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Polyisoprene matrix for progesterone release: *In vitro* and *in vivo* studies

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ABSTRACT

Latex, a polyisoprene (PI) hydrophobic elastomer, was evaluated *in vitro* and *in vivo* as a matrix for intravaginal steroid hormone delivery. Matrices containing hormone were prepared by swelling latex in chloroform that contained soluble progesterone (P4). *In vitro* studies demonstrate that P4 release from PI follows a zero order model during at least 100 h and depends on initial load up to 10 mg cm^{-2}. The release of P4 from a PI matrix was found to be two times faster than from a polydimethylsiloxane (PDMS) matrix. FT-IR and X-ray powder diffraction analysis of P4 polymorphs show that when nucleated in PDMS, the hormone crystallizes only in α-form while in latex, crystallizes as a mixture of α- and β-form. *In vivo* studies show that devices with a PI matrix containing 0.5 g of P4 are effective to reach plasma levels above 1 ng ml^{-1} that are needed to synchronize estrous in cattle. Altogether, the results show that PI, a vulcanized polymer with a carbon–carbon backbone, can be used as a new matrix for the intravaginal administration of progesterone with improved release profile than silicone and that the matrix can influence the crystalline state of the hormone.

1. Introduction

Pharmacologic control of reproduction through the delivery of hormones is an area of intense research (Vernon et al., 2004; Biruss and Valenta, 2008). In humans it is mainly used as a contraceptive method while in livestock it is widely used to synchronize estrous associated with artificial insemination for planned conception programs (Rathbone et al., 1997; Vernon et al., 2004). Estrous control can be achieved through the use of commercially available drug delivery systems characterized by a daily release of progesterone (P4) or a synthetic derivative (Rathbone et al., 1997). The best fertility results are obtained when the drug delivery system achieves a 7 or 8 days sustained progesterone delivery and plasma progesterone concentration above 1 ng ml^{-1} (Macmillan et al., 1991; Rathbone et al., 1998a). Silicones, in particular, lend themselves well to the release of steroid molecules (Malcolm et al., 2003). They are thermoset rubbers consisting of three-dimensional polydimethylsiloxane (PDMS) networks held together by chemical bonds. The fabrication of intravaginal devices used to synchronize estrous in cattle consists of dispersing between 1 and 2 g micronized progesterone in a high temperature vulcanizing PDMS that requires a treatment at up to 190 °C during the manufacturing process (Rathbone et al., 1997, 2002a). In a recent study, we characterized the *in vitro* and *in vivo* kinetics of a new intravaginal device consisting of a skin made with room temperature vulcanizing PDMS impregnated with P4, supported on a reusable spine (Heredia et al., 2008). This system was loaded with 6% (w/w) P4 (0.75 g total) and delivered the drug in such a way that the hormone plasma concentration required to synchronize estrous in cattle was achieved and sustained over the period of time needed (Heredia et al., 2008).

Although a significant body of work has been published to date to understand the kinetic release of P4 from PDMS matrices (Rathbone et al., 1997, 2002a; Malcolm et al., 2003; Taghizadeh et al., 2003; Woolfson et al., 2003; Heredia et al., 2008) few attempts have been made to study other polymers as potential P4 carriers (Vernon et al., 2004; Biruss and Valenta, 2008; Wischke and Schwendeman, 2008). One of the few examples is poly(ε-caprolactone) (PCL) that has been used within the veterinary field to engineer a steroid intravaginal delivery system with a high retention rate in the vagina of cows (Rathbone et al., 2002b). This system provided bioequivalent plasma levels to those attained with a commercially available product (CIDR intravaginal insert) (Rathbone et

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al., 2002b). To manufacture intravaginal devices with either PDMS or PCL, micronized P4 is mixed with the polymer before vulcanization. In an attempt to improve the kinetic release, which is driven by the aim of reducing the amount of residual hormone after treatment, we evaluated a different strategy that involved loading the hormone into a polymer already vulcanized by swelling it using a solution of hormone in an organic solvent. Latex is another hydrophobic thermoset elastomer but unlike PDMS it contains a polyisoprene (PI) carbon–carbon backbone and absorbs some organic solvents such as chloroform. These structural differences in the matrix network may result in different interactions between the drug and the matrix that could modify drug release profiles. For these reasons, and in order to evaluate the possibility to use it in the design of a novel intravaginal delivery system for cattle, a latex matrix was studied to characterize the loading and release of P4.

