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Challenges and opportunities in polymer technology applied to veterinary medicine

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An important frontier in the administration of therapeutic drugs to veterinary species is the use of different polymers as drug delivery platforms. The usefulness of polymers as platforms for the administration of pharmaceutical and agricultural agents has been clearly recognized in the recent decades. The chemical versatility of polymers and the wide range of developed controlled-release strategies enhance the possibilities for the formulation of active molecules. In particular, the veterinary area offers opportunities for the development of novel controlled-release drug delivery technologies adapted to livestock or companion animal health needs. In some cases, it also allows to improve profitability in meat production or to meet the safety criteria related to drug residues. A number of factors affect the selection of polymers and subsequent properties of the controlled-release drug delivery system. However, their selection also dictates the release kinetics of the drug from the delivery system. Such choices are therefore crucial as they affect the success and potential of the delivery system for achieving the therapeutic goals of the veterinarian. It is the intention of this review to give an overview of the most relevant polymers, which are used or have been tested as drug delivery release rate modifiers in the veterinary field. The article highlights some recent developments focusing on their advantages and applications and analyzes the future direction of the scientific and technological advancements in this area.

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INTRODUCTION

For more than two decades, the delivery of bioactive agents from polymeric materials has attracted considerable attention from researchers throughout the scientific community. Polymer chemists, chemical engineers, pharmaceutical scientists, and entomologists are among those seeking to design predictable controlled delivery systems for bioactive agents ranging from insulin to rodenticides. This has resulted in a major challenge, as evidenced by the small number of fully developed products based on this concept. One must realize, however, that only in the past 10 years with the rise of biotechnology, research in controlled drug delivery has benefited from an intense dedication of resources. With the availability of new molecules, often with short biological half-lives and relatively high molecular weights, the need for reliable controlled-release systems has significantly increased.

In veterinary medicine, the development of vaccine/drug delivery systems is intended for livestock and companion animal populations. Livestock animals are those that are raised for food or other products, such as meat and dairy. They include not only sheep, cattle, swine, goats, and poultry, but also fish and any other animals that enter the food chain. Among the companion animals (or pets), dogs, cats, and horses comprise the largest part. Other animals such as birds, reptiles, and rabbits can also be considered as companion animals. However, these species represent only a small fraction in this market.

Additional requirements are needed in regard to safety in veterinary drug delivery systems for food-producing animals, compared with those for humans or companion animals. Besides the safety of the target animal, consumer safety is also important, because these animals will enter the food chain, and so both the drugs and the polymers must be designed tak-

ing into account their presence as residues in tissues. Environmental safety should also not be affected.

The use of veterinary drugs and growth-promoting agents is widely extended in farming practice. The estimated annual consumption of antimicrobials in the European Union (EU) and in the USA is around 10 000 metric tons each. About half of the total antibiotics in the EU is used for livestock production (Díaz-Cruz & Barceló, 2005).

Development of suitable carrier systems for pharmaceutical products remains a major challenge. Historically, polymeric devices for implants were prepared from silicon, rubber, and polyethylene. A serious drawback of using these inert polymers as parenteral devices is their nonbiodegradability, and thus, their surgical removal after depletion of the drug is required. To overcome this problem, the concept of biodegradable polymers was first introduced in early 1970s for sustained-release parenteral drug delivery. The use of biomaterials has led to considerable interest, especially after the successful introduction of bioresorbable surgical sutures three decades ago. Since then, biodegradable polymers have become increasingly popular, and several new polymers were synthesized and employed for drug delivery applications. Drug delivery systems based on biodegradable polymers have the potential advantage that the supporting matrix will dissolve after drug release, and so no residual material remains in the tissue. This advantage must be balanced by the potential disadvantage that degrading polymers introduce an additional level of complexity into the design of useful materials.

Formulating a drug into a modified-release veterinary drug delivery systems provides benefits to both the animal and the veterinarian/farmer/pet owner. Such benefits include: (i) the ability to tailor the administration of pharmaceuticals oriented to health and production to the constraints of farm management systems, (ii) reduction in pain and distress of the animals by decreasing the number of times that they are handled and subjected to administration procedures, (iii) financial benefits to the end user as a result of reduced cost of veterinarian and optimization of employees′ time by reducing the time required for the tasks of herding and administration, (iv) an increase in the cost/benefit to the end user, and (v) improved therapeutic outcomes.

It is the intention of this study to give an overview of the polymers, which are used or have been tested in the veterinary field, employed in drug delivery systems. This study will highlight some recent developments in this area and will look into the future to examine the directions in which veterinary pharmaceutics is heading. Examples of currently available and future biodegradable veterinary drug delivery systems will be presented and explained including polydimethylsiloxane, polyurethanes, poly (ethylene glycol), polymethacrylates, polyvinyl alcohol, poloxamer, sugar sucrose acetate isobutyrate, as well as biodegradable polymers, among others.

POLYMERS FOR VETERINARY APPLICATIONS

Because of the low commercial value per unit of sheep, cattle, and pigs and the fact that farmers control large herds or flocks of these animals, the drugs, polymers, and any other excipients used in controlled-release drug delivery systems for this kind of animals need to be cheap to enable low-cost products to be manufactured and retailed. Processing conditions and facilities are important factors that must be considered during development and scale-up. Also, solvents used in many polymer-based microencapsulation processes may require explosion-proof processing areas and special waste handling systems.

Most veterinary drug delivery systems are prepared from polymers that exhibit proven histories of biocompatibility, are biologically inert, have regulatory approval, and are inexpensive. Such polymers can be either biodegradable or nonbiodegradable and include silicone. The classification depends on the key excipients used.

The delivery systems based on polymers must be reasonably aesthetic to appeal to the end user. They must also be easy to administer, adapted to farm management practices, safe to the end user, and cost effective.

On the other hand, the companion animal market is quite different from the food animal one. For example, in food animal industry, the main factor that drives product development is the cost associated with the handling and dosing of the animals. In that industry, the profit margins of the farmers are often quite low. Therefore, the formulations must be inexpensive and able to release the active ingredient over the course of a long period of time to minimize the frequency of dosing and handling of the animals. In contrast, companion animals are often considered as part of the family, and for this reason, the owners are usually willing to support expensive costs of dosage forms. Most companion animals, such as dogs and cats, are physiologically monogastric species. Therefore, formulation scientists face challenges for oral delivery similar to those when developing a formulation for use in humans. Indeed, human medicines are sometimes used for companion animal applications.

Drug delivery in domestic animals include not only all the different types of controlled-release dosage forms used in human medicine, but also unique delivery systems, for example, to control estrous cycle and parasite infections. Differences in anatomical and physiological characteristics of the individuals in each animal species have to be considered in the design of the dosage form, in addition to product stability, reproducibility in processing, and other stringent regulatory requirements. Thus, this segment of the animal health market presents opportunities for research synergies and spin-offs from human health with less consumer safety-orientated regulatory pressure than the livestock animal market.

Although an onlooker may perceive that the challenges, and indeed the objectives, of controlled-release veterinary drug delivery would be similar to those encountered in human medicine, they are in fact very different. This arises because the ‘patients’ contrast markedly in these two fields and because the veterinary field more readily accepts novel approaches to the controlled delivery of drugs to animals. As a result, most controlled-release drug delivery systems developed for animals are very different from those developed for their human counter-

parts. The challenges of this area of drug delivery arise from the unique anatomy and physiology of the target animal, the diversity of species and breeds, the range in body size and regional differences (Ahmed & Kasraian, 2002), and also the cost constraints associated with the value of the animal being treated and the extended periods of time that delivery must be sustained for (often measured in months). For some, these may be seen as limitations, but for others, they are considered opportunities that allow the pharmaceutical scientist to develop innovative solutions to challenging delivery problems.

Controlled-release drug delivery systems for veterinary use are, by necessity, innovative in their design and challenging to formulate due to the implicit drug delivery requirements or the environment in which they will ultimately find themselves (Rathbone, 1997; Baggot & Brown, 1998). The environment, in which the delivery system will be placed, can be harsh (i.e., rumen, which contains abrasive components, elevated pressures, large volumes of fluid, etc.) (Cardinal, 1997; Baggot & Brown, 1998) and could be exposed to the elevated temperature and moisture associated with that administration site for long periods.

The veterinary area is abounding with opportunities for the development of controlled-release drug delivery technologies. It is an area of medicine that is open to the acceptance of novel drug delivery devices and which readily encompasses the use of novel routes of administration. The need for new drug delivery technology for animal health is driven by various factors such as to improve the availability of drugs, to enhance breeder convenience and compliance, to provide product differentiation, and to assure target animal and consumer safety. Although most of the companies active in the field of drug delivery are primarily interested in human medicine, the research of drug delivery systems for veterinary use provides opportunities for initiative and imaginative design in areas that are unavailable in the human pharmaceutical field.

Nonbiodegradable polymers

Synthetic chemistry can be used to obtain polymers having specific three-dimensional structures with defined compositions and specific orientations of functional groups for precise drug conjugation. Polymer–drug conjugates using synthetic polymers as backbones are usually nonbiodegradable. Examples of drug delivery devices based on nonbiodegradable polymers are shown in Table 1.

