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Polymeric rumen-stable delivery systems for delivering nutricines

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ABSTRACT
Ruminants face unique drug and nutrient delivery challenges because of their symbiotic rumen microorganisms. Polymeric rumen-stable delivery systems (RDSs) have emerged as a promising solution for efficiently delivering nutrition and enhancing animal health and productivity. Traditional methods such as heat and chemical treatment have been improved with polymeric coatings that facilitate the slow postruminal release of bioactive substances. Polymeric coatings of nutrients offer significant potential for improving ruminant health, reducing farmer costs, and promoting sustainability in livestock. This paper explores the mechanisms of rumen protection and abomasal release provided by polymeric coatings, discusses other RSDs, and reviews methods for evaluating their performance *in vitro* and *in vivo*. Further research in this area could advance novel nutricine delivery solutions for ruminants**.**
Keywords: Ruminants; Polymeric coatings; Nutricines; Livestock industry.

Introduction

As the global demand for animal food increases, especially in Indonesia, the need for efficient and sustainable methods to improve livestock health and productivity is becoming increasingly important. These methods help reduce malnutrition and increase household and food security (Kappes *et al.*, 2023). Currently, animal husbandry faces several challenges due to a lack of available arable land, clean water, ongoing climate issues, competition for feed and fuel, and a shortage of animal feed ingredients (Malenica *et al.*, 2023). Despite this, the demand for red meat is projected to double in 2050, while national beef production in Indonesia is currently only able to meet around 45% of the demand (Agus and Widi, 2018). A significant proportion of beef production is carried out by smallholders, with commercial entities contributing a small proportion. This presents an excellent opportunity to strengthen the Indonesian beef sector through technological innovation, thereby increasing the productivity and profitability of these smallholder farmers (Burrow, 2019).

Historically, the livestock industry has faced several hurdles, such as limited access to innovative technologies, investment, veterinary drugs, and superior seeds (Jaime *et al.*, 2022). With rapid growth, innovative technologies are playing an increasingly important role. Traditional procedures are labor-intensive, time-consuming, and technical and require skilled specialists and specialized equipment (Akhigbe *et al.*, 2021; Džermeikaitė *et al.*, 2023). Increased investments in technology, veterinary drugs, and superior seeds can reduce the country's dependence on food imports, strengthen the national food security, and improve the welfare of small-scale beef farmers. Because local production cannot meet national food needs, import arrangements are made. However, this policy is unsuitable for the long term because of the risk of dependence on imported food (Zuhud, 2020).

The emerging field of pharmaceutical sciences provides potential solutions to the challenge of effective nutritional delivery. Pharmaceutical sciences deal extensively with biocompatible drug carriers for the transport of molecules in pharmaceutical, cosmetic, and nutraceutical applications. The main advantages of this strategy are increasing efficacy, reducing the dose, and controlling the delivery of bioactive compounds (Halmemies-Beauchet-Filleau *et al.*, 2018). Combining preparation modification and food delivery science will create a new "smart food" system that can improve health and well-being (Martínez-Ballesta *et al.*, 2018). Controlled delivery systems for encapsulating bioactive compounds or nutrients to achieve the desired efficacy in animal feeds. Nanoencapsulation offers better protection, absorption, and delivery of bioactives (Siddiqui *et al.*, 2022).

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Developing systems that can withstand the ruminant digestive system is essential for effective and cost-effective treatment regimens that support animal health and productivity. These delivery systems, made from biodegradable or nonbiodegradable polymers, provide controlled bioactive release, benefiting ruminant health and livestock productivity. Biodegradable materials are gaining attention due to their adaptable characteristics, such as electrical conductivity and biodegradability, which make them attractive in many applications (Bilhalva *et al.*, 2018; Tran and Tran, 2019).

Micronutrients are essential for optimizing animal feed use and represent the most significant single cost in livestock production, often accounting for 60% of the expenses. Micro ingredients such as soy, corn, and wheat can vary significantly in density and nutritional value, and antinutritional factors usually hinder their digestibility. Despite these challenges, advancements in feed technologies have enhanced feed quality and livestock productivity. Many of these technologies have been successfully adopted and scaled up to increase income (Balehegn *et al.*, 2020). A key aspect of these polymeric-controlled delivery systems is the inclusion of nutricines—bioactive substances such as carotenoids, enzymes, fatty acids, flavors, oligosaccharides, organic acids, phospholipids, and polyphenols (Martínez-Ballesta *et al.*, 2018; Borandeh *et al.*, 2021). These components have been extensively researched for their roles in maintaining animal health and preventing disease, making them well-suited for long-term, controlled-release delivery systems (da Silva *et al.*, 2020; Broda *et al.*, 2024). Current methods such as heat and chemical treatments often fail to protect bioactive substances from rumen degradation and ensure their effective release in the abomasum (Iommelli *et al.*, 2022; Pena *et al.*, 2023; Davidson *et al.*, 2024). This gap in effective delivery systems hinders optimal nutrient utilization and increases farmers' costs. Polymeric rumen-stable delivery systems (RDSs) offer a promising solution for the slow, postruminal release of bioactive substances. While these systems show significant potential in improving ruminant health, reducing costs, and promoting sustainability, there is a need for comprehensive research to optimize their performance and explore new materials (Bešlo *et al.*, 2022; Albuquerque *et al.*, 2023).

This study focused on the potential of polymeric RDS for delivering nutrients. We aim to explain how these delivery systems can enhance ruminant health and productivity by addressing the unique challenges of ruminant biology and finding ways to overcome them. As we examine these delivery systems in detail, we highlight their potential for sustainable livestock management, improved animal health, and overall food security.

Rumen-stable Delivery Systems

The digestive system of ruminants

Understanding the unique digestive tract and digestion process of ruminants, along with the harsh conditions of degradation in the rumen environment, is crucial for developing carriers for various active compounds and nutrients (Galyon *et al.*, 2022). The advancement of these preparations offers promising prospects for ruminant drug delivery.

The ruminant rumen hosts a complex ecosystem of bacteria, protozoa, and fungi that break down plant cell walls (Zhang *et al.*, 2022). With their large numbers and diverse metabolic pathways, rumen bacteria dominate this ecosystem. They play a key role in the digestion of cellulose, whereas protists and fungi contribute through various mechanisms (Weimer, 2022). These bacteria break down approximately half of the crude fiber consumed by ruminants. The three most common fiber-degrading rumen bacteria are *Ruminococcus flavefaciens*, *Ruminococcus albus*, and *Fibrobacter succinogenes*. The digestion of cellulose and hemicellulose in food (Hua *et al.*, 2022; Weimer, 2022; Gharechahi *et al.*, 2023). Rumen bacteria help to break down nutrients such as starch, xylan, and pectin. This process is mainly performed by amylolytic bacteria such as *Prevotella ruminicola* and *Streptococcus bovis* (Palevich *et al.*, 2019; Wei *et al.*, 2022). Some bacteria, such as *Fibrobacter succinogenes* and *Butyrivibrio fibrisolvens*, also break down cellulose and starch, contributing further to the complex digestive processes in the rumen (Hua *et al.*, 2022).

Protein degradation is another vital function of rumen bacteria, particularly *Ruminobacter amylophilus* and *Butyrivibrio fibrisolvens* (Liu *et al.*, 2019; Mohamaden *et al.*, 2020). These bacteria convert plant and nonprotein nitrogen, which the host cannot use directly, into microbial protein (Wei *et al.*, 2022; Zhu *et al.*, 2022). Other bacterial species, including *Clostridium spp*., *Eubacterium ruminantium, Prevotella spp*., and *Selenomonas ruminantium*, also play roles in protein degradation (Zhu *et al.*, 2022; Arjun *et al.*, 2023). The distribution of bacteria in the ruminant digestive system is shown in Figure 1.

Several bacteria produce lactic acid, an essential intermediate product, in the rumen. *Lactobacillus*, *Streptococcus*, *Enterococcus*, and *Pediococcus* are the primary lactic acid producers. Excessive lactic acid production due to an imbalance between lactic acid-producing and lactic acid-utilizing bacteria can lead to rumen acidosis (Lee *et al.*, 2019; He *et al.*, 2022; Hu *et al.*, 2022). The rumen hosts methane-producing archaea known as methanogens. Recent studies suggest that feed additives can reduce methane emissions from ruminants, thereby mitigating the environmental impact of ruminant farming (Li *et al.*, 2019b; Getabalew *et al.*, 2020).

Although less numerous than bacteria, protozoa comprise a significant portion of the rumen microbial biomass due to their larger size. Protozoa comprise 50% of the rumen biomass and play a key role in rumen metabolism, contributing significantly to volatile fatty acid (VFA) production through the fermentation of feedstuffs and engulfing bacteria. Removing protozoa

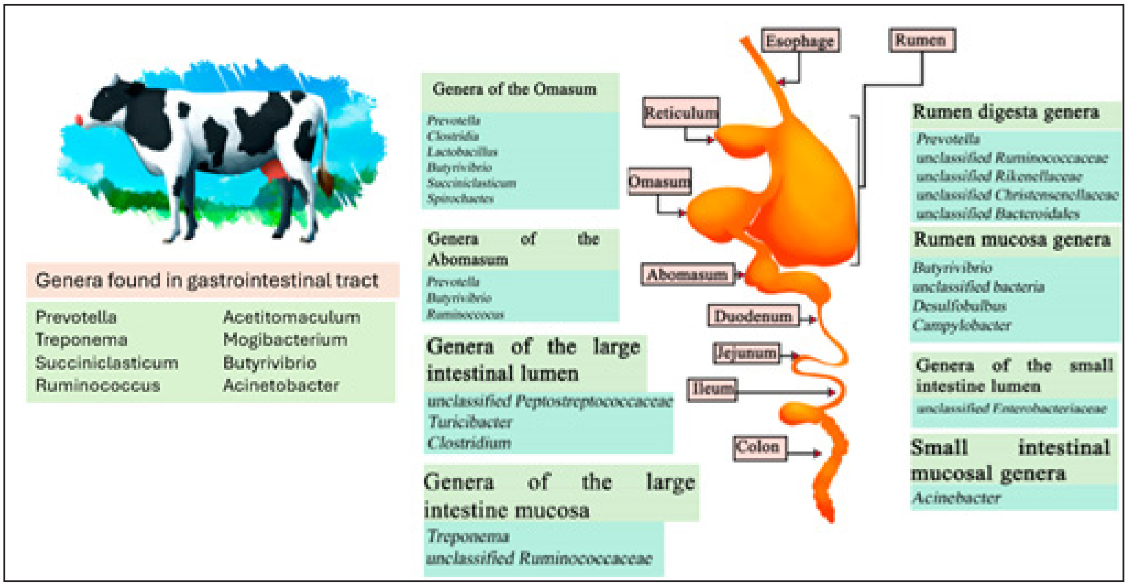

Figure 1. The digestive system of cows. Microorganisms are frequently found in different sections of the gastrointestinal tract compartments (Huaiquipán *et al.*, 2023).

