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Review

Trace mineral controlled-release intraruminal boluses. Review

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Abstract:

Trace minerals are essential nutrients for sustaining life, growth, and reproduction. In ruminants, mineral deficiencies affect the physiologic and metabolic functions that often trigger diseases. The design and use of controlled-release intraruminal boluses (CRIRB) are an alternative to correct the microelement deficiencies in the organism. This review aims to highlight the available information on the different types of trace mineral CRIRB, as well as the manufacturing methods that include hot-melt extrusion, melt granulation, and direct melting techniques. Furthermore, this review describes the effects of CRIRB related to health, productive, and reproductive parameters in ruminants.

Keywords: Intraruminal boluses, Release mechanisms, Mineral concentration, Release kinetics.

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Introduction

Trace mineral deficiencies in pasture and forage from various livestock regions are common around the world and in Mexico. The low mineral concentration in the soils and the antagonism between minerals difficult their availability for plants and animals[1]. Trace minerals like copper (Cu), zinc (Zn), cobalt (Co), selenium (Se), and iodine (I) are deficient in ruminants[2-5] and impair productive and reproductive parameters[1].

Faced with this problem, the food and veterinary pharmaceutical industries have developed products for trace mineral supplementation in the form of mineral premixes, blocks, and injectable solutions; however, frequent dosages are required, and consumption is variable when freely accessible[6,7]. Prolonged-release intraruminal boluses are devices designed for oral administration and must remain in the reticulorumen for periods of three months or up to one year[8,9], considered the most indicated method to correct trace mineral deficiencies in grazing ruminants[6,10,11].

The design of CRIRBs follows basic criteria: dimensions, release system geometry, and density. These characteristics determine the mineral release mechanism; therefore, materials (excipients) with different mechanisms for dosage rate control have been used[8,9]. This review describes the different types of trace mineral CRIRBs, as well as their manufacturing methods, including hot-melt extrusion, melt granulation, and direct melting techniques. Furthermore, this review discusses the effects of CRIRBs on ruminant health, productive, and reproductive parameters.

Controlled-release intraruminal boluses

The CRIRBs are solid devices that can release trace minerals, drugs, growth promoters, and nutrients in the reticulorumen of ruminants[8,9]. These devices must meet specific characteristics to remain in the reticulorumen and release the correct immediate or controlled dose. Their design considers three essential criteria[8,9,12,13]:

Dimensions. The bolus diameter must be of approximately 25 mm with a variable length of 40-100 mm.

Release system geometry. Usually, boluses have a cylindrical or spherical shape, with round tips and a smooth or capsule-shaped surface, for oral administration. However, there are designs with collapsible wings, compressible sheets, and rings that expand to avoid regurgitation and remain in the reticulorumen during treatment.

Density. Must be greater than 2.0 g cm^{-3} to ensure the bolus remains in the reticulorumen. The addition of densifying agents like iron (Fe) or soluble glass to the bolus formulation achieves the required density.

Compressed boluses

This type of bolus consists of a compressed matrix that contains drugs or trace minerals and a polymeric membrane coating[14]. Compressed boluses were designed to dissolve or disintegrate by the mechanic action of the rumen[8]; therefore, the release of drugs or trace minerals occurs through the erosion or diffusion of the bolus during predetermined periods[14]. Densities higher than 2.0 g cm^{-3} were determined to be sufficient to ensure bolus retention in the reticulorumen and prevent regurgitation[15]. For example, in Australia, an erodible bolus based on cobaltic oxide (CO_3O_4) and other diluents was developed to supply Co to grazing ruminants[16]. Boluses contained between 30 to 90 % Co_3O_4, with a variable weight of 5.5 to 30 g, and were efficient for supplying Co for more than a year[16,17]. Although the boluses had a specific weight between 3.5 and 4.1[17], they presented regurgitation problems, as well as the formation of a superficial calcium phosphate layer that prevented their correct dissolution[7,17]. To decrease the incrustation of calcium phosphate in the bolus, the authors decided to administer a steel screw that, when making contact with the bolus would disintegrate the calcium phosphates[17,18]. This problem also occurred in Se pellet boluses formulated with 5 or 10 % of Se and 90 or 95 % of Fe, with an approximate weight of 10 g, a 12-mm diameter, and 15 mm long[19]. However, some formulations were not very effective, confirming that the Se particle size used in the manufacture of the pellets was the limiting factor in the long-term release of Se[18,20]. Similarly, Zn pellet boluses were developed based on the mixture of 5 g of Zn and 5 g of Fe filing. The boluses showed release rates of 10 mg of Zinc per day[21].

Several authors have designed compressed boluses to supply Se to goats[22] and sheep[23,24]. For example, one study demonstrated the effectiveness of 10 g boluses to correct Se deficiency in sheep. The bolus was manufactured with 5.23 % of sodium selenite, 68.77 % of Fe, 25 % of cutin, and 1 % of magnesium stearate[24]. However, with this supplementation strategy, regurgitation problems arose; therefore, the design must consider the geometric shape and density of the bolus. To solve this problem, they designed a bolus with polymeric wings that expand upon contact with the ruminal fluid; this prevents the regurgitation of the bolus. The device contains inside a spring that acts on a plunger that, in turn, exerts pressure on the erodible matrix that may contain drugs or trace minerals. The release occurs when the matrix makes contact with the external environment through a portal at one end of the bolus[8].

