

Review

Present and Future of ZrO₂ Nanostructure as Reservoir for Drug Loading and Release

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Abstract: Extensive research has been conducted on ZrO₂ nanostructures due to their favorable biocompatibility, low toxicity, and promising prospects in various biomedical applications. They can be used as drug carriers, facilitating the administration of therapeutic substances into the body while enhancing their effectiveness and safety. This is achieved by regulating the timing, location, and rate at which drugs are released within the body. Several factors can influence the effectiveness of drug loading onto ZrO₂ nanostructures, such as the physicochemical characteristics of the drugs, the surface properties of the ZrO₂ nanostructures, and the specific methods used for drug loading. A wide range of drugs may be loaded onto ZrO₂ nanostructures including anti-cancer drugs, antibiotics, anti-inflammatory drugs, antifungal drugs, anti-osteoporotic drugs, etc. The release kinetics of drugs can be influenced by different factors, such as the size and shape of ZrO₂ nanostructures, the pH and temperature of the release medium, and the characteristics and molecular weight of the specific drug being released. While ZrO₂ nanostructures have demonstrated significant potential as drug delivery systems, further research on these structures is essential to optimize drug loading and release strategies.

Keywords: ZrO₂ nanostructures; biocompatibility; drug delivery system



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1. Introduction

Drug delivery systems are designed to enhance the therapeutic efficacy of drugs by controlling the delivery of the active ingredient to the target site in the body [1–5]. Traditional drug formulations such as pills, capsules, and injections often suffer from low bioavailability, short half-life, and off-target toxicity, leading to suboptimal treatment outcomes and patient dissatisfaction [6–8]. Drug delivery systems aim to overcome these challenges by providing targeted and sustained drug delivery, reducing side effects, and improving patient compliance [1–5,9–11]. The primary objective in drug delivery is to optimize the effectiveness of medications by efficiently transporting and releasing them (through passive or active means) to the intended location within the body. At the same time, it is crucial to minimize the unintended accumulation of the drug in non-target areas [12]. Drug delivery systems can take many forms, ranging from simple to complex, and can be designed to meet specific therapeutic needs [8]. For example, drug delivery systems can be engineered to improve drug solubility, stability, and bioavailability, or to target specific cells or tissues, such as cancer cells or infected cells [13,14]. They can also be designed to provide controlled release of drugs over time, or to respond to external stimuli such as temperature, pH, or light [12,15].

The development of drug delivery systems has revolutionized the field of medicine, enabling the delivery of drugs to previously inaccessible sites and improving the treatment of many diseases [16–18]. Drug delivery systems have been used to treat a wide range of conditions, including cancer, cardiovascular disease, neurological disorders, and infectious diseases, among others [19–21].

ZrO₂ nanostructures have emerged as a promising drug delivery platform due to their unique properties, such as high surface area, biocompatibility, and tunable surface chemistry [22–25]. The following sections will provide a more detailed overview of ZrO₂ nanostructures as drug delivery vehicles, including their properties, drug loading strategies, drug release mechanisms, and biomedical applications.

Zirconia (ZrO₂) is a biocompatible ceramic material that has attracted significant interest as a drug delivery platform because of its characteristics [26–28]. ZrO₂ nanostructures, in particular, have shown great potential as drug carriers due to their high surface area-to-volume ratio, which allows for high drug loading capacity and controlled release of drugs [22,29,30].

The key points for properties and characteristics of ZrO₂ are listed in Table 1.

Table 1. The key points for properties and characteristics of ZrO₂.

A. Properties of ZrO ₂ Nanostructures [31]	B. Drug Loading Strategies for ZrO ₂ Nanostructures [32–34]	C. Drug Release Mechanisms from ZrO ₂ Nanostructures [35,36]	D. Biomedical Applications of ZrO ₂ Nanostructures as Drug Delivery Vehicles [22,30,37–40]
High surface area Tunable surface chemistry Biocompatibility	Physical adsorption Covalent bonding Electrostatic interactions	Diffusion-controlled release Degradation-controlled release Stimulus-responsive release	Cancer therapy Bone regeneration & Dental applications Wound healing

Based on its structure and band gap ZrO₂ is an important luminescent material with good optical transparency with a high surface area with plenty of oxygen vacancies [41].

Depending on the synthesis procedure polymorph phases can be amorphous, tetragonal, and monoclinic usually as a function of calcination temperature. ZrO₂ is easily functionalized, and such a process enhances the antimicrobial effect in a specific way [42,43].

It is mentioned that various crystalline phases act differently in biological applications having various cell responses [44].

The surface of ZrO₂ nanostructures can be functionalized with various functional groups, such as amino, carboxylic, and thiol groups, which can be used for drug conjugation or electrostatic interactions with drugs (Figure 1) [45,46]. The functional groups used in the functionalization of ZrO₂ nanostructures provide versatility in conjugating other molecules, improving stability [23], targeted delivery, solubility, controlled release, and surface modification, thereby expanding their applications in various fields, including medicine, biotechnology, and materials science [47–49].

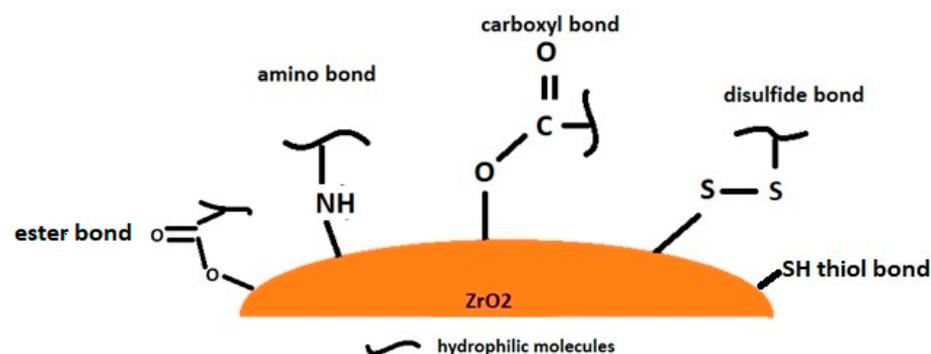


Figure 1. Functionalization of the surface of ZrO₂ nanostructures with functional groups.

