Pharm Res (2014) 31:795–808
DOI 10.1007/s11095-013-1201-6

RESEARCH PAPER

The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model

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Received: 10 May 2013 / Accepted: 31 August 2013 / Published online: 18 October 2013
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ABSTRACT

Purpose Progering® is the only intravaginal ring intended for contraception therapies during lactation. It is made of silicone and releases progesterone through the vaginal walls. However, some drawbacks have been reported in the use of silicone. Therefore, ethylene vinyl acetate copolymer (EVA) was tested in order to replace it.

Methods EVA rings were produced by a hot-melt extrusion procedure. Swelling and degradation assays of these matrices were conducted in different mixtures of ethanol/water. Solubility and partition coefficient of progesterone were measured, together with the initial hormone load and characteristic dimensions. A mathematical model was used to design an EVA ring that releases the hormone at specific rate.

Results An EVA ring releasing progesterone *in vitro* at about 12.05 ± 8.91 mg day^{-1} was successfully designed. This rate of release is similar to that observed for Progering®. In addition, it was observed that as the initial hormone load or ring dimension increases, the rate of release also increases. Also, the device lifetime was extended with a rise in the initial amount of hormone load.

Conclusions EVA rings could be designed to release progesterone *in vitro* at a rate of 12.05 ± 8.91 mg day^{-1}. This ring would be used in contraception therapies during lactation. The use of EVA in this field could have initially several advantages: less initial and residual hormone content in rings, no need for additional steps of curing or crosslinking, less manufacturing time and costs, and the possibility to recycle the used rings.

Electronic supplementary material The online version of this article (doi:10.1007/s11095-013-1201-6) contains supplementary material, which is available to authorized users.

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KEY WORDS controlled release · drug delivery · intravaginal ring · mathematical modeling · progesterone

INTRODUCTION

The vagina is an optimal organ for site of drug administration for therapeutic purposes (1–3). The main advantages of vaginal drug administration are: the ability to by-pass hepatic first pass metabolism, avoid gastrointestinal absorption, enable continuous drug release and lower daily doses, allow systemic and local effect, the high permeability of the vagina to low molecular weight drugs and the easy administration of vaginal products. However, some drawbacks can be mentioned: gender specificity, local irritation, influence of sexual intercourse, variability in drug absorption due to vaginal epithelium thickness changes, cultural sensitivity and personal hygiene.

The vaginal route has been extensively studied as a site for drug administration (2–5). As a consequence, a novel controlled release system known as vaginal ring was developed (6,7). Vaginal rings are torus shaped devices formed by a polymeric material. This material contains the active principle, which will be released. The ring is simply inserted into the vagina and it releases the drug in a controlled manner. The only requirement for correct insertion is the contact with the vaginal epithelium. The rate of release is controlled by several factors like the relationship between the characteristic dimensions, the initial load of active principle, the presence of excipients, and the tissue-material partitioning (8–10). Once the drug is absorbed through the vaginal epithelium, it enters into the systemic circulation (11,12). The use of vaginal rings presents numerous advantages: it permits the controlled release of drug, avoids daily administration, allows the use of low drug dose and the simultaneous administration of several drugs by the same device, it is user controlled, and does not interfere with coition. Some disadvantages are: the increase in

vaginal secretions associated with its use, the possibility of expulsions, and cultural sensibility (13,14).

Vaginal rings can have different configuration: matrix, reservoir or sandwich type. In matrix type rings, the drug is homogeneously dispersed within the polymeric matrix. In reservoir type, the drug is contained in a centralized core and the core is coated with a membrane. Sandwich type devices consist of a drug-containing layer located between a drug-free central core and a outer membrane. In matrix type rings, the drug at the surface of the device is released faster than the drug in the inner layer leading to an initial burst release. In reservoir and sandwich devices, the membrane controls the release rate avoiding the burst effect. However, matrix devices are more secure to be used in human due to the low failure possibilities due to breakage of the device (like cracks or punctures), which would lead to a sudden release of active agents.

Vaginal rings are commonly made of poly(dimethylsiloxane) or silicone. This is due to the advantages that presents the use of silicone in biomedical applications: low toxicity, good thermal and oxidative stability, easy diffusion of low molecular weight and lipophilic drugs, high blood compatibility, physiological inertness, and low modulus (15–18). However, some drawback can be mentioned (19): *i)* silicones are generally cured in a mold at high temperatures (around 150–190°C during 30 min); *ii)* the polymer is post-cured in a oven also at high temperatures (around 180°C to 230°C) for periods of 4–8 h; *iii)* rings manufacturing cost may be high due to curing and post-curing stages; *iv)* the drug to be released may undergo modification and /or degradation due to the high temperatures used during processing; *v)* the silicone is not a reprocessable material, so the entire device has to be discarded after its use; *vi)* there is an important environmental concern on the impact of the use of silicone products due to the non-degradability of the material.

Because of these drawbacks, the trend is to replace the silicone with more beneficial material. The use of elastomeric polymers like ethylene vinyl acetate copolymer (EVA) has been studied (13,20). EVA is a thermoplastic material that can be reprocessed after its use (recycling). In addition, this polymer does not require cured and post-cured steps, which would lower the manufacturing cost. The increase in vinyl acetate content provides several advantages: increased flexibility, improved optical properties, greater adhesion, and increased impact and puncture resistance. A vaginal ring made of EVA releasing etonogestrel and ethinyl estradiol was reported (21–24). The clinical acceptability of this ring has been tested (13,21).

Depending on the active principle that they contain, vaginal rings can be employed for different purposes: hormone replacement therapy (25,26), microbicide (27,28), and contraception therapy (22,29–38). Although many prototypes have been studied for such purposes, only a small number of vaginal rings were approved and are commercialized in the global market. The main relevant devises are: a silicone ring releasing 7.5 μg of estradiol per day (Estring®), a silicone ring releasing 0.05 mg or 0.10 mg of estradiol acetate per day (Femring®), and an EVA ring releasing 120 μg of etonogestrel and 15 μg of ethinyl estradiol per day (Nuvaring®) (27).

A particular interest is the use of vaginal ring for contraception during lactation (36,39–41). Only one vaginal ring known as Progering® was approved for this purpose. Progering® is a silicone vaginal ring that releases progesterone. It was developed by Silesia Laboratory® (Santiago, Chile). The ring is formed by a matrix of silicone containing 2.074 g of progesterone uniformly dispersed in its interior. It is indicated for contraception in women during lactation and it should be placed after 30 to 90 days postpartum. The contraceptive effect is the result of the inhibition of the secretion of LH and FSH at the level of the hypothalamus and the pituitary, thereby inhibiting ovulation. It also has an effect on the cervical mucus making it more dense to prevent the penetration of sperm and inhibiting the proliferation of the endometrium (41). However, the ring has the silicone drawbacks mentioned before. Therefore, the main goal of the present contribution is to evaluate the use EVA to fabricate a vaginal ring. More specifically, it is to fabricate a ring that releases progesterone at proper rate for its use in contraception therapies during lactation. To achieve this goal, the use of mathematical models is crucial.