(defaunation) can reduce animal performance by approximately 10% (Perez *et al.*, 2024). Protozoa and rumen viruses influence the rumen microbiome through interactions between top-down (predation) and bottom-up (metabolic impact). Protozoa regulate other microbes through predation and metabolic effects, whereas viruses act as intracellular predators, lysing cells, and reprogramming host metabolism to enhance ecological fitness (Yu *et al.*, 2024). *Entodinium* and *Epidinium*, two dominant genera of the order Entodiniomorphida, were found in over 99% of 592 rumen samples, with mean abundances of ~38% and 16%, respectively (Andersen *et al.*, 2023). The diverse rumen viruses can infect most lineages of the rumen microbiomes, including 1,051 genera of bacteria, 25 genera of archaea, and 13 genera of protozoa (Yu *et al.*, 2024).

Anaerobic fungi, such as *Neocallimastix*, *Piromyces*, and *Orpinomyces*, are significant in the initial colonization of plant material. Anaerobic fungi (phylum Neocallimastigomycota) inhabit the alimentary tract of herbivores and display multiple adaptive strategies that enable them to survive and thrive in this permanently anoxic, prokaryote-dominated ecosystem (Elshahed *et al.*, 2022). Anaerobic fungi (Neocallimastigomycota) are common in the digestive tracts of mammalian herbivores and can comprise up to 20% of the rumen microbial biomass. They primarily degrade lignocellulosic plant material and have a syntrophic relationship with methanogenic archaea, enhancing fiber degradation (Edwards *et al.*, 2017). Anaerobic gut fungi form rhizoidal structures to enhance plant attachment and colonization, which facilitate taxonomy. Hyphal coils wrap around plant fibers, maximizing contact, while appressoria develop as multilobed vesicles with penetration pegs to aid nutrient absorption (Hanafy *et al.*, 2022). While producing highly active cellulases, ruminal fungi largely degrade plant material through the physical force exerted by growing hyphal tips (appressoria) that fracture plant tissues, facilitating bacterial invasion. This capability gives them a significant role in plant biomass degradation (Weimer, 2022).

Methanogenic archaea are diverse microorganisms crucial to global carbon cycling, producing methane as a by-product of energy production (Volmer *et al.*, 2023). Common species include *Methanobrevibacter ruminantium* and *Methanobacterium formicicum*. Methanogenic archaea in the gut act as a hydrogen sink, facilitating short-chain fatty acid production. Dysbiosis of these methanogens is linked to diseases such as inflammatory bowel disease (IBD). Although archaea diversity is higher in patients with IBD, methanogen prevalence and abundance decrease, particularly in ulcerative colitis (Cisek *et al.*, 2024). Recent advancements in sequencing technology and omics have provided profound insights into the rumen world, wherein a consortium of archaea, bacteria, protozoa, fungi, and viruses exist and interact (Sanjorjo *et al.*, 2023).

Need for rumen-stable delivery systems

Prolonged drug release systems can reduce the need for human intervention in livestock and domestic animals, thereby enhancing therapeutic efficacy while minimizing potential discomfort and stress for the animals (Hayward *et al.*, 2018). The ruminant digestive system presents a unique challenge, as developing delivery systems that can survive the rumen environment and ensure drugs reach the desired absorption site is crucial for effective disease prevention and treatment in ruminants (Fleming *et al.*, 2019).

The development of drug preparations is expected to have a long-term impact. Beyond merely addressing nutritional deficiencies, these systems will significantly contribute to maintaining optimal health and productivity in ruminants (Bionaz *et al.*, 2020; Sprinkle *et al.*, 2021). Long-acting drug delivery systems can also be used to prevent and treat infectious diseases caused by viruses, bacteria, protozoa, and fungi, which can lead to severe health issues if left untreated. Additionally, these systems are effective against parasites such as worms, ticks, and mites, which disrupt livestock productivity by interfering with feeding and resting patterns, thereby reducing feed conversion efficiency and weight gain. Rumen-stable formulations are particularly beneficial for treating conditions such as bloating, ketosis, and acidosis in livestock (Youssef *et al.*, 2019).

Digestive system of ruminants preparation

Physiological considerations

Ruminants, such as cattle, have a unique digestive system with four distinct gastric compartments: the rumen, reticulum, omasum, and abomasum (Lei *et al.*, 2018; Pokhrel and Jiang, 2024). Each compartment plays a different role in digestion. Rumen microbes are crucial for breaking down food into simpler, more digestible components (Xu *et al.*, 2021). Plant nutrients are converted into energy that animals can use efficiently and produce B vitamins, vitamin K, and amino acids, which are vital for animal health and growth (Suarjana *et al.*, 2021). Understanding these microbes will help in designing effective long-term drug delivery systems by considering their interactions to optimize drug delivery in ruminants.

When designing an RDS, it is essential to consider the pH difference between the rumen and the abomasum (Diao *et al.*, 2019; Hu *et al.*, 2019). This pH difference can create a system that remains stable in the rumen and releases the drug into the abomasum, where it can be absorbed. New systems use ingredients sensitive to these pH changes to enable targeted drug or nutrient release. Rumen motility and rumination effects on particle degradation are also crucial. The size and density of particles in the delivery system affect their movement and behavior in the rumen. Recent studies have shown that nano- and microparticles can enhance the effectiveness and stability of drug delivery systems in the rumen. Thus, designing these systems requires consideration of the animal's specific physiological conditions and the drug's characteristics (Vítor *et al.*, 2021).

Ruminants differ from other mammals because most of their food is fermented in the rumen, reticulum, and omasum. Although postgastric fermentation occurs in the cecum and colon, it is less significant than that in other herbivores (Wang *et al.*, 2020; Zou *et al.*, 2020; Soltis *et al.*, 2023). This unique digestive system allows for memorable interactions with dietary supplements. For instance, protein supplements and postruminal amino acids can improve growth and productivity. However, rumen microbes decompose some proteins into ammonia, which is then absorbed and excreted as urea, indicating nitrogen loss from the diet. This highlights the need for stable rumen formulations to ensure efficient nutrient delivery. Changes in the ruminant diet significantly affect the rumen bacterial communities (Ramos *et al.*, 2021).

The brooding process, which involves regurgitation and demystification, increases the substrate surface area for microbial fermentation (Wang *et al.*, 2020; Zou *et al.*, 2020). However, this can damage drug delivery devices, so the technology must be designed to withstand mechanical stress. The gases produced during rumen fermentation can also affect the performance of some delivery systems, presenting another challenge in designing RDS (Hamid *et al.*, 2020; Ungerfeld, 2020). These gases could potentially be used to develop new drug delivery technologies.

Nutrients must be administered orally and consumed in small, frequent doses, emphasizing the need for innovative delivery systems that efficiently and economically provide these additives to grazing ruminants. There is a growing demand for devices that can release therapeutic agents, additives, or nutrients into the rumen in a controlled and sustainable manner. Drug delivery systems are designed to improve user compliance by extending the release of therapeutic agents over time (McGrath *et al.*, 2018; Hu *et al.*, 2019; Fonseca *et al.*, 2023). To achieve optimal drug effectiveness, it is crucial to consider physiological factors that influence drug absorption and distribution. In ruminants such as cattle and sheep, these factors play a key role in the success of drug delivery systems. Interactions between gastric acid, bile from the gallbladder, digestive enzymes from the pancreas, and relatively short retention times in the small intestine contribute to low microbial diversity in the midgut. By precisely analyzing these factors, as illustrated in Figure 2, the rumen conditions and associated challenges, advanced drug delivery systems can be optimized to achieve therapeutic objectives in ruminant animals more effectively (Hua and Lye, 2023).