Using a different approach, Evrard *et al*[23]. designed a bolus for the treatment of coccidiosis in lambs. The bolus consisted of a matrix with 30 % of sodium sulfamethazine, 54.4 % of reduced Fe, 15 % of hydrogenated castor oil, and 0.5 % of magnesium stearate. The average weight of the bolus was 18.5 g, and the density was 2.3 g cm^{-3}. The release of sulfamethazine occurs by diffusion and erosion of the matrix. Furthermore, in this study, the authors determined that the dose regimen of 800 mg kg^{-1} of live weight and compression forces higher than 2,160 kg cm^{-2} were enough to maintain the release rate and the plasmatic concentrations of sulfamethazine (>25 µg ml^{-1}) for up to 100 h, as long as the mechanical strength of the boluses is 33.5 ± 1.2 kg[23]. The boluses formulated with sodium selenite and sulfamethazine have an average weight of 20.13 g, a density of 2.0 g cm^{-3}, a length of 52.05 mm, and a width of 21.22 mm. These boluses were efficient in controlling coccidiosis and maintaining the correct amount of sulfamethazine and selenium in goat kids[22].

Different polymers, insoluble in ruminal fluids, have been used in the manufacture of boluses as a coating for matrices containing drugs or trace minerals. Polymers form a brittle membrane that allows matrix erosion and the release of trace minerals or drugs[25]. An example of this approach is the All-Trace® bolus composed of a 30 g compressed mixture of inorganic salts (copper oxide, sodium selenite, cobalt sulfate, potassium iodide, manganese sulfate, zinc oxide (ZnO), zinc sulfate) and vitamins A, D_3, and E. At one end, the bolus has an 18 g counterweight that ensures the bolus remains in the reticulorumen; at the end of its shelf life, it dissolves entirely without leaving residues. An inert polymer resin coats the bolus, except for the upper end that will be in contact with the ruminal environment, and controls the release of trace minerals for approximately 240 d[26,27].

Extruded boluses

This type of bolus is obtained by extrusion of the trace mineral and polymeric excipient formulation[14]; the process is described in the section of Bolus Manufacturing Methods. This bolus was developed in New Zealand for the treatment of facial eczema. The bolus consists of an extruded ZnO matrix coated with a waxy material and impermeable to ruminal fluid, except for one end which, when in contact with the ruminal fluid, erodes to release the microelement. As the matrix erodes, the waxy coating disintegrates; this ensures the constant exposure of a part of the matrix to the ruminal environment[14,28,29].

Soluble glass boluses

Soluble glass boluses (SGBs) were designed to supply Cu, Zn, Co, Se, and I to grazing ruminants[6,11,30-35]. Their composition consists of phosphorus pentoxide (P_2O_5), sodium oxide (Na_2O), and calcium oxide (CaO) as glass forming and modifying oxides. This composition allows a release rate in the reticulorumen not higher than 25 mg cm^{-2} day^{-1}[36], making possible its administration to ruminants to release trace minerals for more than a year[30,31]. The release of microelements occurs by glass diffusion or dissolution, and to a greater extent by erosion[8,13,30,36,37].

Sheep boluses have a variable weight of 30 to 35 g, a length of 40 to 50 mm, a diameter of 14 to 19 mm, and densities ranging from 2.7 to 4.0 g cm^{-3}; while cattle boluses are bigger, with weights of 100 g, diameters of 24 to 26 mm, and lengths of 80 mm[36]. Other aspects to consider in the bolus design, to achieve the release rate aforementioned, are the particle size and the pH of the harboring environment[37]. The SGBs present multiple advantages; these include less calcium phosphate formation in the bolus[1], which facilitates its dissolution, improved plasmatic profiles[30,31,35], higher productive and reproductive indexes[32,35,38,39], as well as economic benefits[6,11]. However, during the SGB manufacturing process, it is not possible to include materials (excipients or drugs) sensitive or unstable to the high temperatures required for glass formation. Still, pressure-mediated sintering processes can incorporate drugs or other components into the glass[37].

Magnesium boluses

Magnesium (Mg) boluses consist of a cylinder formed by an alloy of Mg, aluminum, and Cu (86, 12, and 2 %, respectively), containing dispersed Fe in the bolus matrix to increase density. Sheep boluses weight around 35 g and erode due to electrochemical influences in the rumen, releasing Mg during approximately three weeks(40). A different example of a magnesium bolus consists of two cylindrical halves linked with a rubber to facilitate its administration. When the bolus reaches the rumen, it opens to avoid regurgitation and releases Mg, by electrolytic action, at an approximate rate of 2 g per device during three months(41).

Capsules with copper oxide wire

Copper oxide (CuO) wires have been used to correct Cu deficiencies in sheep(21,42,43) and cattle(44). They measure between 3 and 12 mm in length, 0.5 to 1 mm in diameter, and have a specific gravity of 6.1 to 6.4 (42,45,46), they are generally covered by a mixture of cupric and cuprous oxide(21) or contained in gelatin capsules(42,46). CuO wires enter the reticulorumen and then flow to the abomasum, where hydrochloric acid dissolves them and release Cu ions, absorbed in normal biochemical processes(41,46). The administration of CuO wire capsules increases the concentration of hepatic Cu during 6 to 12 months; this is due to the relative inertia of the particles in the reticulorumen and the retention in the abomasum(21).

CRIRB manufacturing methods

Hot-melt extrusion

This technique is used to produce pharmaceutical products like tablets, capsules, films, and implants for oral, transdermal, and transmucosal drug administration(47,48). The process consists of pumping raw materials through a screw that rotates at temperatures from 30 up to 250 °C inside a die; this results in a homogeneous mixture of the active compounds and binding agents (thermoplastics and polymers). The equipment commonly used is called an extruder; it consists of a barrel that contains bands that heat, soften, and compress the mixture of chemical compounds. Finally, the extrudate is led to the die to give it the required shape and dimensions[47,49].

