ORAL DRUG DELIVERY SYSTEMS IN RUMINANT ANIMALS

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Abstract:

Ruminant animals like cattle, sheep, goat, etc. are commercially the most essential group of animals and are widely kept by human beings all over the world. With an increase in variety and popularity of products obtained from these species, their health also becomes an important consideration. Ruminants are animals with a distinct digestive system. The unique anatomy and physiology of these animals provides many challenges for their drug delivery. Animals, either large or small are difficult to handle and thus drug administration becomes a hassle for the caretaker and hurtful for the animal. However, the process of rumination along with their unusual four compartmental stomachs offers opportunities for controlled and sustained release delivery of drugs in these animals. This reduces the number of doses and makes the administration of a large variety of drugs possible. Taking advantage of this opportunity many formulations have been developed. However, there still remains tremendous scope for better and more efficient drug delivery systems for ruminants. This article talks about ruminant animals, their healthcare, devices used for drug administration, various oral formulations administered to them, with special emphasis to intraruminal devices- their mechanism and delivery.

1. INTRODUCTION:

The animals of commercial importance are mainly cattle, swine and poultry; hence the control of diseases which directly or indirectly affect the production in these animals is very important. The veterinary market is the "poor cousin" to its human counterpart. 30.5 billion US dollars were spent in 2001 on R&D by research based pharmaceutical companies. Of this amount, only an estimated US $0.6 billion (2%) were spent on pharmaceuticals for veterinary use. Nevertheless, the veterinary

pharmaceutical industry continues to thrive within a population of diverse species. The vast range of animal species and the corresponding anatomical and physiological differences, challenges the development of veterinary pharmaceutical formulations. [1], [2]

2. RUMINANTS:

2.1. An introduction to ruminants

The word "ruminant" comes from the Latin “ruminare”, which means "to chew over again". Physiologically, a ruminant is a mammal of the order Artiodactyla that digests plant-based food by initially softening it within the animal's first stomach, then regurgitating the semi-digested mass, now known as cud, and chewing it again. The process of rechewing the cud to further break down plant matter and stimulate digestion is called "ruminating". There are about 150 species of ruminants which include both domestic and wild species including cattle, goats, sheep, giraffes, bison, moose, yaks, water, buffalo, deer, camels, wildebeest, antelope, etc., the most important ones being the domestic food animals in this class. [3]

2.2. Digestive system of ruminants

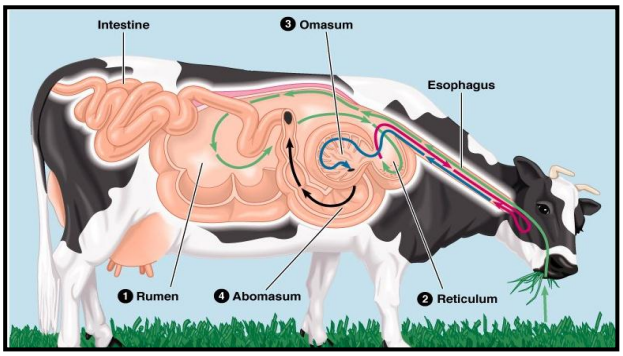

Figure 1: Ruminant digestive system.

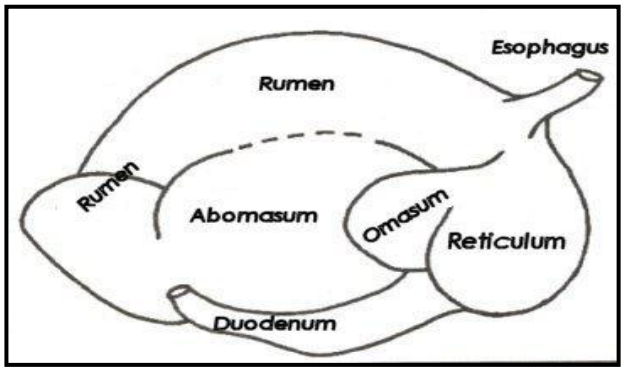

Figure 2: Ruminant Compartmental Stomach.

