Journal of Materials Chemistry B

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Cite this: J. Mater. Chem. B, 2025, 13, 6949

Recent progress in ZIF–polymer composites for advanced drug delivery applications

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This review article provides an in-depth study of recent advancements in ZIF–polymer composites, focusing on their transformative potential in drug delivery systems. It also reveals their multiple advantages, including increased drug loading efficiency, controlled and sustained release, and targeted delivery capabilities. In addition, this article explores various applications of ZIFs in diverse therapeutic areas such as orthopedic, ocular, transdermal, gastrointestinal, and pulmonary drug delivery. This review also offers key insights into the synthesis approaches, current scenario, and future directions of ZIF–polymer composites, along with some aspects of critical factors such as stimuli-responsiveness, stability, and toxicity. Zeolitic imidazolate frameworks (ZIFs), a new subclass of MOFs, are synthesized from tetrahedral metal ions and imidazolate linkers. ZIFs are valued for their exceptional porosity, robust chemical stability, and thermal characteristics. They show excellent compatibility with polymers and fabrication of ZIF–polymer hybrids with high loading efficiency is achieved using methods such as *in situ* synthesis, self-assembly, grafting, electrospinning, and microfluidic synthesis techniques. By consolidating knowledge of the role of ZIF–polymer hybrids in drug delivery, this article provides a valued resource for researchers and scientists seeking to revolutionize patient care through cutting-edge materials. It also emphasizes the potential of ZIF–polymer composites to redefine drug delivery systems and improve clinical outcomes, marking a significant milestone in the quest for ideal drug delivery platforms. In summary, this review emphasizes the importance of innovative ZIF-polymer materials as promising alternatives to conventional therapeutic systems, contributing to the development of advanced healthcare solutions.

Received 21st January 2025,
Accepted 8th May 2025

DOI: 10.1039/d5tb00147a

rsc.li/materials-b

1. Introduction

Ensuring human well-being remains a paramount global concern for researchers. According to global cancer statistics for 2024, the disease accounted for 2 million deaths and 0.6 million new cases in the US,[1] underscoring the urgent need for research into advanced cancer therapies. As reported by Beilei *et al.* (2024)[2] and Neha *et al.* (2024),[3] the most widely adopted cancer treatment modalities include radiation therapy, chemotherapy, surgery, and targeted therapy.[4] The pharmaceutical industry has a significant and ultimate goal of producing drugs with targeted delivery to a particular site in the body in order to maximize the therapeutic effect with minimal side effects. The premise of this idea is as old as Paul Ehrlich's "magic bullet" hypothesis, which was proposed in 1891[5] and mainly focused on bringing the type and quantity of drug to the target location and at the right time. However, the effectiveness of such systems depends on several parameters: drug composition, hydrophilic/hydrophobic nature, molecular size, and affinity to proteins.[6] Chemistry research has revealed a variety of nanoparticles and drug delivery systems (DDS) currently in the discovery and development phase, but only a few of these reach clinical testing. These nanotherapeutic agents, which are built from a variety of materials and possess desirable structural characteristics, are now being employed to deal with particular therapeutic problems. New era biomedical uses such as surgical recovery, tissue engineering, cell support structure and as matrices for drug delivery are increasingly correlated with advanced multifunctional inorganic–organic hybrid materials.[7] In recent years due to enhancement in science and technology, the nanomedicine field has opened a new era in health care delivery systems, treatment approaches and nano-biomedical technology.[8]

Metal–organic frameworks (MOFs), first reported more than two decades ago, have attracted a considerable amount of attention from researchers due to their potential for

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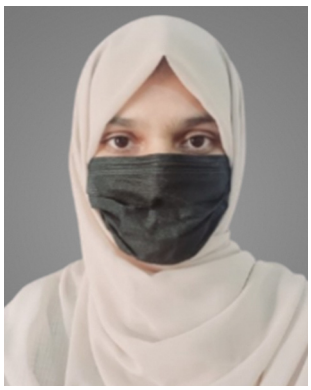
multifunctional uses like drug delivery systems, drug carriers, electron storage systems *etc*.[9] Recently, zeolitic imidazolate frameworks (ZIFs) have shown numerous favourable characteristics including high porosity, large surface areas, chemical and thermal stability, and biocompatibility. These characteristics make ZIFs particularly appropriate for DDS applications, because they allow the efficient loading of the drug and its controlled release. Encapsulation of the drugs can occur through different mechanisms such as hydrogen bonding, van der Waals forces, π–π stacking, coordination chemical bonding and covalent bonding, making the drugs bioavailable as well as improving their therapeutic effects.[10]

Recent incidents, such as drug leakage and instability, have also brought into focus the ability of drug carriers to further



Rimsha Perveen

Rimsha Perveen has completed her MPhil in Analytical Chemistry at the Islamia University of Bahawalpur, Pakistan, under the supervision of Professor Dr Aziz Ur Rehman. Her research focuses on the synthesis of advanced nanomaterials for electrochemical applications. Her research is primarily centered on innovative solutions for water splitting, energy storage, and the development of high-performance sensors. Passionate about pushing the boundaries of materials science, she aims to design and fabricate novel electrode materials with tailored morphologies and enhanced functionalities. She continues to pursue her research ambitions, striving to contribute significantly to the fields of sustainable energy and electrochemical sensing technologies.

Shumaila Bibi

Shumaila Bibi is currently pursuing her PhD in Analytical Chemistry under the supervision of Professor Dr Aziz Ur Rehman at The Islamia University of Bahawalpur and has accomplished her MSc in Chemistry from the same university with an MS in Analytical Chemistry from Government Sadiq College Women University, Bahawalpur. She works as a Research Assistant under the guidance of Professor Dr Aziz Ur Rehman. Her research area is the field of water splitting and energy storage at the forefront intending to develop newest materials with very intriguing characteristics and intricate morphology.

Mohamad A. Saleem

Dr Mohamed Abdel-Rashid Salem is a distinguished scholar in the field of organic chemistry, with a particular emphasis on pharmaceutical organic chemistry. He currently holds the position of Professor of Organic Chemistry in the Department of Chemistry at the Faculty of Science, Al-Azhar University, Cairo. Since 2009, he has also been serving as an Associate Professor at King Khalid University in the Kingdom of Saudi Arabia, where he continues his academic and research endeavors. In 1999, Dr Salem earned his bachelor's degree in special chemistry from the Faculty of Science, followed by both his master's and PhD degrees in Organic Chemistry from Al-Azhar University. His doctoral research focused on the synthesis of heterocyclic organic compounds. His research interests lie primarily in the synthesis of novel heterocyclic compounds with potent biological activities. This includes the development of drug derivatives with a strong focus on their evaluation as antifungal, antimicrobial, and anticancer agents. In addition, Dr Salem is actively involved in organic process development, drug design, and various aspects of medicinal and pharmaceutical chemistry.

Adeel Afzal

Adeel Afzal studied Chemistry at the University of Vienna (Austria) and earned a PhD in 2007. He developed synthetic antibodies as biomimetic coatings for chemical sensors using bulk and surface molecular imprinting techniques. Later, he worked as a Collaborator (Postdoc) at the University of Bari (Italy) and developed nanomaterial-based high-temperature electronic gas sensors. In 2012, he joined the King Fahd University of Petroleum and Minerals affiliated colleges in Hafr Al Batin (Saudi Arabia), which is now known as the University of Hafr Al Batin. He is currently a Professor of Chemistry at the School of Chemistry, University of the Punjab, Quaid-i-Azam Campus (Pakistan). His research interests include the development of imprinted and functional materials for chemical and biosensors and biomedical diagnostics. His academic work is supported by impressive academic metrics, such as a citation count of 4159, an h-index of 32, and an i10-index of 62.

enhance curative effectiveness.[11] There is strong preference for polymers in DDSs due to the enhanced pharmacokinetic profile expressed through the targeting of tissues of interest. They have been applied in polymer therapeutics and nanomedicines and have exhibited advancement in reservoir based drug delivery systems.[12] In DDSs, polymers are preferred over ZIFs due to their superior pharmacokinetic characteristics, as well as their added benefits including targeting ability, drug release characteristics and physiological stability.[13]

Organizing the ZIFs and polymers as one system has expanded the opportunities in the field of DDSs: pH-sensitive nanocomposites and systems with the core–shell structure, with the help of which the best characteristics of both components were used. For example, polymers can improve the stability of ZIFs in the colloidal system, protect ZIFs from degradation and prolong circulation time as well as modify the surface of ZIFs for target-triggered and environmental-sensitive drug delivery.[14–16] However, certain drawbacks like pore blockage and reduced porosity caused by dense polymer coverage still persist, highlighting the need for innovative design and synthesis strategies to fully exploit the potential of ZIF–polymer composites.[17,18]

This review provides a concise overview of recent developments of ZIF–polymer hybrids for enhanced drug delivery systems. Data concerning synthesis structures and properties of ZIF polymers and their nanocomposites are given at the start of this article. After that, the potential of ZIF–polymer hybrids for various DDS applications is discussed, with special attention paid to the key benefits of these materials for drug loading, drug stability, and targeted delivery The focus here is made on the latest trends and advanced approaches, as well as the perspectives for future development of such promising composites in the context of the enhancement of personalized and targeted medicine. Last but not least, the present review intends to shed light on the functionalities of ZIF–polymer nanocomposites in planning and designing for attracting more innovations in drug delivery.

2. ZIF classification based on structure topology

MOFs belong to a category of adaptable micro-porous materials known for nearly a decade after their discovery in the year 1999. MOFs with one-, two-, or three-dimensional structures consist of metal ions coordinated to organic ligands, forming highly ordered porous frameworks.[19–21] MOFs have several benefits and special characteristics, including large surface areas, pore diameters, and morphology that may be controlled by different topologies and unsaturated coordination sites.[21–23] The zeolitic imidazolate framework (ZIF) is a well-known MOF comprising imidazole ligands or imidazole ester bridges connecting inorganic metal nodes as illustrated in Fig. 1.

High chemical and thermal stability and adjustable pore diameters with remarkable gas separation and storage capabilities are just a few of the outstanding qualities of these porous hybrid materials.[24,25] Additionally, ZIFs have unique characteristics that set them apart from many other MOFs and make them very desirable for a variety of applications. These characteristics include varied topological structure, many accessible metal sites, increased micropore volume, ultra-high surface areas, naturally less bulk density, and simple electrostatic interactions having various grafting functional groups. Additionally, ZIFs have gained a lot of attention and experienced rapid development in several fields, like biomedicine, surface-enhanced Raman scattering (SERS)-based sensing, luminescence, chemosensors, drug delivery, gas storage and separation, and luminescence.[11,26–28] Fig. 2 presents a brief visual summary of graphical abstracts from recent publications on ZIFs over the past five years, highlighting the ZIF type, synthesis methods, and their respective applications.

Muhammad Ahmad Wattoo

Muhammad Ahmad Wattoo is a Professor at the Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan and has made significant strides in the field of chemistry with a focus on synthesis and characterization of polymers and their composites. His work, aimed at catalysis, photo-catalysis, and energy storage applications, is supported by over 100 peer-reviewed publications in prestigious international journals. His current studies focus on development of a hybrid heterostructure photocatalyst for proficient dye degradation and preparation of novel bi-metallic hybrid oxide nanocomposites for removal of moxifloxacin pollutants.

Aziz ur Rehman

Aziz ur Rehman is a respected professor at the Institute of Chemistry at the Islamia University of Bahawalpur, Pakistan. He has been awarded a PhD degree from Quaid-i-Azam University, Islamabad, Pakistan. He pursued a Postdoc at the Changchun Institute of Applied Chemistry, China. Dr Rehman has built up a recognized academic and research profile in the synthesis, characterization, and application of nanoparticle composites for the development of water purification, catalysis, photo-catalysis, and energy storage solutions. His academic work is supported by impressive academic metrics, such as a citation count of 2800, an h-index of 34, and an i10-index of 65.

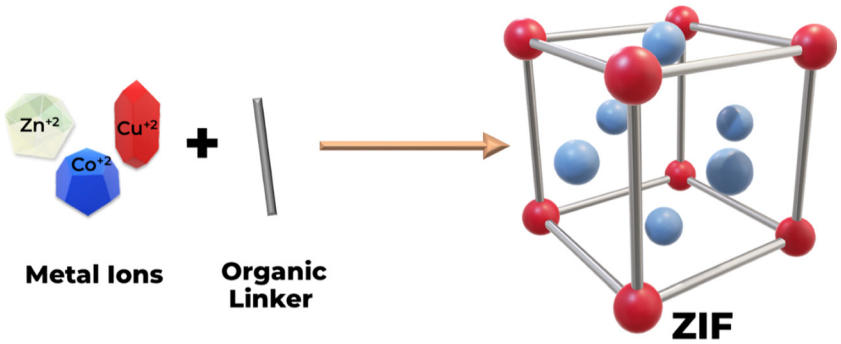


Fig. 1 ZIF 3D structure and metal ions with organic linkers.

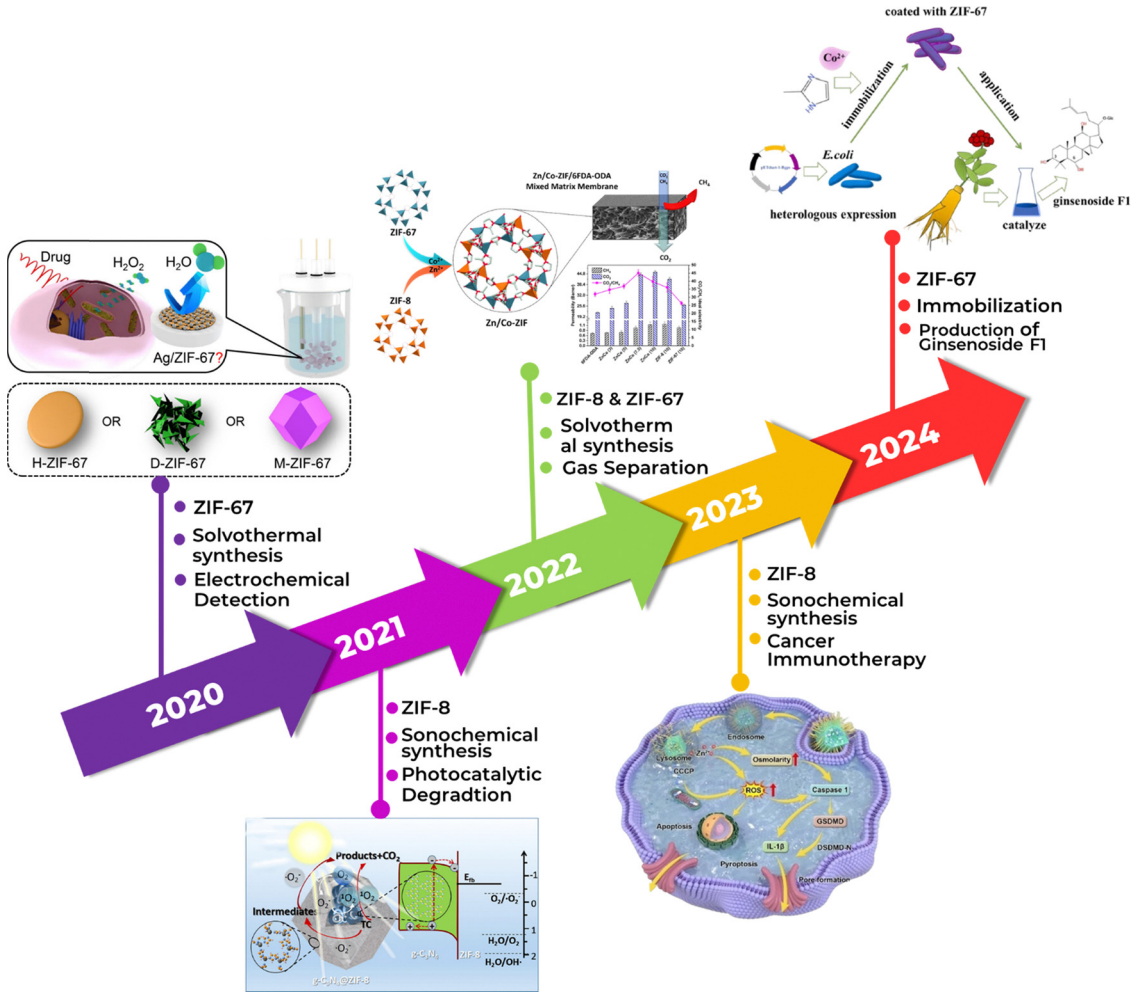


Fig. 2 Illustration of the latest published works on ZIFs with their graphical abstract images.[29–33]

The ZIF's main structural component is $T(IM)_2$ bonding, where T stands for tetrahedrally coordinated metal ions and IM for imidazole and imidazolate derivatives. The T–IM–T has a 145° angle comparable to the $(Si)_2O$ angle seen in zeolites. Greater structural variation in ZIFs can be achieved by taking functionalized imidazolate ligands in their synthesis, as the structure taken by a particular ZIF depends on the kind of imidazolate and solvent used.[34]

ZIF structures are similar to normal zeolites with topologies such as sod, gme, rho, ana, and lta, illustrated in Fig. 3, or they can have structures that are previously unidentified in zeolites that use a combination of two distinct imidazolate ligands. A significant number of novel ZIF structures were identified by the use of high-throughput synthesis techniques, and by 2010, about 105 ZIF materials along with various structures or chemical compositions had been reported.[35] ZIF-8, ZIF-67,

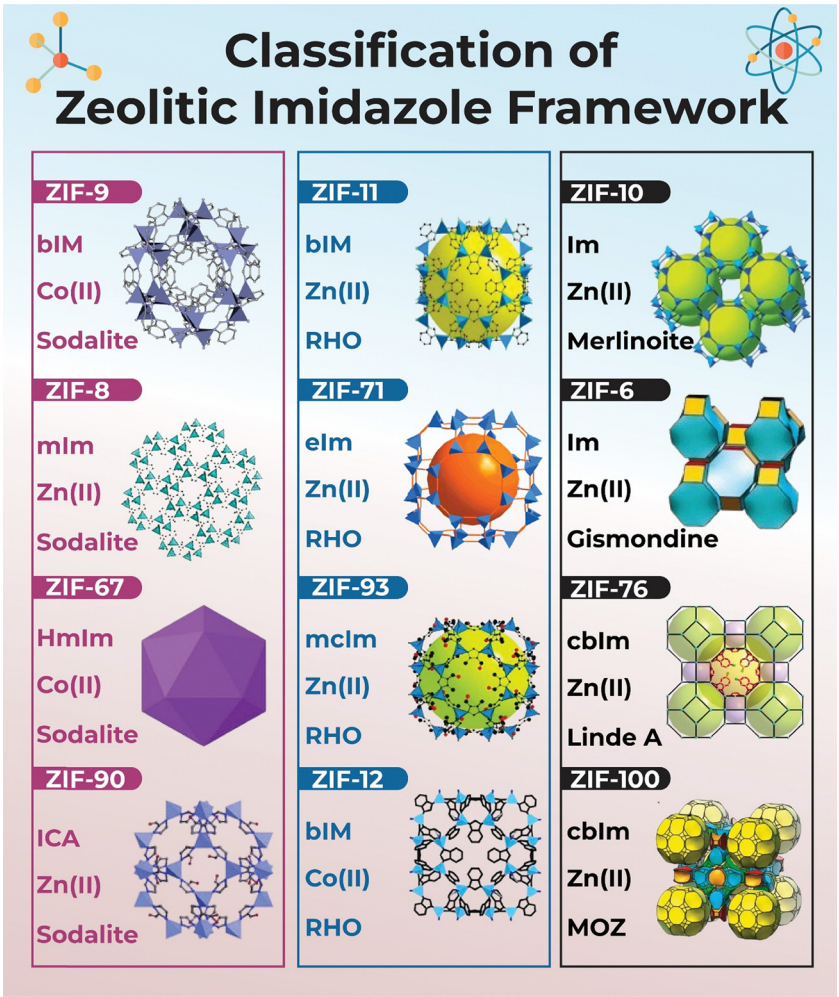


Fig. 3 Classification illustration of widely-used ZIF metalloid linkers of the corresponding ZIFs.

and their variants are most widely used ZIF materials as targeted drug delivery systems for various biological problems. Zinc nitrate and 2-methylimidazole make up ZIF-8 (Zn-based), renowned for having a stable skeleton and consistent internal pore size. ZIF-67 (Co-based), on the other hand, is composed of 2-methylimidazole and cobalt nitrate and is distinguished by its high porosity, wide surface area, and biocompatibility.[11,28,36]

ZIF-8 and ZIF-67 have microstructure cages founded on sodalite topologies, in which neighboring zinc and cobalt ions are linked by 2-methylimidazole, respectively. Reaction parameters can control the ZIF particle size and crystallinity.[37] Numerous additional ZIFs have been synthesized to date. ZIFs are thought to combine the amazing structural variety of MOFs along with the chemical and thermal stability of zeolites. ZIFs have found widespread use across several fields, with drug delivery systems and biomedical engineering being of special interest. Formulated as $Co(PhIm)_2 \cdot (DMF) \cdot (H_2O)$, Co-based ZIF-9 has hexagonal symmetry in its open-framework structure that adopts a sodalite topology. It is made up of benzimidazolate (bIm) anions that bridge and cobalt cations.[38] Recently, Liu *et al.* used solvothermal synthesis of zinc(II) with imidazolate-2-carboxaldehyde (ICA) to create a new SOD structure called ZIF-90.[39]

