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Review

Foundation

Zeolites in drug delivery: Progress, challenges and opportunities

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Highlights

- Zeolites have shown tunable structures, chemical stability and biocompatibility features.
- Zeolites because of various pore sizes and structures have shown a high loading efficacy.
- Zeolites can carry various types of therapeutic agents such as drugs and proteins.
- Zeolite structures can be adjusted on-demand, based on the type of drug and delivery route.
- Zeolite modification can even results in stimuli-responsive carriers for advanced delivery.

There are continuing attempts to achieve appropriate controlled-release therapeutic systems by designing innovative functional drug delivery systems (DDS). Although various types of delivery system have been developed, strategies that have successfully made it to the clinic are rare. Given their diverse structures, zeolites have attracted significant research attention for controlled and targeted drug delivery purposes. The structure of zeolites can be microporous, mesoporous or macroporous, which can be exploited to deliver a variety of therapeutic agents to the target site in a controlled manner. In this review, we introduce the different types of zeolite, and discuss the challenges and opportunities associated with their usage as drug delivery systems.

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Introduction

Biotechnology and biomedical science, especially drug delivery and gene delivery sections, are experiencing rapid development because of their importance to human life 1, 2, 3. Many DDSs (see Glossary) have been suggested, including liposomes, proliposomes, phospholipids, gels, and microspheres, among others 4, 5, 6. Given their unique structural characteristics in addition to their biocompatibility, large surface areas, and ability to control their physicochemical properties, micro- and mesoporous inorganic products, such as zeolites, have been largely used as adjuncts to polymeric substances in a variety of forms, such as composites, blends, hydrogels, and hosts, for drug delivery 7, 8, 9, 10, 11. Zeolites have been a focus of recent drug release system research for the controlled delivery of drugs because of the regular and uniform shape of their pores and their ion exchange abilities 12, 13, 14. The large pore sizes available in some zeolite constructions have been used by engineers to freely release drug molecules. Another primary use of zeolites is their application in the synthesis of hydrogels for biotechnological and therapeutic purposes, which resulted from their highly crystalline form and ability to engineer them to selectively adsorb wanted or unwanted inorganic or organic particles 15, 16, 17. Moreover, in veterinary medicine, zeolites have been exploited with direct benefits on the morphology, performance, and microbial flora of the digestive tract, release of metabolically vital ions, removal of unwanted ions, improvements in the nutrition condition of mammals, enhanced levels of immunity, and removal of toxic products of digestion. Zeolites have additional useful properties, including long-term biological durability and ability to adjust immune system performance, that have attracted significant attention in the biomedical field [18]. In addition, zeolites can be used to deliver DNA to cells because they can be internalized within the cell by endocytosis. The main challenge to the use of zeolites is their cytotoxicity (e.g., erionite can cause cancer). However, such a challenging feature can be exploited in cancer treatment in terms of harnessing the antiproliferative and proapoptotic actions of zeolites [15].

In addition to the features discussed above, zeolites have also attracted research interest because of their low cost, abundance, and high availability. The high specific area and microporous volume of zeolites results from the numerous micro- and mesoporous cavities and pores that they contain [19]. Zeolites are classified according to their chemical composition (Si/Al), pore size, and pore structure. Nano-sized particles are highly applicable for drug delivery, with mesoporous silica-based nanoparticles one of the main candidates in research for drug release 20, 21.

Given the decline in drug development, often as a result of biological issues associated with drug molecules, research interest in the development of nanoscience-based molecules has expanded 22, 23, 24, 25. The use of nanotechnology for medical applications has many advantages, such as: (i) drugs can be released that have poor water solubility; (ii) drug molecules can be directly transferred into a specified cell or tissue; (c) drugs can be transferred across rigid cell borders and tissue walls; (d) successful encapsulation and release of large molecular therapeutics; and (e) simultaneous delivery or release of several drugs with different release rates into one tissue 26, 27, 28.

In this review, we focus on the applications of different synthetic and natural zeolites in medical and drug delivery to highlight the advantages of using zeolites as DDSs.

Zeolites in drug delivery

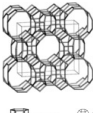
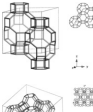
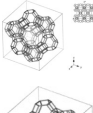
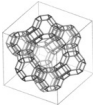
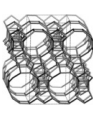
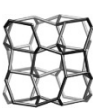
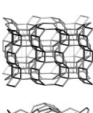
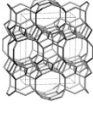
Zeolite can be used as a platform for the delivery of various types of drug. However, because of the small size of the drugs, they can be easily released from the structure. Therefore, the zeolite pore size needs to be adjusted in terms of the desired drug [29]. Moreover, differences in hydrophilicity between zeolites and drugs can limit their loading capacity, although this can be overcome via surface modification of the zeolite 30, 31. Thus, the surface of a zeolite can be adjusted depending on the drug that needs to be delivered. Table 1 details examples of zeolite structures, properties, and applications in biomedical applications.

Table 1. Examples of zeolites used in biomedical applications

Atlas label	Name	Structure	Synthesis method	Application	Refs
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LTL	Zeolite L		Hydrothermal	Cell separation; detection of cancer cells; DNA delivery	60, 127, 128
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Atlas label	Name	Structure	Synthesis method	Application	Refs
LTA	Zeolite A		Hydrothermal Sol-gel [32]	Antimicrobial wound-healing dressing; antimicrobial coating of bone implants; inhibition of osteoclasts	66, 130, 131
HEU	Clinoptilolite		-	Environmental purification; removal of radioactive contaminants; detoxification of organisms; positive effects on nutrition and digestive tract; gastroprotective effects; drug delivery; construction of biosensors; antioxidant, antiapoptotic, anti-inflammatory, and antitumor activity	37, 43, 48, 57, 58, 132, 133, 134, 135, 136, 137, 138
MFI	ZSM-5 Zeolite		Hydrothermal	Drug delivery (gentamycin); antibacterial properties; bone implants; catalyst membrane and energy	7, 105, 144
MOR	Mordenite		-	Drug-delivering biomaterials	[72]
CHA	Chabazite		-	Optical imaging drug delivery	[55]
FAU	Zeolite X		Hydrothermal	Nanocarrier; catalyst	94, 145
FAU	Zeolite Y		Hydrothermal	Drug delivery; adsorption	76, 146
BEA	Beta Zeolite		Microwave; hydrothermal	Toxics adsorption; growth factor delivery	36, 67, 147, 148
ANA	Analcime		One-pot hydrothermal route	Antioxidant	[149]
PHI	Phillipsite		Hydrothermal	Antioxidant	[150]
FER	Ferrierite		-	Antioxidant	
ERI	Erionite		-	Highly carcinogenic	

Natural zeolites

Clinoptilolite

Clinoptilolite (Table 1) is a natural zeolite with a microporous tetrahedral arrangement of silica and alumina. It has the overall formula: $(\text{Na}, \text{K}, \text{and Ca})_{2-3} \text{Al}_3 (\text{Al}, \text{Si})_{2\text{Si}_{13}\text{O}_{36}} \cdot 12\text{H}_2\text{O}$. It appears as white to reddish tabular monoclinic **tectosilicate** crystals with a hardness of 3.5–4 on the Mohs scale, with a specific gravity of 2.1–2.2. It typically occurs as a result of conversion (as a glass) from a vitreous to a crystalline state of volcanic glass shards in tufts and as vesicle fillings in **basalts**, **andesites**, and **rhyolites** 32, 33, 34. The use of clinoptilolite in industry and academia focuses on its ion exchange properties, given that it has a strong exchange affinity for ammonium (NH_4^+). A typical example of this is its use as an enzyme-based urea sensor. It is also used as fertilizer and sold as a deodorizer in the form of pebble-sized chunks contained in a mesh bag 19, 35.

