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The pharmaceutical scientists' role in animal production: An historical and future look at the evolving area of controlled drug delivery in animal production.

M.J. RATHBONE

Director of Research, InterAg, Ruakura Research Centre, P.B. 3123, Hamilton

ABSTRACT

In the field of controlled-release veterinary drug delivery, the utilization of new routes of administration or the development of new delivery systems are of considerable interest. Indeed, because of the large number of production animals and the problems associated with the administration of drugs to these animals, the potential for utilizing novel routes of administration or for developing controlled release products are enormous. However, such a potential will only be fully realized if safe, practical and effective delivery systems are rationally designed and tailored to the end users needs through collaborative efforts between animal, veterinary and pharmaceutical scientists.

The intent of this presentation is to summarize the state of the art of controlled release systems in the veterinary field. It also intends to provide an overview of recent developments in this area and to look toward the future to examine the directions in which veterinary pharmaceuticals is heading. Examples of currently available and future veterinary controlled release drug delivery systems will be given and explained throughout the presentation including ruminal boluses, intravaginal devices, externally applied drug delivery systems, injectable and implantable systems.

Keywords: Controlled release; extended release; prolonged release; veterinary drug delivery.

INTRODUCTION

In the field of controlled-release veterinary drug delivery, the utilization of new routes of administration or the development of new delivery systems are of considerable interest (Rathbone, 1997; Hardee & Bagott, 1998; Rathbone & Cady, 1999; Rathbone & Gurney, 2000). Many controlled release drug delivery systems have been commercialised due to the numerous benefits and opportunities they offer to the end user. Today the major applications of controlled release technology for animal production revolve around the areas of disease prevention/control, growth promotion, oestrous synchronization and supplementation of nutritional agents.

Numerous factors influence the design and development of a controlled release veterinary drug delivery system. A critical evaluation of the products on today's market reveals that the majority were 'animal needs' driven with each serving a solitary purpose: to deliver the single active for which the delivery system was designed. As a result the market is littered with unique and individualised delivery systems, each of which may effectively delivery the single active they were designed to deliver, but which have little practical application for the delivery of other compounds. Recently, however, we have seen a shift in focus in the area of veterinary pharmaceutical research. Several delivery systems have emerged that address drug delivery technology gaps, rather than being developed to deliver a particular drug for a specific clinical condition. This shift in philosophy is the future direction in which this field of pharmaceutical science is heading. It is the aim of this presentation to discuss and expand upon the potential of 'technology driven' veterinary controlled release products.

ORAL FORMULATIONS

Ruminal boluses

Ruminants present significant challenges to the drug delivery scientist, who must develop systems that deliver their contents for very extended periods. Fortunately for

the formulation scientist, ruminants have several useful physiological features. For example, their stomach is composed of four chambers. The largest of these chambers is the rumen which presents the formulator with a region wherein a drug delivery system can be housed and retained. The challenge, therefore, becomes to design a delivery system that not only delivers its active ingredient at the correct rate for the desired duration, but which is also retained in the rumen for the delivery period. The latter is normally achieved by developing delivery systems with sufficient density or that expand in some physical dimension upon entry in the rumen (Cardinal, 1997).

Several approaches have been used to produce expanding delivery systems. The Paratect Flex, Bolus is one example of this type of approach. The unique features of the Paratect Flex, Bolus are its shape, physical construction, drug release profile, method of administration and mathematical equations describing drug release. It was specifically formulated to deliver morantel tartrate. Many others exist in the literature (Cardinal, 1997), but each has in common that they delivery only one drug and have little application beyond that compound.

Examples of high-density delivery systems include Spanbolet, II and Monensin RDD, once again, animal-driven drug delivery systems, which provide little opportunity to deliver any other compound beyond that which they were specifically formulated to deliver.

A critical review of the area suggests that several current and future opportunities exist. These include: (i) the development of versatile drug delivery technologies that are capable of dispensing any drug independent of the environmental conditions found in the rumen, and (ii) the development of drug delivery systems which completely degrade during or following release.

Current efforts to achieve these aims include the Ruminal Therapeutic System (RUTS) Push-Melt% technology (Cardinal, 1997) and the Time Capsule. The Ruminal Therapeutic System (RUTS) Push-Melt%

technology is a versatile drug delivery technology that is claimed to be suitable for the delivery of parasiticides, insecticides, nutritional supplements, antibiotics, growth promoters, repartitioning agents and oestrous suppressants. This osmotic system consists of an injection-moulded, semipermeable membrane that encapsulates an osmotic tablet, a partition layer, drug formulation, and an iron densifier. Two commercial products have been developed and marketed using the RUTS Push-Melt[®] technology. Dura SE, delivers sodium selenite to selenium-deficient cattle for up to 4 months. IVOMEC SR, (ivermectin), delivers the parasiticide ivermectin to cattle for 135 days.

