Review Article

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VETERINARY DEVICES: AN UPDATED COMPILATION

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ABSTRACT:
Animals of different species and breeds have their own specifications for administration of medications and a number of them have not been used for treatment in humans hence, more extensive study and experimentation is yet left to be explored. The drug delivery needs in this segment are once a day or less frequent dosing, palatable products, and ease of dose administration for a successful commercial impact. Topical spot-on formulations are extremely popular as a convenient dosing option exclusively in cats and dogs. The market size of canine veterinary services in the world estimates around USD 324.1 million in 2018. With ever growing industry, the main focus remains towards the increasing prevalence of periodontal diseases. Periodontal diseases comprise of periodontitis and gingivitis. This is the most common condition in small animal. Therefore, effective treatment and prevention of this condition are topics of importance for current research.
Key words: PIPS, PUI, MDA, irrigant.

INTRODUCTION:

Domestication of animals have always been a significant part of human life since they provide us with basic commodities like manual labour, meat and dairy products along with leisures of companionship and recreation. They have been proved to be an integral part in improving the quality of human lifestyle since decades.

Like humans, these animals require medicines and treatments to keep them healthy hence, various veterinary dosage forms are produced for delivery of an active drug. Many similarities are seen between the human health and animal health industries. However, there are also notable differences. Special considerations like cost sensitivity, weather sensitivity, multiple breeds and species, variability in animal weights, consumer compliance and convenience, user and target animal safety and husbandry practices are needed to be considered[1]. The main formulation challenge in the livestock sector is to develop minimum cost and time associated dosage forms with ease of administration on mass treatment of herd, and human safety. Major advantages of administering drug by a controlled release mechanism through various devices, are to reduce animal stress due to restrain, handling and dosing. It also enables administration of a predetermined quantity of drug.

Several challenges involved in the design and development of veterinary products include efficiency of drug, retention time, administration and removal of products from animals that are large in size and tedious to handle. These animals have the capability to cause unintentional harm to the user during forced administration, with limited opportunity of self medication. In such cases, various administrative devices or applicators which facilitate loading of the drug, and then administering on the site of

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administration, which are operated by the user are developed.

These provide us with:

- A form of administration method
- Retention mechanism built into its design
- Human safety

These applicators are mainly balling gun (for rumen products), applicators (for intravaginal products), and implanters (for subcutaneous implants).[2]

The efficacy of any dosage form depends on its retention and absorption from site of administration for the duration of the treatment period. Poor retention rates reduce the overall efficacy of treatment. Rumen products retain in the rumen of the farmed animals either through its innate geometry or by the addition of density agents. Intravaginal drug delivery systems utilize an 'expansion mechanism' to retain the device in the vagina for the duration of treatment. In both cases, the products remain in the animal for the duration of treatment whether this is 7-10 days for intravaginal products or up to 12 months for ruminal products.

Since the majority of products administered to farmed animals are not biodegradable, it requires some means of removal from the animal at the end of the treatment period. Removal must be a simple process, be non-invasive (which do not require surgery) without damaging or harming the animal. The size and shape of an intravaginal and ruminal drug delivery system is complex and key considerations in the final design revolve around it being safe to use and not cause damage to the animal upon insertion, while in place and during removal. Typically tail is added to the design of intravaginal insert to aid the removal easily. The tail should not interfere in the administration procedure, and should be long enough to protrude out of the vulva after the insert has been administered and extrude sufficiently so that an end user can grasp and pull it smoothly out of the vagina without slippage. The tail is usually made of plastic and is blue in color and curved so that it hugs the contour of the rear end of the animal. Interestingly rumen products are not removed after treatment and they remain inside the rumen for the life of the animal. Indeed, 6-10 spent devices can be found in the animal's rumen after dissection.[3]

In addition, a characteristic of a veterinary product is its high drug load. Intravaginal delivery systems are also characterized by poor drug utilization which leads to a high residual content after removal. In contrast, ruminal products exhibit high drug utilization (100%)[4].

Injections, feed additives, ruminal boluses, and topical pour-on are commonly used for drug administration to livestock. Medicated collars, sprays, powders, shampoos, spot-ons and palatable tablets are commonly used for companion animals.

The Federal Food, Drug, and Cosmetic Act defines a veterinary device, as "an instrument, apparatus, implement, machine, contrivance, implant, in-vitro reagent, or other similar or related article, including any component, part, or accessory

thereof, which is intended for use in the diagnosis of disease or other conditions; in the cure, mitigation, treatment, or prevention of disease in man or other animals; or which is intended to affect the structure or any function of the body of man or other animals.[5]

CLASSIFICATION OF VETERINARY DELIVERY DEVICES [6]

Because of the variety of dosage forms in veterinary medicine and the diversity of animal and bird species treated, drug or dosage delivery sometimes requires the development of specific devices to ensure fast, safe, effective and low cost efficient treatment.

There are two ways of classifying veterinary devices:

1. Based on usage,

1.1 Those used to administer the dosage form to the animal.

1.2 Those which meter drug from its site of implantation, insertion, ingestion or attachment to the animal over a potentially long period of time.

