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New Drug Delivery Systems in Livestock Animals

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ABSTRACT

The development of animal husbandry in Indonesia has seen positive progress through government initiatives to increase productivity and efficiency. The field of veterinary medicine plays a vital role in maintaining the health and productivity of livestock, which ultimately impacts the productivity and quality of animal products. However, areas still require improvement, particularly infrastructure, technology, and management. Pharmaceutical science, specifically veterinary pharmacy, focuses on treating animals using different drug delivery systems due to physiological differences. Significant modification in livestock drug delivery involves adjusting medication based on animal needs to improve health and reduce the risk of overmedication and antibiotic resistance. Advancements in technology and medical developments are continuously being reviewed and studied to improve veterinary medicine.

Keywords: Cattle, Bovine, Vaccines, Modified drug delivery, Veteriner.

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1. Introduction

The development of animal husbandry in Indonesia has seen positive progress over the years with various government initiatives aimed at increasing productivity and efficiency. This has increased livestock productivity and the quality of the resulting products [1]. However, areas still require improvement, particularly in infrastructure, technology, and management [2–4]. The field of Veterinary Medicine plays a vital role in maintaining the health and productivity of livestock, which ultimately impacts the productivity and quality of animal products [5,6]. The government and industry players must invest in these areas to ensure long-term sustainability and growth in the livestock sector.

Pharmaceutical science includes veterinary pharmacy, which focuses on treating animals [7]. Treatment for animals is different from humans due to physiological differences. Thus, the drug delivery systems used differ [8–10]. These systems ensure that the drug works optimally and produces the desired response. Various methods, such as oral, topical, injectable, and implantable administration, are used in livestock animals. These systems are used to prevent and treat diseases, improve production efficiency, and ensure the safety and quality of animal products [11].

An importance modification in livestock drug delivery refers to adjusting the amount of animal medication based on their needs and health status [12,13]. This approach ensures that animals receive the appropriate amount of drugs, improving their health and reducing the risk of overmedication and antibiotic resistance [14]. Additionally, it helps optimize resources and reduce costs associated with drug delivery in livestock production.

New Drug Delivery Systems (NDDS) enhance livestock efficiency and sustainability by ensuring targeted, controlled drug delivery. They improve bioavailability, protect active substances, reduce dosages and side effects, and minimize drug residues, boosting food safety. NDDS increases therapy compliance with long-acting systems, optimizes vaccine and nutrient delivery, reduces antimicrobial resistance, and decreases environmental contamination, supporting animal health, productivity, and sustainability.

Designing and delivering drugs for animals requires different considerations and faces more challenges than humans. It is essential to not rely solely on human data. Reviewing New Drug Delivery Systems (NDDS) in livestock is vital to evaluate their benefits, including improved drug efficacy, safety, and productivity, while addressing implementation challenges like cost and feasibility. This supports scientific development, industry adoption, and informed policy-making for sustainable livestock practices.

Common diseases in livestock

Livestock animal health is a critical factor in the success of a farming enterprise. The adage "prevention is better than cure" highlights the importance of proactively improving animal health through actions such as sanitation, vaccination, and proper animal management. Farmers need to be aware of these diseases, as well as the methods of prevention and treatment, to maintain the health and productivity of their livestock [15,16].

