Modified release drug delivery in veterinary medicine

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To successfully research and develop an animal pharmaceutical dosage form, a diverse array of issues covering basic medicine, pharmacology and technology must be addressed. Societal concerns regarding animal and public health, as well as the rapidly changing farming and economic environments, provide additional challenges that require integration into an already complex web of issues. Here, we examine the drive towards reducing the frequency of administration to animals and the closing of gaps between the human and veterinary drug product development.

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▼ 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 2000 accounted for US$3.3 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 115 million dogs and cats recorded as family pets. 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 (http://www.ahi.org/Features/Antibiotics%20and%20Animals%20Fast%20Facts.htm). This range of animal species, and the corresponding anatomical and physiological differences, challenges the development of veterinary pharmaceutical formulations.

Challenges and opportunities

Veterinary needs reflect ongoing changes in human economics and society. For example, as people become progressively enmeshed in modern technology, we find a decrease in extended family structure and an increase in the number of individuals and families leading relatively solitary lives. As a result, companion animals have taken on a growing importance within the human household, with clinical concerns and corresponding therapeutic options becoming increasing similar to that of human medicine. Medications are currently being sought for such veterinary conditions as cancer [1], anxiety [2,3], pain [4,5] and hypertension [6]. This similarity in clinical concerns provides pharmaceutical companies with the opportunity to obtain a greater return on their investment through veterinary spin-offs of their approved human drug products.

Even a casual observer of trends will note that small animal pharmaceuticals constitute a major area of growth within the animal health industry. Based upon a 2001 AHI survey, companion animal product sales have increased to 45% of the market share. Sales from animal health products in the USA during 2000 were US$4.21 billion. Among AHI members (which represent ~80 percent of the US animal health industry), sales for products used in livestock and poultry totalled $1.8 billion, while corresponding companion animal health product sales totalled $1.5 billion (http://www.ahi.org/News%20Room/Press%20Release/2001/July/sales.htm).

On the food-animal side, opportunities closely follow changing consumer expectations and husbandry practices. For example, the drive towards decreased costs and leaner meats have lead to the development of growth-altering drugs to increase lean mass and

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increase feed efficiency [7–9]. The possibility of altering these attributes via genetic modification is also being explored. However, these interventions are not without concern, and consumers have expressed uncertainty regarding the impact of these manipulations on human food safety and to the environment.

The drive for lower costs has also encouraged the growth of mega-farms. However, the presence of large animal populations necessitates careful control over the potential invasion of infectious pathogens. With the resulting need for control and treatment of disease, effective antibiotic therapy is needed. Along with the evolution of these therapies comes the need for establishing guidelines for judicious drug use. In this regard, the prudent use of antibiotics in food-producing animals carries several public health benefits. These include [10]:

(1) Reduction in the incidence of life-threatening infections in large herds and flocks.
(2) Effective treatment of serious systemic infections.
(3) Environmental benefits associated with increase in feed efficiency including a reduction in food requirements, decreased manure production and a decrease in the need for dedicated real estate.
(4) Reduction in the cost of meat, milk and eggs.

Nevertheless, concerns regarding the spread of resistant micro-organisms have severely curtailed the development of new chemical entities (http://www.fda.gov/cvm/index/consumer/ar2001.htm; http://www.cdc.gov/drugresistance/actionplan/). Therefore, pharmaceutical companies are exploring mechanisms to maximize the effectiveness and ease of administration of approved veterinary antibiotic compounds, while minimizing the risk of drug resistance.

