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Controlled release of levamisole from poly-(ϵ-caprolactone) matrices: III. Effects of molecular weight and polymer coating on drug release

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Abstract

Rumino-reticulum devices (RRDs) (oral dosage forms allowing the release of a drug in the first part of the stomach of grazing animals during a prolonged time) in the form of cylindrical matrices were constructed to release orally anthelmintics in large animals during a period of 3–5 months. The aim of this study was to determine the influence of the molecular weight of the poly-(ϵ-caprolactone) (PCL) constituting the polymeric matrix and the influence of coatings on selected RRDs. The influence of the molecular weight and the coating on these RRDs were studied by the rate and the kinetic release of a model anthelmintic compound, levamisole hydrochloride. For the molecular weight, no significant differences ($P > 0.05$) were observed for matrix systems with a molecular weight of 101 100 or 147 000 Da. Conversely, a faster release ($P < 0.05$) was observed for a matrix with a molecular weight of 53 500 Da. Different kinetic release profiles of levamisole were achieved by application of coatings of poly-(ϵ-caprolactone), poly-(L-lactide) (PLA) and poly-(D,L-lactide-co-glycolide) (PLGA). While all coatings of PCL or PLGA reduced the release rate of the drug, only the coatings with PLA induced a lag time (~ 15 days) before the release of the drug. The lag time encountered with PLA coatings was attributed to the crystallinity of the polymer. For the RRDs constructed with different molecular weights and those coated with PCL, fractional release as a function of time is shown to fit the Roseman–Higuchi model. Plots of $(1 - F)\ln(1 - F) + F$ are linear with time where F is the fraction of drug released at time t. In vitro drug release studies were conducted in conditions as near as possible to those encountered in vivo. Based on the typical pH encountered in vivo, complete release of the drug would ensure good bioavailability of the drug following oral administration. Copyright © 1996 Elsevier Science B.V.

Keywords: Biodegradable polymers; Controlled release; Oral drug delivery system; Levamisole; Rumino-reticulum devices

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1. Introduction

Gastrointestinal nematodes are, along with the liver flukes (*Fasciola hepatica*) and pulmonary parasites (*Dictyocaulus viviparus*), the most important agents of parasitic diseases of cattle. These diseases can go unnoticed due to the absence of clinical symptoms prior to mortality. Conversely, the losses in productivity are always present and can be economically substantial. In cattle, Trichostrongilidae (*Trichostrongylus*, *Ostertagia*, *Dictyocaulus*, *Haemonchus*, *Nematodirus*) are the main parasites responsible for helminthiasises. *Dictyocaulus* is specific to the verminous bronchitis. The remaining nematodes may inhabit the entire gastrointestinal tract and can be located in several places of this tract: Rumen, reticulo-rumen, omasum, abomasum and intestine. Among cattle, lung and gastrointestinal helminthiasises are treated with anthelmintics.

Recent progress in the fields of biochemistry, immunology and pharmaceutical technology has provided a means to control the gastrointestinal nematodes in cattle based on the widespread use of anthelmintics administered according to preventive strategic dosing schedules or as intraruminal boluses.

During the last decade, in the veterinary field, major progress has been made in the area of oral drug delivery for grazing animals. The rumino-reticulum, the first portion of the complex stomach system of a ruminant, is especially suitable for long term retention of dosage forms called rumino-reticulum devices (RRDs). Both cost and convenience, make it desirable to minimize the number of times the animal is handled for administering drugs. For these reasons, sustained release devices which deliver drugs for an entire grazing season are ideally suited for the treatment of parasitic diseases in cattle. Since the introduction of this concept of dosage form in the 1980s, several RRDs with anthelmintics were marketed. Different systems were reported: Diffusion throughout a non degradable polymeric matrix (Ascher et al., 1988), osmotic pump (Pope et al., 1985; Zingerman et al., 1992) and intermittent devices (Whitehead and Shepherd, 1987; Duncan and Seymour, 1989; Cardinal and Witchey-Laksmanan, 1992). Diffusion of drugs from variable geometry to obtain the desired release has been studied by different research workers (Boettner et al., 1988; Conrad and Skinner, 1989, Duncan and Seymour, 1989). Strategic administration and construction of RRDs has provided excellent results in preventing production loss in first year grazing cattle (Armour et al., 1987; Jacobs et al., 1987; Vercruysse et al., 1987).