Mathematical models can be divided into two main class: empirical approaches and mechanistic models. In empirical approaches, the equations used do not have theoretical basis. They are purely descriptive and they are not based on real phenomena. Consequently, the drug release mechanisms cannot be known (42). In contrast, mechanistic models are based on real phenomena like dissolution, diffusion, swelling or erosion. The use of mechanistic models in drug delivery presents several advantages (42–44): *i)* the drug release mechanisms from a particular device can be known allowing a better understanding of the real phenomena; *ii)* it allows for the quantitative prediction of the effects of formulation parameters on the resulting drug release kinetics; *iii)* it allows to identify the required composition of the drug delivery system to obtain a specific release rate; *iv)* the number of experimental assays can be minimized decreasing the cost of the product development; *v)* it allows to reduce the time involved in products development.

In our previous study, a mathematical model was developed to predict release kinetics from intravaginal rings (8,10). The model takes into account the specific characteristics of the torus geometry. It was rigorously validated by comparison with experimental data reported in the literature (45–47). The use of this model allows to study the controlled release of solute from rings by computer simulations, minimizing the inconveniences of the *in vitro* and *in vivo* experimentation. It

was successfully used to predict the release of hormones from different rings. These systems included the variation of the polymer, design parameters (initial load of solute and ring dimensions), , experimental parameters like the agitation rate and the release medium, among others (8,10). Consequently, the validity and usefulness of the model were asseverated by the successful results in these assays. Following this line of research, the purpose of the present contribution is to employ our previously developed mechanistic model to evaluate the use of EVA for intravaginal ring fabrication. More specifically, it is to evaluate the design of an intravaginal ring that releases progesterone at a proper rate for its use in contraception therapies during lactation. The use of the model requires that the ring does not swell or degrade in the release media. Therefore, liquid uptake and degradation assays were conducted in order to select the appropriate release media. In addition, partitioning studies and rings characterization were conducted to determine the values of model parameters.

MATERIALS AND METHODS

Materials

Ethylene-vinyl acetate copolymer (EVA, VA content of 28 wt%), Progesterone and Progering® were purchased from Dupont® (Wilmington, USA), Sigma-Aldrich® (St. Louis, USA) and Silesia Laboratory® (Santiago, Chile), respectively. All other reagents used were of analytical grade, except of methanol which was HPLC grade.

Liquid Uptake and Degradation Assays

Ring-shaped EVA matrices were prepared by a hot-melt extrusion procedure. EVA pellets were fed into an industrial extruder (Dr. Collin® GmbH D-85560, Ebersberg, Germany). The extruder was equipped with a cylindrical die of 3.4 mm of diameter. The screw speed was set to 65 rpm. The temperature was adjusted to 155°C, 160°C, 165°C, 170°C and 175°C in the zones of feed, transport, compression, screened plate, and in the head respectively. The extrudates were cooled down to room temperature and manually cut using surgical blades into matrices of specific length. The ends were sealed with heat onto a mold to produce ring-shaped matrices.

The liquid uptake by EVA rings was determined according to the D570 ASTM Standard procedure (48). Matrix samples were dried in a oven at 50°C during 24 h. After cooled to room temperature in a dessicator, the samples were weighed to obtain the initial dry weight (W_0). Then, samples were incubated at 37°C and 100 rpm during 9 weeks in 100 ml of different liquids: ethanol, ultra filtered water and ethanol/water mixtures (ethanol content of 15%, 20%, 40%, 60% and 80% v/v). Samples were taken out at different time intervals and immediately weighed to get the wet weight (W_t). Surface liquid was removed with filter paper before the measure. The liquid uptake by EVA ring was calculated as follows (49):

$$\text{Liquid uptake}(\%) = \frac{(W_t - W_0)}{W_0} 100 \quad (1)$$

where W_t is the wet weight of the matrix at each time point and W_0 is the initial dry weight of the matrix. Finally, matrix samples were dried in a oven at 50°C during 24 h. After cooled to room temperature in a dessicator, samples were weighed to obtain the final dry weight (W_f). The total polymer mass loss was calculated as follows:

$$\text{Total mass loss}(\%) = \frac{(W_0 - W_f)}{W_0} 100 \quad (2)$$

where W_f is the final dry weight of the matrix.

HPLC Determination of Progesterone

Progesterone concentration in the samples was analyzed by a HPLC systems (Prominence LC20A, Shimadzu, Japan) equipped with a ZORBAX® Eclipse XDB-C_{18} column (5 μm particle size, 250×4.6 mm) at the wavelength of 254 nm (50). The mobile phase consisted of a mixture of HPLC grade methanol and ultra filtered water (95:5 v/v). The flow rate was 1.0 ml/min. The column temperature was set to 30°C for all determinations. The progesterone elution time obtained in these condition was 3.7±0.2 min.

Progesterone Solubility in EVA Matrix and in Several Liquids

Films of EVA were prepared by a compression/molding procedure. A mass of 0.1 g of EVA was placed between two Teflon sheets and the whole was introduced into a heated press (Buehler SimpliMet® II, Illinois, USA). The press was heated at 120°C for 5 min. Then, a force of 1,000 N was applied and the EVA was cooled during 10 min under compression. The resulting films presented an average thickness of 220 μm.

The progesterone solubility in EVA was determined according to the technique reported by Wenhui (51). A mass of 0.15 g of progesterone was added to 150 ml of ultra filtered water to obtain a saturated solution. The previously obtained film was cut into pieces of 1.828 cm of diameter and dipped into this solution. The solution was kept at 37°C with a stirring speed of 100 rpm during a specific time. The assay was run in triplicate. To corroborate if the equilibrium condition was reached, each film was withdrawn at different time: 4, 10

and 14 weeks. The hormone contained in each film was extracted with 200 ml of ethanol in a Soxhlet during 24 h at 90°C. After a suitable dilution, progesterone concentration was measured by the HPLC technique detailed previously.

The progesterone solubility in several liquids was determined according to the technique reported in the literature (6,51–53). A mass of 1.0 g of progesterone was added to 5 ml of several solvents: ethanol, ultra filtered water and ethanol/water mixtures (ethanol content of 15%, 20%, 40%, 60% and 80% v/v). The resulting solutions were kept at 37°C with a stirring speed of 100 rpm during 96 h. Thereafter, solutions were filtered with 0.45 μm microfiltration membrane (Microclar®, Buenos Aires, Argentina) to remove the excess of undissolved hormone. After a suitable dilution, progesterone concentration in each solution was measured by the HPLC technique detailed previously. The assay was run in triplicate. In addition, the progesterone partition coefficient between the mentioned solvents and the EVA matrix was calculated as follows:

$$K_1 = \frac{C_a}{C_s} \tag{3}$$

where K_1 is the progesterone partition coefficient between the corresponding solvent and the EVA matrix, and C_a and C_s are the maximum progesterone solubility in each solvent and in the EVA matrix respectively.

Preparation of EVA/Progesterone Rings

A known mass of progesterone was dissolved in dichloromethane. Then, this solution was added to a specific mass of EVA pellets. The system was stirred during 2 h until the pellets absorb all the hormone solution. Thereafter, pellets were first dried in vacuum at 40°C during 1 h and then dried in a oven at 40°C during 48 h to completely evaporate the solvent. The resulted pellets were used to fabricate the rings by a hot-melt extrusion procedure. EVA pellets impregnated with progesterone were fed into an industrial extruder (Dr. Collin® GmbH D-85560, Ebersberg, Germany). The extruder was equipped with a cylindrical die of 3.4 mm of diameter. The screw speed was set to 65 rpm. The temperature was adjusted to 155°C, 160°C, 165°C, 170°C and 175°C in the zones of feed, transport, compression, screened plate, and in the head respectively. The extrudates were cooled down to room temperature and manually cut with surgical blades into matrices of specific length. The matrix ends were sealed with heat onto a mold to produce EVA/progesterone rings of two sizes, identified as Ring A and Ring B, respectively.