Melt granulation

Melt granulation is a technique based on the use of solid binding agents that melt at temperatures between 50 to 80 °C; this allows it to be used for the formulation of drugs or trace minerals sensitive to humidity, avoiding the use of aqueous or organic solvents[50]. The granulation process can consist of a single step; for this, the binding agent is added with the rest of the components of the mixture to a high-speed mixer granulator. The binding agent melts because of the heat generated with the air stream during the mixing, kneading, and drying phase. Finally, the granulate results from the union of the molten binding agent and the powder particles, once dry, the granulate must be sieved to obtain the desired granule size[51]. Depending on the pharmaceutical purpose, the granules can be encapsulated for immediate drug release, or compressed to form controlled-release intraruminal boluses.

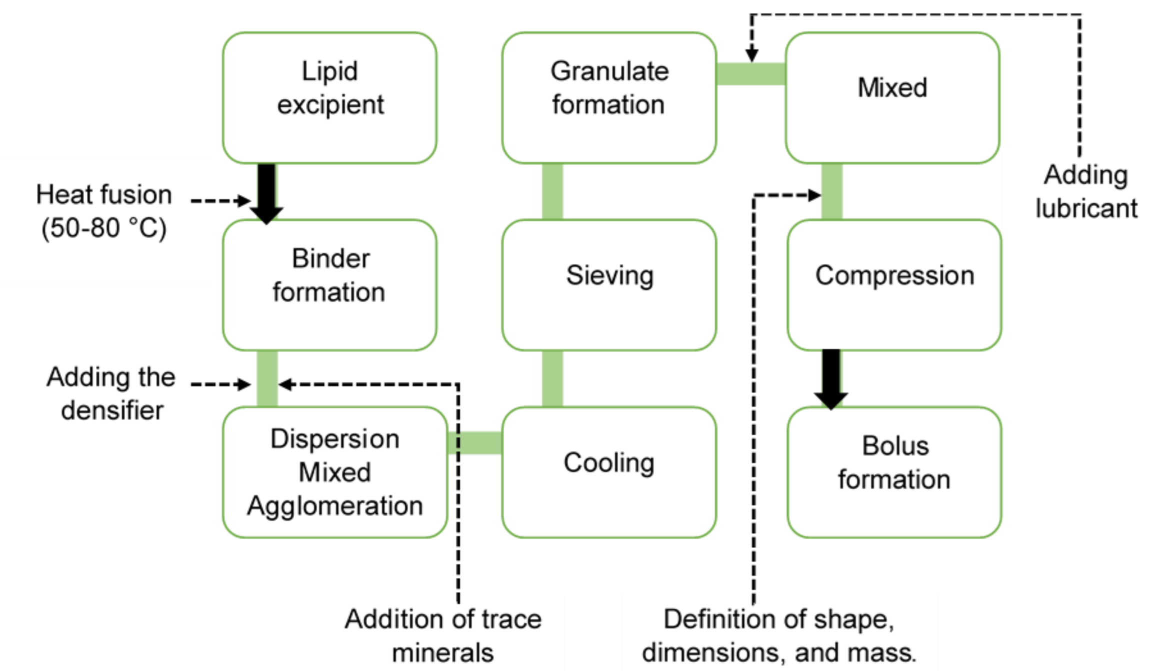
Direct melting

This technique consists of melting the mixture of active components with the excipients at temperatures between 500 to 1,100 °C. The melt is poured into molds to form a final product, for example, glass rods, glass tubes, glass discs, granules, and controlled-release monolithic boluses. Generally, highly soluble glass-forming components are used, such as glass-forming oxides (vitrifying) and modifying oxides (fluxes and stabilizers) that allow the correct formation of the glass network[36,37].

Design of boluses with trace minerals

The present research group proposes an inexpensive and straightforward procedure to prepare trace mineral controlled-release intraruminal boluses. For example, in the design of selenium boluses, the procedure consists of adding amounts of sodium selenite, 13 %, cutin, 32 %; Fe, 54 %, and magnesium stearate, 1 % (Figure 1). Lamb boluses can have an average weight of 8 g, a hardness of 21.17 kp, and a density of 2.08 g cm^{-3}. The recommended density values for retention in the rumen should be greater than 2.0 g cm^{-3}[8,9,15]. The excipient used to form the matrix was suitable for releasing Se.

Figure 1: Diagram of the elaboration process of selenium intraruminal boluses by the melt granulation method



Trace mineral supplementation with CRIRB

Cu, Zn, Co, Se, and I are trace minerals that have been used to produce CRIRB[6,11,21,24,30]. There are several types of commercial boluses with different design, shape, size, weight, concentration of trace minerals (Table 1), and release rates. The latter is essential in the design of boluses since it indicates the daily release of the mineral and the duration of the bolus. In the United Kingdom, a SGB was developed to correct Cu, Co, and Se sheep deficiencies, the bolus was designed to have a release rate of 2.53 mg cm^{-2} d^{-1} in the rumen and supply 11 mg of Cu, 0.5 mg of Co, and 0.21 mg of Se, for up to 6 mo[30,31]. The Cu, Co, and Se requirements in a sheep that consumes 1.5 kg of dry matter (DM) are 10.5, 0.3, and 0.3 ppm, respectively. Zn deficiency in sheep has been treated with a SGB that contains 15.2 % of Zn, 0.5 % of Co, and 0.15 % of Se [32,39]. The daily requirement is 20 to 33 mg of Zn kg^{-1} of DM[52]. According to the bolus manufacturer, the Zn release during 180 days is approximately 28 mg d^{-1}[32], considering the previous example, the sheep would demand a consumption between 30 and 49 mg of Zn, with a deficiency of 2 and 21.5 mg, which can be neutralized by the diet contribution. A different study reported a dissolution rate of 326 mg d^{-1}, equivalent to daily releases of 49.3 mg of Zn, 1.7 mg of Co, and 0.5 mg of Se; thus, the bolus met the daily requirement of sheep[11]. However, the dissolution rate depends on the rumen conditions, such as pH, type of feed, bolus accommodation site, ruminal contractions, as well as on the abrasion effects of other materials in the reticulorumen[8,11,13]. Another type of bolus designed for sheep presented an average rumen release rate of 103.55 mg d^{-1}, equivalent to the daily supply of 23.01 mg of Zn, 0.535 mg of Co, and 0.258 mg of Se[53].