Silicone. Lightly cross-linked polydimethylsiloxane (PDMS) is one of the most commonly used polymeric biomaterials, particularly when it comes to a rubbery material (Smith, 1991; Ward, 2000; Colas & Curtis, 2004; Curtis & Colas, 2004). The backbone structure of PDMS is the most flexible one known among all the synthetic polymers (Fig. 1a). The 'Si'O'Si' bond angle is 143°, which is much greater than the 'C'C'C' bond angle in most other polymers, and the oxygen atom is so small and unhindered relative to the adjacent silicon atoms that the chain is essentially freely rotating. Thus, PDMS has a lower glass transition temperature (Tg ~ −120 °C) than many other polymers. However, its mechanical strength is poor, even when cross-linked, so it is usually used only when it is both cross-linked and reinforced with silica (Colas & Curtis, 2004; Curtis & Colas, 2004). The ability to 'molecularly engineer' its mechanical properties, plus its inertness in biologic media, makes PDMS eminently suitable as a substitute for stiffer tissues such as the ear, nose, and chin. However, its use as breast implant has been controversial (Swanson & LeBeau, 1974; Herdman & Fahey, 2001). The hydrophobic and amorphous low-density properties of PDMS have also made it the material of choice in the drug delivery implant called Norplant®. In this implant, a silicone rubber tube is loaded with a PDMS rod filled with particles of the hydrophobic contraceptive steroid norgestrel, a synthetic progestin, and this drug permeates the tube wall and delivers at constant, steady-state rate over a period as long as five years (Curtis & Colas, 2004).

Many contraception delivery systems are manufactured from silicone. Factors that influence the choice and use of this polymer in an veterinary drug delivery system includes convenience, cost, availability, ease of fabrication, low-cost fabrication methods and manufacturing processes, biocompatibility, international registration status, physical and biological stability, inertness, drug compatibility, and release characteristics. It should be remembered that a delivery system designed and optimized for one species may not necessarily be as effective in a second species, due to several reasons including differences in vaginal size and structure as well as different system designed and optimized for one species dosage requirements. However, the basic design concept or technology used to manufacture an intravaginal veterinary drug delivery system for one particular animal may be able to be applied across species, but that technology will have to be specifically tailored to each individual animal species. An example of this is the CIDR (controlled internal drug release—high-temperature injection molding of progesterone-loaded silicone) technology, where two different-sized devices with different drug loads were needed to be designed for sheep (CIDR-G) and cattle (CIDR-B).

The CIDR-B consists of a preformed T-shaped nylon spine over which is molded a silicone rubber skin containing 1.9 g of progesterone uniformly dispersed throughout silicone (Rathbone *et al.*, 1997, 1998). One end of the device has two flattened wings that are hinged to the body of the device. The wings retain the device in the vagina by gently exerting pressure against the walls of the anterior vagina.

The CIDR-G is essentially a smaller version of the CIDR-B, comprising of a preformed annealed nylon spine, which is coated with silicone impregnated with progesterone. The device has a filament of flexible nylon preformed onto the spine which aids its removal from the animal.

Two types of intravaginal devices loaded with progesterone for estrous synchronization in cattle were studied by Heredia *et al.* (2008 and 2009). To obtain them, room temperature vulcanizing PDMS or latex sheets were impregnated with a solution of the drug in organic solvents, after which the remaining solvent was evaporated using an air steam. The rate

Table 1. Polymers used in veterinary products

Polymer	Polymer functional category	Examples of veterinary products			
		Delivery system	Bioactive molecule	Target species	Marketed (M) or under research (R) (Reference)
(a) Non-biodegradable polymers					
Silicone	Matricial or film component	Spiral intravaginal device (Prid Coil 10™)	Progesterone	Cattle (cows and heifers)	M (http://www.interchem.ie)
	Drug carrier	Reusable intravaginal device	Progesterone	Goats and sheeps	R (Vilariño *et al.*, 2010)
Polyurethane	Drug carrier	Intravaginal sponges (Progespon™)	Progesterone	Ovines and caprines	M (http://www.syntexar.com)
Poly (ethylene glycol)	Viscosity modifier agent Drug solubility enhancer Ointment base Plasticizer Solvent	Wound dressing (Equi-Phar Nitrofurazone)	Nitrofurazone	Companion animals	M (http://www.vedco.com)
		Film-Coated Tablets (Synulox™ Bolus)	Amoxicillin trihydrate, Potassium clavulanate	Calves	M (Veterinary Medicines Directorate, 2013)
Polymethacrylate	Enteric or sustained-release coating, Encapsulating agent Tablet binder Tablet diluent	Oral microparticles	Albendazole sulfoxide	Companion animals and ruminants	R (de Souza & Marchetti, 2011)
		Coated tablet (Cefaseptin™)	Cephalexin monohydrate	Dogs and cats	M (http://www.vetoquinol.mx)
Ethylcellulose	Coating agent Tablet binder Tablet filler Viscosity-increasing agent	Dual-layered coated pellets (Dietary supplement)	L-carnitine	Ruminants	R (Cao *et al.*, 2008)
		Subcutaneous implant (Regulin™ implant)	Melatonin	Sheeps	M (http://www.ceva.com.au)
Ethylene vinyl acetate copolymer	Matricial component	Sterile, cylindrical, sustained release, injectable pellet (Prolaplan™ pellet)	Vitamin B12	Lambs	M (http://www.bayeranimal.co.nz)
Cellulose acetate	Encapsulating agent Nanoparticle stability enhancer, Controlled-release agent Rate-controlling membrane	Redispersible powder or aqueous dispersion containing nanoparticles	Simvastatin (among others)	Mammals	R (Magdassi *et al.*, 2008)
Polyvinyl alcohol	Viscosity-increasing agent lubricant Matricial component	Wound dressing	Nitrofurazone	Companion animals, cattle, among others.	R (Kim *et al.*, 2008)
	Controlled-release agent Coating agent	Film-coated tablet (Forzepril™)	Benazepril Hydrochloride	Dogs	M (http://www.vmd.defra.gov.uk)
Poloxamer	Mucomimetic agent Thermal sensitive carrier	Intramuscular or subcutaneous i njectable gel	Doxycycline hyclate	Bovine	R (Vargas-Estrada *et al.*, 2008)
	Emulsifying agent Solubilizing agent Wetting agent	Subcutaneous long-acting formulation	Difloxacin	Goats	R (Escudero *et al.*, 2011)
(b) Biodegradable polymers					
Polylactic acid	Matricial component Drug carrier Controlled-release agent	Depot nano and microparticles	Model antigen and β-glucan	Fish	R (Fredriksen, 2012)

(continued)

Table 1. (continued)

Polymer	Polymer functional category	Examples of veterinary products			
		Delivery system	Bioactive molecule	Target species	Marketed (M) or under research (R) (Reference)
Poly (lactic-co-glycolic acid)	Controlled-release agent	Parenteral microsphere formulation	Recombinant *staphylococcal enterotoxin* A	Bovine	R (Chen *et al.*, 2012)
Poly (ε-caprolactone)	Controlled-release agent	Microparticles	Brucella ovis	Cattle	R (Estevan *et al.*, 2006, 2008)
		Implant	Praziquantel	Mammals	R (Cheng *et al.*, 2009, 2010)
Chitosan	Drug or vaccine carrier	Microparticles, Gel	Bovine herpesvirus 1 antigen	Cattle	R (Günbeyaz *et al.*, 2010)
	Encapsulating agent Controlled-release agent Clotting agent Viscosity-increasing agent	Wound dressing (granules and gauze) (Celox™ Veterinary)	None	Companion animals, cattle, among others.	M (http://www.dechra.co.uk)