The ruminal delivery system described in this report was developed to provide a continuous dose of an anthelmintic drug, levamisole, to grazing cattle. For the construction of this system, biodegradable polymers eliminate problems associated with residual non degradable polymers encountered during slaughtering of the animal and damage to butchering equipment due to metal containing devices (Zimmerman and Hoberg, 1988). Our previous work supports the conclusions that: (i) PCL keeps good physico-mechanical properties after a prolonged stay in the rumen of fistulated cattle (Vandamme and Legras, 1995a); (ii) the devices constructed with levamisole hydrochloride (the anthelmintic drug in the hydrophilic form) allowed to obtain a release rate of the drug more appropriate for the aim searched than those designed with levamisole base (the organosoluble form of the same drug) (Vandamme and Ngombo, 1996a); (iii) the incorporation of iron powder into the matrix to provide a density of 2.5 increased the rate of the release of the drug (Vandamme and Ngombo, 1996b).

In this report, several RRDs constructed with the same matrix composition but with PCL of different molecular weights were compared to determine the influence of this parameter on the drug release. Also, different coatings were applied on these matrix systems to decrease the release rate of the drug observed with the systems described previously and to prolong the drug release during July and August which have the higher rates of helminthiasis. The coatings also produced a delay before the release of the drug which increases the immunity by allowing contact between the grazing animal and the helminths during the first weeks of the grazing season.

2. Materials and methods

2.1. Materials

PCL (Tone® Polymer P767-E and Tone® Polymer P787-E, Union Carbide Benelux N.V., Belgium), PCL (Capa 650, Solvay, Brussels, Belgium); PLGA 75:25 and 50:50 (Boehringer Ingelheim, Ingelheim, Germany); Ethylcellulose N-22 (Hercules Incorporated, Wilmington, DE, USA) were used as received.

The model drug used was levamisole hydrochloride (Indis, The Netherlands). The iron powder (92% of the particles have a size between 30–50 μm) used for incorporation in the RRDs was of analytical grade and was obtained from Merck (Darmstadt, Germany). The methylene chloride used to solubilize the polymer was of analytical grade and was obtained from UCB (Braine l'Alleud, Belgium).

The L-(−) lactide ((3s)-(*cis*)-3,6-dimethyl-1,4-dioxane-2,5-dione) used for the synthesis of the PLA was purchased from Aldrich (Milwaukee, WI, USA). Stannous 2-ethylhexanoate was obtained from Sigma. All reagents used for the preparation of the dissolution medium were of analytical grade or better.

2.2. Synthesis and purification of PLA

The synthesis of PLA was based on ring opening polymerization of the L-(−) lactide and was carried out in vacuum-sealed glass ampoule at 100°C for 190 h using 0.015% of stannous-2-ethylhexanoate as catalyst. After synthesis, PLA was dissolved in dichloromethane (5 g/dl). This solution was slowly added with continous stirring to methanol in a volume ratio not exceeding 50 ml of polymer solution to 400 ml of methanol. The fibrous precipitate was vacuum dried (< 1 mmHg) at room temperature for 96 h prior to use.

2.3. Physico-chemical characterizations

Polymer molecular weights (M_w) were determined by size exclusion chromatography (SEC) using a Waters 510 pump. Two ultrastyragel linear columns (Waters®, Mildford, USA) were used with tetrahydrofuran (THF) as the eluting solvent at a flow rate of 0.5 ml/min at room temperature with a refractive index detector (Waters 410). The SEC procedure was calibrated using polystyrene standards of different molecular weights (Polymer Laboratories Ltd.). The polymers were dissolved in THF (2 mg/6 ml) and filtered through a 0.45 μm filter, after which 100 μl was injected.

The inherent viscosity [η] of all polymers was determined at 25 ± 0.2°C in THF, using a Desreux-Bischoff type viscometer. The specific viscosity of the polymers were determined for several concentrations, and the inherent viscosity was calculated by extrapolating the specific viscosities to infinite dilution.