The soluble glass technology has allowed the design of boluses of 100 g with 13.4 % of Cu, 0.5 % of Co, and 0.30 % of Se for grazing cattle; according to the manufacturer, two boluses liberated 156, 5.9, and 3.4 mg d^{-1} of Cu, Co, and Se, respectively[33]. The requirement of a 500 kg bovine that consumes 10 kg of DM is 100, 2.5, and 3 mg d^{-1} of Cu, Co, and Se, respectively[54]; therefore, the SGBs are effective in treating trace mineral deficiencies[55,56,57]. The reported daily release of two commercial All-Trace® boluses with trace minerals and vitamins was 138 mg of Cu, 113 mg of Zn, 71 mg of Mn, 2.1 mg of I, 2.0 mg of Co, 2.0 mg of Se, 4,644 IU of vitamin A, 929 IU of vitamin D, and 9 IU of vitamin E during 8 mo[58]; these boluses were designed for cattle with more than 150 kg of LW. While the daily release of two boluses for growing calves was 60 mg of Cu, 1.0 mg of Co, 0.6 mg of Se, 36.8 mg of Mn, 53.3 mg of Zn, 1.25 mg of I, 3033 IU of vitamin A, 607 IU of vitamin D, and 9.1 IU of vitamin E[26]. Approximately half the weight of the bolus matrix (30 g) is released in the first 6 wk; after that, the release rate decreases until the seventh month[27].

Table 1: Trace mineral concentration in different types of controlled-release intraruminal boluses

Product	Copper (mg)	Zinc (mg)	Cobalt (mg)	Selenium (mg)	Iodine (mg)	Manganese (mg)
Cosecure*[34,38]	4356-4900	/	165-220.5	49.5-92.75	/	/
Zincosel[11,32,35,53]	/	3764-5040	94.1-171.6	43.29-49.5	/	/
Cosecure*[33,55]	13400	/	500	300	/	/
All-Trace[58]	16200	13320	236	251	497	8280
smAll-Trace[26,27]	5300-5427	4700-4797	90	50-54	100-225	3200-3312
Tracesure[59]	/	7	1000	1000	6800	/
Ferrobloc[60]	333	36	60	8	24	160
CRIRB+ [61]	3944	4366	95	45	330	3013
CRIRB++ [62]	/	/	582	148	2908	11853

*SGB for sheep; ** SGB for cattle; +CRIRB for sheep; ++CRIRB for cattle.

Some studies show that the supply of trace minerals using CRIRBs increases the blood concentration of minerals[30,31,35], improves productive and reproductive parameters[32,35,38,39], and promotes the humoral immune response in ruminants[11]. Studies have confirmed the effectiveness of SGBs in supplying Cu, Co, and Se to correct and prevent their deficiency in grazing sheep for up to a year[30,31]. Furthermore, they increased the content of Se in the fetus and newborn lambs[38].

The tablets with 25 % CuO, equivalent to 19.3 % of Cu in the active matrix, increased Cu concentrations in blood from 10.4 to 14.0 µmol L^{-1} and in the liver from 120 to 684 mg kg^{-1} of DM in growing sheep[45]. Female lambs in a semi-intensive (semi-stable) system were administered 5 g tablets with 1 and 4.6 % of Se, which were effective for up to 90 days; however, a higher concentration of Se in the blood (182.01 ng g^{-1}) was found in the lambs that received the bolus with 4.6 % of Se[10]. Tablets made of cement-based tile adhesive with 5 and 10 % of Se have been reported to maintain adequate concentrations of Se in the blood (148.49 and 158.48 ng g^{-1}) for up to 120 days[63]. In a different study, the predicted Se release from a bolus with 5.23 % sodium selenite was 0.177 mg d^{-1}. Boluses increase the Se blood content in sheep after 30 d of being administered[24]. In Afshari sheep, Abdollahi *et al.*[60] observed an increase in Cu, Se, and I the mating day and at 90 and 100 d of gestation, using a CRIRB with various minerals (Ca, Mg, Na, Cu, Mn, I, Fe, Co, Zn, and Se). A study suggested that Se, I, Fe, Zn, and Mn are essential for embryo survival and fetus development[64]. Overall, the administration of a CRIRB with several trace minerals to pregnant sheep increases the concentrations of Zn, Cu, Co, and Se in newborn lambs[61]. SGB with Cu, Zn, Co, and Se have been widely used to correct trace mineral deficiencies in semi-intensive lambs[6,32,39], grazing sheep[34], backyard goats[65,66], growing camels[55,67], and grazing cattle[30,68,69].