In vitro testing showed that a matrix of PI loaded with solubilized P4 in an organic solvent resulted in a mixture of α- and β-polymorphs, and was twice as efficient at releasing P4 than a matrix made with room temperature vulcanizing PDMS. Supporting this finding, the *in vivo* studies showed that PI devices containing as low as 0.5 g of P4 resulted in plasma levels (above 1 ng ml^{-1}), suitable to synchronize estrous in cattle.

2. Materials and methods

2.1. Materials

Micronized P4 was obtained from Sigma Chemical Co. (St. Louis, MO, USA). Polyisoprene (PI) sheets with 0.1 mm thickness were obtained from SEISEME S.A. (Buenos Aires, Argentina). Room temperature vulcanizing (RTV) silicone monocomponents of acid reticulation were obtained from Anaerobicos S.A. (Loma Hermosa, Argentina). Chloroform and sulfuric ether of analytical grade were obtained from Ciccarelli (San Lorenzo, Santa Fe, Argentina). The commercial intravaginal insert, DIB®, was obtained from Syntex (Buenos Aires, Argentina).

2.2. Methods

2.2.1. Progesterone loading of latex and silicone matrix

Latex sheets (PI matrix) were loaded as follows: different amounts of P4 were solubilized in chloroform (C) or chloroform:ether 1:10 (v/v) (C/E), then latex was added and gently agitated until the solvent was completely absorbed by the polymeric matrix. Finally, the solvent was evaporated at room temperature using an air stream. Control latex matrices were loaded with C or C/E without P4 and dried with a similar procedure.

Silicone sheets (PDMS matrix) were loaded in three different ways: (1) *Progesterone homogeneously distributed into PDMS matrix*: different amounts of micronized P4 were mixed with a fixed amount of RTV silicone to achieve a homogeneous mixture. The mixture was then placed into a 2 cm × 2 cm × 0.2 cm polyurethane mold and left to vulcanize for 24 h; (2) *Progesterone superficially loaded onto PDMS matrix:* samples of PDMS sheets of 2 cm × 2 cm × 0.2 cm vulcanized for 24 h at room temperature were incubated in a sealed tube with a solution of C/E containing different amounts of P4. Afterwards, the tubes were gently shaken until PDMS absorbed completely the organic solvents and then was dried at room temperature using an air stream; (3) *Progesterone/chloroform solution homogeneously mixed with PDMS:* different amounts of micronized P4 dissolved in C were mixed with a fixed amount of RTV silicone to achieve a homogeneous mixture. The mixture was then placed into a 2 cm × 2 cm × 0.2 cm polyurethane mold and let vulcanize for 24 h. Control matrices were prepared in all cases as described above without P4.

2.2.2. In vitro drug release assessment

The pH values of cow vaginal mucus ranges between 6.0 and 8.5 depending on the stage of the estrous cycle (Senger, 2003). As the solubility of P4 in water does not change within this pH range (data not shown), studies of P4 release from PI or PDMS were carried out in 50 ml phosphate buffer saline (PBS) solution pH 7.0 with 0.02% (w/v) sodium azide. Release medium was sampled and completely renewed every 24 h, over a period of 10 days. The amount of P4 released was quantified by UV analysis at 248 nm using a Beckman DU 650 UV-Vis spectrophotometer. Cumulative P4 release was calculated using a calibration curve of P4 in PBS pH 7.0 with 0.02% (w/v) sodium azide, and plotted against release time.

2.2.3. X-ray diffraction

Samples of PI and PDMS superficially loaded with P4 prepared as described above were analyzed in a Bruker D8-Advance with Cu anode X-ray diffractometer. The polymorphic form was identified by comparing the X-ray powder diffraction pattern with crystallographic data of α- and β-form progesterone polymorphs. (PROGST 10: α-form of P4 data (Campsteyn et al., 1972) and PROGST 01: β-form of P4 data (Foresti Serantoni et al., 1975)).