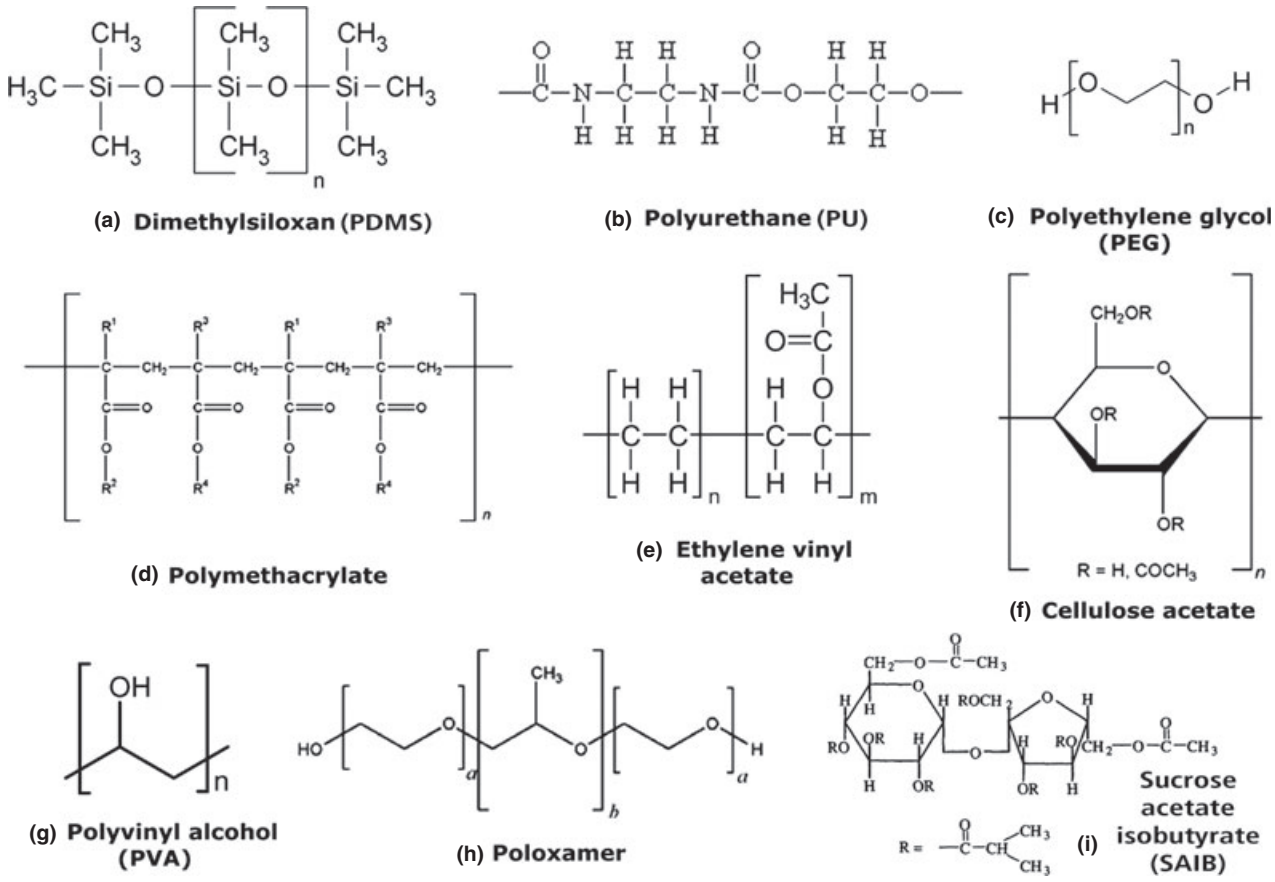

Fig. 1. Some chemical structures of the units of nonbiodegradable polymers.

of progesterone release was modulated by the type of polymer, the exposed surface area, the crystalline state, and the quantity of the drug loaded in the system. The *in vivo* evaluation demonstrated adequate drug levels in plasma. An intravaginal device for goats and sheep, DICO® (Dispositivo Intravaginal Caprino Ovino), based on a medical silicone impregnated with progesterone, was developed to control the serum concentration of the drug, follicular dynamics, and the time for ovulation (Vilariño *et al.*, 2010). The authors claimed that it can be reusable, although further studies would be necessary.

Silicone elastomers are also commonly used for medical devices and external prosthesis. Recently, there has been an increased interest in silicone-based medical devices that control the drug release from the elastomer matrix. In this way, Snorradóttir *et al.* (2011) performed an experimental design for optimizing drug release from a matrix of silicone elastomer. In this study, the release properties of the model drug diclofenac from medical silicone elastomer matrix were optimized, varying the combination of four permeation enhancers as additives, which allowed overcoming constraints in the properties of the material.

Several intravaginal products are commercially available or have been conceptually investigated for the control of the estrous cycle of cattle. The progesterone-releasing intravaginal device (PRID) comprises a stainless steel strip covered on both sides with a matrix comprising silicone and progesterone (Rathbone *et al.*, 1998). The coil is supplied with a hard gelatin capsule containing 10 mg estradiol benzoate glued to its inner surface. A length of string is tied to one end of the device to aid removal. Another interesting approach is the silicone capsules for subcutaneous administration described by Dziuk *et al.* (1966) and Chien (1980) wherein each capsule contains solid drug within its lumen.

A zero-order release kinetic can also be achieved by using reservoir devices based on silicone polymers. The prolonged release of drugs can be controlled either by a diffusion process or by an osmotic mechanism. Chetoni *et al.* (1998) manufactured bioadhesive PDMS rod-shaped inserts maintaining lachrymal concentrations of oxytetracycline above the MIC for at least 3 days. A silicone implant has also been studied for the treatment of glaucoma in dogs (Glover *et al.*, 1995). However, these implants need to be removed surgically once the therapy is complete.

Polyurethane. Polyurethanes (PUs) are most often constructed from polyether diols (Fig. 1b), such as poly (tetramethylene oxide), that have been reacted with an excess of diisocyanates and with chains extended either with diamines to form poly (ether-urea-urethanes) or with diols to form poly (ether-urethanes). Secondary reactions can also lead to branching of the main chains. Thus, PUs are modular polymers with physical properties that can be controlled by varying the molecular weights, compositions, and relative amounts of the original diol, the diisocyanate, and the chain extenders to best match the demands of the end-use application. One example of this principle is the use of PUs as the rate-controlling membrane for water permeation into the osmotic LH-RH (luteinizing hormone-releasing hormone) delivery system, called Duros® implant from Alza Corp. The Duros® implant consists of an outer cylinder that is capped at one end by a semipermeable membrane and at the other end by an exit port. Inside the cylinder, there are an osmotic engine, a piston, and the drug formulation. Drug delivery from the Duros® system is controlled by osmotic principles. The membrane at the end of the implant is permeable to water, but impermeable to the osmotic solutes in the osmotic engine. Therefore, water moves through the membrane in response to the osmotic gradient between the osmotic engine (typically saturated sodium chloride) and the extracellular fluid in the subcutaneous space. The osmotic engine then swells, displacing the piston and thereby decreasing the volume of the compartment that contains the drug formulation. This results in delivery of the drug through the exit port at a precisely controlled rate. The Duros® system can be used for therapies requiring systemic or site-specific administration of a drug. To deliver drugs systemically, the Duros® system is placed just under the skin, for example, in the upper arm, in an outpatient procedure that is completed in just a few minutes using local anesthetic (http://www.durect.com/pdf/duros_fact_sheet2001.pdf). This type of technology was originally designed for human therapy, but can be extrapolated to different animal species.

Polyurethane sponges impregnated with varying amounts of progesterone with different lengths, diameters, and densities have been inserted in cattle (Moore & Smith, 1980; Davis *et al.*, 1983). The sponges exhibited variable retention characteristics depending on different factors such as diameter, length, presence or absence of antibiotic, type of antibiotic applied, animal age, vaginal size, hormone type, rectal palpation, tail characteristics, and sponge density.

Kabadi and Chien (1984 and 1985) described a further approach, which comprised an unloaded polyurethane sponge onto which was adhered a laminate of silicone sheet (immediately adjacent to the sponge), drug-loaded silicone sheet (drug reservoir), and silicone sheet (rate-limiting membrane).

Poly (ethylene glycol). The use of synthetic or natural polymers as chemical conjugates to increase circulating lifetimes of proteins and peptides, as well as to protect them from different solutes, undesirable degradation, immune responses, and other interactions, has been well accepted. Between the different protein polymer conjugates studied, polyethylene glycol (PEG) is the most advanced in clinical terms (Fig. 1c), and it is approved in many human injectable products. Although the use of higher molecular weight PEG polymers to prolong the circulating life of small-molecule drugs has been proposed in the literature and several polymer conjugates have been tested for their cytotoxic activity in clinic assays, less is known about the performance of such conjugates compared with PEG.

A combination of polymethacrylic acid and PEG has been evaluated for its effects on intranasal budesonide delivery in rabbits (Nakamura *et al.*, 1999). Concentrations in the blood remained constant for approximately 45 min after administration.

Another interesting approach has been the development of fast-dissolving molded tablets consisting of drug and PEG blends with a melting point around body temperature. Such systems have been investigated for the delivery of nitroglycerin by Lagas and Duchateau (1988a,b) and progesterone by Maddox *et al.* (1990) with the purpose of obtaining a highly concentrated drug solution rapidly in the buccal cavity, which allows the drug to gain contact with a large mucosal surface.

On the other hand, in a very simple approach, a long-acting delivery system designed as an implant was fabricated to deliver ivermectin to cattle (Miller *et al.*, 1983). The implant containing 20% ivermectin was formulated by dissolving the drug into a high molecular weight PEG. When the loading in this implant was increased to 30% active ingredient and cattle were treated at 400 μg/kg body weight, ticks were controlled for up to 11 weeks.

Other formulations under patent showed interesting approaches. Jun (2006) described paste formulations containing silica useful in the veterinary field that present good chemical and physical stability over a wide temperature range. The formulations included PEG or Poloxamer® (a synthetic block copolymer of ethylene oxide and propylene oxide) in low concentration as excipients to modify the viscosity. Blakely and Cromie (2011) developed a pour-on formulation containing closantel and ivermectin (parasiticidal drugs) suitable for topical administration, to which PEG was added to enhance closantel solubility. This strategy allowed loading more quantity of this drug (from 1% to 30% w/v) in the veterinary formulation.

Polymethacrylates. Polymethacrylates (Fig. 1d) are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be purchased as dry powder, aqueous dispersion, or organic solution. The polymers are regarded as nontoxic and nonirritant and are primarily used as film coatings for solid dosage forms, although they are also used as binders for both aqueous and organic wet granulation processes and as viscosity modifiers in some topical formulations. They have also been tested as the matrix layers in the formulation of transdermal delivery systems (Chang & Shukla, 2003).

