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Design of polymer based inorganic-organic hybrid materials for drug delivery application†

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Inorganic-organic hybrid materials possess multi-functionalities with noteworthy properties due to the combination of their counterparts. The combination of these components is not a physical mixing but an intimate mixture of both moieties which results in the formation of new material with new properties. These materials may find significant application in biomedical technology, specifically in drug delivery process. The polymer based hybrids (Polymer hybrids) are obtained in combination of silica, metal-organic frameworks (MOFs), poly-oxometalates and so on and can be synthesized by various methods. The silica-based hybrids may also incorporate polymers, like synthetic and biopolymers of protein, peptide etc. The hybrids can be obtained in the form of bulk materials or nano-particles of gold/magnetic particles and quantum dots. Zn and Cu-based polymer-MOF hybrids are most common. Recently, extensive studies have been reported for polyoxometalate (POM) based inorganic-organic hybrid materials. The polymer hybrids are biocompatible and involved in a broad area of biomedical applications. This review specially enumerates the design of polymers based inorganic-organic hybrids for drug delivery system.

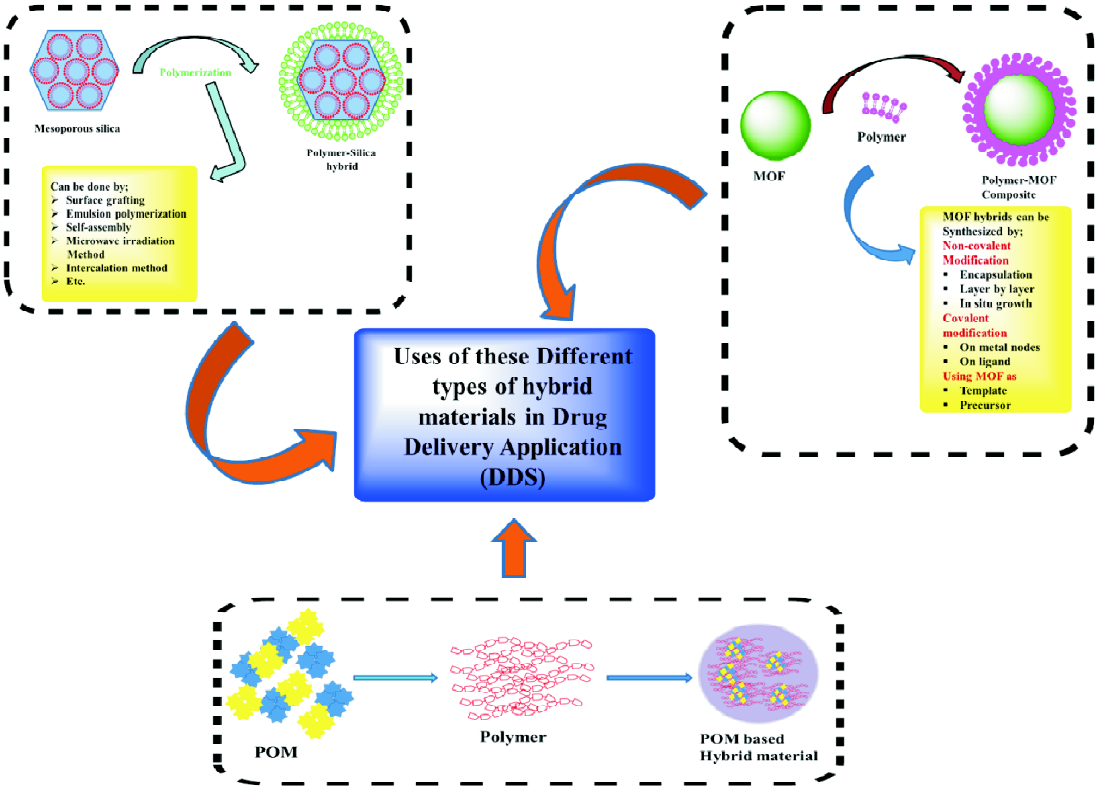
Keywords: Polymers, inorganic-organic hybrid, silica-polymer, MOF-polymer, polyoxometalate, drug-delivery.

Introduction

In the past few years, countless studies have established the great potential of various polymer based inorganic-organic hybrid materials of silica[1], metal-organic framework (MOF)[2], and polyoxometalate (POM)[3] at the research level for biomedical applications. These hybrid materials can be synthesized by combinations of polymers with various inorganic and metal organic hosts, such as mesoporous silica (zeolite), metal oxo clusters, oligosilsesquioxanes derivatives, inorganic clay compounds, calcium carbonate, and metal, or inorganic nano-particles, using different chemical routes and were exploited in different applications. Silica is an inorganic material which in combination with polymer forms various hybrid materials of having large surface area and excellent mechanical properties. The hybrid material can also be functionalized with various organic groups by utilizing silanol groups present on silica surface. Nano silica entities may be used instead to enhance the property. Silica is taken as the main elementary unit for hybrid synthesis because it provides biocompatibility for the system. Polymer incorporated/coated silica hybrids provide great probabilities for the design of novel hybrids for research and their incorporation add new properties and make them suitable for versatile application, specifically in the drug delivery field[4]. The polymers from the polysaccharide family that includes Cyclodextrin, Carrageenan, Cellulose, Chitin, Chitosan, Alginate, Agarose, Pectin, Polylactic acid (PLA), Poly lactic-co-glycolic acid (PLGA), Polyethylene glycol (PEG), Poly vinyl alcohol (PVA), Polycaprolactone (PCL) and heparin have been used for coating the hybrids. The biopolymer embedded hybrids due to their nature and chemical structure formed a better carrier for the controlled drug delivery system. The development of secure and targetable drug carriers is a recent challenge. More recently, the magnetic nano-particle core is coated with silica and this silica coating contains surface silanol groups which can be functionalized with organic groups to which drug molecule can be attached, this resulted in an efficient drug delivery system where the drug may be magnetically targeted with good control over the drug release at the target site[5]. These materials have also shown good antibacterial,

†**Invited Lecture.**

and antioxidant activity and many other applications. For effective drug delivery applications, the material should entrap drugs with high payloads and should control the drug release to prevent the chances of burst effect. The possibility of synthesizing inorganic-organic hybrids with various types of structures, sizes, porosity, and multi-functionality makes