Using a RHO topology, ZIF-11 is made up of big cages with a diameter of 14.6 Å that are joined by tiny holes with 3.0 Å diameter. This creates zeolitic structure that is composed of zinc ions along with nitrogen atoms from benzimidazole (bim) anions.[40] Porous carbons generated from ZIF-11 might keep this sacrificial template ZIF-11's apertures intact; since they are almost the iodine's kinetic diameter of 3.30 Å, they could effectively retain visitor iodine molecules.[41] ZIF-93 [Zn(4-methylimidazolate-5-carbaldehyde)$_2$] and ZIF-71-EIM [Zn(2-ethylimidazolate)$_2$] have RHO topology.[42] ZIF-12, a cubic RHO-type zeolite structure, has 28.76 × 28.76 × 28.76 Å unit cell dimensions. It consists of bIm acting as a linker with cobalt (Co) as a metal atom.[43] Within ZIF-10, every zinc atom is tetrahedrally bonded to four imidazolate linkers, producing a merlinoite (MER) cage with a diameter about 12.1 Å. These cages are bridged by huge windows with 8.2 Å diameter apiece, and each unit cell has two MER cages.[44] One of the more intriguing structures that Marija's group has published is ZIF-76. ZIF-76 is composed of zinc ions coordinated with a combination of 5-chlorobenzimidazole

(5-ClbIm) and imidazole (Im) ligands. The resultant structure has larger pores than similar non-hybrid zeolitic structures, yet it still exhibits LTA topology.[45] Yaghi and colleagues used the reaction of $Zn(O_3SCF_3)_2$ with 5-chlorobenzimidazole (cbIM) to create a new ZIF-100 structure with the composition $Zn_{20}(cbIM)_{39}(OH)$.[46] It was discovered that ZIF-100 has a somewhat complicated structure. ZIF-100 is made up of 7524 atoms and has a MOZ structure in its unit cell. With a diameter of 35.6 Å, the inner sphere of this MOZ cage is huge, while its window aperture is narrow, measuring just 3.35 Å. ZIF-100 has an exceptional capacity and affinity for CO_2, leading to an exceptional absorption of CO_2.[47]

2.1. Synthesis methods of ZIFs

ZIF synthesis has been the topic of several investigations for the last few years. Therefore techniques like sonochemical, mechanochemical, and ionothermal synthesis have been added to traditional hydro- and solvothermal approaches as shown in Fig. 4.[27,34] Due to the field's rapid progress, new ZIF synthesis methodologies have emerged recently. A range of synthesis techniques like solvent-containing and solvent-less procedures have been introduced to produce ZIF-based products. Multiple synthesis techniques have to be applied to produce ZIF containing materials, depending on the type of generated ZIFs.[48]

2.1.1. Solvothermal synthesis. The solvothermal method is widely used for ZIF synthesis, employing organic solvents like DEF, DMF, and NMP. Yaghi *et al.* first synthesized ZIF-1 to ZIF-13 in 2006 and later extended it to ZIF-60 to ZIF-100 using similar solvents.[8] Further researchers synthesized ZIFs utilizing DEF or DMF to study their characteristics and formation. Inspired by Yaghi's approach, several organic amines act as deprotonating agents, like triethylamine (TEA) and pyridine by adding to DMF or DEF solvent. For example, TEA can used to create a ZIF-78 crystal having a micron-sized hexagonal rod shape,[49] while room-temperature pyridine was added to DMF to synthesize ZIF-90.[50] ZIF-8 is made by Swati *et al.* utilizing a straightforward solvothermal technique with DMF, followed by calcination at 150 °C and 300 °C. Her study reported ZIF-8's electrochemical performance and structural retention, along with nanoparticle agglomeration changes, Fig. 5(a).[51] Yueting *et al.* investigated hydrangea-like porous ZIF-8 crystals formed at 110–140 °C without structure-directing agents, which transformed into rhombohedral polyhedrons over time, Fig. 5(b).[52] Qiming *et al.* reported Zif-67@NiCo doped on LDH using methanol as solvent, confirming its rhombic dodecahedron structure *via* SEM, Fig. 5(c).[53]

2.1.2. Hydrothermal synthesis. Even though the solvothermal approach dominated early ZIF research, organic solvents are costly, combustible, and not environmentally friendly. Recent efforts focused on synthesizing ZIFs using minimal or no organic solvents. Pan *et al.* achieved ZIF-8 production for the first time in an aqueous environment at ambient temperature.[54] Hang *et al.* produced ZIF-8 in alcohol at 140 °C using stoichiometric precursors (Zn^{2+}: MIm $\frac{1}{4}$).[55] Honney *et al.* studied a $MoSe_2$/ZIF-8 heterojunction nanocomposite for photocatalytic degradation of dyes and antibiotics, synthesizing it *via* a two-step hydrothermal method. The FESEM image of pure ZIF-8 displayed in Fig. 6(a) shows several smooth-faced dodecahedral crystallites.[56]

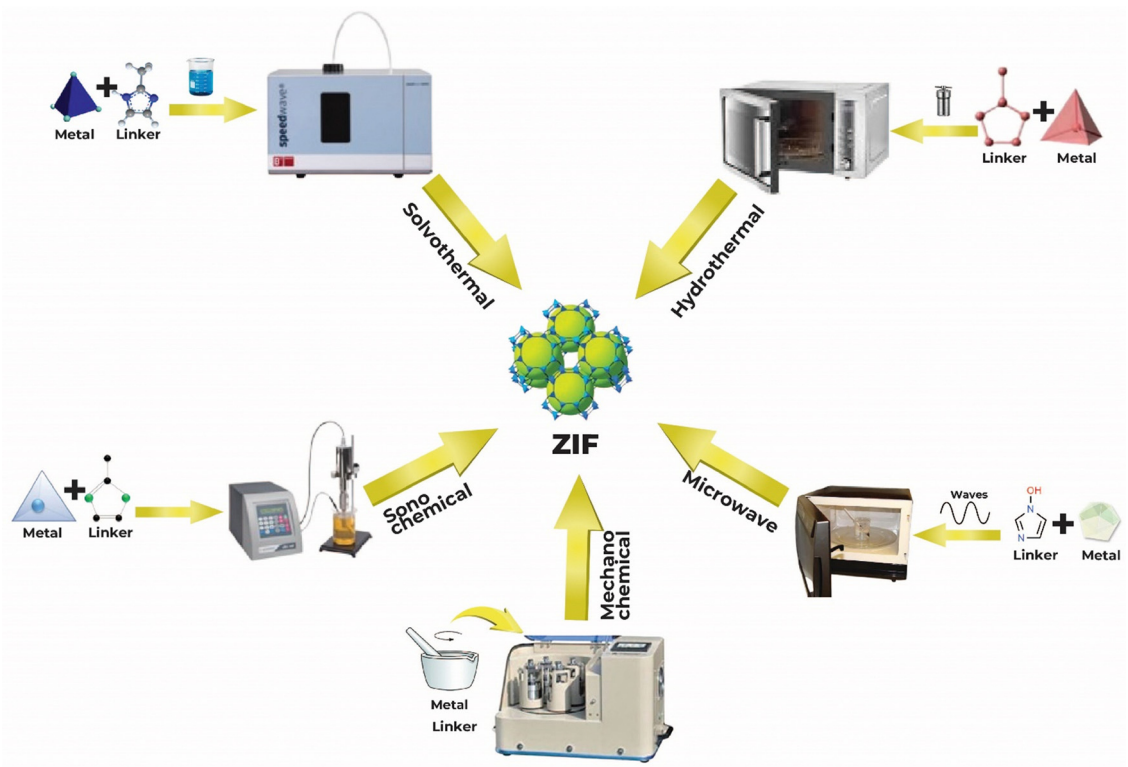


Fig. 4 Different synthesis schemes for the zeolitic imidazole framework.

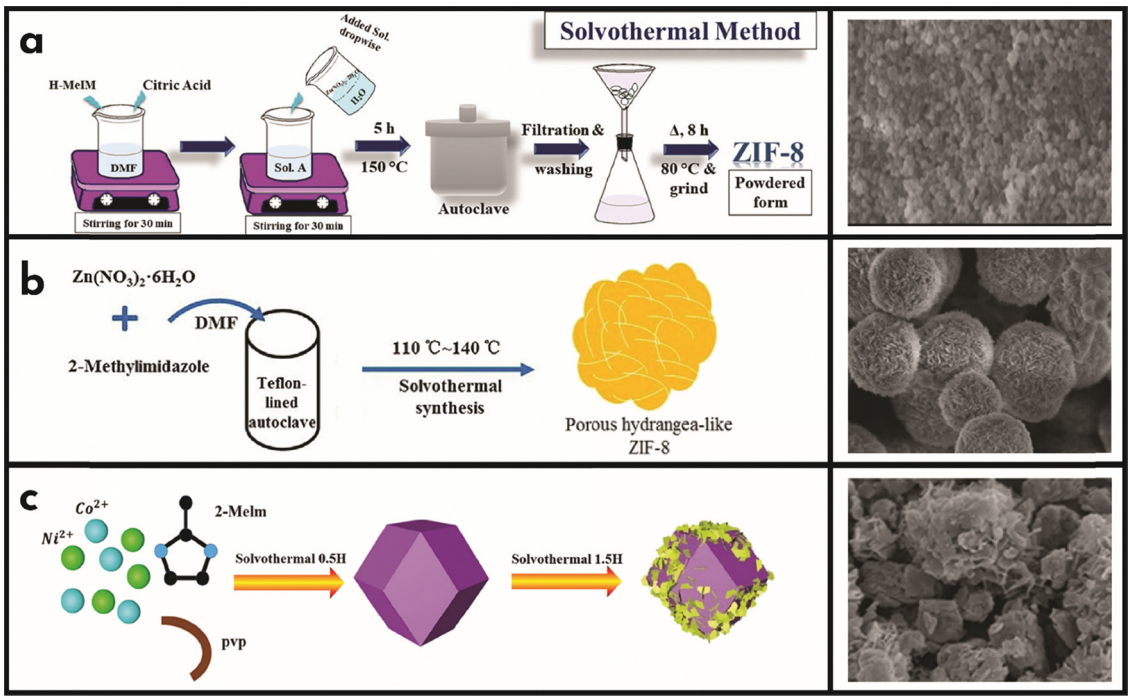


Fig. 5 Solvothermal synthesis of ZIF-8 with SEM of calcined ZIF-8[51] (a), ZIF-8 synthesis using DMF with a SEM image[52] (b), and ZIF-67 synthesis with a SEM image[53] (c).

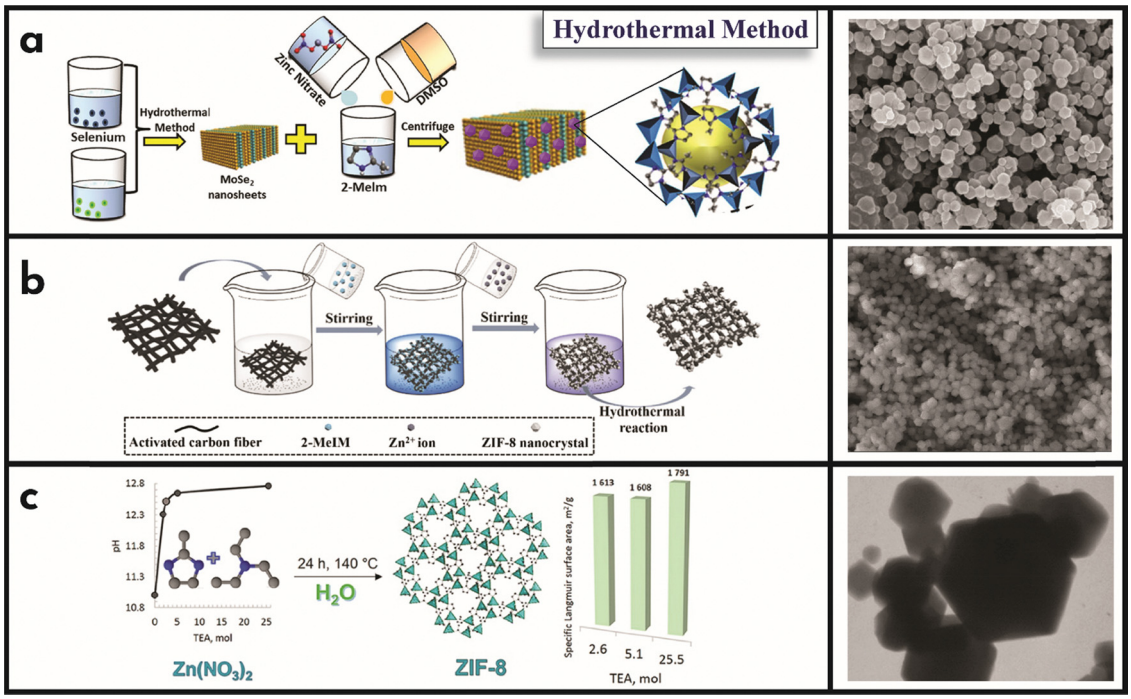


Fig. 6 $MoSe_2$@ZIF-8 synthesis with a ZIF-8 SEM image[56] (a), SEM image of ZIF-8-coated activated carbon fiber[57] (b), and the synthesis process of ZIF-8 by little TEA usage[58] (c).

Lipei *et al.* synthesized ZIF-8 nanocrystals using a hydrothermal technique in an aqueous solution, yielding 100 nm hexagonal and cube-like particles Fig. 6(b).[57] V. V. Butova *et al.* developed a hydrothermal method to produce high-surface-area ZIF-8 (1340 $m^2\ g^{-1}$ by BET) without DMF, using TEA as a structure-directing agent. They examined TEA concentration effects (1.9–25.5) on ZIF-8 formation at 120 °C, confirming particle size and shape *via* TEM, Fig. 6(c).[58]

2.1.3. Mechanochemical synthesis. Mechanochemistry has proven to be a promise as a productive and sustainable material creation process. A mechanochemical synthesis technique (ball milling) for ZIFs was established, with nonporous $Zn(IM)_2$ partially formed in 2006 by grinding ZnO and imidazole (IM).[59] Ivana *et al.* used mamometric studies of a mechanochemical process to obtain $Zn(IM)_2$ materials.[60] The structure of produced ZIFs can be maintained by choosing various salt additions like NH_4NO_3, $(NH_4)_2SO_4$, and $NH_4CH_3SO_3$ and grinding solutions (like ethanol, DMF, and DEF). Friscic *et al.* observed the development of intermediates, and inter-conversion of ZIF topologies *via* high-energy synchrotron X-rays.[61] Cheetham *et al.* reported that ball milling may also produce amorphous ZIFs,[62,63] including ZIF-1, ZIF-3, ZIF-4, ZIF-8 and ZIF-69.[63,64]

Mahya *et al.* synthesized ZIF-67 using a solvent-free ball milling method, a quick and green process that eliminates solvents,[65] with FESEM images in Fig. 7(a) showing spherical primary ZIF-67 particles of 50–100 nm. ZIF-8 was synthesized under high pressure as Lorena *et al.* described,[66] with SEM images in Fig. 7(b) showing a rhombic dodecahedron form. According to Sylwia *et al.*, the best way for immobilizing Candida Rugosa Lipase (CRL) is to use ZIF-8[67] and SEM images of ZIF-8@CRL illustrated in Fig. 7(c) revealed the aggregation after immobilization.

2.1.4. Sonochemical synthesis. Sonocrystallization produces ZIFs by uniformly spreading nucleation and facilitating their formation. Acoustic cavitation in sonochemical synthesis generates high temperatures, pressures, and rapid heating/cooling, making it a quicker, cheaper, cleaner, and greener method.[68] In contrast to traditional solvothermal synthesis, ZIF-7, ZIF-8, ZIF-11, and ZIF-20 crystals were produced through frequency (47 kHz) and ultrasonic radiation (110 W power), at a short time (6–9 h) with low temperature (45–60 °C), according to Seoane's study, yielding smaller crystals with narrower size distribution.[69] Cho *et al.* synthesized high-yield ZIF-8 in DMF through a sonochemical method by using TEA with NaOH.[70]

Hye *et al.* reported ZIF-8 synthesis through a sonochemical method with TEA and NaOH under pH-adjusted conditions, producing needle-shaped particles with altered properties, as shown in Fig. 8(a).[70] However, ZIF-8's textural qualities were preserved by combining a little quantity of TEA with NaOH (aq). Xue *et al.* fabricated TiO_2/ZIF-8 hybrid photocatalysts, with ZIF-8 arranged uniformly on TiO_2 ESNFs to form a bond of N-Ti-O using a sonochemical technique.[71] As seen in Fig. 8(b), when the TiO_2 nanoflowers/2-MI molar ratio was increased up to 1 : 2, ZIF-8 NPs with rhombic dodecahedra morphology were produced intergrownally. Rahul *et al.* synthesized Ni-ZIF-67/WPU nanocomposites *via* a simple ultrasonic process;[68] the SEM image in Fig. 8(c) revealed the nanocomposite film surface.

2.1.5. Microwave-assisted synthesis. The microwave irradiation approach offers higher selectivity, yield, and heating efficiency than traditional solvothermal techniques.[72] Microwave radiation in MOF synthesis is widely used for (I) accelerating crystallization, (II) preparing nanoparticles, (III) improving purity, and (IV) selectively synthesising polymorphs.[73] ZIF-8's strong chemical and thermal stabilities make it one of the most characteristic ZIF materials.[74] While studies exist on morphology-controlled synthesis for ZIFs, little is documented on microwave irradiation synthesis using dual metal ions for hollow and nanoframe-like MOFs effective in Knoevenagel reaction.[75]

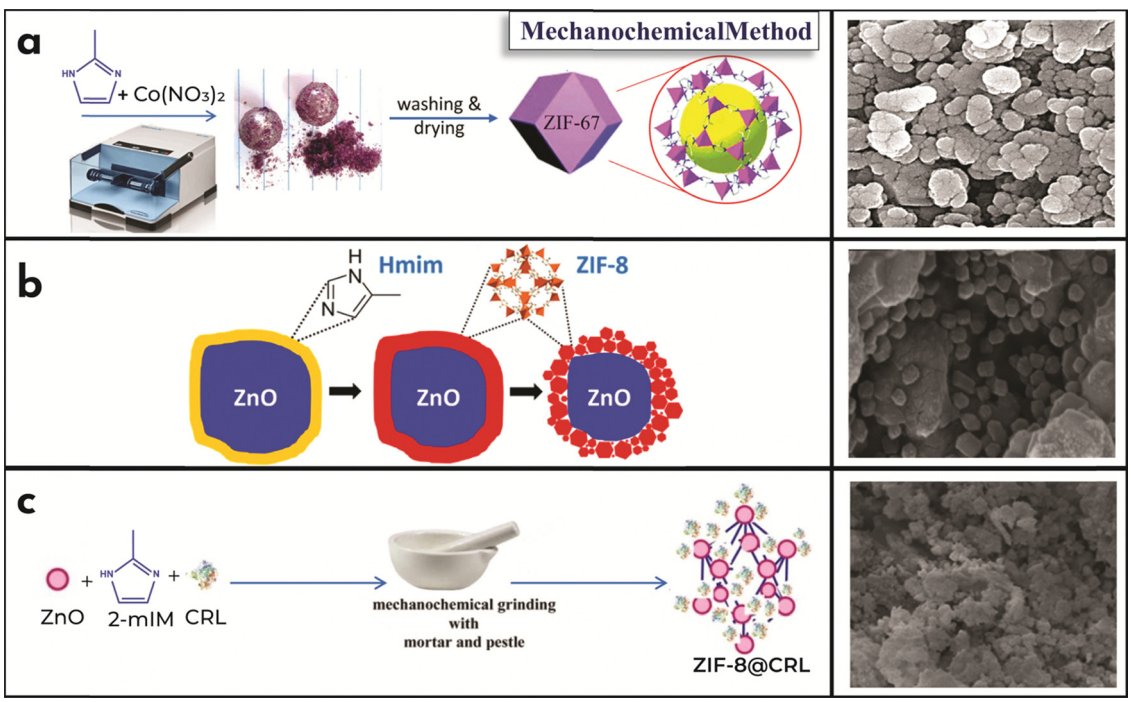


Fig. 7 ZIF-67 synthesis *via* BM with a SEM image[65] (a), solventless high-pressure synthesis of ZIF-8 from ZnO and mIm with a SEM image at 60 min[66] (b), and the encapsulated enzyme ZIF-8@CRL SEM image[67] (c).

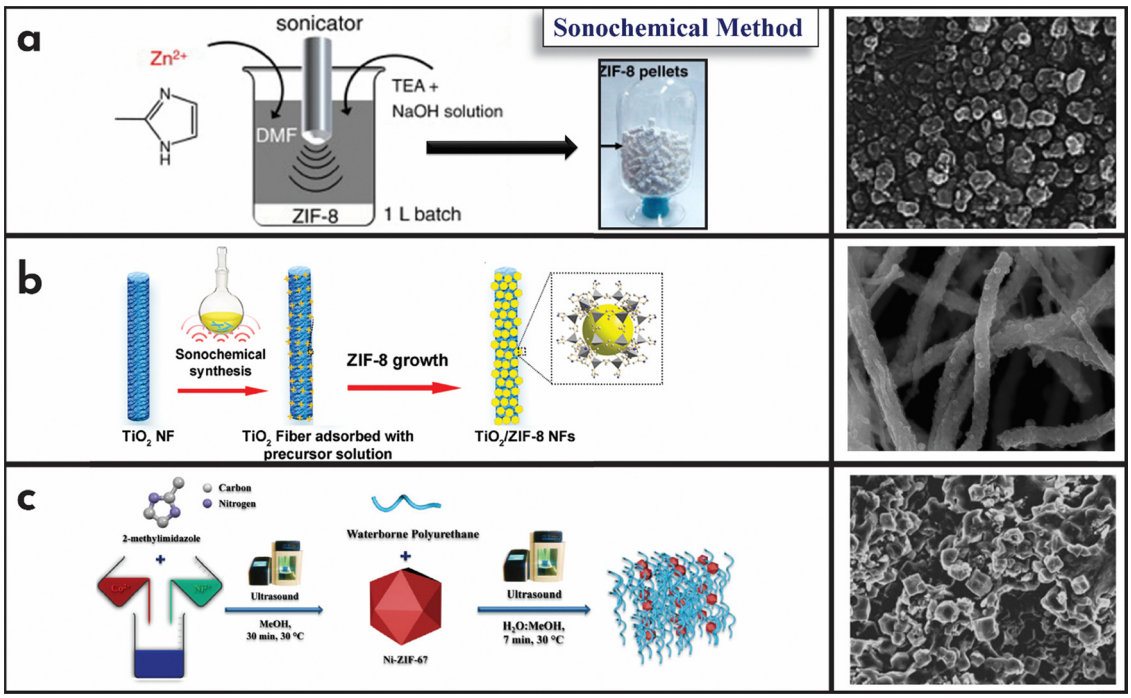


Fig. 8 ZIF-8 synthesis by a sonochemical process with a SEM image[70] (a), TiO_2/ZIF-8 hybrid nanofiber production with a SEM image of TiO_2/ZIF-8-1.3 NFs[71] (b), and Ni-doped ZIF-67/WPU nanocomposite *in situ*, together with an FE-SEM image showing the cracked surfaces of the films[68] (c).