Numerous opportunities exist to develop veterinary drug-delivery systems that fulfill unmet needs for both companion and farmed animals. These, coupled with the aim of less frequent administration, have stimulated the development of modified release drug-delivery systems. Such opportunities have resulted in numerous modified release drug-delivery systems being developed for use in animals [11–13]. To date, the majority of veterinary compounds being targeted for modified (sustained) release include antibiotics, antiparasitic agents, hormones for oestrus synchronization, steroids for fertility control (in companion animals) and growth promotants. Such compounds have been successfully formulated into technologies that include [14]:

- Subcutaneous implantable systems, such as ear implants for hormonal delivery.
- Veterinary implantable therapeutic systems that can release drug in a zero order or pulsatile pattern (e.g. antibiotics, growth promotants, somatotropin and parasiticides).
- Microspheres and microcapsules for direct injection of drug to site-of-action (e.g. equine joints or intramammary administration in the treatment of bovine mastitis).
- Oil-based injectable controlled release formulations (e.g. oxytetracycline).
- Oil-based spot-on formulations that are added directly to the skin and can release drug for one month (e.g. antiparasitic products for use in companion animals).
- Eartags and collars to control flies and ectoparasites in cattle and companion animals, respectively. In both cases, the active agents are released over several months and are made available to the total body surface by normal animal movements.
- Ophthalmic inserts that deliver drug directly to the eye, including antiglaucoma agents, antibacterial drugs, anti-inflammatory compounds and mydriatic agents.
- Oral topical devices that are applied directly to the oral mucosa and are used to prevent or treat gingivitis and periodontal disease in dogs.

Trends in modified release drug-delivery systems

Over the past 50 years or so, substantial research in the human health arena has been focused on the optimization of drug delivery. Traditionally, these delivery systems have been drug-specific, revolving around a particular drug and its clinical application. However, in the past two decades, we have witnessed the emergence of numerous drug-delivery technologies that have been developed independently of any specific compound or disease condition [15]. It is interesting to note that this trend has also been recently observed within the veterinary industry [16].

Oral modified release drug-delivery systems

The basic pharmacoeconomic principles underlying the development and use of human modified release drug-delivery systems include [17]:

- 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).

Similar reasons exist for the use of modified drug-delivery systems in animal species. The potential reduction in animal handling (resulting in decreased animal stress and economic savings) is a major driving force in the development of such systems for farmed animals [14], whereas consumer convenience and compliance are major drivers for companion animals.

In the human arena, the oral route of drug administration represents one of the most attractive and acceptable routes

for the administration of therapeutic compounds. Oral formulations are less expensive to produce because they do not need to be manufactured under sterile conditions [18]. Other advantages include freedom from the pain associated with parenteral administration, zero risk of needle-induced infections and ease of patient administration. This last advantage does not necessarily apply to the veterinary species, which generally need to be restrained to permit drug delivery via the oral route.

Human oral modified release (controlled) drug-delivery systems decrease fluctuations in serum drug concentrations and are invaluable in the treatment of a variety of disease conditions [19]. These systems enable a once- or twice-daily dosing of a drug that could otherwise require three or four administrations per day. In ruminant animals, such extensions in delivery time offer little or no advantage. Consequently, oral (rumenal) modified release (controlled) veterinary drug-delivery systems are developed to deliver their contents over extended periods (up to several months) [20].

The majority of human oral modified release dosage forms fall within one of the following categories [21]:

(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.

A similar categorization can be made for the oral (rumenal) products formulated for animal use [22].

Maximizing the therapeutic effect

Recent advances in human drug-delivery technology enable tailoring the drug release pattern to maximize the therapeutic effect. For example, Geomatrix® systems (SkyePharma; http://www.skyepharma.com) use a multilayer system (active core plus polymeric barriers) to effect a tailored drug release profile. The polymeric barriers consist of hydroxypropyl methylcellulose polymers of varying types, molecular weights and viscosities. These are incorporated into product-specific and drug-specific ratios relative to the desired release pattern, enabling a potential zero-order release rate and the controlled release of two different drugs within a single formulation [23]. Numerous other examples are currently commercialized or under development [15].

