REVIEW ARTICLE

Contribution of Nanotechnology in Animal and Human Health Care

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Nanotechnology is the ability to manipulate individual atoms and molecules in a way to create nano-structured materials and objects from 1 to 100 nanometers. Because of the size new changes in their chemical and physical structure may occur, which could indicate higher reactivity and solubility. Nanotechnology as a new empower technology, has opened up new horizons for applications in many fields including human and veterinary medicine. Examples of potential applications of nanotechnology in the science and engineering include disease treatment, delivery systems, new materials for pathogen detection, etc.The variety of nanomaterials that are used for disease diagnosis, treatment, drug delivery, animal nutrition, animal breeding, reproduction and value addition to animal products; these are metallic nanoparticles, quantum dots, carbon nanotubes, magnetic nanoparticles, nanoporous membranes. For a long time, nanoparticles have been used as diagnostic and therapeutic agents in human and veterinary medicine, although their use in animal production is still relatively new. Areas of particular interest for animal and human health include disease diagnosis, target drug delivery systems, vaccine transfer, and nutrition. Research in the field of nanotechnology will contribute to improving animal and human health and will help to increase livestock production.

Introduction

This century is a good period for the progress of different technologies but the priority is put on the nanotechnologies.

Nanotechnology is the manipulation or self-assembly of individual atoms and molecules into structures to create materials and devices with new different properties.

The word “nano” originates from the greek word meaning “dwarf”. In the technical terms, the word “nano” means 10^{-9} meters.

It is an exciting and rapidly emerging technology allowing working at the molecular level, often atom by atom, to create and manipulate tools, materials and functional structures that have nanometer dimensions.

The unique size dependent properties of nanoparticles have numerous diagnostic applications such as diagnostic biosensors, imaging nano probes for unilamellar with a single lamella of membrane or magnetic resonance imaging contrast agents. Nanotechnology may also be useful to develop nanoscale materials, controlled delivery systems, contaminant detection and to form nano devices for molecular and cellular biology [**1**].

The nanomaterials with their very small size have properties different from those of the traditionally used materials and therefore they have different physico-chemical properties. These properties the researchers use for new tools in diagnostic and medical treatment, drug delivery systems or magnetic resonance imaging contrast agents [**2**].

Nanotechnology has the potential to solve many puzzles related to animal health, production, reproduction, good hygienic practices during rearing and maintaining of food animals, the possible applications of the technology is almost incredible in relation to livestock [**3**].

These various methods of nanotechnology can be a potential therapeutic aid in extenuating the health problems of humans and animals.

This high level technology can provide new tools for molecular and cellular biology, biotechnology, veterinary physiology, animal genetics, reproduction etc. which will allow researchers to handle biological materials such as DNA, proteins or cells in minute quantities usually nano-liters or pico-liters. So there are several areas in which nanotechnology could be applied to the science and engineering of agriculture and food systems, e.g. agricultural and food systems security, disease treatment, delivery systems, and the protection of the environment [**4**].

One particular application in human and veterinary medicine currently being developed involves employing nanoparticles to deliver drugs, heat, light or other substances to specific types of cells (such as cancer cells). Particles are engineered so that they are attracted to diseased cells that allow direct treatment of those cells [**5**].

Nanotechnology is considered as a potential technology to revolutionize veterinary medicine, animal health and other areas of animal production [**6**].

Several decades, to distinguish animal and human pathogens that caused similar diseases, because of unavailability of sensitive diagnostic tools and protocols [**7**].

Nanostructures developed by rational approaches are among the most impressive manmade materials and exhibit unique chemical, physical and/or biological features [**8**]. These features allow the nanostructures to be used for an unprecedented number of applications ranging from electronics and agriculture to medical and health care [**9**].

Actually nanotechnology is not a single discipline it is a combination of disciplines such as chemistry, physics, materials science, and biology to bring together the required collective expertise needed to develop these novel technologies.

The potential impact stems directly from the spatial and temporal scales being considered: materials and devices engineered at the nanometer scale imply controlled manipulation of individual constituent molecules and atoms in how they are arranged to form the bulk macroscopic substrate. This means that nanoengineered substrates can be designed to exhibit very specific and controlled bulk chemical and physical properties as a result of the control over their molecular synthesis and assembly.

