Application of Zeolite in Cancer Therapy

Subjects: Oncology

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Zeolites and zeolitic imidazolate frameworks (ZIFs) are widely studied as drug carrying nanoplatforms to enhance the specificity and efficacy of traditional anticancer drugs.

zeolite | zeolitic imidazolate framework | cancer therapy | drug carrier | pH sensitive | doxorubicin | 5-fluorouracil | curcumin | cisplatin | miR-34a

1. Introduction

Zeolites are minerals with a tetrahedral crystalline structure formed by dense networks of AlO_4 and SiO_4 sharing oxygen atoms [1][2][3]. These aluminosilicate networks create regularly distributed micropores and cavities that range between 4–12 Å in size [4]. The pores and cavities can exchange water, ions, and polar molecules with the surrounding environment, giving zeolites unique ion exchange properties and absorption capacities [2]. Absorption may occur on both the outer and inner surfaces of the material and are governed by the ability of molecules to fit into the micropores [4].

Zeolites were first discovered in the 18th century by Swedish mineralogist Axel Fredrik Crønsted, who introduced the term “zeolite” from the Greek ζέω (zéō), meaning “to boil”, and λίθος (líthos), meaning “stone”, owing to their natural properties he described [4]. Nowadays, zeolites have a wide range of industrial, environmental, and biomedical applications [1][2][3][4][5] and are available as both natural minerals and artificially produced materials. Of the over 40 natural and 230 synthetic zeolites known [4][6], many are subjected to diverse applications that harness the porous characteristic, ion exchange property, and high adsorption capacity of zeolites [3][4][6]. In addition, zeolites possess channels and/or cavities linked by channels, which give it a unique structural feature over other aluminosilicate and crystalline materials.

2. Doxorubicin (DOX)

Doxorubicin (DOX), an anthracycline antibiotic with antineoplastic activity, is frequently used as an anticancer drug in chemotherapy. DOX acts on the human body by intercalating itself between the base pairs of the DNA double helix [7]. This inhibits topoisomerase II activity, prevents DNA replication, and ultimately hinders protein synthesis [8][7]. Despite its prevalence, however, DOX lacks the ability to target certain areas of the body and possesses strong cardiotoxic effects [9]. Therefore, a more effective delivery system is required to mitigate the side effects of DOX on the body.

2.1. The Effects of the pH-Sensitive ZIF-8 and Zeolites on DOX Release

Studies relating to the DOX-releasing properties of ZIF-8 are diverse in nature, but they share a commonality in that the high sensitivity of ZIF-8 to pH makes it possible to accurately release anticancer drugs in the acidic tumor microenvironment [10]. In the study of Tan et al. DOX was loaded into MnO_2@ZIF-8 and utilized a CCK-8 assay to determine that DOX/MnO_2@ZIF-8 can significantly reduce the viability of LLC cells. In addition, mice were subjected to DOX/MnO_2@ZIF-8 and demonstrated a reduction of tumor volume and increase of apoptotic cells. Therefore, MnO_2@ZIF-8 may serve as a nanocarrier of DOX in lung cancer treatment [11]. Sharsheeva et al. combined ZIF-8 with a semiconductor photocatalytic agent that induces a local pH gradient in response to external electromagnetic radiation. This system was found to release DOX in a quantity that successfully suppresses neuroblastoma cells [12]. Kang et al. encapsulated copper bismuth sulfide nanoparticles and rare-earth down-conversion nanoparticles into ZIF-8 before loading the platform with DOX. The encapsulated components were released in response to a change in pH, and a moderate dose inhibited 87.6% of tumors with x-ray irradiation [13]. Li et al. engineered silk sericin into ZIF-8 to overcome poor circulation stability and unexpected drug leakage into blood circulation, both issues that may limit the benefits of chemotherapy. The synthesized nanoplatform has tumor-specific biodegradability induced by the low pH environment, efficient drug uptake, and substantial tumor permeability effects [10]. Moreover, Yan et al. sought to overcome a drawback of ZIF-8, which has low affinity to non-electron rich drugs and lacks surface functional groups. The study modified DOX with a pH-sensitive linker containing two carboxyl groups, which can anchor itself to the ZIF-8 surface to form a prodrug. In an acidic tumor environment, the pH-sensitive linker is cleaved, which yields inherent benefits of more precisely controlling the release of DOX [9]. Finally, Lei et al. grew ZIF-8 on the surface of micelles to form a core-shell nanocomposite. The inner cavity of the micelle acted as a DOX-hydrochloride storage reservoir, while the outer ZIF-8 coating acted as a pH-controlled gatekeeper of drug release. The core-shell nanocomposite can not only be successfully internalized by cancer cells to release DOX under the acidic intracellular environment but can also present lower cytotoxicity compared to free DOX towards normal cells [14].

