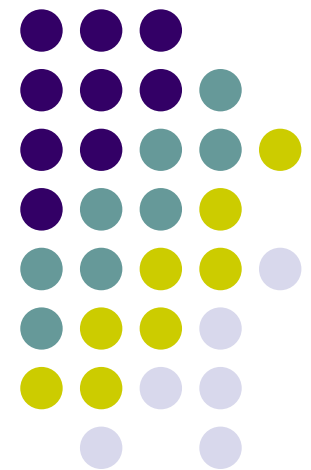
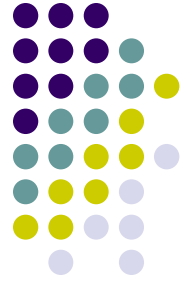


# *Aspects of Veterinary Therapeutics*

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**Robert Falcone**  
**Nice Pak Industries**  
**New Approaches and**  
**Technologies in Oral Drug Delivery**  
**NJCRS Spring 09 Workshop**

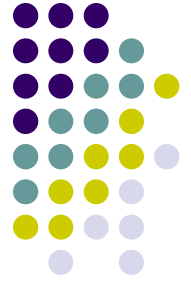




# *Aspects of Veterinary Therapeutics*

## Overview

- **Rationale**
- **Why Oral Route**
- **Current Technologies**
- **Future Trends**
- **Q&A**



# *Aspects of Veterinary Therapeutics*

## Rationale

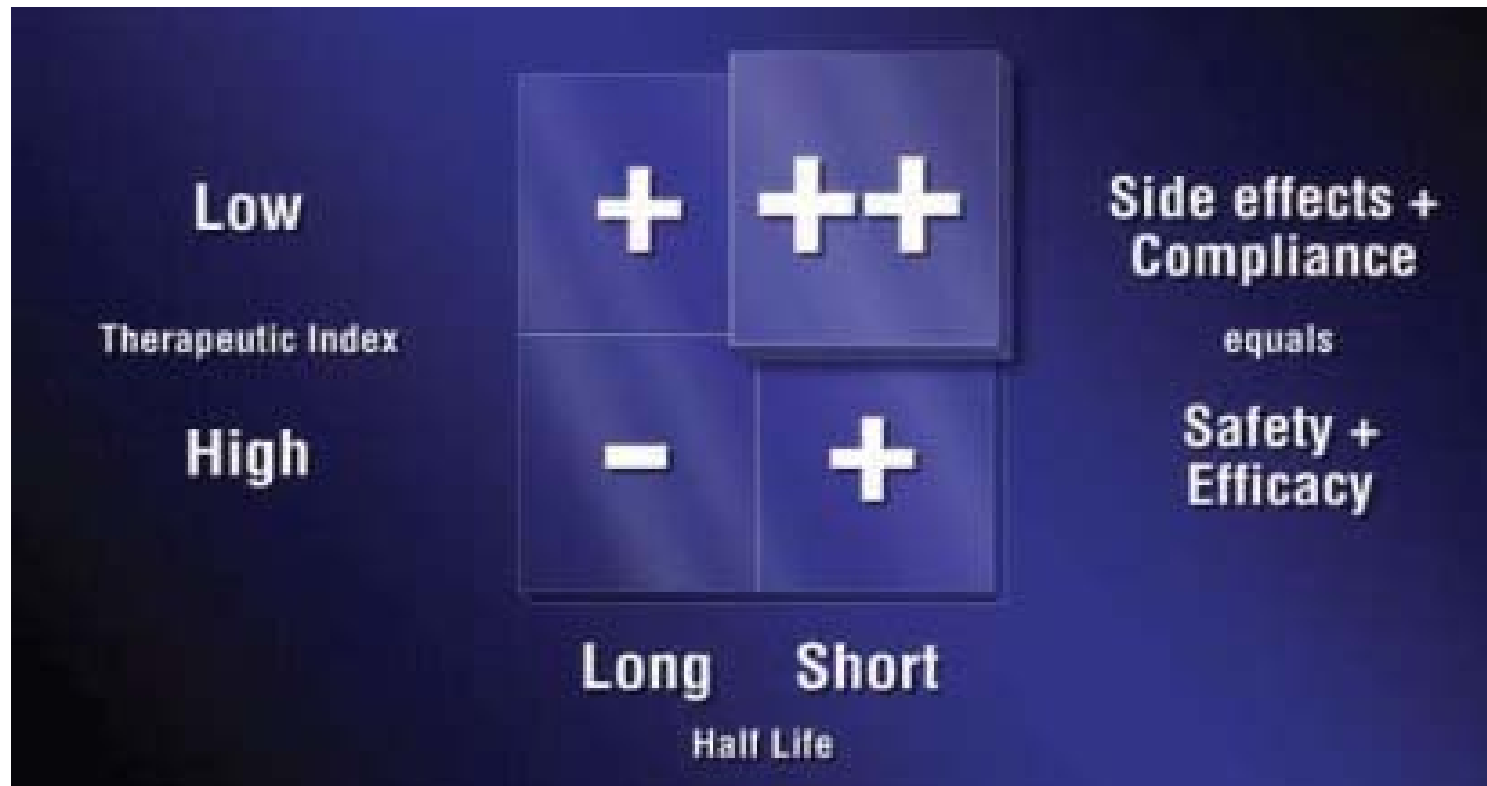
Within the USA, an estimated US\$30.5 billion dollars was spent in 2001 on R&D by research-based pharmaceutical companies. Of this amount, only an estimated US\$0.6 billion dollars was spent on pharmaceuticals for veterinary use (<http://www.Pharma.org/publications/>). The Animal Health Institute (AHI) reports that the total amount of animal health product sales in 2007 accounted for US\$ 19.7 billion US dollars (<http://www.AHI.org>). Statistics like these have propagated the long held perception that veterinary drug delivery is the 'poor cousin' to its human drug counterpart.

