Journal of Advanced Veterinary Research

https://advetresearch.com

Nanoparticles and their Potential Applications in Veterinary Medicine

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ARTICLE INFO

Review Article

Received:
16 August 2020

Accepted:
26 September 2020

Keywords:

Nanotechnology, Medical applications, Veterinary medicine, Animal nutrition, Reproduction

ABSTRACT

Nanotechnology is the innovative and evolving technology with enormous potential for global revolutionization of animal sector. It offers the same opportunities for veterinarians as physicians, including therapy, diagnostics, tissue engineering, manufacturing of vaccines, and modern disinfectants. The nano-applications are already in use in animal health and production, animal husbandry and reproduction and animal nutrition. It has the ability for solving several problems associated with animal health. This review will throw the light on nanoparticles synthesis, classification, characterization, and their applications in veterinary field starting from medical applications to using the nanoparticles in animal nutrition and reproduction.

J. Adv. Vet. Res. (2020), 10 (4),268-273

Introduction

Nanotechnology has been integrated into our everyday life over the last years. Nanotechnology is an increasingly growing technology that has a significant role in numerous disciplines of therapeutic applications (Youssef *et al*., 2019). It is an important area of modern science concerned with synthesis, design, and particle structures manipulation varying from approximately 1-100 nm (Naganathan and Thirunavukkarasu, 2017). A growing number of applications and products have become available containing nanomaterials or at least with nano-based statements (Bleeker *et al*., 2013).

Nanotechnology is the use of a material of at least one dimension of nanometer scale for the development of products, tools or structures of novel or substantially enhanced properties owing to their nano-scale (Yadav *et al*., 2006). The nanomaterials have higher potential than their traditional sources and thus reduce the needed quantity (Torres-Sangiao *et al*., 2016).

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Nanomedicine is nanotechnology application for disease monitoring, diagnosis, control treatment, and prevention (Tinkle *et al*., 2014). Nanomedicine includes the utilization of nano-sized materials in a living organism, such as biocompatible nanoparticles and nanorobots (Hawthorne *et al*., 2017). Nanomedicine was applied to increase the efficacy and reduce adverse reactions by changing the effectiveness, safety, physicochemical and pharmacokinetic / pharmacodynamic properties of the original drugs (Dawidczyk *et al*., 2014).

Advantages of nanoparticles

Throughout the biomedical sector, nanoparticles (NPs) are also structured in a way that drug / bio-molecules can be incorporated and not damaged at undesirable locations that can help the medication enter the target site more effectively. Often, NPs can improve the circulation period of the therapeutic molecules loaded on nanomaterials and improve its residence at the target site through leaky vasculature by enhancing permeation and retention effects (Haley and Frenkel, 2008; Blanco *et al*., 2015). Advantages of nanoparticles are; i) ability to manipulate particle properties such as size and morphology in order to achieve optimum passive/active drug tar-

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geting; ii) different routes of administraions; iii) higher carrier capacity; iv) improved bioavailaility; v) higher mobility and cellular uptake of NPs compared with microparticles; vi) controlled sustained release of the drug at the target site; vii) lower toxicity compared with other compounds; viii) ability to tailor a given particle in order to withstand detirmental pH, processing and enzymatic environments; ix) increasd retention time of NPs at mucosal surface by exploiting mucoadhesive formulation components; and x) increased circulation time so pharmacokinetics and pharmacodynamics were improved (Gelperina *et al.*, 2005; Wang *et al.*, 2007; Nair *et al.*, 2010; Zhang *et al.*, 2011; Yao *et al.*, 2015).

Nanoparticles classification

Nanoparticles are classified numerously based on their origin, form, structure and purpose of administration into:

Organic nanoparticles

Ferritin, dendrimers, micelles, and liposomes, etc. are widely recognized as the organic NPs or polymers. Such NPs are nontoxic, biodegradable, and certain particles like liposomes and micelles have a hollow core, also recognized as nanocapsules, and are vulnerable to light and heat thermal and electromagnetic radiation. Such special features make them an excellent alternative for drug delivery. Apart from their usual characteristics like size, structure, surface morphology, etc., the drug carrying power, its stability and delivery mechanisms, either trapped drug or adsorbed drug system decide their field of application and their performance. The organic NPs are used in biomedicine like drug delivery system as they are effective and also can be injected on specific site (Tiwari *et al.*, 2008).