Effect of CRIRB on the productive and reproductive parameters

There are few published studies about the effects of CRIRB on the productive and reproductive parameters of ruminants. In a study performed in weaned Holstein-Friesian calves fed a balanced diet and administered boluses with several trace minerals and vitamins, the daily weight gain (0.59 kg) of the calves treated with the bolus was higher than that of the animals that did not receive the bolus (0.53 kg)[26]. Similar results were observed with Cu injections (25 mg of Cu mL^{-1}) and boluses of 20 g with CuO micropellets. The authors found no difference in daily weight gain (564.2 g d^{-1}) in Aberdeen Angus and Hereford breed calves; however, they suggested CuO boluses as an alternative to prevent Cu deficiencies[70]. The lambs treated with a SGB containing Zn, Co, and Se presented an improved daily weight gain (153.22 g) compared to the control group (136.61 g), with significant differences during the last fattening stage[11]. Moreover, a study reported that CRIRBs with several minerals improve the performance and nutritional quality of the colostrum (6.70 % of protein, 6.92 % of fat, and 0.59 % of inorganic matter) from Najdi breed sheep; which increases the health and growth of lambs until weaning[61]. Aliarabi *et al*[53] reported birth weights of 4.63 kg and daily weight gains of 0.243 kg in lambs born from females treated with a bolus containing 20 % Zn, 0.50 % Co, and 0.23 % Se. Trace mineral and vitamin supplementation through CRIRBs increased milk production with 8.19 kg day^{-1} cow^{-1}[62].

Sheep treated with a trace mineral and vitamin CRIRB showed twinning rates of 65.5 %, while sheep injected with Cu (12.5 mg of Cu) had 44.8 % of twin births. To confirm the effect of the bolus, the authors administered a CRIRB to sheep with Cu and Se deficiencies, improving twinning rates by 59 %, while in the control group, 11 % of female sheep were sterile[27]. In another study, the authors obtained 80 % of multiple births due to the administration of two CRIRB to sheep before synchronization[60]. Grazing dairy cattle supplemented with two SGBs containing 13.4 % of Cu showed a lower number of services to conception (2.5 ± 0.3 to 1.7 ± 0.2), and the calving interval decreased from 407 to 371 days[68].

Supplementation of Zn, Co, and Se through SGBs has improved the motility and proportion of live sperm cells, as well as the sperm membrane integrity[35,39]. Zn participates in the catabolism of the lipids located in the intermediate part of sperm cells to generate the energy required for sperm motility[71]. Cu, Zn, and Se have antioxidant properties and can reduce reactive oxygen species and avoid the damage to sperm cells[72,73]. Another study evaluated the effect of a bolus with 500 mg of Se on the semen quality of Hampshire and Suffolk sheep; boluses increased the activity of glutathione peroxidase (GSH-Px), motility, number of live sperm cells, and stallion sperm viability[74].

Effect of CRIRB on animal health

Se deficiency is a severe problem that affects animal production. Especially in sheep, the mortality rate of lambs during the perinatal and neonatal stages is 62 %[75], signs of white muscle disease, or nutritional muscular dystrophy are usually evident[4]. In a study with sheep supplemented with a SGB before gestation, the incidence of white muscle disease signs decreased in born lambs[31]. The bolus released 0.21 mg of Se day^{-1}, enough to be transferred to the placenta or colostrum received by the lambs in their first hours of life[31,56]. The Se concentration in milk from cows supplemented with a SGB was higher

(0.0658 µg g^{-1}) than the control group (0.0374 µg g^{-1}) for 7 mo[56]. In a different study, lambs born from sheep treated with a SGB containing 20 % of Zn, 0.50 % of Co, and 0.23 % of Se showed no incidence of white muscle disease, while lambs born from untreated sheep achieved a mortality rate of 10.3 % and signs of white muscle disease by 18 %[53].

Regarding the role of trace minerals in the immune function, some reports indicate that Zn boluses cause a positive effect in the humoral immune response of lambs against the keyhole limpet hemocyanin (KLH) antigen. However, it seems that the joint action of Zn, Co, and Se in the bolus improved the immune response[11]. In camels, a similar effect was found in the humoral immune response as a result of the intravenous injection of 2 mL of a 20 % suspension of sheep red blood cells. Furthermore, a study reported that the SGB improved the cell-mediated immunity, increasing the thickness of skin folds 24 h after the injection of phytohemagglutinin (PHA)[67]. In goat kids, treatment with a bolus of sodium selenite and an injection of Se (0.25 mg kg^{-1} of LW) improved the humoral immune response to immunization with a bacterin-toxoid (*Toxo Bac Neumonias*)[76].

Munday *et al*[28] developed a Zn bolus to protect lambs against facial eczema. The bolus consists of a 43 g core of ZnO covered by a waterproof coating, except for one end which, when in contact with the ruminal fluid, erodes to release a Zn dose of 20 mg kg^{-1} d^{-1}. The boluses with Zn concentrations of 54, 81, and 108 g protected sheep against the sporidesmin produced by the fungus *Pithomyces chartarum*[77]. Calves treated with ZnO boluses and exposed to sporidesmin showed a lower gamma-glutamyl transferase activity in serum than the control group; this demonstrated the effectiveness of boluses in reducing the incidence and severity of facial eczema[29].

Conclusions

Technological innovations used in the manufacturing processes of veterinary pharmaceutical products can contribute to improving mineral supplementation methods. CRIRB are the most effective method to supply trace minerals for up to a year. The controlled-release mechanisms of the intraruminal boluses are practical to correct and prevent the trace mineral deficiencies in grazing ruminants. Several studies demonstrate that CRIRB improve productive and reproductive parameters, as well as the humoral immune activity of ruminants. The use of CRIRB decreases animal handling and stress, as well as economic costs. However, in Latin America, boluses are not a common method for trace mineral supplementation; therefore, further research is necessary for the development of CRIRB based on the deficiency profile of grazing soils and forages.

Literature cited:

1. McDowell LR, Arthington JD. Minerales para rumiantes en pastoreo en regiones tropicales. 4ta ed. Universidad de Florida. Gainsville, Florida. USA; 2005.