2. Based on route of administration,

2.1 Oral devices

2.2 Topical devices

2.3 Nasal and pulmonary dispensers

2.4 Parenteral devices

2.5 Implanting Devices

2.6 Ophthalmic Devices

2.7 Injectable-implantable systems

2.8 Intravaginal drug delivery systems

2.9 Intrauterine Drug dispensers

2.1 Oral devices

These are used for administration of various major oral dosage forms for veterinary use like,

- Tablets and boluses
- Capsules
- Feed additives
- Drinking water medication
- Oral pastes and gels

Devices used for oral delivery include:

a. Balling guns
b. Esophageal delivery devices
c. Drenchers
d. Paste Dispensers
e. Water medication metering devices
f. Rumen lodging devices
g. Hollow bits
h. Non pyloric passage devices
i. Miscellaneous oral dose dispensers
j. Miscellaneous oral dose dispensers

a). Balling guns

Due to the presence of the fact that it is not easy to push a pill or any other medication down a large animal's throat, veterinarians use balling guns. Balling guns are simple to use devices, used for administration of bolus or solid dosage forms to animals and it is available in various sizes for different species. It consists of a tube with a holder for medication, usually a capsule, at one end and the plunger is pushed on the end of the tube to force the medication into the animal. This technique is extensively used for animals like cattle, horses, pigs, sheep and

goats. Depending on the dose balling gun can be classified broadly as,

- a single dose or
- multiple dose

Single dose balling guns have the capability to accommodate bolus of a number of sizes whereas, multiple balling guns can be loaded with one or several boluses of the same size. The boluses are held in the barrel usually by a flexible constriction at the barrel tip. Bolus delivery, which is based upon distance of plunger travel in the barrel, can be adjusted to deliver one or several boluses sequentially. While use, the bolus is placed in the cup or barrel of the balling gun and with the animal's head immobilized, the tube is passed along the midline of the roof of the mouth over the base of the tongue. The tongue may have to be pulled out if it obstructs the tube. When the animal swallows, the tube is pushed gently into the gullet, the handle is squeezed, and the bolus is gently expelled.[7]

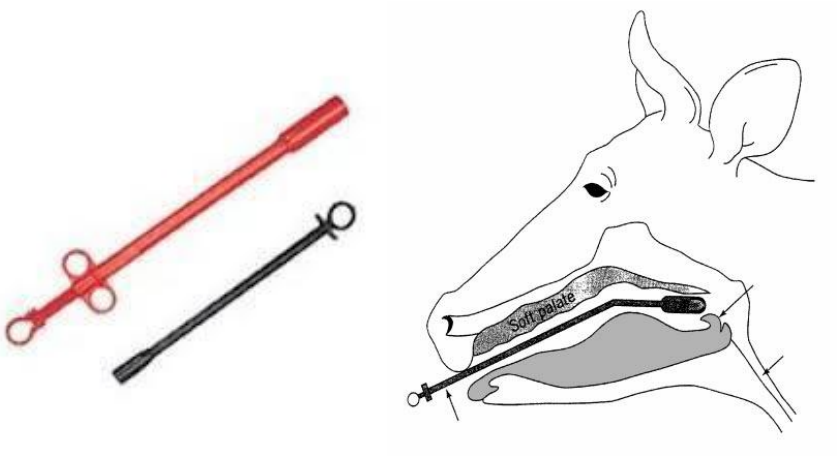

Fig. 1: Balling gun

Source: http://www.southernstates.com/catalog/p-5911-calf-balling-gun-white.aspx

b). Esophageal delivery devices

These are used for direct administration into the stomach of an animal. They are proven to be advantageous for efficient and professional administration, availability of the entire dose into the stomach, substances causing esophageal or pharyngeal irritation and lesions, i.e. carbon sulfide and chloral hydrate are administered successfully. Also used for delivery of feed, water and medication in cases where the animal is unable or refuses to eat.

Esophageal administrative devices of medication are of two types

i. Syringes

ii. Tubes

Syringes- Types of syringes available are,

- Regular dosing syringes, facilitating direct stomach delivery by adaption of a dose tube attached to the barrel outlet. Usually consists of flexible tubes with a rounded or ball tip end for prevention of trauma. Size of the tube could be from 12 inch or more in length and 3/16 to 3/8 inch in external diameter.
- Dose pipe, for delivery of the barrel to stomach through the esophagus.

This syringe consists of a pipe with pear shaped distal end and is generally used on cattle with a body weight >200kg.[8]

Fig. 2: Syringe

Source: http://hambydairysupply.com/xcart/home.php?cat=92

Tubes – It maybe used to deliver liquid medications. Syringes, injections, pumps and funnels are used to deliver the medication to an esophageal tube which is inserted through a speculum either in the mouth or a nostril, completely into the stomach. The tube should be well lubricated so as to fully pass through and reach the stomach. It is advantageous for delivery of substances causing pharyngeal or esophageal irritation. Esophageal tubes may vary in sizes from catheter size for feeding puppies to 1-1/2 inch for washing out of rumen. [8]

Fig. 3: Tube

Source: http://www.bestforbreeder.com

c). Drenchers

Drenching is the administration of drug by pouring down a liquid medication through an animal's throat and drenchers are the devices which facilitate this oral administration of medication in animals using various equipments based on the basic concept of a syringe. They deliver desired volumes of the solution or suspension to the gullet through a preset volume or an adjustable hypo drench. These can be automatic or non automatic.