Thuan *et al.* synthesized ZIF-8 crystals using a microwave-assisted technique (450 W power, 140 °C temperature, and 15 minutes), yielding homogenous particles as shown by Fig. 9(a), with some 200 μm dodecahedron crystals having smooth surfaces and minor defects.[76] Xinlong *et al.* developed a quick, solventless Fe@ZIF-8 synthesis, scalable with ball milling.[77] According to SEM, M_{15}-FeNC-NH_3 has a spongy architecture of macropores and mesopores, as can be seen in Fig. 9(b). According to Yueting *et al.*, ZIF-8 can prepared through microwave-assisted synthesis, taking less than 30 minutes when surfactants

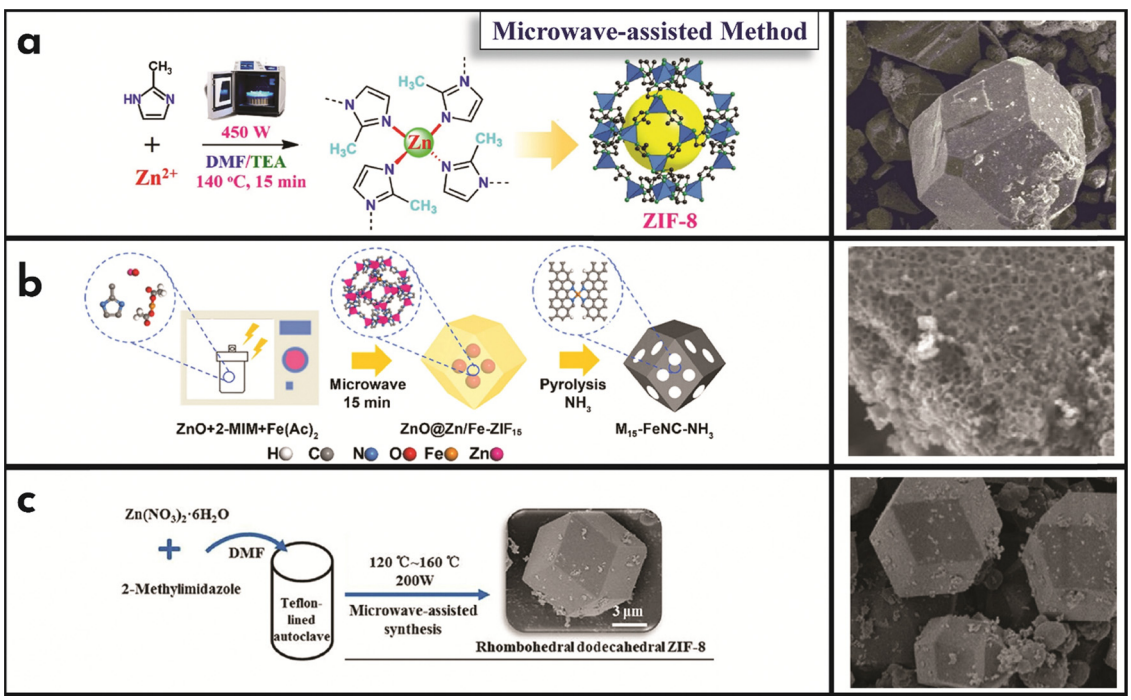


Fig. 9 Schematic of ZnO@Zn/Fe-ZIF and M_{15}-FeNC-NH_3 synthesis[76] (a), ZIF-8 synthesis under microwave irradiation with a SEM image[77] (b), and rhombohedral dodecahedral ZIF-8 synthesis with a SEM image[52] (c).

are present.[52] As the microwave reaction time increases, ZIF-8 crystals grow closer to the polyhedron. ZIF-8 has a rough spherical or rhombohedral polyhedron morphology. The region of 120–140 °C is where the well-architectured ZIF-8 crystal may be achieved. Morphology of ZIF-8 rhombohedral dodecahedral is seen in the SEM picture in Fig. 9(c).

We discussed several strategies for creating ZIFs. Different ZIFs synthesized using these methods are summarized in Table 1. Without question, each strategy has benefits and drawbacks. The solvent-assisted techniques include solvothermal, microwave, ionothermal, hydrothermal, and sonochemical techniques. These innovative methods provide great surface area, scalability, and repeatability quickly. However, these techniques become ineffective when the linker and solvent are used excessively.

2.2. ZIFs for drug delivery

The traditional drug delivery method, which utilizes materials derived from either organic or inorganic sources, has significant drawbacks including cytotoxicity, poor biocompatibility, and uncontrolled drug release. Bringing drugs from synthesis to market is a lengthy and complex process that requires

Table 1 Several approaches used for ZIF synthesis

S. no.	ZIF type	Precursors	Empty cell	Experimental conditions	Synthesis medium	Ref.
Solvothermal synthesis						
1	ZIF-1 to ZIF-12	Zn^{2+}	2-MeIM	120 (°C)	MeOH/EtOH/DMF/DEF/2-propylOH	78
2	ZIF-1to ZIF-12	Zn^{2+}	2-MeIM	140	MeOH	79
	nZIF-8	Zn^{2+}	2-MeIM (40)	60		
3	ZIF-8	Zn^{2+}	Hmim	150	DMF	80
4	ZIF-8	Zn^{2+}	2-MeIM (3.95)HCOONa (7.91)	90	MeOH	81
5	ZIF-8	Zn^{2+}	2-MeIM (23.72)HCOONa (11.86)	90	MeOH	
6	ZIF-8	Zn^{2+}	2-MeIM	40	DES (deep eutectic solvent)	82
7	ZIF-67	Co^{2+}	2-mIm	80	MeOH	83
8	ZIF-95	Zn^{2+}	cbIM (40.0)	120	DMF/H_2O	46
9	ZIF-7 and ZIF-62	Zn^{2+}	L = Im : bIm (9 : 1 to 1 : 9)	110	DMF	84
10	ZIF-95	Zn^{2+}	cbIM (8)	80–120	DMF/H_2O	85 and 86
11	ZIF-9 membrane	Co^{2+}	bIM (4.03)	120	DMF	87
12	ZIF-9 membrane	Co^{2+}	bIM (4.4)	80–130	DMF	88
13	ZIF-90	Zn^{2+}	ICA (0.3)	100	DMF	89
14	ZIF-90	Zn^{2+}	ICA (1.0)	70	MeOH/TEA	90
15	ZIF-76	Zn^{2+}	5-ClbIm	140	GVL/MeOH	45
Hydrothermal synthesis						
16	MXene/ZIF-67	Co^{2+}	bIM	135	DMF	91
17	ZIF-8	Zn^{2+}	2-MeIM (0.06 M)	400	H_2O	92
18	Zif-67@NiCo-LDH	Co^{2+}	MeIM	90	MeOH	93
Sonochemical synthesis						
19	Fe_3O_4@ZIF-8	Zn^{2+}	hmIM	30 min	MeOH	94
20	Ni-ZIF-67	Co^{2+}	mIm	45 min	MeOH	68
21	ZIF-8	Zn^{2+}	2-MeIM (20.3)	—	MeOH	95
22	ZIF-8	Zn^{2+}	2-MeIM (40.2)	30	MeOH	96
23	ZIF-8	Zn^{2+}	mIm	60 min	MeOH	97
24	(a) ZIF-67	(a) Co^{2+}	2-MeIM (16)	(a) —	(a) MeOH	98
	(b) Pd-ZIF-67	(b) Pd^{2+}		(b) 56	(b) acetone	
MW-assisted synthesis						
25	ZIF-9	Co^{2+}	bIm	60 min	DMG	99
26	ZIF-8 CaO/ZnO	Zn^{2+}	2-MeIM	20 min	EtOH	100
27	ZIF-11 crystal	Zn^{2+}	bIM (2)	100	NH_4OH, MeOH, and toluene	101
28	(a) ZIF-67	(a) Co^{2+}	(a) 2-MeIM (10.9)	—	—	102
	(b) Co@ ZIF-8	(b) Zn^{2+}, Co^{2+}	(b) 2-MeIM (9.56)			
29	ZIF-7 crystals	Zn^{2+}	bIM (0.73)	140	DMF/DEF	103
30	(a) ZIF-7-8	(a) Zn^{2+}	(a) 2-MeIM, bIM	100	DMF	104
	(b) CoZn ZIF-7-8	(b) Co^{2+}	(b) 2-MeIM, bIM			
31	ZIF-8	Zn^{2+}	2-MeIM (15.59)	120	MeOH	105
Mechanochemical synthesis						
32	ZIF-8$Zn(EtIm)_2$	Zn^{2+}	HIm (1)2-MeIm (1)HEtIm (1)	27	EtOH, DMF or DEF	106
33	ZIF-8	Zn^{2+}	2-mIm	20 min	H_2O, MeOH	107
34	ZIF-8	Zn^{2+}	2-MeIm (200)	—	—	108
35	ZIF-8	ZnO $Zn(CH_3COO)_2$	2-MeIm (5)	—	—	109
36	(a) Pd@ZnO	(a) ZnO	(a) —	—	(a) —	110
	(b) Pd@ZIF-8	(b) Pd^{2+}	(b) 2-MeIm (200)		(b) EtOH	
37	ZIF-8	Zn^{2+}	2-MeIm (2)	—	EtOH	60
38	ZIF-9	Co^{2+}	bIm	50 min	DMF	111

decades of research. Ultimately, they have significant adverse effects, low effectiveness, and non-specific delivery with elevated cytotoxicity.[112] Precise and focused medication administration that doesn't adversely affect healthy cells to the greatest extent is important to address this shortcoming. The ZIF as a result is the best system for the regulated release of therapeutic molecules. ZIF materials are becoming a potential platform for controlled release of therapeutic molecules or for drug delivery because of their outstanding porosity architectures, remarkable chemical and thermal stabilities, tunable multifunctionalities in the frameworks, and also pH-sensitive release capabilities.[113] ZIF-8 is regarded as a promising option as an anticancer drug delivery system. Sun *et al.* discovered for the first time that ZIF-8 might be employed as a drug delivery carrier because of its pH-sensitive qualities, which are motivated by fact that ZIF-8 is stable in H_2O and NH_4OH solutions but rapidly decomposed in acidic solution.[114] The anticancer medication 5-fluorouracil has also shown a notable loading capacity for ZIF-8 because of its extremely porous structure and superior textural qualities. Two distinct methods for delivery of encapsulated 5-fluorouracil from ZIF-8 are utilized in response to physio-pathological pH signals. Doxorubicin (DOX), another widely used anticancer medication, has been successfully incorporated into the ZIF-8 matrix.[115] When compared to pure DOX, the DOX-loaded ZIF-8 exhibited reduced cytotoxicity toward MCF-7 cell lines and HL-60 while enhancing antitumor potential. It also showed progressive release, with a drug release of about 66% over 30 days and a high DOX loading capacity of about 0.049 g. More recently, ZIF-8-based nanoplatforms have been developed for simultaneous pH-responsive drug administration and cancer cell fluorescence imaging; carbon nanodot doped ZIF-8NPs offer tunable sizes and fluorescence intensity.[116] According to release studies, the carbon nanodots doped on ZIF-8NPs loaded with 5-fluorouracil released slowly at first and more quickly later on (Fig. 10). Beyond anticancer drug delivery, ZIF-8 cages have been used to encapsulate caffeine, an amphiphilic medication with notable lipolytic action.[117] In this instance, the ZIF-8 material was able to regulate the release of caffeine while also shielding the drug molecules from thermal degradation throughout the process.[64]

Moreover, lysozyme (Lys) wrapped around Zn-based ZIF-8 to create Hap doped Lys/ZIF-8 composites by promoting nucleation and development of bone-like hydroxyapatite (HAp) through strong metal ion bonding. According to *in vitro* tests, composites including an HAp shell and a hollow Lys/ZIF-8 core have demonstrated remarkable drug-loading efficiency (56.5%), cytocompatibility, pH-responsive drug delivery and stability in a physiological environment. Using a biomimetic mineralization approach to create ZIF-based composites might pave the way for synthesis of cutting-edge delivery systems in the biomedical industry.[118]

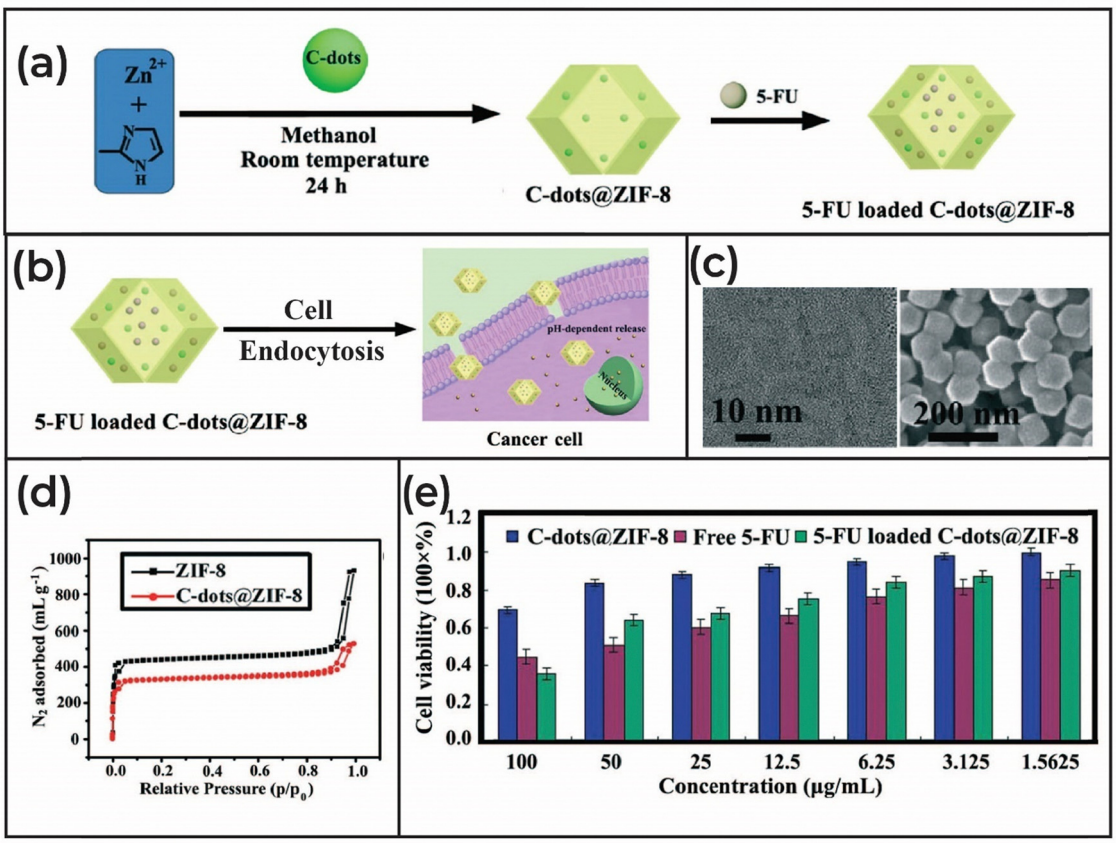


Fig. 10 A schematic of C-dot doped ZIF-8 synthesis[117] (a), pH-responsive drug release profile (b), SEM images of C-dots@ZIF-8 with pure ZIF-8 (c), N_2 sorption isotherms of pure ZIF-8 (black) and C-dots@ZIF-8 (red) (d), and *in vitro* cytotoxicity assay on HeLa cells (e).

3. Polymer classification based on origin

Over the past few decades, polymers have emerged as a highly versatile class of materials, playing a crucial role in transforming various fields, including medicine. However, it was only in the past thirty years that researchers clearly distinguished between their temporary and permanent medicinal applications. The integration of pharmaceutical and polymer sciences has driven scientific advancements in DDSs, allowing for flexibility in the physical state, surface, size and shape. The primary goal of polymeric delivery systems is to control drug administration in a targeted manner, whether spatially or temporally.[119] Since the introduction of the first synthetic polymer DDS using polyglycolic acid, there has been a greater focus on design and synthesis of new biodegradable polymers, which in contrast to nondegradable polymeric systems, do not need any removal after DD. Bioadhesive polymers were designed in response to the realization that close contact between an epithelial cell layer and delivery system will increase both retention time and therapeutic efficiency of the DDS.[120] Further developments in polymeric science have led to creation of polymeric hydrogel systems that can regulate distribution of a bioactive material in response to a particular stimulus. This article discusses many considerations that should be made when selecting and creating polymers in drug delivery applications, given wide classification of synthetic and natural polymers that are now accessible. As illustrated in Fig. 11, polymers are generally classified based on their origin, natural or synthetic. Natural polymers are often biodegradable and highly biocompatible, though they may show variability between batches due to purification challenges. Conversely, man-made polymers come in a vast array of compositions and easily customizable features. Most commonly used polymers in drug delivery applications are chitosan, alginate, collagen, cellulose, hyaluronic acid, gelatin, silk fibroin, polyethylene glycol (PEG), polycaprolactone (PCL), polyether ether ketone (PEEK), polylactic acid (PLA) and various block co-polymers like PCL–PEG–PCL. Many of these polymers are frequently combined with ZIFs to enhance their functionality in drug delivery applications.[121–123]

3.1. Natural polymers

Natural polymers are among the most studied materials for enhancing the therapeutic benefits of drugs. Compared to synthetic resources, they are safer, more biocompatible, and biodegradable and are found in plants, animals, and microorganisms like fungi and bacteria[124] as can seen in Fig. 12. Natural polymers have a wide range of biomedical applications, including regenerative medicine, controlled drug delivery, and gene transport. Their diversity in origin, monomer units, and structures is illustrated in Fig. 12, highlighting their adaptability for various biomedical applications. Their pliability allows customization for various uses, while delicate chemical linkages ensure biocompatibility and biodegradability. Their availability and eco-friendly properties make them ideal for diverse material applications.[125] Natural polymers enable drug delivery applications such as emulsification, suspension, controlled release, film coating, adhesion, encapsulation, and mechanical strengthening.[126,127] Utilization of natural polysaccharides as therapeutic targets for long-term and site-specific illnesses is growing. Novel techniques for medication distribution and customized medications are constantly being investigated about natural polymers.[128]

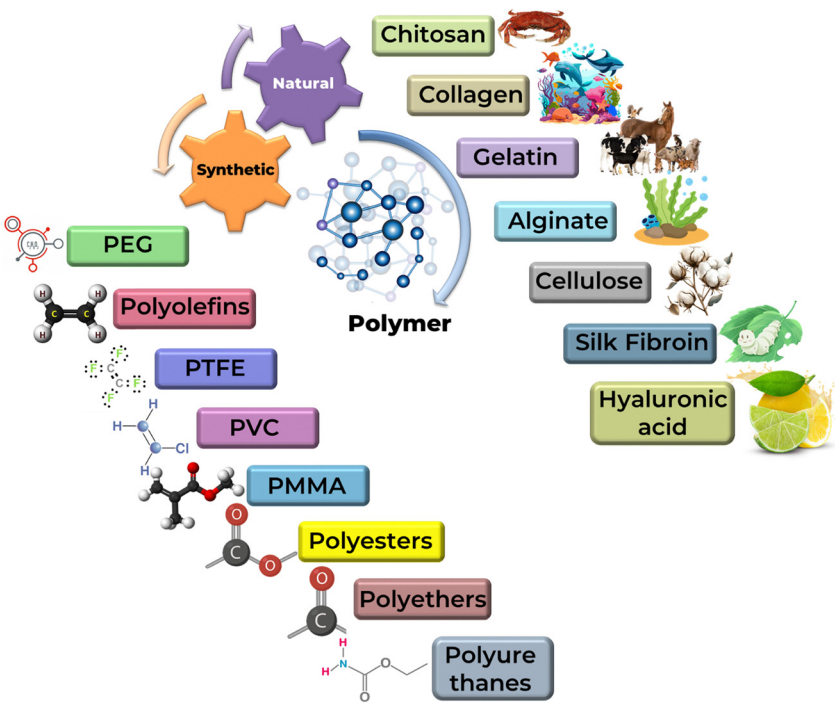


Fig. 11 Classification of polymers on the basis of origin.