Inorganic nanoparticles

Metal based

NPs that are synthesized from metals to nanometric scales by constructive or destructive methods are named as metal based NPs. Almost any of the metals may be synthesized into their NPs. Silver, cadmium, aluminium, cobalt, copper, iron, lead, gold, and zinc are the widely used metals for NPs synthesis (Reverberi *et al.*, 2016).

Metal oxides based

Metal oxide-based NPs are synthesized to change the features of their respective metal-based nanoparticles, such as iron (Fe) nanoparticles instantly oxidizing to $Fe2O3$ in the presence of $O2$ at room temperature, which increases their reactivity compared to iron nanoparticles. Metal oxide NPs are primarily synthesized due to their increased reactivity, and efficiency (Tai *et al.*, 2007).

Carbon based nanoparticles

The nanoparticles made entirely from carbon are known to be carbon based. These can be categorized into fullerenes, graphene, carbon nano tubes, carbon nanofibers and black carbon and often nano-sized activated carbon (Bhaviripudi *et al.*, 2007).

Nanoparticles synthesis

Nanoparticles synthesis is usually performed using chemical, physical, and biological techniques.

Physical methods

For physical methods NPs are prepared by means of evaporation-condensation using a tube furnace at atmospheric pressure. The benefits of physical techniques are speed, radiation used as reduction agents and no dangerous chemicals involved, but the downsides are low yield, high energy consumption, contamination with solvents and lack of uniform distribution (Zhang *et al.*, 2016).

Mechanical pressures, high energy radiation, thermal energy or electric energy are among the physical methods that cause material abrasion, melting, evaporation or condensation to prepare NPs. Such approaches work mainly on top-down technique and are beneficial because they are free of solvents impurities and yield standardized monodisperse NPs. Simultaneously, the abundant waste produced during the synthesis makes physical processes less economical. High energy ball milling, electrospraying, laser ablation, inert gas condensation, laser pyrolysis, physical vapour deposition, flash spray pyrolysis, melt mixing is among the most widely used physical methods to produce NPs (Dhand *et al.*, 2015).

Biological methods

Many surfactants and reductants proved to be toxic for humans and environmentally dangerous. So, many efforts have been recently devoted to the realization of the so-called "green" processes. Therefore, there is an increasing interest to develop sustainable and eco-friendly methods. Although the synthesis of nanoparticles of various compositions, sizes, shapes and controlled dispersion is a significant issue of nanotechnology, new cost-effective strategies are being established. Microbial synthesis of NPs is a green chemistry strategy that connects nanotechnology with microbial biotechnology. Biosynthesis of silver, gold, gold–silver alloy, tellurium, selenium, platinum, silica palladium, titanium, zirconia, quantum dots, uraninite, and magnetite NPs by bacteria, fungi, actinomycetes, viruses, and yeasts have been recorded. Despite the stability, however, bio-nanoparticles are not monodispersed, and production rates are slow. To solve these problems, it is important to optimize several factors such as microbial cultivation methods and extraction techniques and to use the combinatorial approach such as photobiological methods. Cellular, biochemical and molecular processes that mediate the production of biological nanoparticles should be analyzed in depth to increase the synthesis rates and improve NPs properties (Narayanan and Sakthivel, 2010).

Chemical methods

Most of the chemical methods used for the synthesis of nanoparticles are essentially based on reduction processes, as they require a precursor (that is a molecule containing the atoms of the metal whose nanoparticle will be made) dissolved in a solvent and a reducing agent, whose composition depends on the operating conditions at which the reaction is carried out. Very often, a surfactant is added thus preventing the growing particles from reciprocal aggregation. For the choice of reductants, a predictor approach based on a continuum of mathematical modelings is often assessed experimentally for selecting the most suitable surfactant (Reverberi *et al.*, 2016). The list of organic reductants comprises several compounds with various functional groups conditioning their strengths as electron donors, like hydroquinone, secondary alcohols, monosaccharides, ascorbic acid, gallic acid, citrates, aldehydes and ethanolamines (Tan and Cheong, 2013). Among inorganic reductants, alkali metals borohydrides, such as sodium borohydride ($NaBH4$), are powerful reagents

(Paolino *et al*., 2010).