Automatic, in which the drenching syringe refills automatically from an inverted or upright reservoir connected through a tube after each dose has been dispensed and, non automatic, in which the medication is drawn into the barrel by dipping of nozzle into the liquid either by a rubber bulb or a plunger after every dose is administered.

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Fig. 4: Drench syringe

Source: www.agri-pro.com/products

Fig. 5: Drenching gun

Source: www.pinterest.com

Drenchers can also be explained as,

Liquid drench guns

These are guns used for an easy and fast delivery of oral, viscous solutions and suspensions of aqueous or oily nature. Liquid drench guns are of three types

1. Single dose gun, for large volume distribution.
2. Multidose drench gun, for administration of drench in steps.
3. Automatic drench gun, where the chamber is refilled directly from a large volume reservoir.

Powder drench guns

Administration of powder formulations on large animals can be achieved using powder drench guns. The required amount of powder is poured into the barrel and inserted in the mouth, the trigger is pulled and powder sprayed in the mouth. Following administration, powder adheres to inside of the mouth, mixes involuntarily with the saliva and is swallowed.

Fig. 6: Powder drench gun

Source: www.thefarmstore.com

f). Paste Dispensers

Paste dispensers are popular for delivery of formulations of insoluble compounds which can be suspended in pastes or gels. The medication is administered by depositing the dose on the posterior portion of the tongue through interdental spaces. The advantage of a paste formulation being that it cannot be expelled from the mouth as easily as a tablet or capsule. Paste formulation for oral administration to animals may be delivered by,

i. Paste guns
ii. Paste syringes
iii. Squeeze bottles
iv. Squeeze tubes

Fig. 7: Paste dispenser

Source: http://www.bestforbreeder.com

g). Water medication metering devices

The animal might not eat during the illness period but will continue to drink water which seems to be the major advantage of medicating through drinking water. For treating large numbers of animals, automatic metering devices or medication proportioners are used.

Medications formulated as dry powders for reconstitution or concentrated solutions of the medications are dispensed directly in drinking water or injected into the drinking water through the proportioners. Regulated amounts of soluble drug are added to the drinking water for accomplishment of medication of a large number of animals or birds. Since animals drink twice as much water as they consume feed, the drug concentration provided is half of that in the field. Medicaments, vaccines, Wormers, electrolytes, disinfectants and antibloat

surfactants are administered usually through this method.

Fig. 8: Water medication metering device
Source:
http://www.fatcow.com.au/t/Animal-Medical-Supplies

h). Rumen lodging devices

Ruminants are animals with stomachs composed of four chambers. The largest of these chambers is the rumen which is a region where the drug formulation is housed and retained, acting as a drug loading site or a large fermentation tank. The drug formulation is directly injected into the rumen through the flank of the animal. Devices with a sufficient density or having an ability to expand in dimension is a necessity to prevent it from being regurgitated with food or moving through rest of the gastrointestinsla tract. The device is used to administer drugs or minerals to rumen of the ruminant for over a prolonged period.

Some examples of commercially available rumen lodging devices are:

Figure 9: Paratect flux bolus
Source: [2]

The paratect flex bolus is a flat trilaminate sheet rolled into a cylindrical shape prior to administration which allows the device to be administered via back of the throat. Following administration, the water soluble film used to retain its configuration, dissolves and unrolls. It is however withdrawn from the market due to economic reasons.

Figure 10 : Captec device
Source: www.researchgate.net

The captec device comprises of a hollow tube containing drug formulation, a delivery orifice of a fixed diameter at one end and specially designed wings at the other end. The wings are held along with the tube using water soluble tape which upon administration dissolves, allowing the wings to spring open to form a shape that cannot be regurgitated by the animal.[2]

i). Hollow bits

It is a device mainly for administration of medicaments in horses. The active ingredient is incorporated in a compartment in the bit in the form of a confection. Heat from the horse's mouth and its salivary action is responsible for gradual elution of active ingredient through perforations in the hollow bit.

Fig. 11: Hollow bits

Source: www.thefarmstore.com

j). Non pyloric passage devices

Devices larger than the pyloric opening can be retained in the animal's stomach for an extended period of time. However, the major disadvantage being difference in the diameter of pylorus among animal species and large dimensions of the device, making it difficult to swallow.

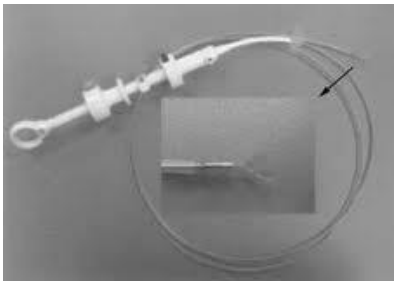

Fig. 12: Non pyloric passage devices

Source: www.thefarmstore.com

k). Miscellaneous oral dose dispensers

i. Pump type dispensers – ball valve dispensers for delivery of 1 ml administration of solutions, suspensions and emulsions to small animals.

ii. Nursers – plastic bottle with a specially designed bottle for easy, nontraumatic delivery.

iii. Droppers – solution of 1 ml or less is dispensed from graduating volume indicators on the dropper tube.