Mesoporous zeolites have been a focus of research to exploit their ability to increase the intestinal absorption of vitamins and minerals. For example, a bentonite clinoptilolite natural zeolite blend was used as a porous carrier for the encapsulation and slow release of vitamin E; thermodynamic investigations revealed the endothermic origin of the automatic encapsulation procedure and showed that the release profile was within the recommended dietary allowance for humans [35]. A novel pathway was proposed for modification of chitosan-attached natural clinoptilolite zeolites for biomedical purposes. In this example, caffeic acid (CA) was efficiently mixed with chitosan via laccase, resulting in the constant generation of hydrogen peroxide, highlighting the use of this system as a beneficial antimicrobial agent [36].

De Gennaro *et al.* modified the clinoptilolite with cetylpyridinium chloride and loaded it with diclofenac sodium to evaluate the release behavior. Drug adsorption followed a pseudo-second order reaction and was controlled by boundary layer diffusion. In addition, the drug release mechanism was controlled by anionic exchange with a rapid final phase resulting in sustained drug release [37]. Pasquino *et al.* modified the clinoptilolite surface to act as a delivery system for nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., Ibuprofen and diclofenac). The results indicated that the molecular conformation of the drugs had an important role in their interaction with the zeolite and the surface modifications resulted in higher binding energy. In addition, the release mechanism was controlled by anion exchange. The drug release behavior was evaluated by using a rheology method, in which the gel-like system was based on a surfactant and a binding salt was used for topical release [38]. Such drugs act as a strongly binding salt, increasing the viscosity of the solution [39]. Counter-ions of such drugs enter the surfactant head groups and alter the packing factor of the micelles, affecting their morphology and rheological behavior [40].

A diclofenac sodium (DS) oral delivery system was also explored by Serri *et al.*, who used cetylpyridinium chloride surfactant-modified zeolites to investigate DS release under pseudo gastric fluid conditions. This system exhibited long-term effective release for the DS-zeolite solution up to 9 h [30]. According to Rodriguez *et al.*, purified natural clinoptilolite zeolites can be used as efficient porous materials in anti-diarrheic applications [41]. Clinoptilolite has also been used as an adjuvant in cancer therapy: treatment with this zeolite prolonged the life-span of, and reduced tumor size, in rat models by decreasing protein kinase B (c-Akt) expression and stimulating the expression of p21WAF1/CIP1 and p27KIP1 tumor suppressor genes [42]. Drug-loaded clinoptilolite also reduced the clinical symptoms and indications related to endoscopically negative gastroesophageal reflux disorder and healing of damages caused by NSAID use. This gastroprotective effect of zeolites, especially clinoptilolite, could stem from the fact that zeolites mainly attach to hydrogen ions and biologically active amines and nitrates [43].

Clinoptilolite was also utilized as a porous platform in an oral DDS for the release of various vitamins (A, D₃ and E). Such zeolites exhibit buffer properties that can protect vitamins in acidic environments and increase their shelf-life. Thus, fat-soluble vitamins show high bioactivity in the presence of zeolites because the latter protect them from the acidity of the gastrointestinal tract [44]. Moreover, magnetic clinoptilolite nano and/or microparticles could be used in novel multimodal investigations for use in optical imaging, MRI, thermo- and phototherapy, hyperthermia, as well as for drug release [45].

Ivkovic *et al.* discussed the synthesis of, and mechanisms involved in, thermomechanically activated zeolites as a new approach for highly efficient drug delivery (e.g., clinoptilolite combined with both synthetic and natural active substances). The authors studied the use of such systems as anti-HIV, antidiabetes, antihypertension and anticancer agents. As a result of their 3D structure and appropriate cellular activity, activated clinoptilolite in combination with natural materials exhibited synergic effects and improved biocompatibility. These results show that it is possible to fabricate novel molecules that work in harmony with natural cell structures, decreasing or even removing complications associated with autoimmune reactions, toxicity, and other impacts [46]. In addition, hemostatic properties of clinoptilolite were compared with those of Quikclot®, a commercially available treatment for external hemorrhage. Mortality in the Quikclot-treated group was ~53%, whereas that in the zeolite group was ~20%. Moreover, the healing process was completed using the zeolite, whereas Quikclot usage resulted in necrotic tissue. This hemostatic mechanism of clinoptilolite is related to its negatively charged framework, which activates the blood-clotting process [47]. When added to the diet of poultry, clinoptilolite improved their intestine health by changing the gut morphology, increasing the villus height and villus to crypt depth, decreasing the pH, and reducing the counts of *Salmonella* and *Escherichia coli* [48]. A Zn ion exchange clinoptilolite (ZnCP) has been used as an alternative to zinc sulfate (ZnSO₄), compared to which it exhibited higher bioavailability, confirmed by increased tissue Zn accumulation and Zn transporter genes expression (*ZnT1*, *ZnT2*, and *MT4*) [49, 50]. In addition, clinoptilolite samples that were loaded with zinc nanoparticles also displayed immune impacts against *Salmonella pullorum* [51].

Mordenite

Mordenite (MOR; [Table 1](#)) is a zeolite mineral with the chemical formula, $(\text{Ca}, \text{Na}_2, \text{K}_2) \text{Al}_2\text{Si}_{10}\text{O}_{24} \cdot 7\text{H}_2\text{O}$. According to Ullmann's Encyclopedia of Industrial Chemistry (2005), it is one of the six most abundant zeolites and is used commercially. MOR is **orthorhombic**. It crystallizes in the form of fibrous aggregates, masses, and vertically striated prismatic crystals. It can be colorless, white, or faintly yellow or pink. It has a Mohs hardness of 5 and a density of 2.1 g/cm^3 . When it forms well-developed crystals, they are hair like, very long, thin, and fragile [19, 34](#). The molecular structure of MOR is a framework containing chains of five-membered rings of linked silicate and aluminate tetrahedral (four oxygen atoms arranged at the points of a triangular pyramid around a central silicon or aluminium atom). Its high ratio of silicon to aluminum atoms makes it more resistant to attack by acids compared with most other zeolites [19, 52](#).

MOR can be used in both biomedical and removal applications. For example, in a study of bovine urine wastewater static adsorption and removal by MOR, the zeolite was shown to absorb increased amounts of waste material into its porous cavities and decrease the concentration of unwanted soluble substances to $<10 \text{ mg/l}$ from an initial concentration of 45 mg/l . This efficient removal and biological waste adsorption was suggested to result from the stable pores of H-beta and H-MOR and the resistance of MOR to a high acid environment, as also indicated by the resulting adsorption isothermal curves [\[53\]](#).

Other natural zeolite compounds

There are many other types of zeolites that can be applied to various areas of science, including biomedical use ([Table 1](#)). Here, we discuss several other zeolites that cannot be categorized only because there are only a few studies of them available thus far compared with other zeolite forms.

Chabazite is a tectosilicate mineral, closely related to geminate, with the formula $(\text{Ca}, \text{Na}_2, \text{K}_2, \text{Mg}) \text{Al}_2\text{Si}_4\text{O}_{12} \cdot 6\text{H}_2\text{O}$. Recognized varieties include Chabazite-Ca, Chabazite-K, Chabazite-Na, and Chabazite-Sr, depending on the prominence of the indicated cation. Chabazite crystallizes in the triclinic crystal system with typically rhombohedral shaped crystals that are pseudocubic. The crystals are typically twinned, and both contact twinning and penetration twinning can be observed. These crystals can be colorless, white, orange, brown, pink, green, or yellow [19, 54](#). The hardness ranges from 3 to 5 and the specific gravity from 2.0 to 2.2. More research is needed into such zeolite-rich rocks for drug delivery purposes, particularly because of toxic compounds (e.g., the Chabazite-rich sample from Bowie). In addition, some other natural materials have been ignored for such applications, because they expressed poor chemical and mineralogical features in terms of cationic distribution, and cation exchange ability [\[55\]](#). In an attempt to understand the release properties of chabazite, it was modified with a cationic surfactant, cetylpyridinium chloride (CP), to evaluate the release of DS. According to the results, DS delivery was regulated mainly by film and particle diffusion mechanisms, whereby the film thickness and distribution coefficient are important for film diffusion mechanism and the effective diffusivity of the exchanging ions is important for particle diffusion [\[56\]](#).

