REVIEW ARTICLE

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# Controlled Drug Delivery Systems for Veterinary Use: A Review

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**Till date, the development of novel drug delivery systems in veterinary medicines is like a dream for Indian scientists, though partially fulfilled in USA and UK. In veterinary medicines, majority of drug formulations are conventional type that fail to deliver and deposit drug molecule at the desired site. Due to wide variation in animal species, body system and its requirement, considerable flexibility exists with regards to the nature and physical structure of the veterinary device. The novel formulation modifications including sustained release devices, implant using biodegradable polymers, site directed formulations and rumen delivery systems could manipulate pharmacokinetic disposition to extend drug availability to the animal at the desired rate for prolonged period. Present review gives insight into controlled drug delivery systems already existing in veterinary field of medicines, however some are in the process of development.**

In human and veterinary medical practice, majority of drugs and their formulations are administered in the form of conventional systems eg. elixirs, infusions, capsules and aqueous or oil-based injections. These conventional systems, fail to deliver and deposit drug molecules at the desired site. Added to this, potent or highly toxic therapeutic agents require careful administration regimens because of their potential untoward side effects.

In India, sustained release formulation or targeted drug delivery systems for veterinary use are not available, although some of them are available in UK and USA. Researchers in many other countries are engaged in the development and investigation of controlled release formulation of veterinary medicines.

In the field of veterinary medicines, presently available controlled release devices are usually restricted to diseases that lead to considerable loss to the animal producer or to situations in which tangible cost effectiveness to the producer is achieved. The design of controlled release systems for animals differs considerably from those intended for human use. Owing to the wide variation in animal species, their body systems and requirements, considerable flexibility exists with regard to the nature and physical structure of the veterinary device. The novel formulation modifications including carrier technology, sustained release devices and site-directed formulations, which had been successfully developed and used in human beings, could be utilized for manipulation of pharmacokinetic disposition of drug to direct or extend bioavailability in the animal.

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## DEVICES USED TO ADMINISTER VETERINARY DRUG FORMULATIONS

The drug delivery system, sometimes, requires specific devices to ensure fast, safe, efficient and cost-effective treatment. Various devices available in the market for specialized oral medication to animals include balling guns, esophageal delivery devices, drench syringes and guns for liquids and powders, paste dispenser, hollow bits, prolonged release devices, nonpyloric passage devices, rumen lodging devices and water-medication metering devices. The devices commonly used for parenteral medication to animals are syringes like single dose, multiple dose, automatic syringes, multi-compartment and pole-mounted syringes and jet injectors. Implanting devices and projectile delivery systems e.g. intrauterine drug dispensers and vaginal drug

dispensers are also common in veterinary practice. The devices for topical medication include teat dips, patches (for spot-on and pour-on), aerosol dispensers, flea and tick collars and percutaneous absorption drug reservoir devices[1].

## CONTROLLED RELEASE FORMULATIONS

In designing a controlled release system for veterinary use, the nature of the compound to be delivered is of prime consideration, but in addition, cognizance must be taken of the best route of delivery, the animal species, optimum release rate, desired duration of response, manufacturability and the potential hazards of violative residue formation. Current technology takes the forms of rumen delivery systems; implant systems or external application systems. For the ruminant species, the drug formulation should be placed at a specific location so that it can function as a drug reservoir. Biodegradable polymers are receiving increasing attention for implants and vaccine bullets. Other important applications of this new technology include delivery of hormones for growth promotion purposes, antibiotic substances for treatment or prophylaxis and trace elements for specific deficiency situations. Relatively potent compounds are only considered potential drug candidates for formulation using this technology, viz. hormones for growth and estrus synchronization, long term delivery of trace elements and nutrients (copper, cobalt, zinc, selenium, amino acids and vitamins). These delivery systems facilitate uniform pharmacological response and reduce labor cost, trauma to animals and frequency of administration. Cost effectiveness is also a major consideration of these delivery systems.

## ORAL FORMULATIONS

### Ruminal boluses:

It is very difficult to hold high concentration of drug for relatively long period in ruminal fluid due to physical dilution in the various compartments of the gastrointestinal tract. In ruminants, the therapeutic efficacy of certain anthelmintics is poor, partially due to non-retention of the therapeutic agent, where worms are residing. Rumen, considered as a large fermentation tank, favors the retention of drug devices for longer periods of time, provided, a suitable method is found to prevent the device from either being ruminated or from moving through remainder of gastrointestinal tract. To increase the retention of drug device in rumen, various methods have been developed. Some of the ruminal boluses of these types are expanding devices, high-density devices and pulsatile boluses[2].