Ruminants have a four-compartment stomach. The four parts of the stomach are a fore-stomach (rumen, reticulum, and omasum) and abomasum. The function of the abomasum is similar to that of the stomach of other mammals. The compartments of the fore-stomach are the primary sites of microbial digestion of the feed. Fibre, especially cellulose and hemi-cellulose, is primarily broken down into the three volatile fatty acids by microbes (bacteria, protozoa, and fungi) in the recticulo-rumen region. Protein and non-structural carbohydrate (pectin, sugars, and starches) are also fermented.

After rumination and microbial digestion, the ruminal content (in the form of a suspension of small particles) passes through the omasum into the abomasum. The abomasum is the sole part of the gastrointestinal tract that secretes gastric juices. The ph is variable, but much lower than the rumen and is generally around a value of 3. Cattle produce about 100-190L of saliva per day. Continuous inflow provides extra fluid for the fermentation and a strong ph buffering of the digesta to optimise the microbial activity. Particles greater than 2mm (cattle) or 1mm (sheep) tend to be excluded from passage through the reticular-omasal orifice; this material is recycled through the rumination process. The abomasum is a true, glandular stomach, which secretes acid and functions in as a manner similar to the stomach of a monogastric. Ingesta are finally subjected to the ruminant's own digestive enzymes. [16], [6], [3], [7].

2.3. Young Ruminants

At birth, the rumen and reticulum are not yet functional. When the lamb or calf sucks its mother's milk, the milk passes directly into the abomasum. The oesophageal groove was the pathway that allowed this to occur. The groove closed when the calf drank the milk. Thus the abomasum in calves is like the human stomach and not the ruminant stomach until they reach maturity. [3]

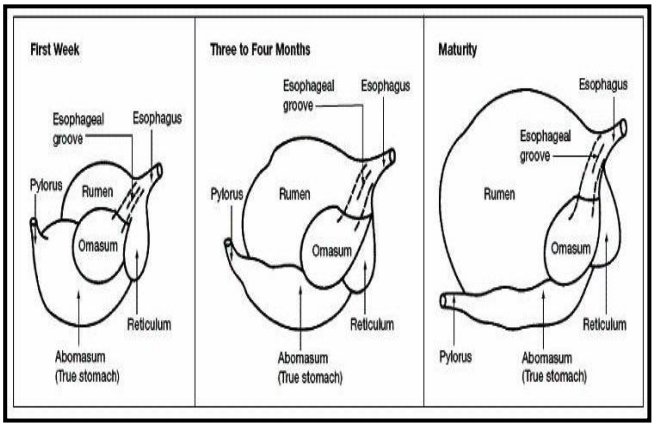

Figure 3: Development of the ruminant stomach compartments from birth to maturity.

3. Oral Formulations For Ruminant Animals:

Figure 4: Oral formulations including boluses, pellets, granules, drenches

3.1. Solids

3.1.1. Conventional Oral Boluses:

Boluses are tablets or caplet-like products that are formulated with very large quantities of drug to be administered once daily. They are 4 inches long weighing 40g for large animals or 2 inches long for smaller ruminants. [8]

3.1.2. Sustained Release Oral Boluses: Rumen Retention Devices.

These are devices that remain in the reticulorumen for prolonged periods due to their density or geometry. These devices are formulated for zero buoyancy and its resulting lodging in the reticulum prevents regurgitation. [12]

3.1.3. Granules and Pellets

These are formulations to be mixed either in the feed or in water. The formation of pellets by pelletisation is an agglomeration process that converts fine powders to granules of bulk drugs and excipients into small, free flowing, spherical and semi spherical units, referred to as pellets.[8],[21]

3.1.4. Capsules for calves

Milk caused closure of the esophageal groove in calves and the milk passes directly into the abomasum. The main component of milk that caused this action is sodium bicarbonate. This effect continues and is effective in calves of upto 2 years of age. Thus in calves of upto 2 years of age these components can be added in capsules in order to close the groove and thus allowing the drug to pass directly to the abomasum.[3]

