Review

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Abstract: Due to the ever-increasing interest in the use of nanomaterials based on rare earth metal nanoparticles in medicine, in this review we considered the interaction of cerium dioxide nanoparticles with the main excipients used in the development of cerium-containing pharmaceutical compositions for biomedical applications. The review was conducted on the international databases PubMed and ScienceDirect, and included original research and literature reviews. Publications devoted to the use of cerium dioxide in disease diagnosis, analysis of other substances, and branches of scientific knowledge other than medicine were excluded. Following the selection process, 171 publications were analyzed, from an initial selection of 3,344 papers. Based on the experimental results and the possibility to extrapolate them to humans, we compared polyacrylate, polyvinylpyrrolidone, dextran, hyaluronic acid, chitosan, polycarboxylic acids, in particular citric acid and its salts, lecithin and phosphatidylcholine in the context of conservation of biological effects of cerium dioxide and its physicochemical properties, as well as the degree of study of these combinations from the standpoint of creating drugs for biomedical use.

Keywords: nanoparticles; excipients; lanthanides; rare earth metals; cerium; nanocerium; cerium dioxide. biopolymers; liposomes; polyvinylpyrrolidone; hyaluronic acid; chitosan; polyacrylate; dextran; citrate; lecithin; phosphatidylcholine; antitumor; antioxidant; antimicrobial; regenerative

1. Introduction

Rare earth metal nanoparticles are becoming increasingly popular in the modern world for solving a number of biomedical problems. The number of data and publications has recently increased significantly, however, there are still many questions and problems regarding the creation of final dosage forms based on them [1]. One of the well-established lanthanides is cerium, a metal possessing labile variable valence and having two oxide forms [2]. The peculiarities of the crystal lattice structure give it antioxidant and enzyme-like activity [3,4]. The most promising form at the moment is recognized as cerium dioxide [5], which, according to many studies, has regenerative [6–9], antimicrobial [10–12] and redox activity [13–16]. According to a number of studies, not only the choice of synthesis method [5,17], but also the choice of excipient [18] are important aspects that ensure and even enhance these effects.

Excipients, which are commonly understood as components that do not have the properties of a drug substance, for a long time were positioned as completely indifferent substances [19], and their main functional values were mainly attributed to the properties of adjusting the organoleptic properties of preparations [20], giving the optimal dosage form [21], increasing the weight of the

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dosage form [22], facilitating dosing [23], providing resistance to adverse environmental factors [24]. Later it was found that many of them have their own pharmacological activity [25], and can reduce [26], and sometimes on the contrary, increase [27,28] the level of toxicity, affect the rate of release [29] and activity of the main active ingredient [30]. It was also shown that new compounds could be formed during the interactions, and, consequently, the properties of the final product changed too [31].

Thus, the selection of an excipient is a very important task, because in addition to providing the proper level of effect, stability, it should also have the property of high biocompatibility, and in the case of lanthanide nanoparticles, and the ability to prevent their aggregation, and therefore to ensure their nanoscale and ability to overcome biological membranes, which also plays a leading role in the realization of the effectiveness of this group of drugs. Given the fact that the effects of rare earth metal nanoparticles and cerium itself are not sufficiently studied, it is not enough to consider only the assumed results of their interaction with excipients, relying only on the data of physical and chemical properties of individual substances.

Due to the combination of these factors, in this review we considered the main excipients (biopolymers, carboxylic acids and their salts, as well as lipid derivatives) used in the synthesis of nanoceria and studies of the properties of cerium dioxide, allowing to preserve its specific physicochemical and biological properties, as well as the degree of investigability of these interactions.

2. Materials and Methods

This review was conducted on the international databases PubMed and ScienceDirect. For the PubMed database, searches were performed using the keywords: “rare earth metals“ and “excipients“, “nanoparticles“ and “efficiency“ and “excipients“ and “medicine“, “cerium“ and “excipients“, “lanthanides” and “excipients”, “cerium oxide” and “hyaluronic acid”, “cerium oxide” and “polyvinylpyrrolidone“, “cerium oxide“ and “chitosan“, “cerium oxide“ and “dextran“, “cerium oxide“ and “lecithin“, “cerium oxide“ and “citrate“, “cerium oxide“ and ‘collagen“, “cerium oxide“ and “gelatin“. For PubMed, the data set was 3, 118, 28, 4, 10, 8, 57, 18, 2, 30, 34, 26 publications, respectively. According to the inclusion and exclusion criteria, the filters “Clinical Trial”, “Meta-Analysis”, “Randomized Controlled Trial”, “Review”, and “Systematic Review” were set. For the categories “cerium” AND “excipients”, “lanthanides” AND “excipients”, “cerium oxide” and “hyaluronic acid”, “cerium oxide” and “polyvinylpyrrolidone”, “cerium oxide” and “chitosan”, “cerium oxide” and “dextran”, “cerium oxide” and “lecithin”, “cerium oxide” and “citrate”, “cerium oxide” and ‘collagen’, ‘cerium oxide’ and ‘gelatin’ search restrictions were not imposed due to the technical absence of classification of publications on this query in the PubMed system. The final number of publications for analysis was 1, 12, 28, 4, 10, 8, 57, 18, 2, 30, 34, 26, respectively.