DSC analysis was carried out with a Dupont Instrument (Model 2000). Samples of ~ 10 mg were put into aluminium pans. The pans were pierced in order to permit gas to leave during the heating process. The instrument was calibrated with an indium standard, and measurements were carried out from −100 to +100°C under nitrogen at a scanning rate of 10°C/min. The crystallinity of the PCL was calculated from totally crystalline PCL for which the enthalpy of fusion is 139.5 J/g (Crescenzi et al., 1972), and the crystallinity of PLA was measured from the enthalpy of melting for 100% crystalline PLA which is 203.4 J/g (Jamshidi et al., 1988).

2.4. Preparation of the RRDs

RRD formulations consisted of levamisole hydrochloride and excipients. Typical matrix devices contained 22.05 g of levamisole hydrochloride, 14.70 g of PCL and 48.89 g of iron powder. For the construction of the devices, the quantity of excipients and drug was 1.5 times as those indicated above. Rumino-reticulum devices were cut after extrusion so that each one contained 22.05 g of drug.

The preparation of the RRDs involve several steps. First, PCL was dissolved in 200 ml of methylene chloride. Secondly, the iron powder and levamisole hydrochloride were added to the polymeric solution. Thirdly, the homogeneized suspension was spread on a teflon plate and the

solvent was evaporated under heat. Finally, the mixture was introduced into the barrel (90 ± 0.2°C) of one extruder constructed by our care. The mixture was compressed at 2000 kg/cm^2. A water-circuit cooled the extruder at a rate of 5°C/min. The RRDs were, driven out by pressure. The length and the diameter of the RRDs are 10.5 ± 0.3 cm and 25 ± 0.2 mm, respectively. Some of the RRDs were coated with bioresorbable polyesters. To realize this, the RRDs were coated by dipping in polymeric solution (5 g/100 ml) followed by solvent evaporation in a dry room (R.H. < 30%). In order to dip the matrix devices with easiness and to allow to withdraw them after the same time, these ones were hung on a magnet. This system allowed also a drying of each RRDs in the same condition.

The thickness of the coatings was measured after each step of drying during all the coating process until the obtaining of the desired thickness (~ 100 μm in the case of PCL and 500 μm in the case of PLA and copolymers). The thickness of each film was measured in ten different places by means of Tesa master micrometer (Tesa, Switzerland) using the relationship:

$$\text{Thickness of the coating} = \frac{(T_1 - T_2)}{2} \quad (1)$$

where T_1 and T_2 are respectively the thicknesses of the coated and uncoated RRDs. The coefficient of variation (CV) determined for each coating was not more than 3.2%. Finally, all of the RRDs were capped on each extremity with a 1 cm hood to prevent release by the ends of the cylindrical matrices and to allow release only by longitudinal area. The hoods were created by cutting some polyethylene scintillation vials (Baxter, Mc Gaw Park, USA) 1 cm from the bottom. Hoods were adhered to both ends of the RRDs using cyanoacrylate glue. Triplicate RRDs were fabricated for each formulation.

2.5. Release methodology

2.5.1. Release process

Release experiments were conducted in an in vitro medium as similar as possible to that encountered in the rumen of cattle (Vandamme and Legras, 1995a). Table 1 shows the composition of the solution for in vitro release studies of levamisole from the RRDs. This solution was prepared by dissolution of the different chemicals and filtering on a Seitz press-filter with K0 Seitz filtersheets. The study was conducted in 1000 ml of the medium in 1200 ml polyethylene flasks. All of these flasks were put in a cabinet inside which there was a heating element. The interior of the cabinet was maintained at 39 ± 0.5°C during the experiment. This cabinet was shaken with the help of a motor. The cycling rate of the cabinet was 60 strokes per minute. Each flask was double capped to prevent the escape of carbon dioxide which would modify the pH. At preset time intervals, the flasks were opened, the pH of the solution was measured and samples of the medium were withdrawn so as to determine the drug levels in the release medium. Samples were filtered through 589^3 Blue Ribbon Schleicher and Schuell Filter Paper circles and assayed for levamisole hydrochloride by high performance liquid chromatography (HPLC). Filtering steps gave quantitative recoveries: 92% of the initial solution were recovered after filtration. Standard curves were linear and passed through origin. The RRDs were withdrawn from the release medium and were put immediately in a similar flask than those used previously and containing a fresh medium.