In addition to harnessing the pH sensitive properties of ZIF-8, ZSM-5, a type of zeolite, can also be used as pH-responsive drug delivery systems. One study fabricated hollow mesoporous ellipsoids with ZSM-5 and chitosan that can load DOX at a 95.8% loading efficiency. In in vitro experiments with healthy blood and tissue-simulating media, the ellipsoids slowly released DOX to the surrounding environment. In contrast, in tumor cells, the ellipsoids rapidly released DOX, which resulted in the considerable apoptosis of MG63 cancer cells [15]. ZSM-5 and chitosan were also combined to form nanodisks, which demonstrated a greater DOX loading efficiency of 97.7%. The nanodisk drug carriers efficiently inhibited tumors with minor side effects, especially in cardiac toxicity [16]. Therefore, both ZIF-8 and ZSM-5 can efficiently be used as pH-sensitive drug carriers to enhance the specificity of DOX release.

2.2. Dual Stimuli to Enhance DOX Release

Apart from solely relying on changes in pH for drug release, studies have utilized dual stimuli to further increase the specificity of the therapeutic platform [17][18][19][20][21]. Wu et al. explored this unique property of ZIF-8 by

synthesizing a pH-responsive nanoplatform that integrated polydopamine, which greatly increased the biocompatibility of ZIF-8 in cytotoxicity and in vivo acute toxicity evaluations. Under the dual stimuli of a near-infrared (NIR) laser and an acidic environment, the DOX release rate increased from 21% to 78% [17]. A similar study exploring the combined effects of pH and a NIR laser constructed ZIF-8 Janus nanoparticles with lactobionic acid-gold nanorods on CT image-guided synergistic chemo-photothermal theranostics. The unique method not only had numerous advantages in cancer imaging, but also significantly inhibited the tumors in vivo by releasing pre-loaded DOX [20]. NIR laser stimuli exhibit promising results not only with pH change, but also with ultrasound stimulation. The multimodal therapy allowed DOX@LTA zeolites to increase its therapeutic efficiency in the deep sites of tumors [18]. Overall, these three studies reveal that the dual integration of a NIR laser and other stimuli allows both zeolites and ZIFs to serve as effective DOX-releasing platforms.

Dual stimulation drug release was also investigated by combining the stimulatory effects of low pH and high levels of glutathione, a compound that is present in high concentrations in tumor cell microenvironments. In this study, molecularly imprinted polymer (MIP)-stabilized fluorescent ZIF-8 was more likely phagocytosed and more lethal to MCF-7 breast cancer cells compared to other cells and nanoparticles. In addition, MIP-stabilized fluorescent ZIF-8 had the best inhibitory effect on the growth of MCF-7 tumors in mice [21]. He et al. examined the control of light and pH on the DOX hydrochloride-releasing properties of Au@ZIF-8. This study demonstrated especially promising results, showing that Au@ZIF-8 with only 10 μM of DOX hydrochloride can result in 98% HeLa cell-killing activity after 30 min of light irradiation [19]. Overall, ZIF-8 as a drug delivery platform can be induced by a variety of stimuli, which further supports promising applications of the nanoplatform in cancer therapeutic delivery.