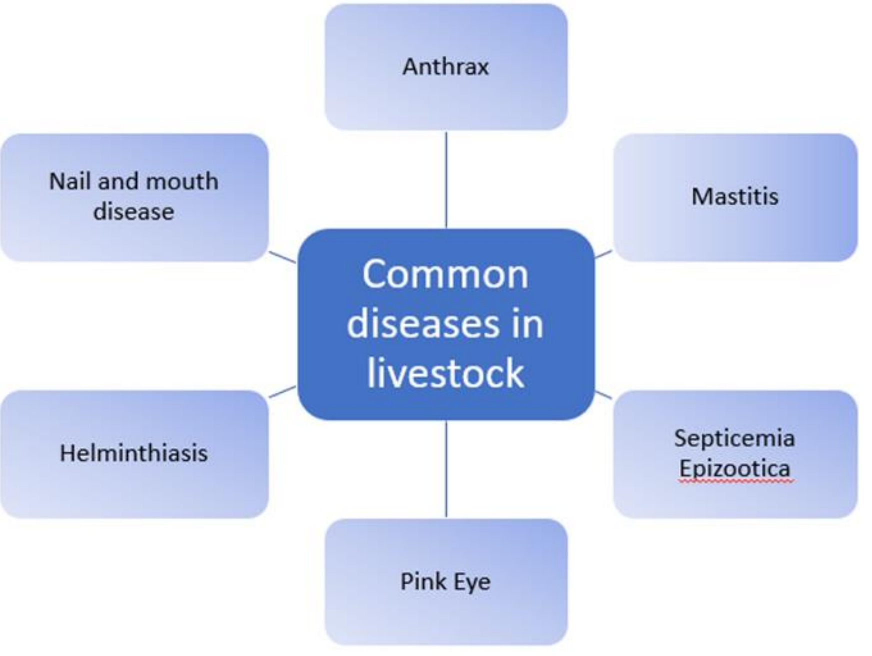

Figure 1. Common diseases in livestock

Anthrax

Anthrax, caused by *Bacillus anthracis* , is a contagious disease affecting livestock and humans in Indonesia. It results in significant livestock deaths, causing labor loss and meat/skin wastage. Transmission occurs through contact with infected animals or contaminated environments [17,18].

Symptoms include high fever, exacerbated by cold weather, food scarcity, and fatigue. The disease is not directly transmitted between animals but is linked to neutral or alkaline limestone soil. In hot climates, flies and contaminated grass can spread it. Awareness among farmers and preventive measures are crucial to control anthrax spread. Anthrax is a contagious disease affecting various livestock animals, including cattle, sheep, goats, horses, pigs, and wild animals such as deer [19,20]. The *Bacillus anthracis* bacteria cause it and has three forms:

1. Peracute form

The disease appears suddenly, and death occurs quickly due to bleeding in the brain, difficulty breathing, trembling, and then collapse, with death occurring within 2-6 hours. This form is commonly seen in cattle and sheep.

2. Acute form

The symptoms in this form include a significant increase in body temperature (fever), restlessness, rapid heartbeat, decreased milk production, yellow or reddish milk, and swelling in the throat and tongue. This form is commonly seen in cattle, sheep, and goats.

3. Chronic form

This form, common in pigs, sheep, goats, horses and other livestock animals, is characterized by limited local sores on the tongue and throat. [21,22] .

It is essential for farmers and those who work with livestock to be aware of the symptoms of anthrax and to take appropriate measures to prevent and control the spread of the disease, such as avoiding contact with contaminated soil, practicing proper sanitation, and seeking veterinary care in case of suspected anthrax infection [21,23].

Anthrax clinical symptoms presents in various forms depending on the route of infection and the species affected:

1. Malignant pustular form: Skin transmission, red bump, erythema; seen in sheep and goats.
1. Septic form: Fever, headache, back and epigastric pain, nausea, bloody diarrhea, cyanosis, sudden death; common in cattle and sheep.
2. Gastroenteritis form: Oral transmission, lower fever, stomach pain, shivering, rapid death; seen in cattle and sheep.
3. Pulmonary form: Inhalation transmission, mild upper respiratory symptoms; common in cattle and sheep.

Mastitis

Mastitis is a common and costly disease of lactating animals, characterized by inflammation of the mammary gland, leading to a reduction in milk production, changes in milk composition, and increased risk of antibiotic residue in milk. The causes of mastitis include multiple factors, such as bacterial infection, physical or chemical injury, and the cow's immune response [24,25].