Nanoparticles characterization

Size and shape affect the functionality of nanoparticles, the drag and diffusion of fluids, the optical properties and the absorption into cells (Zhang *et al*., 2009).

Particle size of nanoparticles

Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the in vivo distribution, biological fate, toxicity and the targeting ability of nanoparticle systems. Also, they can also effect the drug loading, drug release and NPs stability (Panyam and Labhasetwar, 2003). Photon correlation spectroscopy or dynamic light dispersion is the easiest and most regular way of evaluating particle size. The particles size affects the discharge of medication as the bigger surface area is provided by small particles. For a final product, the limit of the drug on it should be exposed to the surface of the molecule so that the drug is discharged easily (Redhead *et al*., 2001).

UV-visible absorption spectroscopy

Absorbance spectroscopy is used to determine a solution's optical properties. A Light is transmitted through the solution of the sample, and the amount of light absorbed is measured. If the wavelength is varied, the absorbance is measured at each wavelength. The absorbance may be used with Beer-Lamberts Law to calculate the concentration of a solution (Subbaiya *et al*., 2014).

Scanning electron Microscope (SEM)

SEM offers a direct perceptive morphological evaluation. They offer bound data on the dispersion of size and the usual of genuine populace. This approach is repetitive, expensive and also needs reciprocal insight to estimate dispersion (Jores *et al*., 2004). The SEM is the instruments used most frequently to characterize nanomaterials. Using a SEM, secondary electron images of organic and inorganic materials with nanoscale resolution can be obtained, enabling topographical and morphological studies to be carried out by scanning an electron probe through a surface and tracking the secondary electrons emitted. Compositional analysis of a sample can also be obtained by measuring the X-rays produced by the interaction between the electron specimens. Thus accurate maps can be created of the elementary distribution. It is primarily used in sensor technology for the study of surfaces of thin films and sensing layers (Butt *et al*., 2003).

Transmission electron microscope (TEM)

TEM is used mainly for recognizable proof of the morphology of the prepared nanoparticles (Pangi *et al*., 2003). In a TEM, A high-energy focused beam is transmitted through a thin sample to reveal information on its shape, crystallography, particle size distribution and elemental composition. This is capable of producing lattice images with atomic resolution, as well as of giving chemical information at a spatial resolution of 1 nm or better. Since nanomaterials' unique physical and chemical properties not only depend on their composition but also on their structures, TEM offers a means to characterize and understand these structures. TEM is unique so it can be used to monitor a single nanoparticle in a sample and to define and measure its chemical and electronic structure directly. The most significant TEM application is the atomic-resolution real-space imaging of NPs (Wang, 2000).

Zeta potential

It used to determine zeta potential value, size of nanoparticles and surface charge (Pangi *et al*., 2003). Zeta potential has been used to determine cell biological activation, agglutination and adhesion that are associated with cell surface charge properties (Perez *et al*., 2002; Fontes *et al*., 2006; Lin *et al*., 2006). It represents the particle's electrical potential and it is affected by the particle composition and the medium that is dispersed within. NPs with a zeta potential above (+/-) 30 mV were shown to be stable in suspension, since the surface charge prevents particle aggregation. The zeta potential is often used to assess whether a charged active material is encapsulated within the center or adsorbed onto the surface of the nanocapsule (Honary and Zahir, 2013).

Infrared Spectroscopy (IR)

Spectroscopy is a common characterization technique where a sample is put in the pathway of an IR radiation source and its absorption is determined at different IR frequencies. Hence, IR spectroscopy can be used to evaluate the form of bond between two or more atoms and to classify functional groups accordingly. IR spectroscopy is also widely used to characterize organic ligands' attachment to organic/inorganic nanoparticles and surfaces. Because IR-spectroscopy is quantitative, the number of a type of bond may be determined (Kendall, 1966).

Uses and applications of nanotechnology in veterinary medicine

Nanotechnology offers the same opportunities for veterinarians as physicians, including therapy, diagnostics, tissue engineering, manufacturing of vaccines, and modern disinfectants. The nano-applications are already in use in animal health and production, animal husbandry and reproduction and animal nutrition (Manuja *et al*., 2012). Within the medicinal field, nanoparticles are also constructed in such a way that drug / bio-molecules can be integrated in and not degraded at undesired sites, which can help the drug reach more effectively the intended site of action. Nanoparticles can often improve the circulation time of the loaded therapeutic molecules and improve their residence at the tumor site by means of leaky vasculature by enhancing permeation and retention effects (Haley and Frenkel, 2008; Blanco *et al*., 2015).