The purpose of various functional groups is to enhance biological performance by altering surface properties. As it is well known, the dose increases to improve antibacterial activity is leading some times to more toxicity [50]. Taking into account that nowadays we are living with more aggressive and more resistant bacteria, functionalization with various groups should be a solution [51].

The functional groups enable the conjugation of other molecules through different types of reactions. The specific reaction used to conjugate other molecules to ZrO₂ nanostructures depends on the functional groups involved. For example, carboxyl groups can

react with amino groups through peptide bond formation or with hydroxyl groups through esterification. Amino groups can react with reactive carbonyl groups through reductive amination or with maleimide groups through thiol-maleimide coupling. Thiol groups can undergo thiol-ene or thiol-disulfide exchange reactions [52–54].

There are several types of nanostructures of zirconium dioxide (ZrO_2), including nanoparticles, nanorods, nanotubes, and nanowires [55–57].

One specific type of ZrO_2 nanostructure that has garnered attention is nanotubes. As ZrO_2 nanotubes, titanium dioxide (TiO_2) nanotubes have also been extensively studied for their potential use in various applications such as sensors, photocatalysis, and drug delivery [58]. While both materials share some similarities in terms of their properties and applications, there are also notable differences between them. For example, TiO_2 nanotubes have a lower band gap energy compared to ZrO_2 nanotubes [59].

The nanotubes obtained on TiZr alloy surfaces using anodization had varying sizes and lengths depending on the anodization conditions and the presence of the nanotubes on the TiZr surface enhanced its antibacterial properties against both Gram-positive and Gram-negative bacteria. These findings could have potential applications in the development of antibacterial coatings for medical implants and devices [60].

The chitosan-coated TiZr nanotubes and nanopores can serve as drug reservoirs (ex: gentamicin), with the ability to control drug release by adjusting the pore size and chitosan coating thickness. The biocompatibility of the chitosan-coated TiZr nanotubes and nanopores makes them a promising candidate for drug delivery applications, having great potential for use in biomedical applications [61].

The formation of nanochannels on a TiZr alloy using an anodization method and their effects on improving the biological response of the material were investigated. The results showed improved hydrophilicity and corrosion resistance of nanochannels compared to compact oxide layers. In vitro experiments on macrophages suggest that the nanochannel architecture may reduce the foreign body reaction against Ti50Zr implants by limiting macrophage proliferation and fusion and thus lowering the inflammatory response. The high aspect ratio of the nanochannels also presents an opportunity for the incorporation of surface biomolecules such as anti-inflammatory drugs or growth factors to further enhance tissue integration [62,63].

The effect of varying anodization potentials on the formation of nanopores and nanotubes on a titanium-zirconium (TiZr) alloy was studied and the results show that the morphology and size of the nanostructures can be controlled by adjusting the anodization potential. The surfaces of all samples were superhydrophilic, and higher applied potentials led to a more amorphous structure and smaller crystal dimensions. The roughest surface was found to have the highest antibacterial effect, with nanotubular areas having approximately 2.5 times the antibacterial index of nanopores surfaces. These results suggest that the nanotubular structure is better suited for orthopedic and dental implant applications, as it has promising bioperformance compared to other structures [64].

The aim of this paper is to provide a comprehensive overview of the present and future use of ZrO_2 nanostructures as reservoirs for drug loading and release and to explore the significance of drug delivery systems and the potential of ZrO_2 nanostructures for biomedical applications. Furthermore, the challenges of using ZrO_2 nanostructures as drug-delivery vehicles will also be presented.

2. Properties of ZrO_2 Nanostructures

2.1. Overview of ZrO_2 Nanostructure Synthesis Methods

Zirconia (ZrO_2) is a versatile material that has found numerous applications in various fields, including drug delivery, due to its physicochemical properties [65]. ZrO_2 nanostructures can be produced by several techniques, such as sol-gel, hydrothermal, and microwave-assisted synthesis [66–71] (Figure 2).

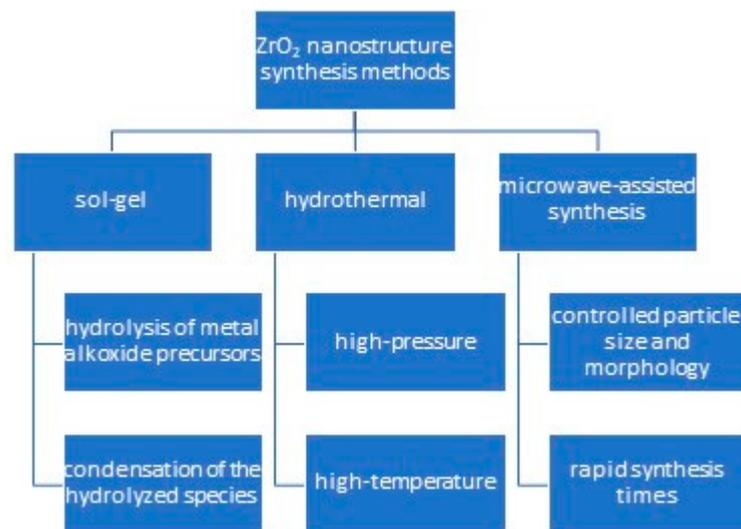


Figure 2. Methods of synthesis for ZrO₂ nanostructures.

