



Aspects in controlled drug delivery for topical applications in veterinary medicine

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ABSTRACT

The controlled release of drugs is an appealing area of research as it provides numerous benefits in veterinary and human medicine. In this paper we attempt to analyze certain aspects related to topical drug delivery systems, their successes and failures, and their place in veterinary medicine. Some emphasis is given to the pharmaceutical aspects of the delivery systems, where the material available made it possible. Purely topical devices, such as cattle ear tags and various collars, as well as some topically administered bioavailable delivery systems are discussed. Special attention is given to hitherto under-evaluated delivery systems, such as topical varnishes. A carefully selected bibliography aims to lead the reader easily to the facts, without providing overwhelming data of varying quality. We believe that the paper may be of interest to practicing veterinarians as well as to pharmaceutical scientists working or considering practice in the area.

Introduction

The veterinary field is an area rich with opportunity for the application of controlled-release (CR) technology (Cardinal, 1985). In veterinary medicine, the main reasons for developing a controlled and/or prolonged-release system are the animals' welfare (the reduction of stress from restraints and handling required for more frequent dosing of conventional formulations), caregiver or veterinarian convenience and reduction in the costs of care. Controlled-release systems are not only more convenient to administer than repeat-injection dosing but also enable the quantity of the drug administered to be known, in contrast to the administration of a drug in drinking water or food. In addition, these dosage forms can also reduce human exposure to veterinary compounds that are sometimes unsafe to handle (Rothen-Weinhold, Gurny & Dahn, 2000). Topical administration for either local or systemic effects often provide additional benefits such as reduction in handling during administration compared with dosing by the oral or injectable routes. One of the benefits of working in the veterinary area is that unlike human medicine, formulations can be tested expediently in the target

species (McDowell & Rathbone, 2014). Nevertheless, many challenges remain, especially in the veterinary arena such as more limited budgets, very cost-competitive product pricing, acquiring registration particularly with regard to human food safety and environmental safety, and sometimes the gap between the perceived and actual market needs (Rathbone & Brayden, 2009).

Veterinary controlled release is a large field that has been extensively reviewed previously (Bilhalva, Finger, Pereira, Corrêa & Burkert Del Pino, 2018; Jain, Kashaw, Rathi & Agrawal, 2003; Rathbone & Brayden, 2009; Rathbone & Witchey-Lakshmanan, 2001; Rathbone, 1997, 2002; Rathbone & Cady, 1999; Rathbone & Martinez, 2004; Rathbone & Witchey-Lakshmanan, 2000). Generally, the area is as large as veterinary pharmacotherapy itself; nevertheless, new developments are rather slow. Given clear advantages that exist to controlled delivery of therapeutics, this apparent stagnation seems perplexing. In this narrative we provide an overview of the published literature on the subject, with specific focus to what appears to us as new concepts, or at least the application of principles known in human pharmaceuticals to veterinary medicine, and yet retaining the decades-proven approaches that are

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unique to veterinary applications. A detailed review of all the possible delivery systems is beyond the scope of our present effort; instead, we will attempt to focus on some aspects of topical controlled-release delivery in veterinary medicine. For this purpose, we searched a variety of databases with keywords, first broadly, then more narrowly and specifically, and reviewed in this manuscript the publications that either presented historical interest to evidence the development of controlled-release delivery systems in veterinary sciences to our days, or publications presenting interesting advances in the field, that could provoke further ideation and research. This narrative relates to a variety of delivery systems presenting some form of control over the drug release, regardless of the terminology used in the publications; the use of the terms “controlled release”, “sustained release”, “prolonged release” and many others, while originally aiming at slightly different phenomena, are now duly used synonymously in pharmaceutical science, and we will observe this practice in the current manuscript.

In general terms, topical delivery systems may be subdivided into two major classes; we will refer to them as the topically administered bioavailable systems and the local delivery systems. The latter are not intended to deliver the drug for systemic circulation, whereas the former will necessarily exert their effect at least partially by absorption and distribution to the target tissues. Incidentally, some of the bioavailable systems may also target external membranes, such as spot-on systems for the treatment and control of, for example both ectoparasites and endoparasites (endectocides).

The drugs used in the topical systems can be largely divided into several classes – pest-control substances, antimicrobial substances, ocular medications, and miscellaneous compounds (reproduction enhancers, analgesics, etc.). New actives of very different modes of action such as RNAi and lethal gene technologies are being explored for applications such as ectoparasite and vector-transmitted pathogen control, and some of these methods may pose new challenges for controlled drug delivery systems (Pérez de León, Mitchell & Watson, 2020).

Non-bioavailable topical devices

The non-bioavailable topical devices mainly include livestock ear tags, companion animals’ collars and topical CR formulations. All these will be addressed briefly below.