iv. Mineral dispensers –constructed of concrete for the delivery of mineral mixes

v. Mouthpieces – specialized dose pipes to ensure entire delivery of liquid down the animal's throat

2.2 Topical devices

The topical dosage forms for veterinary use mainly include solids (dusting powders), semisolids (creams, ointments and pastes) and liquids (suspension concentrates, solutions and emulsion concentrates).

a. Pour on, spot on application

b. Dust bags

c. Spray race and dip

d. Teat dip

e. Flea and tick collars

f. Percutaneous devices

a). Pour on, spot on application

These systems consists of low volume products and are in liquid form that affect the systemic activity after pouring on the animal's backline and are applied as one-spot concentrate on animal rump. The oils from the drug are mixed with the natural oils that are non-toxic to the animal skin and they act as neurotoxin against the ectoparasites. These spot on are generally used in case of cattle in order to control the grubs and lice. Example: levamisole, a broad spectrum antibiotic is used as pour-on/spot-on product. These formulations contain insecticides or anthelmintics dissolved in

organic solvents. The main advantage of this system is that no special skill is required and even sterile precautions are not necessary. The speed of treatment is quick in this case as well.

Fig. 11: Pour on, spot on the application
Source: http://parasitipedia.net

b). Dust bags

The animals are treated with insecticide powders through dust bags. The dosing is achieved through the brushing of animals against the bag while walking or sitting on it. The bag contains inner porous and is protected from the outside elements by an outer protective waterproof layer with an opening at the bottom. The animals can opt for free-choice applicator dust bags. These bags are hung in doorways, lanes, gateways, etc., so that dosing is achieved through passing by of animals.

Fig. 12: Dust bags
Source: www.animalsupply.com

c). Eartags

The flies and ectoparasites can cause problem in the cattle resulting in decreased milk production and weight gain of cows and their calves. So, it is economically important to control flies and ectoparasites. The most common dosage form for the medication to control the livestock pests is monolithic or reservoir structure which can be incorporated into an ear tag. This ear tag can release drug for a prolonged period of time, may be for several months. The active ingredient can be administered or transferred to the animal skin by the natural movement of its ear or movement of the body which can be later transferred to other animals as well. The main challenge faced is that the insects may develop resistance towards the insecticide. To solve such an issue, Herbig et.al developed a membrane based ear tag that released the insecticide for a prolonged period of time at constant rate[9]. The insecticide release can be altered by changing the permeability and geometry of the membrane. Neckband systems have also been developed for the delivery of organophosphorus insecticides in a controlled manner to the cattle[10].

Fig. 13 : Eartags

Source :www.pbsanimalhealth.com

d). Spray race and dip

For controlling of external parasites, dipping is used extensively for sheep and cattle. Dipping vat is a portable unit or a permanent in-ground structure which is protected from direct sunlight by roofing. The chemicals used in dips are usually formulated with aqueous solutions, emulsifiable concentrates or suspension concentrates. All of these are diluted with water prior to use. The dip formulation is diluted with water in a large bath tank and should be deep and long enough so that the animal is completely immersed into it. Challenges such as stability and inactivation of the active pharmaceutical ingredient throughout a range of concentrations and temperatures should be a check. In addition, the formulation should be toxic to the parasites but not to the animal. These formulations are used in both small and large animals.

The concentration of the pesticide should be maintained in case of plunge dips as recommended by the manufacturer. Stripping of the active ingredient is main problem faced in case of dipping of sheep and cattle. In this case pesticide loss from the dip wash occurs at a significant rate than water loss and categorized as mechanical or chemical stripping. Chemical stripping is caused by absorption of pesticide by fleece. Mechanical stripping resulted from the fleece which acts as a sieve towards the active drug. To avoid such stripping, a complex dip management regimen should be carried out. This regimen includes reinforcement and 'topping up'. Reinforcement is referred to as addition of undiluted drug to the dip vat. Proper dip management helps in minimizing the contamination of the dip with organic matter.

Shower dips are referred to as typical shower type sump containing the dip wash, a pump and a showering pen which is constructed with a concrete floor and fitted with an overhead rotating boom with nozzles and fixed nozzles near the ground level. In the case of shower dips, proper dip management requires attention. A special attention in case of dips is that sheep should not be dipped by either plunge or shower dip until the shearing wounds have been healed to avoid infections[11].

Fig. 14: Spray race

Source : http://parasitipedia.net

e). Flea and tick collars

The most commonly used dosage form for ectoparasites control in companion animals such as dogs and cats is the ubiquitous flea and ticks collars. The basic technology in these collars is that the active ingredient is

blended into the plastic solid thermoplastic resin. They are also known as slow release pesticide generators; vaporous and powder producing collars. The vaporous collar contains high pressure liquid pesticide which is mixed evenly in the collar. The active ingredient i.e. the pesticide is released at a slower rate without being toxic to the skin of the animal[12].

The powder producing collars contains solid and non-volatile solution of the drug in the resin. As the two materials are non-compatible, the non-volatile pesticide preferentially diffuses to the surface and gets distributed across the coat. This process is known as "Bloom" resembling a dust or powder on the collar surface. Powder producing collars have an advantage over vaporous that the powder expands the contact area allowing it to continue to control the ticks and fleas[13].

