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REVIEW [REVISIÓN]

NANOTECHNOLOGY ON ANIMAL PRODUCTION

[LA NANOTECNOLOGÍA APLICADA A LA PRODUCCIÓN ANIMAL]

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SUMMARY

Nanotechnology, defined as that technology in which materials and structures are found in nanometric scales, has increased his application and research, since small scales materials have different properties and characteristics compared to those at higher scale. Recently, research on nanobiotechnology has been increased, especially that focused on drugs for human health, and there is the need of applying that knowledge on animal health, in order to improve animal production process. However, there is a lack or null information about it, even though research focused on human health is carried out using animal models. It is important to take into consideration that nanotechnology must include ethical, environmental and food safety factors. Therefore, the objective of this review is to offer a general view on nanotechnology and its application on veterinary and animal production, based on the new challenges to explore new research areas according to actual needs to obtain benefits for the society.

Key words: Nanoparticle; nanomaterial; veterinary; zootechnics.

RESUMEN

La nanotecnología, entendida como aquella tecnología en la cual los materiales y las estructuras se encuentran en escalas nanométricas, posee un campo de aplicación e investigación crecientes, ya que los materiales a escala pequeña adquieren propiedades y características distintas que aquellos a escala mayor. Recientemente, ha incrementado la investigación de los usos de la nanotecnología en el área de la biología, especialmente en la administración de fármacos para seres humanos, y existe la necesidad de aplicar dichos conocimientos en el área zootécnica, particularmente lo que concierne a salud animal, con el objetivo de facilitar y optimizar los procesos de producción de alimentos de origen animal. Sin embargo, existe poca o nula investigación al respecto, a pesar que gran parte de la investigación enfocada a la salud humana se realiza con modelos animales. Esto es de particular interés al considerarse animales destinados a consumo humano, donde deben de tenerse en cuenta factores éticos, ambientales y de seguridad alimentaria. Por lo tanto, el objetivo de esta revisión es proporcionar una visión general de la nanotecnología y sus posibles aplicaciones en las áreas de veterinaria y zootecnia, basado en las necesidades actuales, en la exploración de nuevas áreas de investigación en beneficio de la sociedad.

Palabras clave: Nanopartícula; nanomaterial; veterinaria; zootecnia.

INTRODUCTION

Nanotechnology (from the Latin *nanus*, meaning *dwarf*) is defined as the technology of materials and structures where size is measured in nanometers, with application in diverse areas such as physics, chemistry, and biology (REA, 2001; Buzea *et al*., 2007). This implies a certain understanding and control of matter measuring from 1 to 100 nm, with the capability of having new applications. This is because at sizes so small, the properties of matter can differ considerably from those at larger scale, even in microns. For a better understanding, a nanometer is a billionth of a meter (10^{-9}) and, as reference, the thickness of a sheet of paper measures approximately 100,000 nm (NNI, 2009), and the length of a visible light wave ranges from 400 to 700 nm; also, many biological structures are sized at a few nanometers (Table 1) (Scott, 2005).

Worldwide, financing for research in this area comes from both public and private sources. The United States of America, Japan, and Germany are the countries that have the greatest public investment in Nanotechnology (1,606; 1,100; and 413 million dollars, respectively, in 2005) (NRC, 2006). No Latin American country appears in the list of the 13 countries with the highest budget for nanotechnology studies within that year.

Table 1. Size of different biological structures (nm).

Biological structure	Size, nm
Leucocytes	10,000
Bacteria	1,000 – 10,000
Virus	75 – 100
Protein	5 – 50
DNA (width)	~ 2
Atom	~ 0.1

Source: modified from Scott (2005).

Historically speaking, nanoparticles have existed on the planet for a very long period of time, and they have been created though several natural phenomena, including photochemical reactions, volcanic eruptions, or forest fires (Buzea *et al*., 2007); and, although from recent research, the applications of nanotechnology have been present since ancient times, even if in those days they did not refer to it as such. It is known, for example, that the pigment used for porcelain in the different Chinese Dynasties (since the XVIth century B.C.) contains nanoparticles of gold (Hollister *et al*., 2003). Another case is that of the Lycurgus cup (on exhibition at the British Museum) made during the Roman Empire (IVth century B.C.), which possesses a glass matrix containing nanoparticles of gold and silver, responsible for creating an optical effect in the cup depending on the direction of the light: if the cup reflects the light, it looks green, if it transmits it, it then changes to red (Freestone *et al*., 2007). In the Orient, colloids containing nanoparticles of gold were also used in the treatment of bone ailments such as arthritis (Cao, 2004). Later, in the middle of the XXth century, the physicist Feynman (1959) proposed the possibility of handling matter atom per atom, leaving the door open for the development of a technology at atomic and molecular scale. In 1975, Ringdorf developed a joint pharmaco-polymer model, stressing that the properties of said model can change depending on the properties of the polymer (Sinha *et al*., 2006).