Wearable devices

The idea of using wearable devices for pest-control has been around for many years. The first idea to attach a pesticide-bearing device is over a century old (Day, 1916). The drugs that have been hitherto tested include predominantly antiparasitics and insecticides such as various organophosphates, carbamates, avermectins, benzimidazoles, isoxazolines and pyrethroids. Luckily, many of these penetrate animal skin sufficiently to cause a generalized effect, yet topical systems were studied extensively. Treatment of ectoparasites is important both for the animals and for humans around them, as ectoparasites cause significant disturbances to the animals, cause multiple allergic reactions, and transfer pathogens, some of which are zoonotic. For example, in cattle, injurious ectoparasite infestations impair the productivity of cattle and, in extreme cases, result in mortality. This inflicts significant economic loss on cattle producers around the world. Estimates indicate that ectoparasitic flies and ticks infesting cattle in Brazil cause US\$6.86 billion in economic losses annually. Adopting the principles of integrated pest management to practice integrated ectoparasite management mitigates the risk for the development of resistance to ectoparasiticides while maximizing their longevity as useful tools used rationally with decreased impact on nontarget species (Pérez de León et al., 2020).

The first significant topical CR efficacy was reported by Ahrens (1977), who applied stirophos-polyvinyl chloride tags onto the ears of 70 animals in a herd of cattle suffering from horn fly (*Haematobia*

irritans) infestation. Following application of the tags the flies’ counts were depleted by 95% within 2 weeks. Even better effectiveness was reported with 8% w/w fenvalerate tags (Ahrens & Cocke, 1979) and similar results for season long control of face flies (*Musca autumnalis*) a beef cow and calf suckler herd and for horn fly in a lactating dairy herd where reported by Knapp and Herald (1981). Although the benefits of pest-burden reduction were appreciated at once and their economic implications realized (Byford, Craig & Crosby, 1992), Boland, Scaglia and Umemura (2008) later reported statistically significant correlations between reduction of horn fly burdens and animal well-being when using diazinon 20% w/w and coumaphos 20% w/w ear tags. Harris, Hillerton and Morant (1987) found under United Kingdom conditions that fenvalerate ear tags reduced fly loads on dry dairy cattle by 95% between July and September. Fly dislodging behavior, such as ear flicks which correlated with numbers of *Musca autumnalis* on the face and stamps/kicks which correlated with numbers of *Stomoxys calcitrans* on the legs, was also significantly reduced. There was no significant difference between the tagged and untagged groups in the total time spent grazing each day. Milk yields were not statistically significantly different, but the tagged group showed a greater increase in milk yield between lactations, of 1.45 kg/cow daily in the first 12 weeks of lactation.

In addition to cattle, 10% permethrin ear tags were tested in horses against *Stomoxys calcitrans*, and *Haematopota dissimilis* and found effective for 1,2 months (Parashar, Gupta & Rao, 1989). Tetrachlorvinphos (13.5%) and cypermethrin (8.5%) tags were studied in sheep and found effective against sheep lice (*Damalinea ovis*) for up to 45 weeks (James, Erkerlenz & Meade, 1990; James, Meade & Powell, 1989). Ear tags containing 10% zeta-cypermethrin and 20% piperonyl butoxide (PPB) were found effective in sheep against a variety of mosquitoes (Johnson et al., 2013).

Overviews of commercially available ear tags are extensively provided by many sources; we feel that it may be cumulative to reprint the lists that are prone to changes, as products are being phased out of the market and the availability of each of these may be dictated by local registration processes. The more common active ingredients controlled-release ear tags are presented in Table 1.

Table 1

Active ingredients used in medicated ear tags to control various ectoparasites of livestock.

Active ingredients (% w/v)
Stirofos, 10%
Fenvalerate 8.6%
Diazinon 20% coumaphos 20%
Diazinon 15% coumaphos 35%
Diazinon 20% chlorpyrifos 20%
Diazinon 30% chlorpyrifos 10%
Diazinon 40%
Diazinon 21%
Diazinon 20%
Diazinon % Piperonyl butoxide %
β-cyfluthrin 15%
λ-cyhalothrin 10% Piperonyl butoxide 13%
Pirimiphos methyl 20%
Permethrin 10%
Permethrin 10% chlorpyrifos 6.6 %
Permethrin 10% chlorpyrifos 6.6 %; Piperonyl butoxide
Ethion 36%
Fenthion 20%
Fenthion 20% P Piperonyl butoxide PB 15%
Cyflutrin 10%
Pirimiphos methyl 14% λ -cyhalothrin 6.8%
Abamectin 8% Piperonyl butoxide v20%
Zeta-cypermethrin 10% Piperonyl butoxide 20%
Cypermethrin Chlorpyrifos

