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Review article

Porous alumina as potential nanostructures for drug delivery applications, synthesis and characteristics

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ABSTRACT

One of the inorganic NPs that have recently piqued researchers' interest in different industries is aluminum oxide (alumina). In this review, we go through applications of alumina in biomedical engineering with a focus on drug delivery. Various physical and chemical properties of alumina that have made it a suitable candidate for biomedical applications are investigated. Different phases of this metal oxide are introduced. The most common synthesis methods for obtaining biomedical-grade alumina with suitable properties specific to each field of biomedical engineering are reviewed. Cytotoxicity and biocompatibility of alumina is investigated and properties of alumina that make it biocompatible along with strategies that can make pure alumina more biocompatible are examined. Literature reports on applications of alumina as a drug carrier have been reviewed and novel strategies for enhancing therapeutic efficiency of alumina-based nanocarriers have been introduced through these reports. The goal of this review is to provide the latest achievements in the steaming research conducted on application of alumina as a drug carrier. By reading this paper, readers' knowledge of latest progress made on alumina drug delivery will be updated and the direction for future studies on enhancing biocompatibility and therapeutic efficiency of alumina-based nanocarriers will be clarified.

1. Introduction

Enhancing the efficiency of drug delivery systems has been a major area of focus for researchers over the recent years [1]. Dynamic development of nanotechnology in recent decades and expansion of its applications in disease diagnosis and therapy has proven the promise of nanostructures for biomedical usage and delivering drugs owing to their nanoscale above all [2–4]. Consequently, several research studies have been conducted to fabricate nanomaterials and assess their efficacy as drug carriers. Nanocarriers improve therapeutic and pharmacological features of drugs including controllable solubility; therefore, employing nanocarriers in drug delivery can decrease the required dosage of drugs [3,5–7].

The accumulation of drug in vital organs originated from uncontrollable and non-specific release of drug from nanocarrier, which is typical in passive targeting, has led to the development of active targeting strategies. It is known that exogenous and endogenous are two types of stimuli that can be employed for active targeting [8]. Exogenous is referred to each extra-corporal signals that can trigger the release of drug from nanocarrier, including temperature change, magnetic and electric fields, and ultrasound wave. On the other hand, redox reactions, pH and temperature change, and enzyme transformation has been regarded as endogenous stimuli [9]. Reduction in required dosage and consequent minimized cytotoxicity may be achieved by employing nanocarriers benefiting extended-release and high loading efficiency. Extended relief of symptoms, improved life-cycle management of drugs, and patient compliance are among benefits computed to sustainable drug delivery.

Apart from their applications in catalysis [10] and ceramics industry [11], alumina NPs have attracted scientists due to their extraordinary

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properties in drug delivery applications [12–16]. A porous biocompatible structure along with advantageous characteristics, such as antimicrobial activity and chemical inertness, is essential for any nanocarrier in order for it to transport and release a drug in the site of interest efficiently [17–19]. Moreover, abundance and low cost of alumina eliminates any concerns regarding availability [17]. Consequently, this inorganic compound can be considered as an ideal candidate for drug delivery applications. Alumina has many different phases such as α, γ, θ, δ, and η phase [20]. Characteristics such as excellent mechanical strength, electrical insulation, and very low chemical activity in both oxidizing and reducing environments at temperatures up to 1000 °C, have turned alumina NPs into a promising vessel for loading and delivering therapeutic payloads [21].

Owing to the promising properties of alumina, it has been applied in a wide range of biomedical applications, including drug delivery systems, antimicrobial agents, and food additives [22–24]. In orthopedics, alumina has been successfully applied in prostheses and implants [25]. Moreover, applications of alumina in ceramic and composite substances stemming from its high specific area, controllable microstructure, and high chemical and thermal stability, have paved the way for utilization in dentistry applications [26]. Furthermore, other fields of biomedical engineering such as immunoisolation [27], tissue engineering [28], and cardiology [29] have found usage for alumina NPs. Uniform pore size and density, chemical and thermal stability, stiffness, tunability of pore size through adjusting synthesis factors (voltage, electrolyte and temperature), and modifiability of surface chemistry through chemical methods have created potential applications for alumina NPs in fields such as immunoisolation and tissue engineering. Also, even though alumina is biologically inert, modifying its surface with bioactive agents can make it bioactive [30].

In this review, we discuss promising chemical and physical characteristics of porous alumina nanoparticles and explain how these characteristics contribute to applicability of this nanomaterial in biomedical fields such as tissue engineering and drug delivery. Through investigating literature reports, we introduce different fabrication techniques for porous alumina NPs and investigate the influence of each technique on the properties that the produced NPs obtain. Since the nanoparticles are required to have features specific to the field in which they are being used, choosing the appropriate synthesis method is of paramount importance. We also investigate biocompatibility and cytotoxicity of nanoscale alumina. Since these characteristics are crucial for effective performance of alumina in biomedical fields, strategies for enhancing biocompatibility of alumina NPs and minimizing their cytotoxicity are discussed as well. Finally, we provide a thorough review on literature reports which have investigated use of porous alumina and its composites as a drug delivery system. Several strategies such as caping, surface functionalization, taking advantage of some composites' stimuli-responsiveness, multimodal therapy, and employing target-specific ligands have been exploited.

2. Characteristics and different synthesis methods of alumina

The size and density of alumina NPs follows a uniform distribution. They are not electrically conductive. These NPs can maintain their porous structure at high temperatures and are not considered as reactive compounds. They have high mechanical strength and do not easily disintegrate. The parameters of their synthesis procedures can be adjusted to tune their pore diameter. The NPs have high surface area and their surface can be easily functionalized to adjust them for different applications such as biosensing. Their surface can be modified using biomaterials to make alumina more bioactive. Alumina can have different crystalline formations depending on defect locations of Al atoms. Some of these phases include α, γ, θ, δ, and η phases [17,19,21,30,31].

In this section, we will discuss different methods for alumina synthesis. It is conceivable that due to the specific properties required for each field of application, different classes of alumina with distinct characteristics are producible. Hence, different fabrication techniques exist for adjusting particle size, morphology, surface, and phase homogeneity [12,15]. There are several methods for synthesizing the NPs of a metal oxide, such as sol-gel method [32], co-precipitation [33], combustion [34], vapor deposition [35], and etc. Among all phases of alumina, α- and γ-alumina have gained significant attention because of their unique characteristics. γ-alumina NPs have high surface area and show thermal stability at high temperatures. α-alumina NPs have a more uniform size distribution and are desirably flowable. Also, they have small surface energy. α -alumina is the most thermodynamically stable phase of alumina. As a result, both crystalline structures have found various applications [20,36–38].