2.2.4. Infrared spectroscopy

The spectra were collected on a FT-IR spectrophotometer (FT-IR-8501, Shimadzu, Japan), 4 cm^{-1} resolution for scans. P4 crystals from samples of PDMS or PI matrices loaded with C or C/E were mixed with KBr powder (1/20) and analyzed by diffuse reflectance (DRIFT). The polymorphic form was evaluated by examining the spectral region between 850 and 890 wavenumbers as α- and β-form give characteristic bands at 870 and 864 cm^{-1}, respectively (Payne et al., 1999; Wang et al., 2000).

2.2.5. Optical microscopy

Silicone and latex sheets loaded with P4 were photographed and analyzed without any staining using a stereoscopic magnifier (ST 30 2L, ARCANO) at 20×.

2.2.6. Intravaginal device and in vivo studies

Y-shaped intravaginal devices with PI matrices (150 cm^2) loaded with 0.25, 0.50 or 0.75 g P4 as described before, were tested in ovariectomized cows with mean weight of 450 kg (Heredia et al., 2008). Ovariectomy removed the endogenous source of P4 so that plasma P4 measured can only have come from intravaginal inserts. The control used was a commercially available V-shaped insert DIB with PDMS matrix containing 1.0 g P4 and a surface area of around 150 cm^2. Blood samples were taken during 9 days and the plasma concentrations of P4 were determined by electrochemiluminescence as previously described (Heredia et al., 2008).

3. Results and discussion

3.1. In vitro kinetic of progesterone release from latex matrix

As expected, the *in vitro* release profile of P4 from latex sheets loaded with increasing amounts of the dissolved hormone in chloroform was dependent on the surface area (data not shown) and the initial load of P4. Above the saturating concentration there was no further increment in the release rate (Fig. 1A and B). Latex matrices loaded with 0.55 mg cm^{-2} P4 or more display linear cumulative release (R^2 = 0.99) over 100 h, indicating that zero order release kinetics are being obeyed and that constant source activity is being maintained at least for the period evaluated (Woolfson et al., 2003). However, matrices loaded with 0.28 mg cm^{-2} and 0.14 mg cm^{-2} did not display linear cumulative release versus time profiles (R^2 = 0.86 and 0.67, respectively), indicating that P4 initial load was not enough to release a constant quantity during the period evaluated.

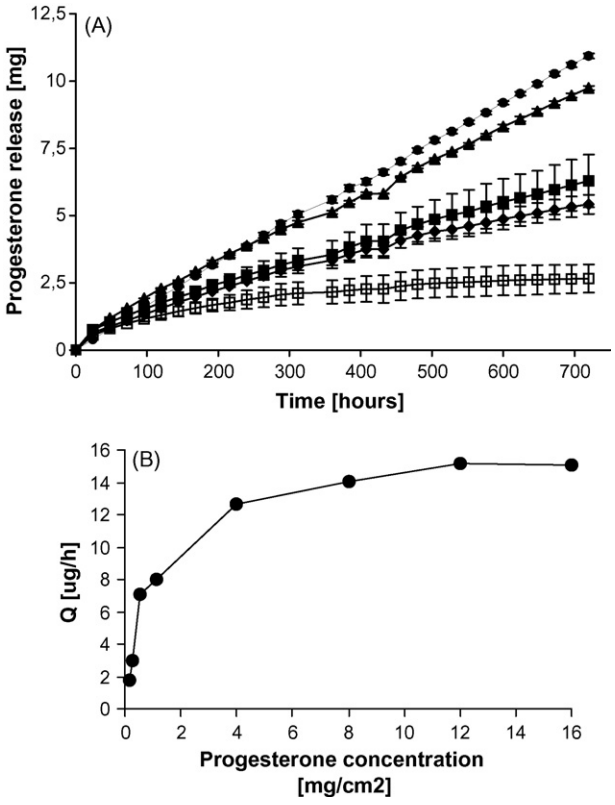

Fig. 1. (A) Cumulative progesterone release profiles from latex matrices with different initial loads. PI loaded with 16 mg cm^{-2} (●), 4 mg cm^{-2} (▲), 1 mg cm^{-2} (■), 0.55 mg cm^{-2} (♦), 0.28 mg cm^{-2} (□); (B) progesterone release rate (Q) from PI matrices as a function of initial progesterone concentration. Data are means ± SD. Errors bars in (B) are smaller than symbol size.