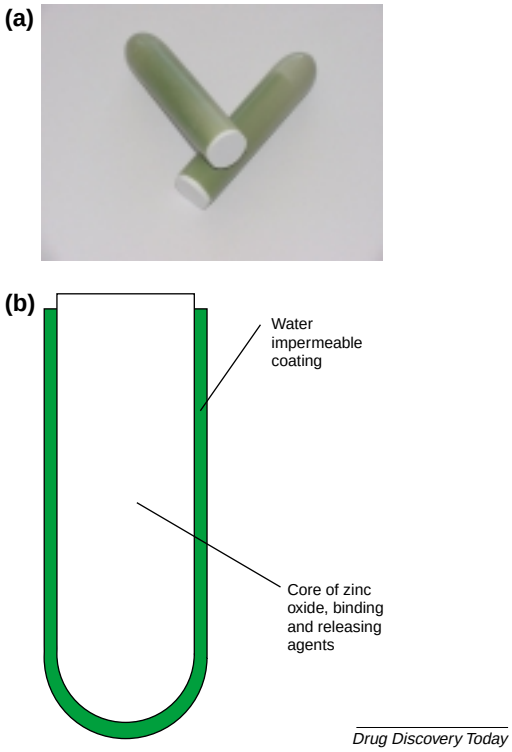

Figure 1. (a) The Time Capsule. **(b)** In the rumen, the zinc oxide slowly erodes from the exposed face for up to 6 weeks. Because the surface area of exposure is constant during erosion, zero-order release is observed. The rate of release is controlled by the rate of dissolution/erosion of the zinc oxide core and the surface area maintained by flaking off of the water impermeable waxy coating.

Similar efforts are being made in the veterinary field to tailor the drug release pattern to maximize the therapeutic effect. To achieve this, the unique anatomical features of the animal are being exploited. The approach, known for many years, involves heavily weighted devices that sink to the bottom of the rumen where it is retained. An example of a recently developed delivery system that was developed to improve the efficacy of an existing drug is the Time Capsule (Celentis; http://www.celentis.com). It delivers zinc oxide for up to 6 weeks in sheep to treat facial eczema [24]. The delivery system comprises a core of zinc oxide, binding and releasing agents (Fig. 1), which are extruded and then dipped into a water impermeable waxy coating.

Another example is the Ruminal Therapeutic System (RUTS) Push-Melt™ technology [13,25,26]. Two drugs, ivermectin and selenium, have been successfully delivered using this technology for periods of up to 135 and 120 days,

respectively [13,25,26]. 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 cap-screen. The release rate can be tailored to maximize the therapeutic effect.

Gastrointestinal transit time

Within human modified release drug-delivery systems, there is the inherent limitation of GI transit time. Therefore, efforts are currently under way within the human field to overcome these inherent physiological challenges. These formulations are intended to either delay product passage through the GI tract, accomplishing a sustained release of drug over a prolonged period of time, or provide for colonic delivery. Examples include:

(1) Pulsincap formulation (RP Scherer; http://www.rpscherer.com) [27]: 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 [28]: 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 [29] 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 [30] 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.

These technologies are highlighted in this article because some might find application for the delivery of drugs to small animals [31], although marked variation in gastric emptying rate both within and between species could make this a challenge [32]. However, for ruminant species, the desired duration of release is generally in the order of weeks and/or months, rather than hours. Therefore, the technologies described are unlikely to find application in this group of animal species.

Parenteral modified release drug-delivery systems

Because of the limitations of transferring human oral technologies to ruminant and monogastric species, parenteral delivery could provide a more favourable option. This route for drug administration was considered at a recent workshop of the *American Association of Pharmaceutical Scientists* [33]. The workshop focused solely on the development and concerns associated with parenteral sustained release products, and, although mainly addressing human pharmaceuticals, veterinary applications were also considered [33]. Included in the discussion were such technologies as microspheres, liposomal preparations, implants and depot injections, all having potential application to both human and veterinary medicine. It is within the area of parenteral drug-delivery technologies that cross-pollination of ideas and technology transfer is most likely to occur.

It should be remarked, however, that veterinary formulation scientists face a specific challenge when developing parenteral pharmaceuticals. This challenge relates to residues

of active ingredient, particularly at the injection site, but also in other tissues, when injectable products are developed for use in food-producing animals. Indeed, several regulations forbid the consumption of meat, milk, fat, eggs, liver and kidney until residues of drug are below a certain limit. Therefore, when an injectable veterinary pharmaceutical product, and particularly a controlled release injectable product, is developed, care must be taken to ensure that the amounts of drug at the injection site remain below the authorized limit because financial losses might occur to the farmer if the animal is slaughtered for any reason.