There are different reports in literature regarding synthesis of alumina and its composites for biomedical applications. Vignesh Raj and coworkers [39] prepared nanocomposites of hydroxyapatite/alumina via stir-type hydrothermal method. Alumina NPs were prepared from a solution of 0.05 M Aluminum nitrate with pH value of 11.0 using co-precipitation method. The solution was mixed with solutions of calcium nitrate and diammonium hydrogen phosphate at same pH value in a stir-type hydrothermal chamber. The resulting nanocomposites were used as bone substitutes. Vijayalakshmi and colleagues [40] fabricated biomedical grade nanocomposites of hydroxyapatite and alumina. In order to prepare alumina NPs, a 0.05 M solution of alumina was prepared by dissolving 4.68 g of aluminum nitrate in 250 mL of deionized water. Then, ammonia solution was added to maintain the pH value at 11.0. The solution was then stirred overnight without disturbance. The final nanocomposites of alumina and hydroxyapatite were used as additive material for bone tissue formation as they showed little biodegradation. Fig. 1.a shows transmission electron microscopy (TEM) images of hydroxyapatite/alumina nanocomposites. Fig. 1.b depicts the X-ray diffraction (XRD) test result for the nanocomposites.

Ahmed et al. [41] fabricated a scaffold of alumina and coated its surface with Au-modified carbonated hydroxyapatite. The goal of the study was to assess applicability of the composite in tissue engineering. In order to fabricate alumina scaffold, butanol, cyclohexane, and triton as surfactant, co-surfactant, and lipophilic phase were mixed magnetically with ratios of 4:20:1. The mixture was stirred until complete transparency was achieved. Then the mixture was divided in two parts. Aluminum nitrate was added to one part, whereas ammonia was added to the other part until the pH value of the latter reached approximately 11.0. Then, the ammonia containing solution was added to the other solution dropwise until pH was between 8.5 and 9.0. The resulting solution was stirred for 1 h and remained undisturbed for a day to age. The precipitation was removed by ethanol. This step was followed by centrifugation. The obtained powder was then dried at 60° of Celsius for 1 h. The dried powder was annealed for 120 min at 900° of Celsius and stable NPs were obtained. Kiradzhiyska and coworkers [42] fabricated Ag-modified anodic alumina and verified its potential biomedical applications by testing its biocompatibility versus NIH/3T3 cell line. In order to prepare anodic alumina, EN AW 1050A aluminum alloy was employed. To remove any defects and impurities, aluminum alloy was pretreated with acetone and nitric acid. Also, the alloy was electro-polished at a mixed solution of ethanol and perchloric acid with a volume ratio of 4:1 at 10 V voltage for 180 s. Next, the alloys were anodized using 1.53 M solution of sulfuric acid at 0.015 A/cm^2 current and temperature of 20° of Celsius. The resulting samples were washed with double distilled water. Fig. 2 depicts SEM image of silver-modified anodic alumina.

Rajan and colleagues [43] synthesized poly(g-glutamic acid)-based alumina NPs and evaluated their efficacy as protein adsorbents. They employed a precipitation-digestion method to prepare γ-alumina NPs. 17.1 g of aluminum sulfate was dissolved in 0.5 L of deionized water and stirred until complete dissolution was achieved. Next, ammonia solution was added to the initial solution dropwise until pH value reached 8.0 and precipitation of alumina started. The stirring solution was kept at

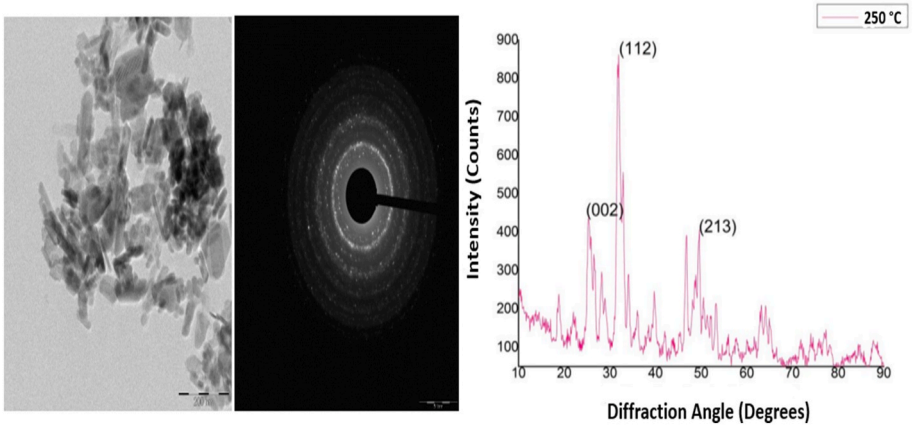

Fig. 1. a) TEM images of hydroxyapatite/alumina nanocomposites at 250° of Celsius b) XRD analysis for hydroxyapatite/alumina nanocomposites at 250° of Celsius [40].

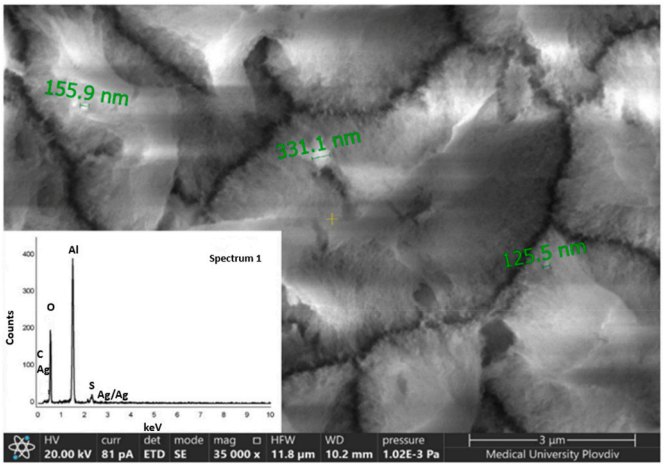

Fig. 2. SEM image of Ag-modified anodic alumina [42].