Given the lack of database specialization in medical, biological and pharmaceutical fields of scientific knowledge, the query was adjusted for ScienceDirect by the keywords: “rare earth metals” and ‘excipients’, ‘metal-based nanoparticles’ and ‘efficiency’ and ‘excipients’ and ‘medicine’, ‘cerium’ and ‘excipients’ and ‘medicine’’, ‘lanthanides’ and ‘excipients’ and ‘medicine’, ‘cerium oxide’ and ‘hyaluronic acid’, “cerium oxide” and ‘polyvinylpyrrolidone’, ‘cerium oxide’ and ‘chitosan’, ‘cerium oxide’ and ‘dextran’, ‘cerium oxide’ and ‘lecithin’, ‘cerium oxide’ and ‘citrate’, ‘cerium oxide’ and ‘collagen’, ‘cerium oxide’ and ‘gelatin’. The number of publications were 77, 34, 273, 190, 644, 750, 2432, 713, 192, 1650, 1085, 1028, respectively. According to the inclusion and exclusion criteria, “Review articles” and “Research articles” filters were applied, resulting in a number of publications of 46, 18, 160, 105, 440, 533, 1598, 471, 112, 1222, 755, 670. In order to limit the data set to the target field of scientific knowledge, additional filters were used: “Biochemistry, Genetics and Molecular Biology”, “Materials Science”, “Pharmacology, Toxicology and Pharmaceutical Science”, “Medicine and Dentistry”, “Immunology and Microbiology”, “Agricultural and Biological Sciences”, “Neuroscience”. The number of publications according to the filters used was 31, 16, 120, 69, 321, 271, 271, 901, 331, 84, 248, 543, 457. No restrictions on the date of publication were imposed.

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Thus, the sum of publications selected for further study was 200 for PubMed and 3144 for ScienceDirect. During the initial analysis, publications considering nanoparticles as a delivery system for other pharmaceutical substances, cerium as an oxidizing agent in the analysis of quantitative content of other pharmacologically active substances or a biosensor, lanthanides as detection reagents were excluded. This work does not exclude from the analysis publications that consider nanoparticles as a non-targeted research object or as model substances, as well as works that are not in the public domain.

Inclusion criteria for this study were as follows: availability of verified assessment of the effect of excipients on the efficacy of the active pharmaceutical substance; type of publications - systematic reviews, meta-analyses, clinical studies; field of research - biology, pharmacology, toxicology, pharmaceutical technology.

The following parameters were identified as exclusion criteria: studies on the application of nanoparticles and rare earth metals in environmental monitoring, analysis of substances using nuclear magnetic resonance and fluorimetry, manufacturing of stents and implants, as well as areas of scientific knowledge not directly related to biomedicine (energy, engineering, physics and astronomy). Publications that are descriptions of individual clinical cases, mini-reviews, patents, methodological guidelines, and conference abstracts. This review also does not consider the issues of diagnostics and application of rare earth metals as tools for instrumental methods of research. Materials devoted to the use of cerium and its derivatives as a fluorescent indicator in determining drug concentrations in biological fluids were not included. The paper does not consider the use of auxiliary substances during the synthesis of nanoparticles and the influence of reagents on the structure of particles.

3. Results

3.1. Results of the Literature Search and the Final Flowchart of the PRISMA Search Strategy

According to the results of the analysis, the number of papers meeting the above criteria amounted to 171 publications from an initial selection of 3,344 papers. Meta-analyses and systematic reviews on the given parameters are absent in the considered databases. Among the original studies, in vitro experiments predominate, the largest number of which falls on the work with cell and tissue cultures. 100% of authors use small rodents (rats, mice) as experimental animals. Studies involving humans are much less common. Among them only 50% are randomized controlled.

Analysis of review articles showed that in 96.52% of cases there is no description of the methodology of literature selection. The remaining 3.48% indicated the databases involved, including a detailed search strategy in 2.61%. Review articles do not aim to assess the effect of excipients on pharmacodynamic, pharmacokinetic and toxic parameters of nanoparticles in 100% of cases. Changes in these parameters are presented in the context of describing the properties of the excipients themselves. The final Flow diagram of the search strategy is presented in Figure 1.