Moreover, Fig. 1B shows that *in vitro* P4 release rate (Q) increases with the initial load up to a concentration of around 10 mg cm^{-2}, suggesting that in this concentration range the system reaches saturation. The increase in release rate as a function of initial load indicates that the receptor phase is not saturated with progesterone under the experimental conditions employed. Furthermore, when loaded with 16 mg cm^{-2}, the peak of progesterone release (i.e. within the first 24–48 h) reaches a hormone concentration below 50% saturation (data not shown). In agreement with these results, when latex was loaded with P4 concentrations of 6 mg cm^{-2} the surface appeared covered with a fine white powder, and with concentrations higher than 8 mg cm^{-2} the surface showed clearly visible crystal structures.

3.2. Effect of swelling latex matrix on the capacity to load and release P4

Latex is composed of a non-covalent interaction of hydrophobic polyisoprene that swells to different sizes when is incubated in the presence of different volumes of chloroform and returns to its original size after solvent is removed. The fact that P4 is soluble in chloroform, suggested the possibility that P4 molecules could be located at different depths into latex as different volumes of solvent were used when loading the matrices. To evaluate this possibility, we analyzed the effect of incubating latex in the presence of increasing volumes of chloroform containing a fixed amount of P4 and then analyzed the *in vitro* release of hormone. Latex matrices with surface area of 10 cm^2 and thickness of 1.6 mm were loaded with two concentrations of P4 (0.5 mg cm^{-2} and 1 mg cm^{-2}), but using different volumes of chloroform. Fig. 2 shows that PI loaded with both concentrations of P4 but with increasing volumes of chloroform did not modify the *in vitro* hormone release kinetic. These results suggest that, under the conditions employed, the final distribution of P4 in PI is independent on the swelling and volume of solvent used. In agreement with these findings, similar release kinetics was observed using latex matrices of different thicknesses (data not shown). These results could be due to a migration of dissolved progesterone with the solvent as it migrates from the interior of the latex matrix to the surface during its evaporation. For this reason, under the different loading conditions employed, most of the hormone likely accumulated near the surface of the latex matrix.

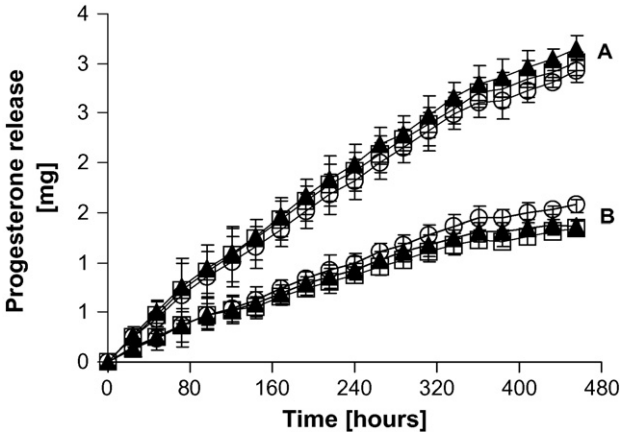

Fig. 2. Progesterone release rate from PI matrices loaded with different solvent quantities: 0.625 ml (▲), 1.25 ml (◯) and 2.50 ml (□). PI loaded with 1 mg cm^{-2} (A) and 0.5 mg cm^{-2} of progesterone (B). Data are means ± SD.

3.3. Comparative analysis of P4 release from latex and polydimethylsiloxane (PDMS) matrix

Most commercial intravaginal devices for P4 release used to synchronize estrous cycle in cows contain a matrix of high temperature vulcanizing PDMS (Rathbone et al., 1997). Recently, we described that polymeric PDMS matrices prepared by vulcanization at room temperature (RTV) show an *in vitro* and *in vivo* behavior similar to those vulcanized at high temperatures (Heredia et al., 2008). A comparative study of P4 release from latex and RTV-PDMS sheets showed that the release rate from latex (1.97 μg cm^{-2} h^{-1}) was two times higher than from RTV-PDMS (0.93 μg cm^{-2} h^{-1}) (Fig. 3). However, it is important to note that silicone matrices are usually loaded using micronized P4 that is mixed with PDMS before polymerization, while vulcanized PI matrices were loaded by swelling them with a solution of the hormone in an organic solvent. We