Formulation considerations

Encapsulation protects vitamins and nutrients from degradation in the ruminant digestive system. Without encapsulation, rumen microorganisms can break down these nutrients before animals fully utilize them. Encapsulation involves coating nutrients with a protective layer that prevents rumen degradation. This ensures that nutrients reach the lower digestive tract where they can be absorbed and utilized by the animal (Mazinani *et al.*, 2020; Besharati *et al.*, 2022; Zabot *et al.*, 2022). Encapsulation allows for the controlled release of nutrients, thereby enhancing efficiency

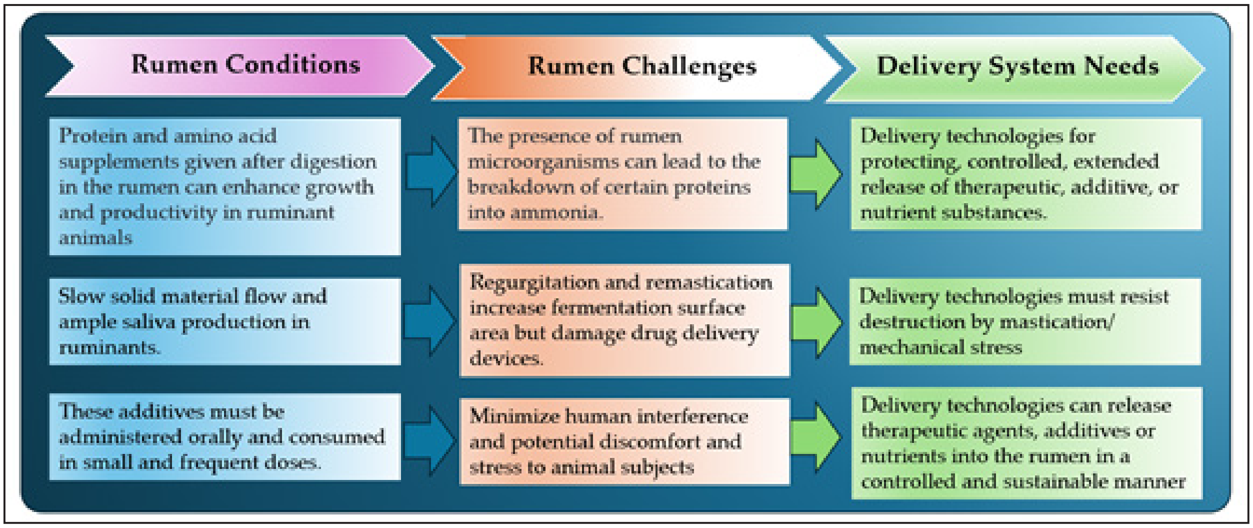

Figure 2. Physiological considerations for designing RDSs.

(Ozturk and Temiz, 2018; Melo *et al.*, 2021; Zabot *et al.*, 2022). It also protects nutrients from environmental factors such as heat, light, and oxygen, during feed storage and processing, ensuring their stability until consumption by ruminants (Piñón-Balderrama *et al.*, 2020; Amin *et al.*, 2021; Zabot *et al.*, 2022).

The appropriate materials, especially polymers, are crucial for developing an RDS. The polymer must be safe and effective and must comply with regulatory requirements. Biocompatible and biodegradable polymers have advanced, offering safe materials with no adverse health effects. The polymer must be physiologically inert, non-absorbable, and unchanged during animal excretion. It should be nonmutagenic and should not cause harmful genetic changes. The polymer should not negatively impact long-term feeding, allowing for the safe and extended use of supplements (Galyon *et al.*, 2023).

Other essential factors include strength, solubility, permeability, stability, and cost. Organic materials such as polylactic acid, glycolic acid copolymers, and polypeptides are preferred for their ease of use, high encapsulation efficiency, and low toxicity (Wei *et al.*, 2022). Inorganic materials such as double metal hydroxides, calcium carbonate, and silicates offer good chemical and thermal stability (Teixeira *et al.*, 2021; Hamimed *et al.*, 2022).

The encapsulation process has progressed from single physical methods to chemical or combinations of both, enhancing efficiency and stability (Reis *et al.*, 2022; Sousa *et al.*, 2022). It is essential to maintain the activity of active ingredients and consider external factors such as touch, light, and pH, which can affect ingredient release. Research has focused on developing more efficient and cost-effective encapsulation techniques for drug delivery and active ingredients for ruminant digestion (Wei *et al.*, 2022).

The thermal stability of a polymer is essential for preventing damage during processing or storage at varying temperatures (Ur Rehman *et al.*, 2020; Wang *et al.*, 2022; Huang *et al.*, 2023). The polymer must dissolve properly—not in rumen fluid but in abomasal fluid—to release active ingredients at the right time (MacHtakova *et al.*, 2022). The coating efficiency depends on the solubility of the active ingredients, pellet size, and pellet surface smoothness (Hiew *et al.*, 2019; Agrawal *et al.*, 2022; Salawi, 2022). The development of pH-dependent coatings has improved the stability and effectiveness of RDSs (Albuquerque *et al.*, 2020; Dijkstra *et al.*, 2020). Consider these factors, as illustrated in Figure 3, and select the appropriate polymer to create a stable and effective RDS.

Routes of administration considerations

When designing a stable RDS, the route of drug administration is crucial. Different methods have benefits and limitations (McGrath *et al.*, 2018; Jeong *et al.*, 2020). Oral administration is commonly used, but it can vary in absorption and interaction with feed, which may affect bioavailability and efficacy (Mileva *et al.*, 2023). In contrast, parenteral administration allows precise dosing with a faster onset but requires expertise in injection techniques, making it impractical for farm animals (Mileva *et al.*, 2023). Topical and inhalation methods have specific purposes, particularly for the local treatment of respiratory problems (Amiri-Farahani *et al.*, 2020; Windsor, 2022). Thus, designing an optimal RDS should ensure consistent and controlled release for sustained therapeutic effects.

The design of the delivery system must also consider ease of use. The system should be user-friendly for farmers or ranchers and require minimal training and equipment (Kopper *et al.*, 2023; Song *et al.*, 2023). Methods such as boluses, implants, and rumen magnets have proven effective, but they require specialized training and consistent monitoring, increasing their complexity (Blakebrough-Hall *et al.*, 2020; Neves *et al.*, 2022). Recent innovations aim to simplify these systems, enhance ease of use, and encourage higher adoption rates.

Furthermore, controlled shipping methods must be adapted to account for variations in animal size, weight, and health concerns. This includes ensuring animal comfort and welfare while maintaining the effectiveness of the drug delivery system. Modern biotechnological tools are increasingly used to create personalized delivery systems that consider each animal's unique physiological and anatomical characteristics (Pech-Cervantes *et al.*, 2020; Lobo and Faciola, 2021). This approach not only enhances treatment effectiveness but also improves animal welfare standards.

Criteria for rumen-stable delivery systems

RDSs are expected to be an alternative to traditional feed, providing medicine or nutrition to ruminants. However, creating a system that ensures sustainable release over long periods is a significant challenge. Differences in drug physiology and pharmacokinetics among species complicate the direct application of controlled-release technologies in livestock. The system must also protect the active ingredients from rumen fermentation and ensure their availability for absorption after passing through the rumen (Diez *et al.*, 2022; Tajima *et al.*, 2023).

Cost-effectiveness is another crucial factor. The costs of manufacturing, distributing, and administering RDS must be justified by the potential economic benefits, such as increased livestock productivity or reduced health expenses. It is essential to compare RDS with conventional methods, which might be cheaper but still provide similar or better benefits at a comparable or lower cost (García-Dios *et al.*, 2020; Ungerfeld and Pitta, 2024).

The environmental impact of RDSs is a critical consideration. Evaluations should include the effects of soil, water, air, and wildlife. Recent advancements aim to develop degradable systems that minimize environmental impact and support more sustainable farming practices. The major criteria considered in RDS planning, including environmental impact, are illustrated in Figure 4 (Smith *et al.*, 2018; Neethirajan, 2024).

Evaluation of rumen-stable delivery systems

Physical characterization

Comprehensive characterization of polymeric delivery systems for rumen applications involves multiple analytical approaches. Modern nanoparticle characterization employs three primary technique categories. Light scattering methods (including

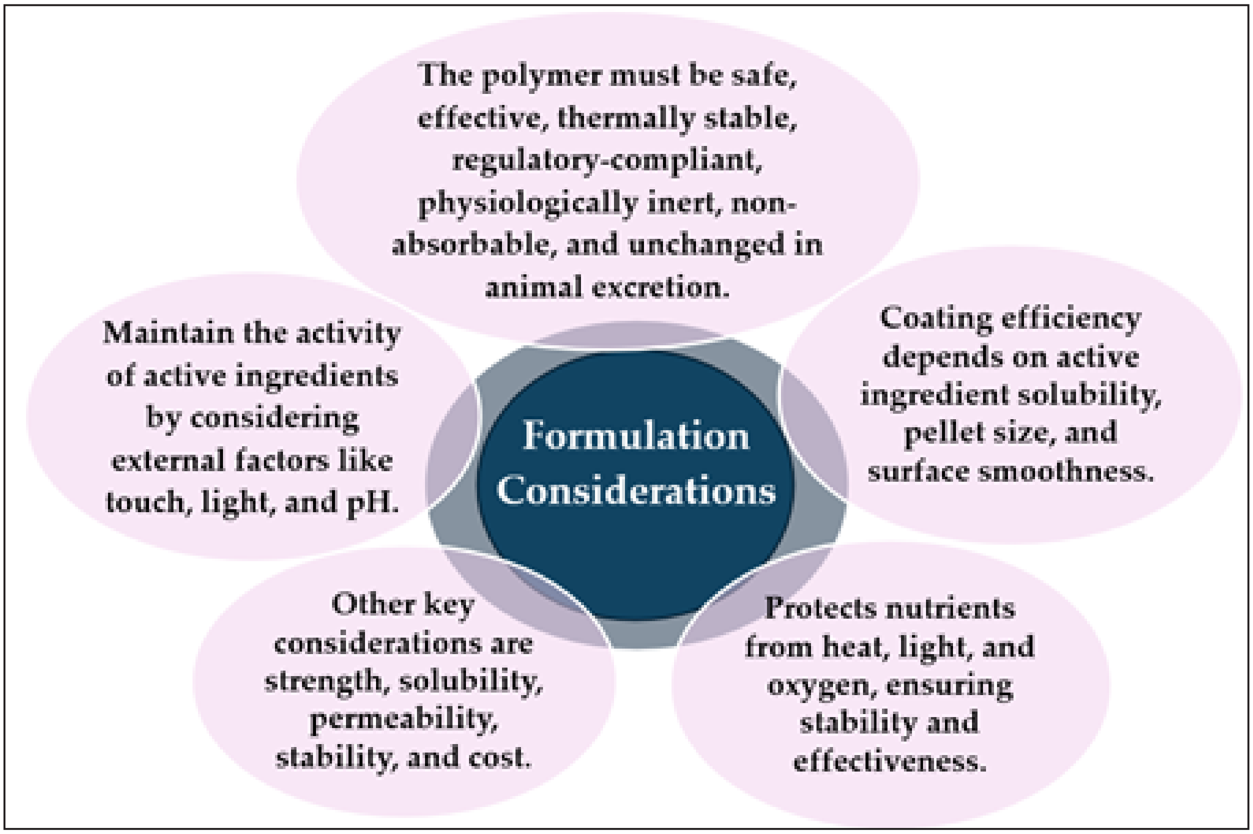

Figure 3. Formulation considerations for designing RDSs.