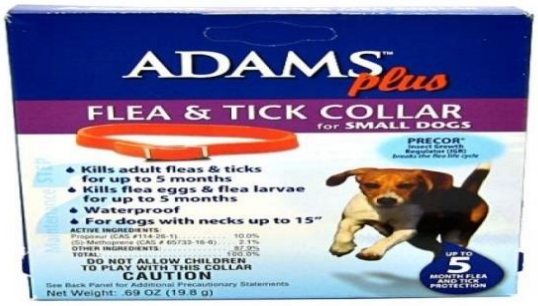

Figure-15 Marketed Flea and Tick collar
Source:http://www.petmountain.com

f). Percutaneous devices [6]

1) Topical reservoir – A depot device on attachment to the skin of an animal enables controlled percutaneous absorption of the active drug moiety. This provides a constant, easily terminated, prophylactic drug delivery over a period of hours, days, weeks or months.

2) Ear tampon – A cylindrical resilient absorbing materials is placed in the ear cavity of animals to deliver growth stimulating hormones, corticosteroids, antibiotics and other medicaments for prolonged periods of time.

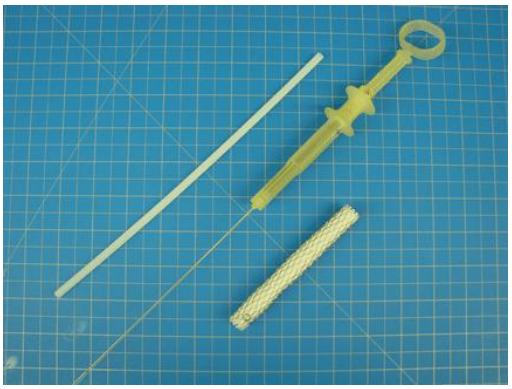

Fig. 16: Percutaneous devices
Source: http://www.atechdesigns.com

2.3 Nasal and pulmonary Dispensers

Aerosol dispensers provide medication in the form of spray, stream, quick break foam or stable foam directly to the affected areas. Also, there are devices exclusively used for local effect in the pulmonary and nasal areas through airway conduct of drugs, inhalation anaesthetics and toxins . Drug inhalation is found to be productive in small animals suffering from canine bronchitis and kennel cough. Species to species designed metered dose nebulizers are also seen to be prevalent. [14]

Fig. 17: Animal nebulizer

Source: http://www.flexineb.co.nz

2.4 Parenteral devices

Though oral route continues to be the primary route of administration, the parenteral route offers diverse advantages in drug delivery. Some of the drawbacks covered by parenteral delivery can be overcoming the physical challenge of oral dosing, minimizing of interspecies variability caused due differences in oral absorption of different species.

a). Single dose syringe

Fig. 18: single dose syringe
Source: http://store.palmtreesaver.com

b). Multiple dose syringes

Multi-dose syringes for use in breeding stock.

Fig. 19: Multiple dose syringes
Source: http://store.palmtreesaver.com

c). Automatic syringes

The vial holder model of this automatic syringe is often used for vaccination or injection of swine.

Fig. 20: Automatic syringe
Source: http://www.nechmad.com

d). Multi compartment syringes

Contains separate compartments to occupy two or more substances.

Fig. 21: Multi compartment syringe
Source: http://www.nechmad.com

e). Pole mounted syringe –Drug formulation can be delivered to remote administration sites. It contains long needles with housing which provides support and prevents its breakage.

f). Mastitis syringes - Used for delivery of drug formulation to the site of infection in a cow with mastitis. Needles can be inserted directly into the mammary gland through the teat canal.

g). Jet injectors – Operates under extremely high pressure to expel out the dose of liquid medicaments against epidermis of the animals. Used for vaccination of a large number of animals and birds.

h). Projectile delivery system - Used to deliver drug parenterally from a distance.

2.5 Implanting devices

These are small sized devices to be incorporated beneath the skin surface, subcutaneously or intramuscularly.

Veterinary implantable therapeutic systems: These systems are small

implantable drug delivery systems in which the active ingredient is kept away from the body aqueous environment until the drug is released. It is designed in such a way that drugs such as somatropins, parasiticides, oestrus suppressants and growth promoters, antibiotics in both food producing and companion animals is released for a longer period upto one year[15]. They have used in the animal health industry since 1950 for production enhancement. Compressed tablet implants of estrogenic anabolic steroids were administered for the improvement in feed conversion and the rate of weight gain in the cattle. The implants are composed of impermeable drug reservoir which contains the drug and a rate controlling membrane. The piston present in the implant isolates the osmotic pressure and the water from the animal's body moves across the membrane wall at a constant rate. The body water displaces the piston towards the drug reservoir and expels the drug out. The drug release is constant and zero order. With the help of implants, small dosages are delivered from microgram to milligram per day[16]. For example: Alzet® osmotic pump is an implantable delivery system releases drug at a predictable rate at fixed time intervals. This system is used in exotic cats and in pony mares to induce fertile ovulation and oestrus.