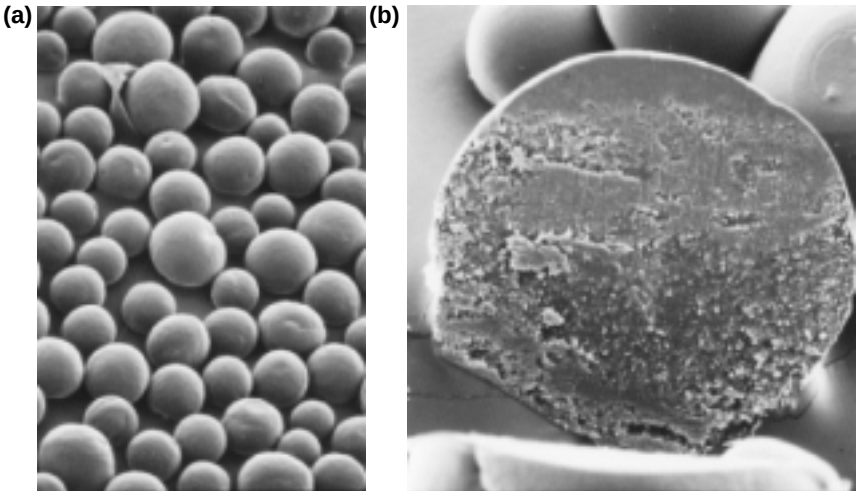

Figure 2. Scanning electron micrograph of biodegradable microspheres containing progesterone and estradiol prepared using a solvent extraction process from poly (DL-lactide). **(a)** Whole microspheres showing a regular spherical appearance (13 mm represents 100 μm). **(b)** Single microspheres cut in half showing their monolithic nature (4 mm represents 10 μm). Figure reproduced, with permission, from Ref. [44].

ATRIGEL®

The ATRIGEL® system (Atrix Laboratories; http://www.atrixlabs.com) consists of biodegradable polymers dissolved in a biocompatible carrier. When the liquid polymer system is injected it forms a solid implant upon contact with the aqueous body fluids. If a drug is incorporated into the polymer solution, it becomes entrapped within the solidified polymer matrix. The drug is then released over time as the polymer biodegrades [34,35].

ATRIGEL® has been investigated for the delivery of complex antigens, such as inactivated pseudorabies virus (PRV) to pigs [36]. The delivery system was produced by mixing the ATRIGEL® polymers (polylactides and polyglycolides) with solvent and vaccine. Upon subcutaneous administration of this liquid preparation, solidification occurred. Subsequent hydrolysis of the co-polymers resulted in an antigen release pattern that resulted in an increase in serum antibody levels for more than 90 days following a single injection.

Microparticles

There are numerous examples of human drug products, both marketed and conceptual in nature, that contain microparticles [37]. Microparticles are small, spherical particles <200 μm in diameter. These microparticles offer the advantage of ease of administration and the ability to tailor the release profile.

There have been several proposed veterinary uses for microsphere formulations. Applications include the delivery of Vitamin B12, moxidectin (http://www.fda.gov/cvm/efoi/section2/141189060601.html), progesterone/estradiol [38–43], estradiol [44] and ivermectin [26].

The first commercially available microparticle-based veterinary product was launched in New Zealand (SMARTShot B_{12}™; http://www.stockguard.co.nz). This injectable product contains Vitamin B12 that is continuously released for >200 days. More recently, the Food and Drug Administration (FDA)/Center for Veterinary Medicine (CVM) has approved ProHeart® 6 (Fort Dodge Animal Health; http://www.wyeth.com/divisions/fort_dodge.asp) (moxidectin) for protection against heartworm disease caused by *Dirofilaria immitis* in dogs. The product is provided in two separate vials that are mixed before use. Subcutaneous administration of this product provides a six month duration of therapeutic activity [44].