2. Ramírez-Orduña R. Ramírez RG, González RH, Haenlein GFW. Mineral content of browse species from Baja California Sur, México. Small Ruminant Res 2005;(57):1-10.

3. Gámez BJR. Diagnóstico del estado mineral de bovinos en San Juan Del Río, Choapam, Oaxaca [tesis maestría]. Chapingo, México: Universidad Autónoma Chapingo; 2009.

4. Ramírez-Bribiesca JE, Tórtora JL, Huerta M, Aguirre A, Hernández LM. Diagnosis of selenium status in grazing dairy goats on the Mexican plateau. Small Ruminant Res 2001;(41):81-85.

5. Vieyra-Alberto R, Domínguez-Vera IA, Olmos-Oropeza G, Martínez-Montoya JF, Borquez-Gastelum JL, Palacio-Núñez J, *et al*. Perfil e interrelación mineral en agua, forraje y suero sanguíneo de bovinos durante dos épocas en la huasteca potosina, México. Agrociencia 2013;(47):121-133.

6. Kendall NR, Mackenzie AM, Telfer SB. Effect of a copper, cobalt and selenium soluble glass bolus given to grazing sheep. Livest Prod Sci 2001;(68):31-39.

7. Grace DN, Knowles SO. Trace supplementation of livestock in New Zealand: meeting the challenges of free-range grazing systems. Vet Med Int 2012;(ID 639472):8.

8. Cardinal JR. Intraruminal decives. In: Rathbone MJ editor. Adv Drug Deliv Rev 1997;(28):303-322.

9. Rathbone MJ, Cardinal JR, Ogle CR. Mechanisms of drug release from veterinary drug delivery systems. In: Rathbone MJ, Gurny R editors. Controlled release veterinary delivery. Biol Pharm Consid: Elsevier Sci; 2000:17-50.

10. Blanco OMA, Spross SAK, Rosiles MR. Evaluación de comprimidos intrarruminales de selenio por concentración sanguínea y lanar de corderas semiestabuladas. Vet Méx 2000;31(2):121-127.

11. Kendall NR, Mackenzie AM, Telfer SB. The trace element and humoral immune response of lambs administered a zinc, cobalt and selenium soluble glass bolus. Livest Sci 2012;(148):81-86.

12. Fan LT, Singh SK. Contolled release: A quantitative treatment. Polymers properties and applications. Berlin Heidelberg: Springer-Verlag; 1997.

13. Cardinal JR. Intraruminal controlled release boluses. In: Rathbone MJ, Gurny R editors. Controlled release veterinary drug delivery. Biol Pharm Con; Elsevier Sci 2000;(36):51-82.

14. Vandamme TF, Rathbone MJ. Long acting rumen drug delivery systems. In: Rathbone MJ, McDowell A editors. Long acting animal health drug products: Fundamentals and applications. Adv Deliv Sci Tech; Springer 2013:221-246.

15. Riner RL, Byford LG, Stratton JA, Hair JA. Influence of density and location on degradation of sustained release boluses given to cattle. Am J Vet Res 1982;43(11):2028-2030.

16. Marston HR. Therapeutic pellets for ruminants. U.S. Patent 3 056 724, 1962.

17. Andrews ED, Isaacs CE, Findlay RJ. Response of cobalt deficient lambs to cobaltic oxide pellets. NZ Vet J 1958;6(5):140-146.

18. Langlands JP, Bowles JE, Donald GE, Smith AJ. Selenium supplements for grazing sheep. 2. Effectiveness of intra-ruminal pellets. Anim Feed Sci Tech 1990;(28):15-28.

19. Millar KR, Meads WJ. The efficacy of intraruminal pellets composed of elemental selenium and iron in sheep. NZ Vet J 1988;36(2):53–55.

20. Langlands JP, Donald GE, Bowles JE, Smith AJ. Selenium supplements for grazing sheep. 1. A comparison between soluble salts and other forms of supplement. Anim Feed Sci Tech 1990;(28):1-13.

21. Judson GJ. Trace element supplements for sheep at pasture. In: Masters DG, White CL editors. Detection and treatment of mineral nutrition problems in grazing sheep. Australian Centre for International Agricultural Research, Canberra, Australia: ACIAR Monograph 1996;(37):57-80.

22. Díaz SVM. Efectos de bolos intrarruminales de sulfas y selenio para el control de la coccidiosis caprina [tesis licenciatura]. Cuautitlán Izcalli, Edo. de México: Universidad Nacional Autónoma de México; 2012.

23. Evrard B, Delahaut P, Hubert P, Crommen J, Delattre L. Biopharmaceutical aspects of the development af a sulfamethazine oral sustained release bolus for lambs. J Contr Rel 1995;(35):107-115.

24. Revilla-Vázquez A, Ramírez-Bribiesca E, López-Arellano R, Hernández-Calva LM, Tórtora-Pérez J, García-García E, *et al*. Suplemento de selenio con bolos intrarruminales de selenito de sodio en ovinos. Agrociencia 2008;(42):629-635.

25. Hemingway RG, Ritchie NS, Parkins JJ, Device for introducing nutrients and/or therapeutic materials into ruminant animals. U.S. Patent 4 732 764, 1988.

26. Hemingway RG, Parkins JJ, Ritchie NS. Sustained-release boluses to supply trace elemnts and vitamins to calves. Vet J 1997;(153):221-224.

27. Hemingway EG, Parkins JJ, Ritchie NS. Enhanced reproductive performance of ewes given a sustained-release multi-trace element/vitamin ruminal bolus. Small Ruminant Res 2001;(39):25-30.

28. Munday R, Thompson AM, Fowke EA, Wesselink C, Smith BL, Towers NR, *et al*. Azinc-containing intraruminal device for facial eczema control in lambs. NZ Vet J 1997;45(3):93-98.