Natural zeolites have the potential to be used for nutrition and dietary purposes in animals to improve their product qualities, such as eggs, meat, or milk, because they can enhance the targeted release strategy for drugs and improve nutrient transfer. They also have the ability to trap and hold nutrients for a long period of time because of their long-term stability and nondegradability; these enable the drug and nutrient to be transferred slowly but constantly to the target areas inside the body [57, 58](#). In addition, the use of porous inorganic zeolites in animals to neutralize the deleterious effects of swallowed toxic substances was investigated by Kececi *et al.*. These authors investigated the ability of zeolite and zeolite-containing composite containers fed directly to animals to scavenge and absorb toxic chemicals in the body fluids and tissues. Zeolite-based materials produced promising effects, attributed mainly to their inertness and nontoxic features and their appropriate pore diameter, which can easily trap and hold toxic chemicals inside the body [\[59\]](#).

Synthetic zeolites

Zeolite Type L

Among the high diversity of natural and synthetic zeolites, Linde Type L (LTL) zeolite ([Table 1](#)) stands out owing to its appealing physicochemical and structural properties and high versatility. LTL zeolite is a crystalline aluminosilicate with a well-defined 3D framework and hexagonal symmetry. It is formed by corner-sharing TO_4 tetrahedral (T being aluminum or silicon) leading to the arrangement of cancrinite cages and the final 3D network. The presence of the trivalent aluminum infers an anionic character to the framework and charge-compensating cations are required to balance the charge of the tetrahedral. This explains

the stoichiometry of LTL zeolites with monovalent charge-compensating cations M^+ ($M9[Al_9Si_{27}O_{72}] \cdot nH_2O$), where the number of water molecules per unit cell is 21 in fully hydrated materials and ~16–20% in relative humidity [19].

Multifunctional porous media, such as zeolites, also can be implemented in novel biomedical areas, such as gene therapy agents. For example, Bertucci *et al.* used zeolite-L as a carrier for peptide nucleic acids (PNAs) and for the delivery of organic molecules inside living cells; Zeolite-L particles were modified by covalently attaching the PNA to their surface, while their channels were occupied with fluorescent dye molecules. Fluorescence colocalization experiments showed that the zeolites bound to PNA were not destroyed after their internalization into the target tissue. This result clearly showed the protective ability of porous zeolites in protecting the encapsulated nucleic acid from unwanted release as a result of their fitted 60-nm channels, which can hold the nucleic acid and enable it to attach properly to other functional groups. Such decoration resulting in a theranostic and gene therapy nanoparticle [60, 61]. Freeze–thaw fabricated poly vinyl alcohol (PVA)/pullulan cryogels were also used to fabricate composite-containing zeolite-L nanoparticles to release enalapril maleate (EM). The addition of the zeolite increased the EM loading efficiency because of its porous structure. The incorporation of zeolite-L powder nanoparticles reduced the humidity absorption capacity of the cryogels and caused a new morphology configuration, which enhanced the release properties. This system obeyed the Korsmeyer–Peppas release model, whereby EM release was controlled by diffusion mechanisms [62].

Zeolite Type A

Zeolite Type A (Table 1) exhibits a Linde Type A (LTA) structure. It has a 3D pore structure with pores running perpendicular to each other in the x, y, and z planes, and comprises secondary building units 4, 6, 8, and 4–4. The pore diameter is defined by an eight-member oxygen ring and is small at 4.2 Å. This leads into a larger cavity with a minimum free diameter of 11.4 Å. The cavity is surrounded by eight sodalite cages (truncated octahedra) connected by their square faces in a cubic structure. The unit cell is cubic ($a = 24.61$ Å) with Fm-3c symmetry. Zeolite A has a void volume fraction of 0.47, with a Si/Al ratio of 1.0. It thermally decomposes at 700 °C. Zeolite A is of interest because its super cage structure is useful for various applications, such as drug delivery, catalysis, and adsorption [19, 63, 64].

In research by Kocaaga *et al.*, hydrogels comprising natural polysaccharide LM pectin and Zn-Na ion-exchanged type A zeolites were synthesized as a wound dressings with sustained drug release. This research showed that using zeolites and inorganic porous materials enhanced the oxygen transmission maintenance properties. Hydrogels containing zeolite A were fabricated by a membrane diffusion approach and showed an ability to release the drug in a constant ratio up to 86% within 5 h. Zeolite A nanoparticles acted as porous drug containers and improved the hydrogel stability by swelling, as well as preserving the oxygen transmission rate [65]. Nitric oxide (NO)-rich, type A zeolite nanoparticles have been explored to understand their effects on antimicrobial and wound-healing characteristics of moisture-sensitive delivery structures against wound pathogens, such as Gram-negative bacteria (*E. coli* and *Acinetobacter baumannii*), Gram-positive bacteria (*Staphylococcus epidermidis* and methicillin-resistant *Staphylococcus aureus*) and a fungus (*Candida albicans*). Adding the nanozeolite into a hydrophobic ointment base decreased the water diffusion properties, altering the rate at which NO was released. The presence of the zeolite regulated the stabilized ointment release into the wound and also controlled the adsorption or delivery of other chemical through porous cavities of the zeolite, which resulted in the faster closure of the treated area [66]. Keeting *et al.* [67] reported that the differentiation and conversion of one structure into another related structure of transforming growth factor beta in target tissues could be improved by using type A zeolite crystals. Their analysis indicated that the presence of zeolite A increased alkaline phosphatase activity and osteocalcin release. However, this action did not notably affect collagen fabrication per individual cell. The porosity and adequate surface area of the zeolites provided a steady-state mRNA conversion rate for TGFβ₁, which extend its release time up to 6 h [67]. In another study, 5-fluorouracil (5-FU), a common anticancer drug, was encapsulated into zeolite 4A nanocomposite magnetic particles, which showed steady fluorescent behavior with near-infrared (NIR) optical features. Cell viability tests revealed that encapsulation of the drug inside the zeolite pores enhanced its cytotoxic properties compared with free 5-FU. The conversion and encapsulation of the drug into zeolitic nanoparticles resulted in regulated and sustained drug release without any sudden release phenomena, because of the channel length of the zeolite and its stable constant slow diffusion rate [68]. Rieger *et al.* analyzed the antimicrobial agent delivery properties of a silver-coated LTA zeolite configuration mounted inside cellulose fibers by an electrospinning process. The electrospun nanofibers exhibited considerable rates of microbial and bacterial inhibition of up to 92%, highlighting the efficiency of the system for the fast delivery of antimicrobial agents to target sites using a modified porous structure. When Ag-LTA-Large zeolites with a lower external surface area were immobilized onto the nanofiber mats, they presented four times-lower antimicrobial behavior compared with Ag-LTA-Small and Ag-LTA-Meso inorganic samples also attached to the nanofiber mats. Notably, the

stabilization of the zeolites significantly enhanced the initial bacteria removal after a relatively limited incubation period. Moreover, it was reported that because of the extra outer surface area and open pores of the zeolites, the zeolite–nanofiber composites provided the composite structure with a longer lasting drug delivery capability, leading to a manageable release system [69].