3.1.1. Chitosan. Chitosan is a naturally occurring cationic biopolymer that is produced when chitin is deacetylated, which is extracted from crabs and shrimps, *etc.* Chitosans are a potential class of natural polymers with good controlled release and absorption-enhancing and bioadhesive qualities. For certain drug-delivery applications, the level of deacetylation and derivatization with different sidechains can be manipulated.[129]

3.1.2. Collagen. One of the natural protein biopolymers is collagen, which serves as a structural component for both the hard and soft tissues of living things.[130] The creation of collagen sponges, tubes, sheets, powders, and injectables is made possible by this special quality. For cosmetic purposes, injectable collagen is frequently used to develop or accumulate skin tissue.[131] Collagen as a suture material has been used for centuries; catgut, for instance, is utilized in surgery. However, usage of collagen increases the risk of infection and inflammation in sutures, which is why synthetic sutures are now far more popular. Collagen products are widely employed in drug delivery systems, wound repair, and fracture healing to recruit fibroblasts.[132]

3.1.3. Gelatin. Gelatin is the hydrolyzed form of collagen and can be obtained from mammals, poultry, fish, and other sources can provide it.[133] It is translucent, flexible, oxygen-impermeable, and water-resistant, with good film-forming properties.[134] Gelatin is utilized in the biomedical industry as an implant matrix, to create customized drug-release profiles in the form of fibers, hydrogels, microparticles, and nanoparticles, and as a stabilizer agent in vaccinations like the mumps, measles, and rubella. Moreover, it may be used more effectively as an adhesive for surgical usage, an absorbent pad, a wound dressing, and a framework for tissue engineering.[135]

3.1.4. Hyaluronic acid. Hyaluronic acid (HA) is an anionic natural glycosaminoglycan polymer that can be naturally extracted from animals like rabbits and mice or acidic fruits like lemons. Additionally, HA-based nanoparticles have demonstrated their efficacy as a delivery system for antibiotics and chemotherapeutics.[136] To successfully induce cartilage tissue growth in tissue engineering, a variety of techniques have been used, such as photo-cross-linked and covalent cross-linked HA scaffolds and HA-modified poly(D,L-lactic acid co glycolic acid) (PLGA) scaffolds.[137] Additionally, HA is a perfect wound-healing biomaterial that helps patients feel less pain and have more mobility in their joints.[138]

3.1.5. Alginate. Alginic acid and its salts are natural anionic polysaccharides obtained biotechnologically from bacteria or different species of brown algae.[139] As a stabilizing agent, alginic acid performs multiple biological functions and has various industrial applications, including a binding agent, viscosity enhancer and drug carrier. Certain alginate dressings have been proposed to promote healing of wounds by inducing monocytes to secrete higher quantities of cytokines such as TNF-α and interleukin-6. Pro-inflammatory elements that aid in healing of wounds are produced at sites of wounds by the production of cytokines.[140] Numerous research has also been conducted on applications of injectable scaffolds based on alginate for bone regeneration.[131]

3.1.6. Cellulose. The most prevalent naturally occurring polysaccharide found in nature is cellulose, which can be obtained from various natural sources. It is mostly used in drug delivery applications due to its accessibility, environmental friendliness and biocompatible properties; natural fibers for example cotton and linen are most frequently used, as well as regenerated fibers like lyocell, rayon, and viscose.[141] Numerous scientists looked at the use of cellulose for various biomedical applications, like bone, cartilage, blood vessels, and cornea engineering, as well as wound healing.[142]

3.1.7. Silk fibroin. A naturally occurring byproduct of silkworms, arthropods, and other spiders including bees and mites is silk fibroin.[143] Similar to other silks, the silk fibroin has nontoxic, biodegradable, and biocompatible qualities, making it appealing for use in biomedical applications. Furthermore, silk fiber exhibits favorable mechanical and chemical

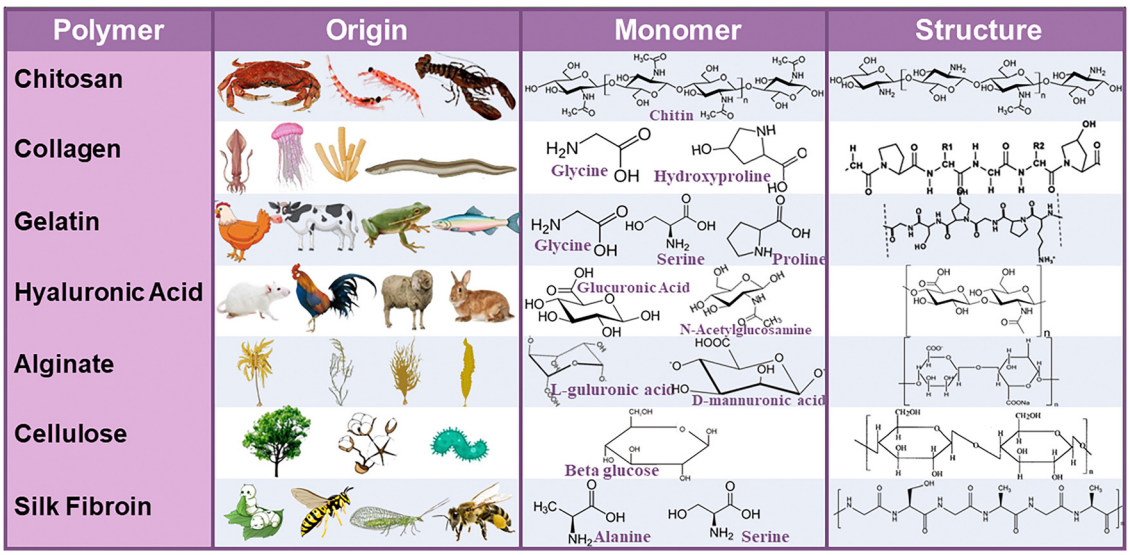


Fig. 12 Natural polymers with their origins, monomers, and structures, highlighting their diversity and applications.

characteristics that render it a superior fiber for a range of uses, including scaffolds, food additives, transdermal drug delivery, cosmetics, and fibers. Due to its great versatility, silk fibroin can also be made into a wide range of products like gels, films, fibers, and powders.[144]

3.1.1.1. Extraction methods of natural polymers. Natural polymer extraction involves both traditional and non-conventional methods, each revealing nature's molecular framework (Fig. 13). Traditional methods, such as solvent extraction and mechanical separation, gently unfold polymers, much like the petals unfurling in spring, relying on solubility and physical properties while maintaining their fundamental characteristics. In contrast, unconventional methods, akin to uncovering buried gems, use cutting-edge technologies like supercritical fluid extraction and enzymatic hydrolysis to isolate polymers and reveal new insights into their crystallinity and usefulness. These techniques blend old and new solutions, enhancing the versatility of natural polymers for optimal benefit.

Conventional extraction involves bioactive chemicals from plant matrices with ordinary solvents with or without heat treatment. The plant matrix is homogeneous and immersed in a solvent, often with continuous stirring, allowing target molecules to diffuse. Soxhlet extraction, while traditional, involves high solvent consumption and typically requires more than 20 hours to complete.[145,146] Maceration uses solvents with or without agitation, heat, or shaking to improve transfer of materials and dissolution of chemicals to extract bioactive molecules from plant or animal sources. The extraction process is given a lengthy time, from several hours to days, allowing the solvent to permeate through animal tissue or plant cell walls to dissolve the chemical components found in those materials.[146,147]

Similarly, percolation, a classic method for separating active compounds from fluid extract, typically uses a narrow, cone-shaped vessel with open ends called a percolator, where eventually mixture seeps down, resulting in the pure extract.[146,148] Decoction, a preparation made from water, is used to draw out chemicals that are soluble in water from medicinal plants and is the best technique for hardy, fiber plants, barks, and roots. Despite the drawbacks, this method has been used with a variety of aromatic and medicinal plants.[149–151] Although these techniques are fairly straightforward, they have shortcomings including low efficiency or excessive solvent usage.[152,153] Decoction and hydro-distillation procedures employ water as a solvent, whereas conventional extraction techniques like percolation, maceration, and soxhlet extraction often use organic solvents, necessarily using specific amounts of solvents and a lengthy period of extraction.[147]

Non-conventional methods improve selectivity and efficiency by utilizing specialized processing aids and energy inputs.[154] Ultrasound- and microwave-assisted extraction enables faster and better recovery of bioactive compounds.[152,153] Microwave-Assisted Extraction (MAE) uses microwaves to heat polar substances in plant and animal materials.[155] While methanol and ethanol absorb less microwave energy than water, they still heat efficiently; non-polar solvents like hexane remain microwave-

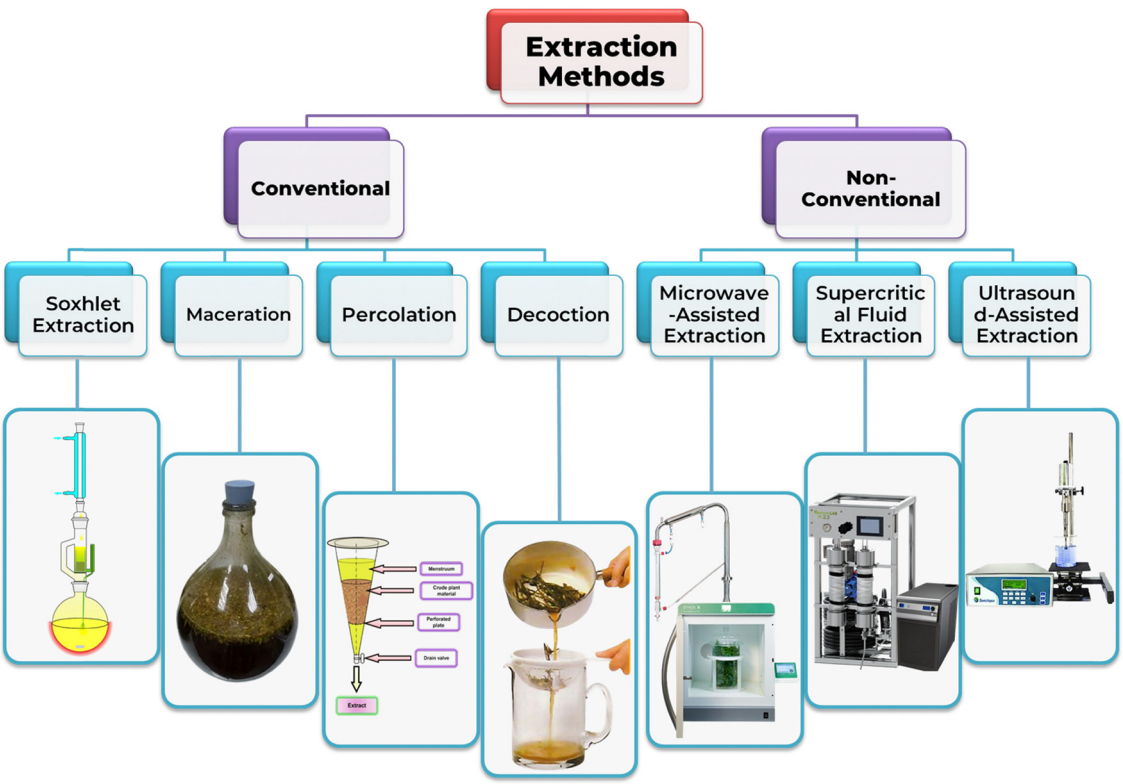


Fig. 13 Flowchart explaining the general process of obtaining natural polymers.

transparent. Since Ganzler *et al.* introduced MAE in 1986, it has been a major alternative to Soxhlet extraction.[156] Supercritical fluid extraction (SFE) uses fluids with gas–liquid properties, where solubility is adjusted by temperature and pressure. Ethanol, as a low-toxicity co-solvent, enhances CO_2 miscibility. Supercritical CO_2 extracts natural products like volatile oils and lipids, offering advantages such as relative affordability, non-flammability, high selectivity, and safety.[146,157] Ultrasound-assisted extraction utilizes ultrasonication at 10 and 1000 W cm^{-2} and frequencies between 20 and 100 kHz. Ultrasonic waves pass through materials, moving molecules *via* compression and rarefaction.[158] Non-conventional methods excel in yield, selectivity and cost-effectiveness, and reduced extraction time.

3.2. Synthetic polymers

Although the number of man-made synthetic polymers is approximately equal to that of natural ones, the greatest advancements occurred during World War II. Newly created polymers, like polyesters and polyamides used in synthetic suture, quickly found medical applications. Most existing technologies enable the synthesis of complex devices, primarily meeting mechanical and structural needs. Mechanical self-reinforcement is achieved by integrating oriented filaments of the same substance into the matrix.[159] Based on degradability, synthetic polymers are classified as degradable and non-degradable polymers [Fig. 14(a)]. Ideally, biodegradable polymers should remain in the body only as long as needed before naturally degrading.[160–163] Beyond degradability, synthetic polymers are also classified by monomeric structure and chemical composition, shaping their properties and applications. Fig. 14(b) shows key polymers with their molecular structures, each tailored for diverse industrial, biomedical, and engineering uses. A detailed discussion on this classification follows in the next section.

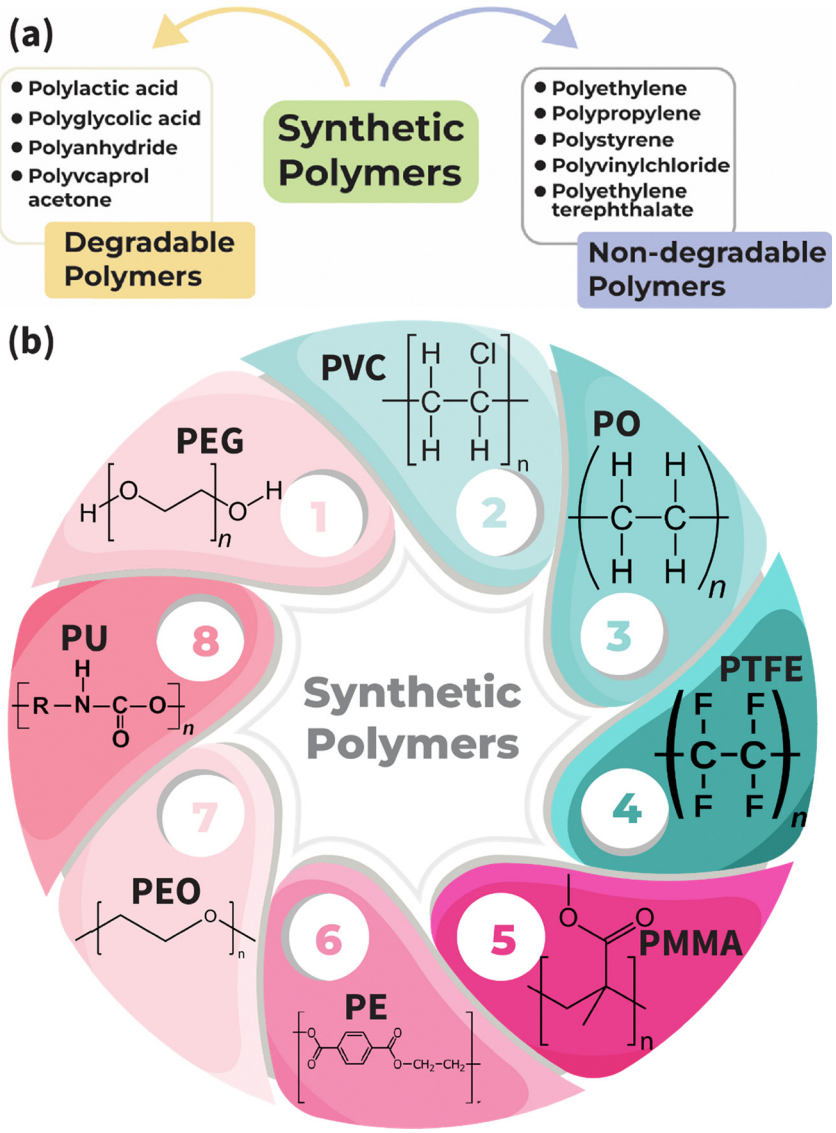


Fig. 14 Classification of synthetic polymers based on degradability (a) and monomeric structure (b).

3.2.1. Polyethylene glycol and polyethylene glycol diacrylate. Polyethylene glycol (PEG) is a well-known non-ionic and hydrophilic polymer with low toxicity or immunogenicity and high solubility in various solvents.[164] It also exhibits strong stiffness in its primary polymer chain, making it highly versatile. Different PEG-containing block copolymers have been developed for injectable drug delivery.[165] The most well-known are triblock copolymers, or poloxamers, composed of one hydrophobic polypropylene oxide (PPO) block and two hydrophilic PEO blocks. The use of polyglycerols, also known as polyglycidols, as a substitute for PEG and PPO has grown. It was discovered that linear polyglycerol had characteristics with PEG in terms of protein absorption resistance and biocompatibility. Furthermore, the materials have thermoresponsive properties.[166]

3.2.2. Poly(vinyl chloride) (PVC). One covalently attached chlorine atom is bonded to the ethylene backbone of PVC. The primary cause for medical concerns with this polymer is that stabilizers and plasticizers are needed during its production and application.[167] Blood storage bags and extracorporeal tubing are made of soft polymers, which are transformed from rigid PVC by plasticizers, most often phthalates. The combination of plasticizers based on phthalates and stabilizers based on tin has been shown to exhibit direct cytotoxicity *in vitro*.[168]

3.2.3. Polyolefins. Polypropylene (PP) and polyethylene (PE) are hydrophobic, inert polyolefins that do not break down in living organisms. PE varies in crystallinity and molecular weight, influencing its properties. Low-density PE (50 000–200 000 MW, 40–50% crystallinity) is the softest (E-modulus: 100–500 MPa) and is mainly used in packaging. PE is prone to oxidation, particularly after gamma sterilization, leading to brittleness, increased hydrophilicity, and recrystallization.[163]

3.2.4. Polytetrafluoroethylene (PTFE). PTFE is composed of four covalently bonded fluorine molecules on an ethylene backbone. It is a very hydrophobic, inert substance.[169] It exhibits some tissue ingrowth and causes very little inflammation in the body. It is mostly used as a graft for veins.[163] Poly(tetrafluoroethylene) (PTFE), often referred to as Teflon (DuPont), may be produced by fluorinating PE and using radical polymerization to create it from liquid tetrafluoroethylene. PTFE is the least frictional polymer known to science, has a high chemical resistance, and is hemocompatible. Meshes made of porous PTFE fiber have gained popularity as a synthetic vascular graft material.[170,171]

3.2.5. Poly(methyl methacrylate). Poly(methyl methacrylate) (PMMA) is a non-degradable polyacrylate widely used in orthopedics and dentistry due to its ability to polymerize into a rigid structure, making it suitable for bone cement and dental applications.[172] They are employed as intraocular lenses because of the optical qualities and the eye's inertness. The hydrophilic nature of hydroxyethyl methacrylate (pHEMA) allows its use in hemocompatible coatings and as a lubricant for contact lenses, offering excellent protein-repellent properties.[163] PMMA is a widely used nonmetallic implant material in orthopedics. PMMA is commonly utilized as a matrix component in composite films, valued for its superior physical, electrical, and mechanical characteristics.[173]

3.2.6. Polyesters. Biomedicine utilizes both biodegradable and biostable polyesters. Poly(ethylene terephthalate) and polycarbonates (PC) are examples of biostable polyesters with aromatic groups (PET, dacron). Conversely, biodegradable polyesters are valued for their susceptibility to nonenzymatic hydrolysis of ester bonds, facilitating controlled degradation in biomedical applications.[104] Based on encouraging findings on the material's biocompatibility, it comprises applications in tissue engineering scaffolds, orthopedic implants, and drug delivery.[170]

3.2.7. Polyethers. Polyethylene oxide (PEO) is a polyether made up of ethylene glycol that is nondegradable.[174] In biomedical applications, PEG hydrogels are usually made of cross-linked polymer chains. Copolymers incorporating degradable or nondegradable hydrophobic polymers, such as PEO and PEG, serve as building blocks for drug delivery systems,[175] gene delivery, tissue engineering scaffolds, implants, and medical devices. To enhance cell adhesion and protein absorption, PEG chains are immobilized on polymeric biomaterial surfaces. Due to the osmotic or entropic mechanism, highly hydrated chains of PEG on the polymer surfaces are responsible for these effects.[176] The two primary examples of this polymer family in biomedicine are polyether sulfone (PES) for dialysis membranes and polyether ether ketone (PEEK), a robust material for orthopedic applications.[163]

3.2.8. Polyurethanes. Numerous chemistries and characteristics are used in the synthesis of polyurethanes (PU). Medical applications include PU based on polycarbonate, polyether, and polyester that contain either aliphatic or aromatic constituents; aromatic formulations have superior biostability. Patients find polyether-based PU more pleasant because they quickly soften in the body, particularly in aliphatic formulations.[163,177] Surface modification of PUs can be used to enhance their interactions with cells and tissues or reduce thrombosis risk. Proteins like fibronectin and adhesion peptides that include integrin-binding peptides have been distributed throughout the PU surface using a variety of techniques, including covalent grafting and adsorption, through the utilization of self-assembled monolayers.[170]

3.2.8.1. Synthesis of synthetic polymers. There are two primary groups into which the processes of polymer synthesis reactions may be divided including chain polymerization and step-growth.[178] The process by which monomers join together as an extension of typical organic condensation processes is known as step-growth polymerization. During this process, side products with less molecular weight, such as water and alcohol, are removed as link is created. Molecules with functional groups such as carboxylic acid, amine, alcohol, or carboxyl derivative may react to produce these reactions. Consequently, addition of the removed small molecules might cause step-growth polymers to break down into their initial monomers. Step-growth polymerization yields the well-known synthetic polymers polyesters, polyamides, and polyurethanes,[179] while opening the double bond between unsaturated monomers is the process of chain polymerization. The developing polymeric chain, which has an all-carbon single-bond backbone, gains monomeric units by adding them to the reactive spots. An initiator that can produce the initial active unit and initiate the chain's development is necessary for this reaction process. A significant portion of the most widely used synthetic polymers,

such as PVC, polyethene, polypropylene, and polystyrene, are produced by chain polymerization.[178]

3.3. Polymer advancements for drug delivery

Recent advancements in biopharmaceuticals like proteins, nucleic acids, peptides, and bioactive materials have significantly improved disease diagnosis and treatment. In order to enhance the pharmacokinetics and pharmacodynamics of innovative medications and biocompatibility, the development of advanced drug delivery systems has become essential. This necessity has driven the evolution of next-generation DDSs with greater control and precision.[180] The selection of polymers for DDS applications focuses on materials that offer non-toxicity, controlled biodegradability, environmental stability, and appropriate wettability.[181,182] Two promising synthetic polymers in biomedical applications include polyvinylpyrrolidone and polyethylene glycol acrylate-based hydrogels. They both combine to produce copolymers with organic macromolecules and are biodegradable. Conversely, natural polymers such as collagen and gelatin offer less immunogenicity and great biocompatibility. Chitosan, alginate, starch pectin, casein, and derivatives of cellulose are some more natural polymers. Due to their complementary qualities, composites made of some aforementioned natural and synthetic polymers provide further benefits as drug delivery vehicles.[183] The conjugated polymers have been used to treat several illnesses, including diabetes, cancer, ischemia, hepatitis B and C, and rheumatoid arthritis.[184] Jiraphong *et al.* explored the fabrication of glycerol-based polyesters by grafting poly(glycerol adipate) (PGA) with tocopherol (TOC) and cholesterol (CHO) to assess their impact on nanoparticle formation, drug release, and cellular responses in cancer and normal cells.[185] Similarly, Surbhi *et al.* designed chitosan-coated PLGA nanoparticles (PAR–CS–PLGA-NPs) to enhance mucoadhesion and colloidal stability, optimizing intranasal delivery for depression treatment.[186] As for progress, progression with practical applications for diagnostics and polymer–drug conjugates, interdisciplinary cooperation between medicinal chemists, polymer chemists, pharmaceutical scientists, clinicians, and biologists is desperately needed. Research is essential to the field's continued expansion. It will yield results in the synthesis of innovative biopharmaceuticals and participate in the advancement of site-specific controlled drug delivery technologies, both of which will improve the health of those suffering from serious illnesses. Table 2 presents an overview of the most recent studies published in the last three years on polymer-based DD applications.