The effect of treatment area

The wearable devices may produce a sustained generalized effect due to the animal behavior. The animal tends to groom itself and thereby effectively distributes the topically released drug over large areas of the body. The drug is usually retained on the fur and thereby exerts its effect beyond the area where it is actually released or applied. Interactions in the herd contribute to the distribution of the drug over various areas of the body, as tagging only half a herd produced gave protection against horn flies (*Haematobia irritans*) to most animals in a herd (Harvey & Brethour, 1981) and produced almost identical drug residues on the bodies and rumps of the untagged animals (Mwangala, Sarna, Galloway & Webster, 1993). It was shown that the distribution pattern of a drug from an ear tag in a single animal is very irregular or spotty (Miller, 2000). This difference may have resulted in showing that udder pest (i.e. *Hydrotaea irritans*) could only be controlled with two tags rather than with one, probably because of poorer distribution to the abdominal regions (Hillerton, Bramley & Yarrow, 1985). Additionally, resistant horn flies were shown to concentrate on ventral regions, where the insecticides concentrations are lowest (Foil & Hogsette, 1994). Delta-methrin 4% eartags have shown only moderate protection against the tsetse flies *Glossina pallidipes* and *Glossina morsitans*, since the preferred landing sites of these pests is lower torso and legs (Thomson, 1987). Nevertheless, as correctly noted by Miller (2000), some pests that move over the animal ultimately come in contact with the treated area, whereas others prefer specific areas of the animal and may appear “resistant” to the treatment. This explains the ear tags’ efficacy against the extremely mobile horn fly (*Haematobia irritans*), and lack of efficacy against lone star tick (*Amblyoma americanum*).

Drug release from ear tags and related farm-animal devices

One of the limitations of the ear tags is their loading capacity, i.e., the amount of the drug that a single tag can contain. It is generally accepted that an ear tag should not weigh more than 17 g., otherwise its weight may cause an enlargement of the punctured hole thus injuring the animal, and eventually the tag might be prematurely lost (Miller, 2000). Neckbands, on the other hand, may weigh as much as 200 g., but they suffer from limited drug distribution, as the necks move less than the ears. Tail tags may also hold considerable weight, but the technique for attaching them securely to withstand the tail switch is still lacking.

The release of the drugs from common ear tags has been shown to follow essentially the first-order diffusion, based on Fick’s diffusion models, with the rapid initial release waning with time (Miller, Oehler & Kunz, 1983). Some authors suggest that the physical incompatibility between the polymer, most commonly polyvinyl chloride, and the drug, as the driving force for the release, and the exudation of the drug, sometimes referred to as “blooming.” However, it should be noted that (a) these are two ways to describe the same process, (b) there may be conceptual concerns whether both assumptions – the incompatibility of the drug with the matrix, and the uniform solid solution of the drug therein – hold true, and (c) to determine the diffusion model, no interaction should occur between the permeator and the matrix but this assumption does not always hold true. For example, the release profiles from ear tags containing permethrin PBB (claimed effectiveness of 5 months) were studied and the effects of the obtained concentrations on the *Haematobia irritans* mortality were evaluated (Li, Allen Miller & Klavons, 2008). The results exhibit clear release arrest of both compounds after about 8 weeks which is corroborated by the results of significantly reduced mortality of the pest when exposed to the ear tags after 8 weeks in both resistant and susceptible strains. Ahrens and Cocks (1979) observed that fenvalerate concentration in the tags after their removal from the animals decreased from 8% to only about 6.5% after almost five months of release. It is not improbable that some commercially available products may show similar polymer-drug interaction after various use periods.

Membrane-controlling devices were previously described, as well as refillable assemblies for the controlled delivery of rotatable formulations (Hogsette, Prichard, Ruff & Jones, 1991; Miller, 2000; Rothen-Weinhold et al., 2000). All these were aimed to provide a near-zero-order release at least over a portion of the drug-release period. To date, none of these is presently on the market. The drug-release rate from the common ear tags appears to be influenced by a number of factors, mainly the ambient temperatures, and the amounts of drug present on an animal are naturally affected by precipitations.

Resistance management and alternative approaches

Many strategies were attempted to overcome the increasing resistance to pyrethroids. Ivermectin pour-on was used in addition to permethrin ear tags to control the generally resistant horn fly populations (Foil et al., 1998). Combinations of organophosphates and pyrethroids were tried, although their use today is discouraged. Another concept to overcome the resistance to pyrethroids is to introduce a synergist – PPB or N-octyl bicycloheptene dicarboximide (MGK-264) – broad-spectrum inhibitors of detoxifying enzymes in the pest. Yet the synergist effect of PPB is not linear, concomitantly reducing the activity of some organophosphates, notably diazinon, probably via inhibition of bio-activation (Li, Guerrero & Pruett, 2007). The most common practice is to rotate the classes of insecticides, and to avoid retaining the tags after the label term is over. However, this approach has not demonstrated the prevention of emerging resistance (Barros, Alison & Foil, 1999), and cross-resistance in the horn flies was reported between pyrethroids and organophosphates.

Alternative strategies for pest control are becoming increasingly popular, including assurance of proper hygiene, selection of the cattle to improve innate resistance to pests, introduction of parasitoids/natural predators, and development of vaccines (Oyarzún, Quiroz & Birkett, 2008). Various surveys in the USA and Australia show that the use of medicated ear tags is at most 20% of all pest-control cases, and in some areas less than 5%, with preference given to either more labor-evident methodology, such as dust bags and insecticide sprays, which are beyond the scope of the present manuscript, or to pour-on formulations. External fly traps and premises sanitizers offer an additional way to control some pests, which, along with a call to ban organophosphates from various environmentalist and animal welfare organizations, may lead to a further decline in the use of medicated ear tags and other wearable devices in farm animals.