29. Munday R, Thompson AM, Smith BL, Towers NR, O'Donnell K, McDonald RM, *et al*. Azinc-containing intraruminal device for prevention of the sporidesmin-induced cholangiopathy of facial eczema in calves. NZ Vet J 2001;49(1):29-33.

30. Telfer SB, Zervas G, Carlos G. Curing or preventing deficiencies in dopper, cobalt and selenium in cattle and sheep using tracerglass. Can J Anim Sci 1984;64(Suppl):234-235.

31. Zervas G. Treatment of dairy sheep with soluble glass boluses containing copper, cobalt and selenium. Anim Feed Sci Technol 1988;(19):79-83.

32. Kendall NR, Telfer SB. Induction of zinc deficiency in sheep and its correction with a soluble glass bolus containing zinc. Vet Rec 2000;(146):634-637.

33. Sprinkle JE, Cuneo SR, Frederick HM, Enns RM, Schafer DW, Carstens GE, *et al*. Effects of long acting trace mineral rumen bolus upon range cow productivity. Proc Western Section, Am Soc Anim Sci 2004;(54).

34. Kendall NR, Jackson DW, Mackenzie AM, Illingworth DV, Gill IM, Telfer SB. The effect of a zinc, cobalt and selenium soluble glass bolus on the trace element status of extensively grazed sheep over winter. Anim Sci 2001;(73):163-169.

35. Kendall NR, McMullen S, Green A, Rodway RG. The effect of zinc, cobalt and selenium soluble glass bolus on trace element status and semen quality of ram lambs. Anim Reprod Sci 2000;(62):277-283.

36. Telfer SB, Zervas G, Knott P. Water soluble glass articles, their manufacture, and their use in the trearment of ruminant animals. U. S. Patent 4 482 541, 1984.

37. Drake CF. Controlled release glass. U.S. Patent 4 350 675, 1982.

38. Zervas G, Telfer SB, Carlos G, Anderson P. The effect of soluble-glass boluses containing copper, cobalt and selenium on the blood composition of ewes. Anim Feed Sci Technol 1988;(21):23-29.

39. Kendall NR, Green A, McMullen S, Rodway RG. The effect of a zinc, cobalt, and selenium bolus on ram semen quality and trace element status. In: Roussel AM, *et al*, editors. Trace elements in man and animals. Boston, MA. Springer, 2002.

40. Sakkinen H, Eloranta E, Vahtila S, Puukka M, Timisjarvi J, Saarela S, *et al*. Effects of magnesium oxide and magnesium alloy rumen boluses on plasma and urinary magnesium and calcium concentrations in reindeer (*Rangifer tarandus tarandus*). Small Riminant Res 2004;(54):69-79.

41. Vandamme TF, Ellis KJ. Issues and challenges in developing ruminal drug delivery systems. Adv Drug Deliv Rev 2004;(56):1415-1436.

42. Dewey DW. An effective method for the administration of trace amounts of copper to ruminants. Search 1977;(8):326-327.

43. Langlands JP, Donald GE, Bowles JE, Smith AJ. Trace element nutrition of grazing ruminants. 3. Copper oxide powder as a copper supplement. Austr J Agr Res 1989;(40):187-193.

44. Burke JM, Miller JE. Control of *Haemonchus contortus* in goats with a sustained-release multi-trace element/vitamin ruminal bolus containing copper. Vet Parasitology 2006;(142):132-137.

45. Parkins JJ, Hemingway RG, Lawson DC, Ritchie NS. The effectiveness of copper oxide powder as a component of a sustained-release multi-trace element and vitamin rumen bolus system for cattle. Br Vet J 1994;(150):547-553.

46. Huerta BM, Amándola MR, Martínez HPA, García MJG, Sánchez RC, Domínguez VI, *et al*. Suplementos minerales para rumiantes. Postgrado de Producción Animal, Departamento de Zootecnia. Universidad Autónoma de Chapingo; 2010.

47. Patil H, Tiwari RV, Repka MA. Hot-melt extrusion: from theory to application in pharmaceutical formulation. AAPS Pharm Sci Tech 2016;(17):20-42.

48. Repka MA, Bandari S, Raman KV, Vo AQ, McFall H, Pimparade MB, *et al*. Melt extrusión with poorly soluble drugs-an integrated review. Int J Pharm 2018;(535):68-85.

49. Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Kumar BS, *et al*. Pharmaceutical applications of hot-melt extrusión: Part I. Drug develop and Pharm 2007;(33):909-926.

50. Ochoa DL, Igartua OM, Hernández MRM, Gascón RA, Pedraz MJL. Granulación por fusión en mezcladores granuladores de alta velocidad. VITAE, Rev Fac Quím Farm 2006;(13):40-47.

51. Rodríguez GA. Validación del proceso de fabricación de bolos intrarruminales de selenio inorgánico. [tesis licenciatura] Cuautitlán Izcalli, Edo. de México: Facultad de Estudios Superiores Cuautitlán, Universidad Nacional Autónoma de México; 2006.

52. NRC. National Research Council. Nutrient requirements of small ruminants: sheep, goats, cervids and new world camelids. Washington, DC, USA: National Academy Press; 2007.

53. Aliarabi H, Fadayifar A, Alimohamady R, Hossein DA. The effect of maternal supplementation of zinc, selenium, and cobalt as slow-release ruminal bolus in late pregnancy on some blood metabolites and performance of ewes and their lambs. Biol Trace Elem Res 2019;(187):403-410.

54. NRC. National Research Council. Nutrient Requirements of Beef Cattle. 7th rev. ed. Washington, DC, USA: National Academy Press, 2000.