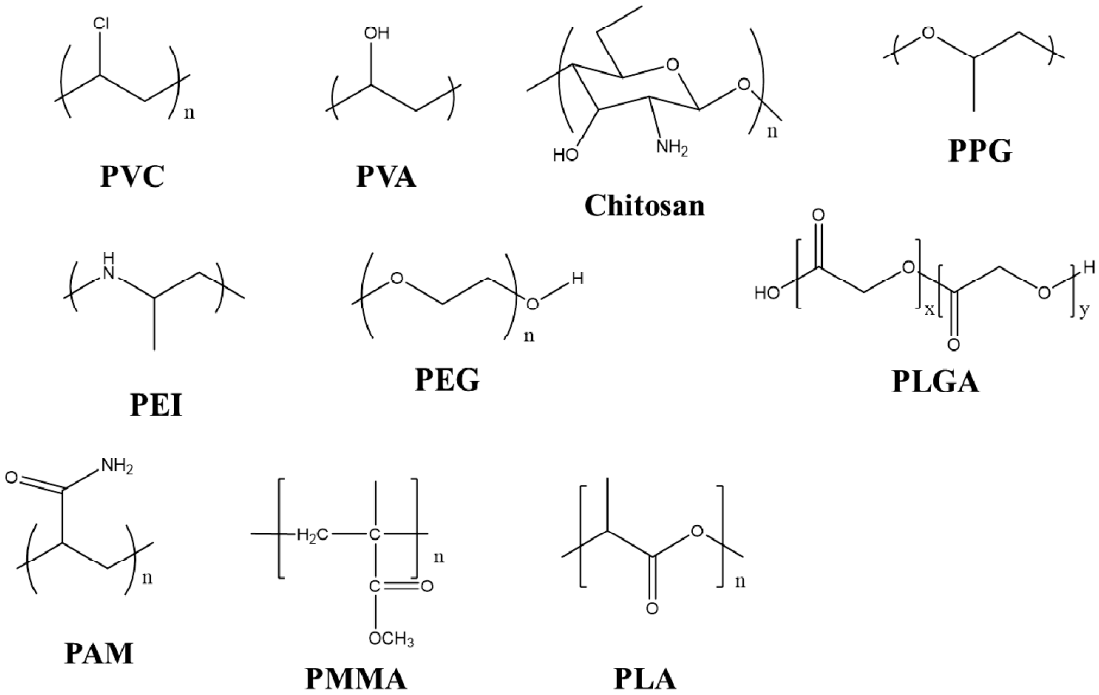


Fig. 1. Schematic representation for synthesis of various polymer hybrid materials and their application in drug delivery system (DDS).

them a promising candidate for biomedical applications[6]. The synthesis of various polymer hybrid materials and their application in drug delivery system (DDS) are shown in Fig. 1. In the present review, we have highlighted the various inorganic and organic counterparts to design the new polymer hybrid materials and their benefits in the field of drug delivery process.

Silica-based inorganic-organic polymer hybrids

Silica-polymer hybrids are an interesting class of inorganic-organic (I-O) hybrids having certain properties which find various applications. Silica is an amorphous inorganic polymer and has been chosen as an inorganic support in the synthesis of hybrid materials due to its various unparalleled properties such as presence of adequate number of silanol groups to which desired organic molecules can be grafted[7]; once grafted these groups show resistance towards their removal from the surface of silica through organic solvents or water. Also, the attachment of organo-functional groups on its surface is easier as compared to that on organic polymer support. Additionally, when silica is chemically modified with functional groups having donor capabilities, it usually facilitates and boosts the attachment of metal ions through coordinate bond, and thereby increasing their life span on silica surface. Considering these, silica based I-O hybrids may have good catalytic activity and may also effectively applied in the field of optical imaging, magnetic resonance imaging (MRI), photodynamic therapy and drug delivery[8]. The various types MSNs, such as MCM-41, SBA-15, TUD-1, MCM-48, HMM-33 and FSM-16 have been fabricated and used for the delivery of drugs. There are different methods for the synthesis of hybrids such as sol-gel, self-assembly, surface-grafting, hydrothermal/solvothermal, intercalation, blending, electrochemical and emulsion method etc. The sol-gel, condensation and self-assembly methods for the synthesis of hybrid materials are the most common and for the synthesis of polymer-silica hybrid materials the procedures are: (1) Sol-gel technique, (2) Blending of particles in polymer matrix used melt and solution blending and (3) *In situ* polymerization method (Fig. 2).

Method of synthesis: Sol-gel technique:

In this method the hydrolysis and polycondensation of the metal alkoxide precursor lead to the transition from a colloidal solution into a solid phase. Many of the preparation methods are described elsewhere[9]. Catauro *et al.* reported the synthesis of SiO_2/PEG (polyethylene glycol) where PEG contains 60 or 70 weight percent[10]. From the literature, we know that PEG is a biocompatible polymer and is mainly used in various matrices for drug delivery. In the synthesis of hybrid material, the two counterparts SiO_2 and PEG linked by hydrogen-bond and hydroxyapatite layer were observed on the surface of SiO_2/PEG hybrid. The cytotoxicity assay shows that the cells treated with hybrid extract/suspension are more viable than the cells grown with culture medium and the best result was shown by SiO_2 + 70% PEG.

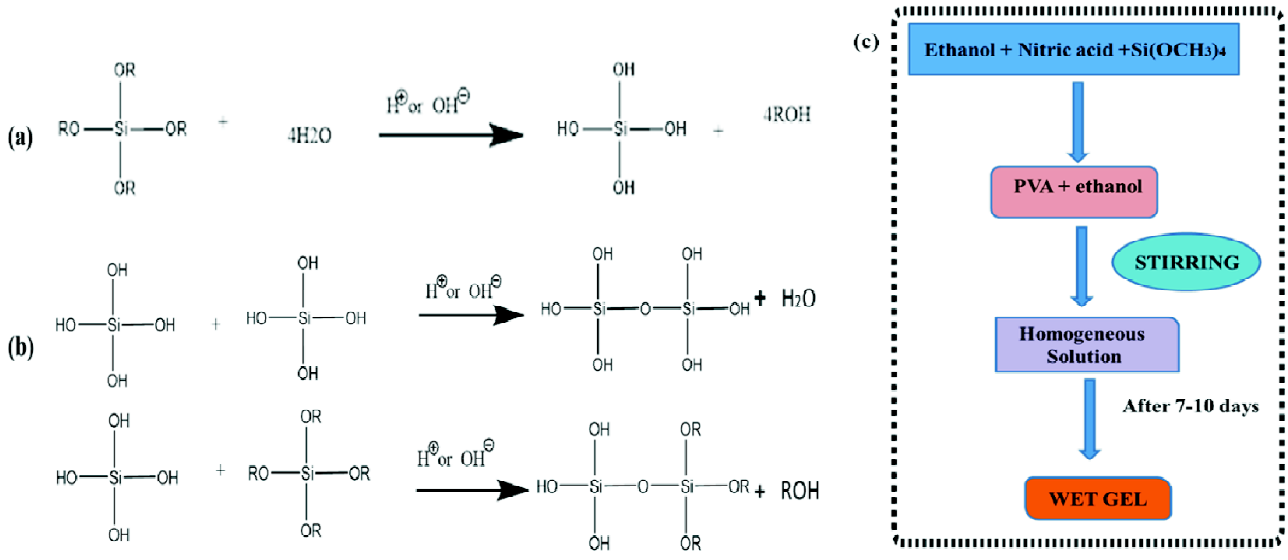


Fig. 2. (a) Hydrolysis and (b) condensation reaction of silicon alkoxide in sol-gel process and (c) flow chart of synthesis of SiO_2/polymer hybrid gel.