Nevertheless, the veterinary pharmaceutical industry continues to thrive within an environment that works on minimum budget and low profit margins, serving an immense population of diverse species. As an example of the diversity and number of animals being cared for, in the USA alone there are over 135 million dogs and cats recorded as family pets ([APPMA / AVMA 2007](#)). For other animal species, there are estimated to be >6.9 million horses, 7.5 billion chickens, 292 million turkeys, 109 million cattle, 92 million pigs and 7 million sheep



# *Aspects of Veterinary Therapeutics*

## *Key Clinical Parameters*



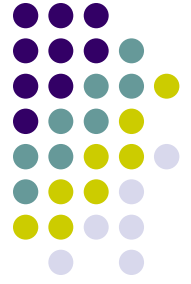


# ***Aspects of Veterinary Therapeutics***

## ***Potential Therapeutic Benefits of Enhanced Medicine Product***



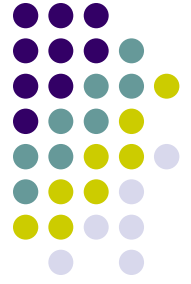
# *Aspects of Veterinary Therapeutics*



## Why Oral Route

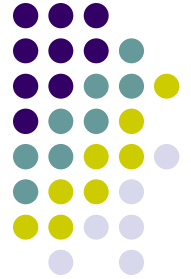
- Improved clinical effectiveness.
- The relative efficiency of reduced dosing regimens (i.e. improved patient compliance).
- Relative savings in patient handling (e.g. nursing or outpatient visits for repeat drug administration) and medical care (e.g. handling of adverse events or side-effects).
- Consumer convenience and compliance are major drivers for companion animals.