Sol-gel synthesis is a simple and versatile method that involves the hydrolysis of metal alkoxide precursors, followed by the condensation of the hydrolyzed species to form a colloidal suspension. The sol-gel method allows for the synthesis of ZrO₂ nanostructures with controlled particle size, shape, and crystallinity and has been widely used for the synthesis of ZrO₂ nanoparticles and nanocrystals [72,73].

Hydrothermal synthesis involves the use of a high-pressure and high-temperature aqueous solution to promote the nucleation and growth of ZrO₂ nanostructures [69,70]. Hydrothermal synthesis allows for the synthesis of ZrO₂ nanostructures with a narrow size distribution, high purity, and controlled morphology and has been used for the synthesis of ZrO₂ nanorods and nanotubes [69,74].

A facile and cost-effective method for the synthesis of ZrO₂ nanosheets is by using a solvothermal technique. The synthesized ZrO₂ nanosheets were characterized by various techniques, including X-ray diffraction (XRD), transmission electron microscopy (TEM), scanning electronic microscopy (SEM), and High-resolution transmission electron microscopy (HRTEM), which confirmed their unique structure and morphology. The synthesized ZrO₂ nanosheets showed potential for use in various applications, such as catalysis, energy storage, and biomedicine [75].

Microwave-assisted synthesis is a relatively new method that involves the use of microwave irradiation to promote the synthesis of ZrO₂ nanostructures. Microwave-assisted synthesis offers several advantages over conventional synthesis methods, including rapid synthesis times and controlled particle size and morphology [71].

ZrO₂ nanostructures can also be synthesized using anodization techniques. Anodization involves the application of a voltage to a metal substrate, causing the formation of an oxide layer on the surface of the substrate. By controlling the anodization conditions, such as the voltage and electrolyte used, the thickness and morphology of the oxide layer can be tuned, leading to the formation of various nanostructures [76,77].

In the case of ZrO₂, anodization is typically carried out on a Zr foil in an electrolyte solution, such as an aqueous solution of H₂SO₄ [78].

Anodization is a simple and cost-effective method for the synthesis of ZrO₂ nanostructures and it allows for the fine-tuning of the morphology and surface chemistry of the nanostructures [79]. However, anodization is limited by the size of the substrate and the thickness of the oxide layer that can be formed [80].

The two-step anodization method can be used in order to obtain ZrO₂ nanotubes on TiZr alloy substrates. The nanotubes exhibited a high degree of uniformity and their size could be controlled by varying the anodization parameters. The ZrO₂ nanotubes

were found to have good biocompatibility and were able to support cell adhesion and proliferation [81].

Another simple and effective approach for the synthesis of ZrO₂ nanoparticles with high purity and crystallinity is the modified co-precipitation method. By modifying the experimental conditions, such as pH and temperature, the particle size and morphology can be controlled. The synthesized ZrO₂ nanoparticles exhibit excellent thermal stability [82].

The synthesis of ZrO₂ nanostructures is an active area of research and various methods have been developed to synthesize ZrO₂ nanostructures with different sizes, shapes, and properties. The choice of synthesis method depends on the desired properties of the ZrO₂ nanostructures and the specific application.

2.2. Explanation of the Structural and Chemical Properties of ZrO₂ Nanostructures

Zirconium (Zr), is a robust metal that possesses comparable chemical and physical characteristics to titanium (Ti) and makes it suitable for medical applications [83]. ZrO₂ nanostructures can be synthesized in various forms, including nanoparticles, nanorods, nanowires, and nanotubes, with sizes ranging from a few nanometers to tens of microns [84].

Post-treatments, such as annealing, significantly allow for the adjustment of roughness and adhesive properties to render the structures suitable for various biomedical applications. The annealed and reduced nanotubes exhibit distinct roughness and hydrophilic balance, with the latter increasing after reduction and decreasing after annealing. While these factors can affect performance, the study reveals only minor changes in cell response. These variations in roughness and wettability also have potential applications beyond the biomedical field [85].

Ti50Zr nanostructures fabricated via two-step anodizing as an alternative to Ti implants in dentistry, offer improved organization due to the nanotexture obtained through ultrasonication between the first and second anodizing steps. The final nanotube coatings exhibit a crystalline phase, with similar values for contact angle, adhesion, and antibacterial activity, but different mechanical properties due to changes in structure after annealing. The decrease in material hardness may be attributed to a decrease in density resulting from an increase in unit cell parameters [86].

The surface roughness parameters for TiZr nanotubes significantly increased after anodizing using a two-step procedure, while the mean adhesion force decreased. The post-treatment further reduced the adhesive properties of the surfaces, which could potentially prevent bacterial adhesion. The scratch hardness values of the coatings were lower than that of the uncoated substrate but still showed reliable mechanical resistance for various biomedical applications. The increase in surface roughness and the decrease in mean adhesion force are favorable for osseointegration and minimizing inflammatory processes at the tissue-implant interface, respectively [87].