dynamic light scattering, nanoparticle tracking analysis, and static light scattering) measure particle size, shape, and motion in systems. Electron microscopy techniques, namely scanning electron microscopy for surface imaging and transmission electron microscopy for internal structure analysis, provide high-resolution visualization at the nanoscale. Surface probing using atomic force microscopy studies particle–environment interactions. Additionally, combined microscopy–spectroscopy approaches enable simultaneous measurements of both physical and chemical properties (Caputo *et al.*, 2019; Qiu *et al.*, 2025). Chemical analysis through FTIR confirms polymer interactions and cross-linking, supported by XRD and DSC/TGA for structural properties (Mahmood *et al.*, 2017). Nanoparticle formulations with zeta potentials beyond ±25 mV exhibit more excellent stability, as these charge levels prevent particle agglomeration and maintain dispersion by overcoming van der Waals attraction forces (Mahmood *et al.*, 2017; Cottet *et al.*, 2023).

The physical characteristics of RDS include hardness, adhesiveness, drying time, flexibility, and elasticity. The hardness and adhesiveness of the coatings were measured using a texture analyzer. Drying time was visually evaluated by assessing uniformity, appearance, and peelability. Stickiness was assessed by applying low-pressure cotton wool. Mechanical properties such as flexibility and elasticity are determined by measuring the tensile strength and elongation at break. Microscopic techniques provide nanoscale information. Instrumental analyses, such as X-ray diffraction, calorimetry, spectroscopy, and nuclear magnetic resonance, may be performed for specific purposes (Tran and Tran, 2019).

Protection against rumen environment

In vitro and *in situ* rumen methods can be used to evaluate RDS stability in the rumen environment. These methods provide information on how rumen conditions, such as pH changes or specific microbial populations, affect the stability and release of the active ingredient (Chen *et al.*, 2024, 2022).

The rumen of ruminants acts as a natural feed fermenter that contains diverse microorganisms such as bacteria, anaerobic fungi, archaea, protozoa, and viruses (Chen *et al.*, 2021; Liu *et al.*, 2023b; Chen *et al.*, 2024). These microorganisms work together to ferment and break down nutrients, providing energy and VFAs for the host (Wei *et al.*, 2022).

Simulated rumen-protection tests are the tests that mimic the rumen environment and allow researchers to analyze key factors such as the release rate, duration of release, and stability of the active ingredient within RDS, as illustrated in Figure 5 (Wei *et al.*, 2022; Silva *et al.*, 2024). Rumen motility, which involves cyclic movements, including primary and secondary contractions, is crucial for ruminant nutrition. This significantly impacts nutrient degradation and can affect the functioning of RDS. For example, the frequency and duration of ruminal contractions typically increase around feeding, potentially influencing the effectiveness of RDS (Wang *et al.*, 2023b). Microbial protein (MCP) synthesis in rumen depends on using ammonia-nitrogen (NH_3-N). Efficient MCP production requires a balanced supply of nitrogen and energy. Rumen motility improves microbial colonization of substrates, which helps synchronize nitrogen and energy release and enhances the effectiveness of RDS in the rumen (Li *et al.*, 2019a).

***In vitro* release**

In vitro and *in situ* rumen methods can be used to evaluate RDS efficacy under actual rumen conditions. *In vitro* rumen methods use rumen fluid from a live animal to replicate rumen conditions in the laboratory. The fluid was incubated with RDS, and the degradation

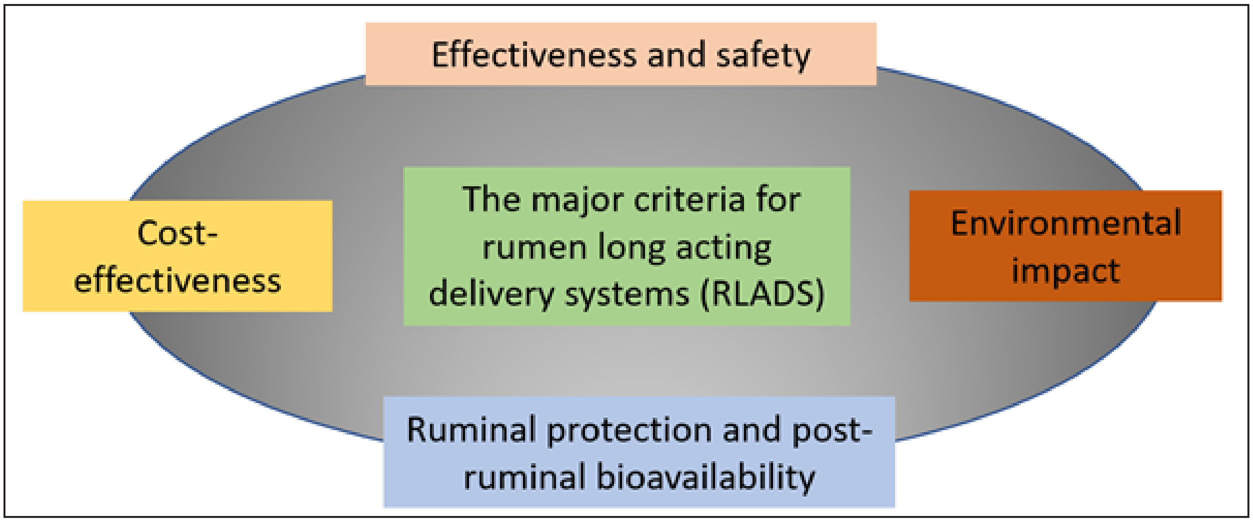

Figure 4. The major criteria for designing a RDSs.

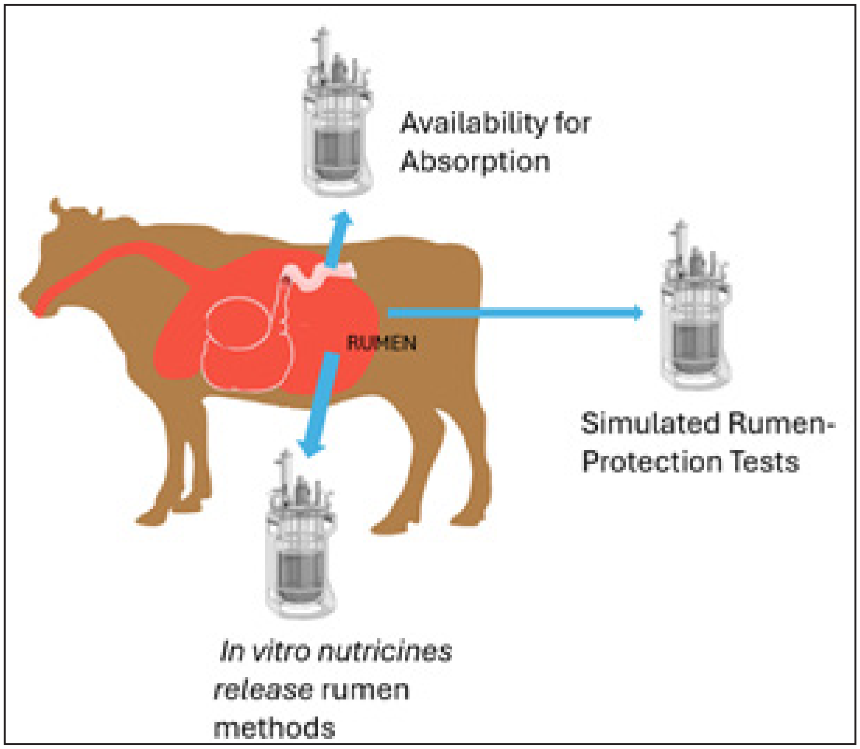

Figure 5. *In vitro* test for protection from rumen, release test, and absorption.

or release of the active ingredient was analyzed. *In situ* rumen methods involve placing a small bag with test material into the rumen of a live animal. After a specific time, the bag is removed, and its contents are analyzed to determine the degradation or release of the active ingredient (Gümüş *et al.*, 2022; Guo *et al.*, 2022).

These methods can be used to assess several RDS-related factors, such as the release rate, duration of release, and active ingredient stability. By analyzing samples taken at various time points, researchers can measure the amount of the active ingredient released over time and its release rate (Gümüş *et al.*, 2022; Guo *et al.*, 2022).

Absorption availability

Simulated abomasal-release test to evaluate the effectiveness of RDS in delivering active ingredients to the small intestine. This test uses a buffer solution with a pH similar to the abomasum's to mimic its environment. RDS was added to this solution and incubated to assess the active ingredient's release rate, duration, and stability. By analyzing samples taken at various time points, researchers can measure the release rate and amount of active ingredients. This test helps determine whether the RDS can protect the active ingredient from rumen degradation and ensure its delivery to the small intestine, thereby improving animal health and productivity (Gümüş *et al.*, 2022; Guo *et al.*, 2022).

Blood responses of ruminant animals

The blood response of ruminant animals evaluates the delivery of active ingredients to the bloodstream. RDS is designed for slow, sustained release, leading to a prolonged blood response. Blood markers, such as glucose, insulin, and amino acids, are measured before and after RDS administration to assess the impacts of metabolism and nutrient utilization. For instance, RDS containing amino acids can improve protein utilization and milk production, as measured by markers such as branched-chain amino acids and milk protein yield. Similarly, related blood markers indicate that RDS supplementation with vitamins or minerals can boost health and productivity (Astuti *et al.*, 2022; Kim *et al.*, 2022). Supplemental enzymes improve metabolic processes by increasing apparent digestibility, optimizing the use of dietary proteins, and enhancing overall nutrient availability (Anil *et al.*, 2022). The blood response to vaccination is shown in Figure 6, which illustrates the changes in blood parameters.