3.2. Liquid

3.2.1. Drenches: These are liquid formulations that are intended to be delivered to the back of the tongue, forcing the animal to swallow the medication. [8], [12]

3.2.2. Syrups, solution, suspensions [8]

3.3. *Semi-solids: Pastes and gels*

4. Special Deliver Devices For Solid Liquid And Semi-Solid Oral Dosage Forms:

For effective drug delivery it is essential that the drug reaches its targeted site, disintegrates and thus displays the desired effect. Other than the physical and chemical parameters of the drugs it is important for the dosage form reach the site correctly. Administration of drugs in animals requires technique to avoid discomfort to the animal, hassle to the farmer and damage to the dosage form. Thus special devices for administration to ruminants help make this process more efficient and less strenuous.

4.1. For Solid Oral Medication

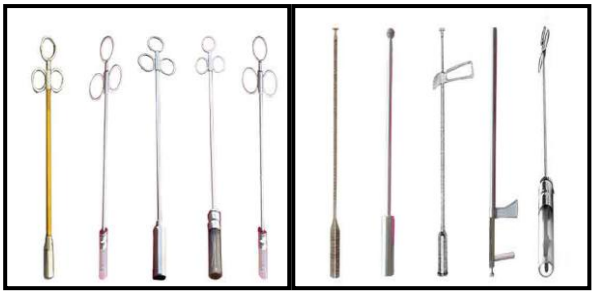

Figure 5: Various types of balling guns.

4.1.1. Conventional Oral Bolus Delivery Device

4.1.2. Sustained Release Oral Bolus Delivery Devices

Both conventional and sustained release oral boluses are delivered with the help of a balling gun. A balling (or bolling gun) is used to administer the bolus dosage form to large animals. The bolus is inserted to the base of

the tongue, and is delivered. After the bolus is placed in the pharynx it is allowed to be swallowed by a reflex action, and then passed into the ruminal sac. [12]

4.2. For Liquid Oral Medication

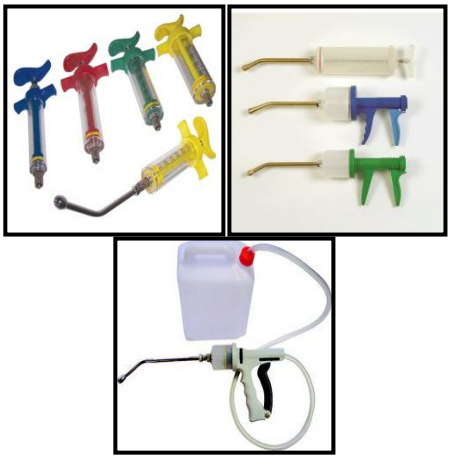

Figure 6: Various drenching devices**.**

4.2.1. Oesophageal Delivery: Most commonly used oesophageal delivery devices are stomach tubes of varying length, internal and external diameters, and composition.

4.2.2. Drenching Devices: Oral liquid medications are administered to cattle, sheep and goats using a method called drenching. Drenching can be done by using drenching syringes or drenching guns.

4.2.1.1. Drenching Syringes

4.2.1.2. Drenching Guns

4.2.1.2.1. Single-Dose Gun

4.2.1.2.2. Multi-Dose Gun

4.2.1.2.3. Automatic Gun

4.3. For Semisolid Oral Medications

Figure 7: Devices for semi-solid dosage forms

4.3.1. Single Dose Syringes.

4.3.2. Multiple Dose Syringes.

[2], [12]

5. INTRARUMINAL BIOACTIVE DELIVERY:

Ruminants possess a unique digestive system. Using the high metabolic potential of the symbiotic microflora of the rumen, ruminants are capable of digesting plant material and obtaining nutrients and energy from this process. Because of the ruminal fermentation, the most bioactives are not stable in the harsh ruminal environment. Major developments in nutritional and veterinary science, which increased substantially productivity of monogastric farm animals, could not be applied directly to ruminants. Rumen fermentation may also destroy or modify nutrients and drugs used to prevent or treat disease. For example, glucose and starch given orally to prevent or help treat ketosis is largely hydrolyzed to short-chain fatty acids. Some potent growth promoters require an effective

oral delivery system to deliver the active agent to the absorption site in the small intestine of the host animal. Thus, it was well recognized very early that there was a need for a rumen-stable delivery system to improve the bioavailability of a bioactive by protecting it from the ruminal digestion. [5], [16].