Even though methacrylate is approved in some commercial products, it is principally marketed by Rohm Pharma (Darmstadt, Germany) under the brand name Eudragit®. The most commonly employed methacrylate polymers are Eudragit® L and Eudragit® S, which are copolymers of methacrylic acid and methyl methacrylate, and are available as fine solids. Their aqueous solubility depends on the ratio of carboxyl to ester groups, being approximately 1:1 in Eudragit® L 100 and 1:2 in Eudragit® S 100. This ratio has a direct effect on solubility with regard to pH sensitivity, and these copolymers dissolve at pH 6 and pH 7, respectively. Certain polymethacrylates are soluble in alkaline pH making them suitable for enteric coatings, as they do not dissolve in the stomach, but dissolve in the more alkaline regions of the gastrointestinal tract. However, by changing the copolymer composition, the polymer may be rendered insoluble and therefore used as an insoluble film coating for sustained-release dosage forms.

Saettone *et al.* (1990) have observed that inserts based on mixtures of polyvinyl alcohol (PVA), glyceryl behenate, and different polymers containing pilocarpine coated with a mixture of Eudragit® RL and RS induced a miotic effect of longer duration in rabbits, compared with the corresponding uncoated products.

Eudragit® delivery systems have also been developed to protect antigens from the acidic pH of the stomach, allowing their later release in the intestine. In this regard, an oral enteric-coated *Vibrio anguillarum* vaccine was prepared by initially coating lyophilized bacteria onto 0.9 mm diameter dextrose sugar beads followed by an Eudragit® coat to serve as enteric protection (Wong *et al.*, 1992). This vaccine was fed to salmonid fish, engendering an active immune response that resulted in protection of fish challenged with the organism.

Eudragit RS PO (cationic polymer) was employed as an encapsulating material in the production of microparticles for oral administration of albendazole sulfoxide, a broad-spectrum antiparasitic drug used in the treatment of infections in companion animals and ruminants. The microparticles were prepared by an emulsificant/solvent evaporation method, achieving entrapment efficiency and process yield in the order of 60% using 1:10 drug/polymer proportion. Although the pure drug has poor solubility, the microparticles enhanced significantly the *in vitro* dissolution by increasing the surface area of the drug (de Souza & Marchetti, 2011). This could lead to an improvement in bioavailability and, consequently, in antiparasitic action.

The model bioactive (phloridizin) was coated using the coating methodology adopted from exploratory studies with model substrates. The bioavailability of protected (coated) phloridizin was assessed by administering directly into the abomasum of fistulated cows.

Formulation of protected phloridizin was used to demonstrate the feasibility of bioactive-controlled delivery based on ART (active rumen technology). This technology uses an elevated gas pressure created by a hydrogen-producing cell to drive a plunger that extrudes bioactive formulation from an intraruminal controlled-release device (Syzov, 2008).

Dual-layered coated pellets of L-carnitine, compound used for dietary supplement in ruminants, were prepared by an extrusion method and then coated with different materials, such as ethylcellulose and various Eudragit® polymers. The systems showed high *in vivo* rumen bypass efficiency in cows compared with nonprotected preparations and were more efficient in retarding the nutrient release in rumen fluid (pH 6.8) than single-layered coated pellets, but they released it faster in the abomasum fluid (pH 1.2) (Cao *et al.*, 2008).

Ethylene vinyl acetate copolymer. Ethylene vinyl acetate copolymer (EVA) is a random copolymer of ethylene and vinyl acetate (Fig. 1e). These copolymers are used as membranes and backings in laminated transdermal drug delivery systems. EVAs have been shown to be an effective matrix and membrane for the controlled delivery of atenolol (Shin & Choi, 2003; Kim & Shin, 2004), triprolidine (Shin & Lee, 2002a,b), and furosemide (Cho *et al.*, 2005). The intrauterine progesterone contraceptive system Progestasert® (Pharriss *et al.*, 1976) and the pilocarpine ocular insert Ocusert® produced by ALZA Corporation in Palo Alto, California

(Friederich, 1974), are examples of commercially introduced sustained-release systems based on EVA. In both cases, EVA is the constituent of a membrane that controls the rate of release of the drug, keeping it almost constant over several days.

A matrix sheet device was also designed for intraruminal administration comprising a trilaminate sheet (Brewer & Griffin, 1980). The veterinary drug should have adequate water solubility and be compatible with the polymer in which it is dispersed. Preferred examples are the anthelmintics, which include morantel or a salt thereof, such as salts with organic acids, for example, citrate and tartrate, and levamisole or a salt thereof such as the hydrochloride. The product consisted of a highly porous EVA drug reservoir coated on both sides with layers of EVA, which incorporated a water-soluble compound such as starch or lactose. The highly water-soluble ingredient dissolved when the device came in contact with ruminal fluids, resulting in a membrane that possessed fluid-filled pores. Drug partitioned from the central drug reservoir into the fluid-filled pores and then diffused through them into the surrounding medium. In addition to these approaches, various collar technologies for the delivery of actives against flies or ticks also utilized this type of systems (von Bittera *et al.*, 1985; Boettcher, 1990).

Cellulose acetate. Cellulose acetate (CA) is cellulose in which a portion or all of the hydroxyl groups are acetylated (Fig. 1f). It is available in a wide range of acetylation levels and chain lengths and thus molecular weights. Cellulose acetate is prepared by the controlled esterification of purified cellulose with anhydride acetic acid. The acetylation of CA is carried out to completion followed by hydrolysis to obtain CAs with lower acetyl contents.

Cellulose acetate is widely used in pharmaceutical formulations both in sustained-release applications and for taste masking. CA and other cellulose esters have also been used to form drug-loaded microparticles with controlled-release characteristics (Soppimath *et al.*, 2001a,b; Magdassi *et al.*, 2008). CA films were used in transdermal drug delivery systems (Rao & Diwan, 1996, 1997). Extended-release tablets can also be formulated with CA as a directly compressible matrix former (Yuan & Wu, 2000).

Several veterinary drug delivery systems utilize the principles of physical erosion for drug release. Such systems are generally characterized by the encasement of the drug formulation (generally manufactured by compression) within a plastic casing, which is impermeable to aqueous fluids. In practice, the erodible composition can be uniform throughout or, for example, a series of compressed tablets that can be placed within the central compartment of a device. In the latter case, the tablets can be prepared to contain active or placebo compositions, and thus, the drug release rate can be made to occur in either a continuous or a pulsatile fashion. The drug/nutrient release rate is controlled via the properties of the erodible composition.

Polyvinyl alcohol. Polyvinyl alcohol (PVA) was introduced in the early 1960s as a means to increase solution viscosity and, hence, prolong precorneal residence time. PVA is a water-soluble synthetic polyhydroxy polymer (Fig. 1g), represented by the formula $(C_2H_4O)_n$. The value of n for commercially available materials lies between 500 and 5000, equivalent to a molecular weight range of approximately 20 000–200 000. PVA is frequently used for drug delivery systems and surgical repair because of its excellent mechanical strength, biocompatibility, and nontoxicity (Martien, 1986). PVA is used as a viscosity-increasing agent for viscous formulations such as ophthalmic products. It is also used in artificial tears and contact lens solutions for lubrication purposes, in sustained-release formulations for oral administration (Carstensen *et al.*, 1981), and in transdermal patches (Wan & Lim, 1992).

The presence of PVA in ophthalmic preparations has been shown to significantly delay precorneal drainage of topically applied formulations and to increase drug bioavailability as well as pharmacological effects such as miotic response to pilocarpine exposure when compared with conventional saline solution (Davies *et al.*, 1991). For example, Hypotears® is a hydrogel for the treatment of keratoconjunctivitis sicca. This formulation has good adhesive quality, excellent contact time, and Newtonian behavior, is an excellent wetting agent, and does not caused blurred vision, but caused discomfort in some cases when PVA was at 4.2% (Ludwig & Van Ooteghem, 1988).

Polyvinyl alcohol/sodium alginate (SA) hydrogel matrix-based wound dressing systems containing nitrofurazone, a topical anti-infective drug, were developed using a freeze–thawing method by Kim *et al.* (2008). The authors concluded that these systems could be a novel approach in wound care. A novel controlled-release wound dressing with an antibiotic delivery system stimulated by microbial infection has also been developed (Tanihara *et al.*, 1999). In this system, gentamicin is incorporated into the dressing by binding it to PVA hydrogels. The drug can only be cleaved by the proteinase that exists in an infected wound. Once cleaved, the drug is free to migrate to the infected area.

Poloxamers. Poloxamers are nonionic triblock copolymers of ethylene oxide and propylene oxide, which exhibit gelling properties when they are heated (Fig. 1h). Their concentration is chosen in accordance with the desired liquid–gel transition temperature. At concentrations above 20% w/w, poloxamers exhibit the phenomenon of reverse thermal gelation, which consists in gelling upon warming up from ambient to body temperature (Gilbert *et al.*, 1987a).

Interestingly, the transition temperature of poloxamers can be regulated by adding solutes or polymers, such as PEGs (Gilbert *et al.*, 1987b), or cellulosic derivatives, such as methylcellulose or hydroxypropylmethylcellulose (Desai & Blanchard, 1998), to the formulation. Poloxamers commercially available as Pluronic®, approved by the USA Food and Drug Administration as food additives and pharmaceutical excipients, are the most commonly used thermosetting polymers in ophthalmology due to their low toxicity, mucomimetic properties, and optical clarity (BASF-Wyandotte, USA). However, the disadvantage of poloxamers compared with gellan gum, which is a

water-soluble polysaccharide commercially known as Gelrite®, lies in their mechanism of gelation. In fact, as solgel transition takes place when the temperature increases, accidental gelation during conservation may occur.