In some cases, zeolite structures can be used with anticancer compounds as DDSs. For example, two different zeolite structures, fugalite (FAU) and LTA, were studied to determine their usefulness as DDSs using α -cyano-4-hydroxycinnamic acid (CHC), an anticancer drug. FAU and LTA exhibited no toxicity to HCT-15 cancer cells individually. Significantly, CHC-loaded zeolites, compared with nonencapsulated drug, enhanced deterrence of cell viability up to 585-fold. The implementation of the zeolite into this system affected and more specifically controlled the solubility rate of the drug in the media by keeping it trapped in its pores, preventing the bulk solubility of the drug and its *in situ* expansion [70]. A sulfonamide polymer composite with zeolite Y was investigated by utilizing variant replacements from aqueous media. The intake properties of five sulfa-containing drugs were found to be considerable because of the porous structure of the zeolite, which could be used for both water purification and drug delivery. In addition, based on numeric modeling, the most persistent tautomeric (amide or imide) kind of each antibiotic was suggested. Given the proper stabilization energy, monomers and dimers of imide sulfathiazole and amidic sulfa-pyridine were set in a zeolite cage, whereas the residual sulfa-containing drugs were absorbed by the monomeric amidic faces. The interactions of these zeolite–drug and drug–drug systems were investigated and showed that sulfonamides with the lowest dimensions (sulfathiazole and sulfa-pyridine) had the ability to generate dimers inside the zeolite cage, in a situation in which those molecules with the biggest size were immobilized as single molecules; thus, this highlights the ability of zeolites to regulate the delivery of both types of sulfonamide [71]. Temozolomide (TMZ) as a chemotherapeutic agent embedded into zeolite Y and MOR was used to treat glioblastoma. TMZ embedded in MOR showed higher efficiency compared with free TMZ both *in vitro* and *in vivo*. Thus, zeolite Y and MOR can be considered as hosts for TMZ delivery. These zeolitic structures were chosen because their Si/Al ratio, and wide and accessible pore configuration were anticipated to be functional for the potentiation of TMZ. In addition, these materials hold the integrity of TMZ without any conversion before their exposure to cancer cells [72].

Zeolite Type Y

Faujasite (FAU) is a mineral group in the zeolite family of silicate minerals. The group comprises FAU-Na, FAU-Mg, and FAU-Ca. They all share the same basic formula: $(\text{Na}, \text{Ca}, \text{Mg}) 3.5 [\text{Al}_7\text{Si}_{17}\text{O}_{48}] \cdot 32(\text{H}_2\text{O})$ but vary in terms of the amounts of sodium, magnesium, and calcium. FAU occurs as a rare mineral in several locations worldwide and is also synthesized industrially [19, 73]. Zeolite Y was first described in 1842 from the Limberg Quarries in Germany. The sodium modifier FAU-Na was added following the discovery of the magnesium and calcium-rich phases during the 1990s. It was named for Barthélemy Faujas de Saint-Fond (1741–1819), a French geologist and volcanologist [19, 74]. The zeolite Y FAU framework comprises sodalite cages connected through hexagonal prisms. The pores are arranged perpendicular to each other. Each pore, which is formed by a 12-membered ring, has a relatively large diameter of 7.4 Å. The inner cavity has a diameter of 12 Å and is surrounded by ten sodalite cages. The unit cell is cubic and its lattice constant is 24.7 Å. Zeolite Y has a void fraction of 48% and a Si/Al ratio of 2.43. It thermally decomposes normally at 793 °C [19].

Karimi *et al.* compared the drug delivery and biomedical properties of the ZSM zeolite, Zeolite Y, and a polyethylene glycol (PEG) nanocomposite structure as anticancer drug carriers. The authors concluded that PEG/ZSM zeolite composite samples showed more antioxidant behavior and consistent release than PEG. The zeolite acted as an efficient platform because of its high surface area and pore availability, as revealed by an nitrogen adsorption–desorption analysis, which indicated that zeolite pore volume and surface area decreased dramatically after introducing the drug into the zeolite solution, indicating that the zeolite pores and particles were successfully occupied by the drug. The truncated octahedron configuration of Zeolite Y also resulted in its high, consistent ability to release curcumin [75]. Zeolitic polymer composites have also received significant attention in recent years. For example, zerumbone is one of the most effective anticancer agents against colon, skin and breast cancers [76, 77]. Salleh *et al.* evaluated the performance of an anticancer DDS based on a zeolite Y gelatin composite loaded with zerumbone. Entrapping zerumbone inside the zeolite improved its release efficiency because of the steady-release configuration, resulting mainly from the inertness of zeolite Y, which acted as both a carrier and support for drug; in addition its pores encapsulated, protected, and controlled the release of the drug [76].

pH-sensitive zeolite Y nanoparticles have also been synthesized hydrothermally to test their drug delivery efficiency. Tannic acid-coated zeolites were prepared to adjust their slow-release behavior in comparison with uncoated porous ze

from zeolites loaded with metronidazole as an antiprotozoan drug showed that such zeolites can be utilized as antitrichomonal agents against *Trichomonas gallinae* [78]. One of the benefits of synthetic zeolites compared with natural forms is their ability to deliver the loaded substances in response to external manipulation release techniques, such as pH or the application of an electric or magnetic field. For example, Paradee and Sirivat synthesized a zeolite Y-alginate hydrogel sample that was ion exchanged with folic acid solution to encapsulate it in the microporous structure of the zeolite. An electric field was used to study its impact on the diffusion rate of the drug, which found to be positive because of the interaction and electrorepulsion between folic acid and the anode section of the field. In addition, the alginate crosslinking ratio and zeolite Al content had a direct influence on the rate of folic acid delivery from the porous zeolite [79].

In another study, the zeolite was used as a porous structure in the system, and zeolite Y-gelatin composite synthesis was reported in the presence of a glutaraldehyde crosslinker. Subsequently, it was revealed that zerumbone can be trapped in porous cavities of zeolite Y. ATR-FTIR spectroscopy was used to characterize the interactions between zerumbone and zeolite Y. Swelling tests showed that the gelatin crosslinked with glutaraldehyde decreased the water penetration of the former. After crosslinking, an increase in the thermal decomposition temperature of the composite occurred that enhanced the composite strength. Results showed that the zeolite did not interact with the drug and no middle chemicals were formed between zerumbone and zeolite Y during the experiment. Given the hygroscopic nature of gelatin, it easily swells and erodes when immersed in water; thus, the incorporation of the zeolite successfully controlled this characteristic by regulating water adsorption via its diverse porous structure [80].

Zeolite Y with varying silica:alumina ratios were selected and loaded with 5-FU. Thermogravimetric probes and nitrogen sorption data showed that 5-FU was absorbed within H type zeolite-Y (HY) pores. In addition, the amount of aluminum was important in specifying the amount of 5-FU delivered. HY-5 with the minimum $\text{SiO}_2/\text{Al}_2\text{O}_3$ ratio did not have the ability to deliver 5-FU, whereas HY-30 and HY-60 delivered nearly 56% and 63% 5-FU, respectively [81]. Vilaca *et al.* similarly investigated the potential of the zeolite NaY as a drug carrier for 5-FU and reported that zeolite-loaded 5-FU nanocarriers showed higher loading content and better release behavior compared with nanocarriers not involving zeolites. A comparison with samples containing rhodamine B embedded in NaY clearly showed that the zeolite particles were able to enter the cytoplasm of human colorectal carcinoma cells. Although this method was only applied to NaY zeolites, it is anticipated that both nano NaY and LTL zeolites might have the ability to enter cells because of their smaller dimensions, such internalization would result in more efficient drug delivery [82]. Research into the ability of silver-coated zeolites to increase the delivery rate of entrapped sulfadiazine revealed a steady release of the drug over a longer period of time. When the drug was loaded in a solution, some of the zeolite silver ions were released into the environment and interacted with sulfadiazine, restricting the bioavailability of the complex. Solid-state deposition of the drug in the pores of the zeolite resulted in interatomic interactions between the drug and Ag^+ and stabilized the total and prolonged drug release, which were not observed in unmodified materials [83].

FAU zeolites have been examined for their potential as DDSs. A DDS was developed by the encapsulation of liquid CHC in empty pores of the zeolite structure at pH 7.0. The molecular behavior and characterization of CHC during the encapsulation process was revealed by magnetic proton magnetic resonance spectrometry (^1H NMR) and UV-Vis spectroscopy. Data analysis of the drug both alone and packaged in NaY showed that CHC and the zeolite framework retained their original structure. The encapsulation of CHC significantly increased its performance as an anticancer drug against human HCT-15 human carcinoma cells. CHC molecules were loaded in zeolite Y super cages, without any structural changes or reduction in the crystallinity of the fabricated zeolite, and the drug molecule also kept its molecular integrity [84]. As an absorber of both UVB and UVA, oxybenzone (OXB) is used as an ingredient in sunscreen, with a maximum permissible concentration of 6% to avoid adverse effects. Accordingly, it was suggested that a porous zeolite could be used to transfer the compound in sunscreen products at a higher concentration. *In vitro* evaluations of encapsulated sunscreens showed that zeolite-loaded OXB exhibited significant anti-UV effects. Photodegradation of OXB was also prevented by using zeolite encapsulation. Moreover, such an approach also avoided any allergy-related effects, which have previously resulted in sunscreens being withdrawn from use [85, 86].