6. INTRARUMINAL DEVICES- PRINCIPLE:

The formulation of protected bioactive can be delivered in the rumen in a controlled manner and over a long period of time Their stomachs have four compartments .of these compartments, the rumen is the largest. It has two small openings: Esophagus & Omasum which allow substances in and out of the rumen. Long term delivery devices can be housed in this large compartment if a suitable method to prevent them from: Regurgitating & moving them into the remainder of the tract. This is possible by producing devices that prevent rumination. Such a device should be a sufficiently high density device so that it is heavy enough to resist the movement out of the rumen; or expandable devices so that when taken in, it increases in size thus not allowing it to leave the rumen. [5], [6] [16]

7. INTRARUMINAL DEVICES & THEIR FUNCTIONING:

Rumino-reticulum devices can be classified into several categories depending upon their release profile: sustained release; controlled but continuous release; pulsed release; novel release patterns**.** Intraruminal devices are solid preparations that deliver the bioactive at required release rate and over required period of time. There are several main design features that are required for any intraruminal devices: A size and shape making them capable of being readily administered orally; Reliability of long term retention in the rumen; a controlled and long term release of the bioactive.

Theoretically there should be no limit to the duration of retention and release, but in practice the device lifetime should match the health condition for which it is designed. For example, treating an infection might need only days or weeks of exposure, an antiparasite drug might be needed for the duration of the grazing season, while a nutrient might be needed for 365 days a year. In practice, most current commercial products have a lifetime of around 100 days, and another device is re-administered if longer term treatment is required.

7.1. Ruminal retention

To avoid regurgitation during rumination, intraruminal devices have to be properly designed. This can generally be achieved either by increasing the density (high density devices) or modifying geometrical parameters of the device. Both approaches can also be combined in a single device.

7.2. Bioactive release mechanism

Various physical and/or chemical processes can be used to release the bioactive from ruminal devices. The simplest mechanism is the erosion of a bolus due to the permanent agitation of the ruminal contents. Another approach uses simple diffusion of a water-soluble bioactive out of the matrix, while an even more sophisticated process relies on osmosis as the release controlling process. All of these types of device can be referred to as "passive" release systems. On the other hand, there are "active" release mechanisms whereby some force is generated to mechanically force bioactive from the device. [6], [7], [16]

8. Different Intraruminal Devices:

8.1. Dispersed Matrix Systems

A dispersed matrix device is defined to be one in which the active species is dispersed within non-biodegradable polymer matrix. Under these conditions drug is released via diffusion processes and the release rates follow the square root of time law. The device is in the form of a large sheet that can be rolled up to form a cylinder. This rolled up device is constrained by a water soluble tape that dissolves following device administration. The device unrolls following removal of the tape. Under these circumstances the unrolled device will have dimensions that are greater than those of the oesophageal channel thereby preventing device regurgitation.

8.1.1. Paratect flex:

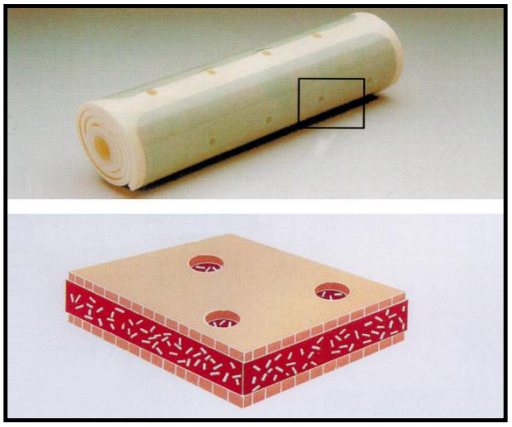

Figure 8: paratect flex.