# *Aspects of Veterinary Therapeutics*



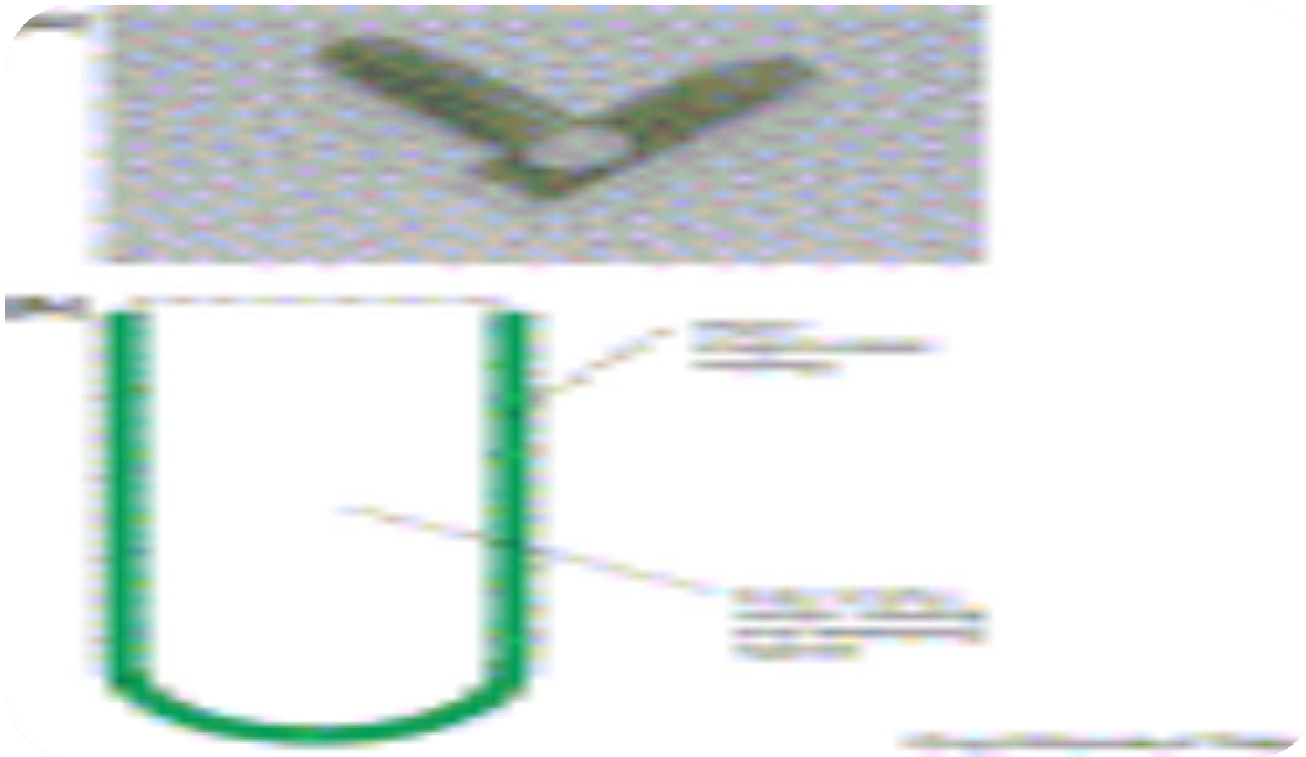
## **Current Technologies**

- 1. Matrix:** drug is embedded in a polymer matrix and the release takes place by partitioning of the drug into the polymer matrix and the release medium. Drug release from this system might be sensitive to food effects and the pH of gastrointestinal (GI) contents.
- 2. Reservoir system:** the dosage form consists of a drug core surrounded by a rate-limiting membrane. Drug release from this system might be sensitive to food effects and the pH of the GI contents.
- 3. Osmotic system:** osmotic pressure is used to fuel drug delivery. This event occurs independently of pH or of other physiological parameters. This mechanism can be used to deliver drug at some predetermined rate.



# *Aspects of Veterinary Therapeutics*

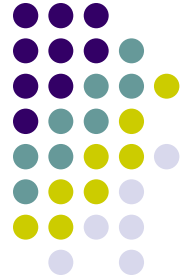
## Matrix Systems



The Time Capsule. **(b)** In the rumen, the zinc oxide slowly erodes from the exposed face for up to 6 weeks.

Because the surface area of exposure is constant during erosion, zero-order release is observed.

The rate of release is controlled by the rate of dissolution/erosion of the zinc oxide core and the surface area maintained by flaking off of the water impermeable waxy coating.



# *Aspects of Veterinary Therapeutics*

## Matrix Systems - Chewables



# *Aspects of Veterinary Therapeutics*



## **Hybrid Matrix Systems**

Development of gingivitis and periodontitis in dogs is related to the multiplication of the microorganisms in dental plaque and the release of the by-products of their metabolism. To prevent or retard the development of these diseases, chlorhexidine has been shown to be the most effective locally applied agent.

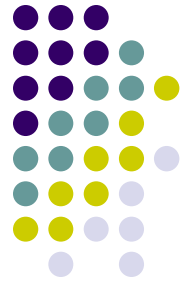
Stomadhex<sup>®</sup> (Vetoquinol) is a tablet with bioadhesive properties enabling it to remain in place on the oral mucosa after hydration of the tablet by oral fluids for several hours. It continuously releases chlorhexidine diacetate for its antimicrobial and anti-inflammatory qualities, and niacinamide for its healing and antifungal qualities. Stomadhex treatment can provide a carry-over effect following dental scaling by reducing oral microflora and retarding the reappearance of dental plaque