Efficacy of rumen delivery systems

The efficacy of RDS depends on the active ingredient or nutrient being delivered and its intended effect on the animal. Generally, RDS offers several benefits, including improved nutrient utilization, sustained release of active ingredients, protection from rumen degradation, reduced feed waste, and minimized environmental impacts. RDS enhances the utilization of proteins, amino acids, vitamins, and minerals, leading

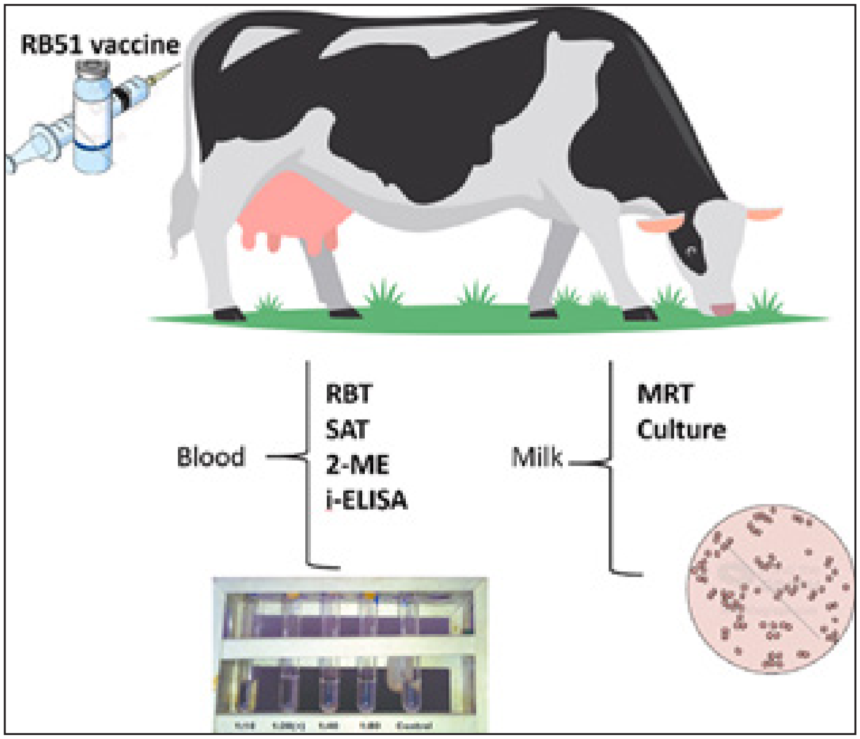

Figure 6. Sample of blood response in ruminant animals evaluation (Abnaroodheleh *et al.*, 2023).

to better animal growth, productivity, and overall health (Hendawy *et al.*, 2022; Ahmed *et al.*, 2024). They can also deliver active ingredients over a longer period, decreasing the need for frequent administration and ensuring that these ingredients reach the small intestine for absorption (Loregian *et al.*, 2023). By improving feed efficiency, RDS reduce feed waste and enhance the economic efficiency of animal production (Nakaishi and Takayabu, 2022; Nath *et al.*, 2023). Overall, RDS contribute to animal health and welfare by providing essential nutrients and active ingredients in a controlled and sustained manner, making them valuable for improving animal production and reducing environmental impact (Cerbu *et al.*, 2021; Jung *et al.*, 2021).

Overall evaluation of the rumen delivery system

Understanding rumen function requires knowledge of different feeds and nutritional assessment systems. *In vitro* gas production (IVGP) is a notable feed evaluation technique. It offers a less tedious and time-consuming alternative to *in vivo* digestibility measurements while showing high correlation with *in vivo* results.

Artificial rumen models were compared with the rumen of dairy cows to assess their ability to support natural rumen microbiota and functions, including the production of VFAs and greenhouse gases (Shaw *et al.*, 2023).

Rumen fermentation parameters such as VFAs, pH, and total gas production are crucial for managing rumen ecology and microorganism growth (Budiman *et al.*, 2024). These parameters help prevent rumen acidosis 12 hours after fermentation. During *in vitro* fermentation, rumen microbes break down complex nutrients such as carbohydrates, proteins, and organic polymers into monomers. These monomers ferment into VFAs, free ammonia (NH_3), carbon dioxide (CO_2), and hydrogen (H_2). Methanogens, including *Methanopyrales*, *Methanocellales*, and *Methanomicrobiales*, then converted CO_2 and H_2 into methane (CH_4) (Phupaboon *et al.*, 2024). Other studies have shown that rumen fermentation can indicate reduced degradability rates and a lower microbial population (Yanza *et al.*, 2021).

In vitro/*in vivo* correlation (*IVIVC*) models are used to demonstrate the relationship between the *in vitro* release profile and *in vivo* performance of dosage forms, especially modified release drug products (Higgins-Gruber *et al.*, 2013). *IVIVC* can be applied to all dosage forms and routes of administration. Developing effective *IVIVC* requires a well-designed, scientifically based approach (Tomic and Cardot, 2022).

Nutricines

Nutricines, derived from "nutrition" and "medicine," are substances incorporated into animal diets to enhance health, performance, and the production of agricultural products, such as milk, meat, fiber, and eggs (Górniak *et al.*, 2018; Ferlisi *et al.*, 2023). These include enzymes, which speed up chemical reactions in digestion; prebiotics, which are nondigestible ingredients that promote beneficial gut bacteria; probiotics, which are live microorganisms that confer health benefits; organic acids, which lower gut pH levels and improve nutrient absorption; plant extracts, which offer various health benefits; and trace elements, which are essential minerals for physiological functions. These substances, as shown in Figure. 7, collectively improve digestion, nutrient absorption, and overall animal health, ultimately resulting in better agricultural production productivity and efficiency (Tran and Tran, 2019; Garba and Firincioğlu, 2023).

Nutricines are not essential for basic metabolism but can greatly enhance the well-being and performance of livestock by improving digestion, promoting better nutrient absorption, boosting immune function, and reducing disease susceptibility (Dell'anno *et al.*, 2021; Dong *et al.*, 2023; Pandey *et al.*, 2023).

Enzymes

Enzymes secreted by microorganisms play crucial roles in plant degradation within the rumen ecosystem. Glycoside hydrolases break down plant biomass, with enzymes such as xylanase degrading β-1,4-xylan in hemicellulose and carboxymethyl cellulase targeting β-1,4-glucan in cellulose fibers. Lipases regulate fatty acid metabolism and control lipolysis, which limits the biohydrogenation of polyunsaturated fatty acids. Additionally, dehydrogenase, urease, and protease interact with protein and urea to supply essential nutrients to the host (Nunes and Kunamneni, 2018; Refat *et al.*, 2021; Vittorazzi *et al.*, 2021; Abid *et al.*, 2023). Enzymes help break down complex dietary components such as proteins, fats, and carbohydrates, making nutrients more available for absorption (Saha and Pathak, 2021).

Nanotechnology can deliver enzymes or digestive aids that improve feed digestion and nutrient utilization in the gastrointestinal tract of ruminants. These are live microorganisms that, when administered in adequate amounts, confer health benefits on the host by maintaining a healthy balance of gut microbiota (Agriopoulou *et al.*, 2023; Gonzalez-bulnes and Hashem, 2023).

Incorporating digestive enzymes such as amylase, protease, cellulase, xylanase, and beta-glucanase into bovine diets enhances growth performance. Exogenous enzymes increase the concentration of short-chain fatty acids in ruminal fluid, improve the proportion of unsaturated fatty acids, and decrease saturated fatty acids in meat. They also positively influence the oxidative stability of meat (Simon *et al.*, 2024). Adding exogenous enzymes to animal feeds has significant potential to boost livestock productivity (Sridar, 2017).

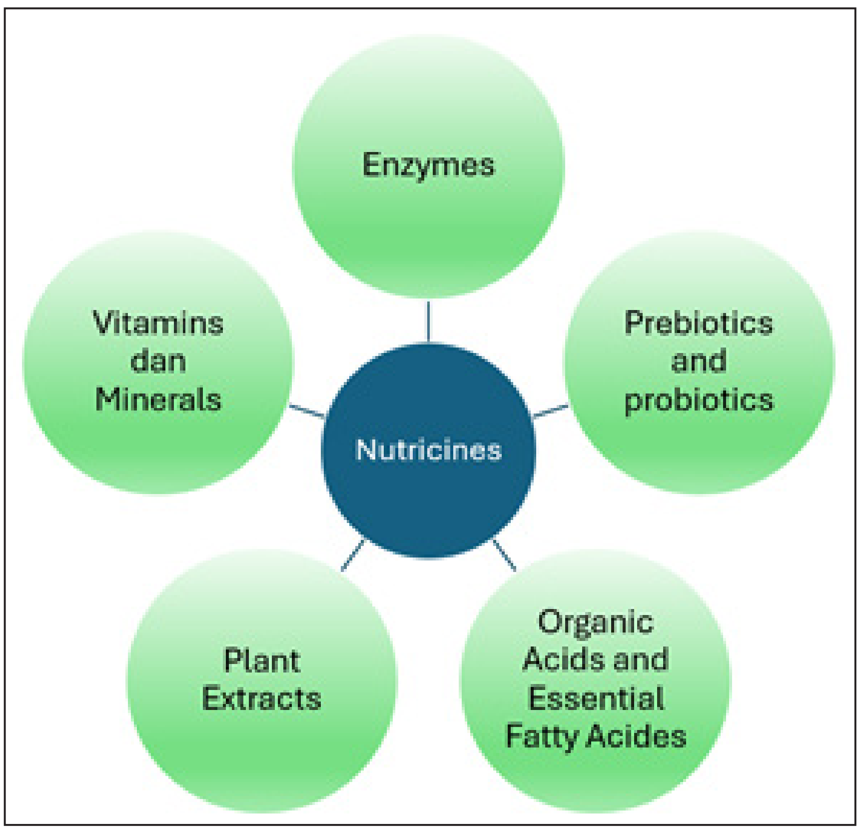

Figure 7. Nutricine components.