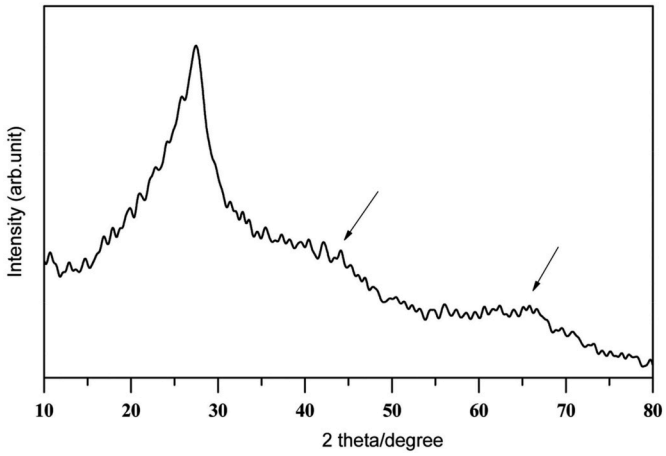

Fig. 3. X-ray diffraction spectra of γ-alumina particles [44].

constant conditions (temperature: 70° of Celsius, pH: 7.0–8.0) for 3 h to obtain NPs with uniform sizes. The particles were separated using centrifuge operation and washed with distilled water and alcohol. Finally, the NPs were dried at 50° of Celsius for a day.

Karim et al. [44] added 35 g of aluminum nitrate nonahydrate to 35 mL distilled water at 22° of Celsius under continuous stirring. Then, to keep the molar ratio of Al^{3+}/urea at 1/13, 72 g urea was added and retained for 1 h. After removing insoluble impurities through filtration, they heated saturated aluminum/urea solution to 90 °C for nearly 12h. The pH increased from 2 to 6 during the reaction in a gradual manner, and the sol became transparent after 3 h of extra heating. Finally, they produced porous γ-alumina powder by drying alumina sol at 280 °C for 1 h in atmospheric conditions. In the next stage, XRD and Fourier transform infrared spectroscopy (FTIR) analysis were applied to determine the characteristics of the produced powder. As shown in the X-ray diffraction pattern in Fig. 3, it is clear that the prepared alumina is entirely amorphous. Two broad peaks at 42° and 65°, as shown by arrows, are the characterizing peaks of the γ-alumina phase. These results are consistent with the XRD analysis of γ-alumina that is reported in the literature [17]. Aluminum ions in octahedral and tetrahedral environments can also be seen in FTIR spectra, where the absorption bands appeared at ~545 and ~788 cm^{-1}. Further investigations illustrate that peaks at 600 and 825 cm^{-1} are respectively pertinent to bending and stretching vibrations of Al–O [45]. The peak located around 3450 cm^{-1} belongs to the stretching vibration of the hydroxyl group bonded to Al^{3+} ions and the hydroxyl group. Finally, the peaks in the range of 1100–1800 cm^{-1} are assigned to the bending vibration of –OH [46].

Solution combustion method has advantages such as saving of energy, eco-friendliness [47], time saving, and effectiveness for producing fine and nanosized oxide powders [48], and can be used for fabricating urea-containing α-Al_2O_3. Zhuravlev et al. [49], synthesized α-Al_2O_3 NPs using solution combustion method. Aluminum nitrate with 99% purity and urea were the initial salts used in the synthesis procedure. The concentration of aluminum nitrate salt in the reaction solution was 228 g/dm^3. Different amounts of urea were used. An open cylindrical chamber was employed as the reactor for the synthesis process. An electric heater was used to heat the reaction mixture from the bottom of the reactor. Tarlani and coworkers [45] used sol-gel method to prepare porous NPs of γ-alumina for drug delivery applications. To fabricate NPs, a mixture consisting of 100 mL of 2-butanol and 11 mL of distilled water was added to 730 mL aluminum-2-butoxide at 75° of Celsius. The resulting gel was stirred and aged for 3 and 100 h, respectively. The final product was calcined at 100° of Celsius while exposed to air, and NPs of γ-alumina were obtained. In another research, Fazli-Abukheyli and colleagues [50] coated the top surface of anodic alumina with electrospinning nanofibers of Polyvinylidene fluoride and polyethylene glycol to obtain a controlled release profile for the model drug, indole-3-acetic acid. Domagalski et al. [51] developed anodic alumina nanotubes via current density-control pulse anodization technique and investigated the influence of variations in different synthesis parameters on physiochemical properties of the nanotubes. Tadic and coworkers [52] coated the surface of α-Fe_2O_3 nanoparticles with alumina through sol-gel combustion method and obtained a nontoxic porous nanocomposite.

The nanocomposite was characterized by XRPD, TEM, SEM, Raman, FTIR, EDS, and BET. Table 1 shows a summary of different synthesis methods for preparing alumina and alumina-containing composites.

3. Biocompatibility and cytotoxicity of porous alumina-based drug carriers

In order to use any material as a drug carrier, it is essential for that material to be biocompatible. Proteins are key players in determining biocompatibility of a certain material as they are responsible for initiating interactions between cells and biomaterials. The amount of protein that is present in a solution positively correlates with its adsorption rate on biomaterial surface. Also, smaller proteins have higher diffusion rates and so are adsorbed better on biomaterial surface. Certain driving forces such as formation of ionic bonds and hydrophobic interactions between material surface and proteins lead to higher affinity of some proteins for binding to surfaces. The adsorption of proteins on the biomaterial surface is not permanent either. Generally, proteins with lower molecular weight reach the surface first and bind to it. However, these proteins are later replaced with more heavy proteins that show higher binding affinity towards the surface. Once alumina comes in contact with water, interactions between its surface and water molecules lead to formation of hydroxyl groups. The presence of these hydroxyl groups facilitates interactions between the inorganic surface and proteins. However, the non-bendable property of alumina makes it incompatible with the tissues. It is crucial for alumina to be more bendable so that it can be used in orthopedic applications. Also, the porosity of the structure negatively influences bending property of alumina. Such mechanical properties of alumina can be tailored during synthesis procedure by manipulating synthesis factors. Various factors such as concentration, morphology, size of NPs, and surface area of NPs have an impact on cytotoxicity of alumina. Despite the limited biocompatibility of pure alumina, its surface can be modified with various biomolecules to improve cell response. Functionalizing alumina's surface with different biomolecules can make it more adhesive, bioactive, and improve adsorption of proteins [55–60].