EVA/Progesterone Rings and Progering® Characterization

The weight of the commercial ring and EVA rings were recorded. The outer, inner and cross-sectional diameters of each ring were measured using a Vernier caliper. Parameters R_e, R_g and R_0 were calculated using this data (8–10). Rings density was calculated by the ratio between mass and volume of rings. The hormone contained in each ring was extracted with 200 ml of ethanol in a Soxhlet during 48 h at 90°C. Progesterone concentration was measured by the HPLC technique detailed previously after a suitable dilution and the initial amount of hormone loaded was calculated. The assay was run in triplicate.

In Vitro Drug Release Assays

The progesterone released from EVA rings and from the commercial ring Progering® was studied using a Hanson Research SR8-Plus Dissolution Test Station (Chatsworth, USA). Each ring was placed in a stainless steel basket and the basket was attached to the rotating shaft. Dissolution glass vessel (7000-G, Hanson Research, USA) of 1,000 ml of capacity were employed. The release medium consisted of 1,000 ml of a mixture of ethanol and ultra filtered water with an ethanol content of 20% v/v. Release assays were performed at 37°C. Two stirring speed were evaluated: 25 rpm and 100 rpm. Aliquots of 5 ml were withdrawn at different time points and replaced with fresh release medium to maintain a constant volume. The progesterone concentration was measured by the HPLC technique detailed previously. In addition, the entire release media was removed every 24 h and replaced with fresh release media to maintain sink condition.

The mechanistic model developed in our previous study was used to predict the *in vitro* progesterone released from EVA rings and from the commercial ring Progering®. To achieve this goal, simulations were made in the software Matlab®. A comparison between experimental data of release and theoretical predictions was performed. f_1 and f_2 factors were used in order to measure quantitatively the fit of the theoretical prediction to the experimental data, (8–10,54–56). The experimental data was selected as the reference product while the model prediction was chosen as the test product.

Model Application to Design a Controlled Release Device

The model developed was used to study the effect of different design parameters over the release of progesterone from EVA rings. The effect of ring dimensions and the initial load of hormone were analyzed. Simulations were made in the software Matlab®. In addition, the model was used to design a particular EVA ring that releases the hormone at a proper

rate for its use in contraception therapies during lactation. The initial load of hormone was optimized using a Matlab® routine. The mean *in vitro* release rate from Progering® was used as reference. A comparison between release rate from both rings was performed. f_1 and f_2 factors were used to measure quantitatively the similitude between both profiles. The Progering® profile was selected as the reference profile while the optimized EVA ring profile was chosen as the test profile.

RESULTS AND DISCUSSION

Mathematical Model

A mathematical model was developed in our previous work to predict the amount of drug released from rings (8). The ring is schematically illustrated in Fig. 1a. When the ring is placed in the release medium, the liquid takes contact with the device over its entire surface. As the liquid contacts the device, the solid drug particles dissolve in and then diffuse out of the matrix. The discrete crystals in the layer closer to the ring surface are the first to elute. When this layer becomes "exhausted", solid drugs in the next layer begin to be depleted. So, a drug depletion zone is created. The thickness of this zone increases with time and as more solid drugs elute out of the device, thus leading to the inward advancement of the interface of the dispersed–drug zone/depleted drug zone, phenomenon commonly referred to as "dissolution–diffusion moving front" (8).

The general assumptions made for the model derivation are well detailed in our previous work (8). Figure 1b presents the dissolved-drug concentration profile in the considered section of the ring. Parameters present in the figure are: r is the spatial coordinates, R_g is the distance from the rotation axis to the center of the generating circle, $S(t)$ is the position of the "dissolution-diffusion moving front", R_e is the distance from the rotation axis to the external surface of the matrix, h_a is the thickness of the external resistance layer, C_t is the dissolved-drug concentration in the matrix, C_s is the maximum solubility of drug in the polymeric matrix, $C_{eq,1}$ is the dissolved-drug concentration in matrix at the matrix-external resistance layer interface, C_{bl} is the dissolved-drug concentration in the external resistance layer and $C_{a,1}$ is the dissolved-drug concentration in the external resistance layer at the matrix-external resistance layer interface. The presence of the external resistance layer depends on the conditions under which the *in vitro* release test is performed. Chien reported about the dependency of stagnant liquid layer with the viscosity, drug diffusion coefficient, and the agitation speed of the release media (57). For example, low stirring speed leads to the formation of a stagnant liquid layer that acts as an external resistance to mass transfer (57).

The governing equation for drug diffusion in the depletion zone is (8):

$$\frac{\partial C_t}{\partial t} = \frac{D_p}{r(R_g + r)} \frac{\partial}{\partial r}\left(r(R_g + r)\frac{\partial C_t}{\partial r}\right) \quad t > 0 \quad S(t) \le r \le R_e \tag{4}$$

where t is the time and D_p is the drug diffusion coefficient in the polymeric matrix. Assuming equilibrium between the surface of the device and the external fluid at all t, the initial and boundary conditions are (8):

$$C_t = C_s \quad t = 0 \quad R_g \le r \le R_e \tag{5}$$

$$C_t = C_s \quad t > 0 \quad R_g \le r \le S(t) \tag{6}$$

$$C_t = C_{eq,1} \quad t > 0 \quad r = R_e \tag{7}$$

With $\partial C_t / \partial t$ in Eq. (4) being fixed at zero according to the pseudo steady-state approximation (PSSA) and with the boundary conditions presented in Eqs. (5, 6 and 7), the concentration distribution of dissolved-drug in the depletion zone can be obtained (8):

$$C_t = C_s \left[1 - \left(1 - \frac{C_{eq,1}}{C_s}\right) \frac{ln\left(\frac{(R_g + S)r}{S(R_g + r)}\right)}{ln\left(\frac{(R_g + S)R_e}{S(R_g + R_e)}\right)}\right] \quad t > 0 \quad S(t) \le r \le R_e \tag{8}$$

To use Eq. (8), the expression for $C_{eq,1}$ must be known. This expression was reported in our previous work (8). Using

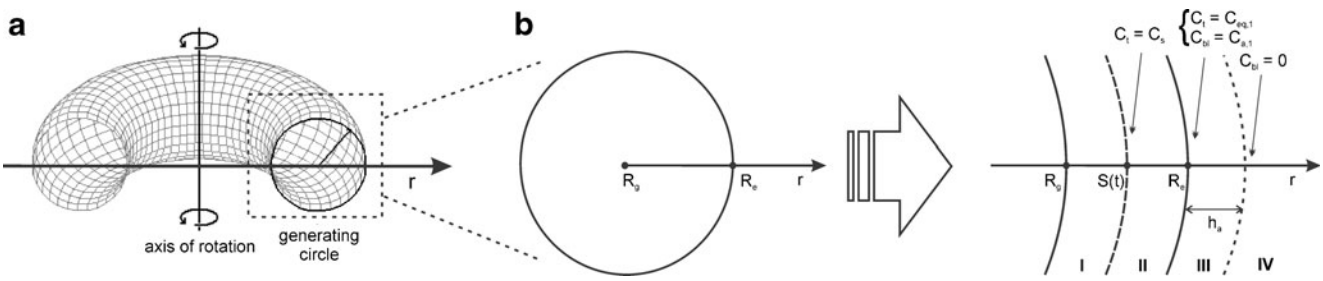

Fig. 1 (**a**) Schematic illustration of the ring. (**b**) Dissolved-drug concentration profile in the considered section of the ring.