Regarding poloxamers use as ocular drug delivery systems, Miller and Donovan (1982) reported enhanced activity of pilocarpine in Poloxamer 407 (P 407) gels when compared with a simple solution. The mucomimetic property of poloxamers is supposed to be due to their hydrophobic and hydrophilic sequences simulating mucin action by adsorption of the aqueous layer of tears on the hydrophobic epithelium. Owing to their protective and mucomimetic action, poloxamers have also been evaluated for the treatment of dry eye (Gilbert *et al.*, 1987b). Furthermore, it was also reported that Pluronic F68 (Poloxamer 188) can be used as a carrier for topical gene delivery in eyedrop formulation (Liaw *et al.*, 2001). The mechanism by which the Pluronic® block copolymers enhance gene delivery *in vivo* is still unknown.

An attractive thermosensitive hydrogel, called Smart Hydrogel, composed of a polymeric network of poly (acrylic acid) and poloxamer, has been described by Gilchrist *et al.* (1997). After its use in rabbits, no clinical signs of irritation appeared. Furthermore, gamma scintigraphic assessment demonstrated a significant increase in the precorneal residence time, and the half-life time of elimination was multiplied by 25 when compared with a saline solution.

Puolakkainen *et al.* (1995) performed a study in which transforming growth factor-beta 1 (TGF-beta1) was incorporated into a poloxamer gel that provided a sustained release of TGF-beta1 and a significant enhancement in wound healing.

The immune response in mice to a DNA vaccine formulated in a self-assembling system containing Poloxamer CRL 1005 and benzalkonium chloride was studied by Hartikka *et al.* (2008). The DNA was bound by electrostatic interaction with the cationic surfactant present in the poloxamer particle surface. The system was stable and enhanced the levels of antigen-specific cellular and humoral immune responses.

Cafaggi *et al.* (2008) demonstrated the usefulness of P 407 as a gel base to improve the apparent solubility of tolfenamic acid, an anti-inflammatory, analgesic, and antipyretic drug widely used in human and veterinary medicine. P 407 considerably enhanced the solubility of this anti-inflammatory agent, by increasing its concentration in aqueous solution at least 2000-fold at 25 °C. The poloxamer micellar phase was directly involved in the late stage of drug release, thus indicating that a strong interaction occurred in the gel between the poloxamer and the tolfenamic acid. The results pointed out the possibility of both the systemic and topical administration of tolfenamic acid by means of aqueous solutions or gels containing P 407 at an adequate concentration.

A cyclodextrin–poloxamer-based matrix was developed to overcome tissue irritation caused by intramuscular or subcutaneous injection of doxycycline hyclate in Wistar rats (Vargas-Estrada *et al.*, 2008). However, clinical trials and residue studies are needed to assess whether this preparation can be potentially useful in bovine medicine.

In addition, a difloxacin formulation based on P 407 and carboxymethylcellulose was studied by Escudero *et al.* (2011). The authors explored the effect of the subcutaneous long-acting formulation on the pharmacokinetic and milk penetration behavior in lactating goats. The formulation was effective against mastitis pathogens, and no local or systemic adverse reaction signs appeared.

Another interesting study was conducted by Castro *et al.* (2013) by preparing solid dispersions containing the anthelmintic compound albendazole (ABZ) and either Pluronic 188 (P 188) or polyethylene glycol 6000 (PEG 6000) as hydrophilic carriers. The results showed that the addition of P 188 as carrier in the solid dispersions containing ABZ markedly improved its dissolution properties. This can be mainly attributed to the surfactant properties of this polymer, which is able to increase wettability and solubilization of ABZ. The authors assumed that this improvement in the dissolution rate was the cause of the increased ABZ bioavailability observed in *in vivo* pharmacokinetic studies performed in mice.

Sucrose acetate isobutyrate. Sucrose acetate isobutyrate (SAIB) (Fig. 1i) has attained regulatory status in several countries worldwide. It is approved as a direct food additive in parts of Europe, Asia, the Middle East, and South America, and it was granted USA approval as a direct food additive in 1999. SAIB has several properties which combine to make it a unique platform for drug delivery. The unusual properties of SAIB, specifically high hydrophobicity and viscosity, can be exploited to provide sustained drug delivery for periods ranging from a few hours to several weeks.

The SABER delivery system comprises a unique high-viscosity base compound (SAIB) which, when mixed with a small amount of solvent, converts to an easily injectable liquid (Betschart *et al.*, 1998). However, following administration, it solidifies to form a semisolid biodegradable implant which acts as a platform for the delivery of the drug or antigen it has been formulated with. SABER formulations can be administered by multiple routes including intramuscular, subcutaneous, intranasal, intravaginal, or intrauterine. Moreover, unlike the very complex and costly processes associated with microsphere formulations, the production of SABER formulations involves a simple mix and fill operation. This system has been investigated as a more cost-effective platform than microspheres to deliver several important reproductive hormones including the potent GnRH analogue deslorelin for a period of hours for induction of ovulation in estrus mares with preovulatory follicles (Bums *et al.*, 1997) and estradiol to mares for a period of several weeks (Johnson *et al.*, 1999).

The use of injectable gel technology to control estrus in horses has also been explored (Fleury *et al.*, 1998). This system consists of an easily injectable solution of the active agent with SAIB. Upon injection, the sucrose derivative gels in the presence of physiological fluids. The active agent then slowly release from the hardened mass. Over time, SAIB completely degrades into innocuous esters. In these recent studies, it was shown that the estrus of mares can be successfully controlled using this technology.

Another interesting approach was conducted by Lu *et al.* (2008). The authors have evaluated SAIB as an *in situ* forming system for the sustained release of risperidone (RSP). The formulation contained SAIB, solvents, such as ethanol, and PLA as a release regulator. The initial *in vivo* studies suggest that RSP–SAIB *in situ* forming system could be used as a formulation for sustained drug release.

The SABER technology is also the basis for SucroMate™ Equine, an injectable animal health drug to deliver deslorelin acetate for precise induction of ovulation. This is the first FDA-approved SABER-injectable product, and it is manufactured by CreoSalus and marketed by Bioniche Animal Health (USA).

Biodegradable polymers

Unfortunately, researches seeking advanced drug delivery systems are severely limited in available polymeric materials as evidenced by the relatively small number of systems described in this review. Historically, designers of drug delivery systems have 'borrowed' polymeric materials originally developed for other applications. Only one or two synthetic polymers have been developed specifically for use in controlled-release formulations. Furthermore, the trend in drug delivery technology has geared toward biodegradable polymer chemistry, whose advantages have been extensively described (Heller, 1984; Baker, 1987; Hsieh, 1988).

Such delivery systems offer a distinct benefit over nonerodible implant formulations. Because the delivery system erodes after the delivery period has been completed, there is no need to surgically remove it after administration. Consequently, drug release can be tailored to the desired rate and duration, and the depleted polymer remains in the animal for varying periods of time after the therapy has been completed during which time it erodes to its toxicologically innocuous products, which can be eliminated by normal metabolic processes.

So far, regarding biodegradable polymers, only drug delivery devices based on polymers and copolymers derived from lactic acid enantiomers, glycolic acid, and ε-caprolactone (PLA, PGA, and PCL, respectively) have been commercialized. The prospective applications include devices with drugs for contraception, infection treatment and vaccination. A number of products are commercially available such as Decapeptyl®, Lupron Depot®, Zoladex®, Adriamycin®, and Capronor® (Dunn, 1995).

In the veterinary area, there are several examples of delivery systems that use bulk eroding polymers to form a rate-controlling membrane around the drug, which are then usually prepared for administration in the form of a subcutaneous or intramuscular injection. Examples of drug delivery devices based on biodegradable polymers are shown in Table 1.

Polyesters. Better control and flexibility over the physicomechanical properties of synthetically prepared biodegradable polymers have made them superior resources for polymer scientists and material designers. During the last years, a battery of advancements has taken place in the area of synthetic biodegradable polymers. This category comprises a broad family of polyesters such as PGA, PLA, and their copolymers, PCL, polyanhydrides, and polyorthoesters. Representative structures of synthetic polymers are given in Fig. 2.

PLA and PGA are the first polymeric materials that have been used successfully as sutures in the last two decades, and their degradation products are known to be nontoxic, and their metabolic pathways are well established. The homopolymers of PLA and PGA are also known as polylactides and polyglycolides.