Herein, we shall investigate some of the literature reports on drug delivery applications of alumina from the angle of biocompatibility and cytotoxicity. In some studies, it has been reported that nano anodic alumina (NAA) in the form of nano-porous coatings is safe for drug delivery applications [61–63]. Wang and coworkers [54] evaluated potential application of anodic alumina nanotubes as drug carriers in cancer therapy. They studied cytotoxicity of alumina nanotubes by treating HFF and THP-1 cells with this nanomaterial. The cell viability figures did not show any noticeable reduction after 3 days of treatment with alumina nanotubes at a dose of 100 μg/mL. Upon absorption by the cells, the alumina nanotubes induced autophagy. It was hypothesized that the maintained cell viability figures are the result of induced autophagy which protects the cells from alumina cytotoxicity.

In another research, Nematollahi et al. [17] synthesized quercetin (QC)-loaded pH-sensitive carrier made of chitosan (CS) and polyvinylpyrrolidone (PVP) coated in nano-porous γ-alumina through a double emulsification method. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was employed to determine the viability of the MCF-7 cells treated with free QC and QC-loaded CS/PVP/γ-alumina. Cytotoxicity figures of nanocomposites implies that alumina-free nanocarrier is nontoxic as the corresponding viability figure was as high as 80%. After adding γ-alumina to the nanocarrier, significant cell death was induced, which confirms that alumina has toxic properties for cancerous cells. In the next stage, to distinguish whether the cytotoxic effects were associated with apoptosis cell death mechanism or necrosis, flow cytometry test was performed. MCF-7 cells were seeded in 6-well plates followed by free drug, drug-loaded-copolymer, drug-loaded alumina-incorporated copolymer, and unloaded alumina-incorporated copolymer treating. Results showed that γ-alumina induced apoptosis in the cancerous cells. The Overall results were in alignment with the results of the work of Alarifi et al. [64]. They focused their study on the DNA damage on human hepatocarcinoma cells (HepG2). By assessing the cellular toxicity and genotoxic potential of alumina NPs, it was concluded that the NPs have cytotoxic and genotoxic effects on HepG2 cells. Moreover, the mechanism of cell death was apoptosis, which was mediated by the reactive oxygen species-triggered mitochondrial pathway.

More confirmatory research is exhibited in Fig. 4 prepared by Ebadi et al. [65]. They conducted a study in which magnesium-aluminum film was used as an agent for drug delivery and the cytotoxicity assay results illustrated the sizeable impact of the nanocarrier in cell viability. Fig. 4.a proves the biocompatibility of the constructed drug since the cell viability of fibroblast cells was more than 70% after 72 h of incubation whereas Fig. 4.b shows that compared to the free drug, the NPs demonstrated substantially stronger anticancer activity. In another study, Sun and coworkers [66] reported on fabrication of one-dimensional anodic alumina nanotubes with high biocompatibility and insignificant toxicity. Park and colleagues [67] conducted a comparative study to assess bovine serum albumin (BSA) protein adsorption on alumina and silica nanoparticles. Based on the outcome of their experiments, they hypothesized that electrostatic forces grant alumina nanoparticles high efficiency in terms of adsorbing the studied protein. Shapovalova et al. [68] prepared nanocomposites of alumina and iron (III) oxide and loaded them with doxorubicin (DOX). Incubating the nanocomposite with HeLa cell line revealed excellent biocompatibility of the synthesized nanoplatform.

To improve immunotherapeutic efficiency of subunit vaccines, Wang and coworkers [69] used alumina as an adjuvant delivery system. To make alumina more biocompatible and suppress inflammatory responses, the surface of the vaccine-adjuvant system was covered with phospholipid bilayers and further modified using PEG. Fig. 5 demonstrates TEM images of non-PEGylated and PEGylated formulations.

Kiradzhiyska and colleagues [70] employed thermal reduction technique to produced highly biocompatible Ag-doped anodic alumina for antibacterial applications. Incubation of the samples fabricated via thermal reduction method and electroplating method with human fibroblasts and NIH/3T3 cell lines revealed superior biocompatibility of

Table 1
A summary of different synthesis methods for preparing alumina and alumina-containing composites.

Target product	Synthesis method	Product Application/ Results	Ref
Nanocomposite of hydroxyapatite/ alumina	Co-precipitation	Bone substitutes	[39]
Nanocomposite of hydroxyapatite/ alumina	Hydrothermal	Additive for bone tissue formation	[40]
Alumina scaffold coated with Au-modified carbonated hydroxyapatite	Co-precipitation	Tissue engineering	[41]
Ag-modified anodic alumina	Electrochemical anodization	Biocompatible and adhesive towards cells for biomedical applications	[42]
poly(g-glutamic acid)-based alumina NPs	Precipitation-digestion	Protein adsorbent and anticancer activity	[43]
γ-alumina powder	Sol-gel	–	[44]
α-Al_2O_3 powder	Solution combustion	–	[53]
Alumina-ibuprofen nanocomposite	Sol-gel	Controlled drug release	[45]
Alumina nanotubes	Electrochemical anodization	Drug delivery	[54]
Alumina scaffold	Evaporation induced self-assembly	Drug delivery system for drugs with low water-solubility	[46]