In the last years, the tremendous evolution in nanotechnology enabled the production of smart therapeutic/diagnostic substance delivery assays. They can diagnose diseases before the symptoms occur, treat infected malignant cells selectively and avoid healthy ones, supply hormones, or enzymes if deficient and can even do more. Through their response to changes in pH value, temperature, or the presence of certain chemicals, the smart delivery systems can be designed to make their decision independently through self-regulatory mechanisms [**10, 11**].

The present review pays particular attention on the contributions of nanotechnology in veterinary and human medicine including nanoparticles for drug delivery, diagnostics and therapy as well as for animal nutrition and production.

Nanomaterials

Nanomaterials are materials that provide the potential to manipulate structures or other particles at the nanoscale level, to control and catalyse chemical reactions. Nowadays they are of great use in animal and human medicine. Specific examples of nanomaterials are nanosensors, nanotubes, nanoshells, nanorods and nanoparticles, each of which is described in more details bellow [**12**]. In **Table 1** are indicated the meaning of the nanomaterials and their application.

Table 1. Presentation of the most applicable nanomaterials in animal and human health.

Type	Definition	Application
Nanosensors	Nanosensors are devices or systems with devices that measure or detect a chemical with the use of a biological material or tissue.	Detection of very small amounts of a chemical contaminant, virus, or bacteria in agricultural and food systems [**13**].
Carbon nanotubes	Carbon nanotubes are natural choice for interfacing with the biological world because of their molecular scale, biocompatibility and stability in aqueous environments [**14**].	Functionalized carbon nanotubes hold strong promise as novel systems for the delivery of drugs, antigens and genes [**15**].
Nanoclays	Nanoclays are nanoparticles of layered mineral silicates.	Nanoclays have great potential for drug delivery application [**16**]. They are drug delivery vehicle for controlled release of therapeutic agent [**17**].
Nanoshells	Nanoshells are concentric spherical nanoparticles (about 100 nm diameter) composed of a dielectric (typically gold sulfide or silica) core and a metal (gold) shell.	The specific properties of nanoshells allow for absorption of directed energy, creating an intense heat that selectively kills tumour cells [**18**].
Nanorods	One morphology nanoscale objects with dimensions 1-100 nm.	Absorbing in the near-infrared range for *in vivo* laser closure of a rabbit carotid artery represented a step forward toward the introduction of nano-technology-based therapies in minimally invasive clinical practices [**19**].
Biological nanoparticles	Naturally occurring nanoparticles with diverse structures and biological roles.	Hold promise as drug delivery systems for parenteral, peroral and ocular administration as well as adjuvant for vaccines [**20**].
Metallic nanoparticles	Particles with metal core with dimensions between 1-100 nm.	Precluding a harmful environmental effect [**21**] and have been used to rapidly detect respiratory syncytial virus *in vitro* and *in vivo* [**22**].

Among of the presented nanomaterials the greatest application has nanoparticles. Some of the major applications are depicted in **Fig. 1**.

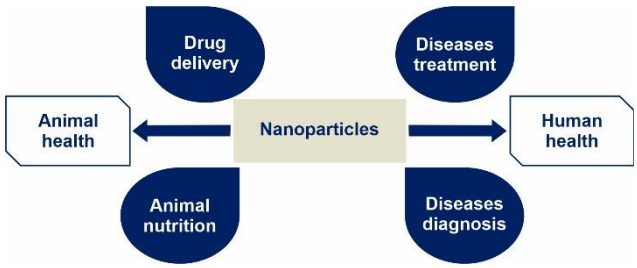

Fig. 1. Schematic depiction of nanoparticles application in animal and human health.

Although much research and major company developments are necessary before nanotechnology is

common place in veterinary medicine. Further, nanotechnology tools like microfluidics, nanomaterials, bioanalytical nanosensors, etc. has the potential to solve many more puzzles related to drug delivery, disease diagnosis and treatment, animal nutrition, animal production and breeding [**23**].

Some applications are discussed in the next sections.

Nanotechnology and animal health

One particular contribution of nanotechnology in medicine currently being developed involves employing nanoparticles to deliver drugs, heat, light or other substances to specific type of cells (such as cancer cells). Such technique reduces damage of healthy cells and allows earlier detection of disease.