Table 1
Composition of the in vitro medium for the release experiments

Chemicals	Weight (g)
$Na_2HPO_4 \cdot 12H_2O$	9.3
$NaHCO_3$	9.8
NaCl	4.7
KCl	5.7
$CaCl_2 \cdot 2H_2O$	53×10^{-3}
$MgCl_2 \cdot 6H_2O$	128×10^{-3}
$FeSO_4 \cdot 7H_2O$	75×10^{-3}
$MnSO_4 \cdot H_2O$	4×10^{-3}
Urea	7×10^{-2}
Water, 1000 ml, pH fixed at 6.9 with CO_2	

2.5.2. Mathematical analysis

The release data of the matrix-type devices was fitted to the relationship (Ritger and Peppas, 1987)

$$\frac{M_t}{M_\infty} = Kt^n \quad (2)$$

Where M_t is the amount of drug released at time t, M_∞ is the total amount of drug released, k is the release rate constant of nth order incorporating characteristics of the macromolecular network system and the drug, and n is the diffusional exponent, which is indicative of the transport mechanism, with $n = 0.45$ for cylindrical samples showing a Fickian diffusion and $n = 1.0$ for zero-order release.

2.6. Analytical method

The levamisole hydrochloride concentration was determined by an HPLC method due to the fact that the interactions of drug-excipients did not permit use of the spectrophotometric method (Vandamme and Ngombo, 1996b). The HPLC assays of levamisole concentrations were determined as described previously including the modifications that follow (Vandamme et al., 1995b). The quantitative determination of levamisole was accomplished with a HPLC-Waters delivery system (pump M45, injector U6K, detector M481, integrator baseline 810, sensitivity at 0.01 A.U.F.S). The analytical column (C18 Nova-Pak®: 3.9 mm i.d. × 150 mm, 4 μm particle size and a porosity of 60 Å) was used for analytical determination. The mobile phase consisted of 15% (v/v) acetonitrile and 85% (v/v) aqueous solution of 0.05 M potassium dihydrogen phosphate. The paired-ion agent (1-pentanesulfonic acid sodium salt) was used at 0.005 M in the aqueous phase. The pH of the mobile phase was adjusted to three with phosphoric acid. The flow rate was maintained at 1.0 ml/min and the levamisole concentration quantified by using peak area ratios (UV absorbance detection, 225 nm) of levamisole to the quinine, the internal standard. Under these conditions, the retention times for levamisole and quinine were respectively ~4.73 and 10.38 min.

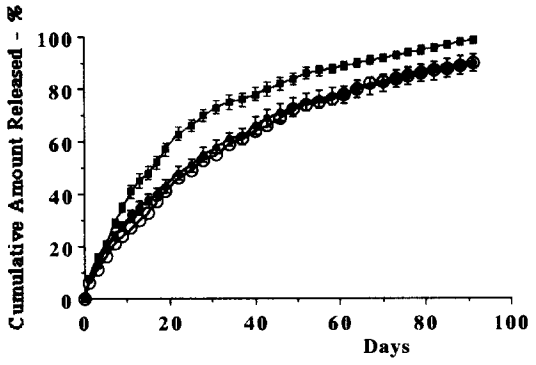

Fig. 1. Cumulative release of levamisole from RRDs having a molecular weight of (■) 53 500; (●) 101 100; (○) 147 000.

2.7. Statistical analysis

All data are expressed as cumulative release % ± S.D. Statistical evaluation of the data used either Student's t-test (where comparisons were made between two groups) or analysis of variance (ANOVA) (for comparisons between more than two groups). These tests allowed comparison of the % drug released from the formulations with the different molecular weights of PCL constituting the matrix of the device and the formulations with the different coatings. P values of 0.05 or less were considered significant.

3. Results and discussion

3.1. Influence of the molecular weight

Fig. 1 shows the release profiles obtained from the systems constructed with 60% of levamisole hydrochloride, 40% of PCL having different molecular weights (Table 2) and iron powder dispersed homogeneously in the matrix system to obtain a density of 2.5. The release of levamisole hydrochloride from the systems containing PCL having a molecular weight of 101 100 and 147 000 Da is not discernibly different ($P > 0.05$). 90% of the total loading of the drug was released in both cases after 91 days. Conversely, the RRDs constructed with a molecular weight of 53 500 Da show a different rate of release. The release is, in this case, faster. It is a drug delivery system for

Table 2
Different molecular weights of poly-(ε-caprolactone) used for the construction of the RRDs containing levamisole hydrochloride

Polymer	M_w (Da)	M_n (Da)	M_z (Da)	δ (M_w/M_n)
PCL (Capa 650) (Solvay)	53 500	32 600	50 200	1.6
PCL (P767-E) (Union Carbide)	101 100	49 900	91 300	2.0
PCL (P787-E) (Union Carbide)	147 000	50 600	126 000	2.9

which the drug release is less prolonged compared to the release of the other matrix systems with a higher molecular weight ($P < 0.05$). 94% of the total loading of the drug was released in this case after 91 days.