# ***Aspects of Veterinary Therapeutics***

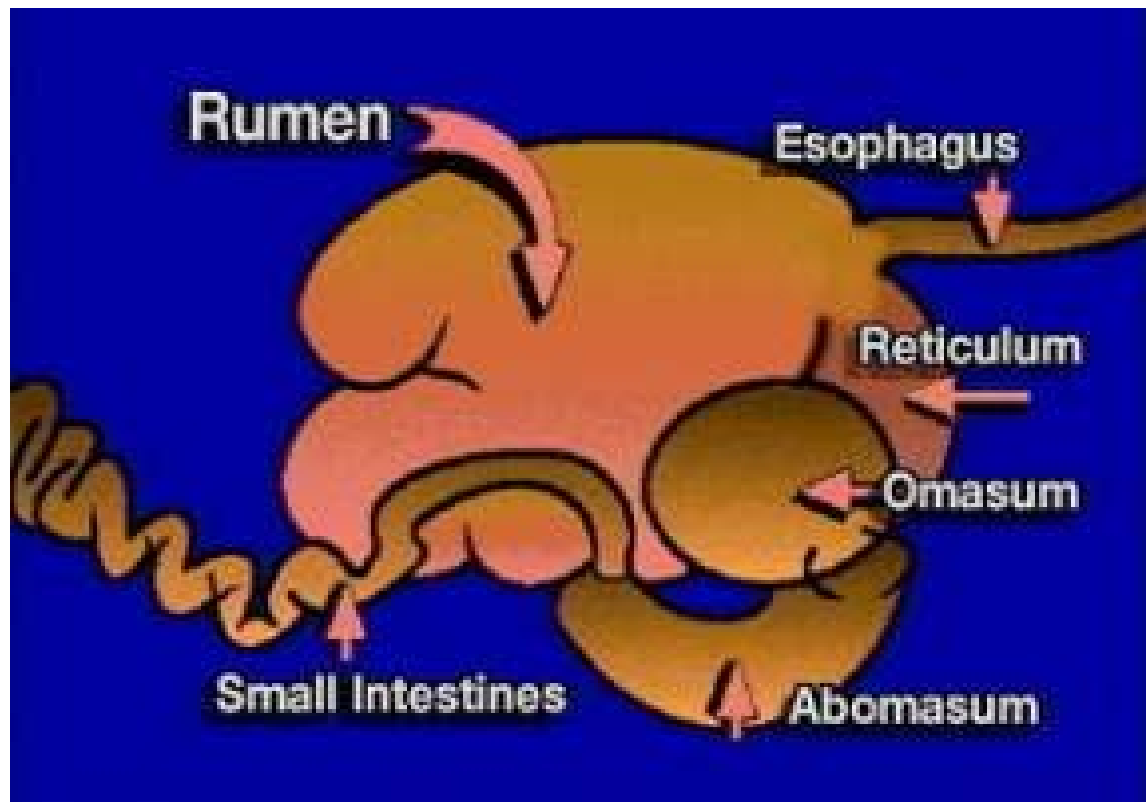
## **Matrix Systems - Capsules**

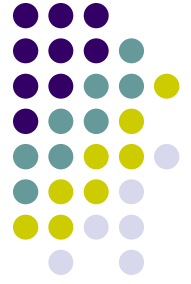




# *Aspects of Veterinary Therapeutics*

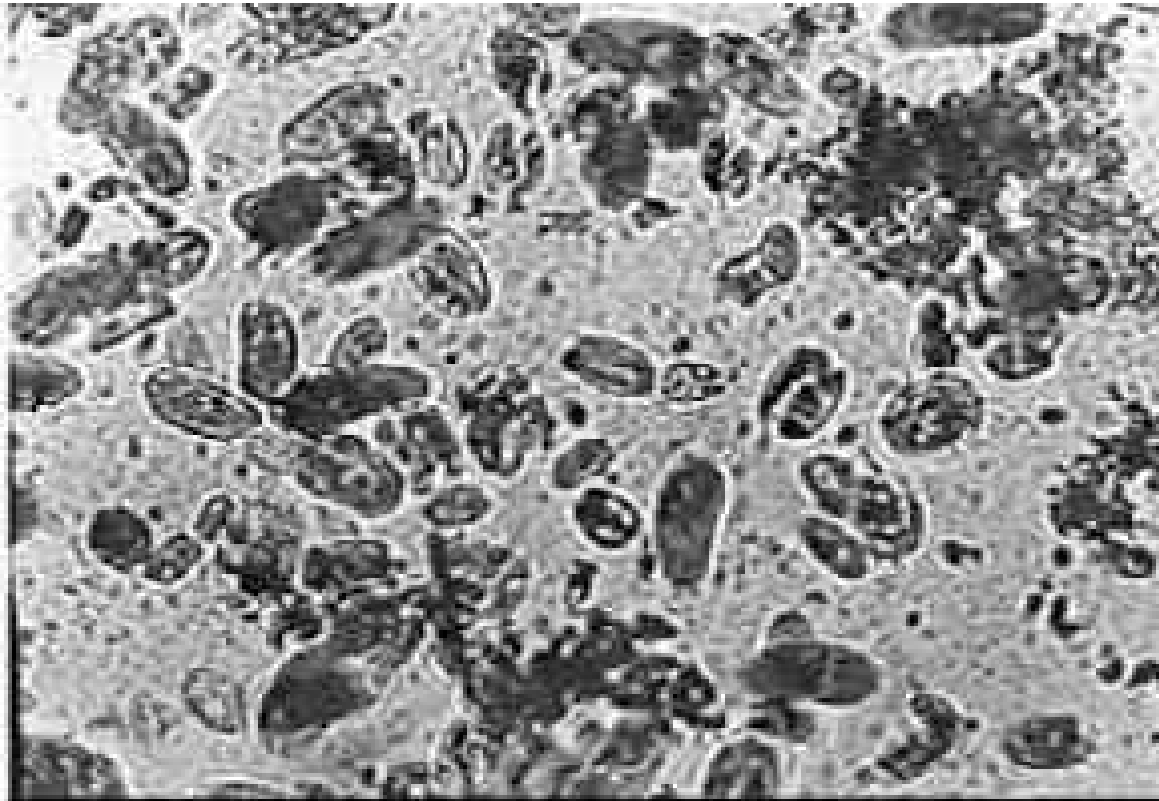
## Reservoir system – Ruminant Digestive System





# ***Aspects of Veterinary Therapeutics***

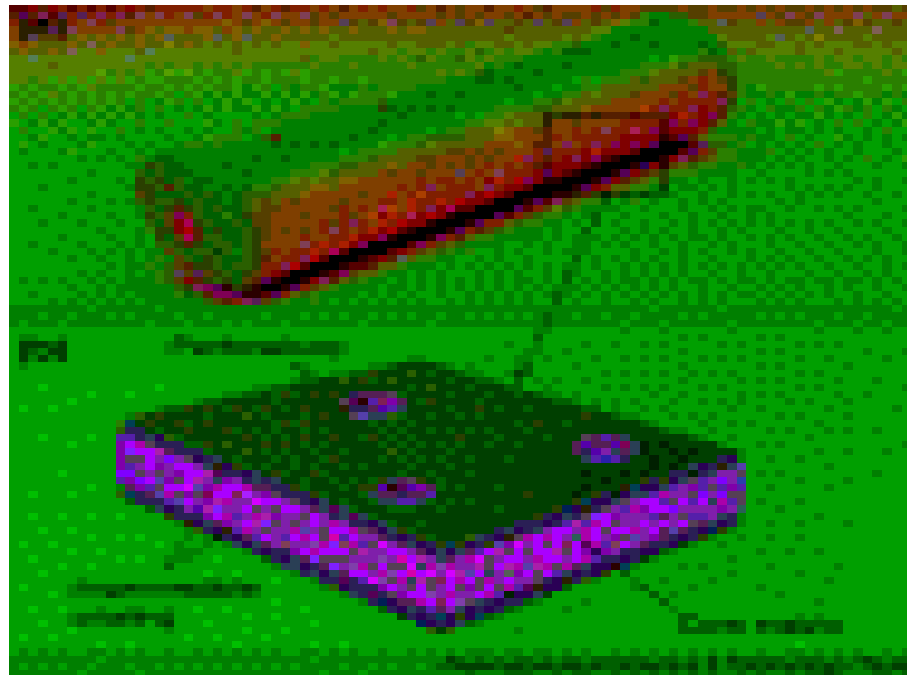
## **Reservoir system – Ruminant Digestive System**