Recent research has identified new potential causes of mastitis, such as environmental factors and genetics. Environmental factors such as poor hygiene, overcrowding, and high-stress levels have been found to increase the risk of mastitis. In contrast, genetic factors such as variations in mammary gland structure, genetics of the cow's immune system, and genetic variants of the bacteria involved in the infection are important in susceptibility to the disease [25,26].

Recent research has also highlighted the importance of understanding the dynamics of bacterial communities (microbiota) within the mammary gland and the interactions between the host, the environment, and the microbiota, which can impact the development of mastitis. Studies have shown that the diversity and composition of the mammary gland microbiota can affect the host's susceptibility to infection and that certain bacteria can act as protective or risk factors for developing the disease.

It is important to note that the most common bacterial causes of mastitis are *Staphylococcus aureus, Streptococcus agalactiae*, and *Escherichia coli*. However, other bacteria, yeast and fungi also can cause the disease [24].

Clinical symptoms of mastitis in livestock animals can be divided into three categories: acute, subacute, and chronic.

1.Acute mastitis is characterized by a sudden inflammation in the mammary gland, leading to swelling, warmth, pain, redness, and changes in the milk produced, such as broken and mixed with sediment or fibrin clots.

2.Subacute mastitis is a less severe form of the disease, where the animal may not show any clinical signs of inflammation during examination. However, there are still changes in the milk produced.

3.Chronic mastitis is a long-term infection in the mammary gland, often recurring from one lactation period to the next, and can eventually lead to the atrophy of the mammary gland.

Mastitis can be diagnosed by several methods, such as observation of clinical signs of inflammation and changes in the color of the milk produced and field testing using the California Mastitis Test or the Whiteside Test. Additionally, laboratory tests such as bacterial culture, PCR, and milk somatic cell count are commonly used to confirm the diagnosis and identify the cause of the infection [27,28].

Septicemia Epizootica

In Indonesia, regular vaccination programs have led to a decrease in the occurrence of *septicemia epizootica* (SE). However, outbreaks of SE still occur, particularly in the Nusa Tenggara regions, such as Sumba, Timor, and Sumbawa. The disease typically occurs at the beginning of the rainy season. The cause of SE is a bacterium called *Pasteurella multocida*, which is a small, bipolar coccobacillus that has several types. Transmission of SE can occur through various factors, such as fatigue, cold temperatures, transportation, and unvaccinated animals. The disease primarily affects cattle aged 6-24 months and is characterized by symptoms such as high fever, trembling, dull and watery eyes, loss of appetite, and digestive disorders [29,30].

Recent research on SE in livestock has focused on developing new diagnostic methods, using precision farming technology to detect early signs of the disease, and exploring new treatment options, such as using bacteriophages and natural compounds. Additionally, researchers are investigating new vaccination strategies and identifying genetic factors that make animals more resistant to SE. Studies also examine the relationship between SE outbreaks and environmental factors such as temperature and humidity, and management practices that may contribute to the spread of the disease [30,31].

Pink Eye

Pink Eye, also known as infectious bovine keratoconjunctivitis (IBK), is a contagious disease that affects cattle, sheep, and goats. The leading cause is a bacterium called *Moraxella bovis*. Symptoms include redness and swelling of the eyes, squinting to avoid bright light, cloudy corneas, and the formation of ulcers or holes in the cornea. These ulcers can cause blindness. Recovery typically takes 1-4 weeks. To prevent the spread of the disease, it's essential to diagnose and treat it quickly and to practice proper hygiene and biosecurity measures [32,33].

Recent research on Pink Eye has focused on developing new diagnostic methods and treatments and identifying risk factors for the disease. For example, new diagnostic tools such as PCR-based methods and metagenomic sequencing have been used to determine the causative agents of Pink Eye and to monitor the spread of the disease within a herd [34,35].