Prebiotics and probiotics

Probiotic additives are beneficial, nondigestible food ingredients that selectively stimulate specific bacteria in the colon to improve host health. Encapsulation technology enhances the effectiveness, stability, and survival of probiotics during processing, storage, and gastrointestinal transit. Encapsulating probiotics in microspheres or microcapsules with materials such as alginate, chitosan, gelatin, plant mucilage, whey proteins, and polysaccharides protects probiotics from harsh conditions during fermentation. Chitosan nanoparticles can further protect probiotics, enhance their stability, and offer controlled release during fermentation (Agriopoulou *et al.*, 2023).

Phytobiotic additives, which are rich in secondary plant metabolites or phytochemicals, also support host health. Found in legume trees, medicinal plants, spices, and agricultural by-products, these phytobiotics can be combined with probiotics. The encapsulation of these combined additives ensures better stability, controlled release, and improved effectiveness in promoting a healthy gut microbiome (Ahmed *et al.*, 2024).

Organic acids and essential fatty acids

Alternative feed additives could offer nutritional strategies that help prevent metabolic disorders in ruminants by improving their metabolic and immune status. These additives lower the pH of the gut, which inhibits the growth of pathogenic bacteria and promotes digestion. Organic acids, such as citric acid and sorbic acid, and pure botanicals, such as thymol and vanillin, are widely used in animal nutrition because of their positive effects on production performance and their known impact on metabolic and immune status (Nkosi *et al.*, 2021; Giorgino *et al.*, 2023).

Organic acids and essential oils are effective alternatives to antibiotic growth promoters in pig production due to their antibacterial, antiviral, and antioxidant properties (Nhara *et al.*, 2024). Essential fatty acids, such as omega-3 and omega-6, play crucial roles in metabolic processes, including immune function and inflammation regulation. Nanoencapsulation protects these fatty acids from oxidation and enhances their delivery to animals (Tolve *et al.*, 2021; Dumlu, 2024).

Plant extracts

Phytogenic extracts provide unique benefits as natural, abundant, renewable, and pollution-free sources with low-residue anti-inflammatory, antioxidant, and antimicrobial properties. They also stimulate appetite and enhance digestion (Piao *et al.*, 2023; Orzuna-orzuna *et al.*, 2024; Yang and Park, 2024).

In addition to traditional vitamins and minerals, nanotechnology can deliver other bioactive compounds with potential health benefits, such as antioxidants, polyphenols, and probiotics. Nanoencapsulation protects these compounds from degradation and enhances their stability during storage and digestion (Pateiro *et al.*, 2021; Andrade *et al.*, 2024).

Vitamins and minerals

Adequate mineral supplementation in small ruminants is crucial for proper physiological processes. Too little or too much supplementation can impair immune function, reproduction, and growth (Radke, 2021). The bioavailability of fat-soluble nutrients depends on their ability to form micelles (Borel and Desmarchelier, 2018; Šimoliūnas *et al.*, 2019). Mineral bioavailability can be influenced by competition for binding sites and nutritional status, such as the effect of vitamin A on iron absorption. Chelation with dietary polyphenols can reduce iron uptake. Physiological factors such as gastric and intestinal secretions, mucosal cell regulation, and microflora also play a role. For instance, vitamin B12 absorption relies on gastric acid and intrinsic factor production (Brugger *et al.*, 2022; Byrne and Murphy, 2022).

Current delivery systems for rumen nutricine are limited (Garba and Firincioğlu, 2023). Enzymes are challenged by rapid proteolytic degradation, pH instability, and thermal sensitivity during feed processing while maintaining optimal concentrations remains difficult (Morgavi *et al.*, 2000; Dijkstra *et al.*, 2014; López-Trujillo *et al.*, 2023). Prebiotics suffer from uncontrolled fermentation and nonspecific microbial stimulation, with the effectiveness of these interventions varying based on the existing microbiota. Probiotics are limited by poor survival during processing and storage, weak colonization in mature rumen, and frequent dosing requirements. The challenge is to establish ideal fermentative processes in which the maximal cell growth and biomass yield are in equilibrium with cell metabolism and stress tolerance (Mendonça *et al.*, 2023; Rana *et al.*, 2024). Organic acids are rapidly absorbed and neutralized (a rapidly fermentable substrate), requiring careful dosing to avoid pH disruption. However, their corrosive nature and short duration of action present practical challenges (Carro and Ungerfeld, 2015). Herbal extracts, despite their potential benefits, face issues with variable composition, inconsistent bioavailability, rapid degradation in the rumen, and possible interactions with other feed components (Alem, 2024; Subbiah *et al.*, 2024; Wang *et al.*, 2024). The former usually leads to inadequate dietary formulations that, in turn, cause unbalanced AA levels in the plasma (Albuquerque *et al.*, 2023). These limitations highlight the need for improved delivery systems to enhance the efficacy of rumen nutricine.

Different nutrients can work better together in the rumen. When enzymes and probiotics are combined, they collaborate to break down feed more effectively. The enzymes first break down complex plant materials, making it easier for beneficial bacteria to use them (Khademi *et al.*, 2022; Mousa *et al.*, 2022). Adding herbal extracts to enzymes can help protect the enzymes from breaking down too quickly in the rumen, while also providing extra benefits such as fighting harmful bacteria or acting as antioxidants (Yang and Park, 2024). When probiotics are paired with prebiotics (called synbiotics), the prebiotics act like a targeted food source, helping the good bacteria survive and thrive better in the rumen. Synbiotic formulation of 6 g FOS + *L. plantarum* CRD-7 in dairy calves improved digestibility, antioxidant enzymes, and immune status, as well as modulated the fecal microbiota and decreased diarrhea incidence (Sharma *et al.*, 2023). Mixing herbal extracts with organic acids can help control harmful bacteria for longer periods while keeping the rumen pH stable (Ahmed *et al.*, 2022; Okoye *et al.*, 2023). Cinnamon extract can be used as an alternative antibiotic to monensin extract to control ruminal acidosis when corn is used as a basal diet (Ahmed *et al.*, 2022). However, we need to be careful when mixing these ingredients: they need to be properly formulated to work well together and avoid any negative interactions that could make them less effective.

In livestock, low levels of pasture micronutrients and gastrointestinal antagonisms can affect absorption. Direct supplementation helps prevent deficiencies, and animal excreta contributes micronutrients to the pasture. More research is needed to understand how feed and supplements affect micronutrient content in excreta and soil. Designing multispecies swards for optimal ruminant health requires understanding soil properties, forage types, and environmental conditions (Pinotti *et al.*, 2020).

Nuticine Rumen-Stable Delivery Systems

Nuticine RDSs

Nanoengineering involves creating materials with unique properties using both organic and inorganic substances (Khan *et al.*, 2019; Khalid *et al.*, 2020). These materials enhance bioavailability, protect against gastrointestinal tract conditions, and enable controlled release. Key factors affecting nutritional value include particle size, physical state, and surface properties (Wang *et al.*, 2023a; Altemimi *et al.*, 2024). Coating materials used to protect core nutrients or feed from ruminal degradation should have specific properties:

- Insolubility in the rumen environment where the pH exceeds 6.
- Solubility in acidic conditions (pH 1.5–2) of the abomasum.
- Resistance to microbial attack.
- Adequate mechanical properties, including flexibility and strength, are necessary to endure stress and prevent breakage (Belverdy *et al.*, 2019).

Encapsulated nanoparticles improve the delivery of vitamins D and E in supplements. Compared with high-dose salts, nanosized ZnO/Cu particles in piglet diets enhance growth and reduce environmental impact. Amino acid chelates improve mineral absorption, promoting animal performance and bone health while reducing trace mineral excretion (Upadhaya and Kim, 2020).

Nutricines in RDS enhance rumen health, nutrient utilization, and animal performance. Careful formulation and testing are essential for ensuring stability, bioavailability, and efficacy. Antioxidant supplementation and methyl group status enhancement with vitamin E, selenium, and choline are recommended for stable metabolic health and optimized milk production (Pinotti *et al.*, 2020).

Table 1 illustrates the effectiveness of polymeric nutricine delivery systems. Specifically, the use of polymers in nutricine enhances the protection of active substances by ensuring stability within the rumen, regulates the controlled release of these substances, and mitigates environmental impacts such as methane emissions. The table further demonstrates the prevalent use of alginate and chitosan polymers in these systems. Alginate's interaction with cationic compounds enhances its protective properties by improving its resistance to acidic pH and reducing porosity. Chitosan, known for its biocompatibility and gel-forming ability, is particularly suitable for targeted release applications. Modified chitosan particles are frequently employed as coatings in bioactive material delivery systems because of their controlled release. Chitosan dissolves at pH < 6 and can undergo polymerization through anionic cross-linking, which improves the survival of active substances, colon-targeted delivery, and thermal stability in applications across food, medicine, and agriculture (Sadeghi *et al.*, 2024).

Chitosan is an effective material for RDSs due to its distinctive properties. In the alkaline environment of the rumen, chitosan remains stable, preventing the premature release of encapsulated substances (Almassri *et al.*, 2024). As the material progresses into the acidic abomasum, the chitosan dissolves, allowing for a controlled release of the nutrients. Additionally, chitosan is hydrolyzed by specific enzymes present in the abomasum, which enhances the targeted release of the encapsulated bioactives (Anil, 2022). Chitosan's ability to form gels creates protective coatings around the nutrients, while its bioadhesive characteristics improve adherence to the intestinal walls, thereby increasing nutrient absorption. Moreover, chitosan's biodegradable nature ensures a gradual breakdown over time without environmental accumulation, thereby optimizing the controlled release of nutrients throughout the digestive tract (Souza *et al.*, 2020). Chauhan *et al.* revealed that the release of amino acids in rumen mimic solution, despite using the same coating agents, is significantly influenced by the type of technology used (Chauhan and Kumar, 2020).