Companion animal collars

Despite the disadvantages of ear tags in livestock, flea and tick collars have found wide use in companion animals. The reasons for this difference in attitude are multiple. First, companion animals principally, cats and dogs are not normally consumed for food in Western culture, allowing for a larger variety of medicated products to be used for the treatment of various conditions. Second, as companion animals normally reside with their owners, the tolerance for pests is significantly lower than for farm animals. Third, companion animal products are often less cost sensitive than livestock products may provide better remuneration despite significantly lower absolute numbers of companion animals in comparison to cattle. The global market for companion animal healthcare was valued at US\$ 8.518.7 billion in 2020 and is growing 9.2% a year (Grand View Research, 2021).

An excellent and comprehensive overview of the collar technology was published by Withey-Lakshmanan (1999). The history of their development and the technological highlights were discussed. Generally, these technologies started with the delivery of volatile organophosphates from PVC matrices, and then evolved through the delivery of less volatile compounds, including carbamates, with the necessary modifications of porosity of the collar matrix. The various formulation problems – including initiation of the drug release from the moment of

production and possible implications in the toxicity of the drug to the host – were discussed. Alternative matrices, such as polyurethanes and ethylene vinyl acetate, as well as reservoir technology, ultrasound-repelling devices, and mechanical traps, were discussed in detail.

The most common arthropod ectoparasites of companion animals and livestock are presented in Table 2. Many of these parasites are vectors of important diseases and control of the ectoparasites provide additional methods of control of vector-borne diseases. Biology and the life cycle of many common companion animal ectoparasites have been reviewed extensively along with a general summary of the practices to manage these pests (Blagburn & Dryden, 2009; Dryden & Payne, 2004; ESCCAP, 2018; Pérez de León et al., 2020; Rust, 2020; Starkey & Little, 2012; Starkey & Stewart, 2015).

Several collar formulations were investigated against a variety of pests in companion animals. Table 3 represents some of the available collars. These include deltamethrin, amitraz, s-methoprene/pyriproxyfen combinations, propoxur, propoxur/flumethrin combination, tetrachlorvinphos, fipronil (Jeannin, 2000), and lately imidacloprid/flumethrin combination. By way of example, we have gathered the information on the latter combination, since the data on it are most readily available and this fixed-combination collar is probably one of the most studied anti-ectoparasite products. Developed by Bayer Animal Health and now marketed by Elanco Animal Health under the brand name Seresto™, it contains an insect anticholinergic neurotoxin (imidacloprid) and a synthetic pyrethroid (flumethrin), and has shown efficacy on dogs and cats against a variety of pests, principally fleas and ticks and, importantly has shown good efficacy in the prevention of several vector-transmitted infections (Table 4). Additional information including safety precautions and provided on the local product labels.

The synergy between imidacloprid and flumethrin was shown in an *in-vitro* isolated insect nerve model (Stanneck et al., 2012a). The efficacy of the combination in collars for was shown to reduce tick counts by at least 90% and flea counts by at least 95% for a period of at least 7,8 months in cats and dogs under field conditions (Stanneck et al., 2012b), and was shown to be effective in preventing some parasite-borne infections such as *Ehrlichia* (Stanneck & Fourie, 2013), *Anaplasma platys* and *Babesia vogeli* (Dantas-Torres et al., 2013), *Dipylidium caninum* (Fourie, Crafford, Horak & Stanneck, 2013), *Babesia canis* (Fourie, Stanneck & Jongejan, 2013) and *Leishmania infantum* (Brianti et al., 2014) in dogs, and of *Bartonella henselae* (Lappin et al., 2013) in cats, but not of *Mycoplasma haemofelis*.

The use of collars in companion animals is not only limited to parasite control. Numerous works have suggested using collars with dog appeasing pheromone (DAP, at loading 2.5%) to treat stress-related disorders in canines. The feline counterpart (feline facial pheromone, FFP), and other species' equivalents, are used as immediate-release formulations only. A meta-analysis of the DAP and FFP efficacy was

Table 3

Examples of active ingredients in medicated collars used for companion animals.

Active ingredient	Effective against	Target species (claimed duration of activity)
Dog appeasing pheromone (DAP) 2.5%	Canine stress	Dogs (1 month)
Amitraz 9%	Fleas, ticks and mites	Dogs > 12 weeks (3 months)
Imidacloprid 10% & Flumethrin 4.5%	Refer to Table 4	Dogs >7 weeks (7,8 months) Cats >10 weeks (7,8 months)
Methoprene 2.1% & Propoxur 10 %	Fleas' eggs and larvae, fleas, ticks, mites	Cats >12 weeks Dogs >12 weeks
Methoprene 2.1% or 1.02%, & Tetrachlorvinphos 14.55 %	Fleas, ticks, mites	Dogs > 6 weeks
Pyriproxyfen 0.5%	Flea eggs and larvae, adult fleas, ticks, mites	Dogs > 3 months up to 1 year Cats up to 1 year
Flumethrin 2.25% & Propoxur 10 %	Fleas and ticks	Dogs (5–7 months)
Propoxur 9.4% or 9.87%	Fleas and ticks	Dogs, cats (3–5 months)
Deltamethrin 4%	Fleas and ticks	Dogs > 12 weeks (6 months)

reported by Frank, Beauchamp and Palestini (2010).