It is a slow release device and takes over 90 days to release its drug content. It is a triaminate sheet that is rolled into a cylindrical shape for easy administration and is retained in this form by a water soluble adhesive bandage. In the ruminal Fluid, the band dissolves and allows it to assume its expanded form to prevent regurgitation. The active escapes through the holes in the sheet from the middle layers. The ruminal environment controls its release. [7] [12]

8.2. Continuous controlled release

8.2.1. Laby device:

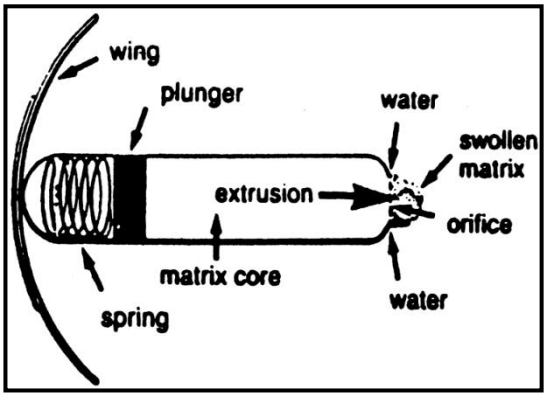

Figure 9: laby device.

It consists of a hollow cylinder capped at both ends. One of its end is closed and serve to help constrain a spring which acts as a piston. The polymeric wings attached to the cylinder expand and serve as a means to retain drug delivery device within the rumen. The density of the erodible composition helps to determine the target location of the device in the Reticulorumen. It dissolves or abrades due to mechanical action of rumen. [6], [7]

8.2.2. IVOMEC SR Bolus:

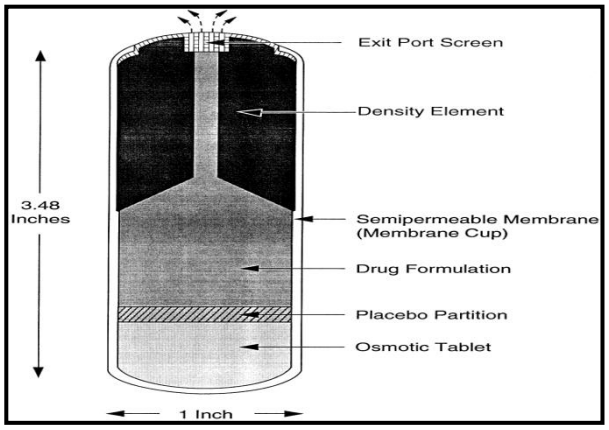

Figure 10: IVOMEC SR Bolus

It delivers ivermectitin for full grazing season. It is a continuous controlled release bolus. It consists of a membrane cup (semipermeable membrane) that contains an osmotic table, partition layer, drug layer and a densifier. The drug can be in the form of a suspension @31-35C or it can be a fluid. Densifier made of sintered iron fillings ensures retention. The entry of water through osmosis results in the swelling of the osmotic table by imbibitions. The osmotic table swells due to entry of water, and thus pushes the drug content while swelling through the exit port, slowly and continuously over about 135 days. Temperature in the rumen allows flow of the drug suspension. Concentration of the ruminal fluids controls the release. [6], [7], [18]

8.2.3. Erodible glass bolus: The Elemental Bolus.

Figure 11: The elemental bolus.

The elemental bolus is a continuous controlled release type of bolus. They are unique in that they are made of compressed glass. As the glass dissolves the copper, cobalt and selenium ions are released into the rumen. The bolus dissolves completely so there is no remaining residue. This is a great advantage of this bolus. The provision of a continual source of copper ions in the rumen is another unique feature of elemental boluses. The copper ions are available around the clock to bind to thiomolybdates and ensure they are passed out of the body rather than be absorbed to exert their toxic effect. Selenium ions are continually available in the rumen from the dissolving elemental boluses and are available for rumen microbes to convert into

selenomethionine and selenocystine which can be absorbed by the animal as organic selenium. A lack of selenium has been shown to increase the incidence of retained foetal membranes (placentas) and endometritis. Selenium deficiency can also reduce immunity and ability to fight infections such as mastitis and pneumonia. Elemental boluses are for use in ruminating cattle weighing over 100 kg. The expected period of protection is four to six months - six months in pasture fed conditions but the boluses will dissolve faster when supplements or concentrates are fed resulting in the rumen being more acidic. Administering to dairy cows at drying off will protect through mating. The boluses may crack if warmed too quickly. Thus it must be at room temperature (15 to 20°C) prior to administration. With an excellent retention rate, elemental boluses offer peace of mind from knowing each animal is getting the required daily dose. [22]