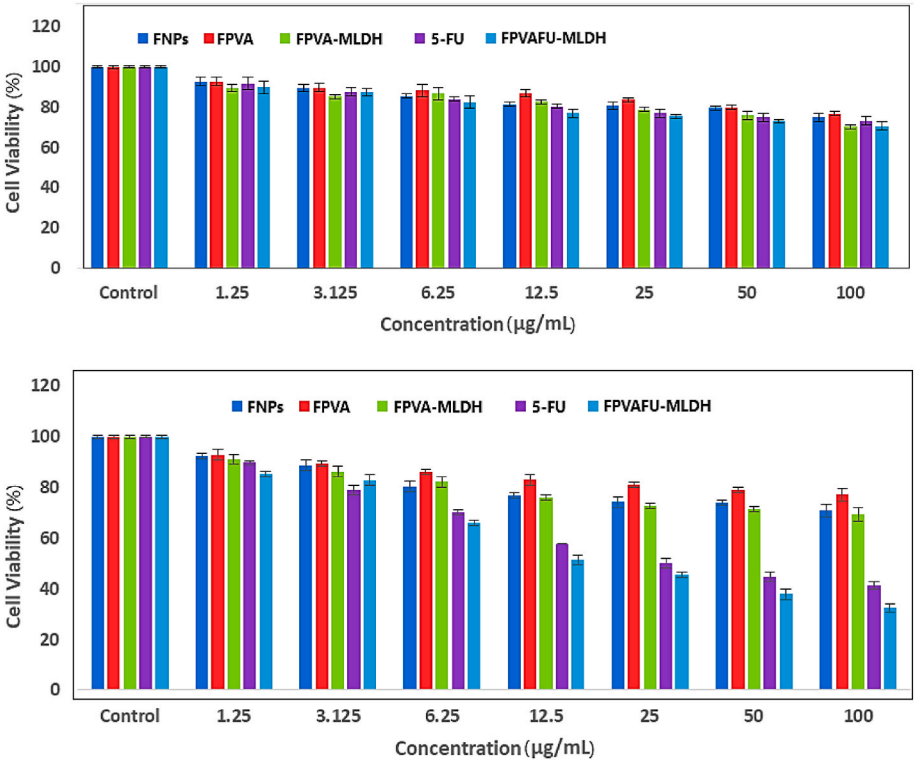

Fig. 4. a) Cytotoxicity assay of free drug 5-fluorouracil (5-FU), magnetite (FNPs) and nanocarrier constructed from polyvinyl alcohol (PVA) and Mg–Al-layered double hydroxide (MLDH), FPVA-MLDH, NPs (FPVA-FU-MLDH) against normal 3T3 fibroblast cells at 72 h of incubation. b) Cytotoxicity assay of magnetite (FNPs); FPVA; FPVA-MLDH; 5FU; FPVA-FU-MLDH against normal HepG2 cells at 72 h incubation [65].

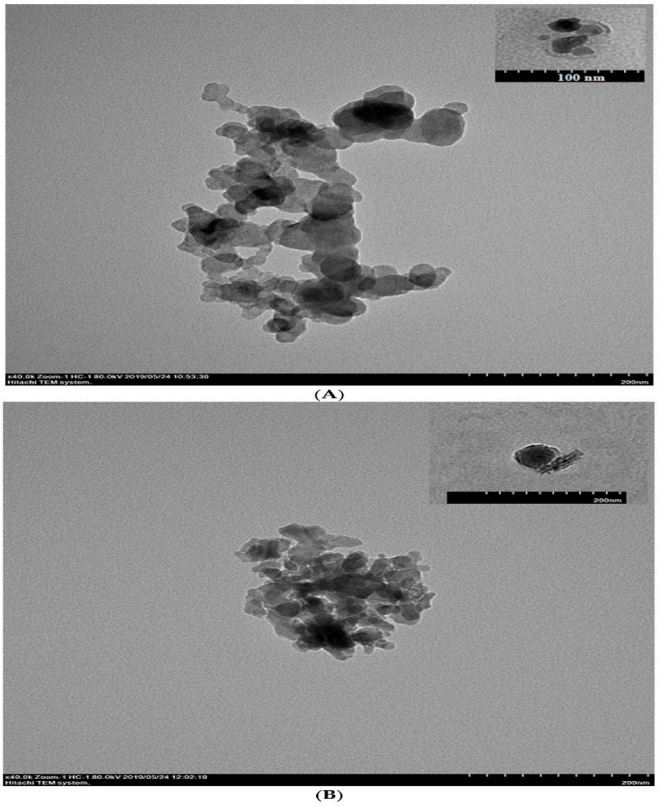

Fig. 5. TEM image of a) phospholipid bilayer-coated vaccine-alumina adjuvant b) phospholipid bilayer-coated PEGylated vaccine-alumina adjuvant [69].

the sample prepared by the former technique as indicated in Fig. 6.

4. Drug delivery applications of porous alumina nanocomposites

Among various materials used in developing drug carriers, mesoporous substances are emerging as appealing candidates for designing novel drug delivery systems. The capability to design their porous structure with specific pore geometries and sizes allows for the entrapment of numerous cutting-edge drug molecules and presents rational and desired release behavior. Mesoporous substances represent the main area of focus in recent studies on drug delivery systems. Owing to their

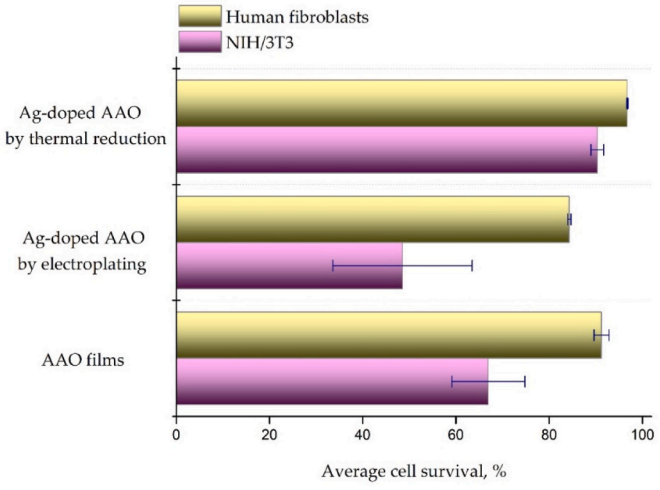

Fig. 6. Cell viability figures for Ag-doped anodic alumina prepared via different methods [70].

high-surface-region and tunable pore shape, they can be involved in initiating a brand new generation in contemporary nanotechnology [71, 72]. Mesoporous alumina (MeAl) is a favorable candidate for drug delivery applications because it has remarkable lateral surfaces with expanded regions, huge pore size, chemical stability, biocompatibility, thermal stability, non-toxicity, economic advantage, and desirable mechanical strength. Because of the promising results acquired from studies on alumina nanocomposites over the past few years, they have been extensively researched as a new drug nanocarrier for encapsulating different drugs, including anticancer drugs, insoluble drugs, antibiotics, peptides [73,74] and their applications in the fields of gene expression [75], wound healing [76], tissue engineering [28], diverse biosensors [77], and antimicrobial platforms [78].