Polumbo *et al.*[11] prepared biologically active glass and Martin *et al.* reviewed the bio-active glasses as bone replacement and regeneration materials and can be used in many other biomedical field[12]. Malik *et al*. proposed sol-gel derived nanostructured tin dioxide (SnO_2) encapsulated into biopolymer (guar gum) used as electrochemical hydrazine sensor for the determination of hydrazine[13].

Blending method:

In blending method polymers are directly mixed to silica particle via melt blending and solution blending and this is the simplest method to form polymer hybrid materials. Choi *et al.* (2017) proposed a supertough hybrid hydrogel that consists of alginate/polyacrylamide double-network hydrogels embedded with mesoporous silica particles (SBA-15). This leads to various types of bonding such as ionic interaction of alginate, hydrogen bonding between SBA-15 and polymers, Van der Waal interactions, and covalent bonding of polyacrylamide[14]. It also exhibit high stability under physiological conditions (both *in vitro* and *in vivo*). On-demand *in vitro* study of release profile using mechanically stable Alg/PAM/S-15 loaded with fluorescence labeled model proteins. The result shows that hybrid hydrogels can be used in a controlled drug delivery system, can store drugs without any stimulation and released when required.

Ramamurty *et al.* prepared silica/cyclic olefin copolymer (COC) nano-hybrid material or films through solution blending process[15]. The synthesized material helps to reduce the degradation of electronic devices because COC played as encapsulating material into electronic devices for lowering the risk of degradation. Adachi *et al.*[16] reported the preparation of organic-inorganic polymer hybrids from different organic polymer such as poly(ethylene oxide) (PEO) and poly(N-vinylpyrrolidone) (PVP) with 500 W, 2.45 GHz of microwave irradiation method where the dried glassy polymer hybrid films were obtained within 5 min.

In situ polymerization:

The process organizes the different building blocks at the same molecular level into the composite, including micro, meso and macro-scopic length and giving rise to the synthesis of multi-functional nanohybrid materials with new and better properties. Jamwal *et al.* (2018) reported two new hybrid nanomaterials, poly(methacrylic acid-*co*-(2-dimethylamino)ethyl methacrylate)/silica [P(MAA-DMAEM)/SiO_2] and poly(methacrylic acid)/silica [P(MAA)/SiO_2] by emulsion polymerization[17] where P(MAA)/SiO_2 showed slow drug release efficiency (60%) than P(MAA-DMAEM)/SiO_2 hybrid (96%) and fluorescein used as a model drug. Guo *et al.* (2018) prepared poly(butyl acrylate)/silicon dioxide (PBA/SiO_2) core-shell composite hybrid with good stability and biocompatibility by using ultrasonically initiated encapsulation emulsion polymerization[18], and the synthesized hybrids used as a carrier for controlled release and as enzyme immobilization. Naz *et al.* (2017) reported a new hybrid (3-aminopropyl)triethoxysilane (APTES) by grafting of O-carboxy methyl chitosan (OCMC) onto amine-modified nano-silica silane (SiO_2*NH_2), which was further metallated with Cu(II) and 2-hydroxy-1-naphthaldehyde (HN) for Schiff's base formation (OCMC*HN)[19]. The increased diameter of silica can be utilized for drug loading and drug delivery application. The hybrid showed better zone of inhibition (ZOI) in *Bacillus subtilis* than *Escherichia coli*. Likewise, Nhavene *et al.* (2018) synthesized chitosan grafted mesoporous silica nanoparticles, MCM-41 + GPTMS + CS. The density functional theory (DFT) and EFTEM were used to investigate the structural and energetic properties of the reaction between chitosan, GPTMS, succinic anhydride, and benznidazole (model drug) molecules for targeted drug and gene delivery in controlled manner[20]. An schematic representation of synthesis of hybrid nano-carrier for controlled and targated drug delivery in cell for Chaga disease is depicted in Fig. 3.

Polymer/MOF nano-composites:

The MOF hybrids combine with any polymer such as chitosan, poly-methacrylic acid (PMAA) and thus give rise to a new hybrid material with excellent performance than their parent materials. They have a unique property of porosity, and it might have resistant to structural collapse upon evacuation of small trapped or occluded molecules. The organic ligands with their specific functional groups viz. pyridyl, amino, OH, carboxylate and amide etc. that can coordinate to metal centres then assembled into one, two or three dimensional structure.

The preparation of polymer/MOF hybrid materials by covalent and non-covalent modifications or using MOF as templates or precursors are reported[21], further, these MOFs can be conveniently synthesized as nano-MOFs. The MOFs are being used as drug delivery vehicles, because of its have a large cavities inside and therefore can accommodate good amount drug in these cavities and tunable structure make

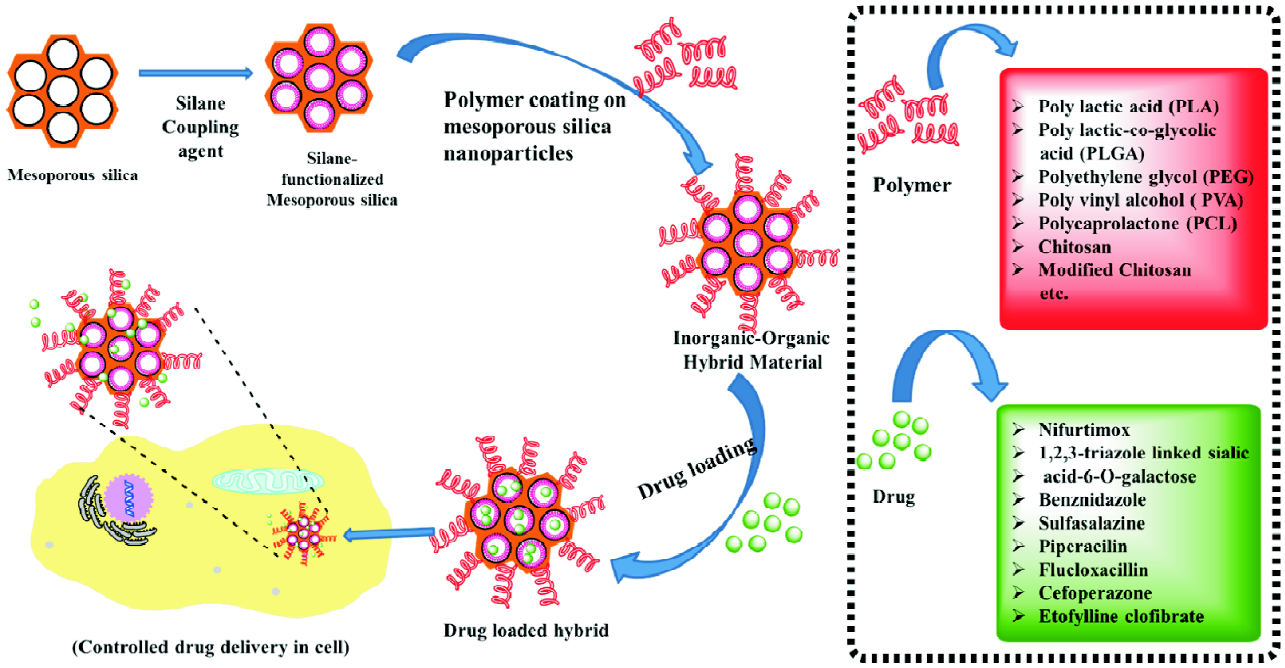


Fig. 3. Schematic representation of synthesis of hybrid nano-carrier for controlled and targated drug delivery in cell for Chaga disease.