Eq. (8), the position of the "dissolution–diffusion moving front" (S) can be obtained (8):

$$\frac{R_e(R_g+R_e)-S(R_g+S)}{6}+\frac{R_g^2}{6}ln\left(\frac{R_g+S}{R_g+R_e}\right)-\left(\frac{S^3}{3R_g}+\frac{S^2}{2}\right)ln\left(\frac{(R_g+S)R_e}{S(R_g+R_e)}\right)+\frac{D_p}{D_aK_1}ln\left(\frac{(R_g+R_e)(R_e+h_a)}{R_e(R_g+R_e+h_a)}\right)\left(\frac{(R_e^3-S^3)}{3R_g}+\frac{(R_e^2-S^2)}{2}\right)=\frac{D_pt}{\left(\frac{A}{C_s}-1\right)} \quad (9)$$

where A is the initial drug loading in the device, D_a is the drug diffusion coefficient in the external resistance layer, and K_1 is the drug partition coefficient at the matrix-external resistance layer interface. The value of S for each time point considered can be obtained from Eq. (9) using an adequate computational software that finds zeros of a function of one variable. The cumulative amount of solute released (m) in a given time can be calculated from (8):

$$m=2\pi^2R_g\left[A\left(R_0^2-\left(S-R_g\right)^2\right)-C_{eq,1}R_e\left(R_e-2R_g\right)+\frac{C_sS(S-2R_g)ln\left(\frac{(R_g+S)R_e}{S(R_g+R_e)}\right)-(C_s-C_{eq,1})\left(R_g(R_e-S)+3R_g^2ln\left(\frac{R_g+S}{R_g+R_e}\right)\right)}{ln\left(\frac{(R_g+S)R_e}{S(R_g+R_e)}\right)}\right] \quad (10)$$

where R_0 is the radius of the generating circle. This equation allows to calculate the cumulative amount of drug released in a given time from rings considering the existence of an external layer that acts as a resistance to the mass transfer.

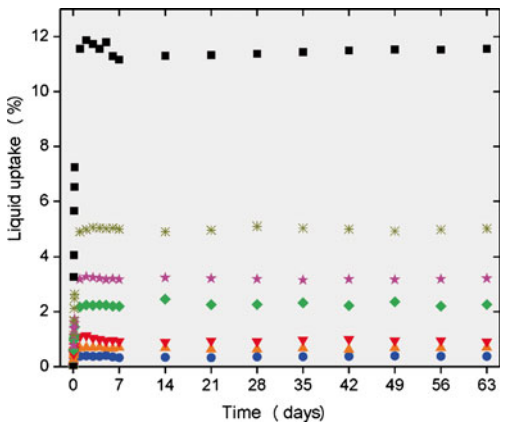

Fig. 2 Liquid uptake by EVA rings in several liquid media: (■) Ethanol. (✳) Ethanol-water 80:20. (★) Ethanol-water 60:40. (♦) Ethanol-water 40:60. (▼) Ethanol-water 20:80. (▲) Ethanol-water 15:85. (●) Ultra filtered water.

Liquid Uptake and Degradation Assays

Figure 2 shows the percentage of liquid uptake by EVA rings. Similar behavior was observed for all media studied. For each system, a maximum value of absorbed liquid was reached at around 24 h and then it kept constant. The liquid uptake by the polymer was similar in ultra filtered water and ethanol/water with an ethanol content of 15%. The maximum percentage of liquid uptake in these media was less than 0.7%. These results are similar of those reported in the literature (49). The percentage of liquid uptake in ethanol was substantially greater reaching a maximum of approximately 11% of liquid uptake. An intermediate behavior was observed for ethanol/water mixtures. As ethanol content in release media increases, the maximum percentage of liquid uptake by EVA also increases. This percentage was 1.13%, 2.46%, 3.27%, and 5.11% for mixtures of ethanol/water with an ethanol content of 20%, 40%, 60%, and 80% v/v respectively.

Table I presents the total polymer mass loss after 9 weeks. It was less than 0.8% for all liquids analyzed. Thus, it can be concluded that EVA rings do not degrade in the liquid media analyzed under the experimental conditions established. In summary, EVA matrix exhibits least percentage of liquid uptake in ultra filtered water, ethanol-water 15:85, and ethanol-water 20:80. In addition, EVA rings do not degrade in these liquid media. Therefore, these liquids can be considered initially as a good candidate for release media for *in vitro* release assays. It can be noted that, in order to use the mathematical model to predict the release kinetics from rings, the matrix do not swell or degrade in the release media to satisfy the assumption made in the model derivation (8,10). The liquid uptake and degradation assays were performed with the aim of determine the appropriate liquid media for the release assays.

Table I Degradation of EVA Rings in Different Liquids

	Ultra filtered water	Et-Wa 15:85	Et-Wa 20:80	Et-Wa 40:60	Et-Wa 60:40	Et-Wa 80:20	Ethanol
Total mass loss (%)	0.00	0.00	0.08	0.04	0.05	0.22	0.79

Progesterone Solubility in EVA Matrix and in Several Liquids

The content of hormone in EVA films incubated for 4, 10 and 14 weeks were very similar allowing to conclude that the equilibrium condition was reached on or before the fourth week. The progesterone solubility was 0.026 ± 0.003 g of hormone per grams of EVA matrix. Using the matrix density, the solubility was $C_s = 25.39 \pm 3.01$ mg of progesterone per cm^3 of EVA matrix. Table II shows the progesterone solubility in several liquids. As ethanol content in liquid media increases, progesterone solubility also increases. The obtained values are very similar to those reported in the literature for progesterone solubility in ethanol-water mixtures (58) and in pure water (58,59). In addition, Table II presents the progesterone partition coefficient between the corresponding solvent and EVA matrix. As mentioned before, ultra filtered water, ethanol-water 15:85, and ethanol-water 20:80 can be initially good candidates for release media of *in vitro* assays. However, the low solubility of progesterone in ultra filtered water and ethanol-water 15:85 makes difficult to maintain sink condition. Therefore, ethanol-water 20:80 was chosen as the release media for all *in vitro* drug release assays.

Preparation of EVA/Progesterone Rings

The dissolution of progesterone in dichloromethane was rapidly and completely. EVA pellets absorbed the hormone solution after 2 h. Solvent evaporation was made slowly to avoid the entrainment of progesterone particles out of the pellets by the evaporated solvent flow. EVA pellets with progesterone have white color while pellets without the hormone have a translucent appearance. This difference can be observed in Fig. 3. It can be concluded that progesterone was successfully incorporated into EVA pellets.

Figure 4 shows EVA rings produced by the hot-melt extrusion procedure. Progesterone incorporation clearly modifies rings appearance. These differences are in agreement with those observed previously for pellets. Resulting rings are whitish and have soft and flexible texture.