Even though numerous common drug carriers have demonstrated benefits such as drug dissolution and long-term circulation, their effectiveness is considerably limited by their inability to encapsulate large quantities of their payload and target tumor sites specifically. This is because of their restricted loading capacity and low degree of performance. In addition, inadequate cellular uptake reduces the therapeutic efficiency of the antitumor agent, and overall aggregation in healthy organs brings about significant side effects, which finally results in limiting its clinical use. Therefore, development of efficient carriers capable of increasing the amount of drug absorbed by the cells, and releasing their cargo at the required sites is crucial. A renowned master plan for acquiring effective tumor selection is to bind drug nanocarriers to special ligands that are capable of detecting receptors at the tumor platform. The target ligands may be flexible, inclusive of hyaluronic acid, peptides, transporters, folic acid, and monoclonal antibodies [79–81]. Another way to ensure high therapeutic efficiency and low side effects is to take advantage of stimuli-responsiveness of alumina. Using the influence of different internal or external factors such as pH or ultrasound can help to the release of the drug in the target site and not in healthy tissues [82,83].

Herein, a number of case studies on the use of alumina for fabricating smart drug delivery systems with minimal side effects are provided.

A drug transport system using alumina NPs was developed by Khodabandeh et al. [84]. They prepared zinc-capped alumina and titanium dioxide nano-porous clusters for pH-sensitive drug release. The nano-porous structural pattern of alumina consisted of closely packed hexagonal nanopores with vitamin C as the model drug. The nano-porous alumina structure was immersed in vitamin C solution in order for alumina pores to be loaded with vitamin C. The nanopores were then covered using zinc ions. The zinc ions were deposited on the alumina pores using direct electrical current. Regarding in vitro drug release studies, two solutions with pH values of 7.0 and 5.0 were employed. While the former was the representative of normal tissue conditions, the later represented cancerous tissues. No drug was released from Zn-covered alumina nanopores in the neutral solution. However, half of the loaded drug was released from nanopores in acidic solution within 10 h. Hence, a pH-responsive nanocarrier was fabricated that could contribute to reducing side effects of the therapy. Ajalli and coworkers [12] developed nanocomposites consisting of chitosan, alumina, and magnetite for 5-FU delivery. The prepared nanostructure pH-responsive and released more amount of its payload at acidic environment of tumor compared with neutral medium. MTT assay and flow cytometry test revealed superiority of this nanoplatform in terms of apoptosis induction on breast cancer cells compared to free 5-FU. Fig. 7 shows Chitosan/Alumina/Fe_3O_4@5-FU nanocomposite entrapped in a water-in-oil-in-water emulsion [12].

Chen and colleagues [85] prepared NPs of alumina covered with polydopamine for skin cancer therapy using both photothermal therapy and immunotherapy approaches. The prepared NPs had a mean

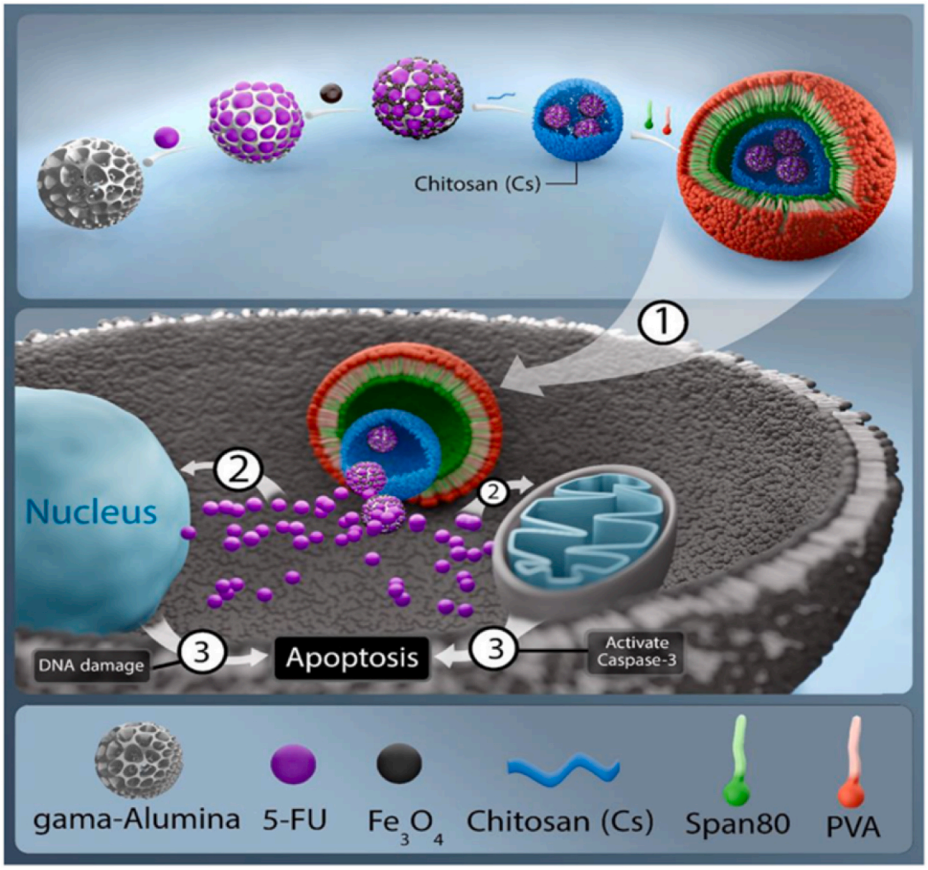

Fig. 7. Chitosan/Alumina/Fe_3O_4@5-FU nanocomposite entrapped in a water-in-oil-in-water emulsion [12].

diameter of approximately 344 nm. Regarding photothermal therapy, the NPs demonstrated the best absorption in the infrared range at a dose of 1000 μg/mL. Also, upon exposure to light, the temperature of NPs can rise by 30° of Celsius within 5 min. Since cancerous tumors can be exterminated after 5 min at a temperature of 50° of Celsius, use of these NPs for photothermal therapy is a highly efficient way of eliminating tumors. Furthermore, they attempted to combine photothermal therapy and immunotherapy to further increase therapeutic efficiency. First polydopamine-coated alumina NPs were injected into the tumors and irradiated until tumors were destroyed and their related antigens were released. These antigens are absorbed by immature dendritic cells, and once these cells are mature, the antigens will be on their surface. The presence of these antigens on the surface of mature dendritic cells will trigger immune responses. The experiments of Chen's team proved that adding a relevant immune adjuvant can further enhance the immune response. Fig. 8 depicts the overall mechanism of combined photothermal therapy and immunotherapy.