them ideal materials for drug delivery. These are generally crystalline in nature and self-assembled structure of metal ions and organic ligands. The metal centers can coordinate with organic ligands both through covalent or non-covalent linkages (hydrogen bonding etc.) and are known as 'supramolecules' or through co-ordinate bond known as 'co-ordination polymers'. In order to synthesize MOFs, it is compulsory to react with labile metal ions of organic bridging ligands[22]. These are also known as porous coordination polymers (PCPs) or porous coordination networks (PCNs). The covalent modification can be done by "grafting to" and "grafting from" methods while the non-covalent modification can be done by Encapsulation, Layer by layer deposition, and *in situ* growth synthesis process[23].

Non-covalent interaction:

Liu *et al.* reported the non-covalent interactions between copolymers [poly(oligoethylene glycol monomethyl ether methacrylate) (pOEGMA) and poly(2-aminoethyl methacrylate) (pAEMA)] and iron(III) carboxylate nano-MOFs MIL-101-NH_2(Fe)[24] to study the surface binding or assembly process and degradation of MIL-101-NH_2(Fe) in the aqueous. The synergistic binding and restricted diffusion in a solution of MIL-101-NH_2(Fe) with copolymers represent that this surface-modified nano-MOFs with improved property can serve as superior carriers for efficient controlled drug delivery.

Azizi Vahed *et al.* reported iron based MOF polymerized with alginate encapsulated by Metformin (Fe)MIL-100 Met@alginate via non-covalent interaction and used as carrier for the pH controlled release of metformin[25]. Sodium alginate was taken as polymer which is helpful for the pH-controlled release of drug molecules due to presence of carboxylic acid group. Wang *et al.* synthesized polymer-coated MOF having stimuli responsive features as better drug delivery device. MIL-101-NH_2(Fe) MOF nanoparticle azide functionalized by post-synthetic modification by PEG polymerization where β-CD (cyclodextrin) and DOX used. β-CD and PEG are important materials in polymer-MOF hybrid for the controlled drug delivery system[26] because of stimuli-responsive behavior of benzoic-imine bonds of PEG and β-CD for disulfide bond. The step wise synthesis of polymer/MOF hybrid is shown in Fig. 4.

Covalent interaction:

Covalent interaction/modification are large group of post-synthetic modifications (PSMs). These are chemical modification of MOF network following the synthesis via two types of covalent modifications. One type of covalent modification

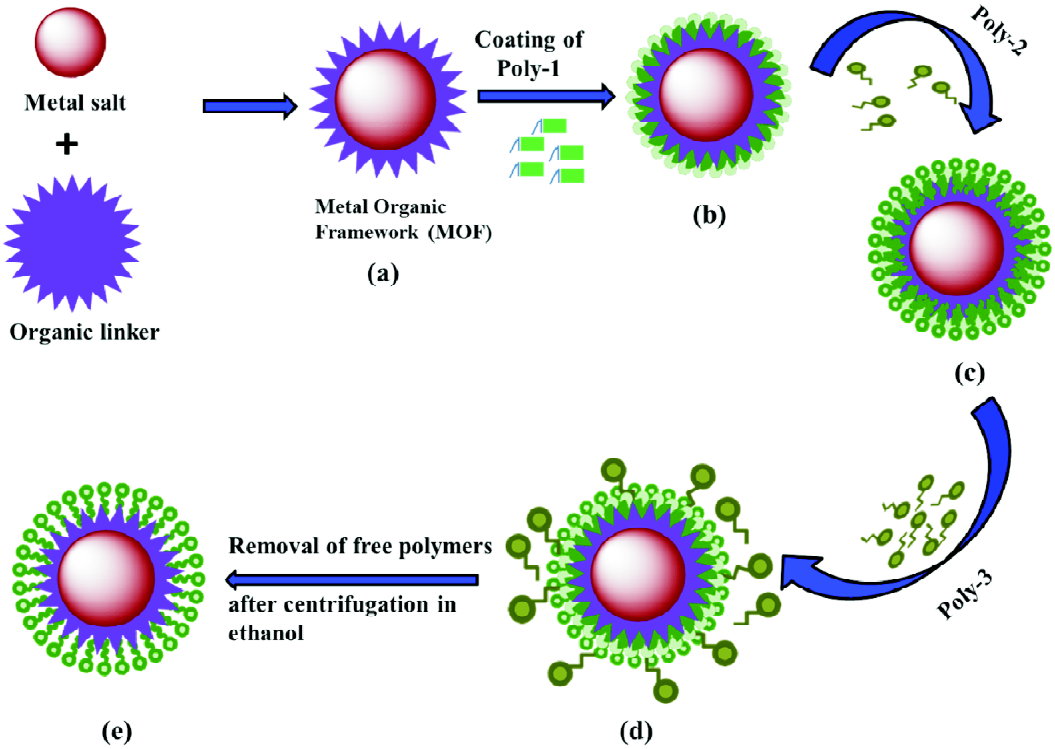


Fig. 4. Representation of synthesis of polymer/MOF hybrid: (a) synthesis of MOF, (b), (c) and (d) MOF coated by different cocentrations of polymers, (e) surface polymer grafted hybrid after removal of free polymers.

is on metal nodes or metal clusters (or grafting from) and the other one is on ligands (or grafting to). In this modification organic moieties or functional groups are covalently attached to metal nodes or ligands of MOF, therefore MOF hybrid materials are synthesized.