The applications of nanotechnology are indeed very varied. For example, it is used in electronics for the fabrication of processors, hard drives, and batteries; in ecology it is used to eliminate certain pollutants from the air and water; in the cosmetics industry it is used to make products such as sunscreen creams, make-up, hair dyes, and certain creams containing nanoparticles; there are even many industrial paints and lubricants containing these particles in order to obtain products with specific characteristics (Buzea *et al*., 2007), such as “intelligent” packages that alert consumers if the product is somehow contaminated (ETC, 2004); in agriculture it is used in the form of nanofertilizers, water catchers, and trappers of toxic substances (Lal, 2007); and there are many other uses. Nevertheless, one of the most important and extensive uses of nanotechnology is in the area of human medicine, where it has allowed the development of nanoparticles for the controlled liberation of cancer medication (Sinha *et al*., 2006), nutrients (Ross *et al*., 2004), hormones (Schaffazick *et al*., 2006), gene therapy (Bowman and Leong, 2006), and as a contrast medium for image studies (McNeil, 2005), among others. In the area of veterinary medicine and animal production, there is a growing interest in the application of nanotechnology in its processes. However, research in this field is still very limited.

Differences between nanomaterials and larger materials

The physical, chemical, electrical, optical, mechanical, and magnetic properties (as well as others, still unknown) at an atomic scale are quite different from those present at a greater scale, even when compared with those present at a scale of microns (10^{-6}) (Buzea *et al*., 2007; Cao, 2004). The reason that nanomaterials are so different from larger ones is, according to Roduner, because of two effects:

1. Surface. The atoms of nanomaterials are less stable than those of larger structures since the energy required to join adjacent atoms is less. As a consequence of this, the fusion point of a given element changes. For example, the fusion point of a gold particle measuring 2.5 nm is about 930K (≈ 657°C), which is much lower than 1336K (≈ 1,063°C), the normal fusion point of this metal at greater volumes. To this regard, Cao (2004) mentions that this phenomenon is characteristic in metals, inert gases, semiconductors, and molecular crystals when the size of the particle is less than 100 nm.

2. Quantum effects. Quantum points are a type of nanostructures, just a few nanometers in size, that show a behavior similar to a single atom. Their spatial arrangement allows them to have properties not proper to the element, such as magnetism in metals like gold or platinum when they are in the form of nanoparticles.

Moreover, nanoparticles have a surface area much larger than microparticles. To illustrate this point, a carbon microparticle with a diameter of 60 µm has a mass of 0.3 µg, and a surface area of 0.01 mm^2; the same mass of carbon forms 1 trillion particles, 60 nm in diameter, with a surface area of 11.3 mm^2. This indicates that as the size of the nanoparticles decreases, the surface area for chemical reactions increases, thus reactivity increases about 1,000 times (Buzea *et al*., 2007). The aforementioned can be compared with the function of cilia and micro-cilia of the intestinal tract, present in every animal species, including man. The intestinal tract is covered with epithelial projections called cilia, which increase the surface area 10 to 14 times more than if it were a flat surface. Also, these cilia are covered with microscopic micro-cilia that increase even more the total surface area (Cunningham, 1999).

Preparation and design of microparticles

There are different methods for the preparation of nanoparticles. The selection of any of these methods depends on the particular objectives and conditions for where and how the obtained particles are meant to be used. Thus, it is necessary to consider the physical and chemical stability of the active agent, as well as its toxicity, its liberation profile, among many other considerations. Agnihotri *et al*. (2004) specifies some common methods for the preparation of nanoparticles, such as:

1. **Cross-linking emulsion**: in this method, a water-oil (w/o) emulsion is prepared through emulsification of a watery solution in an oily phase, which when shaken vigorously separates and hardens the particles. It requires the use of agents that facilitate the union of the involved agents.

2. **Precipitation/coacervation**: in this case, the particles are produced by "blowing" the interest agent in an alkaline solution. The separation and purification of the particles is done through filtration and centrifugation, followed by rinsing with hot and cold water.

3. **Spray-Drying**: this is one of the best-known techniques used to produce dusts, granules, or agglomerates, besides being an easy and quick way to do it. It is based on the drying of droplets sprayed into compressed hot air. It requires the use of a solvent (for example, a solution of acetic acid), which is instantly evaporated, allowing the formation of particles.