2.3. Co-Delivering DOX with Other Anticancer Drugs

ZIFs have also been demonstrated to co-deliver DOX alongside other therapeutics [22][23][24]. Multidrug resistance is one of the main causes of chemotherapy failure in cancer, with the primary reason being the overexpression of active efflux transporters such as the P-glycoprotein [24]. Co-delivering drugs through a zeolitic framework holds the potential of overcoming multidrug resistance and increasing the targeting ability of the drugs. Zhang et al. utilized methoxy poly(ethylene glycol)-folate stabilized ZIF-8 to efficiently co-deliver verapamil hydrochloride as a P-glycoprotein inhibitor along with DOX hydrochloride. The multidrug delivery system demonstrated much safer and more effective therapeutic properties and can be used as a promising formulation in reversing the multidrug resistance for targeted cancer therapy [24]. Shen et al. co-delivered two drugs with distinct properties—the hydrophilic DOX with the hydrophobic near-infrared photosensitizer dye IR780. The combined effects of the two drugs not only significantly improved the pH-responsive drug release of ZIF-90, but also facilitated precise drug delivery to CD-44 overexpressed tumors [23]. Finally, Yan et al. reported a unique approach to the dual-drug delivery system by loading a photosensitizer (chlorin e6) and DOX with the ZIF-8 coating layer on E. coli via the biomimetic mineralization method. MOF-engineered bacteria preserved its tumor selectivity and exhibited strong therapeutic effects in both in vitro and in vivo experiments [22].

2.4. Impact of MOF Size on DOX Delivery

Another important property to consider for MOFs in drug delivery is its size, which is commonly less than 200 nm to improve cellular uptake and blood-circulation time [25][26]. Yan et al. fabricated nanoscale size controllable and surface modifiable ZIF-8-poly (acrylic acid sodium salt) nanocomposites that ranged from 30 to 200 nm. These nanocomposites exhibited various crystallinity and pH sensitivity and retained their therapeutic efficacy when delivering DOX to cell lines and mice models [27]. Duan et al. proposed a one-pot, rapid, and completely aqueous approach to tune the size of DOX-loaded ZIFs. It was found that the 4T1 murine breast cancer cells tested were able to take up the DOX-loaded ZIFs in a size-dependent manner. In addition, an optimal size of 60 nm ZIF was shown to have longer blood circulation and over 50% higher tumor accumulation than its 130 nm counterpart [28]. Collectively the two studies showed that a biocompatible method to precisely control the size of ZIFs holds great potential in constructing multifunctional delivery systems for cancer theranostics and various other applications.

2.5. Impact of PLNPs on DOX Release

Persistent luminescent nanoparticles (PLNPs) have been incorporated into the metal-organic framework of ZIF-8 to form multifunctional theranostic nanoplatforms that can improve the effectiveness and accuracy of tumor treatments [29][30]. Lv et al. constructed a ZIF-8 shell with PLNPs that possessed the dual functionalities of tumor imaging and pH-responsive drug delivery. The loading content of DOX on the nanoplatform reached a high percentage of 93.2%, and the release of DOX was greatly accelerated in the acidic environments created by tumor cells [29]. Similarly, Zhao et al. reported the anticancer properties of DOX-incorporated ZIF-8 with PLNPs. The theranostic platform can not only play a critical role in tumor imaging, but also showed anticancer drug loading capacity, acidity-responsive drug release behavior, and significant anti-tumor effect [30].

2.6. Other Methods to Enhance Drug Release

Despite the advantages presented by ZIF-8 as a drug delivery system, it still possesses certain drawbacks, such as poor tumor targeting and short blood circulation time, that may reduce drug delivery efficiency [31]. To address this issue, a phosphorylcholine-based zwitterionic copolymer coated ZIF-8 nano-drug was developed. In the systemic circulation, the zwitterion can effectively extend blood circulation time to enhance tumor accumulation of the nanodrug. At the tumor site, the zwitterion can then rapidly convert to a positive charge, thereby enhancing tumor cellular uptake. This nanodrug is shown to have a 93.2% tumor inhibition rate on A549-bearing tumors with negligible side effects, suggesting great potential for this method of improving the efficiency of ZIF-8 [31].