The Time Capsule, developed in New Zealand, is a world-leading effort to develop a ruminal delivery system that is capable of delivering active for prolonged periods (up to 6 weeks), and yet completely disappears following release. Currently this product may be viewed as an animal-needs-driven product – it is specifically formulated to deliver zinc for facial eczema - however, the basic principles of this product has the potential to be turned into a technology offering the opportunity of delivering a wide range of drug candidates.

Systems to bypass the rumen

These systems are intended to pass through the rumen without releasing drug, and then to release drug in the lower GI tract in areas such as the abomasum. Heat, chemical treatment and the synthesis of low soluble analogues have been the traditional approaches to produce rumen by-pass systems (Wu & Papas, 1997). A critical review of the area suggests that several current and future opportunities exist in this area. This is a challenging area that has received little research. The opportunity for more extensive fundamental investigations combined with the use of novel polymers is only over ridden by the requirement in this area of drug delivery to make very inexpensive preparations. To date, a too demanding challenge. However, recent advances have been made in this area. Pellets have been developed using specially selected polymers, pigments and aliphatic acids. The ingredients used and the manufacturing methods are all, by necessity, inexpensive, making this technology viable for the delivery of methionine, to increase wool production in treated animals. This approach is a further example of a technology - the concept can potentially be applied to many different compounds.

INTRAVAGINAL DRUG DELIVERY SYSTEMS

Several commercially available intravaginal products have been marketed which include CIDR, polyurethane sponges, CueMate, and PRID (Rathbone *et al.*, 1997a; Rathbone *et al.*, 1997b; Rathbone *et al.*, 1998; Eichman *et al.*, 1999). The principles behind the formulation and delivery of progestagens from these silicone or polyurethane based delivery systems have been established since the early 1970s. Indeed, it is only recently that developments in this area of veterinary medicine have been forthcoming. These have been in the form of technologies that specifically address the current and future needs of this area including (i) the development of drug delivery technologies that are

capable of delivering progestagens in a more controllable manner, (ii) the development of drug delivery technologies that are capable of extending the list of drug candidates that can be delivered intravaginally, (iii) the development of the physical shape and retention characteristics of current intravaginal delivery systems to permit their use in other animal species, and (iv) the development of drug delivery systems that can release multiple drugs either simultaneously or consecutively, hours or weeks apart in a slow or immediate (pulsed) manner.

The most recent and technologically advanced controlled release drug delivery system available for the control of the cattle oestrous cycle is the Intelligent Breeding Device (IBD; Rathbone *et al.*, 1997a; Rathbone *et al.*, 1997b; Rathbone *et al.*, 1998). The unique features of this delivery system are that drug delivery is controlled through electronics that control the rate and time of release of the active compounds. The IBD is designed to continuously deliver progesterone from the large drug reservoir over a 10-day period, a pulsed dose of estradiol 1 hour after administration and a pulsed dose of prostaglandin 6 days after administration, to precisely control the oestrous cycle. This device is an example of a technology. Its current format is designed for oestrous control, however, it has the capability to be tailored to the delivery of any drug that elicits a biological response following intravaginal administration.

Recently poly(ϵ -caprolactone) intravaginal inserts have been described (Bunt *et al.*, 1999a; Bunt *et al.*, 1999b; Ogle *et al.*, 1999). Once again progesterone was incorporated into the insert to demonstrate its capability of delivering progesterone to control the oestrous cycle of cattle or sheep. However, the low moulding temperature (Ogle *et al.*, 1999) and capability to add excipients (Bunt *et al.*, 1999b) result in it being a technology that is capable of delivering a list of different compounds, and to control their rate of release.

Following extensive fundamental investigations into the anatomy and physiology of the pig vagina, coupled with an understanding of its daily physical habits, a delivery system based on the CIDR technology has recently been developed for use in gilts to control the oestrous cycle (Burggraaf *et al.*, 1999).

INJECTABLE SYSTEMS

A number of successful controlled-release products are commercially available which provide controlled release via injectable systems (Cardinal & Witchev-Lakshmann, 1992). These animal-driven products use relatively simple approaches. For example, a long-acting injectable of oxytetracycline was prepared in 2-pyrrolidone. The theory was to prepare a solution of drug that was close to saturation, so that, upon injection, the drug would slowly deposit a fine precipitate, creating a drug suspension depot at the injection site. The resulting formulation succeeded in providing release of drug over 2 to 3 days. Ivermectin has been formulated into propylene glycol and glycerol formal and administered subcutaneously to cattle and pigs. The half-life of the drug, combined with its formulation into a nonaqueous vehicle (which allows for the creation of a depot at the site of injection), prolongs the action of the drug for over a month.