Nanoparticles have long been used in the human medical field as diagnostic and therapeutic agents, but their use in veterinary medicine and in animal processing is still fairly recent. Owing to increasing concern about microbial antibiotic resistance, development demands on the livestock industry have recently centered on the use of antibiotics as growth promoters, which lead to antibiotic resistance development (Hill and Li, 2017). Thus we need antibiotic alternatives as nanoparticles to be used as antimicrobials. Nanotechnology is thought to play an important role in global veterinary practice (Scott, 2005). Nanotechnology has recently helped to establish non-toxic antimicrobial agents to resolve antibiotic resistance by using devastating dose of antibiotics used against various pathogens that cause chronic animal infections, including *Brucella*, *Mycobacterium bovis, Streptococcus* and *Rhodococcus equi* (Muktar *et al*., 2015).

Nanotechnology has enhanced the medical field by use of nanoparticles in drug delivery. The drug can be delivered to specific cells by using nanoparticles (Ganesh and Archana, 2013). The total consumption and side effects of drugs are significantly reduced by placing the drug in the required area by the required dose. By this way the cost and side effects are reduced. With the aid of nanotechnology, the regeneration and repair of damaged tissue (Tissue Engineering) can be carried out. Tissue engineering can replace the traditional treatments such as artificial implants and organ transplants. One such example is the growth of carbon nanotube scaffolds in bones (Mudshinge *et al*., 2011).

Across several areas, nanotechnology has a profound impact on veterinary medication integrating treatment, diagnostics, tissue building, vaccine production, and disinfectants. The medicine's vehicle directly into the target cells enables exceptionally low dosages to be used that gradually decrease the amount of medication and the withdrawal period in homestead animals (El-Sayed and Kamel, 2018).

Nanotechnology brings us innovative approaches to conventional veterinary problems. This holds a boundless promise for different branches of veterinary medicine and animal welfare. NPs can be guided to remove various animal pathogens, including those that cause chronic robust infections, intracellular pathogens, and parasites in the blood. Nanotechnology provides innovative approaches to the veterinarians' most severe issues, such as tuberculosis, brucellosis, methicillin-resistant *Staphylococcus (S.) aureus*, foot and mouth disease, and also intracellular or blood pathogens infections. Trials are under investigation to direct the administered agents towards mastitic udders (Greenwood *et al*., 2008; Kroubi *et al*., 2010). Mastitis is probably one of the main challenges of dairy livestock production. Traditional antibiotics for this disease cannot be used because many pathogens are resistant. Researchers have therefore been focused to look for new solutions, and metal NPs have been found to be the most appropriate agents. Kalińska *et al*. (2019) evaluated the effect of silver NPs; copper NPs, and silver-copper NPs on pathogen species (e.g., *S. aureus* and *E. coli*) that commonly implicated in udder inflammation. They found that commercially available NPs were of good quality and did not have a toxic effect on mammary gland tissue. Furthermore, the tested NPs decreased the viability of pathogens. Yuan *et al*. (2017) assessed the efficacy of biologically synthesized silver NPs against two multiple drug-resistant strains of *Pseudomonas* (P.) *aeruginosa* and *S. aureus*, which were isolated from mastitis-infected goats milk samples. They recorded that the MICs of silver NPs against *P. aeruginosa* and *S. aureus* were found to be 1 and 2 µg/mL, respectively.

The nanoparticles are widely used in the preparation of veterinary vaccines. These have essential immunomodulatory roles that can potentiate the immune response. They increase peptide cross presentation and activate / modulate the antigen presenting cells. They can also act as adjuvants to delay antigens release, which increases the vaccine efficiency (Kim *et al*., 2010; Awate *et al*., 2013; Torres-Sangiao *et al*., 2016). Li *et al*. (2018) designed a novel infectious bronchitis virus (IBV) vaccine alternative using a highly innovative platform called self-assembling protein NPs (SAPN). They recorded that the IBV-Flagellin-SAPN might be a promising vaccine for IBV as the chickens vaccinated with IBV-Flagellin-SAPN showed marked reduction of tracheal virus shedding and tracheal lesion scores compared to non-vaccinated chickens. Lopes *et al.* (2018) stated that administration of IBV vaccine encapsulated in chitosan nanoparticles either alone or combined with a live attenuated heterologous vaccine by oculo-nasal route to chickens caused both humoral and cell-mediated immune responses, and provided an effective protection against IBV infection at local and systemic sites.