In addition to the most common types of zeolites and ZIFs used, there are also some types, namely clinoptilolite and zeolite NaX, that have few previous studies on DOX release. For the first time, zinc-clinoptilolite/graphene oxide was fabricated and its cytocompatibility and drug loading capacity were investigated. The toxicity of the DOX-incorporated nanocomposite was also compared to that of pure DOX. The nanocomposite exhibited promising drug loading capacity and no toxic effects towards cells, especially below 16 mg/mL in concentration. In addition, the DOX-incorporated nanocomposite exhibited more cytotoxicity towards A549 lung tumor cells than free DOX [32]. Finally, magnetic zeolite NaX was combined with PLA/chitosan, Fe_3O_4, and/or ferrite with or without the presence of a magnetic field [33]. DOX loaded chitosan/PLA/NaX/ferrite with an external magnetic field after 7 days of

treatment killed the most H1355 cancer cells (82% cell death) compared to all the groups. Overall, preliminary studies show that clinoptilolite and zeolite NaX also possess great potential in drug delivery and should be a topic of further investigation.

3. 5-Fluorouracil (5-FU)

5-fluorouracil (5-FU), an antimetabolite drug, is widely used in the treatment of cancer. 5-FU inhibits the activity of thymidylate synthase and incorporates its metabolites into RNA and DNA, thereby exerting anticancer effects [34]. Incorporating 5-FU into ZIF-7 modified with both metal ions and organic ligands showed a synergistic therapeutic effect in damaging the DNA and inhibiting the chemokine receptor 4 of esophageal squamous cancer cells [35]. In addition, Jiang et al. utilized pressure-induced amorphization to load a large amount of 5-FU into amorphous ZIF-8. Amorphous ZIF-8/5-FU was shown to have significant therapeutic efficacy in tumor-bearing mice due to less drug released during circulation, longer circulation time, and great biocompatibility [36]. Furthermore, Kulkarni et al. characterized 5-FU in the ZIF-8 framework using techniques such as FTIR, PXRD, Raman spectroscopy, EDX, and UV-NIR spectroscopy as well as morphological techniques such as SEM, TEM, and AFM [37].

Like those utilizing DOX, the ZIF studies incorporating 5-FU also harnessed the pH sensitivity of ZIF to produce a pH sensitive nanoplatform. Pandey et al. combined proteins, biopolymers, and ZIF-8 to construct a pH responsive nanoplatform for effective therapy against glioblastoma. In vitro cell line studies showed increased cancer cell cytotoxicity, which was further supported by the generation of cellular and surface reactive oxygen species by the nanocomposite [38]. Xiao et al. designed a novel ZIF-90@zinc oxide drug carrier that has a high 5-FU loading rate of 39%, which it will release in the acidic tumor microenvironment. Interestingly, the zinc oxide can decompose into Zn^{2+}, which acts as an alternative therapeutic agent to overcome potential tumor resistance to 5-FU [39].

In addition to ZIFs, studies have also investigated how the unique properties of different types of zeolites affect loading capacity and release potential of 5-FU [40][41]. Vilaca et al. studied the drug delivery properties of FAU (zeolite NaY and zeolite nano NaY) and Linde Type L on colorectal cancer cell lines. In the first 10 min, in vitro drug release studies showed that 80–90% of 5-FU were released from the zeolites [40]. In addition, the differing pore sizes of various types of zeolites (FAU, BEA, MFI, LTA) were demonstrated to influence the loading capacity and release profile of 5-FU [41][42]. Sagir et al. found that 5-FU loaded magnetite-zeolite nanocomposites effectively inhibited the proliferation of gastric cancer cells lines through apoptotic mechanisms in vitro and may be a beneficial therapeutic agent against cancer [43]. Finally, Abd-Elsatar et al. showed that the release of 5-FU from zeolites (ZSM-5, zeolite A, FAU) are also pH dependent. The drug release occurred in two stages, and there was a significantly higher concentration of drugs in the more acidic media of gastric solution (pH 1.6) compared to a mildly acidic one (pH 5) [44]. Overall, 5-FU loaded zeolites hold as great a potential as 5-FU loaded ZIFs, and further animal studies should be conducted to determine its tumor inhibiting effects in vivo.