### Expanding devices:

These may be designed such that the geometry i.e. size and shape serve as retention mechanism (Captec device, Alza) or may use wings that remain folded during administration but unfold and spread out afterwards, enabling their retention in rumen (Rumensin ABC, Lilly). The use of recently developed device to deliver morantel tartrate to grazing cattle, termed as Paratect Flex Bolus (Pfizer), used in strategic treatment system to provide an unconventional, but successful method to remove existing worm burdens to prevent the re-establishment of new parasitic infections over an extended period of time[3]. The device consists of a polymer matrix containing water-soluble drug coated with a polymer impermeable to the drug, on its outer surface, but not on the edges. Release of soluble drug occurs via diffusion within water-filled channels of porous core matrix to uncoated edges of the device or to the uncoated edges of a series of holes punched through the coat. For a given drug-polymer matrix, the release rate can easily be controlled by variation in the number and dimensions of holes and by coating the perimeter edge. Another means of controlling the release is drug solubility (fig. 1).

The other device developed by Lilly (USA), utilizes wings that remain folded during administration but spread out after administration so that the device is retained in the rumen. Drug is incorporated into a bioerodible matrix to control the rate and duration of drug delivery. A spring is placed inside the device to push the matrix firmly to the opening, thereby maintaining a constant exposed surface area and therefore, a constant release rate. This device has been utilized for the delivery of oxfendazole (an anthelmintic) for the control of gastrointestinal disease in sheep. It has also

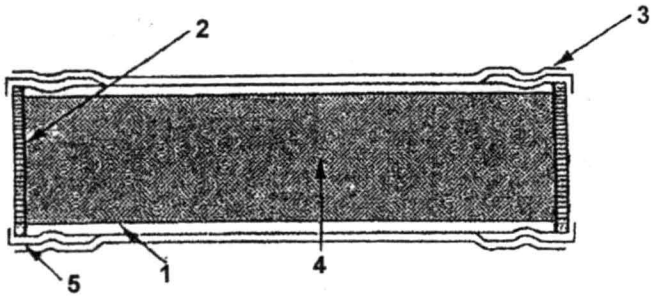


**Fig. 1: Sketch of Paratect Flex Bolus.**

**1. Stainless steel tube, 2. Sintered polythene discs impregnated with cellulose triacetate hydrogel, 3. Heat strunk poly-olefin band, 4. Drug blend (morantel tartrate, polyethylene glycol 400, sodium metaphosphate) and 5. Coating of drug blend.**

been evaluated in Australia by Lilly for the delivery of monensin to control bloat in cattle (fig. 2)[4].

**High density devices:**

These consist of either slow erosion (Spanbolet II) or osmotic (Ivomac SR) systems. Ivomac utilized the osmotic technology originally developed by Alza. The drug delivery rate is controlled by a cellulose acetate cup of sufficient thickness to give the mechanical integrity to the device, when placed in the rumen. Water from the ruminal fluid diffuses through the cup into a tablet composed of a salt and a swelling hydrogel. The tablet expands as the hydrogel absorbs water. The expansion of tablet forces a vehicle-containing drug through an exit port in the top of the bolus. This exit port is a passageway through a metal element placed at the top of the bolus. The metal element called a densifier, is included to increase the density of the bolus and thereby prevent regurgitation from the rumen. Claerebout *et al.*[5] developed the Rumisert bolus of ivermectin and studied the *in vitro* release for about 110 d. The device was developed to deliver ivermectin for the control of ecto-and endo-parasites in cattle (fig. 3). The Alza corporation (USA) has developed a similar device for the release of selenium to grazing cattle. Selenium is a critical growth component for cattle that is often missing from natural food sources.