Topical varnishes and controlled delivery systems for oral cavity

Another class of topical delivery systems has recently emerged in the veterinary field. The idea of the topical application of viscous formulations that dry out to form controlled-release delivery systems *in situ* has been around for some time and found wide acceptance in human medicine, mainly in dentistry (Balanyk & Sandham, 1985; Kolehmainen, 1981; Newman, 1986) and in nail infections (Murdan, 2002). Animals were not infrequently used as models for these studies (Kozlovsky, Sintov, Zubery & Tal, 1991), and readily-available *ex-vivo* tissues or synthetic surrogates were also used for the research. The first veterinary application of an oral bioadhesive tablet for the treatment of gingivitis in dogs, releasing chlorhexidine and niacinamide (Gruet, Maincent, Berthelot & Kaltsatos, 2001) was previously reviewed (Rothen-Weinhold et al., 2000). The tablets were used daily for 14 days and demonstrated a statistically significant reduction of dental plaque, quantitative periodontopathogen counts and total anaerobic bacterial counts, spirochetes, and halitosis; however, they failed to reduce gingivitis. We have also previously reported a study of triclosan, cetylpyridinium chloride and chlorhexidine varnishes against common oral pathogens in dogs (Lavy, Ezroni, Friedman & Steinberg, 2012). Various drug loadings and the

Table 2

Common arthropod ectoparasites of livestock and companion animals that are targeted by topical ectoparasiticides.

Fleas	Ticks	Mites	Lice	Flies
<i>Archaeopsylla erinace</i>	<i>Amblyomma</i>	<i>Chorioptes bovis</i>	<i>Bovicola bovis</i>	<i>Culicoides spp</i>
<i>Ctenocephalides canis</i>	<i>Americanum</i>	<i>Demodex canis</i>	<i>Felicola</i>	<i>Glossina spp</i>
<i>Ctenocephalides felis</i>	<i>A. maculatum</i>	<i>D. cati</i>	<i>subrostratus</i>	<i>Haematobia irritans</i>
<i>Echidnophaga gallinacea</i>	<i>Dermacentor reticulatus</i>	<i>D. gatoi</i>	<i>Trichodectes canis</i>	<i>Hypoderma spp</i>
<i>Pulex irritans</i>	<i>Haemaphysalis</i>	<i>Cheyletiella blakei</i>	<i>Haematopinus spp</i>	<i>Mosquitoes (e.g Culex, Aedes, and Anopheles spp)</i>
<i>P. simulans</i>	<i>longicornis</i>	<i>C. yasguri</i>		<i>Musca autumnalis</i>
	<i>Ixodes hexagonus</i>	<i>Lynxacarus</i>		<i>Phlebotomus</i>
	<i>I. ricinus</i>	<i>radovskyi</i>		<i>Stomoxys calcitrans</i>
	<i>I. scapularis</i>	<i>Neotrombiculi spp</i>		<i>Tabanids spp</i>
	<i>I. pacificus</i>	<i>Notoedres cati</i>		
	<i>I. holocyclus</i>	<i>Otodectes cynotis</i>		
	<i>Otobius megnini</i>	<i>Psoptes ovis</i>		
	<i>Rhipicephalus sanguineus</i>	<i>Sarcoptes scabiei</i>		
	<i>R. turanicus</i>			
	and others			

Table 4

Efficacy studies on imidacloprid plus flumethrin in medicated collars (Seresto™) on ecto-parasites of dogs and cats, and prevention of vector-transmitted infections.

Species	Pest	Number of animals	Duration	Study
Dogs	<i>Phlebotomus perniciosus</i> (and prevention of <i>Leishmania infantum</i>)	219	300 days	Brianti et al. (2014)
Dog	<i>I. holocyclus</i>	36	227 days	Smith et al. (2013)
Dogs	<i>R. sanguineus</i> (and prevention of <i>Ehrlichia canis</i>)	8 (+35 control)	378 days	Stanneck and Fourie (2013)
Dogs	<i>D. reticulatus</i> (and prevention of <i>Babesia canis</i>)	8 (+8 controls)	1 month	Fourie et al. (2013b)
Dogs	<i>C. felis</i> , (and prevention of <i>Dipylidium caninum</i>)	16	74 days	Fourie et al. (2013a)
Dogs and cats	<i>C. felis</i> , <i>C. canis</i> , <i>A. erinacei</i> , <i>P. irritans</i> , <i>D. reticulatus</i> , <i>I. hexagonus</i> , <i>I. ricinus</i>	313 (cats) 400 (dogs)	8 months	Stanneck et al. (2012a)
Cats	<i>C. felis</i>	8	8 months	Lappin (2013)
Cats	<i>A. americanum</i>	20	2 days*	Reichard (2013)

* attachment study

duration of the effect were investigated. Some varnishes allowed for up to 10 days' control of common oral pathogens (two powers of magnitude reduction of bacterial counts) after a single application.