A review of polymeric materials for rumen-protected delivery systems reveals two primary categories: natural and synthetic polymers, each with distinct physicochemical properties and applications (Ghasemiyeh and Mohammadi-Samani, 2021; Zhou

Table 1. Encapsulation of nutrition with several polymers.

Substance	Polymer	Application	Result	References
Lavender essential oil (LO)	A double-layered microcapsule comprises β-cyclodextrin as the inner layer and chitosan and sodium alginate as the outer layer.	The microcapsules were spherical with a particle size distribution ranging from 2 to 6 µm and demonstrated good thermal stability. They exhibited an encapsulation efficiency up to 80%.	The double-layered mi-crocapsules released the active ingredients of essential oils continuously over extended periods under both normal and high temperatures.	Zhang *et al.*, 2020
Peanut oil is rich in polyunsaturated fatty acids (PUFAs) and	Protein isolate (WPI), microcrystalline cellulose (MCC), and maltodextrin. EDLEPO enhances rumen degradability without adverse effects on fermentation.	The double-layer encapsulation of emulsified peanut oil (EDLEPO) traps it, ensuring it does not interfere with digestibility and fiber digestion, enabling slow passage of the emulsion into the postrumen.	EDLEPO enhances rumen degradability without adverse effects on fermentation	Budiman *et al.*, 2024
Glycerol	Sodium alginate-glycerol (AG) and alginate-chitosan-glycerol (ACG) polymers	AG and ACG exhibit high loading capacity and efficiency. ACG exhibited stronger ionic bonds. Glycerol was released at pH 6, with minimal release at pH 2 and substantial release at pH 8. *In vitro* microbial data indicate decreased fermentation of encapsulated glycerol after 24 h.	The AC polymer provided greater protection at acidic pH with a gradual release of intact glycerol when exposed to an alkaline pH.	Gawad and Fellner, 2019
Yeast or feed enzyme (FE)	Barley protein hordein and glutelin	The stability of the encapsulated products in the rumen was measured as dry matter disappearance in batch culture.	Encapsulated yeast products were stable in the rumen.	Garba and Firincioğlu, 2023
Lactobacillus and *Bacillus subtilis*	Sodium alginate, methylcellulose, and fiber nanocrystals	Wall materials for the bilayer microencapsules.	In simulated gastric juice, the activity was still strong 60 min after embedding.	Zhao *et al.*, 2020
Lemongrass powder and mangosteen peel (LEMANGOS pellets)	Chitosan	LEMANGOS significantly improves *in vitro* rumen fermentation, increases fermentation end-products and microbial protein synthesis, and reduces methanogen population and methane production. This highlights the notable impact of antibiotic action mechanisms compared to standard. These supplements effectively reduce methane production and can serve as valuable additives in ruminant feed, acting as antimicrobial agents. These supplements effectively reduce methane production and can serve as valuable additives in ruminant feed, acting as antimicrobial agents.	These supplements effectively reduce methane production and could serve as valuable additives in ruminant feed, also acting as antimicrobial agents.	Phupaboon *et al.*, 2024

(Continued)

Substance	Polymer	Application	Result	References
Flaxseed oil	Chitosan and calcium alginate NPs.	Prepared separately using an oil-in-water emulsion containing chitosan and calcium alginate	Encapsulating flaxseed oil with chitosan reduces the ruminal biohydrogenation of unsaturated fatty acids.	Besharati *et al.*, 2022
Lysine	Arachidic or stearic acid as the solid lipid and Tween® 60 as the surfactant	Rumen-resistant nanoparticles show promise as oral lysine delivery systems for dairy cattle	Nanoparticles can resist ruminal digestion and withstand temperatures as high as 60 °C. Lyo-philization studies showed that they can be used as powders instead of liquids. SLNs retained their physical properties for up to a month at room temperature.	Albuquerque *et al.*, 2023
Methionine and lysine	Benzaldehyde and glutaraldehyde	The essential AA methionine and lysine were reacted with benzaldehyde and glutaraldehyde to create ligands for producing protected AAs.	Energy consumption, dry matter intake, and blood metabolites were similar between the six groups. The highest total protein content was observed with methionine and lysine glutaraldehyde, whereas the lowest was observed in the control.	Mazinani *et al.*, 2020
Fish oil	Gelatin treated with alcoholic solutions of flavoring agents followed by drying	The results suggest that capsules treated with reduced shell abrasion resistance slightly prevented fish oil release into the rumen.	Feeding untreated or treated capsules did not affect animal performance or milk composition. However, fish oil capsules consistently increased total trans-C18:1 isomers and DHA levels in rumen and milk fat compared with controls.	Pena *et al.*, 2023
Glycerol	Alginate (A) and alginate-chitosan (AC) polymers	Calcium chloride solution as a crosslinker	In vitro data show reduced fermentation of encapsulated glycerol after 24 hours. The AC polymer offered better protection under acidic conditions and gradually released intact glycerol at alkaline pH.	Gawad and Fellner, 2019
Methionine and lysine	Manufactured using solid dispersion, fluid bed processing, and spray congealing techniques (same polymer).	The release of amino acids in rumen mimic solution coated with the same type of coating agent depends on the type of technology employed.	Products coated with fluid bed top-spray technology had the lowest degradation in rumen mimic solution and highest rumen bypass efficacy, whereas those coated with solid dispersion technology had the highest degradation and lowest efficacy.	Chauhan and Kumar, 2020
Heme and nonheme iron	Spray drying of maltodextrin	The parenteral group showed a higher resting time (46.5% *vs*. 42.4%, peaking at 51.9% *vs*. 33.8% post-supplementation), whereas oral administration increased suckling (27.8% *vs*. 24.6%).	Oral iron supplementation caused more behavioral issues in piglets due to longer administration times and poor palatability.	Valenzuela *et al.*, 2016

(Continued)

Substance	Polymer	Application	Result	References
Proteins	PLGA is an oil/water (o/w) single emulsion-solvent evaporation technique.	The generated microparticles had good size and encapsulation efficiency.	The encapsulation of proteins is presented here as an excellent alternative for evaluating the antigenicity of proteins from parasites of medical importance such as *L. panamensis.*	Ospina-Villa *et al.*, 2019
Yucca schidigera extract (YSE)	Pluronic F127®	The particle size and polydispersity index (PDI) of Chitosan-Yucca schidigera nanoemulsion were measured using photon correlation spectroscopy (Zetasizer Ver. 7.11, Malvern) at 25 °C.	Chitosan encapsulation of Yucca schidigera extract may limit rumen fermentation effects unless the extract type, dose, and dietary carbohydrate levels are optimized.	Botia Carreño *et al.*, 2024
Curcumin	Ethyl polymethacrylate (Eudragit L-100) nanocapsules	A 17-day trial of ethyl polymethacrylate curcumin nanocapsules (N-CU) in 32 Lacaune lambs at doses of 0–4 mg/kg feed. The 2-mg/kg dose optimized weight gain and blood parameters, which were aligned with the calculated optimal dose of 1.89 mg/kg. While supplementation enhanced antioxidant activity, the 4 mg/kg dose showed no advantages.	Low-dose nanocapsulated curcumin in lamb feed enhances health by reducing oxidative stress and inflammation, leading to improved weight gain. This delivery system has promise as an innovative animal nutrition tool.	Marcon *et al.*, 2021

et al., 2024). Natural polymers exhibit specialized physicochemical properties: chitosan exhibits pH-dependent behavior with documented antimicrobial activity (pKa ≈ 6.5), whereas alginate facilitates gelation via multivalent cationic cross-linking mechanisms (Nasaj *et al.*, 2024; Yilmaz Atay, 2019). Cellulose derivatives manifest thermally induced conformational changes, and zein proteins display pronounced hydrophobicity because of their nonpolar amino acid composition (Carvalho *et al.*, 2021; Giteru *et al.*, 2021; Liu *et al.*, 2023b). Synthetic polymer systems demonstrate complementary characteristics: polymethacrylate (Eudragit) shows pH-dependent dissolution profiles correlating to specific functional group modifications (Patra *et al.*, 2017; Nikam *et al.*, 2023), poly(lactic-co-glycolic acid) undergoes hydrolytic degradation with tunable kinetics, and polyethylene glycol demonstrates enhanced colloidal stabilization through steric hindrance mechanisms (Masoudi *et al.*, 2012; Zaaba and Jaafar, 2020; Lu *et al.*, 2023). Multilayer coating systems, incorporating strategic combinations of these polymers, demonstrate enhanced rumen stability and controlled-release profiles. Examples include chitosan-alginate polyelectrolyte complexes, zein–pectin multilayers (Gawad and Fellner, 2019), and Eudragit-cellulose composite systems (Iffat *et al.*, 2022). The selection of appropriate polymeric materials and coating architectures is governed by factors such as the physicochemical properties of the target nutrient, desired release kinetics, and environmental conditions. Economic viability and manufacturing scalability remain critical considerations for the commercial implementation of these delivery systems.

Scientists have developed novel synthetic polymers by enhancing existing materials: they have modified polyacrylate to be more sensitive to pH changes, created cross-linked methacrylic derivatives that release their contents in a controlled manner, and engineered biodegradable polyesters that break down at precise rates (Patra *et al.*, 2017; Nikam *et al.*, 2023). Researchers have successfully modified chitosan to improve its solubility (through carboxymethylation), enhanced alginate's ability to stick to mucous membranes (via thiolation), created acetylated cellulose that breaks down in a controlled manner, and developed phosphorylated starches for targeted delivery (Herdiana *et al.*, 2023).