4. Curcumin

Curcumin, a natural phenolic drug extracted from turmeric, holds strong bioactive molecules known as curcuminoids to reduce cancers at the initial, promotion, and progression stages of tumor development [45][46]. Curcumin acts on cancers by blocking growth enzymes, modulating cellular progressions, and inhibiting lipid peroxidation and reactive oxygen species production [46]. Despite the promising anticancer effects of curcumin, the drug is poorly soluble in aqueous solutions, resulting in poor bioavailability that is somewhat mitigated by a very high dosage in oral formulations [45]. This traditional method of curcumin administration is not optimal; thus, a new route should be explored to enhance the drug's efficacy. Zeolite may serve as a potential pharmaceutical carrier to increase the dissolution of curcumin as a therapeutic agent.

The surface properties and morphology of curcumin-loaded zeolite 5A was examined by Abadeh et al. using scanning electron microscopy (SEM), powder X-ray diffraction (XRD), differential scanning calorimetry (DSC), and UV-vis spectroscopy. These tests showed promising results by verifying the presence of curcumin in the zeolite framework, thereby supporting the potential use of the nanoplatform in targeted cancer therapeutics [45]. Curcumin-loaded nanoscale ZIF-8 (nZIF-8) and ZIF-8 were reported to have high drug encapsulation efficiency, good chemical stability, and fast drug release in the acidic tumor microenvironments. In addition, both nZIF-8 and ZIF-8 promoted cellular uptake of curcumin, which resulted in higher cytotoxicity towards HeLa cells [47][48]. Similar findings in antitumor efficacy were found in in vivo anticancer experiments of curcumin/nZIF-8 on mice [47]. The results indicate that curcumin-incorporated zeolites and ZIFs have great potential as efficient carriers for passive tumor therapy in future cancer treatments.

5. Cisplatin

Cisplatin is a chemotherapy drug that crosslinks with DNA's purine bases to cause DNA damage and interfere with its repair mechanisms, thereby inducing apoptosis in cancer cells [49]. Cisplatin-loaded ZIF-90 with mitochondrial targeting was shown to have higher cellular uptake and less toxicity than cisplatin alone towards epithelial ovarian cancer cells. Incorporating cisplatin into ZIF-90 can also increase the specificity of drug release by producing a pH- and ATP-responsive nanoplatform [50]. In addition, the drug is often used in combination with other anticancer compounds to overcome tumor drug-resistance and reduce the inherent toxicity of the compound [49]. For example, cisplatin can be co-delivered with oleanolic acid to reverse multidrug resistance and induce apoptosis. Co-delivering the two drugs together in ZIFs yielded greater cancer cell death than the free drugs alone or mono delivery systems [51].

6. miR-34a

MicroRNAs (miRNAs) have become part of a promising class of nucleic acid drugs due to its vital role in miRNA modulation therapy. However, there are certain delivery challenges, mainly due to in vivo instability and low delivery efficiency, that impede the advancement of miRNA therapy [52]. Studies have incorporated miR-34a, a tumor-suppressing microRNA, into zeolites/ZIFs to enhance the tissue-specificity and safety of microRNA modulation therapy [53][52]. These novel nanoplatforms were successfully fabricated both with ZIF-8 and ZSM-5,

thus demonstrating good biocompatibility in both ZIFs and zeolites. Release of the miR-34a-mimic@ZIF-8 complex decreased Bcl-2 expression at both mRNA and protein levels and promoted cellular apoptosis [52]. In vivo mouse model experiments also revealed miR-34a-mimic@ZIF-8 as a promising nanoplatform that can inhibit tumor growth via synergistic gene/chemodynamic therapy [52]. Incorporating miR-34a into ZSM-5 showed similarly promising results both in vitro and in vivo by inhibiting target oncogenes such as AEG-1 and SOX-9 [53]. Overall, miR-34a is a powerful candidate for cancer treatment, and incorporation of the miRNA into zeolites/ZIFs can mitigate the delivery challenges that miRNA therapy faces.