Sustained-release varnishes were also successfully applied to treat lesions caused by *Microsporum canis* dermatophytosis, which had previously shown poor responses to topical griseofulvin, itraconazole and lufenuron in a Siamang primate (*Hylobates Syndactylus*) (Avni-Magen et al., 2008). Although a single animal was treated in that report, it provided an incentive to further study the efficacy of these delivery systems, especially for wildlife animals, as the treatments may persist for prolonged intervals on the animals and provide treatment that would otherwise require recapturing and anesthetizing the animals. Moreover, we have also provided (unpublished data) a compassionate treatment of the same varnish applied to a female brown bear (*Ursus Arctos*), which had an unidentified dermatophyte infestation resistant to the same topical treatment on her nose. The varnish was applied once to the conscious animal using a long brush. The dermatophyte patch resolved within several days without recurrence. Similar compassionate treatments were performed on several mixed-breed dogs (unpublished data). The varnish was applied from one to three days, with complete resolution of the lesions. More recently, efficacy of ivermectin varnish in the treatment of wound myiasis of various severity was assessed in a variety of zoo animals, and it has been demonstrated that the use of a topical ivermectin varnish (with or without concurrent injectable ivermectin) can reduce handling and treatments, had no detectable adverse effects, and had minimal recurrence of the disease when compared with cases treated without it (Avni-Magen et al., 2018).

Furthermore, a sustained-release varnish containing chlorhexidine was used to treat oral necrobacillosis, known as lumpy jaw, in several captive macropods (*Macropus giganteus* and *Macropus rufogriseus fruticis*), shortening the treatment time relative to the literature values (Bakal-Weiss et al., 2010). The study also indicated that the treatment may prevent a recurrence of the condition over time.

The controlled-release varnishes can be coated onto a variety of surfaces, in addition to the skin and the teeth. An effect of coating chlorhexidine varnish onto a urinary catheter was evaluated in the prevention of catheter-associated urinary tract infections in dogs (Lavy, Brinker, Friedman, Steinberg & Segev, 2012) via the prevention of biofilm formation thereon (Segev et al., 2013) and on urethral stents

(Zelichenko et al., 2013). We also tested the efficacy of chlorhexidine varnishes on mastitis prevention when applied on the mammary glands of dry cows (unpublished data). The varnish remains on the teats for a prolonged time interval, providing residual chlorhexidine levels that inhibit bacterial growth even after the varnish peels off from the application site.

We feel that the potential of controlled-release varnishes is yet to be fully realized in the field of veterinary medicine.

Bioavailable systems

Bioavailable drug delivery systems allow for the drug to be absorbed into the bloodstream and to effect its action in systemic manner. The drug affecting the site of action is not being directly applied thereto, as in cases of topical systems reviewed above, but distributed from the site of absorption by the blood flow. Bioavailable systems naturally include oral feeds, tablets, and other conventional delivery systems, which may and may not possess the property of controlled drug delivery. Within the framework of this narrative, however, we will focus on the formulations providing transdermal delivery of the drugs – pour-on formulations and transdermal patches. Unlike the purely topical delivery systems that draw their rationale from the barrier function of the skin and keeping the drug on its surface, the formulations of bioavailable products are expected to effectively permeate the skin barrier and to deliver their payload into the bloodstream.

Pour-on (Spot-on)

These especially attractive dosage forms have evolved over the years due to the appeal to deliver the drug with a small local application of solution on the one hand, and with the lenient requirements for transdermal delivery in the animals on the other. The animals' skin differs significantly in thickness and hair follicles and, consequently, in drug permeation. Despite that, the possibilities for using permeation enhancers and organic solvents have allowed for the rapid and prolific development of various pour-on formulations. The main target remains ectoparasites, although some pour-on / spot-on formulations are proven effective against endoparasites as well (for example, as a single active ingredient, selamectin (Boy et al., 2000), and more recently the use of combinations of actives has increased such as selamectin plus sarolaner and imidacloprid plus moxidectin (Geurden, Becskei, Farkas, Lin & Rugg, 2017). The European Medicines Agency (EMA, 2020) approved a spot-on formulation containing a triple combination of esafloxolaner, eprinomectin and praziquantel and this provides efficacy against a broad range of both ecto- and endo-parasites including cestodes in cats (Beugnet, 2021).

The formulation of these topically administered dosage forms is usually an oily solution or emulsion, sometimes augmented with permeation enhancers. A recent addition to the veterinary arsenal of fentanyl transdermal solution is no exception. In addition to the drug (5%) it contains octyl salicylate and isopropyl alcohol (Freise et al., 2012).