Another important factor to take into account is the shape that the nanoparticles acquire, since it strongly influences its biological behavior. It is important to point out that these particles are not always spherical, as could be expected. There are reports of innumerable shapes, some quite peculiar, of nanoparticles: rectangular discs, cones, canes, "worms", elliptical or circular discs, "rolls", among many others. All these can come up in the 1st, 2nd, or 3rd dimension, depending on the preparation method and the materials used. Concerning this, the viscosity and thickness of the material used determines whether the particle will show sharp or flattened endings. It is even possible that the nanoparticles will show regions with different curvature, texture, concavity, and other characteristics (Champion *et al*., 2007).

Besides capsules, other nanostructured materials can be used, which have the potential of changing the structures of other particles. Some specific examples of these are **fullerenes** (structures made up of 60-80 carbon atoms arranged in spherical shapes, used for the controlled liberation of medication), **dendrimers** (branched structures which, due to their structure, can serve as vehicles for medication, liberating it in a specific location), and **quantum dots** (nanometric crystals designed for optical and electronic applications. When a quantum dot is stimulated, it emits a fluorescence of varying intensity) (ETC, 2004; Scott, 2005).

Possible applications in animal production

A great portion of nanotechnology research applied to human medicine has been tested in lab animals (rats, mice, rabbits, guinea pigs, among other species), and thus these nanotechnological applications are, indeed, susceptible of being studied in species of a zootechnical interest, wild fauna, or pets. It is probable, however, that there lacks a greater interdisciplinary involvement among professionals of biotechnology (including nanotechnologists, of course), veterinary science, zootechnics, agronomy, and akin areas. Regarding this, Scott (2005) points out four possible applications of nanotechnology in animals: 1) administration of medication, nutrients, probiotics, supplements, and other substances, 2) diagnosis and treatment of diseases with nanoparticles that allow the detection and elimination of the cause of the disease without the need for surgery, 3) identity registry that allows a follow up on the history of an animal and its products (meat, milk, eggs, mainly), and 4) management of reproduction with hormonal immunosensors.

An area that is closely linked with livestock raising is agriculture, and according to data from the INEGI (2007) more than 60% of the total surface area of

Mexico has a farming, livestock raising, or forestry activity. Therefore animal production systems, either in stables or free grazing, or mixed, could benefit with this technology by using nanofertilizers that transport nutrients to specific places in the forages, just when they are needed and in the required amounts. This can be done with the aid of magnets (González-Melendi *et al*., 2008; Lal, 2007), improving water catchment in the soil with the use of hydrogels or zeolites, using nanomaterials that absorb toxic substances, and with devices that determine soil properties, among others (Lal, 2007).

Actually, there is already research aimed at animals of zootechnical interest, although the number of studies is still quite reduced. Recently, Romero-Perez *et al.* (2010) designed and evaluated, *in vitro*, sodium selenite nanoparticles for oral use in ruminants using copolymers of metacrylate, sensible to pH, such that they would not be degraded in the rumen (near neutral pH), but would in the abomasums, whose pH is acid due to the secretion of chlorhydric acid, similar to that present in non-ruminant species; however, no *in vivo* tests were done. On the other hand, silver nanoparticles were tested unsuccessfully (with antibacterial aims) in chicken embryos. The particles, although they did not affect embryo development, reduced the number and size of lymph follicles of the bursa of Fabricius (Grodzik and Sawosz, 2006). Also, immunosensors have been developed based on nanostructures capable of detecting the concentration of progesterone in cow milk, facilitating the detection of ovulation in these animals (Carralero *et al*., 2007ab); and of clembuterol, a β-agonist, in meat animal fodder, which is used as a growth promoter, but whose residues in animal tissues can have negative effects on humans (He *et al*., 2009).

A most important aspect to consider is health, both for the protection of the animal itself and for humans. This is why animals are constantly vaccinated against diverse diseases. Vaccines contain other substances besides the antigen; among these are adjuvants, which have the objective of improving the immune response of the individual (Baxter, 2007). However, some of these adjuvants, like aluminum hydroxide, have the disadvantage of having noxious side effects such as tissue irritation, inflammation of the infected site, lower cell immunity, and ineffectiveness to create immunity to certain organisms like viruses. To avoid this, adjuvants have been developed in the form of calcium phosphate nanoparticles, capable of creating an effective antiviral immunity (He *Et al*., 2000). Nevertheless, the development of vaccines against parasites has not been successful mainly due to the complexity of these organisms, much more so than bacteria or viruses (Meeusen and Piedrafita, 2003). Nematodes (round worms of the *phylum* of helminthes) infect almost all plant species and are abundant in all kinds of vertebrate hosts. Of these, *Trichinella spiralis* is the parasite responsible for the disease in humans known as trichinosis, caused by the consumption of undercooked contaminated pork meat, and which can cause the death of the individual in severe cases (Jawetz *et al*., 1996). With regard to this, Deville *et al*. (2005) proved the importance of the adjuvant, and this in the form of nanoparticles showed an adequate induction in the immune response of mice against antigens of *Trichinella*, and a decrease of the larva cargo in their muscle tissue. This is an advance of nanotechnology in animal production.