In addition, new treatment options such as long-acting antibiotics, topical antimicrobial ointments, environmental and vector control. Furthermore, research has also been conducted on using vaccines and other preventive measures to reduce the risk of Pink Eye in cattle, sheep, and goats. It's also essential to implement good management practices, including good hygiene, proper sanitation, and biosecurity measures, as well as providing adequate nutrition and housing to animals to prevent the outbreak of Pink Eye [32,34].

Helminthiasis

Helminthiasis, a parasitic infection commonly seen in young cattle, is often caused by inadequate husbandry practices and is more prevalent during the rainy season or in damp or humid conditions. This infection can lead to severe consequences and high mortality rates. The clinical signs of parasitic infection may include profuse diarrhea, soft to watery feces containing mucus and segments of worms passed through the anus, anorexia, weight loss, and rough, dull, stiff, and standing hair. Furthermore, the infection can decrease feed intake, reduce growth rate, and decrease milk production and reproductive performance [36].

Furthermore, research is also focused on identifying genetic factors that may make certain animals more susceptible to parasitic infections, and on developing new vaccination strategies to prevent the occurrence of helminthiasis. Studies are also investigating the relationship between helminthiasis outbreaks and environmental factors such as temperature and humidity, and management practices that may contribute to the spread of the disease. An integrated approach is required to effectively control helminths, including strategic and tactical use of anthelmintics and careful management of grazing lands, including control of stocking rates and appropriate rotation strategies. Vaccinations may also play a role, as in the case of lungworms [37,38].

Nail and mouth disease (NMD)

Nail and mouth disease is an infection caused by the herpes simplex virus. This virus is spread through direct contact with fluids from infected skin, such as saliva, saliva, or fluids from lesions. The virus can also be spread through contact with contaminated items, such as towels, spoons, or cutlery used by an infected person [39].

The main symptoms of NMD include:

1. into ulcHigh fever
2. Blisters or sores on the tongue, gums, and/or inside of the mouth and the feet, hooves and/or teats
3. Swelling of the lymph nodes.
4. Loss of appetite.
5. Lameness and reluctance to move.
6. Decreased milk production.
7. In severe cases, the blisters can developers, and the animal may have difficulty eating or drinking.

Nail and mouth disease generally doesn't cause serious complications but can cause severe aches and pains around the mouth and lesions. The lesions can spread rapidly and can be spread to other people through physical contact or contact with contaminated items [40]. Available treatments for nail and mouth disease include oral or topical antiviral drugs to relieve symptoms and reduce the duration of the infection. Good cleaning and keeping a distance from infected people can help prevent the spread of infection. In general, to prevent foot and mouth disease, it is recommended to maintain good oral hygiene, avoid contact with infected people, and avoid touching the lesions with hands [41].

Treatment and Drug Delivery System Used

The treatment and drug delivery systems used for the diseases mentioned above vary depending on the disease's severity.

No	Diseases	Treatment
1	Anthrax	Treatment for anthrax typically involves the use of antibiotics such as ciprofloxacin or doxycycline, which are administered orally or intravenously. In severe cases, supportive therapy may also be required [22].

New Drug Delivery System

The rumen, the "first stomach" of ruminant animals such as cows, sheep, and goats, plays a crucial role in their digestion and metabolism. A new drug delivery system for the rumen, also known as "rumensia," would involve a method of administering medication or supplements specifically targeted to the rumen and its unique environment. There are several existing methods of delivering drugs to the rumedahn, including oral drenches and tubing, as well as rumen boluses and implants. However, these methods may have limitations, such as difficulty in ensuring accurate dosing and the potential for decreased drug efficacy due to the harsh conditions of the rumen [49,50].