Due to their established properties, they have been used to develop diagnostic methods, therapeutic targets, and for prevention and vaccination of tropical parasitic diseases. NPs are new drug delivery systems for herbal medicine, which can be used as potent insecticides against the different stages of mosquitoes, i.e. new strategy in the control of vector-transmitted diseases (Abaza, 2016). Nanoparticles, as an evolving novel drug carrier, offer a promising strategy to effectively treat parasitic diseases by addressing the limitations of low bioavailability, poor cellular permeability, unspecific delivery and rapid removal of antiparasitic drugs from the body (Sun *et al*., 2019).

Cancer is a leading cause of deaths in pet animals, even with newly approved veterinary anticancer medications (Biller *et al*., 2016). Zabielska-Koczywąs and Lechowski (2017) reported that the most studied nano-drug delivery systems in veterinary medicine is liposomes. The lack of cardiac toxicity associated with commercially available liposomal doxorubicin indicates that it should be used instead of free doxorubicin in dogs with cardiac disorders. Cisplatin-incorporated hyaluronic acid nanomaterials, cisplatin nanocrystals, and paclitaxel seem to be the most inspiring nano-medicines for use in the treatment of various canine tumors such as oral sarcoma, oral melanoma and anal adenocarcinoma.

Nanotechnology applications in the veterinary sector are not only limited to disease prevention and control, but are also expanded to include other areas that make animal rearing more profitable. Specific nanotechnology uses include animal nutrition, reproduction and even animal health, and safety-derived items such as pet care products such as shampoos and body lotions (Swain *et al*., 2015).

In animal nutrition, nanotechnology is primarily used in the processing of nano-minerals, in particular trace minerals of poor bioavailability. In fact, minerals such as nanoparticles eliminate intestinal mineral antagonism, decreasing excretion and environmental contamination. Studies have proposed that the feeding of nanoparticles enhances digestive capacity, immunity and health in livestock and poultry (Gopi *et al*., 2017). Scientists manage to produce food, meat or milk that is distinguished by a higher mineral content, improved flavor, scent, look and longer storage suitability. To date, several techniques have been created to enhance the composition and consistency of food; nevertheless, the use of feed additives is one of the simplest and most successful approaches. In several experiments, it has been shown that micro-and macro-elements in the form of nanoparticles can be properly ingested by animals, which increases the consistency of the products derived from them (Konkol and Wojnarowski, 2018). Nanomaterials are used in food technology like production of contamination free meat and meat products (Lee *et al*., 2011).

Nanotechnology is also used in animal reproduction. Nanomaterials could be used for cryopreserve of gonadal tissues, sperm, oocytes and embryos that are very important in animal reproduction (Saragusty and Arav, 2011). Nanoparticles are used to potentiate fertilization efficiency, which facilitates the fertilization from a single collection to more females. It had some limitations like; to develop it requires biomarker library and purebred restrictions on artificial insemination (Pawar and Kaul, 2014). Semen nano-purification may be used to differentiate the damaged sperm from the healthy, undamaged sperm. One method for a protein-based removal strategy is to coat magnetic nanoparticles with antibodies against ubiquitin, a surface marker of defective sperm. Nano-purified bull (*Bos taurus*) spermatozoa achieved conception levels equal to those of unpurified semen with no negative limitation at half the concentration reported for inseminated cows or calves (Odhiambo *et al*., 2014).

Nanotechnology for pet animals care was often related to the development of new drugs. Owing to nanoparticles physico-chemical properties, they are used to enhance surface refreshment and disinfectants. For examples, silver nanoparticles for topical use are included in shampoos (Feneque, 2003).

Conclusion

Nanotechnology is a rapidly growing technology that has a significant effect on a variety of therapeutic fields. It is capable of solving numerous animal health and production related problems. In this review, we throw the light on nanoparticles synthesis, classification, characterization, and their applications in veterinary field starting from medical applications to using the nanoparticles in animal nutrition and reproduction.

Acknowledgement

This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that they have no conflict of interests.

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