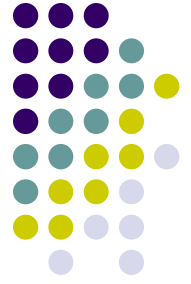


# *Aspects of Veterinary Therapeutics*

## Reservoir system

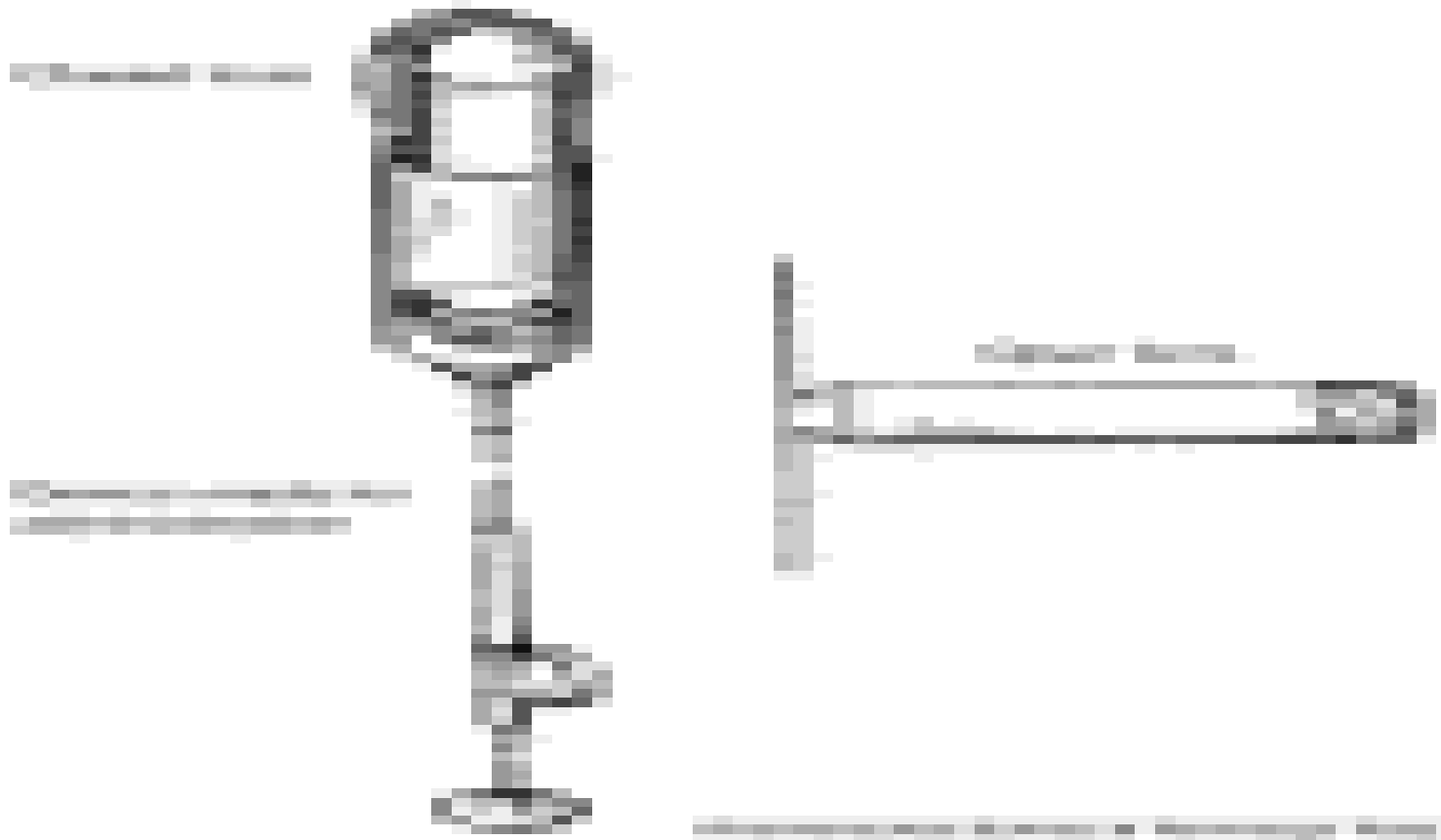


Paratect Flex® (Pfizer Animal Health, New York, NY, USA). Bolus rolled and taped for administration to cattle **(a)** and schematic **(b)**.



# *Aspects of Veterinary Therapeutics*

## Reservoir system



Device containing 'wings' to prevent regurgitation<sup>[9]</sup> (with permission from Pfizer).