When Zr was anodized in H₃PO₄, flake-as α -ZP structures were observed, which became more organized as the voltage was increased. At higher voltages, pores of ZrO₂ began to form. When glycerol was used, auto-organized nanotubes were observed and their formation was found to be directly related to the applied voltage. The type and homogeneity of the structures on the surfaces influenced the roughness, which can be correlated to the wettability and AFM micro adhesion forces and roughness values to some extent. Hydrophilic materials are commonly reported to exhibit better biocompatibility in orthopedic and dental implants due to their ability to enhance initial interaction with biofluids, which in turn promotes osseointegration. The roughness of a biomaterial plays a significant role in its wettability and subsequent cell interaction with the implant surface. These interactions ultimately impact the subsequent integration of tissues [88,89]. The proposed film-forming mechanism for α -ZP and ZrO₂ was based on the experimental data and was found to be correlated with the analyzed surface properties. These findings help in improving our understanding of the necessary properties for the development of thin films that are damage-tolerant and suitable for practical applications [90].

The nanomechanical properties of ZrO₂ nanotubes formed on zirconium via anodization in a mixture of electrolytes with fluoride ions were evaluated. The results showed that the anodization process led to a substantial change in the adhesive properties of Zr. The nano-porous Zr demonstrates a significantly higher mean adhesion force value in comparison to the uncoated Zr. The significant rise in the bacteria growth inhibition index observed in the nanoporous Zr sample, as evaluated against *Escherichia coli* and *Staphylococcus aureus*, may be linked to this phenomenon. It can be inferred that the controlled nano-structuring of Zr has resulted in a substantial decrease in bacteria adherence to Zr. The nano-porous Zr sample showed equivalent mechanical resistance to the uncoated Zr, concerning its mechanical properties [91].

One of the most remarkable properties of ZrO₂ nanostructures is their high surface area-to-volume ratio, which allows for a large number of functional groups to be attached to the surface of the nanoparticles [66]. The surface of ZrO₂ nanostructures can be easily modified by controlling the pH of the synthesis solution, adjusting the annealing temperature, or by functionalizing the surface with different chemical groups, such as carboxyl, amino, and thiol groups, making them highly versatile in various applications, including drug delivery [47,92].

The antimicrobial properties of ZrO₂ nanoparticles (NPs) can be improved by modifying their surface properties. This is achieved by functionalizing the surfaces of ZrO₂ NPs, which are produced via a solvothermal method, with glutamic acid. Glutamic acid is an α -amino acid that contains both COO⁻ and NH₄⁺ ions. The interactions between the nanomaterial and bacteria may have been improved due to a significant increase in the dispersion properties of GA-ZrO₂ in the aqueous solution [42].

ZrO₂ nanostructures also have excellent mechanical properties, such as high fracture toughness, strength, and wear resistance, which makes them highly stable and durable over time [93–97]. ZrO₂ is resistant to corrosion and degradation, which ensures the long-term stability of ZrO₂ nanostructures in biological environments [40,98,99]. These properties are critical for drug delivery applications, as the nanostructures need to maintain their structural integrity and stability to ensure the safe and efficient delivery of drugs to the target site [40,92].

In order to enhance stability and in vitro cell response, it was developed a bioinspired coating on a Zr alloy with increasing chitosan content. The results showed that the chitosan coating significantly enhances the stability of the Zr alloy and promotes the attachment, proliferation, and differentiation of osteoblast cells. The bioinspired coating with chitosan has the potential to improve the performance and longevity of Zr alloy implants in orthopedic and dental applications [100].

The anodization process significantly affects the surface morphology and wettability of the Zr surfaces. The anodization process in the fluoride-containing electrolyte resulted in the formation of a porous nanostructured surface that showed improved electrochemical stability and cell adhesion compared to the other electrolytes. This result suggests that these surfaces have potential applications in biomedical implants and devices, where biocompatibility and corrosion resistance are crucial factors [101].

In addition, ZrO₂ nanostructures exhibit excellent biocompatibility [102], as they do not elicit a negative immune response in the body and can be safely used for various biomedical applications. This property is crucial for drug delivery systems, as it ensures that the nanoparticles do not cause any harm to the body and are well-tolerated [103,104].

The special electronic properties of ZrO₂ nanostructures are also of great interest for drug delivery applications. ZrO₂ is a wide-bandgap semiconductor with a bandgap energy of approximately 5–6 eV [41,59,105,106] which makes it an excellent candidate for photodynamic therapy (PDT) [107]. PDT is a type of cancer therapy that involves the use of photosensitizers to generate reactive oxygen species (ROS) upon irradiation with light [107]. ZrO₂ nanostructures can be functionalized with photosensitizers and used as PDT agents for targeted cancer therapy [107].

The effect of anodization on the surface characteristics and electrochemical behavior of zirconium in artificial saliva were investigated and it was found that anodization treatment caused the formation of a porous oxide layer on the zirconium surface, which improved its electrochemical properties. The anodized samples exhibited higher corrosion resistance and lower passive current densities compared to the untreated samples. The surface morphology of the anodized samples showed a significant increase in surface roughness and the presence of nanoscale pores [108].

2.3. Discussion of the Biocompatibility and Toxicity of ZrO₂ Nanostructures

ZrO₂ nanostructures have been widely investigated for their biocompatibility and potential use in biomedical applications [23,67]. Studies have demonstrated that ZrO₂ nanostructures exhibit low cytotoxicity, making them suitable for use in biomedical applications [102,109]. Additionally, ZrO₂ nanostructures have been shown to have good biocompatibility both in vitro and in vivo, with no significant adverse effects observed [103,109].

Several studies have investigated the potential toxicity of ZrO₂ nanostructures. While some studies have reported the potential toxicity of ZrO₂ nanostructures at high concentrations or under certain conditions [65,110] the overall consensus is that ZrO₂ nanostructures are relatively safe and have low toxicity in comparison to other commonly used nanomaterials [64].