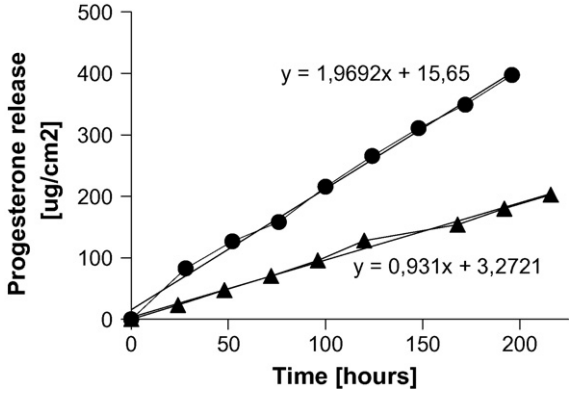

Fig. 3. Cumulative P4 release profile from latex matrices (●) and room temperature vulcanizing PDMS (▲) with equal surface area loaded with 20 mg cm^{-2} P4.

Table 1
Progesterone release rate (Q) from Silicone (PDMS) and latex (PI) matrices loaded with increasing initial load of progesterone (P4). A group of PDMS matrices were loaded mixing micronized P4 with the polymer before vulcanization reaction (Powder). Another group of PDMS matrices and PI matrices were loaded incubating the polymer with a solution of P4 in chloroform:ether 1:10 v/v (C/E) or chloroform alone (C).

Matrix	Method of loading	Q ($\mu g\,cm^{-2}\,h^{-1}$)			
		Initial load of P4 ($mg\,cm^{-2}$)			
		5	10	15	20
PDMS	Powder	0.95 ± 0.05	0.93 ± 0.04	0.93 ± 0.05	0.93 ± 0.04
	C/E	1.25 ± 0.02	1.06 ± 0.02	1.16 ± 0.02	1.17 ± 0.02
	C	0.73 ± 0.01	0.83 ± 0.02	0.77 ± 0.02	0.86 ± 0.01
PI	C/E	1.65 ± 0.03*	1.30 ± 0.06*	ND	ND
	C	1.87 ± 0.05*	1.82 ± 0.03*	1.84 ± 0.05*	1.90 ± 0.04*

Data are means ± S.E.
* Difference versus PDMS C/E, $p < 0.01$.

designed an experiment where both, PI and PDMS already vulcanized, were loaded with P4 dissolved in an organic solvent in order to compare the release kinetics from these matrices under similar loading methods. As polymerized PDMS does not swell in chloroform alone it was necessary to test the ability of different solvents to swell silicone as well as to dissolve P4. We found that a mixture of chloroform and ether (C/E) displayed the capacity to dissolve the hormone and to swell both silicone and latex (data not shown). Therefore, PDMS matrices were loaded using three different procedures: (a) mixing micronized P4 with the polymer before vulcanization, (b) mixing P4 solubilized in chloroform with PDMS before its vulcanization, and (c) incubating vulcanized silicone with P4 dissolved in C/E as described under materials and methods. In order to allow a comparison of solvent and matrix effect on P4 release, PI matrices were swelled either with a solution of C/E or C with increasing amounts of P4. All matrices were evaluated in their capacity to release P4 *in vitro* during 10 days and release rate (Q) was calculated from the P4 release profiles (see Table 1). The results show that release rates from PI matrices loaded with the hormone in C or a mixture of C/E were higher than those from PDMS in all cases (see Table 1). The higher release rate of P4 from latex matrices loaded with an organic solvent compared with that from PDMS matrices loaded with micronized P4 could be due to the final location of the hormone or the physical properties of the granules of powder (i.e. crystal habit, polymorph, granule size) obtained after solvent drying.