4. ZIF–polymer composites

Combining ZIFs with polymers enhances their respective qualities. ZIFs being brittle, powdery, are difficult to process alone, but polymers improve their processability and provide superior mechanical strength, enhancing their use in catalysts, filters, membranes, solid adsorbents, drug delivery vehicles, and so on (Fig. 15). ZIF–polymer core–shell particles have lately surfaced as a novel platform for precision composite design, whereas the majority of composites of ZIF–polymer are haphazard combinations of two materials with limited control over their small structures. While providing the ZIFs with additional qualities including better dispersibility in diverse fluids, adjustable surface energy, higher chemical stability, and controlled guest diffusion, well-defined polymers covering over the ZIFs can preserve rich pore characteristics. However, creation of a workable and generic approach for building ZIF–polymer is severely hampered by structural and chemical complexity of ZIFs.[211]

The representative Zn-ZIF drug delivery carrier ZIF-8 rapidly degrades in acidic environments but is stable in physiological ones. To increase the stability and biocompatibility of ZIFs certain polymers such as polyethylene glycol and alginic acid and their surface functionalities are frequently modified or embellished. The immune system's quick recognition and destruction of these frameworks can be postponed and the drug carriers' longevity increased using a natural polymeric covering.[212,213]

4.1. Synthesis strategies for ZIF–polymer composites

ZIF–polymer composites for drug delivery are synthesized using a number of critical approaches (Fig. 16) that are intended to maximize ZIF integration and interaction with polymer matrices. However, the growth of ZIF thin films on porous or thick polymer substances has only been reported in a few studies. ZIF thin films are commonly fabricated using methods such as interfacial secondary (seeded) growth and layer-by-layer assembly.[214–216] However, ZIF–polymer composite synthesis through techniques like *in situ* polymerization,[217] self-assembly,[218] grafting, electrospinning[219,220] and microfluidic synthesis[221] has only been reported in limited studies.

4.1.1. *In situ* polymerization. Using a modified interfacial reaction, Mohamad *et al.* achieved *in situ* synthesis of ZIF–polymer composites, forming well-dispersed ZIF nanoparticles and intergrown thin films on polyimide at lower temperatures without countercation species.[214] Alginic acid, a naturally degrading polymer, serves as a pH-sensitive drug carrier, forming ZIF-8 coatings *via* interactions with carboxylate groups. Tahereh *et al.* synthesized ZIF-8/alginate composites using ball milling [Fig. 17(a)],[222] while Mohammad *et al.* embedded ZIF-8 in a Pebax matrix [Fig. 17(b)].[217] Similarly, Chaohai *et al.* formed ZIF-8 nanoparticles on PAN fibrous filters [Fig. 17(c)].[223]

4.1.2. Self-assembly. Colloidal particle self-assembly into ordered superstructures opens up new routes for creating sophisticated materials for a vast range of applications, including electronics, catalysis, photonics, sensing, energy storage, energy conversion, diagnostics, and drug or gene delivery. Recent research has shown that polyhedral MOF particles, which possess rich polyhedral forms, porosity, colloidal stability, and size-tunability, might potentially create ordered superstructures.[224] N,N′-dimethylformamide (DMF) was used to dissolve DOX and PEG-PUSeSe-PEG. The resulting solution was then added to water and sonicated. Then, ZIF-8 was induced to develop by using DOX@P as a template, as illustrated in Fig. 18(a). In this instance, 2-methylimidazole combined with DOX@P and linked with Zn^{2+} ions on the micelle

Table 2 Last three years of work published on polymer-based DD applications

S. no.	Polymer	Composite	Drug carrier	Application	Year	Ref.
Natural polymers						
1.	Chitosan	PP-CNPs	Anti-PD-L1peptide (PP), DOX	Cancer immunotherapy	2023	187
2.	Chitosan	Cs-NP loaded Pluronic F127	Imipramine hydrochloride	Major depression, enuresis, and neuropathic pain treatment	2024	188
3.	Chitosan	Transferrin-poloxamer-functionalized chitosan NPs	Metformin	Alzheimer's disease	2023	189
4.	Alginate	Quercetin nanocrystal loaded alginate hydrogel	Quercetin	Wound healing applications	2025	190
5.	Hyaluronic acid	Hyaluronic acid hydrogel	Dopamine	BMSC microenvironment and wound healing	2025	191
6.	Hyaluronic acid	Lipid–polymer hybrid nanoparticles (LPNs)	Dimethyl fumarate	Sclerosis	2025	192
7.	Hyaluronic acid	HP@Nir hydrogel	PARP inhibitors	Ovarian cancer therapy	2024	193
8.	Hyaluronic acid	Liposomes co-modified with Ginsenoside CK and HA	Paclitaxel	Tumor-targeted therapy	2024	194
9.	Chitosan	GO–TiO_2–chitosan–escin	Escin	Colorectal cancer	2023	195
10.	Chitosan	NCTD@CS-DMMA SSME	Norcantharidin	Colorectal carcinoma therapy	2025	196
Synthetic polymers						
11.	PLAG	CZP-PLGA-NPs	Clozapine	Schizophrenia	2024	197
12.	PEI-PLGA	PEI-PLGA/EPI/PFH@Fe_3O_4	GVs-*E. coli*	Tumor therapy	2024	198
13.	PEG	IONP/SA/LS/PEG/SF-MgAl-LDH	SF (Sorafenib)	Cancer treatment	2023	199
14.	EC AND PEO	Janus core@shell	5-Fluorouracil (5-FU)	Oral colon targeted drug-delivery	2023	200
15.	PLGA-PEI	CSP-PLGA-PEI	*Cordyceps militaris*	Immune regulation	2024	201
16.	PVA, Eudragit® RS100	Clotrimazole nanosponges	Clotrimazole	Vaginal candidiasis	2025	202
17.	CMC	FA-CMC-GNA	Gambogenic acid	Lung cancer treatment	2025	203
18.	Copolymers of polymethylacrylate	*B-EUD-NPs*	Clozapine	Schizophrenia	2023	204
19.	PVA, PVP	Clozapine nanosuspension	Clozapine	Schizophrenia	2025	205
20	Eudragit® RS100	RIF-CIP/RS100	Ciprofloxacin and rifampicin	Wound dressings	2023	206
21.	HA, PEGDE	HA/TA2/KR2 cryogel	KR-12	Wound infection with multidrug resistance	2024	207
22.	PLGA	Protamine-coated PLGA	Paclitaxel and imatinib mesylate	Breast cancer	2024	208
23.	Methacrylated gelatin	HDG hydrogel	Polydopamine	Wound infection treatment	2025	209
24.	PLA/PCA	Lyophilized (freeze dried) PLA/PCA	Tolfenamic acid	Targeted drug delivery	2025	210

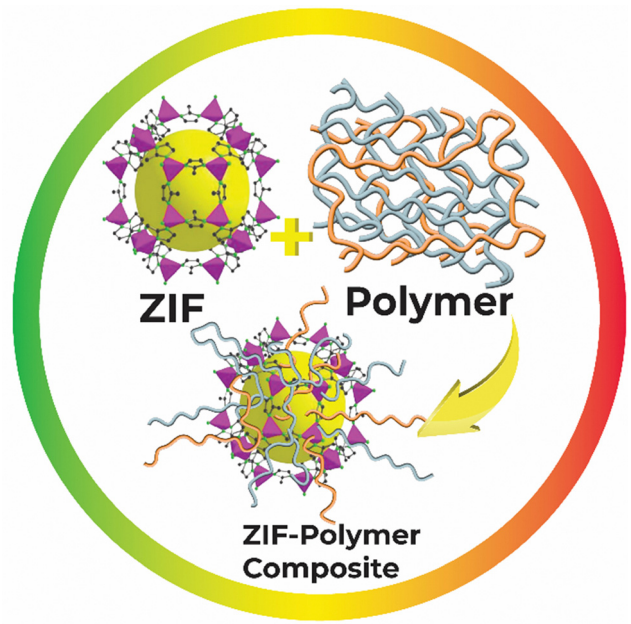


Fig. 15 The binding of ZIFs and polymers to form an advanced drug delivery carrier.

surfaces to create P@ZIF-8 or ZIF-8.[218] Many other composites can also be synthesized by self-assembly techniques, like ZIF-8@PDMS[225] shown in Fig. 18(b) and ZIF-PI nanofibers[226] in Fig. 18(c). Overall, these approaches highlight the versatility of colloidal self-assembly for fabricating multifunctional ZIF–polymer-based materials with enhanced performance across diverse fields.

4.1.3. Grafting techniques. It has been investigated how polymer chains covalently link to ZIF surfaces to improve compatibility with matrix components or enhance material properties. Two common procedures that result in polymer-functionalized surfaces are grafting-to and grafting-from.[227,228] In the grafting-to approach, reactive groups are added to presynthesized polymers, allowing end-functionalization to be grafted. The advantage is that the polymer is fully defined before grafting; however, the bulk fragment is limited due to poor grafting density of grafting-to. The grafting-from approach involves functionalizing the surface with initiator groups, enabling *in situ* polymer growth.[229] A one-pot synthesis method has been discovered, combining ZIF synthesis, PSM with functional groups, and polymer integration. For instance, zinc

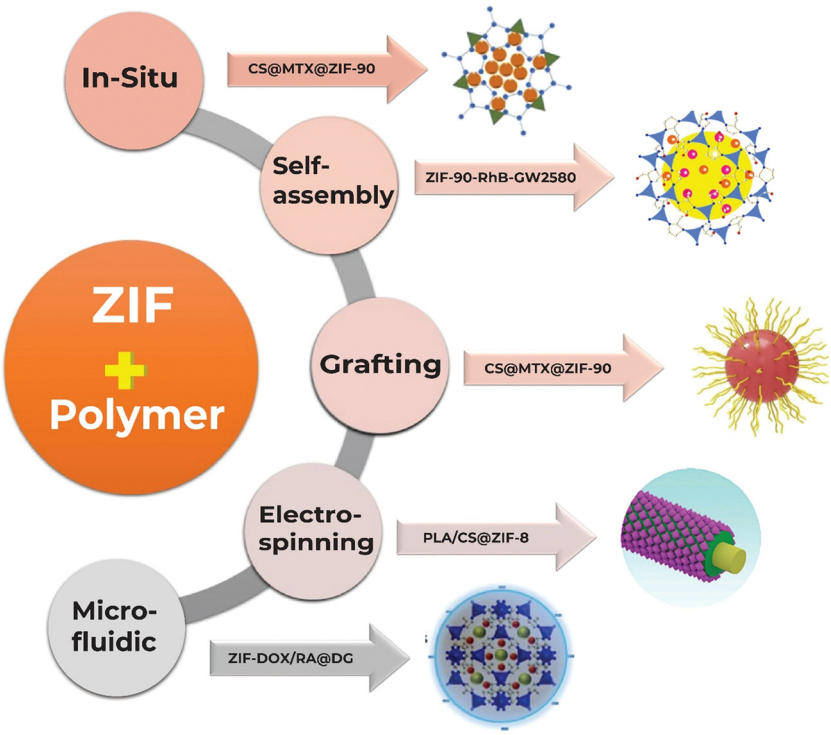


Fig. 16 Various ZIF–polymer composite synthesis approaches.

nitrate, polyethylenimine and 2-methyl imidazole were combined in a one-pot process and subjected to the usual synthesis procedures of ZIF-8.[230] Because PEI shared amine moieties with Hmim, it was incorporated with the ZIF-8 scaffold, resulting in ZIF-8@PEI, which was mixed with polyvinyl amine to form mixed matrix membranes.

Similarly, Yi *et al.* used ZIF-8@PEI as the outer shell to produce polydopamine–TiO_2 doped Fe_3O_4 nanoparticles with magnetic properties and peptide capture capabilities. The ZIF-8@PEI enhanced recovery and separation and provided colloidal stability.[231] Zhirong and associates proposed an interfacial design to improve compatibility between ZIF-8 and the cellulose acetate matrix by grafting PEI onto ZIF-8 particles as illustrated in Fig. 19(a). PEI added to ZIF-8 regulate their surface properties and maintain their pore accessibility.[232] Other composites formed by grafting techniques include ZIF-67 grafted-boehmite-PVA[233] illustrated in Fig. 19(b) and polyether polysiloxane-grafted ZIF-8[234] in Fig. 19(c).

4.1.4. Electrospinning. Electrospinning was used by Kiadeh *et al.* to incorporate a Cu-based ZIF and folic acid into a pectin matrix, aiming to reduce cytotoxicity and drug burst release *in vitro*.[235] Additionally, Lin *et al.* employed coaxial electrospinning to fabricate a dual-drug organized releasing fibrous mat with a shell layer containing deferoxamine and a core layer containing dexamethasone.[236] In actuality, the shell/core structure nanofiber has been extremely important in preventing burst releases, regulating release behavior, and safeguarding sensitive drugs. The core/shell structure nanofiber may be produced *via* coaxial electrospinning or emulsion electrospinning. Emulsion electrospinning, as opposed to coaxial electrospinning, may encapsulate a variety of active substances (drugs, proteins, cells, *etc.*) and is simpler to process with a single nozzle. A variety of composites can be formed by electrospinning like ZIF-67/PAN[237] shown in Fig. 20(a), PAN@ZIF-67[238] in Fig. 20(b) and PAN/ZIF-67[239] in Fig. 20(c). Structural nanofibers have been essential in safeguarding delicate medications and regulating their release. For example, using w/o emulsion electrospinning, Norouzi *et al.* synthesized sodium alginate doped poly(3-caprolactone) nanofibers with a smooth, homogeneous surface, and cylindrical morphology.[219,220]

4.1.5. Microfluidic synthesis. To carry out different biological, chemical, and physical processes, microfluidic technology entails management and operation of tiny volumes of fluids, particularly at the micrometer level. Capillary forces and surface tension, which predominate over gravity at tiny scales, are the distinctive physical features that govern fluid behavior in microfluidics.[240,241] Microfluidic synthesis can be used to synthesize a variety of ZIFs like ZIF-67 decorated PVDF[242] illustrated in Fig. 21(a), At_3 encapsulated ZIF-8[243] in Fig. 21(b), and Trypsin@-ZIF-90[244] in Fig. 21(c). Microchannels, valves, and pumps are used to provide accurate control over mixing, fluid flow, and reactions.[245–247] Jie *et al.* created a brand-new nanocarrier called ZIF@DG that was pH-responsive and biocompatible ZIF-8 NPs co-loaded with small-molecule medications and protein therapies. Notably, the exterior of the ZIF-8 NPs was coated using a dextran-based polymer coating that contained both glutathione (GSH) and acetylated groups. This can be accomplished using a simple and efficient microfluidic nanoprecipitation technique. This method provided dual responsiveness in terms of degradation caused by an acidic environment and γ-glutamyl transpeptidase (GGT)-activatable cationization.[221]

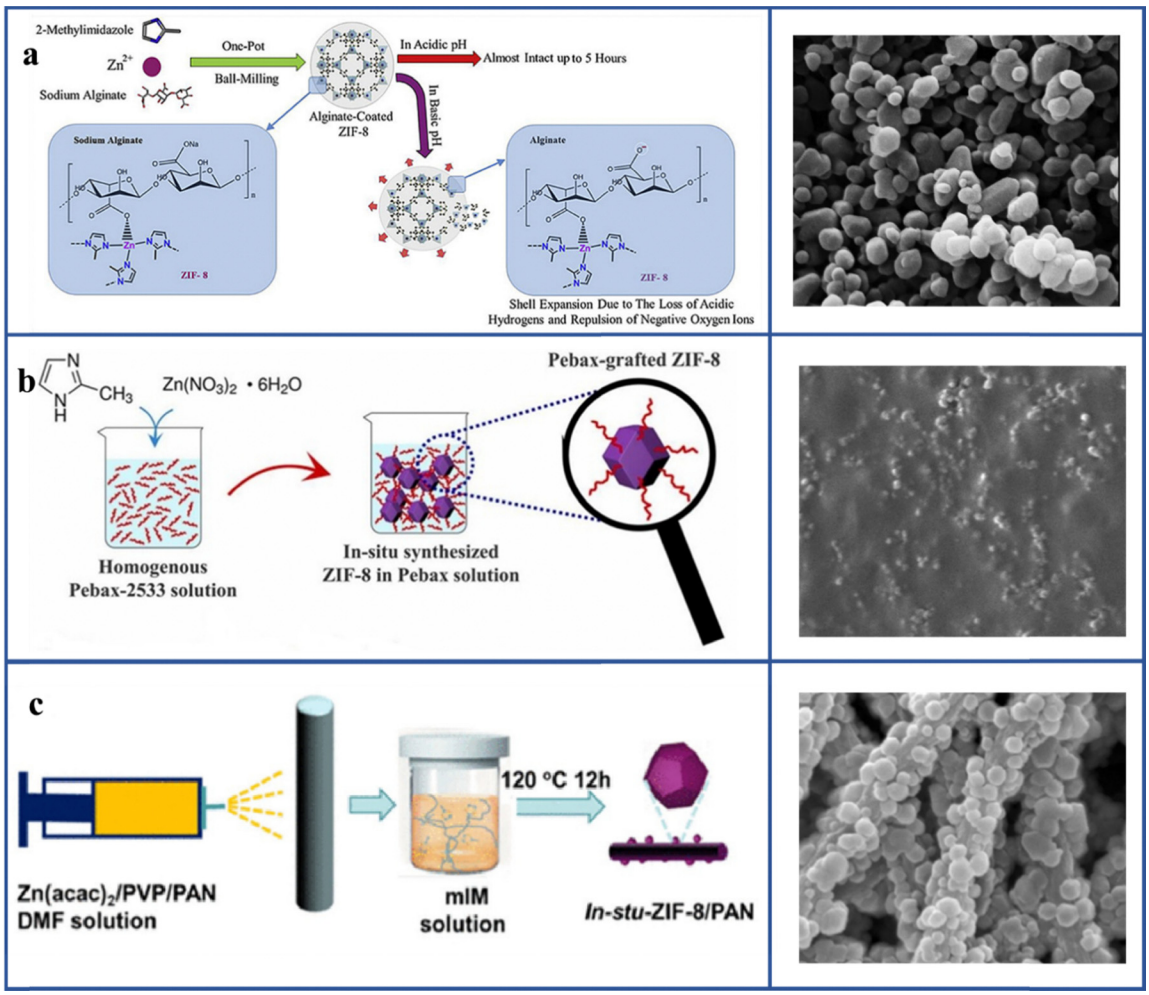


Fig. 17 Illustration of *in situ* formation of alginate-coated ZIF-8[222] (a), ZIF-8 on Pebax[217] (b), and ZIF-8 growth on PAN[223] (c), with the corresponding SEM images.

4.2. Outstanding features of ZIF–polymer for drug delivery applications

Surface characteristics that affect physical attributes like permeability, degradability, and durability also affect biocompatibility with tissues and blood, such as smoothness, hydrophilicity, surface energy and lubricity, which can be enhanced through the combination of ZIFs with polymers.[248,249] In addition, the hydrolytic breakdown and swelling of the polymers are determined by their surface characteristics. Conversely, materials used for life-time, like dental and orthopedic implants, must be water-proof to prevent processes of deterioration or erosion, which causes loss of toughness and mechanical strength. To enhance surface qualities and biocompatibilities, various physical, chemical, and biological methods can be used. "Polymer therapeutics" are medications, antibodies, enzymes, and proteins that are grafted onto the surface of polymers to target organs and cells.[249] Because of their advanced features (*e.g.* well-defined crystallinity, tunable porosity, possibility for potent encapsulation and release of guest materials), ZIFs are used in biomedical applications. In light of these appealing qualities, this section (Fig. 22) outlines the structural and functional aspects of ZIFs/polymer composites.[27] Matrix's micromorphology, structural characteristics and pore size all have a remarkable role in mass transfer of drugs in and out of polymers.