On the other hand, the routine use of antibiotics in animal production systems is a given fact, and these can leave a residue in the products that reach the final consumer. And although there is a variable retirement period before the products of treated animals can be placed into the market, this period is not always respected. However, with the use of nanotechnology, the amount of antibiotics used can be greatly reduced due to the properties that the substances acquire when their size is reduced to a few nanometers. This was proven by Fattal *et al*. (1989) on mice infected with *Salmonella typhimurium*, and treated with different forms and amounts of ampicillin. Those treated with ampicillin joined to nanoparticles had a survival ratio equal to those treated normally; the difference being that the prior required 40 times less antibiotic to achieve the same effect. Moreover, its distribution in the tissues was more specific, thus validating the lower amount of antibiotic required to equal the results.

In the area of nutrition, it is also possible to apply nanotechnology with several goals, such as obtaining information of a nutrient or bioactive component, its liberation in specific sites of action, greater availability, maintenance of adequate levels for longer periods of time, avoiding its degradation, and lower parenteral invasion (Ross *et al*., 2004), thus also reducing the stress implied in animal handling. Minerals are one of the most widely used supplements in animal nutrition; however, the way in which said minerals are found influences their bioavailability, and so, if they have low bioavailability, the animal will not make suitable use of them, and they will be eliminated. An example of this is iron, whose deficiency is still a problem in animal and human nutrition, especially in the earlier stages of life, during gestation, and in parasite infestations (Church *et al*., 2003). One of the most bioavailable sources of this element is in the form of ferrous sulfate (McDowell, 1997), but it has the inconvenience of giving food a metallic taste, and accelerating the oxidation process of fats in cereals, thus making them rancid (Hurrell, 2002). The alternative is to use a less available, but more stable, source of iron such as ferric phosphate ($FePO_4$).

Regarding this, Rohner *et al*. (2007) developed highly available nanoparticles of ferric phosphate, proving that at a nanoscale this source can increase its nutritional value.

Pets are an economically attractive area, given the greater preoccupation of their owners to give them a better quality of life. According to Ostrander and Wayne (2005), millions of dollars are spent annually in the United States on dogs' health. A lot of this money is destined to cancer treatments, heart and autoimmune diseases, epilepsy, and blindness. In fact, dogs develop cancer twice as frequently as humans do, and in the urinary system, the bladder is the most common place for neoplasias, which are generally malign. Malign neoplasias include transitional cell carcinoma, fibrosarcoma, and adenocarcinoma. These can affect any part of the bladder, although transitional cell carcinoma commonly affects the region of the trigone, where a surgical removal of the tumor is not recommended (Cowan, 1996). To this regard, Lu *et al*. (2004) developed nanoparticles of paclitaxel (a potent therapeutic chemical) joined to a gel for the treatment of bladder cancer and, although the goal is human beings, they were tested successfully on bladder tissue of dogs, and are therefore doubtlessly an alternative for this disease.

Safety and toxicity of nanomaterials used in animals

It is important to determine what is the zootechnical use of the species that will be given the nanoparticled component. It is not the same if it is one which will be used as a pet or for exhibition, as in the case of zoo animals, or if it will be used, the animal itself or its products, for human consumption, due to the risks of residues in the tissues. Generally speaking, the toxicity of a nanoparticle depends on several factors, such as dose, the concentration of the interest agent, the type of polymer used to nanoencapsulate, among others. Regarding this, Braydich-Stolle *et al*. (2005) found that nanoparticles of silver negatively affect gametogenesis in mice, and therefore this element should be avoided when using animals destined for reproduction.

CONCLUSIONS

Nanotechnology is in constant development, and its applications are ever more varied and specific, with a high potential for improving livestock production, and animals in general. The study of nanotechnology in these areas is still very limited; regardless, it is feasible to apply it, probably with encouraging results that will allow to carry out processes more quickly and efficiently and, perhaps, at a lower risk to consumers. However, a great amount of research is still required to support the effectiveness, and mainly the safety of nanotechnology, avoiding any harm to the environment or to human beings proper.

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