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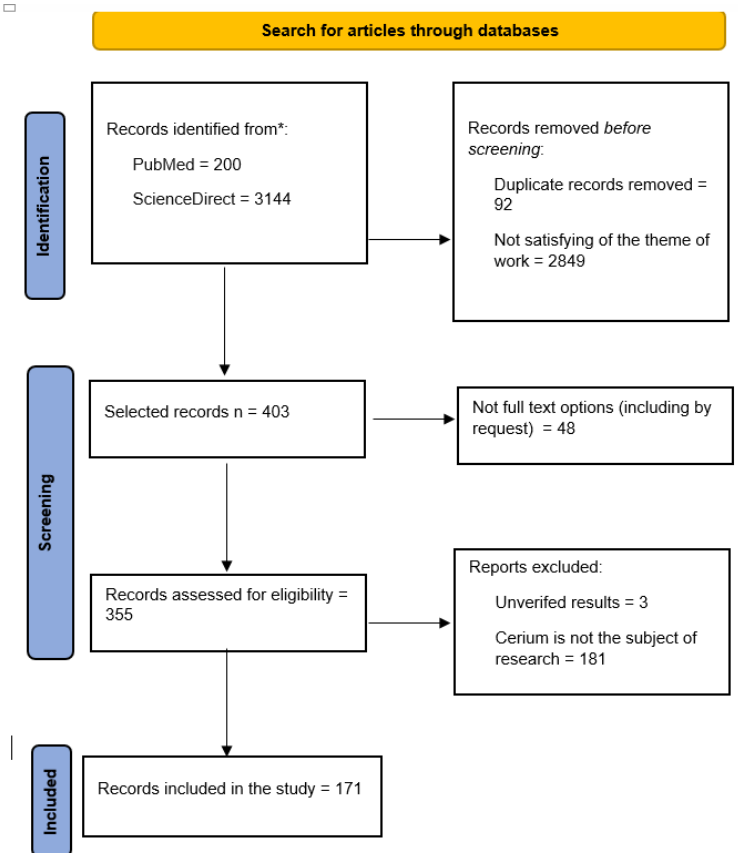

Figure 1. Final flowchart of the search strategy used to identify studies included in this review, based on PRISMA guidelines [Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71; https://creativecommons.org/licenses/by/4.0/.].

3.2. Cerium Dioxide Nanoparticles and Biopolymers

The main biopolymers used to stabilize cerium dioxide nanoparticles are hyaluronic acid, dextran, chitosan, polyacrylate and polyvinylpyrrolidone [32,33]. It has been observed that they can influence the bioavailability values and pharmacological effects of cerium oxide [31,34]. For some biopolymers, such as, for example, polyacrylate, information on these properties is limited to data on cytotoxicity and isolated reports on the intensification of antiviral action of nanoceria [35]. For others, however, the interactions are very specific. These include polyvinylpyrrolidone, a hydrophilic, biodegradable, and nontoxic biopolymer that has good stabilizing properties and is widely used in medicine [36,37]. In particular, polyvinylpyrrolidone-coated cerium oxide shows antioxidant and cytoprotective effects in brain injury in an in vitro study using neuroblastoma and U937 cells and in vivo study involving rats [36,38]. It was observed that the antibacterial and regenerative properties of nanoceria were not reduced by this stabilization approach [38,39]. Limited in vitro studies evaluating the toxicity and toxicokinetics of cerium nanoparticles stabilized with polyvinylpyrrolidone are also mentioned in the literature. They report the absence of signs of cytotoxicity and apoptosis in cell cultures; however, activation of the EB transcription factor was observed, which, on the one hand, may find its application in the development of treatments for diseases associated with impaired lysosome function, and on the other hand, may be one of the early signs of specific toxicity of metal nanoparticles [40].

In contrast to the aforementioned little-studied combinations, the so-called “dextran synthesis” is among the most popular techniques for the preparation of nanoceria due to its high biocompatibility and relative simplicity of the fabrication methodology [31,32,41,42]. In addition to the stabilizing effect itself, the use of dextran increases the antibacterial effect of cerium oxide nanoparticles, including against antibiotic-resistant Escherichia coli (E. coli) biofilms [43]. High pharmacological activity of dextran-nanoceria complex against such microorganisms as S. aureus, S.

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epidermidis, E. coli, E. faecalis and P. aeruginosa has been noted [31,44–47]. It should be noted that its intensity properties of the dextran-nanoceria complex are dose-dependent, and according to several researchers has an optimum of pH=9 [31,45,48].

According to the findings of in vitro experiments by Kim S. J. and Chung B. H., the redox properties of nanoceria also depend on the acidity value of the medium [49]. On the one hand, this imposes certain limitations on the use of cerium oxide as an antioxidant, on the other hand, it opens a prospect as an antitumor agent, since cells of malignant neoplasms have slightly acidic pH [50]. Under in vitro conditions, dextran-coated nanoceria had a highly selective cytotoxic effect on cultures of osteosarcoma, A375 melanoma, and neuroblastoma cells; it did not protect lung carcinoma (A-549) and breast carcinoma (BT-474) cells from oxidative stress, while normal cell cultures remained intact [51–53]. A comparative analysis of the antitumor effect of cerium oxide and cerium oxide coated with dextran was performed using HeLa cells as an example by Miletić M. et al. The latter had a more pronounced cytostatic effect in vitro [54]. The observed phenomenon is probably due to the combination of functional groups on the cerium surface as well as their own redox properties [55,56]. The antitumor effect was also dose-dependent [32].

An alternative biocompatible polymer candidate for the role of excipient for nanoceria is hyaluronic acid. In addition to stabilizing cerium oxide, it has many additional functions. In particular, its compositions have anti-atherosclerotic and anti-inflammatory effects associated with the ability to bind to CD44 receptors of cells [57–59]. Further comparison of nanoceria+hyaluronic acid composition, free nanoceria and its complex with dextran by Wang S. et al. demonstrated greater antiatherosclerotic efficacy of hyaluronic acid. However, the studies were carried out only in vitro on human fibroblast cell cultures, so at the moment it is difficult to assess the scale of prospects for the use of this organometallic complex and its biocompatibility [57].