PLA, PGA, and copolymers of lactide/glycolide (PLGA) are among the most commonly used biomaterials for drug delivery and tissue engineering. The interest in these materials has resulted from several characteristics: (i) they break down into

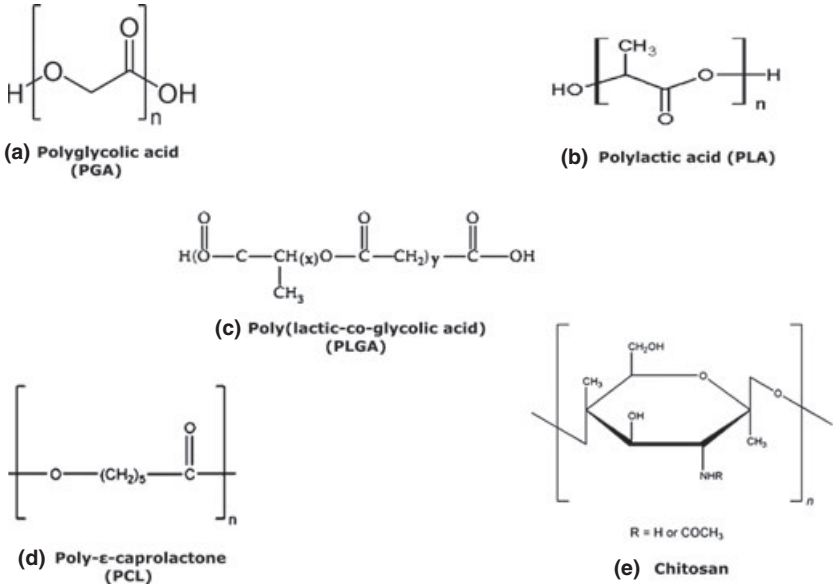

Fig. 2. Some chemical structures of the units of biodegradable polymers.

naturally occurring metabolites, (ii) materials with a variety of useful properties can be produced by copolymerization of the two monomers, (iii) degradation requires only water, and (iv) early development of successful suture materials based on these polymers has led to a great deal of experience with their use in humans, so that their safety is now well documented.

Polyesters and their copolymers have been tested extensively as implants, nanoparticles, and microspheres for the delivery of various drugs, such as narcotic antagonists, contraceptives, local anesthetics, cytotoxics, and antimalarial agents (Wood, 1980; Deasy, 1984).

Features such as biocompatibility, predictability of biodegradation kinetics, ease of fabrication, and regulatory approval in commercial suture applications have attracted investigators to lactic/glycolic polymers.

Poly (glycolic acid). About 30 years ago, a distinction was made between materials for permanent or temporary therapeutic uses. The former requires biostable polymeric materials, and the main problem is their resistance to degradation in the body. By contrast, the latter needs a stable material just for a limited treatment time. In this regard, degradable polymers became of great interest in surgery as well as in pharmacology. The first degradable synthetic polymer was PGA, which appeared in 1954 (Lowe & Buffalo, 1954). This polymer (Fig. 2a) was first discarded because of its poor thermal and hydrolytic stabilities, which precluded any permanent application. However, the hydrolytic sensitivity of PGA was later taken into account to make polymeric devices that can degrade in a humid environment and, thus, in a human body. The drug can be formulated as a solid erodible matrix or as reservoirs encapsulated by a rate-controlling membrane. These advantages were exploited to develop polymers that undergo bulk erosion in aqueous conditions, such as PLA and PLGA. In other studies, a bioabsorbable, injectable microsphere formulation containing ivermectin in PLA/PGA copolymer was developed to provide long-lasting delivery of the drug for control of livestock pests (Miller *et al.*, 1998).

Polylactic acid. Biodegradable Polylactic acid (PLA) polymers (Fig. 2b) used for controlled-release applications are stereoregular and available as D-, L-, and racemic DL-polylactides (Beck & Tice, 1983; Beck *et al.*, 1983). PLA has been reported to exhibit excellent biocompatibility at subcutaneous and other injection sites (Kulkarni *et al.*, 1966). PLA has been extensively studied for controlled-release applications ranging from the oral delivery of simple drugs such as indomethacin (Ammoury *et al.*, 1990) to the parental administration of complex proteins such as insulin (Kwong *et al.*, 1986).

The first reported biomedical applications of PLA polymers involved its use as sutures and prosthetics (Kulkarni *et al.*, 1971). American Cyanamid developed synthetic, degradable sutures composed of PGA in the 1960s (Schmitt & Polistina, 1967), while Ethicon developed similar materials involving PGA and PLA (Schneider, 1967; Wasserman & Levy, 1975). Since their introduction as suture materials, these polymers have been used extensively in biomaterials, particularly as drug delivery devices.

In the early 1970s, patents for PLA/drug mixtures were awarded to DuPont (Boswell & Scribner, 1973). The first applications for controlled drug delivery involved the release of narcotic antagonists from PLA films (Woodland *et al.*, 1973). PLA was used to deliver contraceptive steroids (Jacknicz *et al.*, 1973), and particles of PLA/PGA copolymers (25:75) were used to deliver an antimalarial drug to mice, providing 14 weeks of protection against malarial challenge (Wise *et al.*, 1976). PLA microspheres were employed to deliver the contraceptive steroid norethisterone to baboons, inhibiting ovulation for six months (Beck *et al.*, 1979). In the last 15 years, many different groups have evaluated the use of copolymers of lactide and glycolide for the release of small and large molecules. Products based on this technology are currently available in the USA, including Lupron Depot for endometriosis and prostate cancer.

Other developed products include microspheres for sustained release of biologically active growth hormone, which have been prepared from PLA/PGA copolymers (50:50) using an atomization process in liquid nitrogen (Auer *et al.*, 1994) of glyceryl tristearate or glyceryl distearate using a spray prilling technique (Steber *et al.*, 1989). In the first case, the microspheres were designed, whereas in the second one, they consisted of fat or wax or a mixture and a biologically active protein or peptide suitable for parental administration.

A further example is an intramuscular injection comprising a microsphere formulation manufactured from PLA. This product has been designed to deliver its entire contents of progesterone (1.25 g) and estradiol (100 mg) continuously for a period of time of 12–14 days (Blanchard *et al.*, 1992; Burns *et al.*, 1993, 1994; Fleury *et al.*, 1993; Jasko *et al.*, 1993).

Poly (lactic-co-glycolic acid). PLGA (Fig. 2c) remains the most popular and well-characterized biodegradable polymeric biomaterial. Its degradations properties, biocompatibility, regulatory approval, and extensive database of human use make it an obvious choice in medical applications that range from controlled drug delivery to tissue engineering (Chasin & Langer, 1990; Jain, 2000).

In principle, matrices formed from degradable polymers disappear in one of two idealized patterns: bulk erosion or surface erosion. In bulk erosion, such as occurs with PLGA materials, the polymer disappears uniformly throughout the material; a microporous matrix eventually becomes spongy, with the water-filled holes becoming larger until the matrix is no longer mechanically stable. During surface erosion, the polymer disappears from the surface, so that the matrix becomes progressively smaller over time.

The polymeric devices based on PLGA degrade in an aqueous environment through bulk erosion at a uniform rate throughout the matrix, due to the hydrolysis of the backbone ester linkages (Brannon-Peppas, 1995; Uhrich *et al.*, 1999; Jain, 2000). The degradation process is self-catalyzed as the

number of terminal carboxylic acid groups rises with increasing chain scission, and the acids catalyze the hydrolysis. The degradation is highly dependent on the ratio of lactide to glycolide moieties as lactide is more hydrophobic and reduces the rate of degradation (Mainardes & Silva, 2004). Also, important factors in the degradation process are the degree of crystallinity, the molecular weight, and the glass transition temperature of the polymer (Jain, 2000).

PLGA microspheres have increasingly become the focus of research efforts in the scientific community and pharmaceutical industry. PLGA has been used to encapsulate several drugs and genes in controlled delivery systems for many diseases and other applications; however, only a few will be mentioned here.

Various drugs have been encapsulated into PLGA microspheres in the size range between 1- and 100-μm-diameter PLGA polymers have been extensively used as microparticulate carriers for sustained releases of various small molecular weight drugs, peptides, and proteins (Cleland & Langer, 1994). In particular, various PLGA polymers having different molecular weights and compositions of lactic/glycolic acid ratio have been commercially available, which degrade in a wide range of time intervals suitable for tailoring the drug release period (Lewis, 1990). As PLGAs are biocompatible and biodegradable polymers, they are ideal for injectable and implantable delivery systems.

Microparticle delivery systems (average diameter—20 μm) for leuprolide acetate were produced from PLGA (75:25) with an average molecular weight of 14 kDa (Ogawa *et al.*, 1988); these particles release the peptide hormone for 1 month, providing reasonably constant release throughout this period. This technology is the basis of the Lupron Depot®, a successful clinical product for the treatment of prostatic cancer, precocious puberty, and endometriosis. Further examples on PLGA can be found in the studies from Gupta *et al.* (1993) and Garvin *et al.* (1994), in which microspheres containing clarithromycin or compressed rods with antibiotic to treat osteomyelitis were prepared and administered to dogs. These systems were actually being developed for eventual use in humans; however, they demonstrate the feasibility of such drug delivery approaches in canine medicine.

An interesting approach is commercialized as Zoladex (AstraZeneca), which is a PLGA–goserelin acetate implant. This system is applied subcutaneously with a 16-gauge needle to provide sustained release of goserelin for 28 days in palliative treatment of prostate carcinoma (Okumu & Cleland, 2003).

Another example compound Nutropin™ (Genentech, Inc., South San Francisco, CA), which consists of human growth hormone loaded in PLGA microspheres (Cleland & Jones, 1996), was approved by FDA. However, the initial burst effect was not resolved. Burst release can result in acute overdosage, and this could lead to fluid retention, headache, nausea, vomiting, or hyperglycemia. However, since 2004, the production of this system was discontinued due to commercial reasons.