Furthermore, gene delivery applications of alumina were investigated by Ding et al. [86]. They used metal oxide NPs and alumina NPs in specific to mediate transformation of antibiotic resistant genes (ARGs) in water, and proved that nanoscale metal-organic particles, particularly alumina-based ones can act as carriers interceding the transduction-like ARG change in water. They also proved that nano-alumina can be combined with a plasmid coding for ARGs to make an excessive-density package and keep ARGs away from corruption through the endonuclease. Kusiak N.V et al. [87], synthesized nanocomposite of magnetite/alumina/C and determined its properties by a series of physicochemical strategies. The nanocomposite was of core-shell type and was magnetic-responsive which improves therapeutic efficacy of its cargo.

An easy strategy to synthesize an alumina-containing drug transport vehicle for cancer treatment is encapsulating anti-cancer drug molecules straightly into the porous structure of nanocarrier. Gao et al. [79] synthesized porous NPs of alumina modified by hyaluronic acid and loaded with paclitaxel to treat liver cancer. Coating of pores of alumina NPs with hyaluronic acid controls the drug release rate and the loaded samples demonstrated steady release pattern. Comparative study between free drug and drug-loaded NPs showed that paclitaxel-loaded hyaluronic acid-modified nano-porous alumina had higher cellular uptake and enhanced apoptosis induction. Fig. 9 shows cell inhibition percentage figures for free paclitaxel (PAC), paclitaxel-loaded alumina NP (PAC-MHA), and paclitaxel-loaded hyaluronic acid-modified alumina NP (PAC-HMHA).

Using pH-responsive drug transport structures based on amphipathic copolymers is a novel approach to overcome some of the restrictions in most cancer therapy methods. Nematollahi et al. [17], fabricated a QC-loaded nanocomposite (CS/PVP/γ-alumina) by the dual emulsion method. The purpose of incorporating alumina NPs within the polymeric structure was to increase the loading capacity of the nanocarrier and to ensure that the drug is released in a more sustained manner. Besides that, the γ-alumina NPs were prepared through sol-gel technique with a nano-porous network, excessive surface area, and hydroxyl-rich surface. This novel nanoplatform demonstrated promising results such

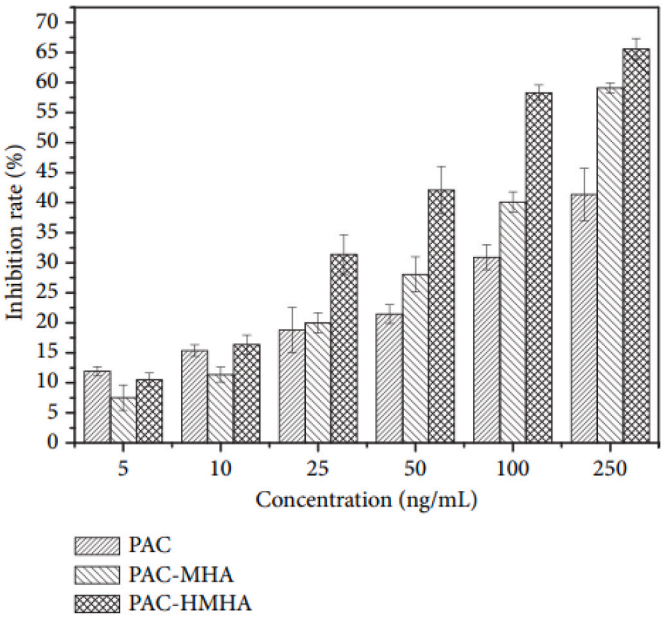

Fig. 9. Cell inhibition percentage figures for free paclitaxel (PAC), paclitaxel-loaded alumina NP (PAC-MHA), and paclitaxel-loaded hyaluronic acid-modified alumina NP (PAC-HMHA) [79].

as reduced side effects through pH-responsive behavior and gradual release profile with a high encapsulation efficiency (95.5%). The results of the MTT assay on MCF-7 cell line indicated 95.33% induced apoptosis. Also, in another study by Talaei et al. [88], alumina NPs were synthesized by laser removal strategy and well-characterized by distinctive strategies. Performing in vitro apoptosis assays indicated that alumina NPs can control and reduce cancer cell proliferation in pre-clinical practices in a dose-dependent manner. Both Talaei results to Nematollahi's study, demonstrated the remarkable effect of alumina present in their components. Moreover, in another study on a nano-porous alumina-containing complex for DOX delivery, Kapruwan et al. [89] employed a sophisticated protocol to manufacture the stacked anodic alumina with a nano-porous structure through a heterogeneous anodization technique, combining sinusoidal cutting-edge-density anodization and constant potential anodization. The organized structures were loaded with the DOX drug through the drop-casting technique, which allows for comparing the reflectance of the relative peak of the PSB with the common reflectance of the spectrum intensity and the alumina had positive effects on the drug release and kinetics.

The study conducted by Lakade et al. [90] resulted in fabrication of MeAl nanocarrier for sustained drug delivery by exploiting a smooth model pathway that was obtained by employing hexadecyltrimethylammonium bromide as a model and chloride of aluminum as a precursor. Also, they achieved a drug loading efficiency of 74.44%. The fabricated formulation demonstrated favorable results in in vitro drug release studies, as it showed sensitivity towards pH value. Since less

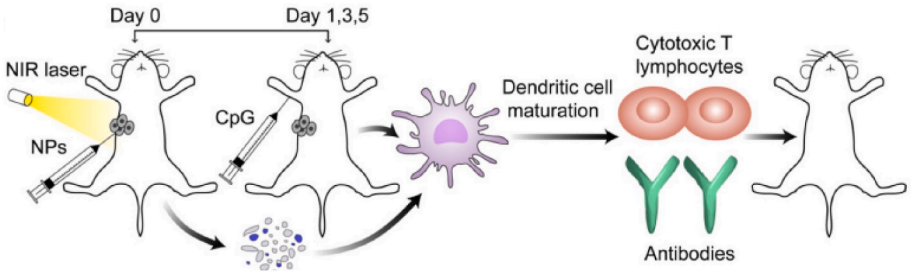

Fig. 8. Overall mechanism of combined photothermal and immunotherapy in tumor bearing mice [85].