In the literature was revealed that Zr NPs have better biocompatibility when compared to other metallic nanoparticles [111–113], but there are some studies with ZrNPs demerits regarding some toxicity in bioapplications, affecting their safety use which was tested with specific in vitro assays. As an example, the article “Zirconia Nanoparticles-Induced Toxic Effects in Osteoblast-Like 3T3-E1 Cells” is an investigation of Zr NPs nanoparticles with sizes between 81 and 94 nm for a longer time and higher concentrations [114]. The research involved TiO₂ and ZrO₂ NPs and showed more potent toxic effects for ZrNPs based on cell viability decrease. Moreover, following the ZrO₂ NP exposure for 48 h, at the concentration of 10 µg/mL, no apoptosis appeared, but the percentage of necrotic cells was 43.7% in 50 µg/mL group in the same period of time [115,116]. As a result of oxidative stress, ZrO₂ NPs induced the increase of membrane microviscosity, changes in cell morphology, and surface cracks in the red blood cells. The ROS (free oxygen radicals) level in 3T3-E1 cells after ZrO₂ NP treatment in concentration-dependent manners was detected [115,116].

The biocompatibility and toxicity of ZrO₂ nanostructures are influenced by a variety of factors, including the size, shape, surface chemistry and concentration of the nanostructures [66,115–117]. It is well known that the general effect of nanosizing in bioapplications is very important as well as phase, shape average size, and concentrations. [118]. It is important to carefully evaluate the biocompatibility and toxicity of ZrO₂ nanostructures before their use in biomedical applications to ensure their safety.

3. Drug Loading onto ZrO₂ Nanostructures

3.1. Overview of the Different Loading Techniques and Strategies

Drug loading onto ZrO₂ nanostructures can be achieved through different techniques, including physical adsorption, covalent bonding, and electrostatic interactions (Table 2) [119–121].

Table 2. Examples of drugs loaded using different strategies.

Method	Drug Loaded	Application	Reference
Adsorption	Doxorubicin	Cancer therapy; Doxorubicin loaded onto NP showed cytotoxic effects against HT-29 colorectal cancer cells.	[122]

Table 2. Cont.

Method	Drug Loaded	Application	Reference
Covalent bonding	Paclitaxel	Cancer therapy; Paclitaxel loaded onto NP has better cytotoxic effects than free Paclitaxel in cancerous cell lines, such as glioma C6 cells, NCI-H69 human small cell lung cancer cells, human breast cancer cell line MCF-7 and HeLa cells	[123]
Covalent bonding	Cisplatin	Cancer therapy; The incorporation of cisplatin onto Zr nanoparticles resulted in a decrease in cell viability by up to 40% on the (MCF-7) human breast cancer cell line.	[124]
Adsorption	5-Fluorouracil	Cancer therapy; The incorporation of 5-Fluorouracil into nanoparticles exhibited potent cytotoxic effects against MCF-7, HCT-116, and HePG-2 cell lines.	[125]
Adsorption	Tetracyclin	Microbial diseases such as malaria, cholera, plague, acne, skin, and respiratory tract infections, etc.; Tetracycline-loaded ZrO ₂ NPs showed zones of inhibition for <i>S. enterica</i> and <i>S. aureus</i>	[126,127]
Absorption	Ampicillin	Bacterial infections; Ampicillin-loaded ZrO ₂ nanoparticles showed zones of inhibition for <i>E. coli</i> and <i>B. cereus</i> .	[128]
Absorption	Erythromycin	Bacterial infections; Erythromycin-loaded ZrO ₂ nanoparticles showed zones of inhibition for <i>E. coli</i> and <i>B. cereus</i> .	[128]
Adsorption	Indomethacin	Inflammatory diseases, neoplastic diseases; Indomethacin encapsulated into NPs induces apoptosis, being an antineoplastic agent (breast cancer, lung cancer colon cancer, leukemia).	[129]
Adsorption	Ibuprofen	Inflammatory diseases; Incorporating Ibuprofen into nanoparticles enhances its solubility, thereby increasing its biological activity.	[130] [131]

Physical adsorption is a simple and effective method that involves the passive accumulation of drugs onto the surface of ZrO₂ nanostructures [132,133] through van der Waals forces, hydrogen bonding, or hydrophobic interactions [134]. This process is accomplished by incubating the nano-carrier with a concentrated solution of the drug [28]. This technique is commonly used for drug loading onto ZrO₂ nanostructures [106], as it is simple and versatile and does not require any chemical modification of the nanostructures or drugs. However, it can suffer from fast initial burst release of drugs [29].

Covalent bonding is a more stable and specific method that involves the chemical attachment of drugs to the surface of ZrO₂ nanostructures through covalent bonds [135]. This can improve the stability and control of drug release, as well as increase the loading capacity of ZrO₂ nanostructures. However, it requires the modification of both the nanostructures and drugs and can be more complex and time-consuming [27,136]. Covalent linking offers several key benefits compared to physical encapsulation. These advantages encompass an extended drug residence time within the body, controlled release, enhanced biodistribution, improved therapeutic efficacy, and mitigated systemic toxicity.

Electrostatic interactions involve the binding of oppositely charged drugs to the surface of ZrO₂ nanostructures through electrostatic forces [119]. Electrostatic interactions provide an alternative method for drug loading, as the oppositely charged drugs can bind to the surface of ZrO₂ nanostructures through electrostatic forces [66–120]. This method can provide high drug loading capacity, as well as control of drug release [136]. However, possible interference from other charged molecules can occur. When electrostatic

interactions were examined at nanoscale levels the results showed that small molecules with three or more charges were capable of mediating interactions between oppositely charged nanoparticles. Conversely, those with one or two charges were unable to do so [136].