PLGA has also been used as the delivery vehicle for LH-RH analogue (Kent *et al.*, 1984). The LH-RH analogue is a profertility agent when administered in a pulsatile manner, but has a contraceptive effect when administered continuously. LH-RH has poor oral bioavailability, so the PLGA system greatly increases its potential as a contraceptive agent. The LH-RH analogue is hydrophilic, as opposed to the lipophilic nature of other steroids commonly used for contraception, and has a rather low diffusivity through PDMS, justifying the choice of PLGA as the delivery vehicle (Vickery *et al.*, 1985).

Norethindrone–PLGA microspheres can be manufactured in a solvent evaporation process. Clinical trials with PLGA spheres loaded with 47% norethindrone (a synthetic progestin) have been conducted in an attempt to optimize the dosage. A release of 100 mg/day appears adequate. The injection is administered with a 21-gauge needle. Serum concentrations of the progestin are 2 ng/mL, about 15–30 times lower than serum concentrations for Depo-Provera. The system approximates to a zero-order release rate, with steadier release of the drug at a concentration low enough to minimize side effects while still maintaining efficacy. The advantages of an injectable contraceptive microsphere delivery system are the ease of administration via single injection, biodegradation of the polymer device, low release of steroid with minimal loading, and long duration of release. However, the disadvantage of any microsphere delivery system is its relative irretrievability after administration (Gabelnick & Hall, 1987; Gu *et al.*, 1992).

The Atrigel™ formulations from Atrix Inc. (Fort Collins, CO) are aliphatic esters dissolved in biocompatible solvents that can be mixed with antigen. In this state, they are stable liquid gels that can be administered to the host as injectable vaccines. When such vaccine formulations are injected into the aqueous environment of the host tissues, the solvent dissipates and the aliphatic ester precipitates. The incorporated vaccine included in the formulation becomes entrapped in the precipitated polymer and is slowly released as the polymer degrades. Candidate polymers for the Atrigel™ delivery system include PLA, PGA, and their copolymer PLGA. Atrigel™ polymers have been demonstrated to deliver complex vaccine antigens such as inactivated pseudorabies (Aujeszky's disease virus) virus vaccines and canine parvovirus (Bowersock & Martin, 1999).

Another interesting approach is the so-called SMART technology used in SMARTShot B12™ (Stockguard Laboratories Ltd, Hamilton, New Zealand). This system consists of vitamin B12 as hydroxocobalamin hydrochloride contained within microspheres of PLGA for extended release, which is controlled by erosion of the polymer and diffusion of the vitamin B12 through its pores. Larger vitamin B12 particles and those particles centrally contained within the larger microspheres are more slowly released, enabling the activity of SMARTShot B12™ to be extended over many months. Grace and Lewis (1999) developed a long-acting vitamin B12 injection for long-term prevention and treatment of cobalt/vitamin B12 deficiencies in sheep, lambs, and calves, particularly when grazing cobalt-deficient pastures. Grace *et al.* (2003) also investigated growth responses of cobalt-deficient lambs to increasing doses of microencapsulated vitamin B12 and the associated changes in serum and liver vitamin B12 concentrations over 243 days.

They concluded that cobalt-deficient lambs' growth was markedly improved by the injection of microencapsulated vitamin B12, and it was related to the vitamin concentration in serum. It was also found that increasing doses of long-acting injectable vitamin B12 plus selenium during premating improved the vitamin B12 and selenium status of ewes and their lambs from birth to weaning (Grace *et al.*, 2006). The results showed that due to the proportional nature of the response to increasing dosage, the dosage of the formulation tested can be adjusted according to the severity of selenium and cobalt deficiency in a flock.

However, in designing degradable polymers for drug delivery, materials that display surface erosion are usually preferred, as drug release from the slowly shrinking matrix should be more predictable. In addition, it is sometimes possible to design drug delivery systems in which erosion kinetics control the rate of drug release from the matrix.

Poly (ε-caprolactone). Another polymer from the polyesters family, which has been evaluated for long-term drug delivery systems, is PCL (Fig. 2d). This polymer is synthesized by a ring-opening polymerization of the monomer ε-caprolactone. It is semicrystalline, rather hydrophobic compared with poly (α-hydroxy acid)s, and has a high molecular weight.

PCL was used in 1973 as a subdermal delivery system for contraceptive steroids, such as the synthetic progestin levonorgestrel (LNG), under the trademark Capronor® (Shelton & Sciarra, 1984). This product was also reported to be clinical testing (Gabelnick & Hall, 1987); however, no current data could be found regarding present development of this device. The contraceptive system consists of a hollow capsule of PCL, which encases about 16 mg of LNG and 61 mg of ethyl oleate as a suspending vehicle. Capronor® is 2.4 mm in diameter and 2.5–4 cm in length depending on the amount of drug to be encapsulated (12 or 21.6 mg LNG), with heat-sealed ends (Sam, 1992). Release rates from this device are about 45 μg/day, and release is governed by diffusion as the polymer degradation rate is relatively slow (18–24 months) (Gabelnick & Hall, 1987).

The implantable PCL reservoirs were also used to successfully deliver insect steroid analogues against ticks (Jaffe *et al.*, 1986).

Dordunoo *et al.* (1997) have developed a PCL-biodegradable paste containing paclitaxel, an antineoplastic agent from the bark of *Taxus brevifolia*. The paste was designed to be spread onto the surface of the pocket left after tumor resection. As PCL melts at temperatures below 60 °C, the paste could therefore be applied to the tumor bed in molten form. These authors have also evaluated various additives to the system, including gelatin, to modulate the release rate of the paclitaxel *in vitro*. The gelatin in the formulation increased the swelling of the paste and accelerated the drug release, allowing for tumoricidal levels of the drug to be achieved at the site of the tumor.

PCL has shown to be suitable for the manufacture of an intravaginal drug delivery system for the delivery of progesterone to control the estrous cycle in cattle (Bunt *et al.*, 1999a,b). Two groups of six ovariectomized cattle were treated for 7 days with either a PCL insert containing 10% w/w progesterone or a CIDR-B containing the same amount of the hormone (Bunt *et al.*, 1999a). The CIDR-B was first marketed in New Zealand in 1987 and originally contained 1.9 g progesterone and was designed for a 12-day insertion period. The PCL intravaginal insert exhibited slightly lower average plasma progesterone concentrations compared with the CIDR-B and released slightly less progesterone (0.68 g) compared with the CIDR-B (0.72 g) over the 7-day insertion period. Further trials demonstrated how progesterone release from the PCL intravaginal inserts could be modified by the addition of various excipients to the insert to elevate plasma progesterone levels (Bunt *et al.*, 1999b). The trial showed that plasma progesterone levels could be elevated and sustained, thus demonstrating the feasibility of using PCL as a platform for the intravaginal delivery of progesterone to cattle.

Ogle *et al.* (1999) also evaluated PCL for fabrication of an intravaginal insert containing progesterone for control of the estrous cycle in sheep. PCL inserts were manufactured and inserted into the vagina of anestrus sheep for 14 days. The plasma profiles created following insertion of the PCL inserts mimicked those observed following insertion of the commercially available silicone product used in sheep, the CIDR-G. The retention rate of the PCL inserts was excellent over the 14-day treatment period, no vaginal damage was observed due to the presence of any inserts over the course of treatment, and discharge was minimal. Further studies showed that plasma levels were affected by both surface area and drug load.

Estevan *et al.* (2008) conducted a stability study of PCL microparticles containing *Brucella ovis*, confirming the preservation of the major antigenic proteins. These particulate systems were previously prepared by solvent extraction/evaporation method and showed efficacy against *Brucella melitensis* in rodents (Estevan *et al.*, 2006).

PCL implants containing praziquantel (PZQ) were tested for the treatment of hydatidosis. Due to the strong hydrophobicity of the PCL matrix, drug release rate fell down quickly after an initial fast release of the drug located on the surface of the implants, and this insufficient drug release may fail to reach the lower limit of the therapeutic window after implantation (Cheng *et al.*, 2009). The authors modified the design of the implants by inclusion of PEG in the composition of the matrix. The crystals of the drug (≤20 μm) were dispersed in PEG and PCL blends of different compositions, and the implants were prepared by twin-screw mixing combined with hot-melt extrusion. *In vitro* drug release could be modified by changes in the proportion of the polymers blends. The devices were implanted subcutaneously in laboratory animals resulting in an adequate drug concentration in plasma for 6 weeks and presented good tissue compatibility (Cheng *et al.*, 2010).

Biodegradable PCL nanoparticles have been shown to increase the oral bioavailability and to control the biodistribution of cyclosporine, thereby potentially reducing the drug toxicity (Molpeceres *et al.*, 2000).

In general, PCL polymers degrade more slowly than comparable PLA or PGA polymers, making them particularly well suited for long-term drug delivery applications. Alternatively,

copolymerization of PCL with other monomers or polymers, including lactide and glycolide, leads to more rapidly degrading materials. Another property of PCL, which has stimulated much research, is its exceptional ability to form compatible blends with a variety of other polymers (Brode & Koleske, 1972; Koleske, 1978). This fact, coupled with a high permeability to many therapeutic drugs and a lack of toxicity, has made PCL and its derivatives well suited for controlled drug delivery. In this regard, a PCL–chitosan composite was fabricated by Im *et al.* (2003) to provide a controlled-release device to induce bone regeneration. The controlled release of PDGF (platelet-derived growth factor) was observed over four weeks at a therapeutic concentration, with bone regeneration seen in rat calvarial defects.