At the same time, the anti-inflammatory effect was demonstrated regardless of the causes of pathology development (from the model of radial tissue damage to osteoarthritis) and was often accompanied by a regenerative effect [60–62]. In addition to favorable effects on cells, several studies indicate the ability of this combination to improve the function of ischemic organs [63–65] as well as modulate the microenvironment [66].

With regard to malignant neoplasms, the role of hyaluronic acid compositions has been described in the context of induction of apoptosis of triple negative breast cancer cells, and as a means of enhancing the efficacy of photodynamic therapy and photothermal therapy [32,67–69]. These directions, as estimated by Zeng L. et al. from 2021, are named as one of the main vectors for the development of effective tumor treatment [70]. The role of hyaluronic acid in the application of this composition in oncology is to provide a targeting effect on tumor tissue [71]. Antibacterial properties of the combination are considered at additional introduction of zinc into the organometallic complex of cerium and hyaluronic acid, thus providing strengthening of antibacterial properties due to synergism of metallic nanoparticles. When studied on a wound surface, the role of hyaluronic acid in this case was to intensify the healing of lesions. The differences with the control group were statistically significant. At the same time, the authors of the work draw attention to the need to balance the target effect and independent toxicity of nanoparticles [72]. Undoubtedly, additional research is required, as the use of nanoceria may become one of the possible ways to overcome antibiotic resistance [31].

One of the most studied at the moment are compositions of cerium oxide nanoparticles with chitosan. They are recognized as biocompatible, possessing a homogeneous structure, and the particle size remains consistently smaller relative to other excipients [32,73,74]. According to the assessment of Fahmy H. M. et al. dated 2020, this is of particular importance for nanoparticles as it is directly related to the risk of toxic effects [75]. It should be noted the good solubility of this combination, as well as betraying the surface of cerium oxide with a positive charge [32,64,76]. It is believed that this approach reduces potential toxicity and also provides good adhesion to mucosal tissues [77,78].

Current publications provide a considerable amount of information on a wide range of antibacterial activity, including for MRSA [39,76,79,80]. Only for chitosan-nanoceria, results on the

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presence of high fungicidal activity against Aspergillus aureus and Agaricus volvaceus were revealed [81,82]. The described effects together with the regenerative properties of cerium oxide are a promising direction for the development of therapy of diabetic wounds, as well as bone tissue engineering - some of the most labor-intensive areas of regenerative medicine [83–88]. Important factors complementing the described pharmacological features are the combined prolonged release of cerium oxide (48 hours), the ease of application in the form of a gel or the possibility of exploitation in the form of a medical device (dressing) [85,89–92]. In all these directions of use, additional cytoprotective action is realized due to antioxidant effect [93]. The preservation of this property of cerium when coated with chitosan, also gives the possibility of using the composition in spinal cord injury, thus realizing a neuroprotective effect [94–97]. Interestingly, of the most investigated interactions of cerium oxide with excipients, only for the chitosan-nanocerium composition, it remains extremely limited considered in the direction of oncology. Targeting retinoblastoma cells has been described in the literature, which presumably should reduce the risk of development and severity of systemic side effects, as well as reduce tumor resistance to existing therapeutic options [98–101]. For advanced breast cancer, a different modification was proposed by Wang S. et al. Rods combining graphene, cerium and chitosan were proposed to target metastatic foci in bone tissue. As a result, this composition induced apoptosis of tumor cells through activation of caspase-3 protease, and also stimulated bone tissue regeneration through the BMP2/Smad signaling pathway [57]. In turn, attempts to combine cerium and chitosan nanoparticles with antimetabolite drugs under in vitro conditions did not demonstrate an increase in efficacy compared to samples containing only fluorouracil and chitosan and supplemented with silver nanoparticles [102].

In contrast, a considerable amount of data addresses the question of the possibility of using nanoceria-chitosan in ophthalmology [103]. The potential for use in the therapy of age-related macular dystrophy has been described due to protection against apoptosis, decreased production of anti-inflammatory cytokines, reduction of oxidative stress, and several other factors [64,104–109]. It is believed that the increase and acceleration of permeability by 42-43 times for cerium oxide is achieved precisely due to the addition of chitosan to the composition [110–113]. The antioxidant properties of nanoceria lead to a decrease in the severity of dry eye syndrome under experimental conditions by increasing the activity of bocaloid cells [114,115]. Improvement of morphological characteristics of conjunctival and corneal cells in vitro and in a mouse model was observed [111,115,116]. Biocompatibility was evaluated on ARPE-19 cell culture. As a result, no signs of inflammatory reactions were found, which emphasizes the promising application of chitosan-containing formulations [117]. The introduction of an additional pharmaceutically active substance (pilocarpine) into the complex of nanoceria and chitosan makes it possible to expand the range of applications in ophthalmology while maintaining the potentiating effect on the permeability of the complex through the cornea. It is claimed that the bioavailability of pilocarpine increased 250-fold under in vivo conditions [111–113]. Thus, such multifunctional systems can provide biocompatibility, reduce oxidative stress, and decrease the effects of inflammatory factors [118]. In addition, compositions containing nanocerium, chitosan and alginate have been developed. The role of cerium was to impart antibacterial effect to the membranes. The organic component provided elasticity of the products and stability under deformation. The additional use of carboxymethylcellulose in the composition brought adhesive properties and gel structure of the complex [119].