4.2.1. Facile crystallization and aggregation control. ZIF-8, comprising Zn^{2+} coordinate clusters linked with 2-methylimidazole in organic solvents (such as CH_3CH_2OH, CH_3OH, DEF, and DMF) at room temperature, is often built amongst various ZIFs. With a pore size of around 1.16 nm, ZIF-8 exhibits a crystalline cubic structure with dynamic porosity. The typical period of ZIF-8 synthesis ranges from less than an hour to several days. Notably, Pan *et al.* pioneered a rapid synthesis approach, achieving the formation of a milky suspension of ZIF-8 crystals in under five minutes by mixing $Zn(NO_3)_2 \cdot 6H_2O$, –MeIM, and H_2O in a 1 : 70 : 1.28 molar ratio at ambient temperature.[54] Over time, the synthesis protocols for ZIF-8 have been optimized to yield nanoscale crystals in organic and aqueous media.[250–252] Excellent structural similarity between ZIF-8 crystals made with different synthesis procedures suggests that these ZIFs are highly reproducible. ZIF-8 crystallizes

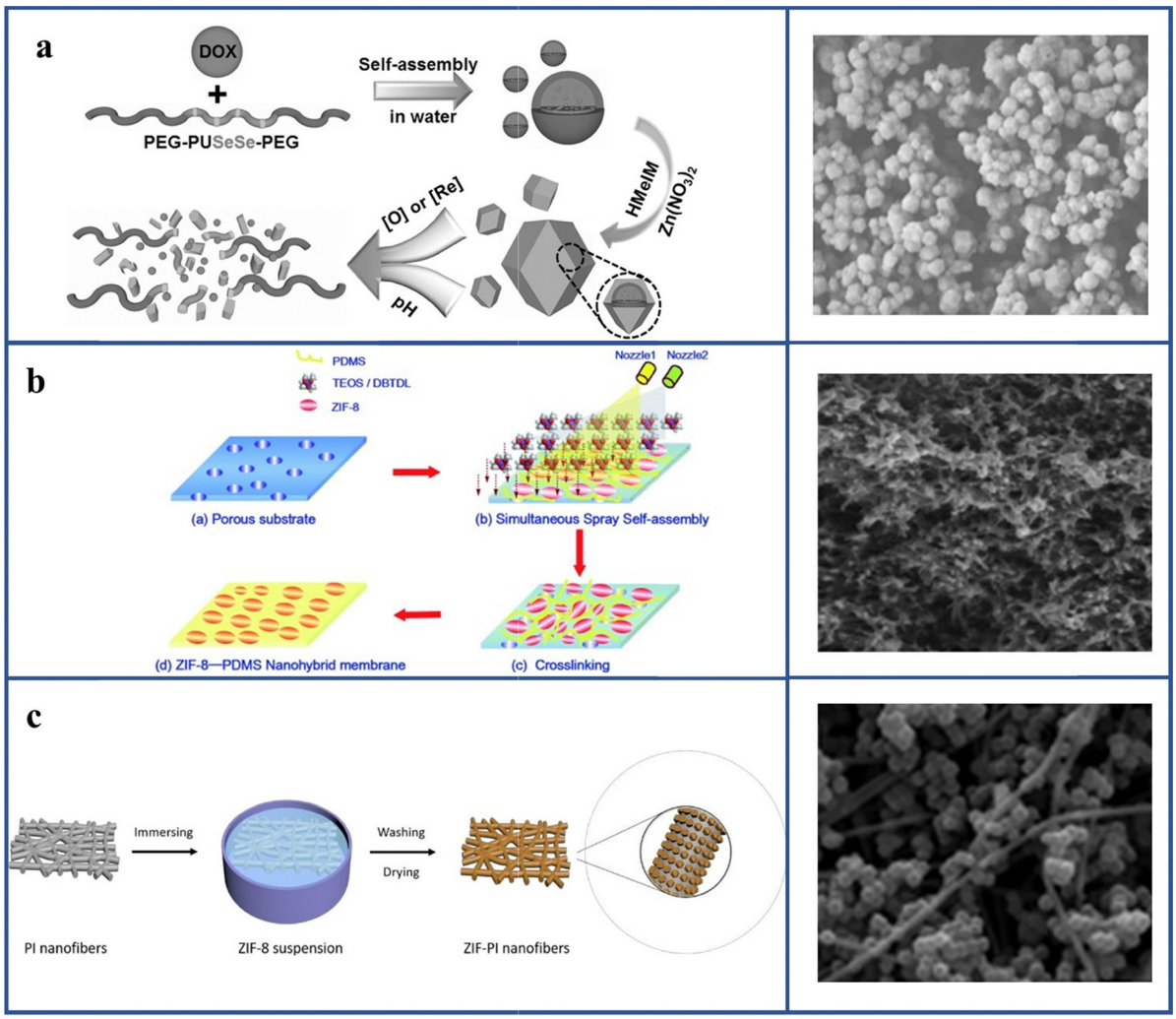


Fig. 18 Self-assembly synthesis of PEG-PUSeSe-PEG@ZIF-8[218] (a) ZIF-8@PDMS[225] (b), and also ZIF-PI nanofibers (c)[226] with their SEM images.

easily and quickly, making it possible to assess both its structural and functional properties. Even with their advantageous qualities, native ZIFs are insufficient for utilization in biological contexts. One common method of altering ZIFs' characteristics is to mix them with polymers to create different hybrid and composite materials. When these materials' surfaces are altered, their hydrophobic or hydrophilic properties change. ZIFs are hydrophobic materials, according to ref. 253.

Aggregation of the ZIF nanoparticles is another issue with ZIFs that might arise under conditions of a lot of water. One major obstacle that restricts the potential uses of ZIFs is their aggregation under aqueous conditions. A ZIF may be made to stop aggregating by adding a polymer to it. Polymers also serve as stabilizers by keeping individual ZIF particles from adhering to one another or clumping together to form bigger clusters.[254] The selection of the polymer is contingent upon requirement of comprehensive biochemical characterization and particular preclinical experiments to validate its safety additionally for its physico-chemical characteristics.[248] When non-ionic polymers like PEG are used to coat ZIF nanoparticles, the result is steric stabilization, which lowers aggregation. This is especially crucial for applications where the ZIF must be uniformly distributed across a coating or solution since aggregation can cause the material to become less effective or perhaps fail completely.[255]

4.2.2. Reducing toxicity and side effects. The challenge of optimizing the effectiveness of ZIFs as medications while reducing their harmful side effects remains a significant concern. In acidic environments, protonation of ligands leads to the breakdown of coordination bonds, resulting in weakened interaction between metal ions and ligands, which triggers drug release. However, this can lead to premature drug release, potentially causing undesirable and harmful effects. The degree of protonation varies among different ZIFs, as does their drug release profile. Consequently, *in vivo* chemical and physical characteristics such as pH, GSH expression levels, and release time vary across different organs, making precise control over the response challenging. Coating the surface of the carrier with protective polymeric shells, like PEG, polymer brush, pectin, chitosan, pH-responsive gelatin polymer, GSH-sensitive polymer, hydrogel, sodium alginate, and similar materials, is one of the

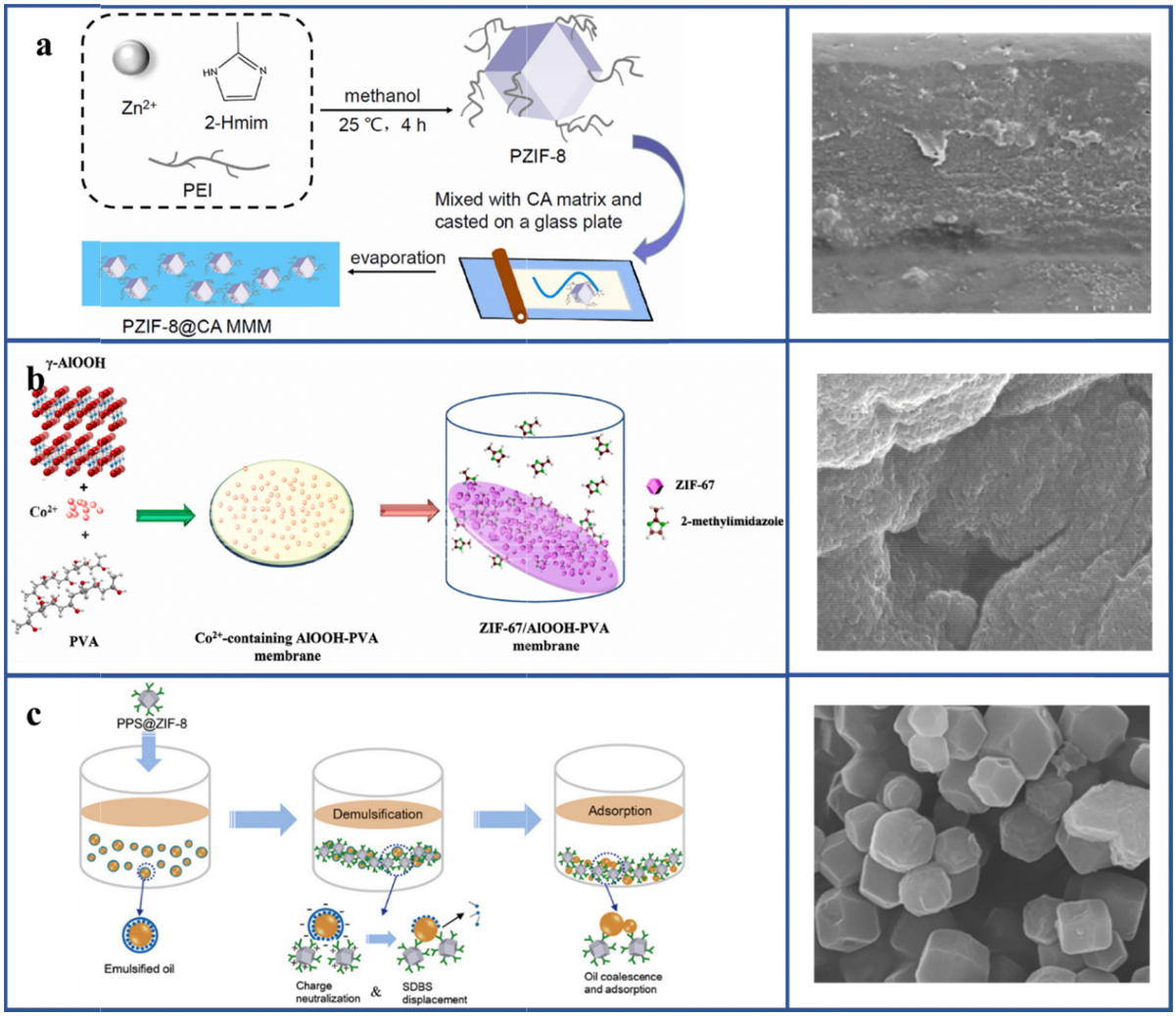


Fig. 19 Grafting of polyethylenimine on ZIF-8@cellulose acetate[232] (a), ZIF-67 grafted-boehmite-PVA[233] (b), and polyether polysiloxane-grafted ZIF-8[234] (c).

most common strategies to extend circulation time, increase biocompatibility, and prevent premature drug release. These coatings help to minimize early clearance and metabolism. Nevertheless, the long-term *in vivo* toxicity of ZIFs has not been thoroughly evaluated,[256] despite it being a critical issue that cannot be overlooked. Thus, further work is needed to assess the acute and chronic toxicity of ZIFs. Additionally, studies into the outcomes of ZIFs in living organisms are necessary to assess their potential and facilitate therapeutic transformation. Since the properties of biomaterials significantly influence on-demand drug release, incorporating additional functional materials is necessary to engineer or modify the MOF structure.[10]

4.2.3. High drug uptake and biocompatibility. The ZIF's ability to be processed through nanoscale modification with polymers enables the highly effective loading of functionally active materials on these crystals. For instance, the ZIF-8 shell and mesoporous silica nanoparticles (MSN) shell-core nanocomposite was synthesized using polydopamine.[257] Two anticancerous drugs, curcumin (CUR) and doxorubicin (DOX), were successively encapsulated within the shell and core of the nanocomposite, respectively. Uptake capacities of CUR and DOX in the nanocomposite were evaluated to be 778 and 607 μg mg^{-1}, respectively. These high drug uptake capacities of ZIF-8 were attributed to non-covalent interactions between the π electron clouds of ZIF-8 and MSN.[257,258] Moreover, studies on *in-vitro* cellular uptake of MCF-7/ADR cancer cells demonstrated effective uptake and significant biocompatibility of the nanocarrier.[257] Numerous researchers have also reported easy encapsulation of ZIF-8 with biologically active molecules (for example proteins, enzymes, and drugs). Additionally, ZIF structures can be modified by adding a polymer to enhance their solubility or stability under specific circumstances, making them more appropriate for targeted applications. Furthermore, ZIFs have been employed to encapsulate other probe molecules, including metal quantum dots, enzymes, and metal ions. Owing to their structural versatility, ZIF frameworks can accommodate a wide range of guest molecules, significantly enhancing their adaptability for diverse sensing applications. When stimuli such as disulfide bonds (GSH), imidazolyl (pH), porphyrin (light), and others are introduced into the ZIF structure,

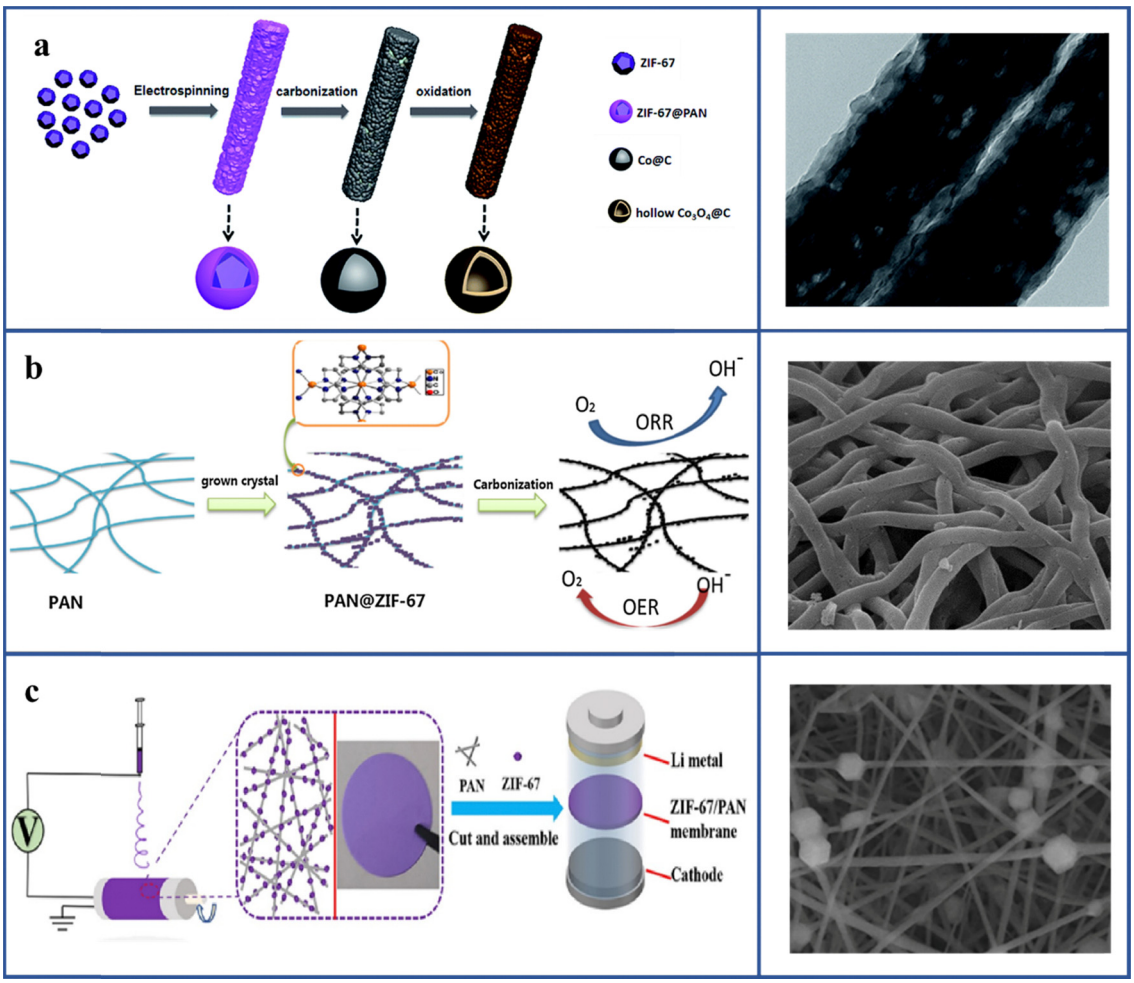


Fig. 20 Electrospinning synthesis of ZIF-67 doped PAN[237] (a), PAN@ZIF-67[238] (b) and PAN-doped ZIF-67[239] (c) with their SEM images.

these smart materials experience molecular configuration changes, hydrolytic cleavage, or protonation, thereby facilitating the controlled release of guest molecules.[10,259]

5. Applications of ZIF–polymer composites for drug delivery

ZIF–polymer nanocomposites have gained significant attention in drug delivery due to their high stability, biocompatibility, and tunable porosity. These hybrid materials offer enhanced drug protection, controlled release, and improved therapeutic efficiency. A key focus has been on delivering protein-based therapeutics, which, despite their high specificity, face challenges such as poor membrane permeability, degradation, and ineffective endosomal escape.[260,261] By leveraging site-specific targeting (SST), ZIF–polymer composites enable precise drug accumulation at diseased sites, minimizing systemic toxicity and maximizing therapeutic outcomes. Historically introduced as the "Magic Bullet" concept, SST has evolved with advancements in biotechnology and nanotechnology, enhancing drug retention and selective release through receptor-mediated mechanisms.[262] ZIF–polymer composites are ideal for orthopedic, ocular, transdermal, gastrointestinal, and pulmonary drug delivery as illustrated in Fig. 23. This classification provides a structured approach to localizing drug action, improving bioavailability, and ensuring sustained therapeutic effects.

5.1. Orthopedic drug delivery

Orthopedic diseases, particularly those affecting the elderly, present significant challenges in modern medicine. Bone defects caused by trauma, infections, and tumor resections often exceed the body's natural regenerative capacity, necessitating the use of implants and biomaterials to support healing.[263] Additionally, implant-related infections, particularly those caused by *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA), pose serious risks, often requiring prolonged antibiotic treatments due to bacterial resistance. The limited ability of traditional implants to promote osteogenesis, angiogenesis, and antibacterial activity has driven the search for advanced biomaterials capable of addressing these challenges.[264] ZIFs offer a promising solution due to their structural tunability, high porosity, and controlled degradation. ZIF-8's ability to release Zn^{2+} ions plays a crucial role in both osteogenesis and antibacterial action,

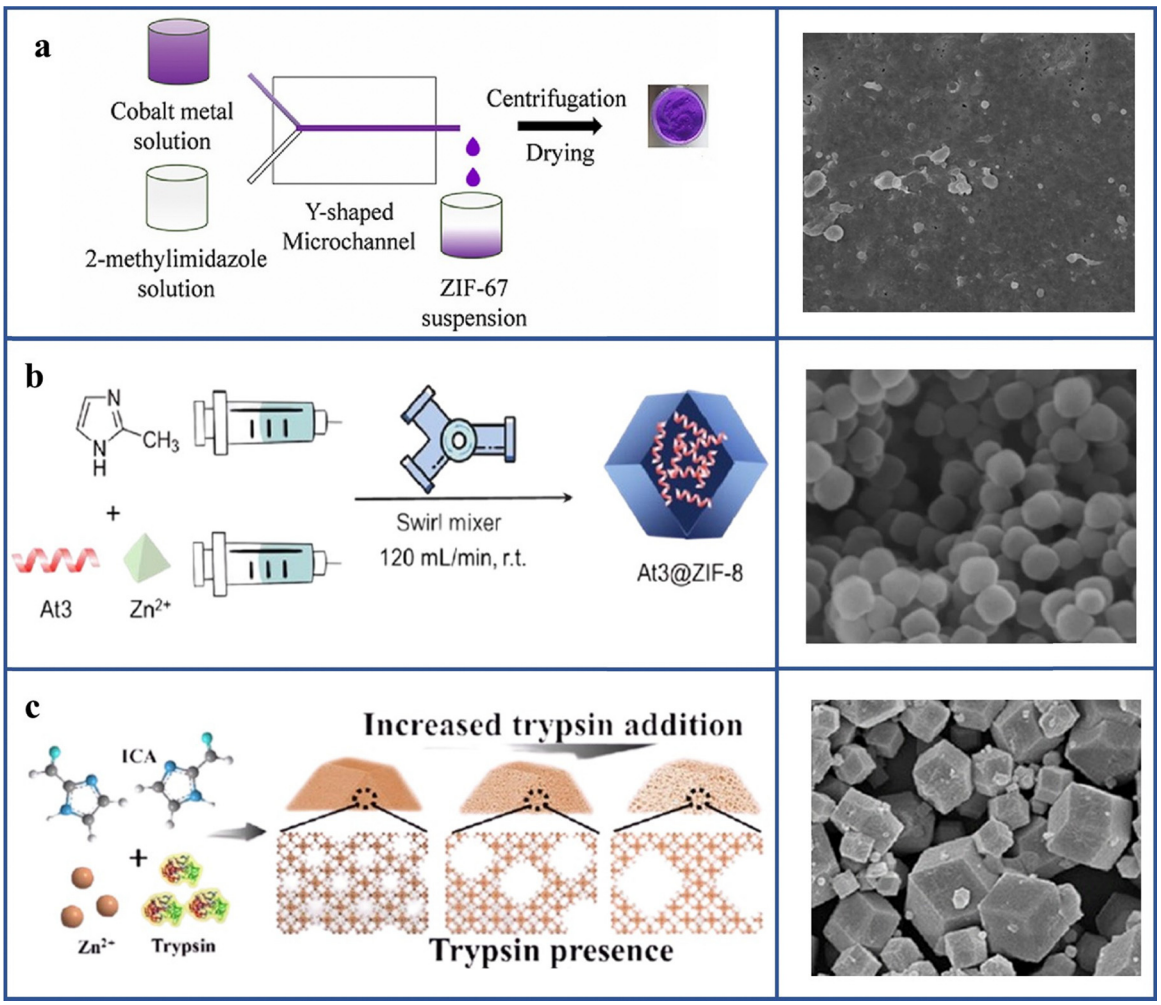


Fig. 21 Microfluidic synthesis of ZIF-67 decorated PVDF[242] (a), At_3 encapsulated ZIF-8[243] (b), and Trypsin@ZIF-90[244] (c) with their SEM images.

making it highly suitable for orthopedic applications. Moreover, its capacity to act as a nanocarrier enables localized and sustained drug delivery, reducing systemic side effects while enhancing bone repair.[265]

Yunhui *et al.* synthesized MV@ZIF-8 using a one-pot method, immobilizing it onto a PDA-coated titanium surface, Fig. 24(a). This modification enhanced the tribocorrosion resistance of Ti_6Al_4V alloys while the nanoporous ZIF-8 enabled controlled release of MV, where Zn^{2+} and MV synergistically inhibited bacterial growth, reducing implant-associated infections.[266] Moreover, Yan *et al.* developed a TNT-based drug delivery system modified with ZIF-8 and silk fibroin, Fig. 24(b). This composite extended drug release, enhanced biocompatibility, and promoted osteogenic activity, as confirmed by increased alkaline phosphatase (ALP) production. The incorporation of silk fibroin stabilized the structure, optimizing drug-loading efficiency and cellular response.[267] Further advancing the multifunctionality of ZIF-8, Qili *et al.* reported systems like 7,8-DHF@ZIF-8, which have been engineered to promote angiogenesis, osteogenesis, and antibacterial activity simultaneously, making them highly effective for treating large bone defects Fig. 24(c). Together, these ZIF-8/polymer composites demonstrate a powerful synergy, improving implant longevity, reducing infection risks, and accelerating bone regeneration, highlighting their transformative potential in orthopedic drug delivery.[265] ZIF–polymer composites offer a multifunctional approach to enhancing orthopedic implants by integrating antimicrobial, osteogenic, and drug delivery properties. These materials improve implant performance and accelerate bone healing, with ongoing research refining their clinical potential.