Nanocomposite technologies have also resulted in the development of samples and scaffolds with a higher elongation and compression ability, enhancing the application of biomedical products [87, 88, 89, 90, 91, 92]. For example, Arruebo *et al.* synthesized magnetite and Y zeolite nano-sized composites with a high active surface area, mechanical capabilities and adsorption content under standard physical conditions and ambient temperature. Benefits of such nanomagnetic composite powders included: (i) uncomplicated synthesis route; (ii) inhibition of the magnetite nanoparticle agglomeration; and (iii) presence of all magnetically produced materials within the aluminosilicate matrix. Moreover, *in vitro* tests revealed that the

nanoparticles were suitable for drug delivery applications because they were able to hold and release large loadings of drugs, such as DOX, because of their high fluid intake value and small pores, which also facilitated the slow release of this drug [93]. Ndiege *et al.* utilized zeolite Y in targeted imaging applications. Using click chemistry, targeting aptamers were linked to the zeolite surface, which then attached to the target cell because of the specific cell biomarkers; thus, zeolites can also be modified for use in both targeted therapy and imaging (Fig. 1) [94].

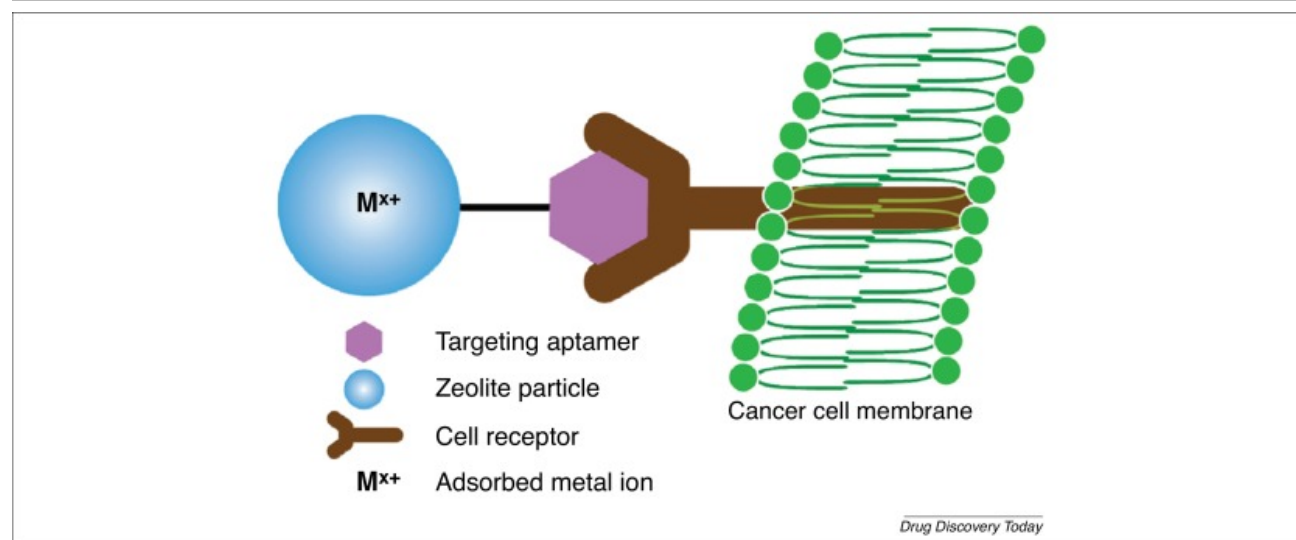


Figure 1. Bifunctional zeolites in targeted therapy and imaging. Reproduced, with permission, from [94].

Zeolite Type X

Zeolite X, alongside zeolite Y, is from the family of aluminosilicate zeolites with a FAU-type framework. Zeolite X differs from zeolite Y in its Si/Al atomic ratio, which is normally in the range of 1–1.5 for zeolite X but higher for zeolite Y. A high Si/Al ratio is favorable for thermal stability applications, a characteristic that is not necessarily required in zeolite X. The 24 tetrahedral cube octahedral units (sodalite cages) in the FAU framework type are similar to the carbon atoms in diamond. They are connected via hexagonal prisms (six double rings) creating a 3D porous channel structure, characterized by 12 oxygen ring openings with a 8 Å gap and super cages of ~12 Å [19, 73]. Two synthetic zeolites were examined to understand their ability to enclose and release anti-inflammatory drugs, such as ketoprofen. Zeolite A and zeolite X powders were used as porous containers with desirable surface morphologies for drug delivery applications. Zeolites cannot retain ketoprofen sodium salt, because of the repulsion of negative charges; thus, ketoprofen loading without activation treatment failed. Activation treatments are essential to remove water molecules from inside the samples to guarantee the entrance of the external ketoprofen molecules into the inner pores [95]. Under oral applications, 10% or less of the drug is able to enter at the gastric level; however, using zeolites resulted in a decrease in the negative impacts of ketoprofen on the stomach because the zeolite-encapsulated drug was able to pass through the stomach and into gastrointestinal tract before release [95]. Hassanvand *et al.* studied the application of ultrasound in enhancing drug delivery and release properties of different mesoporous carriers based on zeolite nanoparticles. Zeolite nanoparticles can pass the blood–brain barrier and enhance the amount of effective drugs reaching the target site. The release profile of the penetrated drug can be controlled by applying ultrasonic waves to stimulate the nanopore zeolite–drug framework; thus, drug-release behavior can be effectively controlled using this technique [96].

In another study, zeolites X and Y were used to determine the abilities of synthetic zeolites to encapsulate and then release diclofenac and piroxicam from their nanometric cavities. Anti-inflammatory drugs are most effective following prolonged slow release in most patients. Zeolites are effective carriers for such drugs because they enable their slow release because of their micro- and mesoporous structures, which prevent the sudden exposure of the drug to the body [97]. Recently, NaX-FAU was loaded with danazol via an incipient wetness approach and its transfer was compared *in vitro* and *ex vivo* with that of oral danazol. The stability of the loaded zeolites was reported to be almost 6 months. In addition, drug delivery tests

initial slow release of loaded danazol, which then increased with time. An everted gut sac model was used for *ex vivo* evaluation and showed that transport of danazol across the intestinal epithelium was enhanced when loaded in zeolites. The authors proposed that microporous NaX-FAU could be utilized as a DDS to facilitate the oral delivery of poorly water-soluble drugs. The synthesized zeolites maintained their natural solid structure under both fasted and fed state conditions, indicating that dissolution of danazol from the inorganic aluminosilicate particles was related to the textural characteristics and encapsulation capacity (pore size) of the mesopore carriers in both environments [98]. Surfactants have also been utilized to enhance the performance of zeolite as drug carriers. Zeolite-surfactant platforms increased chloroquine adsolubilization, which was related to the concentration and chain length of the surfactant and the type of zeolite. However, P and Z type zeolites with sodium/calcium counterion complexes exhibited weak adsolubilization of chloroquine [99].