Development of drug delivery systems based on nanotechnology methods is being tried for conditions like cancer, diabetes, fungal infections and viral infections and in gene therapy. The main advantages of this modality of treatment are targeting of the drug and enhanced safety profile. Nanotechnology has also found its use in diagnostic medicine as contrast agents, fluorescent dyes and magnetic nanoparticles [**24**].

Drug delivery systems

Smart drug delivery systems in animals would most likely contain small, sealed packages of the drug to be delivered. Smart drug deliveries allow judicious use of smaller quantities of antibiotics than would otherwise be possible. A molecular coded 'address label' in the package could allow the package to be delivered to the correct site in the body. Nano and microscale mechanical systems would serve as the 'carriers' in such a system. Smart delivery systems could also contain on-board chemical detection and decision-making capability for self-regulated drug delivery or nutrient treatments as per need. This will aid livestock owners to minimize use of antibiotic and to reduce the expenditure on medication [**23**].

Nanotechnology offers revolutionary solutions for the most serious problems such as tuberculosis, brucellosis, infections with intracellular or blood pathogens.

The delivery of the drugs directly in the target cells enables the use of very low doses, which in turn minimizes the drug residues and withdrawal time in farm animals [**25**].

Delivery of medicines is either provided as a preventative measure or as a treatment once the disease organism has multiplied and symptoms are evident. Nanoscale devices are envisioned that will have the capability to detect and treat an infection, nutrient deficiency, or other health problem, long before symptoms are evident at the macro-scale. This type of treatment could be targeted to the affected area. 'Smart' delivery systems can have multifunctional characteristics to avoid biological barriers to successful targeting. ''Smart'' delivery systems can have multifunctional characteristics to avoid biological barriers to successful targeting [**12**].

Smart delivery systems can also have the capacity to monitor the effects of the delivery of pharmaceuticals, nutraceuticals, nutrients, food supplements, bioactive compounds, probiotics, chemicals and vaccines.

The remote activation and monitoring of intelligent delivery systems will assist livestock producers of the future to minimise antibiotic use.

Disease diagnosis and treatment

The possibility of injecting nanoparticles into an animal and then a week or so later being able to run a light over the animal's body to activate cancer-killing agents to destroy the tumor.

Hirsch *et. al.,* [**18**] have used nanoshells injected into the animal's bloodstream with targeted agents applied to the nanoshells to seek out and attach to the surface receptors of cancer cells. Illumination of the body with infrared light raises the cell temperature about 55°C, which 'burns' and kills the tumor. From another side these nanoparticles when injected in the bloodstream target tumor receptor cells. The nanoparticles are made from iron oxides that when subjected to a magnetic field enhance the ability of the nanoparticles to locate tumor cells. At the site of the tumour the nanoparticles emit an attached drug to kill the cancer cells. It is interesting to note that quantum dots may also be injected into the bloodstream of animals and they may detect cells that are malfunctioning. Because quantum dots respond to light it may be possible to illuminate the body with light and stimulate the quantum dot to heat up enough to kill the cancerous cell [**12**].

From another side early diseases detection in animals could be happen by use of biochips. A Biochip (or microarray) is a device typically made of hundreds or thousands of short strands of artificial DNA deposited precisely on a silicon circuit. Biochips can also be used to trace the source of food and feeds to detect the presence of animal products from different species as a means to locate the source of pathogens a response to public health threats such as avian flu and mad cow disease. In addition to DNA biochips, there are other variations that detect minute quantities of proteins and chemicals in a sample, making them useful for detecting biowarfare agents or disease. Bioanalytical nanosensors are devices or systems that measure or detect a chemical with the use of a biological material or tissue. These will enable us with detection of very small amounts of a chemical contaminant, virus or bacteria in agriculture and livestock system [**3**].

Nanotechnology in animal nutrition

The production of nanominerals provides various advantages for animal feed industry. They are cheaper, needed in lower concentrations, and have growth promoting and immune stimulating effects. Nowadays many nanominerals are now available for commercial use. Liquid vitamins prepared by nanotechnology are available

for poultry feed. The nanosized nutrients are designed to pass through the gastrointestinal tract and deliver the vitamins or other nutrients directly in the bloodstream and therefore increase their bioavailability. They mask undesired tastes and improve the nutrient dispersibility and durability of the feed. In addition, they decrease the need to use preservatives [**26**].