# ***Aspects of Veterinary Therapeutics***

## **Commercially available Reservoir system**

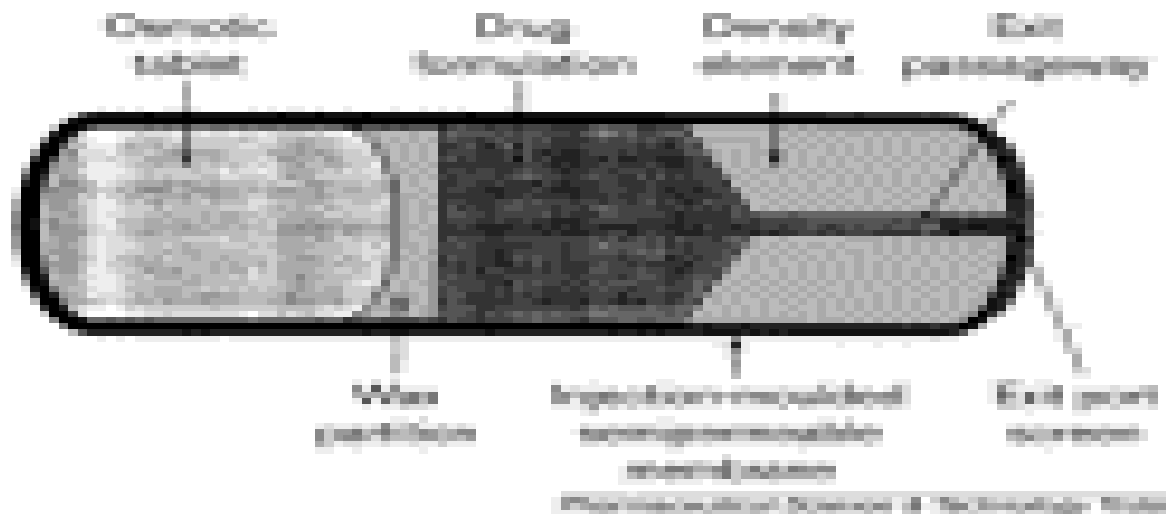
<b>Trade name</b>	<b>Bolus type</b>	<b>Manufacturer</b>	<b>Drug</b>	<b><i>In vivo</i> duration</b>
Paratect Flex <sup>®</sup> Bolus	Expanding device	Pfizer Animal Health (New York, NY, USA)	Morantel tartrate	3 months
Rumensin ABC <sup>®</sup>	Expanding device	Elanco Animal Health, Lilly (Indianapolis, IN, USA)	Monensin sodium	3 months
Monensin RDD <sup>®</sup> (no longer marketed)	High-density device	Elanco Animal Health, Lilly (Indianapolis, IN, USA)	Monensin sodium	3 months
Spanbolet <sup>®</sup> II	High-density device	Norden Laboratories (Lincoln, NE, USA)	Sulfmethazine	3-50 days
Dura SE <sup>®</sup>	High-density device	Schering-Plough Animal Health (Mundelein, IL, USA)	Sodium selenite	4 months
Ivomec SR <sup>®</sup>	High-density device	Merial (Knightsbridge, London, UK)	Ivermectin	4-5 months
Panacur SR <sup>®</sup>	High-density device	Intervet/Hoechst Roussel Vet (Boxmeer, The Netherlands)	Fenbendazole	4-5 months



# Aspects of Veterinary Therapeutics

## Osmotic system

### Ruminal Therapeutic System – RUTS Push Melt™



Cross-section of the ruminal therapeutic system (RUTS) Push-Melt™ system.

Ruminal Therapeutic System (RUTS) Push-Melt™ technology. Two drugs, ivermectin and selenium, have been successfully delivered using this technology for periods of up to 135 and 120 days, respectively. RUTS is an osmotically driven system. Following administration to the rumen, the increase in temperature causes a specially formulated drug layer to melt so that it becomes fluid. Simultaneously, water imbibes across the semipermeable membrane cup resulting in swelling of the osmotic tablet, which pushes a plug comprising paraffin waxes and Cab-O-Sil (silicon dioxide, an inert synthetic thickening agent). The plug behaves as a piston and pushes the now fluid drug layer through an exit port and out of the device through a capscreens. The release rate can be tailored to maximize the therapeutic effect.



# Aspects of Veterinary Therapeutics

## Osmotic / Hybrid systems

1. Pulsincap formulation (RP Scherer; <http://www.rpscherer.com>) : the drug is contained within a water-insoluble body and is sealed into the capsule by an erodible tablet plug. As the capsule moves down the GI tract, the plug erodes away from the mouth of the capsule.

By adjusting the amount of hydroxypropylmethylcellulose and dibasic calcium phosphate, the rate of erosion and release of capsule contents can be modified. Manipulation of the tablet plug formulation enables pulsatile release from the device over a period of 2–12 h, and will enable colonic drug delivery.