''Grafting to" Approaches:

In this process, MOF hybrids are synthesized by covalent interaction on metal nodes in which co-ordinated unsaturated sites (CUSs) are formed by removal of solvent molecules from metal nodes upon heating under vacuum. The resulting CUSs are then co-ordinate with other organic moieties or functional groups and giving rise to formation of new MOF hybrids having improved properties. Lazaro *et al.* (2017) reported the synthesis of Zr-based NMOFs by click modulation method in which the external surfaces of NMOFs were functionalized by modulators [L1(p-azidomethylbenzoic acid) and L2 (p-propargyloxybenzoic acid)] and in the second step further post-synthetic modifications with cargo loaded NMOFs by using high-yielding "click" chemistry[27]. After that, the Zr-MOF UiO-66 was covalently coated with polyethylene glycol (PEG), poly(L-lactide) (PLLA), poly(N-isopropylacrylamide) (PNIPAM), and heparin to enhanced stability and effective application in drug delivery. Because of structure similarities to doxorubicin and dichloroacetic acid (DCA) calcein was chosen as a drug for the investigation of drug delivery potential of the coated MOF nano-particles. The above PEGylated particles showed pH-responsive behavior because faster calcein release (98%) at pH 5.5 as compared to pH 7.4 (40%). The polymer-coated MOFs nano-particles and DCA loaded MOFs show promising candidates as a therapeutic agent.

Further in 2018 Lazaro *et al.* further reported Zr-fumerate MOFs (Zr-fum) incorporated to p-azidomethylbenzoic acid (L1) and also with cancer-targeting folic acid (FA), then transformed by click modulation. Upon PEGylation, colloidal stability was slightly improved and PEGylation of Zr-fum was done by covalently attachment with azide group of the modulator (L1)[28]. From the previous literature we know that the zirconium has excellent biocompatibility, so as compared to UiO-66 MOF nano-particles, Zr-fum MOF nano-particles more efficiently transport the drug mimic calcein into HeLa cells and DCA loaded PEGylated Zr-fum (DCA/Zr-fum-L1-PEG) more effectively reduce MCF-7 cells and HeLa cell prolifera-

tion than the UiO-66 MOF samples. At high concentrations, DCA/Zr-fum-L1-PEG shows cytotoxicity and these all above results indicates that the Zr-fum is an attractive and alternative to UiO-66 for nano-scale drug delivery and that a wide range of *in vitro* experiments are available to greatly inform the design of drug delivery system (DDS) without animal studies.

He *et al.* (2019) introduced a nano-system based on UiO-66 (University of Oslo-66) nano-particles that performs co-delivery of photosensitizer [photochlor (HPPH)] as well as a hypoxia-activated prodrug [banoxantone (AQ4N)] for photodynamic therapy (PDT) and hypoxia-triggered cascade chemotherapy[29]. Zr-clusters as metal nodes together with terephthalic acid and further incorporated with UiO-66 to form Zr-terephthalate UiO-66 nanoparticles were surface-functionalized with photosensitizer photochlor (HPPH) and azide group of p-azidomethyl (as modulators), N_3 via the one-pot solvothermal method. Further, prodrug was encapsulated in nano-particles because of having appropriate porosity. The resulting nano-particles (A/UiO-66-H-P) are phosphate ion-sensitive because the release of AQ4N at a low concentration of phosphate buffer solution (PBS) is very slow while the fast and nearly complete release of AQ4N at high PBS concentration. A schematic illustration of synthesis and surface fuctionalization for an effective drug release with no burst effect in cancer cells is shown in Fig. 5.

"Grafting from" approaches:

In this process, covalent interaction on ligands occurs where ligands already have co-ordinatively unsaturated sites (CUSs) available for modification to synthesized MOF based hybrid materials. Liu *et al.* (2015) developed a reversibly dispersible/collectible MOF system by the modification of MOF nano-particles using grafting copolymerization of 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA) with a molar composition of 90% and 10% oligo(ethylene glycol) methacrylate (OEGMA) on MIL-101-NH_2 through surface-initiated atom transfer radical polymerization (SI-ATRP) approach[30]. The polymers are thermo-responsive and thus in aqueous media modified MOFs have temperature-dependent disparities.

Dong *et al.* (2017) synthesized the dendritic catiomer (UiO-PGMA) by ATRP of poly(glycidyl methacrylate) (PGMA) and UiO-BiBB as initiator[31]. After the synthesis of UiO-PGMA, a ring-opening reaction with ethanolamine bears the synthesis of UiO-PGMA-EA. The cytotoxicity study using A549 cell line was evaluated for UiO-PGMA-EA/pDNA in comparison

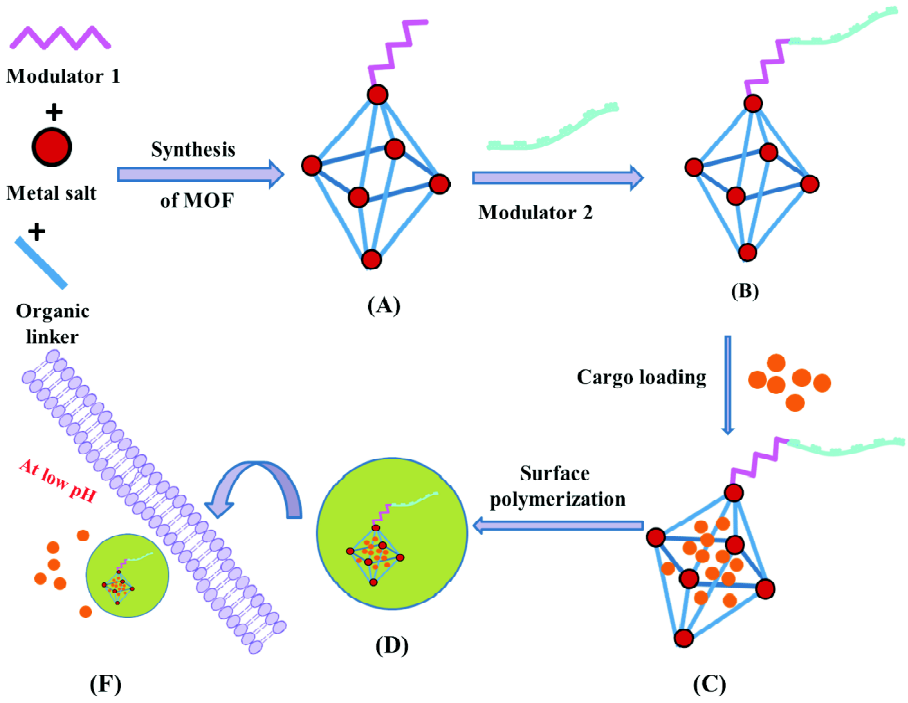


Fig. 5. Synthesis and surface fuctionalization for an effective drug release with no burst effect in cancer cells.

with PEI/pDNA at varying N/P ratios and UiO-PGMA-EA exhibited much reduced cytotoxicity than PEI. Thus UiO-PGMA-EA is to be considered as an efficient gene carrier for delivery of mRNA. Similarly, Chen *et al.* (2018) utilized a new drug delivery platform in which Zr-based MOF nano-particles were functionalized with PGMA[32]. It enhances not only the stability of MOF nano-particles but also DOX release behavior.