Zeolites could be particularly useful for the stable, controlled release of NSAIDs, including indomethacin and ibuprofen, and could also help to avoid the adverse effects of such drugs associated with their oral application. Ibuprofen and indomethacin are popular analgesic and anti-inflammatory medications, with a molecular size of $\sim 10 \times 4.5 \text{ \AA}$ and $13.5 \times 5.5 \text{ \AA}$, respectively. The size of zeolites is the main reason why these drugs are well confined within them and present a slow release behavior. The size of zeolite X pores is $\sim 2 \text{ nm}$ or $20 \text{ \AA}$, which is suitable for biomedical applications and drug delivery purposes [100]. The CuX zeolite porous structure was reported as an anticancer drug transfer system for classifiphosphamide. This platform comprised two ingredients that were physically combined. Data from *in vivo* tests showed that the anticancer impact of drug-encapsulated CuX zeolite particles was similar to that obtained by classifiphosphamide. The potential benefit of CuX zeolites is their constant retention in the blood circulation, their resistance, and their establishment intact at concentrations of $100\text{--}1000 \text{ ng mL}^{-1}$ plasma [101].

MFI Type Zeolites

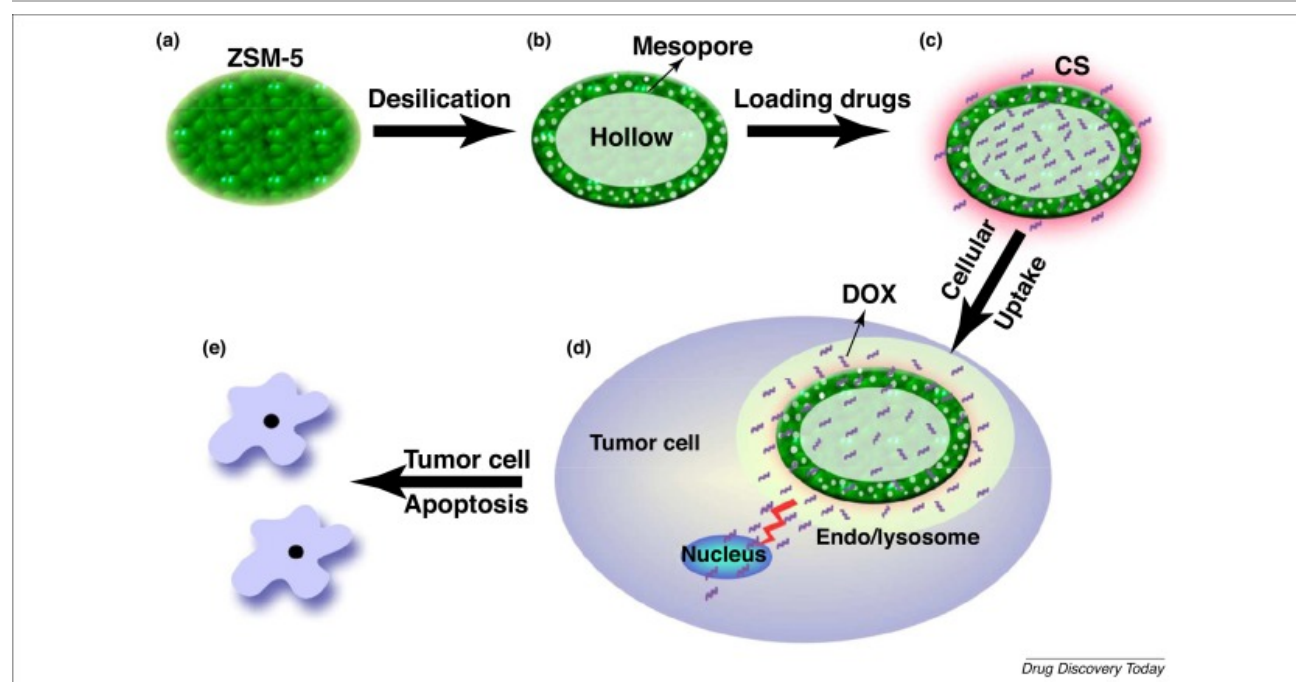
ZSM-5 (framework type MFI from ZSM-5) is an aluminosilicate zeolite belonging to the pentasil family of zeolites. It has a chemical formula of $\text{Na}_n\text{Al}_n\text{Si}_{96-n}\text{O}_{192} \cdot 16\text{H}_2\text{O}$ ($0 < n < 27$) [7, 19]. MFI zeolites comprise several pentasil units linked by oxygen bridges to form pentasil chains. A pentasil unit includes eight five-membered rings. In these rings, the vertices are Al or Si, and an O is assumed to be attached between the vertices. The pentasil chains are interconnected by oxygen bridges to form corrugated sheets with ten-ring holes. Similar to the pentasil units, each ten-ring hole has Al or Si as vertices with an O assumed to be bound between each vertex. Each corrugated sheet is connected by oxygen bridges to form a structure with ten-ring straight channels running parallel to the corrugations and sinusoidal ten-ring channels running perpendicular to the sheets [19, 102]. MFI type zeolite coatings were synthesized on titanium and a titanium alloy (Ti-6Al-4 V) [103]. Adhesion to the titanium substrate section can be created based on the arranged structure of the MFI zeolite. The proposed zeolite showed potential to prevent the release of toxic ions by trapping them in its micro cages and prevented or reduced the release of Al and V ions into human tissue [104].

Avery *et al.* prepared a synthetic silica MFI film to evaluate its use as a lysozyme adsorption structure. This type of synthetic silica-based aluminosilicate can also be considered for use in peripheral medical devices. Although the orientation of the zeolite crystals did not have a significant role in the sorption process, incubation volume and time both impacted sorption [105].

Bone grafting is a routine orthopedic surgical procedure that can facilitate bone formation in bone defects or sections with bone-healing complications. A noticeable problem after bone grafting is postoperative recipient graft site infection, with a high mortality rate and necessitating the increased use of drugs and medical resources. Zeolites show potential in such situations because of their neutral cytotoxicity and bone-like characteristics. Guo *et al.* used the ZSM-5 zeolite as an additive that was synthesized by using a hydrothermal method. The disk-like shape of ZSM-5 zeolites and their 100-nm thickness and 300-nm diameter enable them to encapsulate drugs inside their pores and release them slowly at a desirable rate to treat infections over a significant period of time [106]. The continuous release of gentamicin from ZSM-5 zeolites reduced both bacterial adhesion and biofilm formation substantially. Hence, the gentamicin-loaded ZSM-5 zeolites could be useful DDSs for the treatment of implant-associated infections because of their high biocompatibility, pore size distribution, and functional groups [106].

Hydrothermally synthesized ZSM-5 zeolites, with specific $\text{SiO}_2\text{:Al}_2\text{O}_3$ ratios, have potential as mesoporous drug delivery nanostructures and have been studied to evaluate their release properties for 5-FU. All release profiles showed that 50% of the drug was released to the tissue media in the first 15 min after injection. This was likely because of the 3D pore configurations of the ZSM-5 zeolite and drug coatings in the opening of the pores. By contrast, this kind of zeolite caused a secondary slow release of 5-FU that lasted 2–4 h, related to the drug molecules being deeply adsorbed into the micropores of the zeolite.

successfully developed a ZSM-5–DOX–chitosan composite with an pH sensitivity that was exploited to regulate its release behavior in cancerous and noncancerous cells. The cancerous milieu is more acidic than normal tissue milieu; hence, in the acidic tumor cells, chitosan dissolved, releasing DOX quickly and efficiently. This composite also showed a significantly lower rate of DOX release in healthy tissues because it was unable to diffuse out of the pores of the zeolite. This appropriate drug-release behavior of zeolites is the result, in addition to their porous structures, particle size distribution and surface functionalization, of their enhanced permeability and retention (EPR) effect, modulated drug distribution profiles, long-lasting circulation time, and their adequate intracellular penetration because of their nanometer size (Fig. 2) [108].



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Figure 2. Anticancer drug delivery for cancer therapy using zeolites. Synthesis of zeolite-based drug carrier systems against osteosarcoma: (a) preparation of zeolites by hydrothermal method; (b) formation of hollow zeolites using desilication technology; (c) loading drug and chitosan (CS) coating; (d) cellular uptake of zeolites by tumor cells; and (e) tumor cell apoptosis induced by doxorubicin release from zeolites. Reproduced, with permission, from [108].