Maintaining the structural stability of nanocarriers is crucial to avoiding their rapid degradation in blood serum. If the carrier structure breaks down prematurely, the drug it carries will be released directly into the bloodstream, thereby diminishing its targeted delivery potential. In such cases, cytotoxic drugs may gradually leak from the system, ultimately resulting in the collapse of the entire drug delivery system [27].

In addition to these techniques, other methods have been developed for drug loading onto ZrO₂ nanostructures, including affinity binding [27,137–141] and layer-by-layer assembly [142]. These methods offer different advantages and disadvantages and can be used for different types of drugs and applications.

Overall, the selection of the most appropriate drug loading technique for ZrO₂ nanostructures depends on the specific requirements of the application, such as drug type, loading capacity, release profile, stability, and biocompatibility.

3.2. Discussion of the Factors Affecting Drug Loading Efficiency

The efficiency of drug loading onto ZrO₂ nanostructures can be affected by various factors, including the physicochemical properties of the drugs, the surface properties of the ZrO₂ nanostructures, and the drug loading methods employed [25].

The physicochemical properties of drugs, such as solubility, molecular weight, and charge, can affect their interaction with ZrO₂ nanostructures and, consequently, their loading efficiency [25].

The surface properties of ZrO₂ nanostructures, such as surface area, surface charge, and surface chemistry, can also affect drug loading efficiency. For example, increasing the surface area of ZrO₂ nanostructures can increase their drug loading capacity [103,119,143], while modifying the surface chemistry of ZrO₂ nanostructures can improve their compatibility with specific drugs [144].

The drug loading methods employed can also affect the efficiency of drug loading onto ZrO₂ nanostructures. For instance, physical adsorption is a simple and versatile method for drug loading, but it may result in low drug loading efficiency and poor drug stability [135], while covalent bonding can result in higher drug loading efficiency and improved drug stability [145].

Inorganic hollow mesoporous nanocapsules, specifically hm-ZrO₂, can exhibit varying behavior in cancer and normal cells when loaded with anticancer drugs such as doxorubicin (DOX). The nanocapsules possess high biocompatibility and a substantial capacity for loading DOX. The release of DOX from the mesoporous nanocapsules is pH-dependent, with a faster release rate at lower pH levels. Upon cellular uptake, the loaded DOX is released from the nanocapsules owing to the acidic conditions of the subcellular lysosomal compartments. The results of the flow cytometry experiment indicated that normal cells took up a greater amount of hm-ZrO₂. Because of the acidic nature of tumor cells, hm-ZrO₂ loaded with DOX release a greater amount of drug in cancer cells, but compared to healthy cells over the same time period. This phenomenon resulted in a higher level of cytotoxicity of tumor cells and a lower level of cytotoxicity towards normal cells as compared to free DOX [119].

Understanding the factors affecting drug loading efficiency can help to optimize the drug loading process and improve the efficacy of ZrO₂ nanostructure-based drug delivery systems.

3.3. Description of the Different Types of Drugs Loaded onto ZrO₂ Nanostructures

The most common types of drugs that can be loaded onto ZrO₂ nanostructures are anti-cancer drugs, such as doxorubicin, paclitaxel, and cisplatin which have been shown to exhibit enhanced efficacy when delivered via ZrO₂ nanostructures [146–148].

In addition to anti-cancer drugs, other types of drugs that have been loaded onto ZrO₂ nanostructures include antibiotics (such as tetracycline, ampicillin, and erythromycin), which have demonstrated improved antimicrobial activity when delivered via ZrO₂ nanostructures [127,128].

ZrO₂ nanostructures have also been used to deliver with improved efficacy [67,69] anti-inflammatory drugs (such as ibuprofen and diclofenac) [149,150], curcumin (with anti-inflammatory and antibacterial properties) [151,152], alendronate, itraconazole [153,154].

The use of ZrO₂ nanostructures as drug delivery vehicles has shown promising results for a wide range of drug types and further research is needed to optimize the loading and release properties of these nanostructures for specific drugs and therapeutic applications.

4. Drug Release from ZrO₂ Nanostructures

4.1. Overview of the Different Drug Release Mechanisms

Zirconia nanoparticles have been studied for their use as drug delivery vehicles with various types of drugs [142]. The release of drugs from the ZrO₂ nanocarriers depends on the characteristics of the drug, as well as the properties of the ZrO₂ nanoparticles [155].

Several drug release mechanisms have been identified for ZrO₂ nanoparticles, including diffusion-controlled release [156], swelling-controlled release, and degradation-controlled release [36,157] (Table 3).

Table 3. Examples of drugs with different mechanisms of release.

Method	Drug Loaded	Application	Reference
Diffusion	Doxorubicin	Cancer therapy Doxorubicin loaded onto NP showed cytotoxic effects against HT-29 colorectal cancer cells.	[122]
Degradation	Cisplatin	Cancer therapy The incorporation of cisplatin onto Zr nanoparticles resulted in a decrease in cell viability by up to 40% on the (MCF-7) human breast cancer cell line.	[124]
Diffusion	5-Fluorouracil	Cancer therapy The incorporation of 5-Fluorouracil into nanoparticles exhibited potent cytotoxic effects against MCF-7, HCT-116, and HePG-2 cell lines.	[125]
Diffusion	Ibuprofen	Inflammatory diseases Incorporating Ibuprofen into nanoparticles enhances its solubility, thereby increasing its biological activity.	[130,131]
Diffusion	Indomethacin	Inflammatory diseases Indomethacin encapsulated into NPs induces apoptosis, being an antineoplastic agent (breast cancer, lung cancer colon cancer, leukemia).	[158]

Diffusion-controlled release occurs when the drug molecules diffuse through the nanoparticle matrix and are released into the surrounding environment [158]. Swelling-controlled release occurs when the nanoparticle matrix increases in volume in contact with water, causing the drug to be released [159]. Degradation-controlled release occurs when the nanoparticle matrix degrades over time, releasing the drug [36]. Other factors that can affect drug release from ZrO₂ nanoparticles include pH, temperature, ultrasound, magnetic field, etc. [36].