Ear implants are also used to deliver sufficient quantities of either natural or synthetic progestagen. They are inserted under the skin of the ear. The implants are formulated using progestagen incorporated into one of two polymers, hydron or silicone[17]. For example: Synchro-Mate-B® is an ear implant which is commercially available for cattle. This implant contains norgestomer incorporated with hydron polymer and is implanted into the outer surface of ear. But the main problem is this system is declining of release profile. To overcome such problem Synchro-Mate-C® is formulated using dispersed crystalline norgestomer in the microreservoirs of aqueous polyethylene glycol 400 (PEG 400) throughout the matrix of polymerized silicone. This implant showed a better biological effectiveness. Another example of ear implant is Compudose®, Melovine®, Synovex®, Ralgro® and Crestar® (Fig-21).

Fig. 22: size scale of implants
Source:http://www.web.imu.edu.my)

Table 1: Marketed implants

Trade Name	Company	Dosage Form	Application	Strength

Synovex® S Synovex® C (Progesterone Estradiol Benzoate)	Zoetis Inc.	Subcutaneous Implant (pellet)	Increased rate of weight gain and improved feed efficiency.	100 milligrams progesterone and 10 milligrams estradiol benzoate (one implant consisting of 4 pellets, each pellet containing 25 milligrams progesterone and 2.5 milligrams estradiol benzoate) per implant dose
Ralgro® Magnum Ralgro® Implants (Zeranol)	Intervet, Inc.	Subcutaneous Implant (pellet)	For increased rate of weight gain and improved feed efficiency in steers fed in confinement for slaughter	Each pellet contains 12 milligrams of zeranol

Fig. 23: Marketed Implant
Source: www.valleyvet.com

2.6 Ophthalmic Devices

In veterinary healthcare, the eye infections currently have therapeutic regimen which require instillations of the ophthalmic drop solutions containing antibiotic. But the problem while administration of eye drops is, it leads to poor bioavailability of the drug and needs simultaneously instillations to reach and maintain the therapeutic levels. To overcome such problems, ophthalmic inserts are a good alternative to the eye drops. The advantages of ophthalmic inserts is such that, it requires less frequent administration, increases the adherence time of the drug with the conjunctival tissue, thus ensuring a satisfactory topical or systemic treatment[18]. Ophthalmic inserts are defined as formulations with a solid or semisolid consistency, with shape and size is specifically designed for ophthalmic application. Soluble inserts are mostly used as they get entirely solubilised with time without the need of removal[18]. They are generally placed on the lower fornix of the cornea. Drugs such as antibacterial, anti-glaucoma, anti-inflammatory, anti-viral and mydriatic agents are generally administered by these systems. Example- Biodegradable ocular inserts of gentamycin are used for treatment of infectious bovine keratoconjuctivitis and for treatment in dogs[19] (Vetoquinol, Lure, France; not yet in market).

2.7 Injectable-implantable systems

To control the accurate oestrus and ovulation cycle, such systems are found to be of great importance. The main objective

is to control the oestrus in all selected females in a herd, so that all can be inseminated using the semen at the same time for special breed characteristics[20]. A variety of liquid vehicle hormones are administered through injection in form of controlled release delivery systems for controlling the oestrus cycle mainly of cattle[21].

2.8 Intravaginal drug delivery systems

The vagina of the farmed animals acts as an attractive site for the drug delivery. The advantages of intravaginal delivery of pharmacological active compounds in the veterinary are that this system can be administered with ease and can be removed without any damage to the mucosal tissue[22]. Such damage is associated with injections administration which can be painful and stressful to the animals. The vaginal biological properties are conducive to drug delivery and its ability to retain the delivery systems for prolonged weeks as the vagina of livestock readily tolerates the gentle pressure applied to the mucosa. All the intravaginal inserts produce the required biological responses to control oestrus cycle of farmed female animals. Although this system is sex specific and there is uneven distribution of females within the animal population, thus serving majority of the population owned by the farmers. Drugs those are susceptible to hepatic or gastrointestinal metabolism, vaginal route may provide an alternative to that of the oral administration[4]. Several commercially available intravaginal veterinary drug delivery systems have been developed for the administration of natural and synthetic hormones such as progesterone, estradiol benzoate, methylacetoxy progesterone and fluorogestone acetate. The commercially available inserts are usually in T-shape[23]. These include CIDR®, polyurethane sponges of various sizes, electronically controlled inserts (Intelligent Breeding Device and EMIDD) and PRID. These are capable of delivering multiple drugs at a predefined time, either pulsed or continuous fashion. Progestins are the most commonly used reproductive drugs in the veterinary medicine so, the research of long acting intravaginal inserts incorporating hormones are welcomed for the delivery of progestins[24]. Bunt et.al formulated bovine intravaginal insert for the delivery of progesterone using poly (ε-caprolactone).