3.4. Physical state of progesterone

It is known that among other factors, the release rate of a drug from a matrix may be also regulated by its physical state. In this context, the presence of different P4 polymorphs could affect its bioavailability. Therefore, the next step was to evaluate crystal habit and polymorphism of crystalline material of P4 collected from the matrices prepared as described above. Optical analysis showed that P4 crystal habits varies depending on the nature of the matrix, the quantity of P4 loaded and the presence and nature of solvent used (Fig. 4). In this sense, PDMS matrices loaded with 200 mg P4 dissolved in C/E and PI matrices loaded with the same quantity dissolved in C showed rombic crystals (Fig. 4A and E), while PI matrices loaded with 200 mg P4 dissolved in C/E showed smaller crystals (Fig. 4C). PDMS loaded with 50 mg P4 dissolved in C/E showed a mottled surface where white regions indicate a higher P4 concentration (Fig. 4B). In contrast, PI matrices similarly loaded showed all surface covered with a homogeneous layer of small aggregated crystals (Fig. 4D). PI matrices loaded with the same amount of P4 but dissolved in C showed slender crystals that formed acicular radial oolitic aggregates tightly associated to the matrix (Fig. 4F). Surprisingly, no crystals were seen on the surface of PDMS loaded with P4 dissolved in C. In accordance with this observation the X-ray diffraction analysis of this sample did not reveal the presence of crystalline material on the surface of PDMS (data not shown).

It is well known that P4 exists in two crystal forms of equal physiological activity, which are readily interconverted. The α-form with prism-like crystals and the highest melting point (129 °C) and β-form with needle-like crystals and melting point at 121 °C. The former therefore might be expected to be the thermodynamically stable polymorph (Payne et al., 1999). This is supported by the work of Wang et al. who show that the appearance of α-form is always preceded by the formation of β-form progesterone (Wang et al., 2000). If two polymorphic forms exist, there enthalpy of fusion will be different, and the enthalpy of dissolution depends essentially on this term (Lengendre et al., 2003). Accordingly, preliminary results from our laboratory indicate that the β-form of P4 is more readily soluble in water based buffers than the α-form (Heredia et al., unpublished observations).

As far as we know there is not a classical procedure to obtain single crystals of the metastable β-form of P4 (Fig. 4). Recently, Lancaster et al. was able to produce a co-crystal of β-form with P4 and pregnenolone after failing to produce this form with different manufacturing processes previously reported (Lancaster et al., 2007). To investigate the effect of matrix material on P4 polymorphism, crystalline material found on the surface of silicone and latex that were loaded with P4 was analyzed by X-ray diffraction and Infrared spectroscopy before evaluation of hormone release kinetic. P4 polymorphs found on the surface of PI matrices loaded with different amounts of P4 dissolved in C or C/E are shown in Table 2. Interestingly, the results show that loading PI with 5 $mg\,cm^{-2}$ P4 dissolved in chloroform leads to β-form crystals, the more unstable and soluble P4 polymorph. Although, the higher Q of P4 from PI matrices compared with PDMS observed in this work cannot be fully attributed to the crystalline structure formed in each type of matrix, the appearance of the β-form of P4 was in all cases associated with PI matrices and never with PDMS indicating the strong influence of the matrix on the polymorphic outcome. This result is in agreement with the recent discovery of new polymorphs by templating with polymers (Price et al., 2005) or surfaces (Mitchell et al., 2001). Altogether these results point to an influential role of matrix and/or additives in determining the polymorphic outcome of P4, even under conditions where it is not incorporated into the polymer lattice.

3.5. Effect of formulation variables on progesterone levels in plasma

P4 released upon insertion of an intravaginal device has an important role on ovaric follicular dynamics: supra luteal levels in plasma (>1 $ng\,ml^{-1}$) obtained a few minutes after insertion induce