Some other formulation such as Rumensin ruminal delivery device (RDD) has been developed by Lilly for the long-term delivery of monensin sodium (an antibacterial agent) to promote growth in cattle. The core matrix is a mixture of drug (40%) and a biodegradable copolymer prepared from lactic and glycolic acid (80/20 w/w). To achieve the desired release rate, a relatively low mol. wt. copolymer is utilized. Surface hydrophilic degradation of this copolymer matrix allows the controlled release of drug. Bulk hydration and erosion of the matrix is minimized by the hydrophobicity of monensin sodium and the copolymer. Hot melt adhesives are used to secure the drug-polymer mixture to the interior surface of the cylinder. The ends of the cylinder are covered with a polymer shield to prevent metals and other abrasive ruminal contents from entering the device and physically abrading the core matrix. Drug release rate from this device increases over the first 50 d and is then at a steady state rate, which depends on the average mol. wt. of the copolymer used in the preparation of matrix (fig. 4)[6].

Riner *et al* [7] developed sustained release boluses using carnauba wax, barium sulfate, polyethylene glycol and iron powder with oxytetracycline. Drug release for approximately 50 d has been achieved. Gelatin capsules containing copper oxide needles have been administered to sheep and cattle to provide a long-term protection against copper deficiency. Trace elements can be incorporated into controlled release glasses, which provide protection up to one year. This technique is novel and possesses useful applications in veterinary medicine.

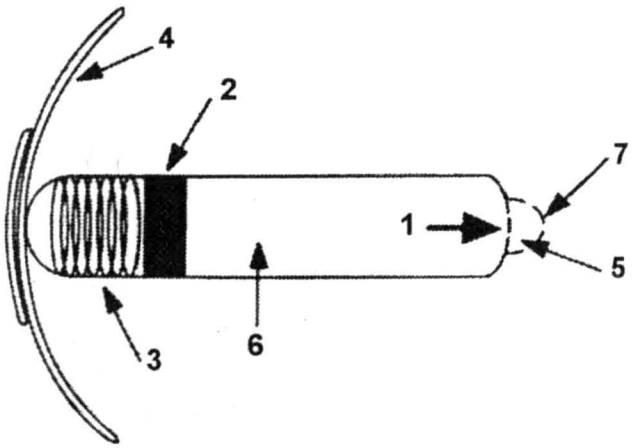


**Fig. 2: Sketch of ruminal bolus, during administration the plastic wing is held against the device by a water dissolvable tape.**

**1. Extrusion, 2. Plunger, 3. Spring, 4. Wing, 5. Orifice, 6. Matrix core and 7. Swollen matrix.**

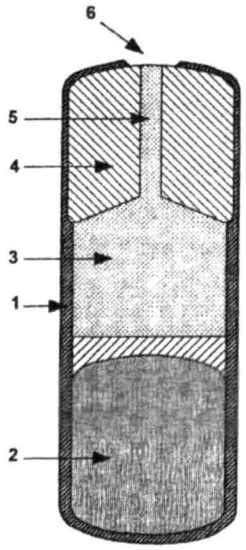


**Fig. 3: Cutaway view showing the components of the Rumisert bolus.**

**1. Injection molded semipermeable membrane, 2. Osmotic driving member (Tablet), 3. Drug + vehicle, 4. Densifier, 5. Exit passageway and 6. Exit pore.**

**Pulsatile boluses:**

Such boluses release therapeutic levels of the drug on a regular basis. A device designed by Holloway[8], has a series of compartments separated by biodegradable partitions, which degrade on exposure to ruminal contents. As successive partition degrades, drug is released periodically. A novel development based on corrosion technology and pulsed release system is the electronic bolus of anthelmintic called Autoworm-5, containing 750 mg of oxfendazole in each of five cells. The device is made up of a series of concentric tablets surrounding a central core of magnesium alloy. The tablets are slated within a series of compartments, each separated by PVC. As the core corrodes in the gastrointestinal tract, tablets are released at precise intervals of time (fig. 5)[9].

**Floating drug delivery system (FDDS):**

These drug delivery systems also called as hydro-dynamically balanced system (HBS) have a bulk density lower than ruminal fluids, and thus remain buoyant in the rumen without affecting the rumen emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate in the rumen. After the release of drug the residual system is emptied from the rumen. Generally speaking in order for a HBS dosage form to float in rumen, the density of the dosage form should be less than rumen contents[10]. Recently Jain and Agrawal have investigated floating flap of albendazole and closantel for the control of helminths in cattle for a prolonged period of 3 mo.