Exogenous fibrolytic enzymes enhance ruminant production and nutrient digestibility, although inconsistent results arise from a limited understanding of enzyme activity factors. These enzymes target the fibrous fraction of forage, which contain 30%–70% NDF, with digestibility typically below 65%. Despite high feed costs, specific enzyme supplementation improves nutritional value, digestion efficiency, and animal performance (Almassri *et al.*, 2024). In many studies, L-tryptophan, L-ascorbic acid, niacin, and omega-3 fatty acids are provided in rumen-protected or coated forms to prevent degradation by rumen microbes (Ballard and Byrd, 2018; Chen *et al.*, 2019). They are then incorporated into the feed (Wu *et al.*, 2022).

Phytochemicals are tested as feed additives for their potential as antioxidants, antimicrobials, immune stimulators, and modulators of rumen fermentation. They can improve metabolism, reduce antibiotic use, modulate appetite and digestion, and enhance immune, endocrine, and metabolic systems, leading to better efficiency, milk yield, and composition (Wu *et al.*, 2022). Supplementation with bypass fat had no adverse effects on rumen fermentation, feed intake, digestibility of nutrients, or blood parameters of dairy animals. The milk yield is increased along with the improvement in postpartum recovery of the body weight, body condition score, and reproductive performance of the dairy animals (Wu *et al.*, 2022).

Commercial challenges in RDSs

The commercialization of RDS and other controlled-release drug delivery technologies in the veterinary field faces several challenges. The limited availability of new active pharmaceutical ingredients has restricted the development of novel RDS formulations. Financial constraints, such as limited research budgets and high development costs, hinder investment in new product development (Kipperman *et al.*, 2022). The complexity of the animal environment necessitates a deep understanding of formulation science to create effective and safe RDS tailored to various animal populations. The aim is to minimize animal handling, reduce stress, and lower treatment costs through sustained and controlled drug release. Flexibility, ease of administration, and safety are key considerations when designing RDS for veterinary use (Lloyd, 2017). Safety, efficacy, and stability are crucial for the development of veterinary products. Veterinary settings have unique environmental conditions, such as temperature fluctuations and pathogen exposure, which require robust formulations that maintain stability and efficacy over time (Francis, 2020; Vidhamaly *et al.*, 2022). Regulatory requirements for veterinary products, similar to those for human drugs, include adherence to good manufacturing practices (GMP), adding complexity to the development and commercialization process. Collaboration, research, and investment from industry, academia, and regulatory bodies are necessary to fully realize the potential of RDS in veterinary medicine (Michael *et al*., 2022; Garba and Firincioğlu, 2023).

Perspective

Smart farming technologies are being adopted to increase food production while minimizing environmental impacts. With the global population projected to reach 10 billion by 2050, the demand for animal products is also rising. However, livestock farming is complex, and production optimization, waste reduction, and cost reduction are essential (Monteiro *et al.*, 2021). These challenges are further complicated by a shrinking workforce and rising production costs. Although meat provides essential nutrients, increasing production is challenging because of limited natural resources (Kumar *et al.*, 2021). Advances in animal health biotechnology, including vaccines, antimicrobials, and diagnostic tools, have supported the growth of livestock systems (Siddiqui *et al.*, 2022). Veterinary drug delivery systems offer benefits such as reduced dosage, minimized side effects, and reduced animal stress, thus increasing profitability (Li *et al.*, 2022).

Encapsulation is essential in ruminant nutrition, optimizing nutrient delivery through appropriate material selection and understanding factors affecting efficiency (Garba and Firincioğlu, 2023). Effective delivery systems for bioactive compounds improve stability, solubility, and targeted delivery, advancing ethnoveterinary medicine, using herbs, offering synthetic drug alternatives, and addressing antimicrobial overuse. Probiotics positively impact the gut microbiota, immune response, nutrient digestibility, absorption, animal growth, and meat quality, thereby improving overall health and productivity (Nwafor and Nwafor, 2022). The encapsulation of feed additives enhances voluntary feed intake and the overall welfare of ruminant livestock (Garba and Firincioğlu, 2023). Nanoparticles play a significant role by protecting encapsulated bioactive compounds from degradation by gastrointestinal digestion and cellular metabolism. They enable controlled release, enhance biodistribution, and target tissues affected by biological disturbances. Nanoparticles also protect the lysine content from the ruminal microbiota (Albuquerque *et al.*, 2020).

Controlled delivery systems offer safer and more effective treatment for chronic diseases than immediate-release drugs. They have prolonged effects, increase efficacy and safety, and improve ruminant nutrition and health. These systems optimize nutrient delivery, control important parameters, and protect high-value nutrients and drugs. Rumen-controlled delivery systems improve animal welfare and production efficiency. Future efforts will focus on optimizing rumen and postrumen function, developing low-cost formulations, and targeting high-value micronutrients and drugs. Cost constraints will shape future developments in this area (Al-Shawi *et al.*, 2020).

Ruminants need coarse "physically effective fiber" (peNDF) to stimulate chewing and ruminal activity. peNDF, defined by particle size, increases saliva flow, the acetate-to-propionate ratio, and milk fat levels, and maintains rumen pH (Belverdy *et al.*, 2019). Fiber enhances chewing, salivation, rumination, and ruminal motility; alleviates rumen acidosis; regulates dietary intake; aids in milk fat synthesis; and promotes solid particle digestion. Evaluating and improving dietary fiber utilization are crucial for formulating ruminant diets (Zhou *et al.*, 2022). Grass–legume mixtures can increase daily intake due to the preference of animals for mixed forage. Legumes with condensed tannins alter ruminal protein degradation by shifting nitrogen excretion from urine to feces, which is environmentally beneficial. Tannin-rich diets also reduce enteric methane emissions per unit of intake. These mixtures benefit animals, increase biomass yield, and reduce fertilizer use (Seoni *et al.*, 2021; O.S. van Cleef *et al.*, 2022).

High-concentration diets fed to finishing beef cattle significantly affect the rumen microbial community. The metabolic activities of these microbial communities, associated with specific basal diets, explain variations in methane and short-chain fatty acid production in cattle. Longitudinal sampling showed that once the rumen microbial community adapts to a dietary change, it maintains a relatively stable state (Snelling *et al.*, 2019). Mathematical modeling and fermentation prediction techniques can help design drug delivery systems and manipulate rumen fermentation (Teixé-Roig *et al.*, 2023).

To meet the increasing demand for large-scale *in vitro* meat production is being explored, leading to self-sufficiency (Kumar *et al.*, 2021). Research has focused on obtaining bioactive compounds from microalgae, agrifood residues, and edible insects as alternative protein sources for functional foods (Teixé-Roig *et al.*, 2023).

Access to veterinary drugs for livestock has become a significant issue, often analyzed in terms of demand and farmer behavior. However, drug use also depends on structural factors that influence the drug supply chain and farmers' access. Veterinary medicine is crucial to the animal-based food chain (van Herten and Meijboom, 2018; Jaime *et al.*, 2022). Many challenges in veterinary drug administration stem from limitations in traditional methods and dosage forms, which lead to compliance issues among animals. These challenges are exacerbated by the lack of suitable dosage forms and control measures for drug release and timing (Unde *et al.*, 2024). Biosafety concerns about the coating materials, their potential adverse effects or unwanted interactions with gut microbiota, and their scalability and cost-effectiveness should be addressed (Sadeghi *et al.*, 2024).

Plant extract is introduced as a green additive and is likely to share similar functions with synthetic additives to enhance the protection ability of the coating. Moreover, they are non-toxic, safe to use, abundant, and environmentally friendly (Wu *et al.*, 2022). *N. oceanica* shows a strong potential to be used as a natural dietary source of eicosapentaenoic acid EPA to ruminants; nevertheless, further studies are needed to verify its protection *in vivo* whole microalga biomass is a natural rumen-protected source of EPA) for ruminants (Alves *et al.*, 2018).

Concerns have arisen regarding drug residues in food products due to their potential adverse health effects and regulatory implications. Residues refer to pharmaceutical compounds or their metabolites found in meat, fish, eggs, poultry, and ready-to-eat foods intended for human consumption (Pratiwi *et al.*, 2023). Reducing methane emissions from ruminants is critical for mitigating the environmental impact of livestock farming. Encapsulation technology has been explored in dairy cows using encapsulated lipids in their diets to inhibit methanogenesis in the rumen. Research has shown a significant reduction in methane production without adverse effects on milk production or cow health (Garba and Firincioğlu, 2023). Encapsulation technology enhances ruminant nutrition and product quality through controlled nutrient delivery, improving stability and targeted release during digestion. This treatment boosts nutrient utilization, reduces wastage, and enhances animal performance. Protecting sensitive compounds such as vitamins and probiotics from degradation ensures optimal health and growth. In ruminant products, they improve taste, texture, and shelf life by masking unpalatable compounds and controlling flavor release, though challenges such as cost and regulatory hurdles remain. Continued research and development are crucial for maximizing the benefits of sustainable ruminant farming.

Conclusion

This study shows that polymeric RDS is a promising method for efficiently delivering nutrients to ruminants. Polymeric coatings for the slow, postruminal release of bioactive substances can greatly improve ruminant health and productivity. The results indicate that polymeric coatings effectively protect nutricine in the rumen and ensure their release in the abomasum. This research highlights the prominent use of alginate and chitosan polymers in RDS. The evaluation of these systems using both *in vitro* and *in vivo* methods provides a thorough understanding of their performance and effectiveness. Future research should focus on optimizing these delivery systems and exploring new materials to further enhance their efficacy and application. The continued development of novel nutricine delivery solutions will advance animal health and benefit the agricultural industry.

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Conflicts of interest

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Authors' contributions

The author is solely responsible for all aspects of this work, including conceptualization, methodology, analysis, and manuscript preparation.

Data availability

All data are presented in the article.

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