5.2. Ocular drug delivery

Ocular drug delivery remains a significant challenge due to the eye's unique anatomy and physiological barriers, which limit drug retention, penetration, and bioavailability. Conventional treatments, such as topical eye drops for anterior segment diseases, suffer from rapid clearance, necessitating frequent administration, while intravitreal injections for posterior segment disorders pose risks like infection, inflammation, and short drug half-life.[269] To address these limitations, advanced DDSs have been explored, among which ZIF–polymer composites have emerged as promising nanocarriers due to their high surface area, tunable porosity, and controlled release properties. These materials provide improved ocular bioavailability, extended drug retention, and targeted delivery, making them ideal for treating

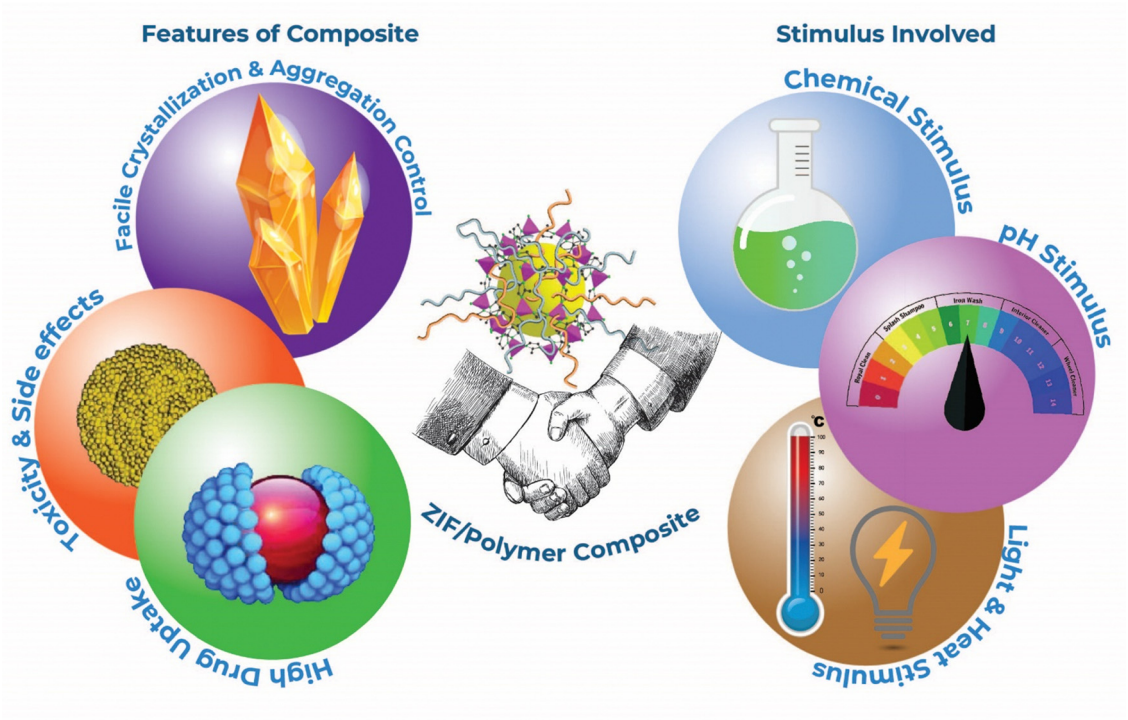


Fig. 22 Featured properties of ZIF–polymer composites.

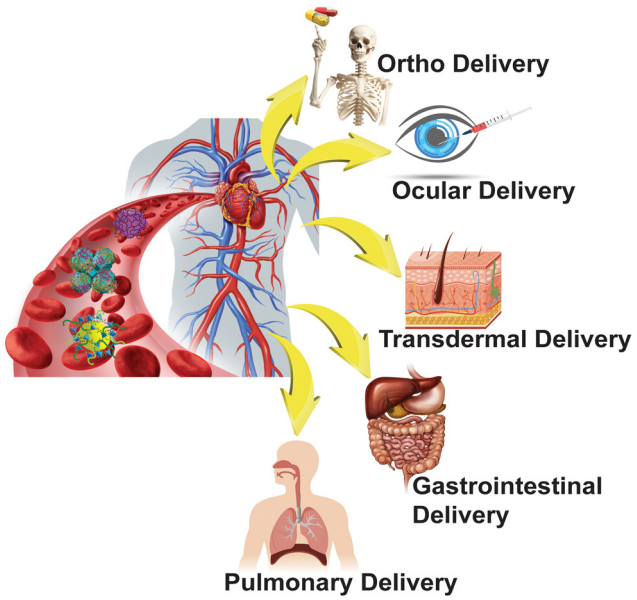


Fig. 23 ZIF–polymer composites in site-targeted drug delivery applications.

bacterial infections, biofilm formation, and degenerative retinal diseases.[270] For instance, the encapsulation of broad-spectrum antibiotic levofloxacin (LEVO) in pH-sensitive ZIF-8 nanocarriers, followed by HA surface modification reported by Yi *et al.*, resulted in a negatively charged system that enhanced corneal adhesion and prolonged drug release, effectively addressing bacterial resistance and corneal infections.[271] Similarly, Hao *et al.* presented a multifunctional hybrid system Fig. 25(a), ZIF-8–polyacrylic acid (PAA), loaded with methylene blue (MB) and further modified with silver nanoparticles (AgNPs) and vancomycin (Van-PEG), demonstrating potent antibacterial and biofilm eradication effects against resistant pathogens such as *S. aureus*, *E. coli*, and MRSA.[272] Beyond antibacterial applications, ZIF-based drug carriers have also shown promise in neuroprotection against photoreceptor degeneration. Peipei *et al.* reported, Fig. 25(b), a zebrafish model of retinal damage, intraocular administration of a ZIF-90 RhB GW2580 nanocomposite enabled sustained drug release, reduced microglial activation, minimized inflammatory response, and ultimately preserved retinal structure and visual function.[273] Moreover, hibiscus-like RF@ZIF-8 NF microspheres were developed by Mohammed *et al.* for corneal cross-linking in keratoconus treatment, enhancing riboflavin-5-phosphate penetration through improved permeability and drug loading, Fig. 25(c).[274] These innovative approaches highlight the potential of ZIF–polymer composites as next-generation ocular drug delivery platforms, overcoming conventional drug delivery challenges and offering novel therapeutic avenues for treating both infectious and degenerative eye diseases.

5.3. Transdermal delivery

The skin serves as a critical barrier, protecting the body from external pathogens while maintaining homeostasis. Injuries like severe burns and trauma severely disrupt skin's natural barrier, leading to serious bacterial infections that significantly hinder the healing process. *Pseudomonas aeruginosa* and *Staphylococcus aureus* bacteria often form biofilms deep within infected wounds, making treatment extremely difficult sometimes nearly impossible. Biofilms form a stubbornly protective

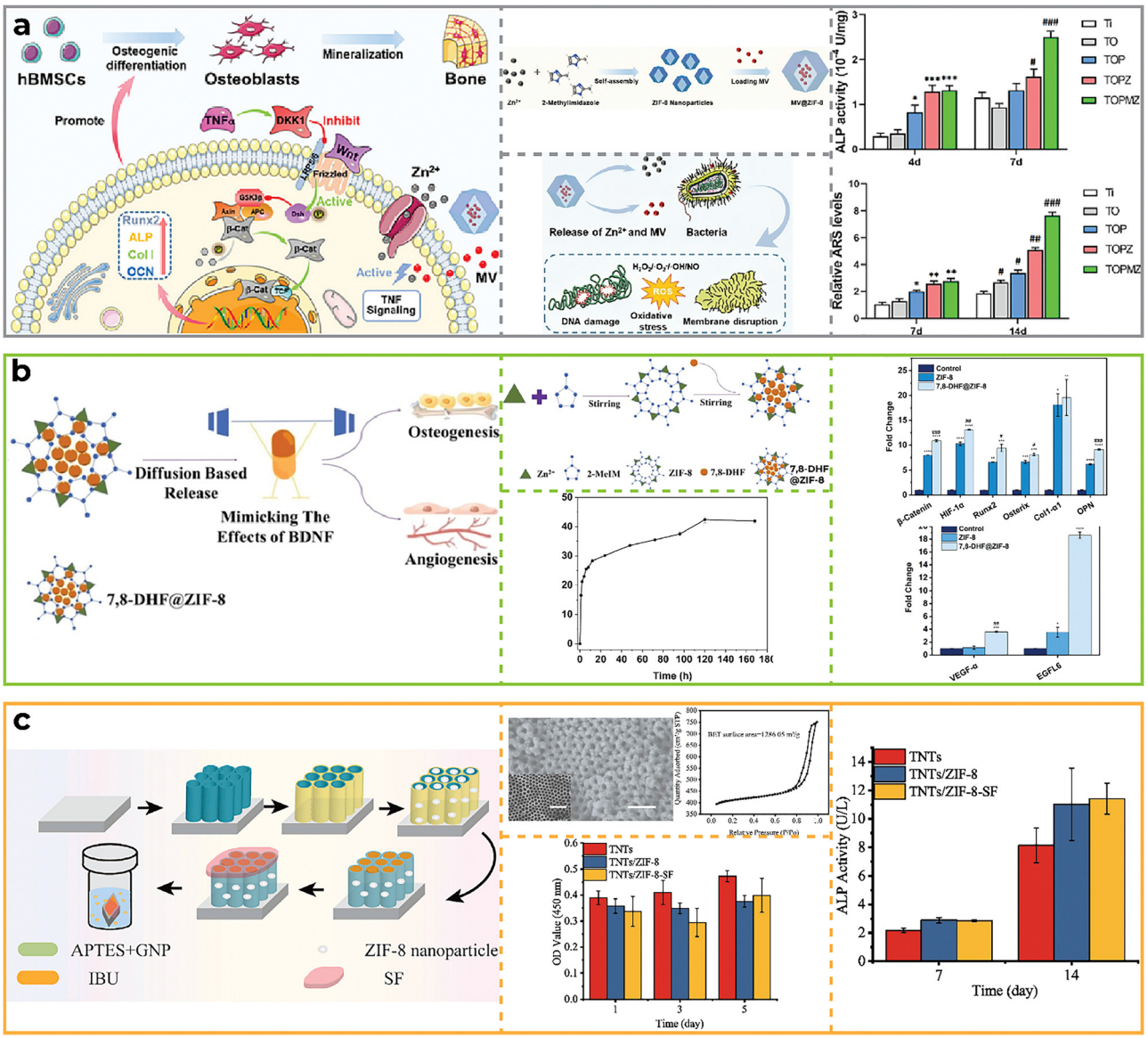


Fig. 24 Osteogenesis in MV@ZIF-8 with ECM mineralization and ALP activity[266] (a), TNTs/ZIF-8-SF drug delivery with release flow and cell proliferation[268] (b), and 7,8-DHF release in PBS with MC3T3-E1 co-culture[267] (c).

barrier significantly limiting penetration of drugs, thereby rendering conventional antibiotics woefully ineffective and bolstering resistance quite rapidly.[275] Traditional wound dressings often falter in providing sustained drug release and moisture retention alongside sufficient antibacterial action necessitating development of superlative wound care materials.[276] ZIFs have garnered considerable attention in transdermal drug delivery owing mainly to unique properties like high porosity and biocompatibility and pH responsiveness. ZIFs boost encapsulation of drugs and their targeted release when merged with various polymers allowing improved penetration through biofilms pretty effectively. Hydrogels incorporating ZIF-8 offer quite an excellent alternative for wound dressing by maintaining moisture quite effectively and facilitating skin regeneration rapidly. Microneedle patches embedded with ZIF-8 offer a surprisingly painless method for directly delivering antimicrobial agents right into wound sites efficiently. Advanced nanocomposite systems boost drug absorption remarkably and tackle antibiotic resistance concerns effectively by enabling localized therapy mostly.[277]

The demand for advanced wound dressings is increasing due to their ability to promote healing and prevent infections. ZIF-8-based dressings offer a controlled drug release system that enhances antibacterial efficacy and tissue regeneration. Lei *et al.* developed a ZIF-8/DMOG-loaded Gel-PCL nanofiber dressing, which synchronizes drug release to match wound-healing stages Fig. 26(a). This dressing eliminates 90% of *E. coli* and *S. aureus* while supporting fibroblast growth, leading to complete wound healing in diabetic rats within two weeks.[278] Similarly, Kang *et al.* designed a microneedle array embedded with pH-responsive ZIF-8 nanoparticles for targeted antimicrobial action and angiogenic control Fig. 26(b). These innovative approaches demonstrate the potential of ZIF-8 in transdermal

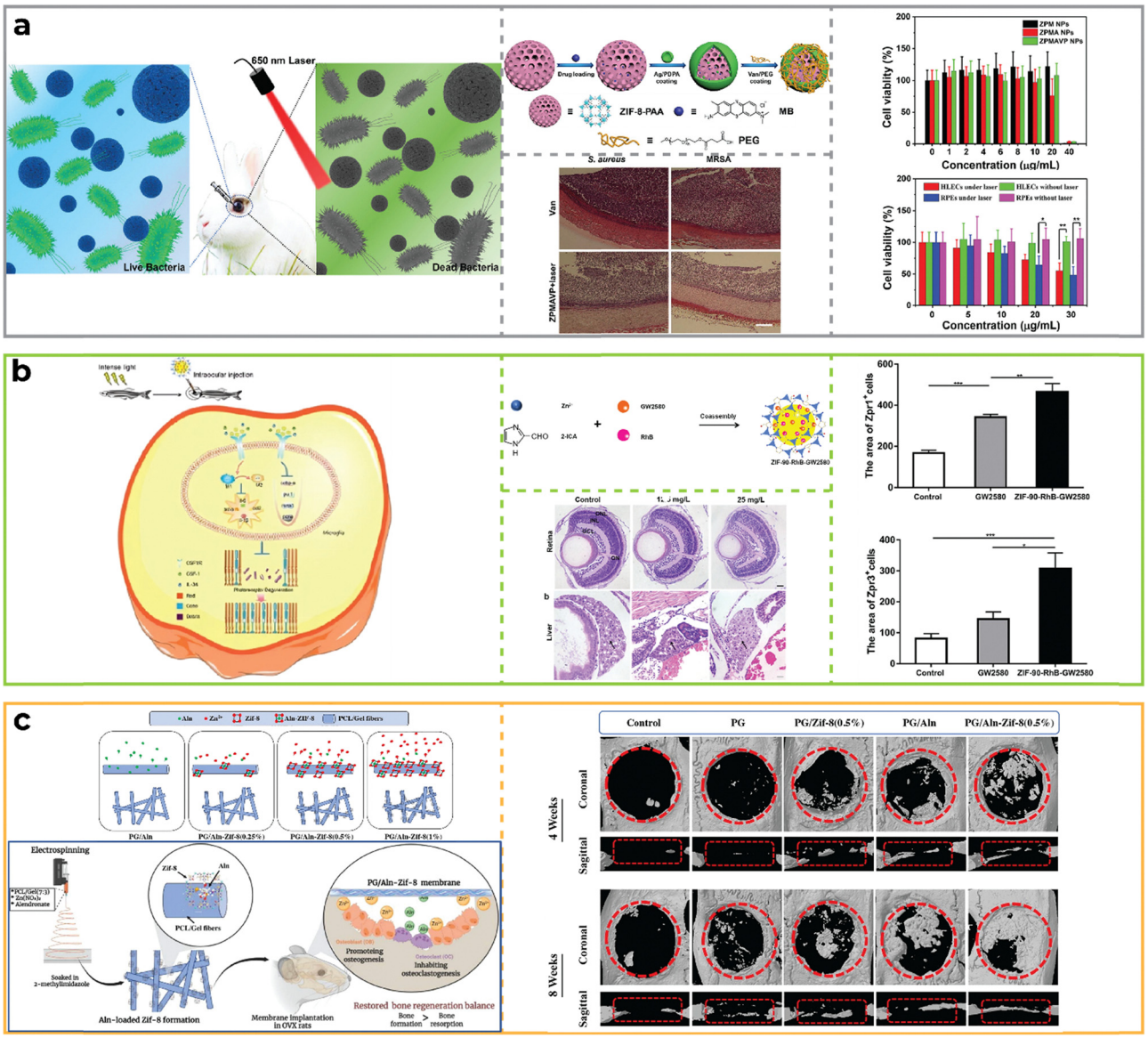


Fig. 25 ZPMAVP for photodynamic therapy and chemotherapy with antibacterial effects[272] (a), ZIF-90-RhB-GW2580 synthesis, biotoxicity, and retinal analysis[273] (b), and PG/Aln-ZIF-8 synthesis with controlled Zn^{2+}/Aln release and cell adhesion[274] (c).

drug delivery, offering a multifunctional, non-invasive solution for chronic wound treatment.[275] Azin *et al.* developed polyethylene glycol-chitosan nanocomposite films incorporating cephalexin and 0–5% ZIF-8 for wound dressing applications Fig. 26(c). Glycerin was added to enhance flexibility, and MTT assays confirmed good cell viability with L929 fibroblast cells, highlighting their potential for antibacterial wound healing.[279] These multifunctional ZIF–polymer based nanocomposites demonstrate significant potential for addressing the challenges of chronic wounds, bacterial infections, and impaired healing, paving the way for next-generation transdermal drug delivery systems.

5.4. Gastrointestinal drug delivery

Oral drug administration dominates therapy, yet the gastrointestinal tract (GIT) presents challenges such as enzymatic degradation, low bioavailability, and drug-induced mucosal injury. NSAIDs, for example, effectively reduce inflammation but cause severe GIT damage, including ulcers and bleeding, with limited solutions beyond dosage reduction. Thus, advanced drug delivery systems are needed to enhance absorption while protecting the GIT.[280] Gastrointestinal infections, such as *Helicobacter pylori*, demand precise drug delivery, yet conventional nanocarriers suffer from non-specific distribution and systemic toxicity. Hetero-hierarchical nanocarriers, particularly ZIFs, provide controlled, sequential drug release, enhancing efficacy while reducing side effects. However, traditional MOF assembly methods lack spatial precision. Recent surfactant-directed assembly techniques improve drug distribution and spatiotemporal release, overcoming gastric barriers. These advancements position MOF-based nanocarriers as a revolutionary tool for targeted gastrointestinal therapies. ZIF has gained attention in GI drug delivery for its porous structure,

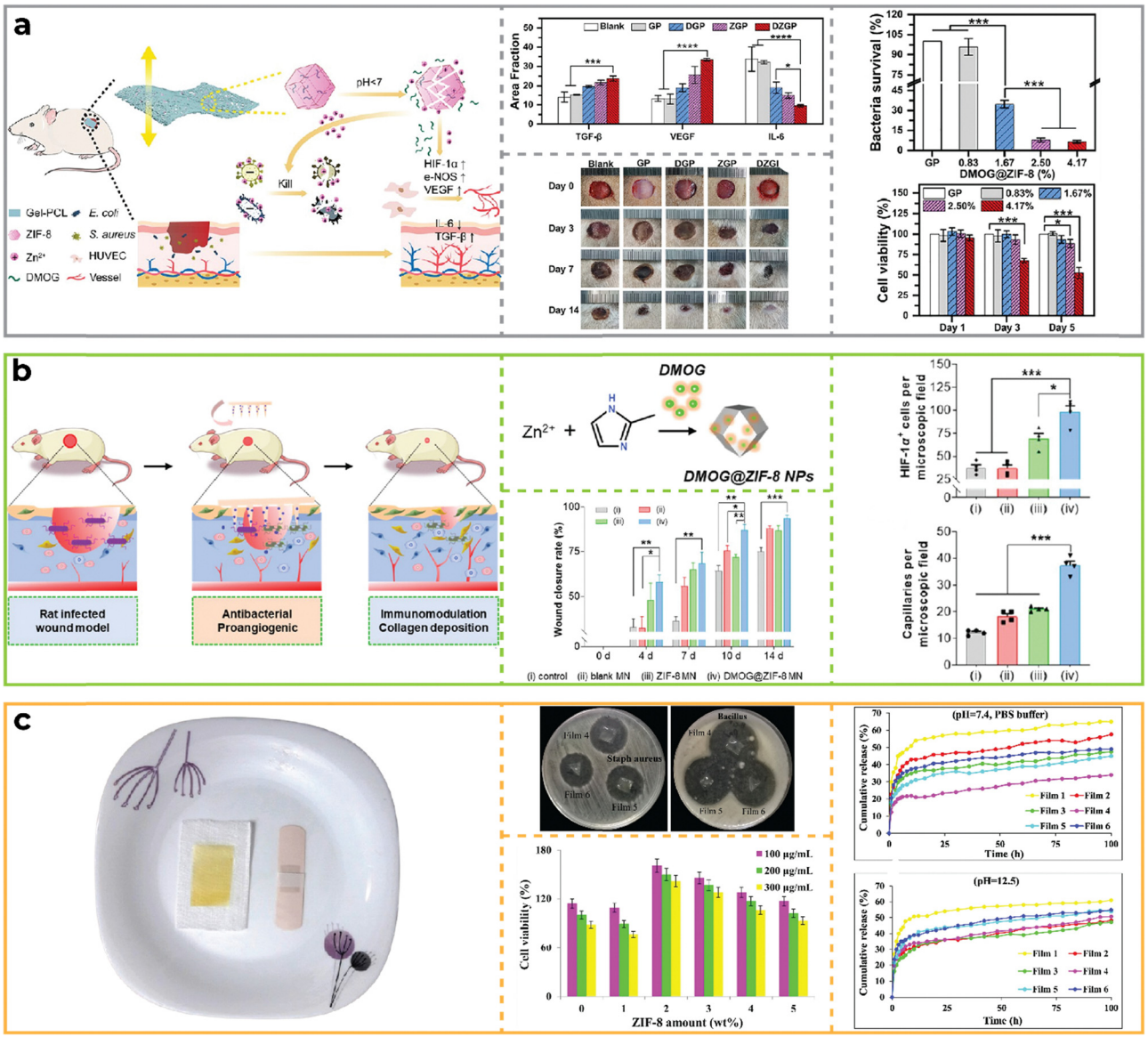


Fig. 26 DMOG@ZIF-8 synthesis, survival rates, and wound healing[278] (a); MN effects on infected wounds, release, and reepithelialization[275] (b); and an ideal film with 4% ZIF-8, cell viability, and antibacterial activity[279] (c).

pH-responsive degradation, and high drug-loading capacity.[281] Combined with polymers, it enhances drug stability and enables sustained release, reducing side effects and improving efficacy. Lei *et al.* reported a multi-level system where hyaluronic acid-modified ZIF-8 (HA/ZIF-8) in a hydrogel sustained lidocaine release, ensuring prolonged analgesia Fig. 27(a). This approach highlights ZIF–polymer composites' potential in enhancing GI drug retention and bioavailability.[282] Zixuan *et al.* reported a cellulose microsphere (CM)-supported ZIF-8 system (CM@ZIF-8) designed for controlled doxorubicin (DOX) release, Fig. 27(b). The CM@ZIF-8-DOX system exhibited sustained drug release, with 81.2% of DOX released over 72 hours in a simulated tumor microenvironment. The release rate was higher under acidic conditions (63.4% at pH 5.0) compared to neutral conditions (37.6% at pH 7.4), demonstrating pH-triggered drug release.[283] Hanieh *et al.* reported the development of pectin (Pec) hydrogel beads incorporating ZIF-8 and tetracycline (TC) for controlled drug release and antibacterial efficacy in gastrointestinal applications Fig. 27(c). Using *in situ* synthesis, ZIF-8 was embedded in the hydrogel matrix, while TC was pre-loaded to enhance antibacterial properties. Simulated digestion studies demonstrated a sustained release of Zn^{2+} and TC over 8 hours (pH 1.2 : 6.8 : 7.4 = 20% : 20% : 60%), ensuring targeted delivery. The system exhibited strong antibacterial activity against *E. coli* and *S. aureus* and maintained high biocompatibility.[284] This highlights ZIF–polymer composites as promising candidates for GI-targeted drug delivery.