Special role in the creation of cerium-containing pharmaceutical compositions is played by such hydrophilic biopolymers as collagen and gelatin [120–122]. Due to their high biocompatibility [95], optimal rheological [123] and stabilizing properties [39], mucoadhesion, and high affinity to the tissues of the wound surface, they have found application in a wide range of directions for the development of agents for use in medicine [124–126]. In particular, optimal values of mechanical strength and porosity have led to the development of agents designed for dentistry and bone tissue engineering [84,126]. According to in vitro and in vivo studies, collagen scaffolds promote accelerated tissue regeneration and differentiation in the injured area [84,126]. According to Chen X.et al. assumption, it is a response to a specific stimulus - generation of reactive oxygen species. Synergism of antioxidant action of nanoceria and biopolymer matrix was noted [127]. When working with

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ovarian cancer cells, it was found that this combination may be a candidate for the role of an antitumor drug [128]. In the study of Zubari W.et al. it was found that when cerium oxide is replaced by its peroxide, it is possible to achieve intensification of angiogenesis processes to improve the healing of chronic wounds [129]. As a result of Inbasekar C. and Fathima N. N. experiment with collagen fibers obtained ex vivo, not only biopolymer has a stabilizing effect on nanocerium [130], but also cerium dioxide increases the stability of collagen at the molecular level [131].

At the same time, a partial hydrolysate of collagen, gelatin, has gained much more popularity in biomedicine. Like its predecessor, gelatin incorporating cerium oxide has been considered as a gel framework in bone engineering [84] and dentistry [132] with pronounced regenerative properties [133]. According to Bhushan S. et al., the specific antioxidant and antibacterial properties of cerium oxide were retained and the proliferative effect on bone tissue was demonstrated under in vitro conditions on cell culture and in ovo [84]. These results are supported by in vivo studies performed on rats [134]. Xuerui Chen et al. and Jain A. et al. mentioned that the combination of gelatin and nanoceria has antihypertrophic properties for cardiomyocytes [135,136]. Regarding the wound surface, the composition under consideration demonstrates regenerative and antioxidant properties [32,137] on 3T3-L1 and HaCaT cell cultures [138,139], as well as in vivo [140,141], including in the presence of concomitant pathology, as shown in several studies using HaCaT, RAW264.7 cultures and in an in vivo model of diabetes [142–144]. Evidence of a favorable antibacterial efficacy profile is currently reported for a significant spectrum of microorganisms such as Pseudomonas aeruginosa [145,146], S. Aureus. E. Coli [147]. It should be noted that gelatin helps to increase the bioavailability and efficacy of nanoparticles and provides prolonged and uniform release, which may provide better tolerability in the long term [148–150]. A much smaller number of studies address the application of the combination of gelatin and nanoceria in other areas of medicine. A number of works provide data on the possibility of using this combination as an antioxidant and regenerative agent for stimulation and regeneration of neurons [64,151,152] on cell cultures and in vivo [153], anti-inflammatory [154], including in lesions of the central nervous system [155], as well as in cardiology [76] and ophthalmology [156].

In summary, it should be noted that numerous studies describe the interaction of cerium oxide and biopolymers. Their use is widespread, but none of them can be characterized only as a stabilizer, since biopolymers themselves are capable of producing additional effects, as well as influencing the efficiency and spectrum of action of cerium dioxide.

3.3. Cerium Dioxide Nanoparticles and Carboxylic Acid Derivatives

The considerable popularity of the use of carboxylic acids and their derivatives as stabilizers of cerium oxide nanoparticles is due to a combination of reasons. First of all, as it was mentioned earlier, the pharmacological effect of nanoceria is best realized at slightly acidic pH value. Another significant factor is the fact that the presence of three or more carboxyl functional groups provides aggregative stability of particles, contributes to the maintenance of biological effects of cerium, and also serves as an additional source of energy for ATP synthesis. [17]. Such stabilizers include mellitic [157] and aconitic acids [158], but at the moment the biological effects and the possibility of using their compounds with cerium in medicine are not considered in the literature. A larger amount of data is presented for L-amino acids. For cerium oxide synthesized with glycine, proline, valine, histidine, cysteine, and glutamic acid, in vitro studies have been carried out and the results showed high stability as well as the possibility of regulating the morphology of nanoparticles [159,160]. For cysteine and glutamic acid, an evaluation of their properties in the context of biomedicine has been carried out. In particular, David Schubert et al. concluded that cerium oxide nanoparticles reduce oxidative stress induced by glutamic acid ingestion in HT22 nerve cell culture [161]. In turn, derivatives of cysteine and cysteine with glutamic acid (acetylcysteine and cysteine-arginine-glutamic acid-lysine-alanine peptide) demonstrated antioxidant effects [162] and targeting effects on tumor tissue [163]. An antitumor effect was also found for acetic acid-stabilized cerium oxide as demonstrated in a study on DMEM, HT-29, NCBI -C466, HFFF2 and NCBI -C163 cell cultures [164]. There are currently no data on experiments evaluating the realization of other pharmacological

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effects of nanoceria. At the same time, 2024 publications indicate a renewed interest of the international scientific community in the application of carboxylic acids. A large-scale in vitro study of compounds with sixteen organic acids on the stability of cerium oxide nanoparticles revealed that nanoceria stabilized by citric, malic, and isolimonoic acids exhibited the highest aggregation stability [165]. For malic acid, high antibacterial activity against E. coli and S. aureus, including the reduction of biofilm formation, was additionally revealed [166].