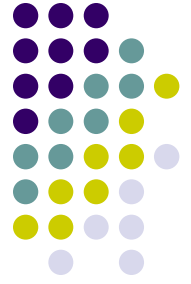
2. Gastric retention devices: to prolong gastric residence and reduce problems associated with erratic gastric emptying times, approaches to increase gastric retention have been pursued. Devices include:

- Floating systems: hydrodynamically balanced systems, such as floating microspheres are multiparticulate drug-delivery systems that have the advantage of gastric retention for up to 12 h in humans. The drug is contained within the hollow inner core of the floating microsphere, and is released within the stomach at a slow rate. After drug release, the residual system is emptied from the stomach. However, most studies indicate that the retention of these systems are strongly affected by patient prandial state and that the device transits more rapidly when consumed under fasted versus fed conditions.
- Swelling system: the device swells to an extent that it is unable to exit the stomach through the pylorus. Consequently, the dosage form is retained in the stomach for a long period of time. Two important properties of these systems are the rate at which the swelling occurs and the device's mechanical strength. In particular, swelling devices need to achieve their fully swollen state before the occurrence of a housekeeper wave (i.e. it must achieve full swelling within 20 min or less). Although still dependent upon the presence of food, the promising finding was that these systems could be retained within the stomach of fed dogs for more than 24 h.
- Bioadhesive systems: the device is formulated to adhere to a targeted site within the GI tract where it delivers the drug.
- Modified shape systems: nondisintegrating shapes that are moulded from silastic elastomer or extruded from polyethylene blends.

Based

upon normal physiological functions, the device is retained within the stomach because of its size, shape or flexibility.

- High-density formulations: the device literally sinks within the stomach, thereby retarding its exit during normal gastric expulsion.
- Ruminally protected amino acid pellets – Smartamine™ (Adisseo – formerly Rhone Poulenc)



# *Aspects of Veterinary Therapeutics*

## **Compounding Options and Benefits Dosage**

### **Form /Administration / Method Ease of Use**

**Suspensions/ Solutions Oral** – Given via oral syringe or added to your pet's food for ingestion. Multiple palatable flavors are available for your pet, including chicken, tuna, cheese, sardine, bacon, various fruits, vegetables, and peanut butter.

**Chewables Oral** – The medication is mixed in a chewable treat base and can be flavored to your pet's preference. A great flavored treat alternative.

**Capsules Oral** – A solid drug form enclosed in a non-flavored, hard or soft gelatinous shell. Dosages are customized for your pet's specific needs. Easy to swallow and masks bitter tastes. Some pet owners also request flavoring so that they can pull the capsule apart and sprinkle the contents on their pet's food. If your pet is taking multiple medications, they may be able to be compounded into just one capsule so you do not have to give several different pills or capsules.

**Concentrated Oils Oral** – Given by dropper on your pet's tongue for ingestion. Medications can be given in higher concentrations, meaning smaller volumes compared to traditional dosage forms. (e.g., some medicines can be given in as little as three drops on your pet's tongue). The oils can also be flavored.

**Disintegrating Oral Tablets Oral** – This is a melt-in-your-mouth tablet that dissolves in seconds and is readily absorbed through the tissues in the mouth. This is a relatively new form of administering medication to your pet. The medication dissolves so quickly that it is difficult for your pet to spit it out. The medicine is then absorbed through the mouth where there is a good supply of saliva and good blood flow to get the drug rapidly into the body. These can be flavored, as well.



# Aspects of Veterinary Therapeutics

## Flavor possibilities for liquid or

Bubblegum Treat  
Butterscotch Topping  
Cheesy Cheddar  
Cherry Blast  
Chicken Pot Pie  
Chopped Liver  
Creamy Caramel  
Crispy Bacon  
Crunchy Celery  
Fish Chowder  
Fruit Supreme  
Grilled Tuna  
Goosey Molasses  
Groovy Grape  
Leapin' Licorice

## suspension prescription medications include:

Lemon Meringue  
Mandarin Orange  
Mom's Banana Bread  
Mother's Milk  
Radical Raspberry  
Red Angus Beef  
Roasted Lamb  
Salmon Steak  
Sardine Splendor  
Shrimp Cocktail  
Strawberry Shortcake  
Tangy Apple  
Watermelon Passion  
Whitefish Salad

## Flavor possibilities for liquid or suspension prescription medications include:

**Dogs** prefer meats, sweet, and cheese.

**Cats** prefer fish, meat and peanut butter.

**Birds** like fruity and sweet treats.

**Rabbits** like fruit or veggie treats.

**Rodents** like sweet or cheesy intense aromas.

**Iguanas** react to sweet, fruity aromas.

**Ferrets** like sweet flavors.

**Gerbils** like fruity sweet flavors.

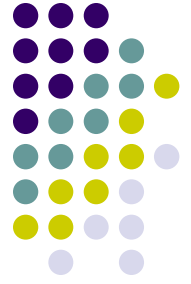


# ***Aspects of Veterinary Therapeutics***

## Characteristics of fast dissolving systems – Edible Films

Table 1.	
Special features	Advantages
<ul style="list-style-type: none"><li>• Thin elegant film</li><li>• Various sizes and shapes</li><li>• Unobstructive</li><li>• Mucoadhesion</li><li>• Fast disintegration</li><li>• Quick dissolving</li><li>• Rapid release</li></ul>	<ul style="list-style-type: none"><li>• Convenient dosing</li><li>• No water needed</li><li>• No risk of choking</li><li>• Taste masking</li><li>• Enhanced stability</li><li>• Improved patient compliance</li><li>• Life cycle management</li></ul>