5.5. Pulmonary drug delivery

The complex architecture of the pulmonary system poses significant challenges for effective drug delivery, particularly in achieving high therapeutic efficacy while minimizing systemic

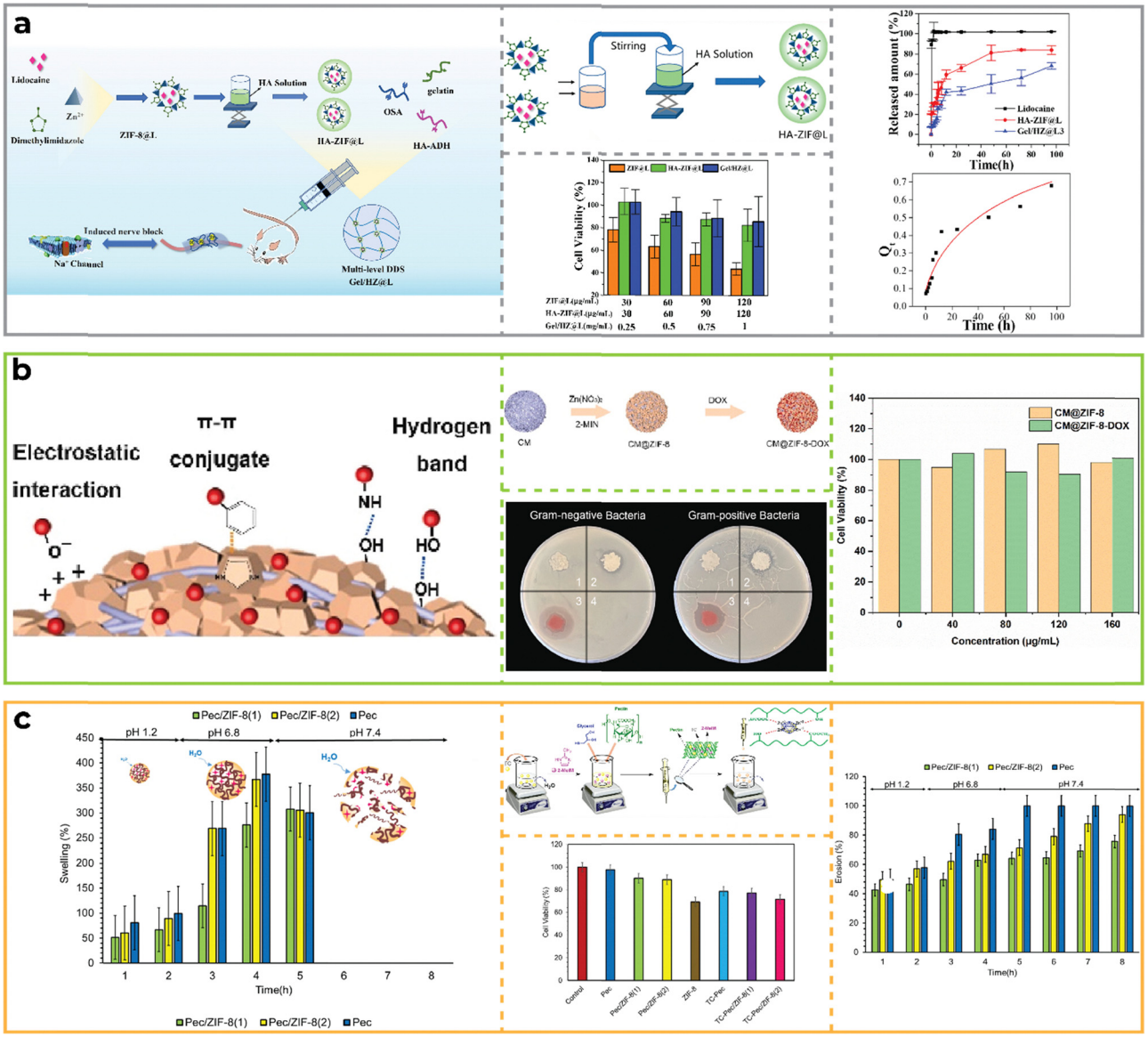


Fig. 27 Multi-level drug delivery, cytotoxicity, and release studies of HA-ZIF[282] (a), CM@ZIF-8[283] (b), and Pec/ZIF-8 composites[284] (c).

toxicity. Traditional oral and intravenous administration methods often struggle to provide sufficient drug bioavailability in the lungs, leading to suboptimal treatment outcomes for respiratory diseases. Moreover, the natural defense mechanisms of the lungs, such as mucociliary clearance and enzymatic degradation, further hinder drug retention and absorption, necessitating the development of advanced pulmonary drug delivery strategies.[285]

To overcome these challenges, inhalable drug delivery systems have emerged as a promising alternative, allowing for localized drug deposition, improved bioavailability, and reduced systemic side effects. MOFs, particularly ZIF, offer a highly adaptable platform for pulmonary drug delivery due to their exceptional porosity, high drug-loading capacity, and tunable degradation properties. ZIF-8 remains stable under physiological conditions but undergoes controlled degradation in response to environmental stimuli, making it ideal for sustained drug release. Additionally, surface modifications with hydrophilic polymers, such as hyaluronic acid (HA), can enhance biocompatibility, prolong nanoparticle circulation time, and enable targeted delivery through receptor-mediated interactions.

A notable example of this approach is the use of HA-modified ZIF-8 (ZIF-8/HA) loaded with doxorubicin (DOX) reported by Yuzhuo *et al.*, which enhances targeted lung cancer therapy by improving drug loading efficiency and enabling controlled release in the acidic tumor microenvironment, reducing off-target toxicity, Fig. 28(a). HA-functionalized ZIF-8 nanoparticles actively target cancer cells *via* CD44 receptors, enhancing drug accumulation at the tumor site.[286] Hamed *et al.* reported that Fe_3O_4@UiO-66 (>200 nm) and Fe_3O_4@PAA/AuNCs/ZIF-8 (<200 nm) nanocarriers improved pulmonary drug delivery by optimizing carrier size and drug loading Fig. 28(b). Magnetic field enhanced adhesion to lung branches increases drug

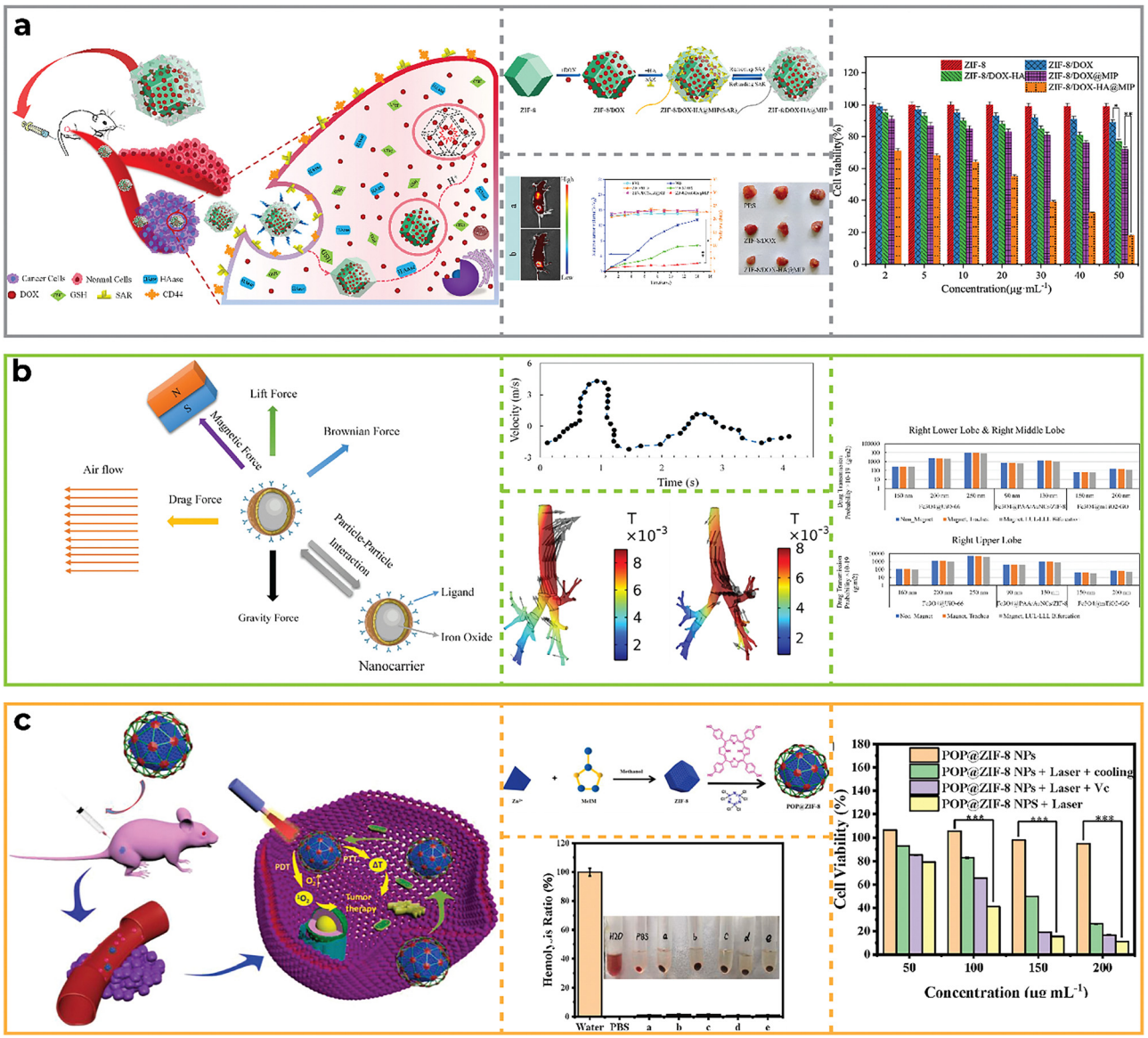


Fig. 28 Targeted drug delivery, cytotoxicity, and tumor analysis of ZIF-8/DOX-HA@MIP[286] (a), NC adhesion and drug transmission in lung tissues[287] (b), and POP@ZIF-8 NPs for combination therapy[288] (c).

targeting while reducing systemic toxicity.[287] Yue *et al.* reported a porphyrin-based polymer-coated ZIF-8 (POP@ZIF-8) hybrid for lung cancer treatment Fig. 28(c). This pH-responsive system enables targeted drug delivery while synergistically triggering photodynamic and photothermal therapy under laser irradiation for enhanced therapeutic efficacy.[288] These intelligent delivery systems not only enhance drug stability but also enable precise targeting of respiratory ailments, offering a promising solution for improving pulmonary drug therapy.

6. Summary and outlook

The development of efficient and selective drug carriers remains a significant challenge in biomedical research. Many conventional carriers suffer from low drug loading capacities and uncontrolled drug release, limiting their therapeutic effectiveness. In recent years, ZIFs have gained substantial attention in drug delivery due to their high porosity, tunable apertures, and excellent biocompatibility. However, controlling the pore diameter of ZIFs remains crucial, as it directly affects drug loading and release profiles. The sensitivity of Zn-based MOFs towards environmental factors also influences their practical applications. Optimization of the structural properties of ZIFs, such as morphology, crystallinity, chemical composition, and active surface areas, is crucial for maximizing the performance of these materials as drug carriers. Furthermore, ZIFs have better drug encapsulation properties and enhanced stability and pH sensitivity, rendering them more useful in controlled and target drug delivery. Post-synthetic modifications, such as functional group addition, further enhance stability, porosity, and drug loading capacity, though maintaining structural integrity during these processes is still a technical challenge.

Combining ZIFs with polymers such as cellulose, chitosan, alginate, polyethylene glycol, polystyrene, and polylactic acid enhances drug stability and circulation time and improves targeting efficiency. Such hybridization not only improves biocompatibility but also minimizes cytotoxicity and enhances long-term stability under physiological conditions. These attributes make ZIF–polymer based systems potential candidates for the next generation drug delivery carriers providing viable solutions to the challenges posed by the existing small molecule drug carriers. Understanding how these properties influence drug delivery efficacy will be key to further improving ZIF–polymer-based systems.

This review provides an in-depth discussion of ZIF–polymer composites (Fig. 29), focusing on their synthesis, functional modifications, and diverse applications in biomedical drug delivery. Various fabrication techniques, such as *in situ* polymerization, self-assembly, electrospinning, grafting, and microfluidic synthesis, have been explored to optimize their physicochemical properties and drug encapsulation efficiency. ZIF–polymer composites have shown remarkable potential in multiple drug delivery systems, including anticancer therapies, transdermal delivery, ocular and orthopedic applications, and targeted drug release, highlighting their versatility in advanced healthcare materials. Precise control over pore size, surface chemistry, and external stimuli responsiveness (*e.g.*, pH, temperature, light, magnetic fields, and enzymatic reactions) enables accurate regulation of drug release kinetics and minimizes burst release phenomena. This allows precise drug release at specific target sites while minimizing toxicity to healthy tissues.

However, despite the numerous advantages, several challenges remain to be addressed for the practical implementation of ZIF–polymer composites in biomedical applications. Although ZIFs exhibit promising biocompatibility, extensive long-term *in vivo* studies are essential to understand cytotoxicity, biodegradation pathways, and potential immune responses. Additionally, the challenge of achieving high loading efficiency, especially for hydrophilic and large molecules, remains a concern. Also, the optimality of the properties of ZIF–polymer composites in a physiological environment and the stability of their characteristics has been a continued problem in the current development of these materials for clinical practice. Targeting specificity, particularly for cancer treatments, also requires enhancement to achieve precise delivery and imaging of diseased cells. Moreover, the heterogeneity of the tumor microenvironment poses an additional barrier to efficient drug penetration and release, often leading to suboptimal therapeutic outcomes. Furthermore, finding new efficient and green synthesis processes, which would allow their larger scale production, is another critical issue in the

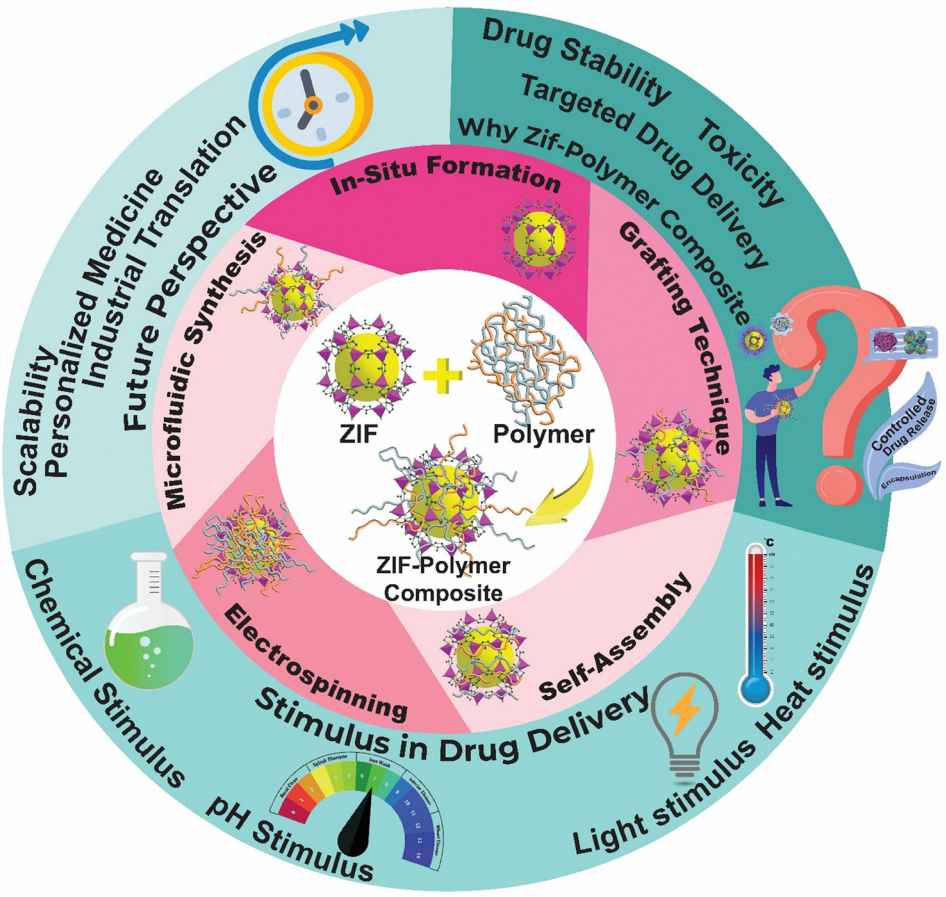


Fig. 29 Summary of ZIF–polymer composites including synthesis, properties, and future perspectives.

further application of these compounds in medicine. Furthermore, batch-to-batch variability during synthesis remains a substantial limitation, causing inconsistencies in drug loading capacity, release behavior, and biological response. The potential leaching of metal ions from ZIF frameworks under physiological conditions raises toxicity concerns, necessitating rigorous stability evaluation and surface passivation strategies. Another critical challenge is the scalability and cost-effectiveness of advanced functionalization techniques, such as stimuli-responsive modifications, which are currently expensive and technically demanding.

Solving the existing problems at this stage, using the characteristics of ZIF–polymer composites, this technology undoubtedly can become the new generation of drug delivery systems, providing better treatment outcomes and reducing side effects associated with conventional therapies. Improvements in controlled drug release, structural stability, and biocompatibility will set the highest standards of modern medicine for targeted interventions. Finally with ongoing evolution and development, ZIF–polymer composites may gradually be introduced as an innovative approach in the drug delivery field, offering a potential pathway for more specific, and effective treatments for a wide range of diseases.

Further studies must develop ZIF–polymer synergistic materials that combine both therapeutic and diagnostic properties that facilitate synchronous tracking and drug release. Integrating imaging functionalities will enable real-time monitoring of drug release and treatment progress. This can only be achieved through strong collaboration between chemistry, materials science and biomedical experts from different disciplines, so as to enhance the mechanical properties of these composites, as well as to enhance biocompatibility for effective clinical applications. In addition, regulatory challenges for clinical translation must be systematically addressed, including establishing standardized protocols for characterization, toxicity assessment, and long-term *in vivo* evaluation. As research progresses, it is anticipated that ZIF–polymer composites will find applications beyond biomedicine, in areas such as environmental remediation, biosensing, and catalysis, further expanding their impact across various fields.

Author contributions

Rimsha Perveen: conceptualization, visualization, and writing - original draft; Shumaila Bibi: investigation, validation, writing – reviewing and editing; Mohamed A. Salem and Mohamed H. Helal: writing, reviewing and editing; Adeel Afzal: investigation and validation; Ahmad Wattoo: investigation and validation; and Aziz ur Rehman: conceptualization, editing, and supervision. All authors have read and agreed to the published version of the manuscript.

Data availability

This is a review article; no new data were created or analyzed in this study. All data discussed in this article are derived from previously published sources and appropriately cited in the manuscript following the guidelines.

Conflicts of interest

No potential conflict of interest was reported by the author(s).

Acknowledgements

The authors also appreciatively acknowledge the PhD Analytical Laboratory, Institute of Chemistry, and The Islamia University of Bahawalpur for providing the necessary resources and environment for this work. The authors extend their appreciation to the Deanship of Scientific Research at Northern Border University, Arar, KSA for funding this research work through the project number ''NBU-FFR-2025-540-05''.

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