8.3. Pulsatile Systems

Boluses which release multiple doses at pre-programmed intervals have been termed pulsatile or intermittent release systems. The major impetus for the development of these systems has been the desire to have systems which better mimic current practices of multiple doses of immediate release products given at specific time intervals.

8.3.1. Castex device:

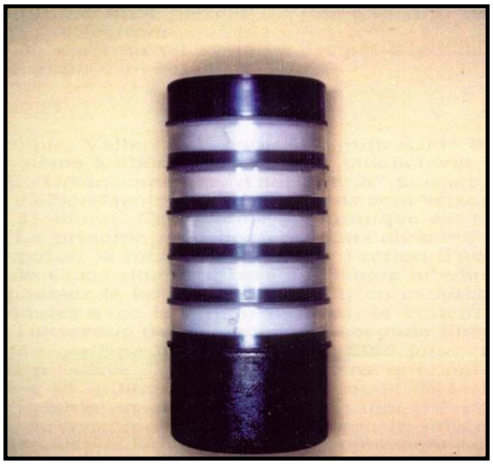

Figure 12: Castex device.

It is a pulsatile system that intermittently releases the drug at regular intervals. One end of this device remains closed while the other end slowly starts disintegrating because of the rumen environmental conditions. It is made of iron which acts as the “density element” allowing the device to be retained in the rumen. The central core is made of a magnesium alloy with the drug. The galvanic coupling allows the ruminal fluid to act as a conductor for the release of electrons and thus the disintegration of the core. It is ph dependent. It allows for the release of 5-6 tablets every 21- 23 days. [5], [6], [7]

8.3.2. Vandamme system:

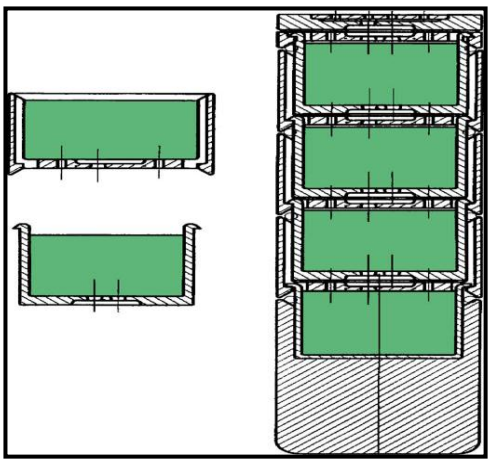

Figure 13: Vandamme system.

The vandamme system, also a pulsatile system contains series of compartments containing an antihelminthic drug, bound to each other with a biogradable monofilament located in the centre of the device. The closed end is made of iron which acts as the "iron density element" which ensures that the device is retained. The biodegradable microfilament when exposed to the rumen fluid allows drug release in intervals. Thus the release of the drug depends on the ruminal environment. Depending on the nature of the monofilament, the device can release the drug after a long (86 days) or short (21 days) period. [6], [7].

8.3.3. The Electronic Bolus:

Figure 14: the electronic bolus.

The E-Bolus is an intermittent release Reticulo-ruminal device (RRD) that releases three therapeutic doses of the anthelmintic albendazole separated by 31 day intervals. Timing for the device is controlled by a custom integrated circuit, and power is provided by alkaline watch batteries. The drug, contained in each of the three adjacent tubes is expelled at once by the action of a gas generator situated at the bottom of each tube. After immersion in the conductive ruminal fluid for a continuous 10 minute period a sensed by two conductive rubber electrodes, the device turns itself on , shuts off the external sensor and begins counting for 31 days. After this time, logic on the chip routes battery energy to the first gas generator, which releases gas, predominantly carbon dioxide sufficient to expel the medication and a protecting rubber stopper. The device then resets, counts an additional 31 days, routes energy to the second gas generator, whereupon the second dose is released on day 62 and this is repeated for the last release on day 93. Accuracy is provided by a quartz crystal, so that precision of release is within 15 min for the final release. Am impervious casing of polypropylene protects the drug and electronics from ruminal fluid and the device operates independently of any changes within the rumen environment. [12], [5]