55. Liu ZP, Xiong GL. The effect of a copper, selenium and cobalt soluble glass bolus on the trace element status of Bactrian camels. J Anim Feed Sci 2007;(Suppl 1):313-317.

56. Hidiroglou M, Proulx J, Jolette J. Effect of intraruminally administered, selenium soluble-glass boluse on selenium status in cows and their calves. J Anim Sci 1987;(65):815-820.

57. Hidiroglou M, Proulx J. Evaluation of a long-acting selenium and copper preparation for intraruminal adminitration to cattle. Ann Rech Vet 1988;(19):187-191.

58. Baumgurtel KL, Judson GJ. Evaluation of a sustained release bolus to supply trace elements and vitamins beef cattle. Anim Prod Austr 1998;(22):133-136.

59. Rose M, Pearson S, Cratchley T. Effect of iodine, selenium and cobalt rumen boluses given to dry dairy cows on the immunoglobulin and thyroid hormone status of calves. Anim Sci J 2012;(83):543-548.

60. Abdollahi E, Kohram H, Shahir MH, Nemati MH. The influence of a slow-release multi-trace element ruminal bolus on trace element status, number of ovarian follicles and pregnancy outcomes in synchronized Afshari ewes. Iranian J Vet Res 2015;16(1):63-68.

61. Abdelrahman MM, Aljumaah RS, Ullah KR. Effects of prepartum sustained-release trace elements ruminal bolus on performance, calustrum composition and blood metabolites in Najdi ewes. Environ Sci Pollut Res 2017;(24):9675-9680.

62. Pulgar AR, Vera VR, Serrano CE. Efectos de la utilización de bolos intraruminales a base de oligoelementos, sobre indicadores reproductivos y productivos en vacas lecheras de alta producción. Sitio Arg Prod Anim 2013;51-52.

63. Gutiérrez OC, Spross SAK, Rosiles MR, Ducoing WA, Ortiz HA. Selenio sanguíneo y fecal en ovinos a partir de comprimidos inorgánicos intrarruminales. Vet Mex 2005;36(3):313-324.

64. Hostetler CE, Kincaid RL, Mirando MA. The role of essential trace elements in embryonic and fetal development in livestock. Vet J 2003;(166):125-139.

65. Serra AB, Serra SD, Nakamura K, Orden EA, Cruz LC, Fujihara T. Effect of selenium in soluble glass bolus on selenium content of milk and blood of goats. Biol Trace Elem Res 1996;(55):207-212.

66. Hayashida M, Orden EA, Cruz EM, Cruz LC, Fujihara T. Effects of intraruminal soluble glass bolus on blood selenium and plasma mineral level of grazing does under Backyard conditions in selected áreas in Nueva Ecija, Philippines. Asian-Aust J Anim Sci 2003;16(2):187-197.

67. Alhidary IA, Abdelrahman MM, Harron RM. Effects of a long-acting trace mineral rumen bolus supplement on growth performance, metabolic profiles, and trace mineral status of growing camels. Trop Anim Health Prod 2016;(48):763-768.

68. Moeini MM, Telfer SB, Sanjabi MR. The effect of Cosecure® supplementation on the copper status and fertility of grazing Holstein-Friesian dairy cattle. Acta Vet Scand 2003;(Suppl 98):257.

69. Sprinkle JE, Cuneo SP, Frederick HM, Enns RM, Schefer DW, Carstens GE, *et al.* Effect of a long-acting, trace mineral, reticulorumen bolus a range cow productivity and trace mineral profiles. J Anim Sci 2006;(84):1439-1453.

70. Pechin GH, Sánchez LO, Cseh S. Evaluación de dos formas de administración (bolos de liberación lenta vs. EDTA Cu inyectable) en la prevención de la deficiencia de cobre en bovinos para carne. Ciencia Vet 2006;8(1):5-15.

71. Roy B, Baghel RPS, Mohanty TK, Mondal G. Zinc and male reproduction in domestic animals: A review. Indian J Anim Nutr 2013;(30):339-350.

72. Suttle NF. Mineral nutrition of livestock. 4th ed. London, UK. CABI Publishing. United Kingdom; 2010.

73. Zhao CY, Tan SX, Xiao XY, Qiu XS, Pan JQ, Tang ZX. Effects of dietary zinc oxide nanoparticles on growth performance and antioxidative status in broilers. Biol Trace Elem Res 2014;(160): 361-377.

74. Carrillo-Nieto O, Domínguez-Vera IA, Huerta-Bravo M, Jaramillo-Escutia G, Díaz-Zarco S, Vázquez-Armijo JF, *et al*. Actividad de GSX-Px, concentración de selenio y calidad del eyaculado en sementales ovinos suplementados con selenio durante la época reproductiva. Agrociencia 2018;(52):827-839.

75. Ramírez-Bribiesca E, Hernández-Camacho E, Hernández-Calva LM, Tórtora-Pérez JL. Efecto de un suplemento parenteral con selenito de sodio en la mortalidad de corderos y los valores hemáticos de selenio. Agrociencia 2004;(38):43-51.

76. Díaz-Sánchez V, Rodríguez PG, Ramírez-Bribiesca E, Morales-Álvarez J, López-Arrellano R. Evaluación de bolos selenio sobre parámetros productivos e IgG en cabritos inmunizados con bacterina-toxoide. Abanico Veterinario 2018;8(3):118-129.

77. Bennison JJ, Nottingham RM, Key EL, Parkins JJ. The effect of zinc oxide and elemental zinc boluses on the concentrations of Zn in serum and faeces, and on providing protection from natural *Pithomyces chartarum* challenge in sheep. NZ Vet J 2010;58(4):201-206.