# ***Aspects of Veterinary Therapeutics***

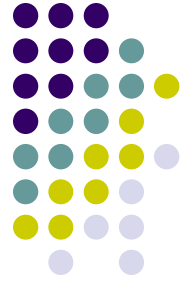


## **Sustained Release Technology**

**Oral: (MacroMed (SQ2Gel); Altus Biologics (Crystalized proteins); Alkermes (PLG microspheres); Spherics(sticky spheres); DepoMed (GR System)**

## **Enhanced Absorption/Transport Technology**

**Enhanced transmucosal absorption: Generex Biotechnology (oral mucosa target); Anesta Corp. (OTS oral mucosa target)**



# ***Aspects of Veterinary Therapeutics***

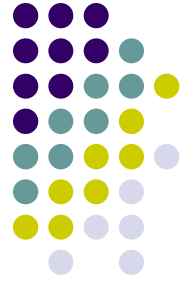
## ***Chronotherapeutic Drug Delivery***



Core containing 'active'

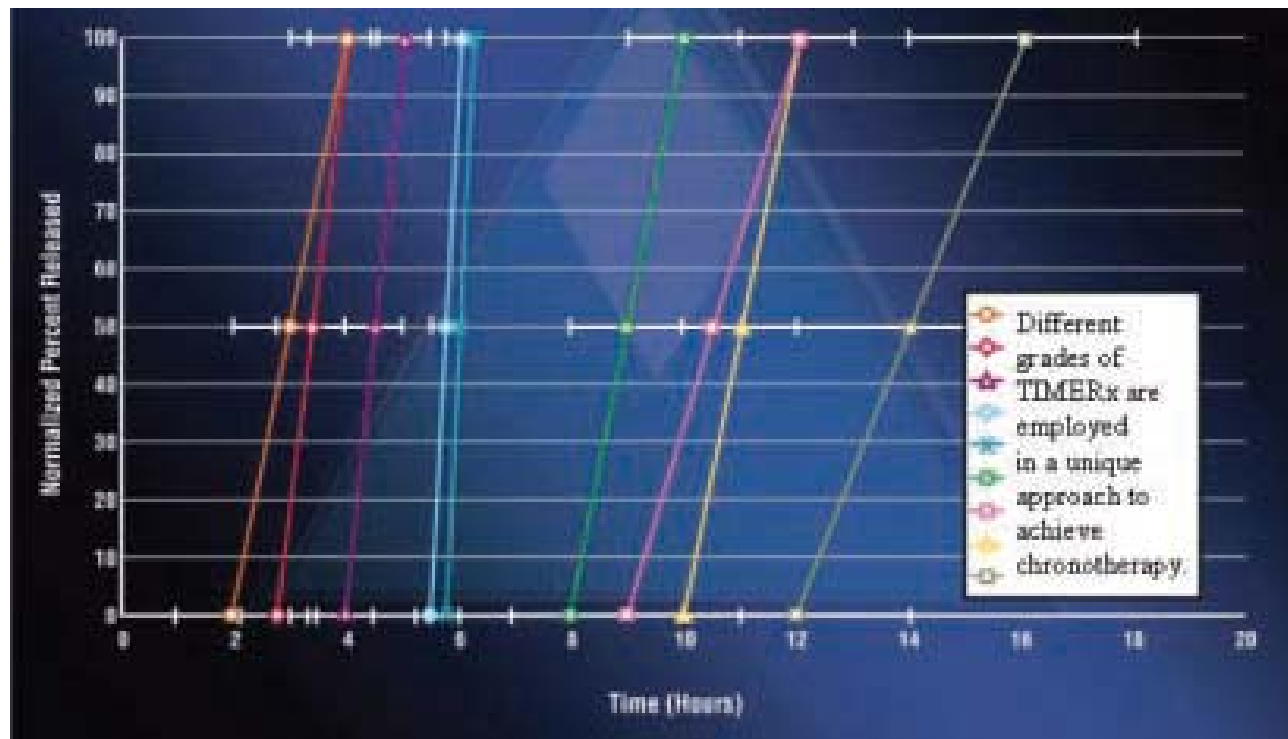
TIMERx<sup>®</sup> based  
compression coating

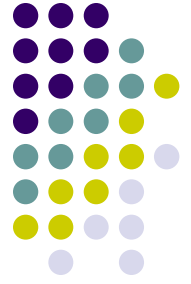
- 'Tablet within a tablet' - core compression technique.
- Inner core - immediate release phase containing 'active'.
- Coating- time lag variation based on different TIMERx<sup>®</sup> grades.



# Aspects of Veterinary Therapeutics

## Chronotherapeutic Delivery of AD121 Using TIMERx

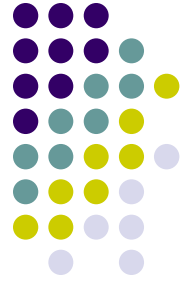




# *Aspects of Veterinary Therapeutics*

## Future Trends

- Duodenal Bioadhesive for Oncological / IBS
- Edible films – dental / NSAIDs / calming / seizures
- Bucal Bioadhesives – dental / calming / seizures
- Hydrogels – pH – “new enteric systems”
- Oral iontophoresis – insulin / anthelmintics / oncology
- Oral proteins – US patent 6874444 – **Diltiazem** for hypertension - Oral spheroids



# *Aspects of Veterinary Therapeutics*

## Q&A



**Thanks!**