The most studied as a stabilizer of cerium dioxide nanoparticles for medical applications is citric acid and its salts, which are highly biocompatible [167–169]. The addition of citrate makes it possible to achieve an optimal particle size (in the range from 1 to 7 nm), and also contributes to an increase in the permeability of cerium oxide through cell membranes due to the negative zeta potential and, as a consequence, intensification of the antioxidant effect and a significant reduction in toxicity [170–173]. A comparative analysis of cellular uptake of nanoceria stabilized by polymers and citric acid demonstrated the greater efficiency of the latter [174,175]. It should be noted that there is no universal way to realize the regenerative properties of cerium oxide + citrate at any phase of wound healing: biological activity can take opposite effects depending on the method of synthesis and the nanoparticle concentration used [17]. It is worth noting that citrate-stabilized nanoceria can be incorporated into polymeric pharmaceutical compositions by integrating into hydrogel matrix or microspheres c preserving antioxidant and regenerative effects [73,176,177]. The results of experiments on the antibacterial effect of citrate-stabilized cerium dioxide are currently contradictory. In an extensive study using 6 strains of bacteria and 2 strains of fungi, a dose-dependent antimicrobial effect was found, most significant for E. coli [178]. In another work, dated 1999, there was information about the low ability of citrate nanoceria to exert bacteriostatic or bactericidal effect [179]. This phenomenon can be explained by the fact that standard methods for assessing antimicrobial activity are not relevant for cerium oxide nanoparticles. Another way to solve the problem may be the correct selection of doses, as well as the connection with polymer carriers for increasing antibacterial activity and penetration the blood-brain barrier [178,180]. Pharmacokinetic parameters (in particular, distribution) may also be dose-dependent and correlate with the route of administration [181].

The unique spectrum of pharmacological effects noted for citrate-stabilized cerium dioxide is of particular interest. Current literature provides data on immunomodulatory and antiviral [35], prophylactic in sunburns [182], therapeutic in multiple sclerosis [183–185], as well as in reproductive disorders in males [186], and many other pathologies [98]. At the same time, the literature mentions contradictory data on the prooxidant, cytotoxic effect of citrate-stabilized cerium nanoparticles on the brain and liver parenchyma, which requires additional study of the safety profile [167,187–189].

3.4. Cerium Dioxide Nanoparticles and Liposomes

Like other representatives of rare earth metals, cerium nanoparticles have a high affinity for lipid compounds. It would be expected to offer an option for the production of liposomal forms of cerium nanoparticles. Such an approach has been investigated by coating the surface of cerium nanoparticles with surfactant (composed predominantly of lipids, among which phosphatidylcholine and lecithin predominate) [190–192]. According to the researchers' claims, such coating promotes endocytosis of the active compound. At the same time, a limitation was identified: the risk of aggregation of nanoparticles with proteins and lipids in the alveoli and, as a consequence, the risk of developing lung function disorders [192]. It should be noted that the studies were conducted using computer modeling, which introduces additional nuances when extrapolating the data to a real organism. The issue of private interaction between nanoceria and lecithin, a surface-active phospholipid that is a part of cell membranes of all living organisms, has been considered more fully in the literature. The data of in vitro studies of this composition turned out to be quite contradictory: no signs of cytotoxicity were revealed, but the antioxidant properties of cerium were also not manifested [193]. Opposite results with respect to free radicals were obtained with betaTC-tet insulinoma cells, as well as with respect to cytotoxicity in an in vivo study [188,194]. At the same time, lecithin has its own antioxidant properties [195]. It is worth noting that cerium also has an effect on lecithin, promoting

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its conversion to an organogel [196]. The combination of lecithin nanoliposomes and gel demonstrated synergistic antioxidant and anti-inflammatory effects when applied as a transdermal therapeutic system [197]. Consequently, it can be concluded that the interaction between cerium and lecithin is difficult to predict and ambiguous.

Separately, the combination of cerium and phosphatidylcholine was also considered, highlighting another potential problem for the embodiment of a technological solution: according to the results, cerium IV causes hydrolysis of phosphatidylcholine and other phosphoric acid esters at both acidic and slightly alkaline pH values. On the other hand, this observation may provide a foundation for the development of treatments for lysosomal accumulation diseases [198,199].

Thus, working with cerium poses additional problems to researchers that do not arise when working with other nanoparticles, including other lanthanides: preservation of the full range of its pharmacological effects, limitation of routes of administration due to the risk of adverse reactions in contact with surfactant, difficulties in selecting the composition to create biocompatible liposomal forms with satisfactory performance and stability. The main results of studies of interaction between cerium dioxide nanoparticles and excipients are summarized in Table 1.