amount of payload was released at acidic environment (pH = 1.2) which is equivalent to stomach media, it is rational to expect that uncontrolled release of the drug in stomach will not be an issue. In another study, Singh et al. [91], fabricated nano-porous alumina and modified it by β-cyclodextrin (BCD) for delivery of amoxicillin. It was observed that the activation of the drug loading in the mesoporous matrices occurred when amino acids provided molecular help. The intermolecular interactions between the medication and the specific amino acids are thought to be the cause of the molecular assistance effect, and these interactions have also been supported by many spectroscopic experiments. Also the drug-loaded BCD-modified system exhibited a sustained release pattern. Taking advantage of the porous network of alumina, da Costa et al. [92] added different percentages of starch to the inorganic particles and created a highly porous structure which showed a sustained and gradual release profile. They also achieved that increase in temperature led to decrease in porosity, thereby lowering the absorption Bupivacaine hydrochloride. In another work, Teixeira et al. [73] synthesized a composite of hydroxyapatite and alumina to enhance the physical characteristics of hydroxyapatite which lacks satisfying mechanical strength. Hydroxyapatite/alumina complex was fabricated in diverse component ratios and the resulting formulations exhibited a controlled drug release pattern for ampicillin. As alumina increased in the component, the strength began to rise until the limit of 15%. Further increase did not conform the same trend due to the large porosity followed by higher salt precipitate amounts during preparation. Moreover, the potential of mesoporous anodic alumina for the sustained and gradual release of pesticides and insecticides, which are rich in 3-Indoleacetic acid (IAA) and bentazon was evaluated by Fazli-Abukheyli et al. [93]. They took into consideration the fact that the growth in the pore diameter results in an improvement of the release rate; whereas an increase in the pore length leads to a reduction in release rate. Their second experiment employed nano-porous anodic alumina as a membrane to configure and shape a stock device for the release of bentazon. They concluded that the growth in the pore diameter causes a rise in the amount of released drug, whilst an opposite result is obtained with growing of the pore length. In another study, Ali [94] and coworkers functionalized alumina whiskers with PEG for delivery of photosensitizer agents. The PEG was used to ameliorate the biocompatibility. With the pore size of 62 nm, the outcome initially exhibits a burst release before approaching a consistent value, while being biocompatible. Table 2 shows a summary of application of alumina-based nanocarrier in drug delivery.

5. Conclusions and perspectives

Thanks to the exceptional structural and chemical characteristics of alumina, its application for drug transport has increased in recent years. Alumina NPs possess several suitable properties such as thermal stability, mechanical strength, high surface area, adjustable pore size, and modifiable surface. Regarding the mentioned capabilities whether in shape or physical properties, it is expected that further applications of this particular material would be utilized in loading process of the pharmaceutical drugs and achieve more information about the behavior in load into and release from its nanoporous formation. Moreover, mechanisms of anticancer and antibacterial activities are suggested to be concerned in vitro and especially in vivo. In vivo tests offer a better understanding of the immunological reactions to the biomaterial, despite the fact that in vitro trials may aid in understanding the overall cell responses to the material. Simple in vitro experiments like MTT, in particular when used to alumina nanoparticles, were unable to accurately predict the biological reactions to the wear particle surface. Moreover, there were still some issues with its clinical application. More research should be assessed on some factors, such as the method used to process the powder, the sintering temperature, rate, and time, and the chemistry present at the grain boundaries, which affect how alumina behaves when it is being produced.

Considering the fact that biocompatibility could be a key challenge for pure alumina, it is also crucial to make some additional suggestions or possibly change the ones that have already been studied in order to treat its surface and achieve outstanding immune system responses. Alumina's surface can be modified by biomolecules to make it more bioactive and facilitate protein adsorption on its surface. Hence, interactions between alumina and biological cells can be improved this way. MeAl can be used in pure form or in a nanocomposite as a drug carrier. Its high surface area can ensure desirable loading capacity for the cargo. Various ligands with sensitivity to receptors of cancerous cells can be attached to its surface to help it distinguish healthy cells from cancerous ones. In this way, the cellular uptake of the loaded drug and therapeutic efficiency will increase significantly. Also, the side effects will be minimized. Furthermore, based on the investigated reports of the

Table 2
A summary of application of alumina-based nanocarrier in drug delivery.

Formulation	Drug	Particle size (nm)	ZP (mV)	Entrapment efficiency (EE) and drug loading (DL) %	Study route	Release	Major results	Ref
CS/PVP/γ-alumina	QC	141	−47	EE = 95.5% and DL = 63%	In vitro	Within 24 h, 27% of QC was released at Ph = 7.4, while 59% of QC was released at Ph = 5.4 at the same time.	Less release in normal cells and more release in cancer media	[17]
Hydroxyapatite/alumina	Ampicillin	603	–	–	In vitro	Within 24 h, 5.29% of the drug was released at Ph = 7.4.	Improved strength and managed drug release pattern	[73]
Hyaluronic acid/alumina	PAC	–	–	DL = 29.45	In vitro	Within 24 h, 89.03of PAC was released at Ph = 7.4.	Sustained release, prevention from PAC	[79]
Zinc/alumina/titanium dioxide	Vitamin C	30–40 nm	–	0.12 μg in Al_2O_3, 0.7 μg in TiO_2	In vitro	Within 15 h, 50% of Vitamin C from Al_2O_3 was released at Ph = 7, while this amount of release is for within 10 h at Ph = 5.	Ph-sensitive release	[84]
Polydopamine/alumina	–	344.4	−2.48	–	In vitro-In vivo	–	High photothermal efficiency	[85]
Mesoporous alumina/BCD	Amoxicillin	–	–	DL = 36%	In vitro	Within 1 h, 15% of amoxicillin was released at Ph = 1.75.	Slow and sustained drug release	[91]
Alumina/starch	Bupivacaine	–	–	15.84% loading in alumina with 10% starch.	In vitro	80% of the drug was released from alumina with 10% starch.	Better absorption and release in the sample with the highest starch concentration	[92]
NAA	IAA, bentazon	–	–	100–106 mg/ml initial load for IAA	In vitro	70% of IAA was released in the first 2–3 h and 80% of bentazon was released in the first 24 h.	Two-stage mechanism for release rate	[93]

literature, some alumina-containing composites are responsive to certain stimuli such as pH or temperature. This will further help to controlled release of the drug in the intended sites.

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.

Data availability

The authors are unable or have chosen not to specify which data has been used.

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