Polyoxometalates based inorganic-organic polymer hybrids

Recently, polyoxometalates (POMs) based inorganic-organic polymeric hybrids have emerged as a new class of hybrid crystalline materials for potential applications. The main strategy explored as to incorporate POM into organic or inorganic (such as silica) polymer matrices to design novel polymer hybrid material for the purpose to release drugs in controlled manner[33]. POMs are transition metal oxide clusters with sizes ranging from one to several nanometers having transition metal (mostly W, Mo, V) in their higher oxidation states with variety in composition and size, formed by metal cations that are bridged by oxide anions. These are a prominent class of anionic oxo-clusters consist of diversity in topologies with chemical and electronic properties and promising characters of POMs in antibacterial, drug delivery and any other biological activities regained considerable interest. The excellent toughness, ductility, easy processability and redox ability of POMs can be utilized for building organic-inorganic polymer based hybrid materials and have attracted towards an interest in both basic research and practical applications[34]. Some organic polymers such as poly(methylmethacrylate) (PMMA) and polyaniline are used to demonstrate the optical and electrical properties of POMs. Newly established polymer capsules or biocompatible polymers can be used as matrices for POMs and applicable in coatings, nano-medicines, and biological activities[35]. From the literature, we can understand that several typical and different strategies for the fabrication of polyoxometalates/polymer hybrid material such as physical blending, covalent bonding, supramolecular modifications and *in situ* polymerization have been developed.

Arun *et al.* reported the synthesis of nano-hybrid CS-Eu-Si-POM in which firstly europium substituted POM $K_4H[Eu(\alpha\text{-}SiW_{11}O_{39})\text{-}(H_2O)_2].17H_2O$ (Eu-Si-POM) was synthesized and further Eu-Si-POM encapsulated into biocompatible polymer i.e. chitosan (CS), through ionotropic gelation technique[36]. Eu-Si-POM shows major antibacterial activity with chitosan because chitosan has potential antibacterial and antimicrobial properties due to the presence of charged groups, formed by protonation of amino groups [NH^{3+}] which forms ionic in-

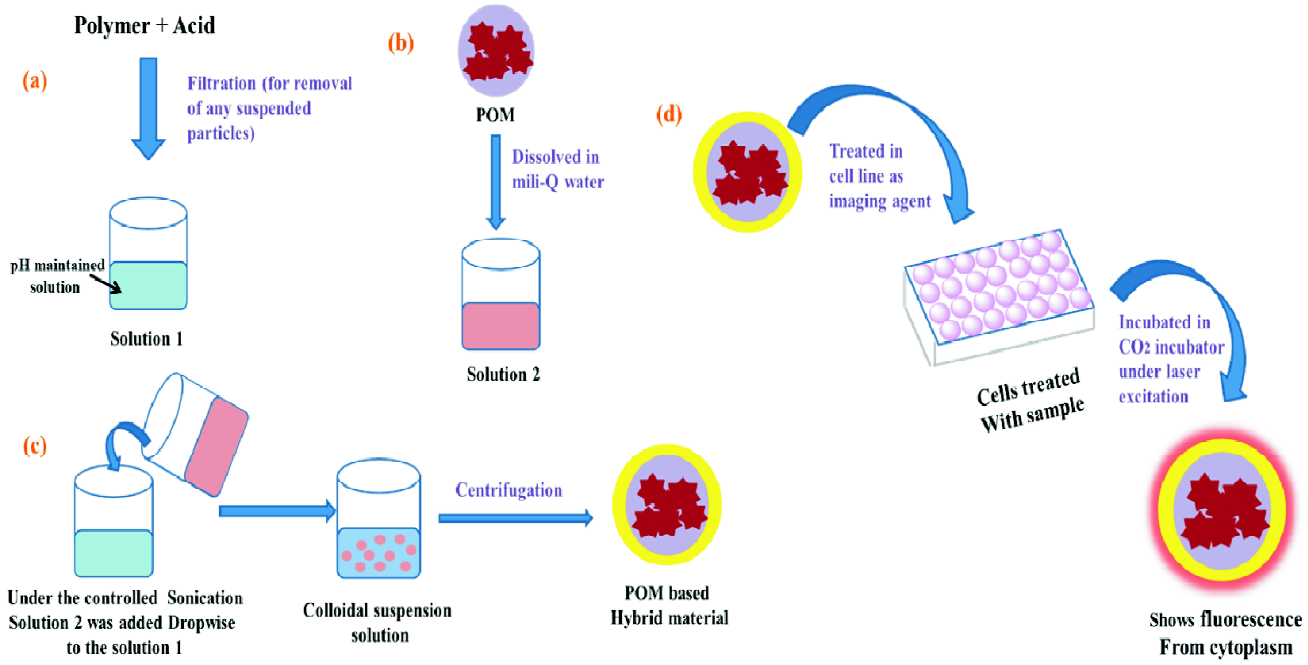


Fig. 6. A systematic synthesis (a), (b) and (c) of CS-Eu-Si-POM and (d) cell line evaluation.

teraction with bacteria wall constituents. CS-Eu-Si-POM nano-hybrid could be efficiently uptaken by A549 cells and further make nano-hybrid promising optical nanoprobes for bio-imaging purpose. A systematic synthesis of CS-Eu-Si-POM and cell line evaluation is shown in Fig. 6.

Chai *et al.* synthesize mobile-ligand nano-particles system built by electrostatic interaction between anionic POM and cationic terminated polymer chains. This multiscale self-assembled NPs represents hierarchical morphologies with reinforced mechanical performance. The mobile-ligand nano-composites provide new idea to design functionalized polymers with new improved optical and electrical properties. These multiscale mobile-ligand particles can be used for drug delivery due to their multiscale sizes[37]. Zheng *et al.* reported sub-nanometer scaled metal-oxide cluster ($PW_{12}O_{40}^{3-}$) and tested their solubility in polyethylene glycol (PEG), while semi-solid nano-composite of cluster is good proton conductive electrolytes. The oxide clusters are dispersed homogeneously in PEG with high loading ~70% and without aggregation can be stable for months[38]. Due to high loading capacity and solubility in PEG clusters can be a good nanocarrier for drug delivery. Yan *et al.* reviewed POM modified metallopolymers, their synthetic stretegies, modification methods, novel POMs based metallopolymers and applications. Metallopolymers are very important for the metal-containing monomers because it is a type of new building block for POMs[39].

Guo *et al.* (2011) proposed an environmentally friendly and very straightforward approach for the preparation of surfactant-free polymer/POM hybrid nano-particles by utilizing the electrostatic interaction between anionic HM and the zwitterionic gelation[40]. Gelatin is a natural polymer, biocompatible and ammonium heptamolybdate (AHM) reported in the literature that it shows good antitumoral activity and in the hybrid HM acts as an active agent as well as an indispensable building block of such polyelectrolyte complex nano-particles. The resultant hybrid nano-particles have a high percentage of HM loading which is about 70% and tunable particle size. The above feature of hybrid is very desirable for the colloidal drug delivery system. *In vitro* cytotoxicity test of nano-particles shows that at higher concentrations gelatin/HM had higher cytotoxicity to cancer cells than the pure AHM solution while *in vivo* study exhibits much higher antitumor efficacy than the plain AHM solution in terms of suppressing tumor growth.