Table 2: Example of an intravaginal insert

Trade Name	**Company**	**Dosage Form**	**Application**	**Strength**
EAZI-BREED™ CIDR® Cattle Insert (Progesterone)	Zoetis Inc.	Intravaginal insert	Improve the effectiveness of reproduction programs	Each insert contains 1.38 grams of progesterone in molded silicone over a nylon spine

a) Controlled internal drug release dispenser (CIDR®)

It is a T-shaped insert which is constructed of medical silicone elastomer moulded over a nylon core comprising a homogenous dispersion of 10% w/w progesterone. These include CIDR-B (CIDR 1900) (figure-12) for cattle, CIDR-G for goats and CIDR-S for sheep. CIDR-S is no longer available in the market[25]. Other species such as deer, horses and buffalos have been under observation for the potential application of these intravaginal drug delivery systems[26]. INVAS is also an intravaginal system which consists of a flexible T-shaped spine coated with silicone matrix in which progesterone is homogeneously dispersed. This system offers an advantage over CDIR-B is that the material used for the spine does not have to exhibit high heat resistance, allowing a wider range of materials to be used[25]. PCL intravaginal insert is also T-shaped and the insert is a single piece injection moulded device comprising of homogenous dispersion of 10%w/w progesterone using biodegradable polymer polycaprolactone. It can be formulated at around 80ºC temperature. During insertion, it retains its physical properties due to slow rate of degradation, but after insertion it gets completely degraded[26].

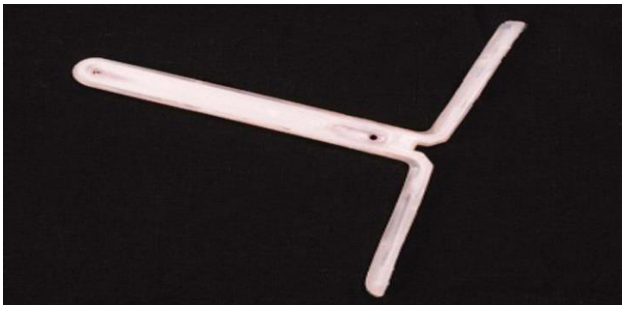

Figure-23

(Source:http://www.web.imu.edu.my)

b) Sponges

These systems are cylindrical shaped polyurethane sponges which are impregnated with varying quantities of synthetic progestogens[27]. Some factors are varied in order to explain the variable retention characteristics of progestagen – loaded sponges used in cattle. Factors are diameter, length, presence or absence of antibiotic, type of antibiotic applied, age of the animal, size of vagina, hormone type, rectal palpitation, tail characteristics and sponge density[28]. Commercially available sponges for sheep and cattle are Synchro-Part and Synchro-Part PMSG (pregnant mare's serum gonadotrophin, CEVA).

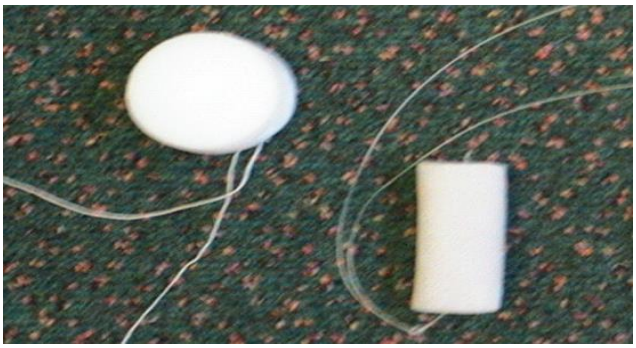

Figure-24

(Source:http://www.web.imu.edu.my)

c) Progesterone-releasing intravaginal device (PRID)

PRID is commercially available, was first developed for cattle which is now under investigation for buffalo and horses. PRID is comprised of silicone rubber impregnated throughout with micronized progesterone which is moulded into a stainless-steel spiral coiled to produce a spiral-shaped cylinder.

This delivery system has a hard gelatin capsule which is attached to its inner surface and a string for easy removal. PRID delta is also available which is a triangular in shape[29]

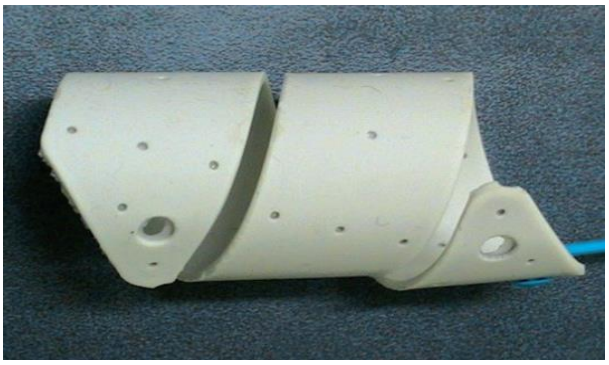

Figure-25

(Source:http://www.web.imu.edu.my)

d) Intelligent breeding device (IBD)

It is the most recent and technological upgraded controlled-release drug delivery system which is used to control the oestrus cycle in cattle. It has an 'umbrella' retention mechanism. This innovative system uses electronics in order to control the release of progesterone from the intravaginal insert. It comprises an outer plastic sheath which is designed to control the electronics which control the rate and time of release of the actives, four drug reservoirs, a retention mechanism and a tail. To control the oestrus cycle precisely, IBD system is designed in order to deliver progesterone continuously from the large drug reservoir over a ten-day period, a pulsed dose of prostaglandin six days after administration and a pulsed dose of estradiol one hour after administration. The product was redeveloped and was re-introduced as the Smart-1 in the market of New Zealand. This product has specially designed rubber retention mechanism which is glued to the back of the animal, rather having wings for retention inside the vagina of an animal during insertion[22].