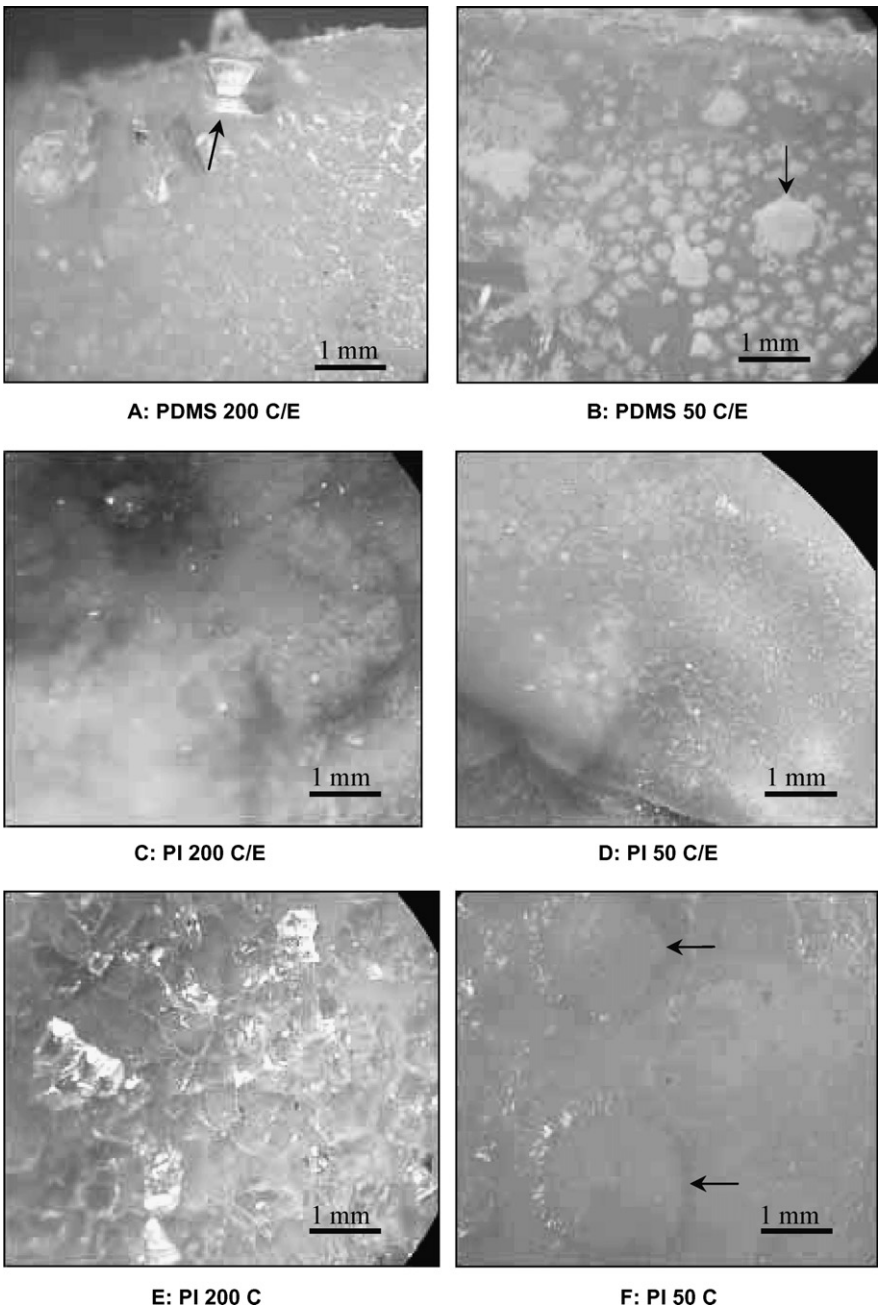

Fig. 4. Photographs of Progesterone crystals formed on different polymeric matrices with different hormone quantities. (A) PDMS 200 C/E: silicone matrices loaded with 200 mg progesterone dissolved in chloroform:ether 1:10 (v/v) (20 mg cm^{-2}); (B) PDMS 50 C/E: silicone matrices loaded with 50 mg progesterone dissolved in chloroform:ether 1:10 (v/v) (5 mg cm^{-2}); (C) PI 200 C/E: latex matrices loaded with 200 mg progesterone dissolved in chloroform:ether 1:10 (v/v) (20 mg cm^{-2}); (D) PI 50 C/E: latex matrices loaded with 50 mg progesterone dissolved in chloroform:ether 1:10 (v/v) (5 mg cm^{-2}); (E) PI 200 C: latex matrices loaded with 200 mg progesterone dissolved in chloroform (20 mg cm^{-2}); (F) PI 50 C: latex matrices loaded with 50 mg progesterone dissolved in chloroform (5 mg cm^{-2}).

Table 2
Polymorph found on Silicone (PDMS) and Latex (PI) matrices loaded with increasing initial load of progesterone (P4). PDMS and PI matrices were incubated with a solution of P4 and chloroform:ether 1:10 (v/v) (C/E).