Table 1. The result of the interaction of excipients and nanoceria.

Class of excipient	Excipient	Adding excipient before/after synthesis CeO_2	Effects	Methods	Sources
Biopolymers	Polyacrylate	Not synthesized	Growth inhibition	In vitro Chlamydomonas reinhardtii	[34]
	Polyacrylate	After synthesis	Antiviral	In vitro. L929, EPT and Vero cells	[35]
	Polyvinylpyrrolidone	Before synthesis	Negative impact on the growth and development of larvae	In vitro. Drosophila melanogaster	[37]
			Antioxidant	U937 cell line. in vivo	[36]
	Dextran	Before synthesis	High aggregative stability	In vitro	[31]
			Antimicrobial	E. coli P. aeruginosa, S. epidermidis E. faecalis	[31,45–47]
			Regenerative	Human fibroblasts	[31]
			Antioxidant	MIN6, NIH3T3, HEK293T, Osteoblasts	[41,49,51]
			Biocompatibility	Human fibroblasts HGF-1	[42]
			Cytotoxicity to tumor cells	Osteosarcoma cells MG-63	[51]
			Less absorption by cells compared to other stabilizers	BGC-803	[55]
			photosensitivity	HUVEC, CCL-30	[56]
	Dextran	After synthesis	High aggregative stability	In vitro	[43]
			Antimicrobial	E. coli, S. aureus	[43,44]

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		Regenerative	NIH 3T3, In vivo	[44]
		Antioxidant	NIH 3T3, In vivo	[44]
		Slow release	neuroblastoma cells	[53]
		Cytotoxicity to tumor cells	neuroblastoma cells, HeLa	[53,54]
Dextran	Not synthesized	Cytotoxicity to tumor cells	A549, HCT116, Hep3B, Caco-2 и HeLa	[52]
Hyaluronic acid	Before synthesis	Cytotoxicity to tumor cells	In vivo, MCF-7	[70]
		Anti-inflammatory	In vivo, ARPE-19, L929, RAW264.7, BV2	[66]
		Anti-atherosclerotic	In vivo, MOVAS, RAW 264.7	[57]
Hyaluronic acid	After synthesis	Antioxidant	In vivo, HucMSC, Chondrocytes, Fibroblasts	[57,59,65]
		Cytotoxicity to tumor cells	Fibroblasts, MDA-MB-231, KB, CT-26, MDA-MB-231	[59,68,71]
Chitosan	Before synthesis	Biocompatibility	WEHI 164, ARPE-19	[74,108]
		Cytoprotective	ARPE-19, umbilical cord endothelium	[108]
		Antimicrobial	S. aureus, E. coli	[85]
		Antioxidant	In vivo	[115]
Chitosan	After synthesis	Antioxidant	In vivo, in vitro	[78,83,90]
		Antimicrobial	S. aureus, E. coli, B. subtilis, MSSA, MRSA	[78,79,81,83,84,86,90]
		Regenerative	Fibroblasts, In vivo, human mesenchymal stem cells, ex vivo, L929, MC3T3-E1 cell	[73,78,83,84,90,97]
		Biocompatibility	In vivo, mesenchymal stem cells, MC3T3-E1	[73,77,84,87,90]
Collagen	Before synthesis	Stabilization of collagen fibers	Ex vivo	[131]
Collagen	After synthesis	Antioxidant	in vivo, Ovarian cancer cells	[127,128]
		Regenerative	hDPSC, in vivo	[126,127]
		Anti-inflammatory	in vivo	[127]
		Acceleration of angiogenesis	in vivo	[129]
Gelatin	Before synthesis	Antioxidant, antihypertrophic	ex vivo	[136]

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	Gelatin	After synthesis	Antioxidant	MC3T3-E1, In-ovo, L929, MG-63, HaCaT	[84,133,139,147]
			Anti-inflammatory	in vivo	[155]
			Antimicrobial	S. Aureus. E. Coli	[84,139,147]
			Regenerative	in vivo, HaCaT, RAW264.7, MG-63, MC3T3-E1	[133,134,139,141,142,144]
	Gelatin	Not synthesized	Antioxidant	SH-SY5Y	[151]
			Regenerative	in vivo	[153]
			Antimicrobial	P. aeruginosa	[146]
Fatty substances	Lecithin	After synthesis	Biocompatibility	ram sperm	[193]
			Antioxidant	ram sperm, HaCat	[193,197]
Phospholipids	Phosphatidylcholine	Before synthesis	Antioxidant	betaTC-tet	[194]
Polycarboxylic acids	Mellitic acid	Before synthesis	Stability	In vitro	[157]
Dicarboxylic acids	Malic acid	After synthesis	Stability	In vitro	[165]
Monocarboxylic acids	Acetic acid	After synthesis	Antitumor	DMEM, HT-29, NCBI -C466, HFFF2, NCBI -C163	[164]
Polycarboxylic acids	Citrate	Before synthesis	Antioxidant	In vivo	[170,176,186]
			Regenerative	Fibroblasts, human mesenchymal stem cells, human keratinocytes In vivo	[17,176]
			Antimicrobial	B. subtilis, B. cereus, S. aureus, P. aeruginosa, E. coli, P. vulgaris, C. albicans, A. brasielensis	[178]
			Stimulation of bacterial growth	E. coli, B. pyocyaneus, S. aureus, Leuconostoc, Streptococcus faecalis	[179]
			Lack of pro- or antioxidant	In vivo	[180]
			Prooxidant	In vivo	[187]
			Cytoprotective	L929, VERO	[182]
	Citrate	After synthesis	High cellular uptake	NIH/3T3	[174]
			Toxicity in high doses	NIH/3T3	[175]
			Prooxidant	NIH/3T3, In vivo	[175,188]