Application in drug delivery

Silica-polymer, polymer/MOFs and polyoxometalates based inorganic-organic hybrid materials as designed by different synthetic strategies have played significant role in controlled drug delivery process. Here we specifically discuss on various methodology like drug release kinetics in a simulated body fluid (SBF), the amount of drug entrapped and release with time, pH-responsiveness, mechanisms for burst effect followed by a gradual decrease, diffusion controlled

Table 1. Drug delivery via polymer based matrices

Hybrid	Polymer	Type of matrix used	Drug	Synthesis/ process strategy	Drug delivery rate and mechanism involved	Ref.
Alginate/polyacrylamide/SBA-15 (Alg/PAM/S15) hybrid hydrogels	Alginate and polyacrylamide	SBA-15	Fluorescently labeled model protein and BSA	A supertough hybrid hydrogel Alg/PAM/S15 was synthesized and used for store fluorescently labeled model protein and BSA and controlled release when they required	The releasing rate of proteins was enhanced by ~70% after 210 min in external mechanical stimulation while without external stimulation it was very slow about 19.8% in same time	14
(P(MAA-DMAEM)/SiO_2) and P(MAA)/SiO_2	Poly(methacrylic acid-*co*-(2-dimethylamino) ethyl methacrylate) and poly (methacrylic acid)	SiO_2	Fluorescein	New polymer hybrid P(MAA-DMAEM)/SiO_2 and P (MAA)/SiO_2 were synthesized via emulsion polymerization and used as drug delivery system for loading and release of fluorescein as drug and diagnostic agent	The diffusion controlled release was slow and follows Korsemeyer-peppas model mechanism	17

Table-1 (contd.)

Chitosan-silica hybrid	Chitosan	Mesoporous silica	Benznidazol	Silica was functionalized with chitosan and used in drug delivery for Chaga disease	This hybrid showed efficient delivery of benznidazol and treated for chronic phase disease	20
(Fe)MIL-100-Met@alginate	Sodium alginate	MIL-100	Metformin	(Fe)MIL-100-Met@alginate used for pH-controlled drug release behavior	Drug loaded MOFs showed 87% release at pH 8 in 8h with no burst release in controlled manner	25
PEGylated UiO-66	Poly(ethylene glycol) (PEG)	UiO-66	Dichloroacetic acid (DCA)	PEGylated UiO-66 hybrid was prepared by using surface-modification or click modulation method and it was used to enhanced stability cell uptake and pH-responsive drug delivery	Release of calcein from coated and uncoated sample at pH 7.4 found very slow ~30% after 5 days while they rapidly released 80% after 2 days at a cancerous environment of pH 5.5	27
PEG/IDA-MSNs	Polyethylene glycol (PEG), iminodiaotic acid (IDA)	Mesoporous silica nanoparticles (MSNs)	Doxorubicin (DOX)	The external surface of MSNs was modified by PEG, and then IDA grafted on the surface of mesopores as ligand, thus DOX were loaded via coordinate bonds. PEG/IDA modified MSNs possessed pH-responsive release behaviour and as an anticancer drug delivery carrier	The pH-responsive release behavior of DOX@PEG-MSNs-IDA/Cu^{2+} at pH 7.4 only 5% while at pH 5 the releasing efficiency was 45%	41
ROSP@MSN	Benzyl acrylate modified polymers (temperature and ROS-responsive polymer)	Mesoporous silica nanoparticles (MSNs)	Doxorubicin (DOX)	Reactive oxygen species responsive co-polymers (ROSP) with mesoporous silica loaded with DOX (ROSP@MSN@DOX). It showed good release behaviour at physiological conditions	Fluorescence mechanism of sample showed that DOX could release from mesoporous in the presence of H_2O_2	42
MSN-cPLGA particles	Poly(L-glutamic acid) (PLGA)	Mesoporous silica nanoparticles (MSNs)	5-Fluorouracil	On the surface of MSNs, PLGA was grafted which were cross-linked with cystamine, and thus used for the controlled release of 5-fluorouracil	The drug delivery rate from MSN-cPLGA without the addition of DTT (dithiothreitol) is only 7.1% while with existence of DTT, 80.4% of 5-Fu drug was released	43
MSN/CS-PMAA .	Chitosan/poly (methacrylic acid) (CS-PMAA)	Mesoporous silica	Doxorubicin hydrochloride	Mesoporous silica nano-particles was coated by pH-responsive polymer shell chitosan/poly(methacrylic acid) MSN/CS-PMAA hybrid was used for doxorubicin (DOX) drug delivery and release behaviour for cancer therapy	The release rate of DOX from DOX@MSNs/CS-PMAA was studied at pH 7.4 and pH 5.5	44

Table-1 (contd.)

DOX@MBC-MSN	Poly(ethylene glycol)/poly(epsilon-capro lactone)(PEG/PCL) multi-block (temperature sensitive)	Mesoporous silica nanoparticles (MSNs)	Doxorubicin (DOX)	MSN were functionalized with PEG/PCL multiblock copolymer (MBC), loaded with doxorubicin DOX@MBC-MSN synthesized for carriers of heat shock responsive drug delivery	In the absence of heat shock loaded drug released from DOX10@MBC-MSN was low whereas in presence of heat-shock entire loaded DOX was released at 45°C	45
MSNs@PDA-PEG-FA	Polyethylene glycol-folic acid (PEG-FA) conjugate on the surface of polydopamine (PDA)	Mesoporous silica nanoparticles (MSNs)	Doxorubicin (DOX)	To prepare a novel nano-particle (NP) MSN was modified by PDA and then polymerized with poly(ethylene glycol)-folic acid (PEG-FA), therefore MSNs@PDA-PEG-FA hybrid was formed and used for drug delivery in cervical therapy	The controlled drug delivery rate of MSNs-DOX@PDA was 27.9% and 28.5% at pH 7.4 from MSNs-DOX@PDA-PEG-FA after 190 h while at pH 5.6 and pH 2 it is 37.2% and 51.1% from former and 38.3% and 49.5% from later matrix	46
MSN-PEG-acrylate	Temperature responsive PEG-acrylate macro-monomers	Mesoporous silica nanoparticles (MSNs)	Sulforhodamine B	MSNs functionalized with PEG-acrylate and at low temperature polymer shell of MSN-PEG acrylate becomes hydrophilic and expanded, while on above room temperature it becomes hydrophobic and release the cargo by sponge-like squeezing effect	Temperature dependent release behavior was shown by sulphodamine B drug from PEG-acrylate and at low temperature releasing efficiency was good in controlled manner	47
FePt@mSiO$_2$@PDA-polyethylene glycol .	Poly-dopamine (PDA)-polyethylene glycol	Mesoporous silica nanoparticles (MSNs)	Doxorubicin (DOX)	FePt@mSiO$_2$@PDA-PEG polymer-hybrid was synthesized for pH responsive controlled release of encapsulated DOX. The above system enhanced PDA loading and had capability of MRI/CT imaging	pH responsive behavior of DOX revealed that at low pH 5 drug releasing efficiency is greater in comparison to pH 7.4	
MSNs-DOX@PDA-PEG	Polydopamine (PDA) and polyethylene glycol (PEG)	Mesoporous silica nanoparticles (MSNs)	Doxorubicin (DOX)	Multifunctional nano drug delivery carriers (MSNs-DOX@PDA-PEG) has been synthesized by DOX loaded with MSN and then coated with polydopamine (PDA) and polyethylene glycol (PEG) for the treatment of breast cancer	DOX release from hybrid was more rapid at pH 5 than pH 7.4	49
P(NIPAM-*co*-MAA)/MGNSs	P(NIPAM-*co*-MAA)	Mesoporous silica nanoparticles (MSNs)	Doxorubicin (DOX)	Magnetic and gold nano-particles embedded silica nanoshuttles (MGNSs) were encapsulated in polymer P(NIPAM-*co*-MAA) and then loaded with DOX. This hybrid perform controlled release of drug at heat and pH changes	The temperature dependent DOX release from MCNS/DOX was 90% at 42°C in 96 h while at 37°C in same time 83% drug released. At pH 7.4, pH 6.8 and pH 5.5 drug released rate was 9%, 31%, 56% respectively	50