A new drug delivery system for rumensia could include the development of new formulations such as microparticles, nanoparticles, or liposomes that can protect the drugs from the harsh conditions of the rumen and target specific cells or regions of the rumen for maximum efficacy. Using controlled release systems, such as pH-sensitive or temperature-sensitive polymers, may also help increase the drugs' stability and effectiveness in the rumen [51,52]. Research and development in this field is ongoing. Discoveries in drug delivery systems, such as probiotics or other microbial-based systems, may also have potential applications in rumensia. Probiotics are live microorganisms that confer health benefits to their animal host by balancing the composition of its gastrointestinal microbiota, modulating its immune response, and improving production performance [53–55].

To develop a new drug delivery system for rumensia, it would be necessary first to understand the unique characteristics and requirements of the rumen environment [51]. This includes factors such as pH, microbial population, and the physical movement of the rumen contents. Additionally, it would be essential to consider the specific drug or treatment being delivered and its optimal conditions for efficacy and stability [49].
It would also be essential to conduct thorough in-vivo testing to ensure that the new drug delivery system effectively reaches the target site and has the desired therapeutic effect. This would involve working closely with veterinarians and animal nutritionists to conduct controlled trials in live animals [56].

Drug Delivery System	Description	Advantages	Application Examples	Studies Conducted
Microparticles & Nanoparticles	Micro/nanoparticles used as drug carriers for controlled release	Increases bioavailability, prolongs drug release, reduces dosing frequency	Livestock vaccination, bacterial infection treatment	Chitosan nanoparticles for oral poultry vaccines [57]
Liposomes	Lipid-based vesicles that encapsulate drugs	Enhances drug stability, reduces toxicity, improves delivery efficiency	Antibiotics for bovine mastitis, oral vaccines	The use of liposomal-entrapped gentamicin in the treatment of bovine Staphylococcus aureus mastitis [58]
Polymeric Implants	Polymer-based implants that gradually release drugs	Long-term drug release reduces stress from repeated injections	Growth hormone for cattle, antiparasitic therapy	Ivermectin controlled release implants based on poly-D,l-lactide, and poly-ε-caprolactone [59]

Smart Hydrogels	Polymer gels that respond to pH or body temperature	Controlled drug delivery based on body conditions	Anti-inflammatory drug delivery in cattle and sheep	Thermosensitive bovine lactoferricin-loaded chitosan hydrogels for sustained antibacterial release [60]
Transdermal Patches	Patches delivering drugs through the skin	Reduces stress from injections, increases farmer compliance	Pain management in cattle, antiparasitic treatment for sheep	Transdermal flunixin patches for pain management in cattle [61]
Biodegradable Injectables	Injectable formulations that naturally degrade in the body	Reduces side effects, no need for device removal	Livestock vaccines, long-acting antibiotic therapy	Long-acting injectable (LAI) depots of polylactide-co-glycolide (PLGA) or polylactic acid (PLA) based microspheres have been developed for controlled drug delivery [61]
In-Situ Forming Gels	Liquid formulations that form gels upon injection for sustained drug release	Facilitates high-dose administration, improves drug stability	Reproductive hormone delivery for cattle, anti-inflammatory therapy	Control of ovarian function using non-injection technologies for GnRH administration [62]
Oral Nanocarriers	Nanoparticles that improve drug absorption in the digestive tract	Enhances oral drug effectiveness, protects drugs from digestive degradation	Livestock nutritional supplements, oral vaccines	Chitosan-based nanoparticles to improve vitamin absorption in poultry [63]
Floating Drug Delivery System	A system that retains the drug in the stomach to enhance absorption	Increases drug bioavailability with slow-release	Antiparasitic drugs for ruminants	Solidified floating organic droplet for anthelmintic drugs in cattle [64]
Inhalable Drug Delivery	Drug delivery through aerosol or nebulizer	Fast-acting reduces animal stress	Antibiotics for respiratory diseases in cattle	Nebulized florfenicol for pneumonia treatment in Bovine Respiratory Disease Complex [65]

The advancement of New Drug Delivery Systems (NDDS) in livestock medicine has significantly improved drug administration, enhancing efficacy, safety, and animal welfare. Traditional drug delivery methods, such as oral and injectable routes, often present challenges, including poor bioavailability, rapid drug degradation, and the need for frequent dosing. NDDS addresses these limitations by offering innovative solutions such as nanoparticles, polymer-based implants, and transdermal patches that optimize drug release and improve treatment outcomes. These technologies increase therapeutic effectiveness, reduce animal stress, and minimize labor for farmers [63].