A sterile injection called P+ (originally named Lutamete Plus, Thorn Bioscience LLC; http://www.thornbiosciencellc.com) was developed for use in cyclic and late transitional phase non-cyclic mares [38–43]. The preparation consisted of biodegradable poly (DL-lactide) microspheres containing 100 mg estradiol and 1.25 g progesterone, which were administered as a single intramuscular injection. The microsphere monolithic system (Fig. 2) was formulated to release its load and suddenly terminate delivery, providing a drop in progesterone levels. Estradiol has also been formulated into poly (DL-lactide) microspheres for use in cycling gilts. When the biodegradable microspheres are administered intramuscularly they induce pseudopregnancy [44].

In addition, a biodegradable injectable microsphere preparation containing ivermectin in poly (lactide-co-glycolide) co-polymer has been developed to provide prolonged delivery of ivermectin for control of livestock pests [26,45].

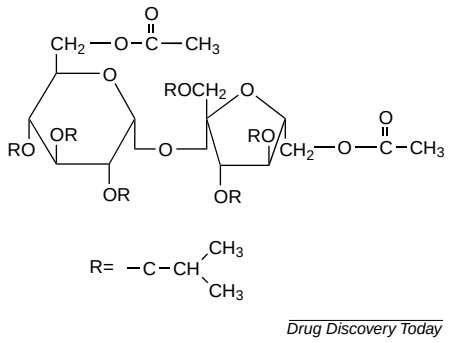

Figure 3. Sucrose acetate isobutyrate (SAIB)

Sucrose acetate isobutyrate

Sucrose acetate isobutyrate (SAIB, Eastman Chemical Company; http://www.eastman.com) [46] is an hydrophobic, fully esterified sucrose derivative (Fig. 3). SAIB possesses some unusual properties including high hydrophobicity and high viscosity. These properties can be exploited to provide sustained drug delivery for periods ranging from a few hours to several weeks [44].

A US Patent [47] discloses several possible approaches to formulate SAIB into a drug-delivery system, but the simplest approach involves mixing the high-viscosity SAIB with a pharmaceutically acceptable solvent [48]. The resultant SAIB–solvent solution possesses a low viscosity into which a drug can be readily dissolved or dispersed. The low viscosity also facilitates drug administration via either the subcutaneous or intramuscular routes. Upon injection, the hydrophobic SAIB forms a high viscosity depot from which drug slowly diffuses. Additives can be combined into this simple formulation to modify drug release kinetics or drug stability.

SAIB is currently being investigated by Thorn Bioscience LLC for use in veterinary medicine. This technology has been investigated for the delivery of deslorelin, a potent gonadotrophin releasing hormone (GnRH) analogue, to induce ovulation at a precise and predictable time in mares and in swine before artificial insemination. Other products currently under investigation using this technology include SABER Mate B (Bovine), a short acting controlled release deslorelin acetate formulation for use in the OVSYNCH® treatment protocol (GnRH/$PGF_{2\alpha}$/GnRH), which was developed by Wiltbank and Pursley [49] at the University of Madison College of Agriculture and Life Sciences (http://www.cals.wisc.edu). This product provides for the synchronization of follicular development, luteal regression and ovulation, thereby enabling timed insemination to occur within 12–24 h after the completion of the OVSYNCH® treatment protocol. A SABER Mate P (Porcine) has also been described [44]. This is a short-acting controlled release deslorelin acetate–SAIB formulation for stimulation of ovulation within 40 h in oestrus gilts and sows [44]. An experimental SABER formulation containing various amounts of estradiol has also been reported in the literature for maintaining pseudopregnancy in gilts [44].

Concluding remarks

This brief overview has highlighted the diverse formulation opportunities available to the veterinary pharmaceutical industry. The development of innovative modified release drug-delivery systems would be invaluable to helping animal health scientists fulfill unmet animal needs. In the future we might see more human drug-delivery technologies adapted for use in animal medicine. However, in the short term, cost constraints and a more lucrative human market are the major obstacles for this occurrence. Nevertheless, the innovative formulation scientist interested in modified release drug-delivery systems has many opportunities to make a significant contribution to the area of animal health.

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