In the above formulations, levamisole hydrochloride powder is homogeneously dispersed throughout the polymeric matrix. In order to determine if the release mechanism is governed by diffusion, the results were analysed following the theoretical model of release from cylindrical matrix systems developed by Roseman and Higuchi (1970). This model assumes a retreating boundary separating an outer zone of drug depletion from an inner zone in which drug is present at essentially its original concentration. An equation describing the fraction of drug released in terms of the radius of the inner zone was derived as follows (Hsu et al., 1994):

$$2a_0^2 \ln\left(\frac{a}{a_0}\right) + (a_0^2 - a^2) = \frac{4CDt}{A} \quad (3)$$

where a_0 is the outer radius of the cylinder (also radius of inner zone at time $t = 0$), cm; a is the radius of inner zone at time t; C is the solubility of the drug in the polymer, mg/cm^3; D is the diffusivity of drug in polymer, cm^2/day; and A is the total initial content of drug in polymer, mg/cm^3.

The fraction of drug released at any time t, F, may be stated in terms of the radii of the cylinder and the inner zone, a_0 and a, as:

$$F = \frac{(a_0^2 - a^2)}{a_0^2} \quad (4)$$

and thus the fraction of drug remaining in the cylinder at time t will be $1 - F$. As shown by Roseman (1972), dividing Eq. (3) by a_0^2 and making appropriate substitutions for F and $1 - F$ yields:

$$(1 - F)\ln(1 - F) + F = \frac{4CDt}{Aa_0^2} \quad (5)$$

Thus, if a plot of the left-hand side of Eq. (5) versus time is linear, this can be accepted as evidence of a diffusion controlled release in which matrix degradation is much slower than diffusion.

Plots of $(1 - F)\ln(1 - F) + F$ versus time for RRDs differing only by the molecular weight of the polymer used for the construction of the matrix are illustrated in Fig. 2. The slopes of these lines are $4CD/Aa_0^2$. These ones allow to reflect that no difference in fractional release rates was observed in the case of the devices constructed with a molecular weight of 101 100 and 147 000 Da whereas a difference in fractional release rate was observed with the devices constructed with a molecular weight of 53 500 Da. Results of the slopes are presented in Table 3. Values of the diffusivity, D, of the levamisole hydrochloride (Leva · HCl) in the matrix are calculated from the slopes and the loading. The solubility of levamisole hydrochloride in the polymer was estimated previously (Vandamme and Ngombo, 1996a). Levamisole hydrochloride solubility in

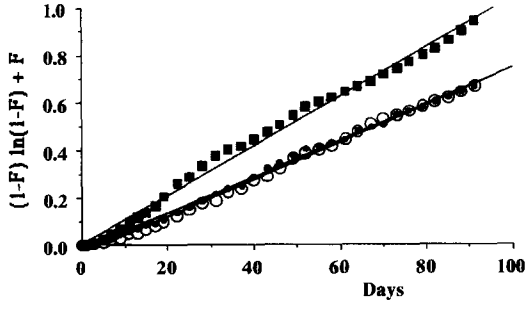

Fig. 2. Effect of molecular weight on release profile: fractional release function $(1 - F)\ln(1 - F) + F$ as a function of time for cylindrical matrices for which PCL has a molecular weight of (■) 53 500 Da; (●) 101 100 Da; (○) 147 000 Da.