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			Accumulation in the reticuloendothelial system	In vivo	[167]
			Regenerative	Fibroblasts, human mesenchymal stem cells, human keratinocytes	[17]
			Antioxidant	In vivo, RAW264.7, Hippocampal ischemia-based model of oxidative stress ex vivo	[183,184]
			Antioxidant	In vivo	[171]
	Citrate	Not synthesized	Reduced toxicity	Caco-2	[173]
			Pharmacokinetics dependence on the route of administration and dose	In silico	[181]
			High aggregative stability	In vitro	[34]
Amino acids	Glutamic acid	After synthesis	Antioxidant	HT22	[161]
Amino acid derivatives	N-acetylcysteine	Not synthesized	Antioxidant	SMMC-7721	[162]

In summary, it should be noted that the original studies are represented mainly by in vitro studies, which makes it difficult to draw conclusions regarding the behavior of the considered pharmaceutical compositions in the human body. The interaction between nanoparticles (including cerium oxide nanoparticles) and excipients has not been studied at the moment, this issue is only indirectly addressed.

4. Discussion

In this work, we did not consider the intrinsic pharmacological activity of cerium, but we considered the final set of possible effects when adding different excipients. In analyzing the literature data from a number of studies, we focused on the requirements of excipients and their significant effects when interacting with cerium dioxide, namely:

1) Maintaining nanoscale dimensionality. To this end, various stabilizers are used, introduced before or after synthesis to prevent particle aggregation.

2) Biocompatibility. For metallic nanoparticles, the main critical parameter is the absence of cytotoxicity to normal body cells.

3) Preservation of intrinsic pharmacological activity of nanoceria. The realization of this requirement is based on the need to maintain the optimal amount of the introduced excipient in order to avoid blocking access to the site of application of the effect (e.g., bacteria or body cells. In this case, the formation of new nanocomposites with enhanced or completely new properties is possible as in the case of dextran [31].

Various biopolymers as well as citric acid and its salts fulfill these requirements to a greater or lesser extent. The choice of the optimal excipient from this range of compounds may differ depending on the purpose of application as well as on the dosage form. Dextran should be considered the most studied and promising at the moment. There are enough studies in the literature describing the preservation of the main therapeutic properties of cerium dioxide, in particular, antioxidant

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[41,43,44,49,51], antibacterial [31,45–47] and regenerative [31,44]. The biocompatibility and efficacy of dextran stabilization are also unquestionable based on a significant number of studies on various cell cultures [31,41,42,44,49,51]. The optimal way of introducing this stabilizer from the position of efficiency of the final composition, is the addition of dextran before the synthesis process [31,41,42,45–47,49,51]. At the same time, similar data were obtained for nanocomposites obtained by stabilization after synthesis, but in a much smaller volume, which requires additional studies [43,44,53,54]. The second potential candidate is chitosan. Being biocompatible [73,74,77,84,87,90,108] and having its own antibacterial properties, it also retains all the main effects of cerium dioxide [78,79,81,83–86,90,97,108,115]. However, unlike dextran, there is no sufficient data on its ability to have a selective cytotoxic effect on tumor cells, as well as prolonged release.

Information on the interaction of other excipients with cerium dioxide is rather limited. In particular, hyaluronic acid may be an optimal solution when setting the task of realizing the antioxidant effect of nanoceria [57,59,65]. Citric acid, despite the high popularity of its use as a stabilizer, demonstrates very contradictory biological effects (both toxic [175] and opposite to those typical for cerium [175,179,187,188]) in vivo, which creates a primary need for a full-fledged and multistage assessment of acute and chronic toxicity of citrate-stabilized cerium dioxide, as well as a more detailed study of its effect on bacteria.

The biological interaction of nanoceria compounds with other excipients such as polyacrylate [34,35], polyvinylpyrrolidone [36,37], phosphatidylcholine [194] and lecithin [193,197] etc. is currently insufficiently studied and does not allow us to draw a reasonable conclusion about the safety and efficacy of these pharmaceutical compositions.

5. Conclusions

In connection with the above, it can be concluded that the development of specific forms of drugs and products for medical use requires careful selection of excipients and a complete step-by-step study of them under in vitro, ex vivo and in vivo conditions. At the moment, the most studied and safe excipients are biopolymers, in particular, dextran and chitosan. According to the results of the analysis, they allow to maintain all specific biological effects known for cerium dioxide, do not adversely affect the physicochemical properties of the nanoparticle, and have a satisfactory safety profile. The possibility of using other excipients requires additional studies.

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