu - Gold-Copper; Au-In - Gold-Indium; Cu - Copper; Cu-Fe - Copper-iron; Cu-Mn - Copper-Manganese; CuO - Copper oxide; Fe - Iron; HMS – Hexagonal mesoporous silica; MCM-41 – Mobil composition of matter No. 41; Mn-Fe - Manganese- Iron; Mn-Manganese; MNP - Metal nanoparticles; MoO_3 - Molybdenum trioxide; MSNs - Mesoporous silica nanoparticles; Ni - Nickel; NiO - Nickel oxide; Pd - Palladium; SBA-15 – Santa Barbara amorphous-type material; V - Vanadium~~;~~ Zr - Zirconium.

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Author Biography

Ranjith Kumar Kankala

Ranjith K. Kankala is an Associate Professor in the Institute of Biomaterials and Tissue Engineering at Huaqiao University, P. R. China. He received his B.S. and M.S. degrees in Pharmaceutical Sciences from Kakatiya University, India in 2009 and 2012, respectively, and earned his Ph.D. degree in 2016 in the field of nanomedicine from the National Dong Hwa University, Taiwan. His expertise relates to the preparation of cutting-edge multifunctional nanocomposites and engineered inorganic nano-/micro- hybrid systems with optimized properties for innovative biomedical applications.

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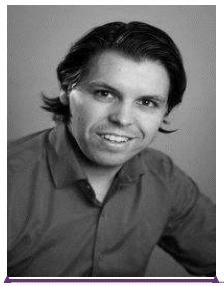
Hélder A. Santos



Hélder A. Santos obtained his Doctor of Science in Technology (Chemical Engineering) in 2007 from the Helsinki University of Technology. Currently, he is the Head of the Division of Pharmaceutical Chemistry and Technology, the Head of the Preclinical Drug Formulation and Analysis Group, and the Head of the Nanomedicines and Biomedical Engineering Group, all at the Faculty of Pharmacy, University of Helsinki. Prof. Santos is also a HiLIFE Fellow. His scientific expertise lies in the development of nanoparticles/nanomedicines for biomedical applications, particularly porous silicon nanomaterials for simultaneous controlled drug delivery, diagnostic, and treatment of cancer, diabetes, and cardiovascular diseases.

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Ai-Zheng Chen

Ai-Zheng Chen received his Ph.D. in Biomedical Engineering from Sichuan University in 2007. After completing the postdoctoral research at The Hong Kong Polytechnic University, he joined Huaqiao University, where he is now a professor at College of Chemical Engineering and Director of Institute of Biomaterials and Tissue Engineering. He was a visiting research professor for one year in Prof. Ali Khademhosseini Laboratory at Harvard Medical School. His research interests include fabrication of biomaterials using supercritical fluid technology, for use in drug delivery and tissue engineering.

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