8.4. Controlled bioactive delivery using ART

Not yet commercially available, is another plunger driven system, Active Rumen Technology. It uses a galvanic cell to release up to 160 ml of hydrogen. Elevated pressure resulted causes the plunger to extrude bioactive formulation. Previous work has demonstrated the feasibility of linear and

reproducible release of placebo formulation out of an ART device over an extended period of time. The Active Rumen Technology may have a number of advantages over existing controlled-release technologies: The gas cell occupies a very small volume in the device so a larger bioactive payload is possible; Gas production rate is independent of the ruminal environment; there is a potential to modulate the bioactive release rate by remote control. [16]

8.5. Other approaches to ruminal delivery

a. A pH sensitive polymer coating is used where a ph difference between abomasum and rumen is considered for effective coating.
b. An increased amount of protein that by-pass the rumen fermentation process may be used.
c. Coating with substances that is less soluble than the active.
d. Substances inert in the rumen e.g. Copper oxide, are in the rumen and are a source of copper ions in the abomasum.
e. Increase in temperature in the rumen decreases the rate of degradation of bioactive.
f. Coating with lipids protects the bioactive from degradation in the rumen. However they have poor post ruminal absorption rates.

During production of Pellets and granules for ruminal animals, the fine powders are microencapsulated with materials that are inert to the rumen environment to increase their strength. *[1], [6], [7], [16], [20]*

Type of device	Name	Company	Active
Matrix device.	Spanbolet	Smithkline	Sulfomathazine
Diffusion device	Paratect.	Pfizer	Antihelminthic agent-morantel.
Laby device.	Rumensin	Elanco	To reduce subclinical ketosis.
Osmotic pump.	Alzet 2ML4.	Merck	Ivomec- anti parasitic.
Castex	Repidose	Coopers.	Oxfendazole.

device	5

Table 1: Various Intraruminal devices.

9. APPLICATIONS OF RUMINANT HEALTH CARE:

Like humans, animals need supplementary nutrients and pharmaceuticals that help to maintain good health and prevent or combat diseases. While the medication of humans is aimed to improve quality of live, intervention with bioactives in ruminants is primarily aimed to increase their production. Thus**,** all the approaches in medication and/or supplementation using bioactives or feed

additives to ruminants have an economical motivation. The factors that can influence the animal production include: Nutritional deficiency, Infectious diseases, Parasites (internal and external), Metabolic disorders, Controlling reproduction and Manipulating animal growth. These factors when taken care of help in the improvement of animal health thus increasing human benefits. [16]

10. CONCLUSION:

The development of specialized dosage forms to treat a variety of animals thus results in the need for efficient administration devices. The advent of controlled release implantable devices and rumen retention devices has hastened the need for the development of product specific administration devices. Innovation in the administrative device area will continue to satisfy the needs of the veterinary drug formulator and drug user to provide the tools that will permit precise administration of the desired drug to the animal in need of treatment. The ruminant animal is particularly amenable to the application of new systems, and one can expect new technologies to be applied to RRDs as the success of the current market introductions becomes apparent.

The foregoing account has demonstrated that a large number of intraruminal boluses have been designed using a variety of technologies that range from uncomplicated i.e., erodible systems to more complex eg. Osmotic systems. Each of the technologies has specific benefits and drawbacks. Each of these technologies has shown commercial products that have shown to be highly beneficial to the practice of animal husbandry. While current technologies represent a major advance over immediate release systems it is clear that more work needs to be done to

develop systems which provide better control of release rate at lower costs.

The oral drug delivery system for ruminant animals provides major challenges and opportunities which hopefully will be achieved in the near future.

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