Matrix	Solvents	Polymorph			
		Initial load of P4 (mg cm^{-2})			
		5	10	15	20
PDMS	C/E	ALFA[a]	ALFA[a]	ALFA[b]	ALFA[a+b]
PI	C/E	ALFA[b]	ALFA[b]	ND	ND
	C	BETA[a+b]	ALFA[a+b]	ALFA[b]	ALFA[a+b]

[a] DRX.
[b] IR.

the regression of the dominant follicle, providing a potent suppression of estrous and ovulation. The extraction of the intravaginal device at the end of the treatment period, results in a rapid drop in concentrations of P4 in circulation that promotes a synchronous estrous within the herd, allowing for mass artificial insemination to take place (Macmillan et al., 1991; Rathbone et al., 1998a,b). In order to explore the possible use of this matrix in the design of a delivery vehicle for P4 we evaluated the *in vivo* release of P4 from PI. For this purpose, Y-shaped polypropylene inert inserts already described (Heredia et al., 2008) were covered with PI sheaths loaded with 0.25, 0.50 and 0.75 g of P4 and the levels of P4 in plasma were evaluated in comparison with a commercial PDMS device with 1.0 g of P4 (DIB) (Fig. 5). Table 3 shows that it is possible to attain plasma

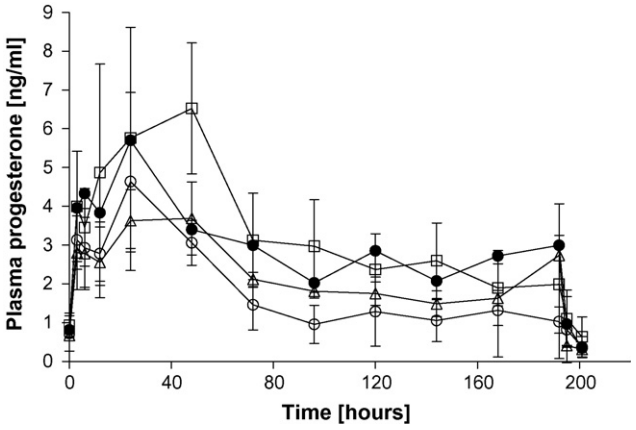

Fig. 5. Plasma progesterone profile form commercially available DIB® insert (●), and PI intravaginal devices loaded with 250 mg (○), 500 mg (△) and 750 mg (□) progesterone initial loadings ($n = 3$). Data are means ± SD.

Table 3
Area under the curve data for *in vivo* plasma profiles of Silicone (DIB®) intravaginal insert loaded with 1.0 g of progesterone and latex (PI) intravaginal insert loaded with 0.25, 0.5 0 and 0.75 g of progesterone for a 8-day insertion period ($n = 3$).

Formulation	AUC (average ± SD)
DIB insert with 1.0 g P4	573 ± 39
PI insert with 0.75 g P4	675 ± 13
PI insert with 0.5 g P4	412 ± 35
PI insert with 0.25 g P4	282 ± 54*

Data are means ± S.E.
* Difference versus DIB, $p < 0.05$.

concentrations similar to those of a commercial PDMS device with PI loaded with initial loads as low as 0.50 g.

4. Conclusions

The *in vitro* controlled release of P4 from latex matrices has been investigated for its possible application in the design of a delivery device for estrous synchronization treatment for cattle. The results indicate that the release rate of P4 is directly related to surface area and to the drug load up to a saturating initial concentration of around 10 mg cm^{-2}. Loading the hormone from a solvent solution proved to be a suitable strategy that may even enhance P4 release from silicone matrices. Moreover, the release rate from latex matrices could be modified changing the composition of the organic solvent used to load the matrix. Loading silicone or latex with P4 dissolved in an organic solvent is related to the appearance of P4 crystals on the surface of the matrix whose polymorphic state is dependent not only on the concentration of P4 but on the polymer support. *In vivo* studies show that plasma levels of P4 observed in cows treated with PI devices containing 0.75 and 0.50 g of P4 are always well above 1 ng ml^{-1} that is the level required to be attained during the 7–8 days of treatment in order to synchronize the estrous cycle. Given the hydrophobic nature of progesterone, it is highly probable that the limiting step in its transfer from an intravaginal device to the blood would be its dissolution in the water phase. Therefore, in an attempt to reduce the residual amount of progesterone after using the intravaginal device, further studies are in progress to characterize drug distribution and crystalline structure or polymorphs of P4 in these delivery systems and their effect on release rate. Altogether, the results show that latex can be used as a new matrix for the intravaginal administration of progesterone with improved release profile than silicone and that the matrix can modify the crystalline state of the hormone.

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