Understanding the different drug release mechanisms is important for the development of effective drug delivery systems using ZrO₂ nanoparticles.

4.2. Discussion of the Factors Affecting Drug Release Kinetics

The factors that can affect drug release kinetics include the size and shape of the ZrO₂ nanostructures [160,161], the pH and temperature of the release medium, and the type and molecular weight of the drug [162,163].

Several studies have reported that the size and shape of ZrO₂ nanostructures can significantly affect drug release kinetics. The size of the nanoparticle affects the surface area and pore size, which, in turn, influences the drug loading and release rate. In general,

smaller nanoparticles have higher surface area and pore volume, which leads to higher drug loading and faster release kinetics. On the other hand, the shape of the ZrO₂ nanostructure can affect the porosity and surface chemistry, which can also affect drug loading and release rate [160,161].

The type and molecular weight of the drug also play a significant role in drug release kinetics [164]. The hydrophilicity and hydrophobicity of the drug molecules can affect their interaction with the ZrO₂ nanostructures, which can influence the drug loading and release kinetics [165,166]. In addition, the molecular weight of the drug can affect the diffusion rate, which can influence the release kinetics [167]. The pH and temperature of the release medium are also important factors affecting drug release kinetics from ZrO₂ nanostructures [168]. The pH can affect the charge of the drug and the surface of the ZrO₂ nanostructure, which can influence drug loading and release [169]. Temperature can also affect the diffusion rate and the rate of chemical reactions that can affect drug release kinetics [130].

Overall, a comprehensive understanding of these factors is important for designing ZrO₂ nanostructures as drug delivery vehicles with optimal drug loading and release properties.

4.3. Comparison of the Drug Release Profiles of ZrO₂ Nanostructures with Other Drug Delivery Systems

Several studies have shown that ZrO₂ nanostructures exhibit sustained release of drugs over a period of time [119]. For example, one study demonstrated sustained release of doxorubicin from ZrO₂ nanostructures, with a cumulative release ratio of approximately 35.5% after 24 h. A reduction in tumor volume was observed on day 7, and the reduction was significant on day 14 [139]. Another study found that Zr-MOFs (Metal-organic frameworks) loaded with ibuprofen exhibited sustained release of the drug for a period of 10 days [170]. An additional investigation discovered that the sustained release of indomethacin from ZrO₂ nanostructures reached a plateau within a range of 13 to 17 days [171].

Compared to other drug delivery systems such as liposomes and polymeric nanoparticles, ZrO₂ nanostructures have been shown to have longer drug release profiles, which may be advantageous for certain applications. For example, a study found that NP micelle loaded with doxorubicin exhibited sustained release of the drug over a period of 48 h [172], while another study found that the release of the ibuprofen from polymeric nanoparticles occurs during the initial 80–120 min [173]. In other investigations, the loading and release efficiencies of a wide range of drugs such as ibuprofen, N-acetyl-L-cysteine, vancomycin, gentamicin, nitrofurantoin, and indomethacin characterized by a large range of polarity, molecular weight, and various functional groups were studied [25].

However, it should be noted that the drug release profiles of ZrO₂ nanostructures can be affected by various factors such as particle size, surface charge, the method of synthesis, the drug loading technique, and the physicochemical properties of the drug. These factors can be fine-tuned to achieve specific drug release profiles [25]. Although ZrO₂ nanostructures offer a promising platform for drug delivery due to their unique properties and ability to achieve controlled drug release, further studies are needed to fully evaluate the potential of ZrO₂ nanostructures as drug delivery systems.

5. Applications of ZrO₂ Nanostructures in Drug Delivery

5.1. Overview of the Different Biomedical Applications of ZrO₂ Nanostructures

ZrO₂ nanostructures can be used in various biomedical applications, such as tissue engineering [174], cancer therapy [175,176], bone regeneration [177], dental applications [178,179], wound healing [128,180], antimicrobial applications [181] and imaging [182,183].

In bone regeneration, ZrO₂ nanostructures have been used to promote osseointegration of the implanted material and bone reconstruction [184]. In dental applications, ZrO₂ nanostructures have been used as antimicrobial agents for the prevention of dental enamel

corrosion [185]. In wound healing, ZrO₂ nanostructures have been used to facilitate the closure of skin lesions and antibiotics-loaded ZrO₂ nanoparticles inhibit pathogens and can be used to treat infected wounds [128].

Tissue engineering is an area where ZrO₂ nanostructures have shown potential as a scaffold material due to their biocompatibility and mechanical properties [178]. ZrO₂ nanostructures can mimic the natural extracellular matrix (ECM) of tissues, providing a suitable environment for cells to adhere, proliferate and differentiate [186].

In cancer therapy, ZrO₂ nanostructures have been investigated for their potential to deliver anticancer drugs to tumor cells, in order to improve drug efficacy and to reduce toxicity [103]. ZrO₂ nanostructures can be used for targeted drug delivery [103,187], as well as for photodynamic therapy [106] and radiotherapy [188].

ZrO₂ nanostructures also show promise as antimicrobial agents, with the ability to inhibit the growth of bacteria. Several studies have investigated the use of ZrO₂ nanostructures for dental, where infection prevention is critical [127].