EVA/Progesterone Rings and Progering® Characterization

Table III presents EVA rings dimensions. Both rings have similar cross-sectional radius (R_0) but ring B is greater in size than ring A. This difference is due to the greater outer radius of ring B. Geometric constraints can be disregarded if circumference is much larger than the cross-sectional radius of the ring. The ratio between circumference and cross-sectional radius was approximately 61 and 84 for ring A and ring B respectively. Therefore, geometric constraints can be disregarded. The initial load of hormone in EVA rings was 0.099 ± 0.001 g of progesterone per grams of EVA matrix. Using the matrix density, the initial load was $A = 95.75 \pm 1.08$ mg of progesterone per cm^3 of EVA matrix for both, ring A and ring B. The A/C_s ratio was 3.77.

Progering® dimensions are also presented in Table III. The ratio between circumference and cross-sectional radius was approximately 43. Hence, geometric constraints can be disregarded. Progering® density was 1109.02 ± 0.03 mg cm^{-3} and the initial load of hormone was 0.222 ± 0.001 g of progesterone per grams of matrix. Using the matrix density, the initial load of progesterone was $A = 246.13 \pm 0.01$ mg cm^{-3}. The progesterone solubility in silicon rubber was reported previously by Chien (57). The author reported a value of $C_s = 0.5947$ mg cm^{-3} (57). The progesterone partition coefficient between ethanol-water mixture with 20% v/v of ethanol and silicone rubber matrix can be calculated using the reported value of C_s, resulting in $K_1 = C_a/C_s = 0.3060$. The A/C_s ratio was 413.87. Values of A, C_s, K_1 and the parameters presented in Table III were determined since they are required to use the model for theoretical prediction.

Model Validation

EVA rings of different sizes were fabricated and experimental data of release were compared with model prediction to establish the validity of Eq. (10). This comparison is presented in Fig. 5. Figure 5a presents the cumulative progesterone released from both EVA rings at two stirring speed. The release follows typical matrix-type release kinetic for all systems. As expected, ring B releases more hormone than ring A according to their difference in size. A good agreement can be observed between model prediction and experimental data.

Table II Progesterone Solubility in Different Liquids

	Ultra filtered water	Et-Wa 15:85	Et-Wa 20:80	Et-Wa 40:60	Et-Wa 60:40	Et-Wa 80:20	Ethanol
C_a (mg cm^{-3})	0.007 ± 0.001	0.078 ± 0.005	0.18 ± 0.01	2.87 ± 0.06	20.42 ± 0.02	70.28 ± 0.07	128.12 ± 0.09
K_1 (dimensionless)	0.0003	0.0031	0.0071	0.1130	0.8042	2.7680	5.0459

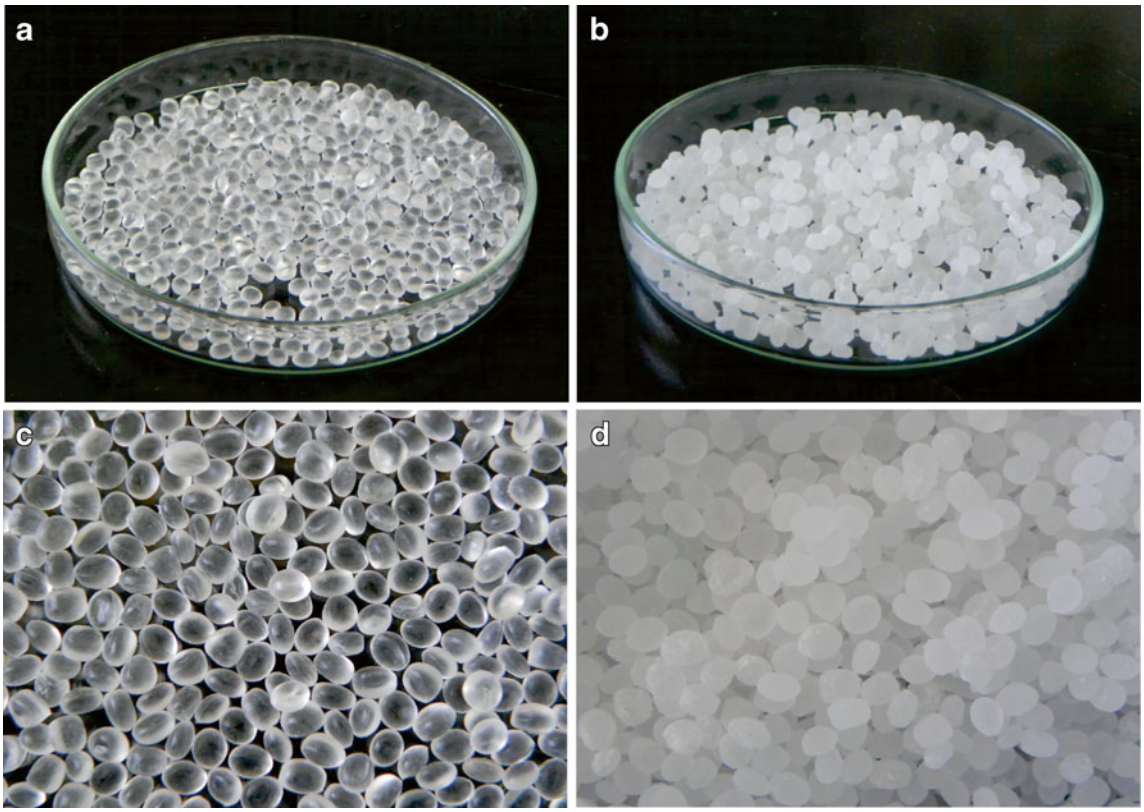

Fig. 3 EVA impregnation with progesterone: (**a**, **c**) EVA pellets without progesterone. **b**, **d**) EVA pellets with progesterone.

In addition, the release is influenced by the stirring speed. As stirring speed decreases, the progesterone released from rings also decreases. This phenomena can be observed for both rings (A and B). This fact can be due to the formation of a stagnant liquid layer of greater thickness over the surface of the device when stirring speed diminishes. This observation is consistent with that reported by other authors for different solutes (57,60). Again, Eq. (10) predicts successfully the experimental data of release. Consequently, release assays can be performed at any agitation speed since the model contemplates this situation. Figure 5b presents the fraction of hormone released for both EVA rings at the two stirring speed studied. As can be observed, the fraction released is independent of R_e for a fixed R_0. The release profiles of both rings are

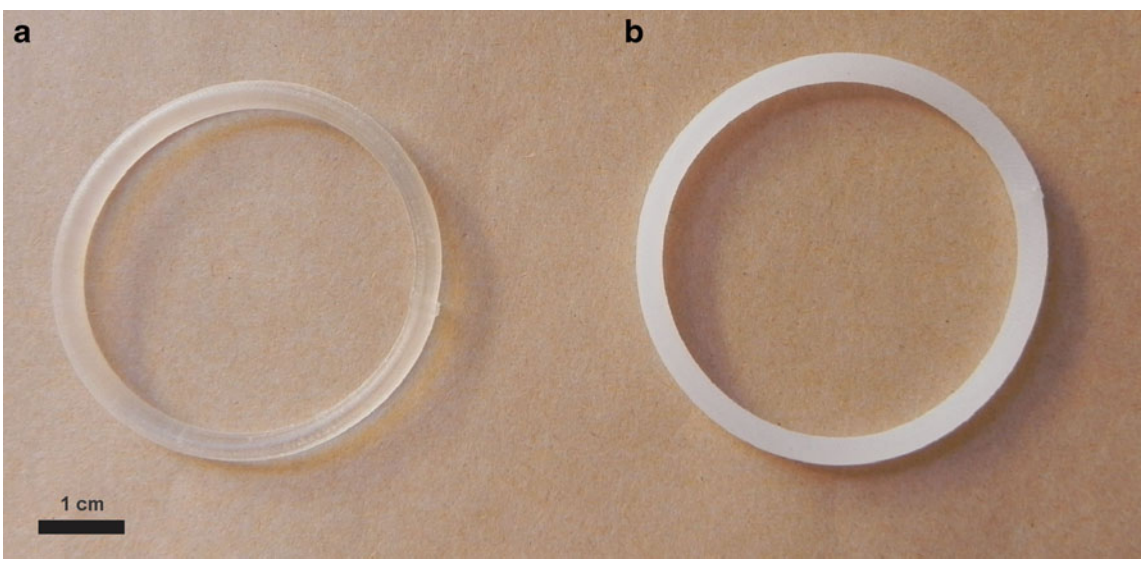

Fig. 4 EVA rings: (**a**) Without progesterone. (**b**) With progesterone.