Generally, the application is made at one spot (hence the name), but sometimes several spots are required to provide the optimal distribution over the animal, or the dose. The drugs in some instances remain on the fur and in the sebum of the animals (e.g. fipronil), but eventually are absorbed and form a depot in the dermis, wherefrom they are gradually released, thereby providing for the extended nature of the release. Depending on the extent of the absorption and on the sebaceous-dermal circulation, various formulations provide coverage from several weeks to several months. The insecticides released from the spot-ons are usually active on contact with the pest, but sometimes a blood meal is required to deliver the lethal dose. The frequency of application may range from once a month to once in several months.

A wide variety of dosage forms have been evaluated and exist on the market. An attempt to amass all the available data on these formulations

would have required a separate volume. A short list of the active ingredients and their concentrations in pour-on formulations is presented in Table 5. These vary in pest specificity and host species' toxicity, and the practitioner is always encouraged to review the label of a specific product.

Transdermal patches

An overview of studies on the use of transdermal patches for veterinary applications was recently published (Brayden, Oudot & Baird, 2010). Briefly, due to the interspecies variability and variability between sites on an animal in the skin thickness and chemistry, as well as the external coat, the success in developing a veterinary transdermal patch was hitherto rather limited. Various patches containing primarily fentanyl, buprenorphine and lidocaine were studied. Human-approved patches were usually studied without reference to the veterinary species' skin properties. The attraction of using patches for continuous delivery of analgesia over several days is particularly evident for post operative use (Mirschberger et al., 2020).

Additionally, a comparison was made between the use of the fentanyl patch and fentanyl spot-on in dogs (Kukanich & Clark, 2012). There has been ongoing research in an attempt to develop suitable formulations for each species. Buprenorphine in dogs (Moll, Fresno, García, Prandi & Andaluz, 2011; Pieper, Schuster, Levionnois, Matis & Bergadano, 2011), lidocaine in horses (Andreoni & Giorgi, 2009), pilsicainide in dogs

Table 5

Representative spot-on / pour-on formulations (w/v) available in commercial formulations for livestock and companion animals (availability may vary by locality).

Target animals	Active ingredients w/v%	
Livestock	Permethrin 1% Piperonyl butoxide 1%	
	Permethrin 5% Piperonyl butoxide 5%	
	Permethrin 40%	
	Permethrin 5%	
	Permethrin 10%	
	Fenvalerate 10%	
	λ -cyhalothrin 1% Piperonyl butoxide 5%	
	λ -cyhalothrin 1%	
	Fenthion 7.6%	
	Cypermethrin 5% Piperonyl butoxide 5%	
	Doramectin 0.5%	
	Eprinomectin 0.5%	
	Famphur 13.2% (in xylenes 46.2%)	
	Permethrin 45%	
	Companion animals	Permethrin 65%
		Indoxacarb 13.01% permethrin 42.5%
		Permethrin 45% pyriproxyfen 5%
Pyriproxyfen 5.3%		
Dinotefuran 4.95% permethrin 36.08% pyriproxyfen 0.44 %		
Cyflutrin 1%		
Moxidectin 0.5%		
Indoxacarb 19.53%		
Imidacloprid 9.1%		
Imidacloprid 10 % permethrin 50%		
Imidacloprid 8.8 %, permethrin 44%		
Imidacloprid 10 %, moxidectin 1%		
Imidacloprid 10 %, moxidectin 2.5%		
Fipronil 10%		
Fipronil 9.8% and methoprene 8.8%		
Methoprene 2.3%, phenotrin 85.7%		
Metaflumizone 9.1%		
Amitraz 15% and metaflumizone 15%		
Amitraz 7.6, fipronil 6.4% and methoprene 5.8 %		
Phytosphingosine 1% (with ethyl diethylene glycol permeation enhancer)		
Ivermectin 1%		
Emodepside 1.98% praziquantel 7.94%		
Selamectin 6%, 12%		
Selamectin 6% sarolaner 1%		
Esafoxolaner 1.2% eprinomectin 0.4% praziquantel 8.3%		

(Iwasaki et al., 2009), calcitriol in cattle (Yamagishi et al., 2009), fentanyl in rabbits (Mirschberger et al., 2020) and even the ubiquitous fentanyl patch in prehensile-tailed skinks (Gamble, 2008), were all studied with encouraging results. Therefore, a species-oriented approach is necessary to develop a suitable transdermal patch.

Other delivery systems

Intramammary

Another route of administration amenable to topical, controlled-release attention is intracisternal administration in the mammary glands, predominantly of cattle. Many aspects of intramammary delivery were reviewed by Gruet et al. (2001) and Brayden et al. (2010), whereas an overview of the need for intramammary delivery was provided by Alany, Bhattarai, Pranatharthiharan and Devarajan (2013). A wide variety of intramammary formulations exist on the market, primarily antibiotics and antiseptics, with varying milking delay and slaughter delay requirements due to the possibility of residues in milk, and also in meat (via systemic absorption). Most of the products are provided either as solutions or as lipid-based liquid formulations, although the possibility for exploiting microparticulate systems is acknowledged. Inspired by this, perhaps, a study was performed with povidone-iodine microencapsulated into polyglycolides (Park & Han, 2002). Microspheres measuring between 25 and 155 μ m yielded a burst effect *in vitro*, releasing over 50% of the iodine immediately, and the remainder over 28 days, indicating its possible utility in the treatment of mastitis in the dry period.