**Enteric coated devices:**

Wu and Sandhu[11] developed an oral delivery system for sheep or cattle that permits the system (usually a multiparticulate) to pass through the rumen without releasing the drug, and to release drug in lower gastrointestinal areas such as abomasum. One application of this technology is in the delivery of methionine to ruminants. Methionine is degraded by exposure to the microbial flora of the rumen. To prevent drug release in rumen, Wu and Sandhu used amine-containing polymers with a pKa of about 4.0, so that the polymer is non-ionized at rumen pH (approximately 5.5 to 7.0), but ionized at pH 3.0 of gastrointestinal tract. These polymers when used alone or with waxes prevent the dissolution of the coating in rumen fluids. The waxes decrease swelling of the polymer and/or drug core in the aqueous environment. Polymers such as cellulose propionate-3-morpholinobutyrate (CPMB) or poly (2-methyl-5-vinylpyridine styrene 80/20) are useful in these applications.

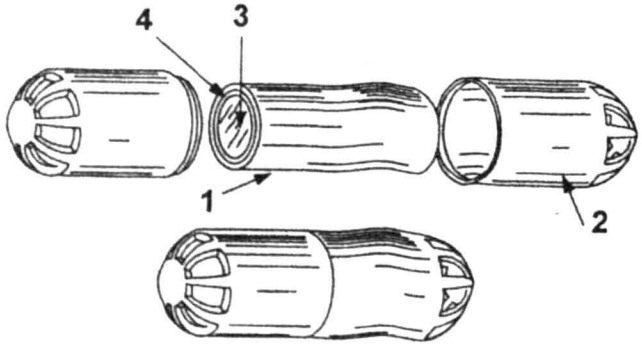


**Fig. 4: Sketch of the Rumensin ruminal delivery device (RDD) for cattle.**

**1. Metal pipe, 2. Plastic end cap, 3. Monensin core matrix and 4. Adhesive filling.**

**INTRAVAGINAL SYSTEMS**

Commercially available intravaginal drug delivery systems include;

**Controlled internal drug release (CIDR) dispensers:**

These are T-shaped devices made up of drug-impregnated elastomer coated on nylon-core. The drugs are delivered slowly over prolonged period of time. Mostly steroidal drugs are given by this device system for contraception in animals[12].

**Sponges:**

These are cylindrical-shaped polyurethane sponges impregnated with varying quantities of synthetic progesterones. Factors such as diameter and length of sponge, presence or absence of antibiotic, type of antibiotic, hormone type, age of animal, size of vagina, rectal palpitation, tail-characteristics and the sponge density, have all been used to investigate the retention characteristics[13].

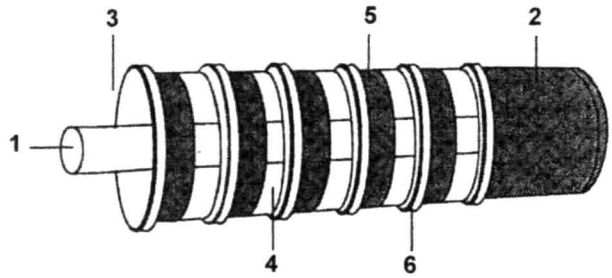


**Fig. 5: Diagram of pulsatile bolus for grazing cattle.**

**1. Core magnesium alloy spindle, 2. Steel end weight, 3. PVC starting section, 4. PVC wall segment, 5. Synanthic tablet and 6. Closing ring.**

**Intelligent breeding devices (IBD):**

This is the most recent and technologically advanced drug delivery system available for control of cattle's oestrus cycle. For example, this system delivers a pulsed dose of prostaglandin after six days and progesterone continuously over a ten day period from administration[14].

## SUBCUTANEOUS SYSTEMS

Under this category ear implants, veterinary implantable therapeutic systems (VITS) and depot injectable systems are covered. The depot preparation may contain microspheres, microcapsules and oil-based liquids of the drug substances.

**Ear implants:**

These are developed for steroids and other water-soluble compounds to enhance the production and growth. Polymers are used to sustain the delivery of drug from implants. For example, subcutaneous implants of progestogens are made by incorporating them either in hydron or in silicon[15].