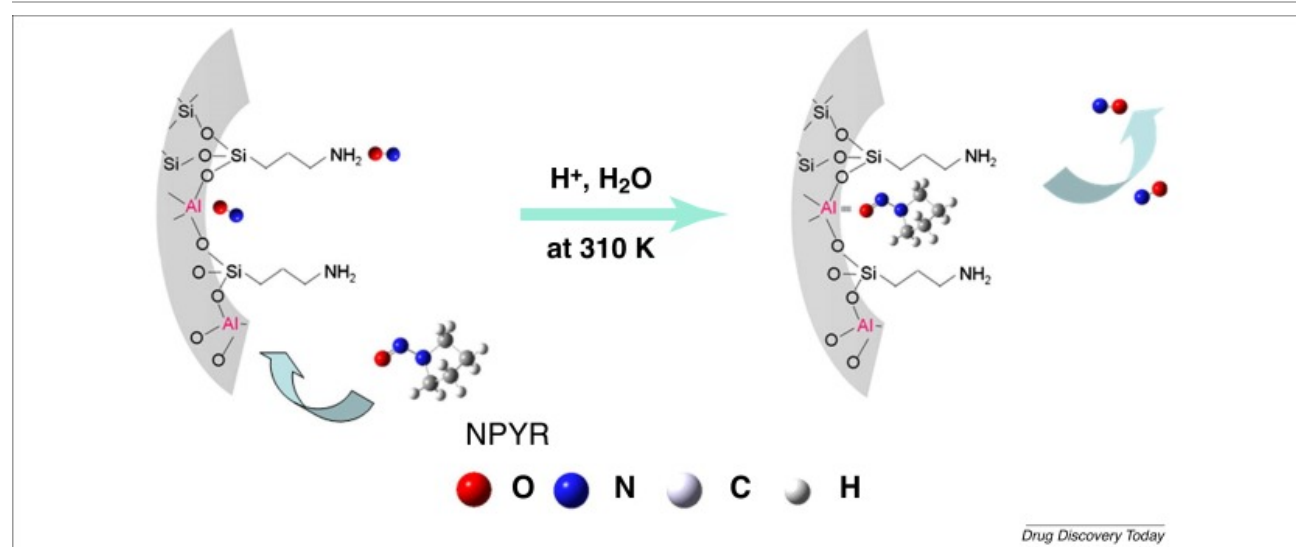
Microneedles based on microporous zeolites have also been fabricated for transdermal drug delivery. Polymer-templated zeolitic microneedles were formed through a UV exposure crosslinking procedure in which regular cylindrical pseudo MFI zeolite needles were shaped on a substrate of silicon. Such zeolite microneedles were tested for use for saline fluid delivery into fresh pig skin. This microneedles displayed better penetration because of the smaller particle size of the zeolites, which enabled them to cross the tissue barriers and effectively guide the drug to its desired destination, where polymer composites presented lower cross-diffusion because of their bigger unit sizes and longer chains, restricting their diffusion rate [109, 110].

MFI-type borosilicate zeolites with a variable Si/B content were combined in a hydrothermal procedure by utilizing silicic acid and sodium tetraborate decahydrate. The authors examined the synthesized borosilicate zeolites as DDSs for the delivery of DOX. The results indicated that the quantity of released drug increased by reducing the pH. *In vitro* tests of the samples based on MTT tests showed that the amount of boron could be regulated by different synthesis parameters, such as adjusting the pore size according to the diameter of the drug by altering the crystallization time and precursor gel pH. Thus, borosilicate particles with well-organized rectangular-shaped nanocrystals and large external surface area demonstrated higher drug delivery capacities [111]. The drug loading volume of boroferrosilicates with varying Fe/B contents developed using a hydrothermal procedure was investigated with DOX. The loading yield was reduced by enhancing the iron ratio: for specimens with Fe/B = ∞, the loading yield increased significantly. However, given the interaction between drug and heteroatom-substituted zeolites, the release amount was low. Although zeolite pores showed a high degree of absorption, the release rates were not c

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Fe/B, because the desorption of DOX molecules from surface of the zeolites was prevented by the strong interaction of the drug molecules and the surface of the heteroatom-changed zeolites; thus, the release rate for all boroferrisilicate zeolites is assumed to be low [112].

Chemotherapy is an important treatment for metastatic cancer, but often results in significant adverse effects on nontarget tissues. In a recent study, the combination of mesoporous ZSM-5/CS/DOX nanodisks as DDSs for osteosarcoma was investigated. The pH-responsive ZSM-5/CS/DOX nanodisks showed a high drug loading output and quickly delivered DOX to acidic target tissues, such as tumor cells. In addition, as reducing the tumor growth rate, these pH-responsive zeolite drug carriers also demonstrated fewer adverse effects, particularly cardiac toxicity, which was confirmed by pharmacokinetic studies, serological examinations, and H&E staining assays. Thus, the ZSM-5/CS/DOX nanodisks could be useful pH-responsive drug carriers for targeted cancer therapy [113]. Delivery of NO and simultaneous absorption of nitrosamine by MFI zeolites in a proposed digestive system have also been evaluated. Three types of aluminosilicate zeolites, including HZSM-5 zeolites, mesoporous zeolites, and mesoporous MCM-41 silica, were shown to transfer and absorb NO particles in gastric tissues (Fig. 3). Investigation of the influence of the amount of (3-aminopropyl)triethoxysilane (APTS) on the structure of zeolite pores and morphological state of silica and other mesoporous samples showed that hierarchical zeolites have a crucial role in the controllable modification of APTS, where numerous amino propyl groups can be grafted in mesopores while the aluminosilicate structure is maintained. The resulting structure exhibited the potential to release NO and consequently adsorb nitrosamines [114].



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Figure 3. Nitric oxide (NO) release and nitrosamine capture by an amino propyl-functionalized silica matrix in gastric fluid. Reproduced, with permission, from [114].

BEA-type Zeolites

Zeolite beta is an old zeolite discovered before Mobil began the ‘ZSM’ naming sequence. As the name implies, it was the second in an earlier sequence. The structure of zeolite beta was only recently determined because the structure is complex and interest only increased in it once it had become important for dewaxing operations. Zeolite beta comprises an intergrowth of two distinct structures: Polymorphs A and B. The polymorphs grow as 2D sheets and the sheets randomly alternate between the two. Both polymorphs have a 3D network of 12-ring pores. The pores in two of the dimensions are not significantly impacted by the intergrowth of the polymorphs; however, the pore becomes tortuous in the direction of the faulting, although it does not become blocked [19, 115].

In some cases, zeolites can improve the physical behavior of the DDS to effectively transfer drugs that cannot be delivered in normal conditions alone. For example, Karavasili *et al.* investigated the ability of BEA zeolites to facilitate the dis

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nifedipine, which is poorly soluble and is associated with numerous difficulties in terms of its local delivery. The data showed a complete encapsulation rate for the drug in the presence of the zeolite and an increase in drug delivery in both gastric and intestinal environments compared with direct utilization of the drug. The positive effect of the DDS was attributed to the availability of a more active surface area in the zeolites compared with the simple drug absorption route; this increased surface area slowed the aggregation of the drug particles and resulted in their amorphization [116]. Karavasili *et al.* studied three synthetic zeolite types (BEA-ZSM-NaX) to understand their effect on the solubility of indomethacin and its release characteristics when it was coated inside the zeolites. Drug delivery analysis indicated that the release rates of this highly insoluble drug were well regulated by zeolites with different microstructures, whereas cytocompatibility tests showed that these zeolite particles had no toxic effects on human cells *in vitro*; thus, these zeolites could be suitable DDSs because of their fine pore size and active outer surface area [117]. Mitoxantrone-loaded beta zeolite nanoparticles also showed significant cytotoxic effects on cancer tissues. Mitoxantrone is thought to attach to the zeolite via interactions in the b-hydroxyketone of the anthraquinone framework of the drug with zeolite aluminum, where relatively strong binding enables the drug to be released slowly [118]. Molecular dynamics (MD) have also been used to understand the diffusion rates of salbutamol and theophylline inside BEA zeolites. MD analysis revealed that the salbutamol and theophylline presented different diffusion patterns, with salbutamol diffusing more freely compared with theophylline. The authors suggested that modeling should be used more proactively when designing and analyzing zeolite–drug combinations ahead of any experimental investigation. Nevertheless, BEA zeolites show significant potential as DDS and for use in other bioapplications [119]. Table 2 summarizes the properties and performance of the various zeolites discussed in this review.