7. Miscellaneous Drugs

In addition to DOX, 5-FU, curcumin, cisplatin, and miR-34a, a variety of other drugs have been studied with zeolites/ZIFs acting as nanocarriers, with ZIF-8 being the most popular choice. Faraji Dizaji et al. loaded Paclitaxel into zeolite (ZSM-5) and MOFs (MIL-101 and ZIF-8) and saw that the MOFs had higher loading and more sustained release of the drug compared to their zeolite counterparts [54]. ZIF-8 can also be successfully used to deliver camptothecin [55], arsenic trioxide species [56], rapamycin [8], RNase A [57], gemcitabine [58], melittin [59], and lactate oxidase & Fe_3O_4 nanoparticles [60]. The nanoplatforms modified by camptothecin, arsenic trioxide, and rapamycin showed excellent pH-responsive hydrophobic anticancer drug delivery [8][55][56]. ZIF-8 is especially promising in delivering melittin, a hemolytic peptide whose conventional clinical applications are severely restricted due to its nonspecific hemolysis properties. The formation of a melittin@ZIF-8 complex can efficiently inhibit the hemolysis bioactivity of melittin until the nanocarrier reaches the desired location of a tumor microenvironment. This greatly increases the efficacy of the melittin@ZIF-8 complex towards the targeted induction of cancer cell apoptosis and tumor inhibition [59]. Zhou et al. simultaneously loaded lactate oxidase and Fe3O4 nanoparticles into ZIF-8 for a dual-modal therapeutic role. The combined effects of the two compounds is able to provide a simple, safe, and effective method to suppress rapid tumor growth and kill tumor cells [60].

In addition to ZIF-8, Zeolite Y (faujasite) has also been used as a popular carrier in anticancer drug delivery research. Amorim et al. investigated the suitability of α-cyano-4-hydroxycinnamic acid (CHC), an experimental anticancer drug, in zeolite NaY and zeolite NaA (LTA). CHC@zeolite exhibited up to 585 times the cytotoxic effects of the non-encapsulated drug, indicating its great potential in enhancing the effects of CHC [61]. Zeolite NaY was also successfully used to incorporate docetaxel, an anticancer drug, and protoporphyrin IX, a photosensitizer in a combined therapy using photodynamic therapy and chemotherapy [62]. Finally, zeolite Y was loaded with temozolomide (TMZ), a chemotherapeutic drug conventionally used to treat glioblastoma brain tumors. However, TMZ@zeolite Y did not have as strong of a cytotoxic effect as TMZ@mordenite, a natural zeolite [63]. Other natural zeolites that have been investigated are clinoptilolite, chabazite, and natrolite, which possess inherent cytotoxic properties and can reduce colorectal cancer Caco2 cell viability by 30, 40, and 60%, respectively. The toxicity of clinoptilolite and chabazite can be enhanced to 57 and 60%, respectively, with the binding and subsequent release of binase [64]. Clinoptilolite has also been modified with quercetin and quercetin dihydrate, both pharmaceutically active flavonoids. Although both drugs showed enhanced cytotoxicity, quercetin dihydrate@clinoptilolite showed greater cytotoxicity than quercetin@clinoptilolite [65]. Overall, drug-

loaded natural zeolites also possess strong anticancer properties like their synthetic counterparts, and further research should be conducted to compare the difference in effectiveness of natural and synthetic zeolites in delivering various anticancer drugs.

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