Aspects of Veterinary Therapeutics

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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
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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$0.6 billion dollars was spent on pharmaceuticals for veterinary use (http://www.Phrma.org/publications/). The Animal Health Institute (AHI) reports that the total amount of animal health product sales in 2007 accounted for US$ 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.
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Key Clinical Parameters

- Low Therapeutic Index
- High Therapeutic Index

Side effects + Compliance equals Safety + Efficacy

Long Short Half Life
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Potential Therapeutic Benefits of Enhanced Medicine Product
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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.
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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.
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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.
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Matrix Systems - Chewables
Development of gingivitis and periodontis 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® (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.
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Matrix Systems - Capsules
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Reservoir system – Ruminant Digestive System
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Reservoir system – Ruminant Digestive System
Paratect Flex® (Pfizer Animal Health, New York, NY, USA). Bolus rolled and taped for administration to cattle (a) and schematic (b).
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Reservoir system

Device containing ‘wings’ to prevent regurgitation[9] (with permission from Pfizer).
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Commercially available Reservoir system

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Bolus type</th>
<th>Manufacturer</th>
<th>Drug</th>
<th>In vivo duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paratect Flex® Bolus</td>
<td>Expanding device</td>
<td>Pfizer Animal Health (New York, NY, USA)</td>
<td>Morantel tartrate</td>
<td>3 months</td>
</tr>
<tr>
<td>Rumensin ABC™</td>
<td>Expanding device</td>
<td>Elanco Animal Health, Lilly (Indianapolis, IN, USA)</td>
<td>Monensin sodium</td>
<td>3 months</td>
</tr>
<tr>
<td>Monensin RDD™ (no longer marketed)</td>
<td>High-density device</td>
<td>Elanco Animal Health, Lilly (Indianapolis, IN, USA)</td>
<td>Monensin sodium</td>
<td>3 months</td>
</tr>
<tr>
<td>Spanbolet® II</td>
<td>High-density device</td>
<td>Norden Laboratories (Lincoln, NE, USA)</td>
<td>Sulfmethazine</td>
<td>3–50 days</td>
</tr>
<tr>
<td>Dura SE®</td>
<td>High-density device</td>
<td>Schering-Plough Animal Health (Mundelein, IL, USA)</td>
<td>Sodium selenite</td>
<td>4 months</td>
</tr>
<tr>
<td>Ivomec SR®</td>
<td>High-density device</td>
<td>Merial (Knightsbridge, London, UK)</td>
<td>Ivermectin</td>
<td>4–5 months</td>
</tr>
<tr>
<td>Panacur SR®</td>
<td>High-density device</td>
<td>Intervet/Hoechst Roussel Vet (Boxmeer, The Netherlands)</td>
<td>Fenbendazole</td>
<td>4–5 months</td>
</tr>
</tbody>
</table>
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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 (silicone 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 capscrew. The release rate can be tailored to maximize the therapeutic effect.
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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 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)
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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.
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*Flavor possibilities for liquid or suspension prescription medications include:*

<table>
<thead>
<tr>
<th>Flavor</th>
<th>Flavor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bubblegum Treat</td>
<td>Lemon Meringue</td>
</tr>
<tr>
<td>Butterscotch Topping</td>
<td>Mandarin Orange</td>
</tr>
<tr>
<td>Cheesy Cheddar</td>
<td>Mom’s Banana Bread</td>
</tr>
<tr>
<td>Cherry Blast</td>
<td>Mother’s Milk</td>
</tr>
<tr>
<td>Chicken Pot Pie</td>
<td>Radical Raspberry</td>
</tr>
<tr>
<td>Chopped Liver</td>
<td>Red Angus Beef</td>
</tr>
<tr>
<td>Creamy Caramel</td>
<td>Roasted Lamb</td>
</tr>
<tr>
<td>Crispy Bacon</td>
<td>Salmon Steak</td>
</tr>
<tr>
<td>Crunchy Celery</td>
<td>Sardine Splendor</td>
</tr>
<tr>
<td>Fish Chowder</td>
<td>Shrimp Cocktail</td>
</tr>
<tr>
<td>Fruit Supreme</td>
<td>Strawberry Shortcake</td>
</tr>
<tr>
<td>Grilled Tuna</td>
<td>Tangy Apple</td>
</tr>
<tr>
<td>Gooey Molasses</td>
<td>Watermelon Passion</td>
</tr>
<tr>
<td>Groovy Grape</td>
<td>Whitefish Salad</td>
</tr>
<tr>
<td>Leapin’ Licorice</td>
<td></td>
</tr>
</tbody>
</table>

*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.
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Characteristics of fast dissolving systems – Edible Films

<table>
<thead>
<tr>
<th>Special features</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin elegant film</td>
<td>Convenient dosing</td>
</tr>
<tr>
<td>Various sizes and shapes</td>
<td>No water needed</td>
</tr>
<tr>
<td>Unobstructive</td>
<td>No risk of choking</td>
</tr>
<tr>
<td>Mucoadhesion</td>
<td>Taste masking</td>
</tr>
<tr>
<td>Fast disintegration</td>
<td>Enhanced stability</td>
</tr>
<tr>
<td>Quick dissolving</td>
<td>Improved patient compliance</td>
</tr>
<tr>
<td>Rapid release</td>
<td>Life cycle management</td>
</tr>
</tbody>
</table>
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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)
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Chronotherapeutic Drug Delivery

- 'Tablet within a tablet' - core compression technique.
- Inner core - immediate release phase containing 'active'.
- Coating - time lag variation based on different TIMERx® grades.
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Chronotherapeutic Delivery of AD121 Using TIMERx
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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
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Q&A

Thanks!