Table III Rings Dimensions

Parameters	Ring A	Ring B	Progering®
R_e (cm)	1.63	2.27	2.84
R_g (cm)	1.46	2.10	2.42
R_0 (cm)	0.17	0.17	0.42

similar at a fixed stirring speed. Therefore, the two sets of data can be considered equivalent.

Figure 6 presents the experimental data of progesterone released from Progering® and the theoretical prediction of Eq. (10). The release follows typical matrix-type release kinetic. A good agreement can be observed between theoretical prediction and experimental data.

Table IV presents the values of the model parameters used in the simulations presented in Figs. 5 and 6. The values of A, C_s, R_e, R_0 and K_1 were determined previously in "Progesterone Solubility in EVA Matrix and in Several Liquids" and "EVA/Progesterone Rings and Progering® Characterization" by experimental assays. The diffusion coefficient of progesterone in the release media (D_a) was calculated using the Stokes-Einstein equation (61), the dynamic viscosity of the release media reported in the literature, and the molecular weight and density of progesterone (Supplementary Material Appendix A). The effective thickness of the stagnant liquid layer (h_a) was calculated employing the Levich equation (57), the dynamic viscosity of the release media reported in the literature, and the stirring speed used in the *in vitro* assays of "*In Vitro* Drug Release Assays" (Supplementary Material Appendix A). The solubility of progesterone in silicone matrix was reported previously by Chien (57). The diffusion coefficient of progesterone in the EVA matrix (D_p) was obtained from the model adjustment to the experimental data of release. Its value was very similar for ring A and ring B. This result is consistent since both types of rings (A and B) have

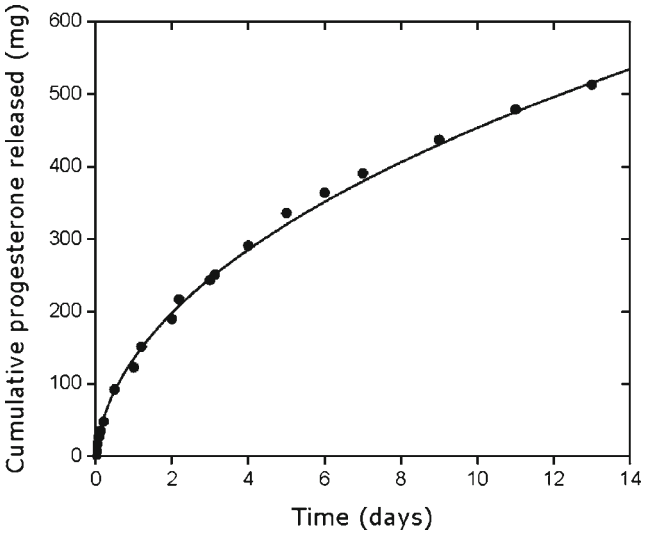

Fig. 6 Comparison between the experimental data obtained in the *in vitro* release assays (●) and the theoretical prediction of Eq. (10) for progesterone release from the commercial ring Progering®.

the same composition and the difference between them lies only in the outer diameter. Therefore, the value of D_p must be very similar for both devices. The diffusion coefficient of progesterone in the silicone matrix of Progering® was also obtained from the model adjustment to the experimental data of release. It was $D_p = 6.2\ 10^{-7}$ cm^2 s^{-1}. This value is similar to the diffusion coefficient of $6.5\ 10^{-7}$ cm^2 s^{-1} reported by Mazan *et al*. (62).

In order to measure quantitatively the fit of the theoretical model to the experimental data, the *difference factor* (f_1) and the *similarity factor* (f_2) were used. The f_1 measures the percent error between two curves over all time points while f_2 is a logarithmic transformation of the sum-squared error of differences between both curves over all time points. The procedure for calculating these factors was reported in the literature (54–56). The f_1 is zero when test and reference profiles are identical and increases

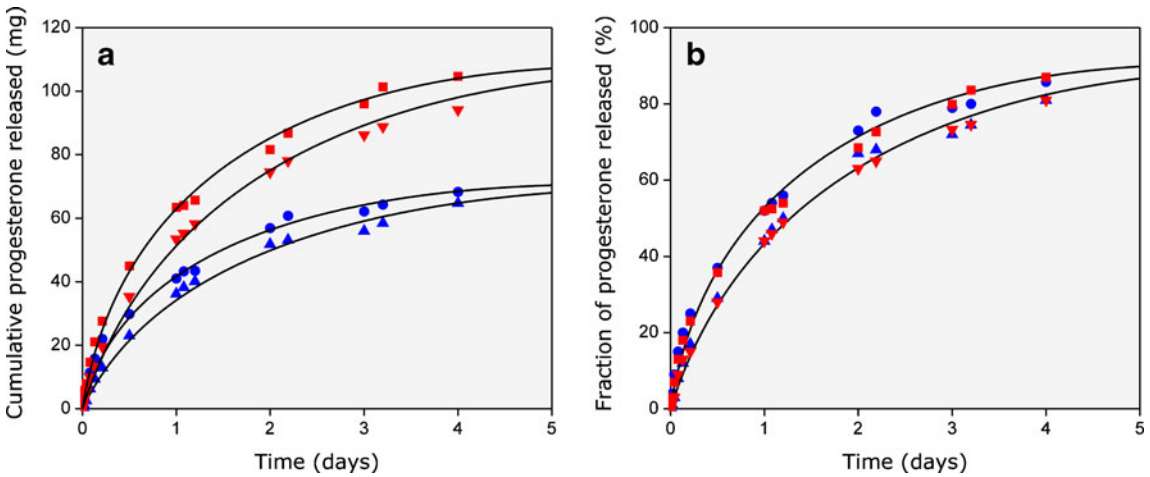

Fig. 5 Comparison between the experimental data obtained in the *in vitro* release assays (*symbols*) and the theoretical predictions of Eq. (10). (**a**) Cumulative progesterone released: Ring A: (●) 100 rpm. (▲) 25 rpm. Ring B: (■) 100 rpm. (▼) 25 rpm. (**b**) Fraction of progesterone released: Ring A: (●) 100 rpm. (▲) 25 rpm. Ring B: (■) 100 rpm. (▼) 25 rpm.