Table 2. General perspectives on the properties and performance of different forms of zeolite^a

Structure	Zeolite type	Biological properties				Chemical properties		Physical properties			
		Biocompatibility	Antibacterial	Drug delivery	Wound dressing	Coatability	Adsorption	No. of rings	No. of dimensions	No. of channels	Pore size (Å)
Synthetic											
LTL	Zeolite L	✓	×	✓	×	×	✓	12	3	1	7.1 Å
LTA	Zeolite A	✓		✓	✓	✓	✓	8	3	1	4/1 × 4/1
MFI	ZSM-5 Zeolite	✓		✓	×	✓	✓	10	3	2	5/1 × 5/5; 5/3 × 5/6
FAU	Zeolite X	✓	×	✓	×	×	×	12	3	1	7/4 × 7/4
	Zeolite Y	✓		✓	✓	×	✓	12	3	1	7/4 × 7/4
BEA	Beta zeolite	✓	×	✓	×	×	✓	12	3	2	6/6 × 6/7; 5/×5/6
Natural											
HEU	Clinoptilolite	✓	✓	✓	✓	×	✓	8	2	3	3/1 × 7/5; 3/6 × 4/6; 2/8 × 4/7
MOR	Mordenite	✓	×	✓	×	×	✓	12	1	2	6/5 × 7; 2/6 × 5/87
CHA	Chabazite	✓	×	✓	×	×	×	6	2	3	3.8 × 3.8; 3.8 × 3.8; 3.8 × 3.8

a

Data from [19].

Concluding remarks: challenges and future directions

Despite the numerous advantages of zeolites as DDS, the usage of such systems have been associated with some challenges. One of the main challenges is controlling the release profile, for which the main mechanism is diffusion. The pore size of zeolites is usually larger than that of the drug molecules or particles, which can then be released rapidly as a result. Therefore, the textural characteristics of the zeolite should be modified to achieve a controlled release profile [29, 120]. In addition, some zeolites might also induce cytotoxic and carcinogenic effects. As a brittle and wool-like fibrous zeolite, erionite has similar properties to asbestos and results in lung cancer and malignant mesothelioma. The cytotoxicity of erionite affects the cytosol and, at nucleus level, results in cell necrosis [121, 122]. Other fibrous zeolites, such as offretite and skolecite, might also exhibit cytotoxicity that disrupts the cell structure and results in swollen mitochondria and squared cells [123]. NaA zeolites perturb mineral metabolism and tissue mineral composition, and Al can be detected in all tissues and Si concentration can be increased in spleen, muscle, aorta, lung, and kidney tissues [124].

The addition of clinoptilolite to cell culture media in the form of nanoparticles can increase cell apoptosis and decrease DNA synthesis. Thus, such zeolites can be used as adjuvant cancer treatments if they can be delivered to cancerous cells. Clinoptilolite decreases the activity of epidermal growth factor receptors, and also the activity of PKB/Akt and NF- κ B, as a result of its adsorptive and ion exchange features [125]. EGF reduction by such zeolites influences the calcium level, impacting signaling pathways [126]. Moreover, clinoptilolite decreases protein kinase B expression, induces the expression of p21WAF1/CIP1 and p27KIP1 tumor suppressor proteins, and blocks growth in several cancer cell lines [42]. However, higher dosages of clinoptilolite can cause inflammatory responses in the intestine and damage the intestinal barrier. This type of inflammatory reaction is mediated by the increase in CD4-positive and CD25-positive T and B lymphocytes and by higher serum concentrations of IL-2 and IL-10 [127].

As a porous structure, zeolites have attracted significant research attentions in DDSs, because of the ability to enhance their loading capacity and control the drug release rate. Zeolites are able to carry different types of drugs and biological molecules to targeted tissues and organs. Surface modification can endow zeolites with various attributes that can be utilized in drug delivery. It is expected that research on the surface modification of zeolites will be expanded in the future specially for cancer therapy. Some innovative surface modifications can not only enhance the delivery ability, but also induce specific therapeutic characteristics based on the composition of the materials used. Moreover, adjusting the particle size of the zeolites enables them to enter living cells. This class of materials can be also used as theragnostic agents for therapeutic and imaging applications.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Glossary

Andesite

an extrusive igneous, volcanic rock, of intermediate composition, with an aphanitic to porphyritic texture.

Basalt

mafic extrusive igneous rock formed by the rapid cooling of magnesium-rich and iron-rich lava exposed at or very near the surface of a terrestrial planet or a moon; >90% of all volcanic rock on Earth is basalt.

Chabazite

tectosilicate mineral of the zeolite group, closely related to gmelinite; formula $\text{Al}_2\text{Si}_4\text{O}_{12} \cdot 6\text{H}_2\text{O}$; recognized varieties include Chabazite-Ca, Chabazite-K, Chabazite-Na, and Chabazite-Sr, depending on the prominence of the indicated cation.

Clinoptilolite

(from the heulandite group); the most common and suitable natural zeolite for commercial and industrial applications.

Drug

delivery systems (DDSs): drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect.

Mesoporous

containing pores with diameters between 2 and 50 nm, according to IUPAC nomenclature.

Mordenite

zeolite mineral with the chemical formula, $\text{Al}_2\text{Si}_{10}\text{O}_{24}\cdot 7\text{H}_2\text{O}$. It is one of the six most abundant zeolites and is used commercially.

Nanotechnology

science, engineering, and technology conducted at the nanoscale ($\sim 1\text{--}100\text{ nm}$).

Orthorhombic

in crystallography, the orthorhombic crystal system is one of seven crystal systems. Orthorhombic lattices result from stretching a cubic lattice along two of its orthogonal pairs by two different factors, resulting in a rectangular prism with a rectangular base and height, such that a, b, and c are distinct.

Rhyolites

igneous, volcanic rock, of felsic composition. It can have any texture from glassy to aphanitic to porphyritic. The mineral assemblage is usually quartz, sanidine, and plagioclase. Biotite and hornblende are common accessory minerals. It is the extrusive equivalent to granite.

Tectosilicate

formerly called polysilicate; any member of a group of compounds with structures that have silicate tetrahedrons (each of which comprises a central silicon atom surrounded by four oxygen atoms at the corners of the tetrahedron) arranged in a 3D lattice.

Zeolite

any of a large group of minerals comprising hydrated aluminosilicates of sodium, potassium, calcium, and barium. They can be readily dehydrated and rehydrated, and are used as cation exchangers and molecular sieves.



Payam Zarrintaj is an experienced polymer engineer received his BSc degree from Amirkabir University of Technology, followed by a MSc (2013) and PhD (2018) from Tehran University. He is currently a postdoctoral research fellow at School of Chemical Engineering, Oklahoma State University. His research interests include smart hydrogel/polymers and nanoparticles with well-controlled microstructures and properties for biomedical applications.



Mohammad Reza Saeb was awarded a PhD in polymer engineering in 2008 by Amirkabir University of Technology (Tehran Polytechnic). After several years as an invited lecturer in different local academic centers, he was employed as a faculty member at the Institute for Color Science and Technology in 2013. His research focuses on the analysis of experimental outcomes using multicomponent polymer systems and principles of modeling and simulation of molecular-level events in polymer systems.



Masoud Mozafari is a fellow of Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto. His research focuses on the development of strategies to treat damaged tissues and/or organs. He is a recipient of the WIPO Medal for Inventors awarded by the World Intellectual Property Organization (WIPO) – the United Nations (UN), for inventions that significantly contribute to economic and technological development in the field of biomaterials.

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