Among the most promising NDDS approaches are microparticles and nanoparticles, which provide controlled and targeted drug release. These systems protect active pharmaceutical ingredients from degradation and enhance their absorption in the body. For example, chitosan nanoparticles have been studied for oral vaccine delivery in poultry, demonstrating improved immune response compared to conventional vaccines. Similarly, liposomes, lipid-based vesicles, have been developed to deliver antibiotics more efficiently, reducing the required dosage and minimizing the risk of antimicrobial resistance. One study has shown that liposome-encapsulated gentamicin effectively treats cattle mastitis, highlighting this technology's potential in livestock healthcare [35,66].

Another innovative approach is using polymeric implants and biodegradable injectables, which provide long-term drug release and eliminate the need for repeated administration. This is particularly beneficial in growth hormone therapy and antiparasitic treatments for cattle, where maintaining consistent drug levels is crucial. Research on biodegradable ivermectin implants has shown extended efficacy in controlling parasites and reducing environmental contamination from excessive drug use [59,67]. In addition, in-situ forming gels, which transform into a gel-like structure upon injection, have been explored for delivering reproductive hormones such as GnRH in cattle, improving estrus synchronization programs [68].

The transdermal patch system is another breakthrough that enhances drug delivery without requiring injections. These patches allow medications to be absorbed through the skin, reducing animal stress and improving compliance. Studies on flunixin transdermal patches for pain management in cattle have demonstrated effective absorption and prolonged analgesic effects. Similarly, smart hydrogels, which respond to body temperature or pH, have been designed to release anti-inflammatory drugs in cattle and sheep, ensuring sustained therapeutic effects with minimal intervention [69].

Nanocarriers and floating drug delivery systems are gaining traction in veterinary medicine for oral drug delivery. Chitosan-based nanoparticles have been tested to enhance vitamin absorption in poultry, ensuring better nutritional intake. Meanwhile, floating drug delivery systems have been developed for ruminants to prolong drug retention in the stomach, increasing absorption efficiency for antiparasitic treatments. These advancements improve the effectiveness of orally administered drugs, which traditionally suffer from low bioavailability due to rapid degradation in the digestive system [63].

Finally, inhalable drug delivery systems offer a fast and efficient method of treating respiratory diseases in livestock. By delivering drugs directly to the lungs through nebulization, these systems ensure rapid absorption and high local drug concentrations, improving treatment outcomes for pneumonia and other respiratory infections. Studies on nebulized florfenicol for bovine pneumonia have shown promising results, reducing the need for systemic antibiotics and lowering the risk of antimicrobial resistance. The continuous development of NDDS in livestock enhances treatment effectiveness and contributes to sustainable and responsible veterinary medicine [65].

2. Conclusion

Developing New Drug Delivery Systems (NDDS) has revolutionized livestock healthcare by improving drug efficacy, reducing animal stress, and minimizing dosing frequency. Innovations such as nanoparticles, liposomes, polymeric implants, transdermal patches, and inhalable drug delivery enhance bioavailability, e nable controlled drug release, and offer targeted treatment for a r ang of conditions, from infections to pain management. Research has confirmed the effectiveness of these technologies in improving treatment outcomes while supporting sustainable and responsible veterinary medicine, including reducing antimicrobial resistance and enhancing animal welfare. As NDDS continues to evolve, collaboration between scientists, veterinarians, and the pharmaceutical industry is essential to expand its application, ensuring better livestock health, increased productivity, and improved food safety worldwide.

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