Table 3
Results of in vitro release measurements

RRDs	Slope K (day^{-1})	r^{2a}	Diameter (mm)	[Leva·HCl] (mg/cm^3)	D (cm^2/day)^b
PCL (M_w: 53 500) uncoated	0.01037	0.992	25	428.025	1.926×10^{-3}
PCL (M_w: 101 000) uncoated	0.00784	0.996	25	428.025	1.426×10^{-3}
PCL (M_w: 147 000) uncoated	0.00769	0.997	25	428.025	1.429×10^{-3}
PCL (M_w: 101 000) coated	0.00469	0.993	25	428.025	1.970×10^{-2}

[a] Correlation coefficient for linear regression of $(1-F)\ln(1-F)+F$ versus time.
[b] Diffusion constant calculated from slope, K.

PCL was estimated by casting and heating films from methylene chloride solution and examining the films microscopically using light polarized microscopy and scanning electron microscopy (SEM) for particles of precipitated drug. Precipitated crystals were observed at 0.9 wt.%.

The linearity observed in Fig. 2 confirms that the release mechanism is diffusion controlled and thus polymer degradation proceeds much more slowly than drug release and therefore can be considered as inert during the release of drug.

The application of Eq. (2) to the fraction of levamisole hydrochloride released from the RRDs constructed with different molecular weights has allowed us to determine the values of the exponent n which are 0.455 and 0.456 for the matrices having a molecular weight respectively of 101 100 and 147 000 Da. An exponent n of 0.472 was found for the devices constructed with a molecular weight of 53 500 Da. These values confirm that the release is controlled by non-steady state diffusion or Fickian diffusion.

3.2. Effect of the coating

Figs. 3 and 4 show the release kinetics of levamisole hydrochloride from the matrices coated and uncoated. The RRDs coated with bioresorbable polyesters allow to envision the possibility to make RRDs with two kinds of kinetics: (i) an immediate release followed by a decrease of the release rate; (ii) a delayed release.

A lag time (~ 15 days) before the release of the drug was observed for the RRDs coated (~ 500 μm with PLA (Fig. 4). Conversely, as seen in Figs. 3 and 4, no delayed release was observed by application of a coating of copolymers of lactic acid and glycolic acid or PCL. The matrix devices coated with PLGA 50:50 and PLGA 75:25 shows a release of the drug following a sigmoidal curve.

In order to explain the differences of the release of the drug from the RRDs coated with PLA and PLGA, physico-chemical characteristics of the polymers constituting the coating were determined and are summarized in Table 4. The PLA has a glass transition temperature (T_g) of 60°C and a crystallinity of 37%. The copolymers of lactic acid and glycolic acid 50:50 and 75:25 have, respectively, a T_g of 44°C and 52°C. These copolymers are devoid of crystallinity and are therefore in an amorphous state. The presence of a lag time observed by application of the homopolymer of L-lactic acid on the RRDs cannot be attributed to the T_g: other poly-α-hydroxyacids used in this study are also below their T_g at the experimental temperature (39 ± 0.5°C). The crystallinity of the homopolymer, the differences in the chemistry of the homopolymer and the copolymers, coupled

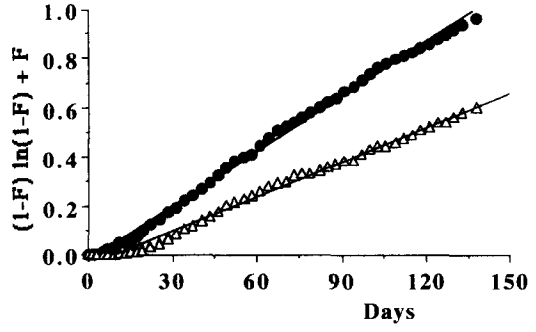

Fig. 3. Effect of coating of PLC on release profile: fractional release function $(1-F)\ln(1-F)+F$ as a function of time for cylindrical matrices (●) uncoated, (△) coated with 100 μm of PCL P767-E.

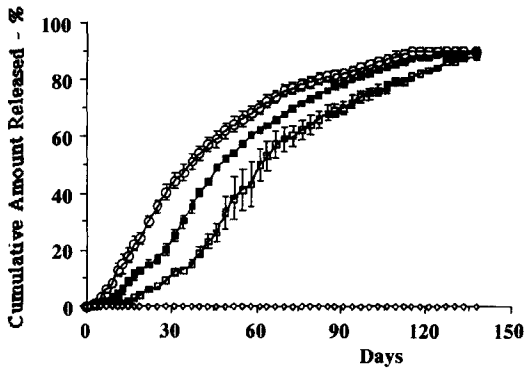

Fig. 4. Cumulative release of levamisole from RRDs coated with: (○) PLGA 50:50, (■) PLGA 75:25, (□) PLA, (◇) ethylcellulose N-22 (inner coating, 50 μm) and polylactide (outside coating, 500 μm).

with different physico-mechanical properties can only explain the delayed release.