Table IV Model Parameters Values Employed in the Prediction of Progesterone Release from the Rings

Parameters	Ring A	Ring B	Progering®
A (mg cm^{-3})	95.75	95.75	246.13
C_s (mg cm^{-3})	25.39	25.39	0.5947
R_e (cm)	1.63	2.27	2.84
R_0 (cm)	0.17	0.17	0.42
K_1 (dimensionless)	0.0071	0.0071	0.3060
D_a (cm^2 s^{-1})	3.02×10^{-6}	3.02×10^{-6}	3.02×10^{-6}
h_a (cm)	0.0036; 0.0073	0.0036; 0.0073	0.0036
D_p (cm^2 s^{-1})	1.02×10^{-7}	1.08×10^{-7}	6.20×10^{-7}

proportionally with the dissimilarity between them. The f_2 is 100 when the test and reference profiles are identical and tends to 0 as the dissimilarity increases. In general, f_1 values lower than 15 (0–15) and f_2 values higher than 50 (50–100) show the similarity between profiles (54–56). Table V shows the obtained results. The experimental data was selected as the reference profile while the model prediction was chosen as the test profile. For all comparison, f_1 was lower than 15 and f_2 was higher than 50. Therefore, compared profiles can be considered similar. It can be concluded based on this rigorous quantitative analysis that the model developed predicts satisfactorily the experimental release profiles obtained in the *in vitro* assays, establishing the validity of Eq. (10).

Model Application to Design a Controlled Release Device

Mathematical model is a valuable tool in the design, manufacturing, and optimization process of drug delivery devices (63,64). Once the model is validated, it can be used to study and optimize the release process from devices. The validity of Eq. (10) was ascertained in the previous section. Therefore, this equation can be used to study the progesterone release from EVA rings and to help the design of a ring that releases the hormone at a specific rate for its use in contraception therapies during lactation.

Consequently, release process from EVA rings was firstly studied. The effect of different parameters on the progesterone release rate is presented in Fig. 7. Simulations were performed in the software Matlab®. Since devices are composed by the same polymeric material (EVA) and they release the same drug (progesterone) in the same release media, the values of C_s, K_1, D_a, h_a and D_p remain constant. The initial load of hormone (A) and the ring dimension (R_e and R_0, represented by ring area) are the only parameters that can be modified. Figure 7a presents the effect of ring area on the hormone release. As ring area increases, the amount of hormone released also increases. This observation is logical since the release rate is directly proportional to the release area. However, the fraction of drug released is independent of R_e for a fixed R_0. Figure 7b shows the effect of the initial load of hormone over the release process. As the initial load increases, the release also increases. This is because as the initial load of hormone in the device increases, more molecules of drug are available to be release per unit of ring volume. Figure 7c presents the ring lifetime for different initial load of progesterone. As can be observed, the release duration increases with the rise in the initial load of hormone. Therefore, a rise in the initial load extends the lifetime of the device.

Table V The Difference and Similarity Factors for Experimental and Theoretical Drug Release Profiles Comparison

Figure	Ring	Stirring speed (rpm)	f_1	f_2
5.a	A	100	5.33	80.04
5.a	A	25	5.45	83.72
5.a	B	100	3.72	81.50
5.a	B	25	4.53	80.42
6	Progering®	100	2.94	65.19

Once the model was validated and the effect of parameters over release process was studied, the next step is the application of the equation to design a particular controlled release device. The focus was to design an EVA ring that releases the hormone at specific rate for its use in contraception during lactation. To date, only Progering® is manufactured for contraception therapies during lactation. This ring is used to extend the contraceptive effectiveness of lactational amenorrhea among breastfeeding women. It is inserted in the vagina for continuous use for up to 3 months and replaced with a new ring if breastfeeding is continued and extended contraception is desired. The ring releases progesterone by diffusion, maintaining a continuous flow of progesterone through the vaginal walls of about 10 mg day^{-1} (29,65). Once absorbed, the progesterone enters the bloodstream and regulates the woman's fertility by suppressing ovulation. Progesterone also thickens the cervical mucus, inhibiting sperm penetration into the uterus (29). The success of Progering® therapy has been proven (29,65).

Figure 8 presents the *in vitro* progesterone released from Progering® during 90 days. Figure 8a shows the release rate while Fig. 8b shows the cumulative amount of hormone released over time. A period of 90 days was used because this is the time of use of the ring. A high release rate can be observed at early times. Then, a rapid decline in the rate was observed until it reaches a relatively constant value. This profile is typical of matrix-type devices. The high release rate observed at the initial times is associated with the well known burst effect usual of matrix-type devices (66–68). The mean *in vitro* release rate of Progering® was approximately 11.77 ± 7.89 mg day^{-1}. This mean value was obtained for *in vitro* assays performed in ethanol-water 20:80, at 37°C and 100 rpm of agitation speed. As this mean release rate corresponds to an

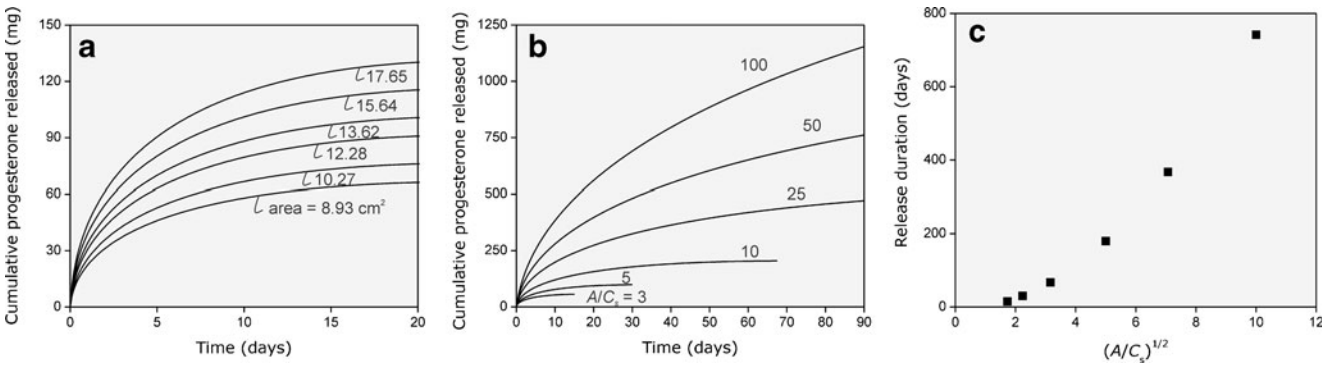

Fig. 7 Effect of different parameters on the release of progesterone from the matrix: (**a**) Effect of ring area. (**b**) Effect of initial load of hormone. (**c**) Effect of initial load of hormone over ring lifetime.

in vitro release, its value depends upon the conditions used in the assays. If experimental conditions are identical to the previously mentioned, the expected *in vitro* release rate of Progering® will be very close to 11.77 ± 7.89 mg day^{-1}. If the condition used in the *in vitro* assays differs from those previously mentioned, the mean rate will be different from the value reported in the present work. The variation of the release media, stirring speed, temperature of the liquid media and else experimental conditions affect the release rate.

Since the *in vivo* successful of Progering® has been proved and the average *in vitro* release rate for a particular set of conditions was established, this value was used as reference in the design of EVA rings. For Progering, it is known that the *in vivo* performance is successful and for a particular set of conditions the mean *in vitro* release rate is 11.77 ± 7.89 mg day^{-1}. Therefore, an initial approach can be done: an EVA ring designed to release progesterone *in vitro* at approximately 11–12 mg day^{-1} during 90 days under the conditions previously mentioned could have successful performance in contraception therapies during lactation.