Nano-additives can also be incorporated in micelles or capsules of protein or another natural food/feed ingredient. Micelles are tiny spheres of oil or fat coated with a thin layer of bipolar molecules of which one end is soluble in fat and the other in water. The micelles are suspended in water, or conversely, water is encapsulated in micelles and suspended in oil. Such nanocapsules can contain healthy omega 3 fish oil (ώ3 fatty acids) which has a strong and unpleasant taste and only release it in the stomach [**27**]. The physical, chemical and biological properties of the materials at their nanoscale usually vary from those of their counterparts. Due to size reduction, the molecules become more reactive (bio-active) and better soluble. They are more stable and less affected by oxidative inactivation and their potential increases. The applications of nanotechnology in the veterinary field are not only restricted to disease prevention and control but are also extended to cover other fields which makes animal rearing more profitable for farmers. Additional contributions of nanotechnology are connected with animal production, reproduction and breeding even animal welfare and in safety derived products [**28**].

Nanotechnology in animal production

Nanomaterials find an application in animal production and feed industry. Therefore animal production systems, either in stables or free grazing, or mixed, could benefit with this technology by using Nano fertilizers 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. From another side is possible to improve 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 [**29**].

In milk production

Nanotechnology is a new technological tool in modern raw milk production and pasteurization. Ongoing advancing in biomedical technology may assist in advancing of disease prevention as well as medical diagnostic and therapeutic [**30**].

Nanotechnology have the potential to advance nutrition and health science in many aspects of relevance for modern milk production [**31**].

Nanotechnology can also help to ensure that the quality of milk is safe for human consumption through novel foodborne pathogen detection techniques.

Nano ZnO is found to enhance growth, improve the feed efficiency in piglets and poultry [**32**]. Nano Zn improves the immunity of the animals. For instance, a reduction in somatic cell count in subclinical mastitis cow and an increase in milk production was observed due to supplementation of nano ZnO [**33**]. Nano Zn also changes the rumen fermentation kinetics in ruminants and also found to alter the proportion of the volatile fatty acids produced. Supplementation of nano ZnO, in vitro, showed an improvement in the growth of ruminal microorganisms, ruminal microbial protein synthesis, and energy utilization efficiency in the early phase of incubation [**34**]. On the other hand, the routine use 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.

Meat and egg quality

The possibility of using nanoparticles to enhance meat and egg quality has also been investigated. For example, Wang and Xu [**35**] demonstrated that when finishing pigs destined for market were given chromium nanoparticles (200 μg/kg) in feed, they were 14.06% leaner at slaughter than control pigs fed a basic diet of corn-soybean meal.

An increase in skeletal muscle mass and improved pork quality were achieved, with similar effects found when finishing pigs were fed chitosan nanoparticle supplements loaded with chromium. These chromium-loaded chitosan NPs elevated the activity of hormone-sensitive lipase in adipose tissue while decreasing fatty acid synthase activity and boosting blood serum immune components [**36**]. These data provide a compelling insight into the mechanism of action these NPs have in pigs, and how they affect meat quality.

Breeding and reproduction

Nanotechnology in animal breeding

Management of breeding is an expensive and time-consuming problem for dairy and swine farmers. One solution that is currently being studied is a nanotube implanted under the skin to provide real time measurement of changes in the level of estradiol in the blood. The nanotubes are used as a means of tracking estrus in animals because these tubes have the capacity to bind and detect the estradiol antibody at the time of estrus by near infrared fluorescence. The signal from this sensor will be incorporated as a part of a central monitoring and control system to actuate breeding [**37**].

Microfluidics are used today in animal science to significantly simplify traditional in vitro fertilization procedures used in animal breeding. It is being used in livestock breeding to physically sort sperm and eggs [**3**]. Nanotechnology can make poultry and meat products cost-effective with the natural properties and the differentiation

in qualities of the products can easily to be made by nanotechnology based techniques [**38**].