During the in vitro experiment, poor adhesion of the coating of PLA has been observed. After several days of incubation of the RRDs coated with PLA, the coating breaks loose of the matrix. Therefore the phenomenon which can explain the ~ 15 days lag time would be the necessary time for penetration of the coating followed by lack of adhesion of PLA on a matrix constructed with PCL. This fact was confirmed by application of a coating of ethylcellulose (~ 50 μm) on the matrix devices before coating with PLA. In this case, good adhesion on the matrix was observed. Furthermore, the PLA coating was not degraded ($P > 0.05$) and no drug was released from the RRDs (Fig. 4) during the time of the experiment.

PCL coatings on RRDs adhered well, unlike poly-α-hydroxyacids coatings which peeled off after a few days. The matrix systems coated with PCL give a kinetic release which is nearly first-order release. These matrix systems released 62.9% during the first 60 days. In spite of the high crystallinity (49.3%) of the PCL, this one shows a greater permeability compared to the PLA due to its low T_g (− 61.9°C).

The release profile from a reservoir device, in which the thermodynamic activity of the drug in a polymer does not remain constant as the drug is released from the device, will follow first-order and not zero-order kinetics. The fractional release, F, at any time t can be expressed by the following equation:

$$F = 1 - \exp\left(\frac{-ADKt}{Vl}\right) \quad (6)$$

where A is the surface area of the membrane, D is the diffusivity of the drug in the membrane, V is the volume of the drug reservoir, K is the reservoir/membrane distribution coefficients and l the thickness of the membrane (Franz et al., 1992). In this particular case, the obtained diffusion coefficients for the coated devices are apparent values. Plots of $(1 - F)\ln(1 - F) + F$ versus time for matrices coated with PCL are illustrated in Fig. 3. Results are presented in Table 3. Values of the diffusivity, D, of levamisole hydrochloride in PCL are calculated from the slopes, the estimated solubility of levamisole hydrochloride in the polymer, and the loading.

The application of a coating of PCL yielded results in accordance with the theory of diffusion. The linearity supports the conclusion that the release mechanism is diffusion controlled over the full range of the release curve confirming that the drug release mechanism is based on Fickian diffusion.

4. Conclusions

Construction of RRDs with a biodegradable polymer matrix such as PCL having a molecular weight of 53 500 Da was shown to modulate significantly the drug release profile ($P < 0.05$) in comparison with the same systems designed with a matrix having a molecular weight of 101 100 and 147 000 Da.

Coating of the RRDs with different polymers provided two different release kinetics. In all systems, application of a coating on the RRDs provides a sustained-release system which allows to decrease the release rate of the drug observed with the RRDs without coatings. Whereas drug delivery systems coated with PLA were able to show a lag time (~ 15 days) before the release of the drug, the RRDs coated with PCL and PLGA were only able to decrease the release rate of the drug but were unable to induce a lag time before the release of the drug.

Table 4
Physicochemical characteristics of the polymers used for the coating of the RRDs

Polymer	$[\eta]$ (dl/g)	M_w (Da)	δ (M_w/M_n)	Crystallinity (%)	T_g (°C)
PLA	0.90	100 700	2.18	37	60
PLGA 75:25	0.80	85 200	2.08	—	52
PLGA 50:50	0.66	63 000	1.99	—	44
PCL	0.71	101 100	2.00	49.3	−61.9

In vitro release kinetics of the levamisole/PCL matrix systems uncoated and coated with PCL follow the Roseman–Higuchi model indicating that the release mechanism is in both cases diffusion controlled. Conversely, the matrix systems coated with PLGA showed a release of the drug following a sigmoidal curve.

Oral administration of the devices designed above to some cattle are in progress. It will allow to estimate the efficiency of these devices in vivo by quantitative determination of the level of the drug in the plasma, counting of the eggs and larvae on the grass and in the faeces of the cattle. It will also allow to appreciate the increase of the weight of the animals during the grazing season.

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