Therefore, the goal was to design a ring made of EVA that releases the hormone at 11–12 mg day^{-1} during *in vitro* tests performed in ethanol-water 20:80, at 37°C and 100 rpm of agitation speed. To achieve this goal, simulations were performed in the software Matlab®. The values of C_s, K_1, D_a, h_a and D_p were calculated in the previous section. The ring dimensions were adopted from the commercial ring Nuvaring® (Organon Int., Oss, The Netherlands), since this ring in the only EVA ring approved for use in human. Nuvaring® dimensions were studied previously and excellent results were obtained with regard to retention time, expulsion rate, acceptability, and tolerability (23,24,69–72). Therefore, the values of R_e and R_0 were 2.70 cm and 0.20 cm, respectively. The ratio between circumference and cross-sectional radius was approximately 85. Hence, geometric constraints can be disregarded. The initial hormone load was optimized using a Matlab® routine that minimizes the difference between the mean release rate of EVA ring and the reference value of 11.77 ± 7.89 mg day^{-1} for Progering®. Results are presented in Fig. 8. Figure 8a shows the release rate while Fig. 8b shows the cumulative amount of hormone released over time. The release rate of EVA ring and Progering® are similar. The mean *in vitro* release rate for the optimized EVA rings was 12.05 ± 8.91 mg day^{-1}. f_1 and f_2 factors were used to measures quantitatively the similitude between both

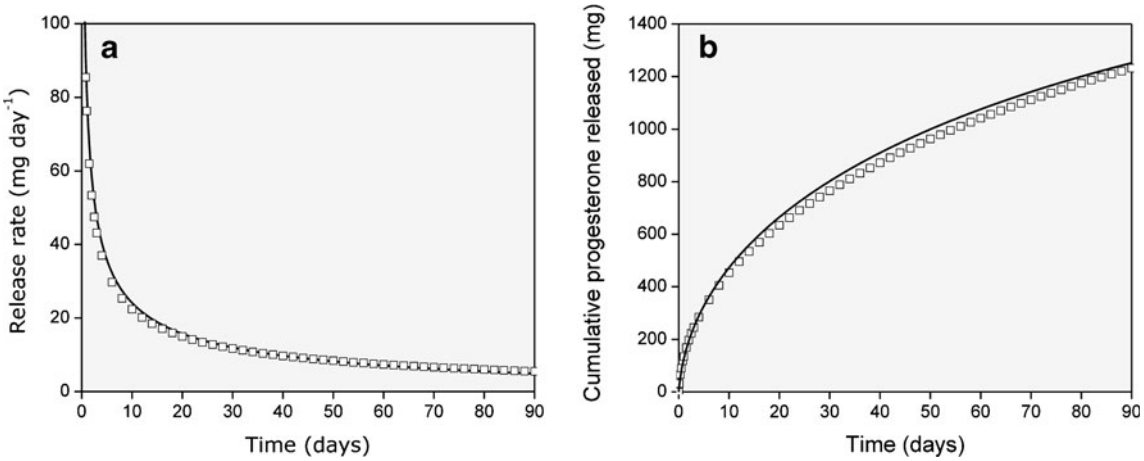

Fig. 8 Comparison between the *in vitro* release of progesterone from the commercial ring Progering® (□) and from the optimized EVA ring (−): (**a**) Release rate. (**b**) Cumulative amount of hormone released.

profiles. Progering® profile was selected as the reference profile while the optimized EVA ring profile was chosen as the test profile. f_1 and f_2 values were 3.39 and 75.87 respectively. Therefore, the two profiles can be considered similar.

In summary, using the Eq. (10) as a tool, an optimized EVA ring was designed to release progesterone *in vitro* at a rate of 12.05 ± 8.91 mg day^{-1}. The optimized EVA ring has initially several advantages: *(i)* EVA does not require additional step of curing or cross linking as it is required when silicone is used. This reduces the manufacturing time and costs. Silicones are generally cured in a mold at temperatures between 150 and 190°C during 30 min and then it requires post-curing process in a oven at temperatures around 180–230°C for periods of 4–8 h. Sometimes, even curing and post-curing are conducted at temperatures above 230°C. These high temperatures along with processing times may result in progesterone changes that may decrease the effectiveness of hormonal therapies. *(ii)* The optimized EVA ring requires less initial amount of progesterone than Progering® to obtain approximately the same *in vitro* release rate. The optimized ring has 18.03% less of progesterone than the commercial ring. However, the mean release rate is slightly higher. This represents a great economical advantage due to the reduction of manufacturing costs. *(iii)* The residual content of hormone after the *in vitro* release process was 40.60% and 26.35% for Progering® and optimized EVA ring, respectively. This reduction in the residual content demonstrates that the optimized ring has a better *in vitro* performance than the commercial device. *(iv)* The lowest initial and residual load of hormone increase the cost-benefit ratio. In addition, it decreases the environmental risks associated with the ring storage, handling, use, and deposition of used devices. *(v)* Silicone rubbers are not thermoplastic polymers. Therefore, they cannot be reprocessed after their use. They require incineration for disposal. In contrast, EVA is a thermoplastic material that can be recycled after its use. *(vi)* As mentioned, EVA copolymer has been successfully used in the past for the manufacture of Nuvaring®, a combined contraceptive vaginal ring. The polymer was approved for its use in human and does not represent a risk for woman health.

Based on the obtained results, EVA may be a good candidate material to replace the silicone in the intravaginal rings. As was mentioned, an optimized EVA ring was designed using the mathematical model as a tool to guide its development. Both rings (EVA and commercial) release the hormone *in vitro* at a similar rate. However, the *in vivo* performance of the optimized EVA ring must be addressed. The initial approach was that if the *in vitro* rate of both rings was similar, their *in vivo* performance will be close too. However, issues like differences in the tissue-material partitioning and/or in the mixing/permeability of the surrounding environment could affect the *in vivo* release. Besides, these could lead to differences in the *in vivo* performance of both rings. The *in vivo* correlation between silicone and EVA rings must be evaluated in Pharmacokinetics studies to ensure the successful of the therapy.

CONCLUSIONS

The use of mathematical models allows not only to predict the release kinetics from controlled release devices but also to determine and study the interrelationships between different factors that make up the system. This knowledge allows to adjust the composition of devices to achieve specific release rates. In this context, a mathematical model was used to study the *in vitro* release kinetics of progesterone from EVA rings and from a commercial intravaginal ring. Firstly, the model was validated with several experimental profiles. Then, the release process of the hormone from EVA rings was studied. The relationship between design parameters and release rate was established. Finally, the equation was used to help the design of a particular EVA ring that releases the hormone at a specific rate. The designed ring presented similar *in vitro* rate than the silicone device, but it would offer certain advantages: less initial hormone load, less residual hormone content, no need for additional steps of curing or cross linking, less manufacturing time and costs, better cost-benefit ratio, lower environmental risks and the possibility to be recycled after its use. Based on these results, EVA can be considered a good candidate material to replace silicone in the intravaginal rings. However, the *in vivo* performance of the optimized EVA rings needs to be addressed by pharmacokinetics studies to ensure therapy successful. In addition, other studies like system stability and mechanical properties have to be performed. These assays will allow the optimization of the device lead to new levels.

ACKNOWLEDGMENTS AND DISCLOSURES

The authors wish to express their gratitude to Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), and to Universidad Nacional del Litoral (UNL) of Argentina, for the financial support granted to this contribution.

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