Nanotechnology and animal reproduction

The nanoparticles can also be used for sustained release of reproductive hormones. They provide the protection of the given hormones and vitamins from inactivation and degradation by oxidation (e.g., vitamins and steroid hormones) or hydrolysis (e.g., gonadotropic hormones) [**39**]. The nanoparticles can also be used for animal sterilization as contraceptives depending of the toxicity of some metallic nanoaprticles such as cadmium when given in low doses. The metal nanoparticles are directed to the reproductive tract of the animals to exert their effect there. They may also use antibodies conjugated to nanoparticles or heating the gonads using external magnetic field to avoid the use of toxic nanoparticles approach [**40**]. Similarly, the nanotubes can be used in the detection of estrus. The tubes are implanted under the cattle skin and fluorescence when the cows come in estrus. The test is based on estradiol sensors measuring the hormone level in the blood and sending real-time readings of the cows to a central computer for cow monitoring. For cow fertilization, nanocapsules loaded with bull semen can be directed to the ovum. Nanotechnology can be used in sorting the sperms and oocytes. Biochips are under development to enable choosing the sex of the fetus [**23**].

Nanotechnology in human health

Nanotechnology extending rapidly in animal health applications but it should be mentioned that it is at the cutting edge of many potential human health benefits.

Diseases diagnosis

Nowadays there is an urgent need in the developing world for better disease diagnosis, and nanotechnology offers options for detecting diseases. One way of doing this is by using quantum dots - nanosized semiconductors that can be used as biosensors to find disease and which can be made to fluoresce. Known as nanocrystals, quantum dots have significant advantages over traditional organic dyes as their luminescence can be tuned to a wide range of frequencies, and they degrade much more slowly in the body. Fluorescent quantum dots can be tagged to antibodies that target cancerous cells or cells infected with other diseases as tuberculosis or HIV [**41**].

Another type of particles which have an application in human medicine is perfluorohydrocarbons nanoparticles. They are suitable as an ultrasonic contrast agent [**42**]. As it is known gadolinium compounds or radioactive substances such as technetium-99 are combined with the lipid layer of the nanoparticles are suitable for MRI, or scintigraphy imaging [**43**].

Today magnetic nanoparticles are interesting because their heat generation potential appears beneficial and they provide the opportunity of direct tumor targeting through blood circulation [**44**]. From another side super paramagnetic nanoparticles of iron oxide are now being used clinically as MRI contrast agent. They accumulate after intravenous administration in the liver, the spleen, and the lymph glands, thereby enabling studies of those organs. Patient-based research has indicated that they can also increase detectability of tumor metastases in lymph glands [**45**].

Drug delivery

The first clinical trial of magnetically targeted drug delivery was performed by Lubbe *et. al.*, in 1996 [**46**]. In this study, epirubicine was complexed to nanoparticles on the basis of electrostatic interactions between phosphate groups bound to the surface of particles and amino sugars present within the drug. Similarly, few more clinical trials have been performed with promising results [**47**], thus promoting magnetic nanoparticles as another tool for treatment of variety of diseases. The scope for using other, especially inorganic, nanoparticles is smaller. Most delivery systems are currently being developed for transporting antitumor agents, genetic material (gene therapy), as well as proteins and peptides. Nanoparticles of polymers as delivery systems for active substances have been taking place since the mid-1970s. The usefulness of other systems, such as nanoparticles of solid fat, dendrimers, fullerenes, and nanocrystals of the active substance, only began to be studied in the early or mid-1990s. There are now various medicines with delivery systems on the market and many are in the clinical study phase [**48**]. Magnetic nanoparticles stand first in this classification. Some drugs can now be delivered through "nanovehicles''. For example liposomes, which can deliver the drug payload by fusing with cell membranes, have been used to encapsulate HIV drugs such as stavudine and zidovudine in vehicles ranging from 120 to 200 nanometers in size [**49**]. It is interesting to mention that nanobiomagnets which carry drugs, for cancer for instance, into the body and are held at the target site by an external magnet. The purpose of this is to concentrate the drug at the tumor site for long enough for it to be absorbed.