Chitosan. Chitosan (Fig. 2e) is a polysaccharide derived by deacetylation of chitin, which is a copolymer of N-acetyl-glucosamine and N-glucosamine units distributed randomly or block distributed throughout the polymeric chain (Khor & Lim, 2003). Chitosan has been shown to have potential use for the development of controlled-release systems capable of delivering drugs within a broad range of applications (Singla & Chawla, 2001; Olmez *et al.*, 2007). It offers several advantages over other biodegradable polymers, especially in regard to the stability of the drugs. Chitosan biocompatibility, biodegradability, bioactivity, and lack of toxicity and allergenicity make it very attractive for diverse applications as a biomaterial in the pharmaceutical and medical fields (Senel & McClure, 2004). There have been numerous reports on the use of chitosan and its complexes in a number of biomedical applications, including drug delivery systems, tissue engineering (Dhiman *et al.*, 2005), and orthopedics (Wang *et al.*, 2003).

Polymers such as chitosan and its derivatives are being explored as permeation enhancers chiefly owing to their lack of cytotoxicity and minimal absorption (Thanou *et al.*, 2001).

There has been much interest in the application of this polymer in veterinary medicine for its bioactive properties such as wound healing, tissue regeneration, and hemostatic and antimicrobial effects, and also for its potential applications for drug and vaccine delivery in veterinary species.

Research on chitosan-based delivery systems is undergoing rapid expansion. Recent human and animal studies have indicated that chitosan-based delivery systems are promising alternatives to conventional formulation approaches, in particular, for the mucosal delivery of biotechnology drugs, such as proteins and genes (Bowman & Leong, 2006; Lai & Lin, 2009).

The chitosan-based formulations like solutions, suspensions, tablets, gels, dispersions, films, sponges, patches, fibers, and particulate (nano- and micro-) systems for both conventional and modified releases seem to be advantageous for oral, dermal, and mucosal administration in animals.

It is interesting to remark that chitosan has emerged as one of the promising enhancers for oral absorption of macromolecular drugs because of its ability to open tight junctions, outstanding biocompatibility, and moderate biodegradability (Thanou *et al.*, 2001). The electrostatic interactions between the positively charged chitosan and the negatively charged surfaces of epithelial cells may be responsible for a structural reorganization of tight junction-associated proteins, thus enhancing paracellular transport of poorly absorbable drugs (Schipper *et al.*, 1997).

Among the natural polymers, chitosan and its derivatives have shown pronounced mucoadhesion in contact with GI mucosa (Bernkop-Schnürch & Krajicek, 1998). Intestinal absorption of insulin loaded in chitosan-coated liposomes was demonstrated (Takeuchi *et al.*, 1996). Blood glucose levels were reduced significantly after the administration of a single dose of these liposomes in rats.

Chitosan has often been employed as a coating material for the colon-targeted delivery of drugs because of its pH sensitivity, its complete digestion by the colonic bacteria, and its low toxicity (Shimono *et al.*, 2002).

Microparticles made of chitosan and coated with paraffin or PLA to stabilize them retained diptheria toxoid for 6 months and could maintain an immune response in rats for at least 5 months (Jameela *et al.*, 1994). Chitosan nanoparticles coated with ethylene oxide–propylene oxide coblock polymer retained tetanus toxin for at least 15 days *in vitro*, releasing antigen at a constant rate (Calvo *et al.*, 1997).

Microparticles of chitosan were also developed by Günbeyaz *et al.* (2010) for mucosal immunization against bovine herpesvirus 1 (BHV-1). The particulate systems were prepared by spray drying and loaded with the BHV-1 virus antigen through incubation method to avoid its denaturalization. The height efficiency of loading was attributed to the interaction between the positive surface charge of the particle and the negative charges of the antigen. Particles were taken up by cells and maintain cell viability and antigen integrity.

The presence of amino groups in chitosan gives it also the ability to condense DNA. This polymer was first reported as a gene delivery tool in the mid-1990s (Mumper *et al.*, 1995; Murata *et al.*, 1996). Chitosan is one of the few agents that is capable of gene transfer via the oral route (Roy *et al.*, 1999). It is attractive as a gene delivery tool because of its good biocompatibility profile when compared with cationic liposomes (Thanou *et al.*, 2002; Corsi *et al.*, 2003; Gao *et al.*, 2003; Li *et al.*, 2003), polyamine polymers (Kim *et al.*, 2003), and polyamine dendrimers (Li *et al.*, 2003). Its favorable biocompatibility has prompted researchers to find ways to optimize gene transfer with this agent, and controlling its molecular weight appears to be the key. An optimum gene transfer activity lies in a degree of polymerization between 7 and 635 (MacLaughlin *et al.*, 1998; Ishii *et al.*, 2001; Sato *et al.*, 2001; Uchegbu *et al.*, 2004). Additionally, increasing the charge density by incorporating a permanent positive charge in the molecule in the form of a trimethyl quaternary ammonium group appears to offer some marginal benefit (Thanou *et al.*, 2002), and the incorporation of targeting groups, such as galactose, improves targeting to hepatocytes (Gao *et al.*, 2003). Chitosan coupled with urocanic acid was successfully prepared and used as an effective gene delivery system by Kim *et al.* (2003). It showed great ability to form complexes with

DNA and exhibited much enhanced gene transfer efficiency than chitosan itself.

Oral gene delivery using chitosan is particularly interesting because the chitosan has been used as a potent absorption enhancer for many bioactive materials owing to its mucoadhesive characteristic. *In vivo* oral delivery of the chitosan–Arah2 antigen gene complex to mice was performed, and at a challenge test, the anaphylactic response was reduced significantly in the chitosan–antigen gene group, but not in the naked DNA group (Roy *et al.*, 1998).

The preparation of chitosan–DNA nanospheres by using a novel and simple osmosis-based method is recently been patented (Masotti *et al.*, 2008). With this method, authors were able to prepare chitosan–DNA particles of spherical morphology with an average diameter of 38 ± 4 nm. Also, the DNA incorporation was pretty high (up to 30%), and the release process was gradual and prolonged in time. Fascinated by the properties of chitosan, few researchers have explored the possibility of surface modification of PLGA nanosphere platform with chitosan for gene delivery by using the emulsion solvent diffusion method (Tahara *et al.*, 2008). By coating the PLGA nanospheres with chitosan, the loading efficiency of nucleic acid in the modified nanospheres was found to increase significantly. The release profile of nucleic acid from PLGA nanospheres exhibited sustained release after initial burst, while coating with chitosan reduced the initial burst of nucleic acid release and prolonged the drug releasing at later stage.

The results using chitosan to produce gene medicines or gene-based vaccines appear promising. However, chitosan, although able to achieve gene transfer to some extent, appears to lack the required level of efficiency that would be needed to allow it to be developed for the clinical delivery of genes. On the other hand, many of the ideal characteristics of a gene delivery system are provided. Chitosan is readily available, inexpensive, and relatively nontoxic. Complexes of controllable sizes and high colloidal stability can be readily formulated, which have the potential for further modification for more specific cell targeting. The high stability and low expression achieved *in vivo* suggest that uptake and/or decomplexation, but to a lesser extent endosomal release, may be critical rate-limiting steps. These issues will have to be addressed to optimize that type of polymeric delivery system.

It has to be mentioned that chitosan is still under research and has not been yet tested in veterinary medicine. However, it has a great potential, especially as oral applications have great relevance to many vaccine applications.

CONCLUSIONS

Over the past decade, the use of polymers for the administration of pharmaceutical and agricultural agents has increased dramatically. The chemical versatility of polymers and the wide range of designs of controlled-release systems offer numerous possibilities for the formulation of therapeutic agents and the creation of tailor-made materials to match the diversity of molecules in drug development, biotechnology, and therapy.

The veterinary area provides opportunities for the development of controlled-release drug delivery technologies. It is an area of medicine with less regulatory pressure, which is open to the acceptance of novel drug delivery devices and which readily encompasses the use of novel routes of administration. But it is also an area of many unmet needs, most of which offer opportunities and unique challenges for the innovative formulation scientist to provide solutions. These opportunities arise from the diverse nature of the field, the desire of the end user to fit drug therapy around farm management practices, and the anatomical and physiological peculiarities of individual animal species. Differences in anatomical and physiological characteristics of the individual animal species have to be considered in the dosage form design, in addition to product stability, reproducibility in processing, and other stringent regulatory requirements. Many technologies have already been developed to overcome the challenges associated with the drug delivery systems in veterinary use.

It is clear that biodegradable drug delivery systems have begun to be taken into account in the area of estrus and ovulation control. However, concerns over cost will limit success to products, if they cannot offer reduced production costs and enhanced profitability to the end user.

Issues related to inflammation at the site of injection, reproducibility of drug release, and scale-up of laboratory preparation batches to industrially feasible production batches, however, need to be addressed to extend the benefits of biodegradable drug delivery systems to a large group of drugs and therapeutic conditions.

An ideal gene delivery system has to be able to shuttle the gene safely to the nuclei of its target tissue with the travelling gene having limited encounters with degradative influences. Therapeutic applications of gene therapy in animals are currently limited, except for the genetically engineered vaccines. However, the number of applications of nucleic acid probes or recombinant DNA products for clinical or diagnostic use in veterinary medicine is increasing rapidly. New drug delivery systems will be developed during the next decade by interdisciplinary collaboration of material scientists, engineers, biologists, and pharmaceutical scientists.

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