ZrO₂ exhibited several beneficial effects in mice infected with H5N1, including a reduction in mouse mortality, mitigation of respiratory pathological changes, and inhibition of viral replication within the lungs. Administration of ZrO₂ prior to influenza infection prompted a rapid initiation of the host's antiviral response and alleviated the harm caused by cytokine storms during H5N1 infection [189].

ZrO₂ nanostructures have also applications in imaging, where their unique optical properties can be leveraged for diagnostic and therapeutic purposes [106]. There are studies where ZrO₂ nanoparticles using was investigated in magnetic resonance imaging (MRI) [190,191] and photothermal therapy [192].

Zr/ZrO₂ nanotubes were used to develop a sensitive and selective electrochemical sensor for heavy metal ion detection, such as Pb²⁺, Cd²⁺ and Hg²⁺. The excellent performance of the sensor was attributed to the high surface area and unique morphology of the Zr/ZrO₂ nanotubes, which provided a large number of active sites for ion adsorption [193].

5.2. Description of the Advantages and Limitations of Using ZrO₂ Nanostructures for Drug Delivery

The advantages of using ZrO₂ nanostructures for drug delivery [188,194–199] include their biocompatibility, stability, and versatility in carrying a wide range of drugs (Figure 3) [25].

ZrO₂ is also highly stable, maintaining its structural and chemical properties over time [200]. However, there are also limitations to using ZrO₂ nanostructures for drug delivery. One major limitation is the challenge in controlling drug release kinetics, as the release of drugs is influenced by several factors, such as nanoparticle size, porosity of the nanostructures, etc. [160,161]. Another limitation is the potential for toxicity, as there is a risk of the nanoparticles accumulating in certain tissues and causing harm [65].

It is to notice as one of the main limitations of the absence of in vitro and in vivo experiments, preclinical and clinical trials represent “obligatory passage” for medical research progress, concerning the status of materials and drugs as well. The ethical side of biomedical research in general, clinical trials, and the law settles, are developed within a restricted framework. Zirconium nanostructures are nowadays developed especially for dental implants [195,201–204], so more research is needed to evaluate their clinical perspective. It is a challenge, and more investigations are required to compare their behavior to other biomaterials used in the dental field and find the best safe usage conditions. As an example, Zirconium nanoparticles have no standard for production leading to specific characteristics and functionality and such things should be solved [128,205,206].

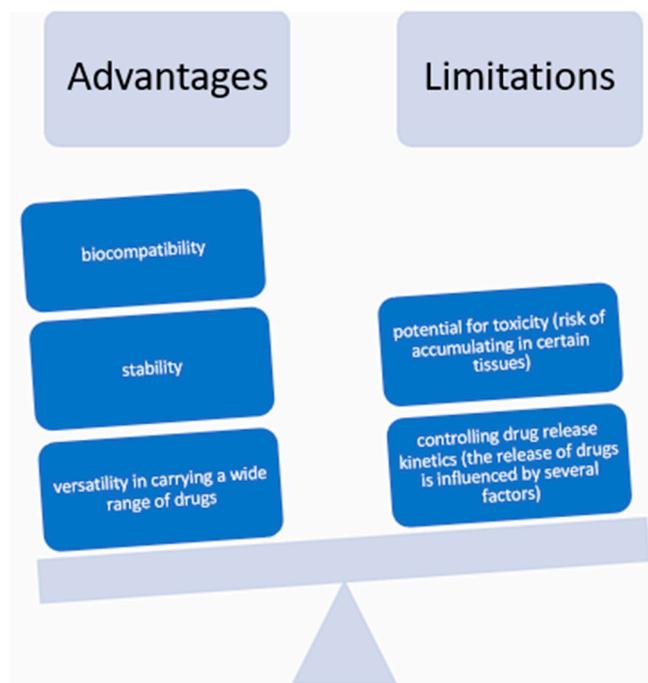


Figure 3. Advantages and limitations of using ZrO₂ nanostructures for drug delivery.

6. Conclusions

6.1. Summary of the Key Points of the Paper

This review highlights the potential of ZrO₂ nanostructures as drug delivery vehicles and the progress that has been made in understanding their properties, drug loading and release mechanisms, biocompatibility, and toxicity. It also acknowledges the challenges that remain in controlling drug release kinetics and optimizing the drug delivery efficiency of ZrO₂ nanostructures.

6.2. Future Directions for Research on ZrO₂ Nanostructures as Drug Delivery Vehicles

ZrO₂ nanostructures have shown great potential as drug delivery systems and there is a growing interest in their development for biomedical applications. Future directions for research on ZrO₂ nanostructures as drug delivery vehicles may include further optimization of drug loading and release strategies, particularly by exploring novel approaches to functionalizing the surface of the nanoparticles. Another area of interest is in the development of targeted drug delivery systems using ZrO₂ nanostructures, which could be achieved through the use of specific ligands or antibodies that bind to cell surface receptors.

Furthermore, there is a need to investigate the long-term effects of ZrO₂ nanostructures on the body, including their potential toxicity. This will require comprehensive *in vivo* studies to assess the safety and efficacy of ZrO₂ nanostructures for drug delivery.

In addition, there is a need for more studies on the biodistribution and pharmacokinetics of ZrO₂ nanostructures in the body, along with their potential interactions with cells and tissues. Other areas of potential research include exploring the use of ZrO₂ nanostructures in combination with other drug delivery systems, such as liposomes or dendrimers, to enhance drug delivery efficiency.

Overall, the future prospects of ZrO₂ nanostructures as drug delivery systems are promising and could have a significant impact on the field of medicine. However, further research is needed to fully understand and optimize their properties and behavior *in vivo*.

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