Diseases treatment

Drugs carried by polymer-coated nanoparticles have been used to treat multidrug-resistant breast and ovarian cancer with the chemotherapies paclitaxel, which inhibits cell division, and lonidamine, which suppresses energy metabolism in cancer cells. The nanoparticles are designed to target an epidermal growth factor receptor, which is overexpressed in tumor cells [**50**].

Besides acting as a delivery system, in some cases nanoparticles can act as an active substance. Once they have found their way through the bloodstream into a tumor, or have been injected directly into it, metal-containing nanoparticles can be heated using near-infrared radiation [**51**] or a rapidly oscillating magnetic field so that the tumor cells die.

Another new method applied for cancer detection is by using nanoporous alumina membrane.

The membrane is chemically modified with poly (acrylic acid) in a way to understand the effect of this chemical modification on the protein detection sensitivity. This kind of system could be used as cancer markers for early breast cancer detection [**52**].

Similarly, carbon nanotubes, and nanowires, have been used as biosensors to detect diseases such cancer. Cancer biosensors can be made, for instance, by attaching nucleic acid probes to the ends of nanowires. These probes are specifically designed to bond to biomarkers that indicate cancer such as mutated RNA. When mutated RNA in a sample interacts with the probes, electric currents are induced along the nanowire, which is detected by the silicon chip in which the biosensor is embedded [**49**].

Concerning the diagnosis detection it should be mentioned that is also possible malaria to be detected by fluorescent quantum dots by making them target the protein that forms a mesh in the blood cell's inner membrane. The shape of this protein network changes when cells are infected with malaria, so scientists are able to spot malaria infection from the shape produced by the dots [**53**].

From another side nanostructured materials with sizes 1 to 100 nm can have other applications. They act as new and effective constituents of bone materials, because bone is also made up of nanosized organic and mineral phases. Several studies have reported improved osteointegration on nanostructure surfaces created from a wide range of chemistries including ceramics, metals, polymers, and composites. For instance, studies show that alumina nanometer fibers significantly stimulate osteoblast responses such as adhesion, alkaline phosphatase activity, and calcium deposition, when compared with conventional grain size alumina [**54**].

Nanomaterials, nanopolymers, carbon nanofibers, nanotubes, and nanocomposites of ceramics will also lead to more efficient deposition of calcium-containing minerals on the implants [**55**].

The benefits of nanotechnology which are widely discussed are just in the beginning. It has to be mentioned that besides benefits the nanomaterials could have disadvantages too. In **Table 2** are summarized some advantages and disadvantages of nanomaterials.

Table 2. Some advantages and disadvantages of nanomaterials.

Advantages	Disadvantages
Fast delivery and diseases treatment	Possible accumulation in some organs
Low concentration of surfactant	Toxicity effect of kidney, liver
Control of nanoparticles size	Impurity Difficulty in synthesis
Dispersion difficulties	May lead to allergic reactions
Easy control of physical properties	May cause infection of lungs
Stable drug release	No degradable need to remove surgically
Biocompatibility	Conjugate low amounts of drugs
Easily scaled for synthesis	Limited application
Good tissue permeability	Limited storage conditions

Conclusion

Nanotechnology in animal and human health is a growing field that plays a great role in diagnostics and therapeutics of some diseases and adds to for improving livestock production and reproduction.

Nanomaterials offer a big number of breakthroughs like cost effective, lower risk to consumers and faster access.

The technology, although still in the early stages of its development but it opens the door for significant benefits in healthcare and animal medicine.

Nanotechnology provided advances of veterinary medicine such as diagnosis, treatment, vaccination, animal production and reproduction, feeding, and hygiene as well as in human health. It could be expect that in the next couple of decade's nanobiotechnology industries and unique developments will be revolutionizing animal and human health and medicine.

However, a great amount of research is still required to support the effectiveness, and mainly the safety of nanotechnology, avoiding any harm to the livestock, environment and to human beings.

Conflicts of interest

"There are no conflicts to declare".

Keywords

Animal health, human health, nanomaterials, nanotechnology

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Graphical abstract

In the last decades nanotechnology find applications in different fields and the most important are in animal and human health. Nanomaterials has contributions in diseases diagnosis and diseases treatment, in drug delivery system, in animal nutrition, production and breeding. In addition to human health care, they also enter people's lifestyles.