A review of the recent literature suggests that this area of veterinary medicine is heading in the direction of biodegradable technologies. Several microsphere products have been emerging in the literature for the delivery of antibiotics into the synovial fluid of equine joints and steroids to control oestrus and ovulation in mares and gilts (Burns, 1999). Microspheres consist of a multiplicity of small spherical particles each less than 200 µm in diameter. They are monolithic systems consisting of a polymeric matrix in which the drug substance is either dispersed or dissolved, depending on its solubility. The microspheres are then administered as a sterile, water-based injection. By necessity, this is a technology-driven area. Commercial manufacturing methods for microspheres are covered by a limited number of patents that extensively describe the technology necessary to manufacture a microparticle.

IMPLANTABLE SYSTEMS

Various implants that contain drugs to promote growth of the animal e.g., Synovex, Ralgro, or control the oestrous cycle, e.g., SYNCRO-MATE-B, and Crestar, have become commercially available over the years. A review of the area suggests that although the products were clinically effective, several opportunities existed for the pharmaceutical scientist to intervene to improve aspects of those products. These included improved drug utilisation and improved release profiles. A critical review of the area suggests several avenues for future work. These include (i) that the basic formulation approaches taken were adequate for the formulation of stable molecules, but are inadequate for the formulation of proteins and peptides and (ii) the implants were manufactured using polymers that did not degrade and required removal, the opportunity exists therefore to develop biodegradable implants that release their contents and then degrade away leaving no residual drug or delivery system.

SYNCRO-MATE-B, and Crestar, are subcutaneous implants for oestrous control. The (pharmaceutical) deficiencies of these two delivery systems are that their release profiles occur in a declining fashion, thus, high doses of drug are delivered following administration, but as time goes by, the amount of drug released each day declines. To overcome this problem, the SYNCRO-MATE-C, implant was developed. It utilizes the microsealed drug delivery, (MDD) technology, and consists of dispersed crystalline norgestomet in microreservoirs of aqueous PEG 400 throughout a matrix of polymerized silicone. The implant delivers drug constantly over the entire insertion period.

COMPUDOSE, is a controlled-release implant made by coating a non-medicated silicone rubber core with a thin layer of silicone rubber which contains micronized crystalline estradiol-17β. It was originally designed as a solid monolith, but was redeveloped into its current form to improve its drug utilisation. This was achieved following an in-depth investigation of its mechanism of release which defined the areas of the implant where drug was released.

The delivery of peptides and proteins is a challenging one to the formulation scientist. In addition to the normal challenges, proteins and peptides are subject to conformational instability, are readily degraded in the contents of the stomach and, being very large molecules,

do not readily absorb. Attempts to develop a drug delivery technology capable of delivering proteins and peptides resulted in the VITS device. This device is a small, implantable drug delivery system in which the active drug is kept isolated from the body's aqueous environment until release. It is designed to provide controlled delivery of drugs for periods of 1 day to 1 year. Its composition is such that it operates via an osmotic energy source. Typically release from the VITS is constant, but declining or pulsatile release profiles can also be designed.

The SABER™ delivery system is an example of a biodegradable implantable delivery system. It utilises a unique high-viscosity base compound to provide controlled release of the drug over a specified period of time. The use of different solvents and additives can alter the duration of release from the SABER™ delivery system from hours to months. This delivery system has been used to deliver deslorelin, a potent GnRH analogue, to induce ovulation at a precise and predictable time in mares and in swine prior to artificial insemination.

EXTERNALLY APPLIED DRUG DELIVERY SYSTEMS

Methods such as spraying, backrubbers and dustbags have been employed by farmers to control ectoparasites. In addition, several externally applied controlled-release technologies have been developed for the administration of insecticides. These have included ear tags, neck bands and tail tags. Recent approaches, however, have focused on the formulation of injectable microsphere preparations containing control agents (e.g., ivermectin) that are systemically effective against blood-feeding ectoparasites.

CONCLUSION

Controlled-release delivery systems for drugs remain in their infancy in the veterinary area. This area offers unique opportunities to the formulation scientist in terms of the diverse nature of the field and anatomical and physiological peculiarities of an individual animal species.

Today's trend in controlled-release veterinary drug delivery appears to be that of pharmaceutical scientists developing veterinary drug delivery systems independent of any clinical application. However, turning those technologies into products that do have a clinical application will require the collaborative efforts of animal, veterinary and pharmaceutical scientists. The success of these technologies will depend to a large degree upon animal scientists recognising the clinical opportunities for such technologies.

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