**Veterinary implantable therapeutic systems (VITS):**

It is a small, implantable drug delivery system in which the active drug is kept isolated from body's aqueous environment, same as osmotic system, until released. After implantation, water from host's tissue moves across the membrane wall at a constant rate (governed by the thickness and composition of the wall); the drug reservoir and the drug is expelled through the exit-port. This system is used for delivery of proteins and peptides. From a typical VITS, the drug release is at constant and zero order, but declining and/or pulsatile release profiles can also be designed[16]. A number of highly successful implantable products have been utilized for promoting growth in cattle. These systems employ conventional technology that is proprietary to deliver hormones for growth promotion. Synovex S (marketed by Syntex) releases estradiol benzoate and progesterone for steers, while Synovex H (Syntex) releases estradiol benzoate and testosterone propionate. Ralgro (marketed by IMC) releases the synthetic hormone zeranol, which is reported to induce the release of growth hormone somatotropin from the pituitary[17].

A non-erodible system for similar application is the Compudose. This product marketed by Lilly, is a silastic implant that releases estradiol for upto one year[18]. Another sustained release formulation of reproductive hormones deposited intravaginally has been used for breeding control programmes in cattle and sheep.

**Microspheres and microcapsules as implants:**

Microspheres are monolithic systems consisting of a polymeric matrix in which the drug substance is either dissolved or dispersed, depending on its solubility. Microcapsules are reservoir systems consisting of a drug-containing core that is coated by a rate controlling biodegradable membrane. Both, microspheres and microcapsules are tested and used to deliver antibiotics, steroids and hormones in various animals[19].

**Oil-based liquids:**

Tetracycline is the best example of long acting drug formulation of this type. This antibiotic is a drug of choice for treating many enteric, respiratory and hemoprotozoal livestock diseases. It was found that the doses required were 2-3 times a day as injectables. To overcome the pain and necrosis after injection, long acting injectable was required. For that, a number of complexing agents were evaluated to increase the aqueous solubility of oxytetracycline. The caprolactum and 2-pyrrolidone were found to be excellent solubilizers. On this basis, Liquamycin® LA-200 was developed and tested. Perhaps the simplest of injectable system is the approach used by Pfizer and other companies in the development of long acting formulations of oxytetracycline[20]. A number of animal health products utilize the sesame oil approach to prolong the release of either anabolic steroids or corticosteroids.

## TOPICAL DOSAGE FORMS

For the local treatment, type of formulation and its intended use are extremely important. Various novel methods for prolonging the topical delivery of therapeutic agents over longer periods of time have been developed. Some of them are pour-on and spot-on systems, ear tags, and collars. Slow releasing pesticides for external application can take many forms including tags, strips and collars containing potent pyrethroids. Biodegradable polymers, liposomes and microcapsulated drugs under development include products for brucellosis mastitis and infectious keratoconjuctivitis.

**Pour-on and spot-on systems:**

Both these applications are dosage forms, consisting of low volume products that are applied directly over the back of animals. The staying power of these medications depends on the unique properties of the active agents and excipients that promote the adhesion of the drug to the skin.

For example, in Fontline Top Spot (Merial, London), the active ingredient gets sequestered into the sebaceous oils of the animal and gets released slowly from there[21].

**Tags:**

For the control of livestock pests, and the ectoparasites, a monolithic reservoir structure, molded into an ear tag, is stuck on the ear, similar to numbered identification tag. The tag then releases the active agent over a prolonged period of time. In most of currently available ear tags, the insecticide release profile is characterized by an initially high release rate that decreases considerably with time and eventually falls below effective levels. Membrane-based ear tags, which release insecticides at a constant rate for nearly the entire duration of release, are improved in that respect. The insecticide release is determined and adjusted by the permeability and geometry of the membrane[22]. Neckbands are also developed for controlled release of organophosphorus insecticides to cattle[23].

**Collars:**

These topical, slow-release pesticide generators are usually manufactured from a plasticized solid thermoplastic resin having either a high vapor pressure liquid pesticide distributed throughout the resin or a solid solution of an ectoparasiticide in the resin. The former releases drug vapors to the surroundings while the later releases molecules or particles of pesticide forming coating of them on the surface of collar for subsequent dispersal. Resin collars for flea and tick control in dogs and cats contain various volatile organophosphate agents.

## CONCLUSIONS

It is apparent that numerous approaches or formulations are being developed and evaluated for the veterinary use. There are a few products available in the market of European countries and many are still in the preliminary stages in the process of their development. Therefore, there is lot of scope for developing successful controlled release formulations for veterinary use for the treatment of helminthes and population control. Therefore, there is a definite need for research with an aim to develop controlled release formulations in the field of veterinary medicine.

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