Several polymeric systems were investigated as potential carriers for controlled-release intramammary delivery (Bhattarai, Bunt, Rathbone & Alany, 2011). These included hypromellose, sodium carmellose, xanthan gum and sodium alginate, in various solvent systems. The systems exhibited pseudoplastic behavior with thixotropy. A follow-up study (Bhattarai, Alany, Bunt, Abdelkader & Rathbone, 2015) of intramammary inserts based on hot-melt extruded polyethylene oxide and hypromellose, containing salicylic acid as a bacteriostatic agent, speculated that these inserts may provide sealing of the teat channel and inhibit bacterial colonization of the mammary gland. The drug release profiles were demonstrated (up to 4 h), and fitting to the Higuchi model (Higuchi, 1961) of suspended drug released from ointment base was claimed. The postulated mechanism of release was by passive diffusion through the viscous boundary layer of a hydrated polymer. We observe, however, that the molecular weight of the polymer had no effect on the drug release kinetics (in fact, it was opposite to that expected, if the claimed mechanism were true). Moreover, we question whether fitting of the data of the first 4 h bears any meaning to the overall drug release profile. Finally, we further question whether or not the swelling layer may retain constant thickness for the studied insert, and therefore the very conclusion of Higuchi behavior. Yet, it is encouraging to see the area revitalized, as the controlled release may provide better solutions for the prevention and treatment of cattle mastitis than hitherto provided.

Intravaginal delivery systems

Intravaginal devices are widely used in veterinary medicine, primarily to deliver progesterone for estrus synchronization and induction. These controlled release systems have been recently and previously reviewed, for example, Rathbone and Burke (2013) and we feel that the reader should refer to this authoritative text for a comprehensive review on this subject. An overview of the vaginal anatomy and physiology, the factors that make animals' vagina an especially convenient locale for drug delivery, and a thorough review of the existing technologies are given. We will only mention that despite the great variety of currently available devices, there still remain challenges for a pharmaceutical scientist to face in this area.

Ophthalmic implants

There are three main routes for the delivery of drugs to the eye: topical, systemic, and intra-ocular injection. The tissue barriers limit the access of drugs to their targets (Conway, 2008; Urtti, 2006). The corneal and conjunctival epithelial barriers cover the ocular surface. The blood aqueous barrier, composed of the uveal capillary endothelia and ciliary epithelia, limits the access of compounds from the systemic blood to the retina and vice versa. After topical eye-drop administration, less than 5% of the dose is absorbed into the eye. The dose is mostly absorbed into the systemic blood circulation via the conjunctival and nasal blood vessels. Eye drops are used only for the treatment of anterior segment disorders, since adequate drug concentrations are not reached in the exterior tissues using this drug delivery method (Del Amo & Urtti, 2008). Sustained release delivery systems can be applied to the exterior segment of the eye for treatment of conditions affecting the anterior segment of the eye (Conway, 2008). The challenge is to provide a system with improved ocular drug bioavailability and prolonged duration of activity, but still with a minimum risk of ocular complications (Davis, Gilger & Robinson, 2004).

During recent years, several methods have been evaluated in veterinary medicine. The goal of the intraocular implant design is to provide prolonged activity with controlled drug release from the polymeric implant material. Intraocular administration of the implants always required minor surgery. The long-term toxicity of an intravitreal implant releasing continuous cyclosporine in normal horses was determined by Gilger et al. (2000). Other clinical studies include: the use of a bio-erodible, deep scleral, lamellar cyclosporine implant for the treatment of horses suffering from uveitis (Gilger et al., 2006); the use of a subconjunctival cyclosporine implant for the treatment of keratoconjunctivitis sicca (KCS) in a red wolf (Acton, Beale, Gilger & Stoskopf, 2006), and the use of an episcleral cyclosporine implant for treatment of the same problem (KCS) in dogs with preliminary good results (Barachetti, Rampazzo, Mortellaro, Scevola & Gilger, 2015). Pijls et al. (2005) described another device named OphthaCoil that was studied in dogs, and consisted of a drug-loaded adherent hydrogel coating on a thin metallic coiled wire that was placed in the conjunctival sac. The study describes the drug levels of pradofloxacin in the tear fluids of the dogs. Unfortunately, in that study the devices were lost when left overnight, due to the third eyelid (which does not exist in humans) pushing the device out of the conjunctival sac during sleep.

Conclusions

A certain increase in interest in topically administered controlled-release dosage forms for veterinary medicine has been observed during the last decade. Despite some progress that has been made in the field, and despite the favorable and somewhat lenient statute of veterinary regulation, the controlled-release delivery systems are in their infancy in the veterinary area (Rothen-Weinhold et al., 2000) and have not yet reached their full potential.

Declaration of Competing Interest

The authors declare no competing interests.

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