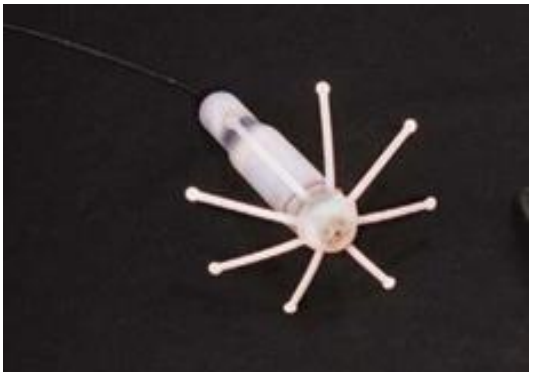

Figure-26 Intelligent Breeding Device

(Source:http://www.web.imu.edu.my)

e) Others

Few other intravaginal inserts include the Cue-mate, which is a wishbone-shaped intravaginal insert is used to provide an opportunity to re-use the supporting spine upon which removable silicone fluted pods is fixed onto. TRIU-B intravaginal insert has a unique cross-shaped structure which is purported to allow for a better anchorage, while minimizing the device losses and local inflammatory reactions. Another shape included the DIB-V intravaginal insert which has a V-shape design[2].

Figure: 27 Cue-mate

Source: http://www.web.imu.edu.my

2.8 Intrauterine drug dispenser

Intrauterine drugs dispensers in animals have a similar effect as that in humans' i.e.

to release its cellular and humoral components into the uterine cavity due to the induction of a local inflammatory reaction[30]. They are useful in local and systemic delivery in animals for local effect of prostaglandins, anti fertility agents and oxytocic agents. Drugs with short biological half life can be also act as a candidates for intrauterine delivery.[6]

2.9 Updated options for periodontal therapy veterinary devices

The market size of veterinary dental equipment in the world was around USD 324.1 million in 2018. Further growth of about 7 -8 % is expected during the upcoming period. The growth rate would primarily be driven by increasing prevalence of periodontal diseases. Periodontal diseases comprise of periodontitis and gingivitis. Periodontal disease is the most common diagnosed problem in small animal veterinary medicine. Therefore, effective treatment and prevention of this condition are topics of importance for current research.

BONE REGENERATION

Bone Regeneration lost through periodontal disease is an important targeted therapy. Guided tissue regeneration (GTR) has been existing for a long time, but recent innovations in bone grafting and barriers have highly increased the success rates. Regardless, very limited conditions qualify as good prognosis for bone regeneration. The most suitable prognosis is seen with walled periodontal pockets typically seen on the palatal aspect of the maxillary canine and distal aspect of the distal root of the mandibular first molar and lesions with Stage 2 furcation. Those are the most common conditions in small breed dogs. Numerous patients can be treated through these procedures [31-33].

The theory of GTR is that the downward growth of faster healing soft tissue must be inhibited to attain the slow growing bone. This facilitates periodontal ligament to repopulate the periodontally induced bony defect. The procedure involves Creating a periodontal flap, performing open root planning, create a clean root surface for healing, Filling the defect with bone augmentation, Placing a barrier membrane. Numerous products are used in humans, but the products of choice for most veterinary dentists are cancellous freeze-dried demineralized bone for the graft and demineralized laminar bone sheets as the membrane[31-34].

Numerous products have been explored in addition to the current therapies for the treatment of periodontal disease [34]. These approaches can be classified into four different areas:

1. Removal of infectious agents (pathogen control)

2. Reduction of inflammation and/or bone destruction by the host (host modulation)

3. Regeneration of lost alveolar bone (guided tissue regeneration)

4. Consideration of implants.

Therefore, they provide a good option for maintaining teeth and removing a potentially infected or painful tooth earlier

in the course of disease. If an implant could be performed

in a pet with advanced disease, it may convince the client to remove an infected tooth.

Some have voiced concerns that there is minimal clinical evidence that these procedures work in veterinary patients. However, most research for humans was performed on dogs, and the results were very positive. The other issue with this form of therapy is the numerous anesthesias required, but advances in technology and techniques will likely improve this in the near future. Adequate bone density is needed to accommodate this type of therapy.

CONCLUSION:

Animals of different species and breeds have their own specifications for administration of medications and a number of them have not been used for treatment in humans hence, more extensive study and experimentation is yet left to be explored. Obstacles mainly include the varying anatomy and physiology, varying sizes and weights of animals giving the need to devise some method of administering the product into the animal.

The drug delivery needs in this segment are once a day or less frequent dosing, palatable products, and ease of dose administration for a successful commercial impact. Topical spot-on formulations are extremely popular as a convenient dosing option exclusively in cats and dogs. There is a continuing need for long acting injections and implants. Whereas, intravaginal delivery are advantageous in less stressful administration as compared to injections and provides the privilege of termination of delivery at will.

Recently approaches have been more inclined toward controlled drug delivery systems since it provides unique opportunities to the formulation scientist therefore, several potential opportunities exist for application of drug delivery in animals. Development of biodegradable and non surgical dosing of implants also show a promising future since dosing of herds with implants are particularly challenging.

Also, 'No needles' is seen as a high priority need in livestock animals due to several reasons like:

- Meat consumer safety concern
- Laborious and requires animal restraints
- Risk of injury

Conclusively, animal health sector remain a fertile area for formulation and drug delivery research since human health and animal health move in synergy in terms of therapeutic area and animals are a value added to human life.

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