Table-1 (contd.)

MSN-P (NIPAm-*co*-MAA)	Poly[(N-isopropyl acryl amide-*co*-(methacrylate acid)] (P(NIPAm-*co*-MAA)	Mesoporous silica nanoparticles (MSNs)	Chlorin e6 (Ce6), carbon dots (CDs) and Gd(III)	Mesoporous silica functionalized by Chlorin e6 (Ce6), carbon dots (CDs) and Gd(III) ions and then coated with polymer [P(NIPAm-*co*-MAA)]. The synthesized system perform thermo/pH-sensitive drug release induced controlled chemotherapy and synergistic therapeutic efficacy	The laser radiation enhanced drug delivery rate of DOX because at 980 nm with radiation DOX release upto 53.32% while without radiation only 16.49%	51
PLGA/DOX@MSN and CPT@HANPs	Poly (DL-lactide-*co*-glycolide) (PLGA)	Mesoporous silica nanoparticles (MSNs)	Doxorubicin (DOX) and Camptothecin (CPT)	The dual drug loaded nanofibers were prepared in which DOX and CPT were loaded into mesoporous silica and hydroxyapatite and then incorporated simultaneously into PLGA. The above nanofiber then used for co-delivery of dual drug and therapeutic effect in cancer therapy	CPT release rate is much more greater than the release rate of DOX. CPT released 84.1% after 192 h from PLGA/CPT@HANPs nanofibres while DOX released after 288 h only 25.7% from PLGA/DOX@MSNs	52
Fe_3O_4@OCMC @IRMOF-3/FA-CDs	Chitosan	IRMOF-3	Doxorubicin	Carbon dots embedded MNPs@CS@MOF polymer/MOF hybrid was synthesized and shows enhanced doxorubicin loading efficiency and pH responsive drug-release	Drug delivery rates are 22.5% and 26.72% at pH 7.4 after 12 h and 24 h, while at pH 5.5 release was 47.92% and 55.1% after 12 h and 24 h respectively	53
SBA-15-PEI-C_{60}	Polyethyleneimine	Mesostructured SBA-15	Methylprednisalone sodium succinate	PEI incorporated with SBA-15 then followed by incorporation fullerene groups and the formed PEI-modified material incorporated with C_{60}-fullerene shows better control of drug release	Drug release rate of methylpredni-solone from SBA-15-PEI-1-C60 and SBA-15-PEI-2-C_{60} in 8 days were 90%	54
MCF-PLA/PLGA: (75/25)	Poly(L-lactide) (PLA) and poly (DL-lactide-*co*-glycolide) (PLGA)	Mesoporous silica foam	Paliperidone	Paliperidone was firstly loaded with MCF silica and then encapsulated into PLA and PLGA 75/25 w/w copolymer. It was used for delivery of antipsychotic drug paliperidone for bipolar disorder	The dissolution apparatus was used to check the releasing profile of drug 90% in 10 days at pH 7.2 and 37°C	55
MNPs-NIPAAm DMAEMA/MSNs	N,N-Dimethyl amino ethyl methacrylate (DMAEMA) and N-isopropyl acrylamide (NIPAAm) (pH-thermo responsive polymer)	Msoporous silica nanoparticles (MSNs)	Methotroxate (MTX)	Synthesize pH and thermo-sensitive MTX loaded magnetic nano-composites and employed in targeted drug delivery and MRI	The drug release rate at pH 5 and 40°C was highest ~92.3% due to combination of pH and thermo-sensitive properties of synthesized molecules	56

Table-1 (contd.)

MS/PNIPAM-MAA/EuW_{10}	Poly(N-isopropylacrylamide-*co*-methacrylic acid) [PNIPAM]	Mesoporous silica and lanthanide-POMs	Doxorubicin	MSNs encapsulated in PNIPAM-MAA shell and Eu-POMs grafted on composite and this hybrid was used as stimuli-responsive drug delivery system	Drug delivery rate of DOX at pH 7.4 and 25°C only 14% in 24 h, while at the same pH but at 45°C release reached 59.5% after 24 h	57
CeAP-L-PEG/MSNs	Polyethylene glycol conjugation through bis (alkyl thiol) alkene linker	Mesoporous silica nanoparticles (MSNs)	Doxorubicin/Ce6	Chlorin e6 with mesoporous silica nano-particles (MSNs) covered by polyethylene glycol shell which was then conjugated via bis(alkyl thiol) alkene linker. The doxorubicin release triggered by red light irradiation observed by *in vitro* and *in vivo*	Photo-dynamically assisted drug release behaviour was shown by designed nanoparticles	58

release etc. to understand the drug functioning behavior. The types of different matrices (silica-polymer, polymer/MOFs and POMs) containing drugs also help to understand new strategies of nano-medicine for controlled drug delivery application (Table 1).

Conclusion

The various combinations of inorganic and organic precursors have been described in detail and the future challenges in this area are also mentioned. From the literature, we conclude that active efforts are needed in this area of research to achieve the new strategies for controlled drug delivery system design. Very little literature is available for synthesis and applications of organically modified polyoxometalates and their applications in drug delivery, it is therefore a challenge for the researchers. Similarly, very few methods are available for encapsulation of these materials into natural biopolymers which generally enhance the bio-compatibility and prevent burst release. The study outlines the synthesis and designing of polymer based hybrid materials to enhance drug delivery in a controlled manner.

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