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Research paper

Evaluation and optimization of progesterone release from intravaginal rings using response surface methodology

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ABSTRACT

Response surface methodology was successfully used to study effect of formulation parameters on progesterone release from rings made of ethylene-vinyl acetate copolymers. Significant effects were estimated by an analyses of variance (ANOVA) and statistical model was constructed. Model predictions showed good agreement with experimental data. Results showed that mass of progesterone released can be enhanced by several strategies. In addition, model behavior was compared with previously validated model reported in the literature obtaining satisfactory results. The statistical model was also employed to optimize formulation parameters with the aim to reach release rate of about 3.545 ± 0.020 mg cm^{-2} $days^{-1/2}$. Optimized prototype was tested in vitro. Results showed that optimized IVR has similar profiles than the commercial silicone device used as reference. Optimized ring would have several advantages over commercial one like lower initial and residual content of progesterone and the possibility of recycling rings after their usage avoiding incineration of used device (as in the case of silicone commercial device). Pharmacokinetics studies must be done to corroborate in vivo performance of optimized IVRs made of EVA.

1. Introduction

Statistical design of experiments (DOE) is a common practice in pharmaceutical product development. Its main objective is to find and estimate the relationship between experimental factors or conditions and desired responses. DOE includes several strategies like screening and mixture designs, variance component analysis, evolutionary operation and response surface methodology [1,2].

Response surface methodology (RSM) is the most used DOE in pharmaceutical area. RSM involves systematic procedures to study the effect of parameters on one or more responses of interest [3,4]. Usually, it is used to study main and interaction effects [5]. It combines experimental strategy, mathematical methods and statistical inference allowing to empirically describe the procedure under analysis [4]. The final aim of RSM is to obtain statistical models from experimental design [6]. Statistical models can be used to describe systems within study range and more important they can be employed to optimize desired responses [6]. It has been reported the use of RSM in the optimization of numerous process and systems [3,7–14]. In drug delivery field, RSM has been employed successfully to optimize sustained release from microspheres [15,16], beads [17–20], matrix tablet [21–23] and from oral delivery system [24].

Although it has been used for many systems, RMS has not been used yet to analyze and optimize drug delivery from intravaginal rings (IVR). IVRs are ring-shaped devices delivering one or more hormones in a controlled manner. Release rate commonly depends on factors like the relationship between the characteristic dimensions, release area, the initial content of hormone, the presence of excipients and the tissue-material partitioning [25–27]. IVRs have been used in hormone replacement therapy [28–30], microbicide [31,32] and contraception therapy [33,34]. A particular interest is the use of IVRs for contraception purpose during lactation [35,36]. Progering® is a commercial IVR approved for this purpose [37–40]. It is formed by a matrix of silicone containing 2.074 g of progesterone uniformly dispersed in its interior. However, some drawbacks related to its use can be mentioned [41]: (i) The initial content of progesterone in the device is high. (ii) Silicone is not a recyclable material. (iii) Silicone IVRs have to be discarded after its use by incineration. (iv) There is an important environmental concern on the impact of the use of silicone products due to the nondegradability of the material.

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Therefore, it is necessary the development of IVRs made of recyclable material as an alternative of non-recyclable silicone IVRs. Ethylene vinyl acetate copolymer (EVA) is a synthetic polymer that can be reprocessed by thermal treatment allowing material recycling. In our previous study, the use of EVA to fabricate IVRs was evaluated [42]. In addition, several simulations were performed to predict the effect of release area and dispersed drug/dissolved drug ratio on release rate [42]. However, main factors affecting drug delivery were not identify and no experimental tests were done to corroborate theoretical predictions. Several simulations were performed to optimize release rate from IVRs made of EVA [42]. However, optimization was done only on initial content of hormone. Optimization of others parameters like ring dimensions was not conducted.

The purpose of present contribution is to identify main factors that affect release rate from IVRs made of EVA and optimize all of them to achieve a specific delivery profile. The best choice to accomplish this goal is to conduct an experimental design based on RMS. This experimental design allows to identify relevant factors and optimize them in a suitable manner.

2. Materials and methods

2.1. 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 methanol which was HPLC grade.

2.2. 3-level factorial design

Response surface methodology was used to evaluate effects of ring parameters on progesterone release rate. Three parameters were analyzed: ring outer radius (R_e), ring cross-sectional radius (R_0) and initial content of progesterone (A). A 3-level factorial design was used. Factors levels and factorial design are presented in Tables 1 and 2 respectively.

2.3. EVA rings fabrication

Rings fabrication was done according to 3-level factorial design (section 2.2). Progesterone was incorporated into EVA pellets by an impregnation process [42]. Different mass of hormone were dissolved in dichloromethane and then added to EVA pellets. Systems were stirred during 2 h. During this time, pellets swell and absorb all hormone solution. Thereafter, an evaporation step was conducted to eliminate dichloromethane and precipitate the hormone inside pellets. This step was realized slowly to avoid higher efflux of solvent that could drag hormone out of pellets. Hence, pellets were first dried in vacuum at 40 °C during 1 h and then dried in oven at 40 °C until constant weight. Complete solvent evaporation was corroborated gravimetrically. Impregnated pellets were used to fabricate rings by hot-melt extrusion procedure. Rings with R_0 = 0.17 cm were fabricated using an industrial extruder (Dr. Collin® GmbH D-85560, Ebersberg, Germany). Pellets were fed into the extruder equipped with a cylindrical die of 0.34 cm of diameter and the screw speed was set to 65 rpm. Rings with R_0 = 0.34 cm and 0.51 cm were fabricated employing a lab-scale extruder with a cylindrical die of 0.68 cm and 1.02 cm respectively. 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. All extrudates were cooled down to room temperature and manually cut using surgical blades into matrices of specific length according to experimental design. Matrices were placed onto stainless steel molds of required sizes. Matrix ends were sealed with heat at 170 °C during approximately 1–2 min and cooled down to room temperature to produce rings.

Table 2
3-Level factorial design.

Run	Factor			Release rate (mg cm^{-2} days$^{-1/2}$)	Adj R^2
	R_e	R_0	A		
1	−1	−1	−1	3.307 ± 0.169	0.979
2	0	−1	−1	3.369 ± 0.176	0.979
3	+1	−1	−1	3.424 ± 0.179	0.979
4	−1	0	−1	3.824 ± 0.101	0.991
5	0	0	−1	3.941 ± 0.105	0.991
6	+1	0	−1	3.837 ± 0.051	0.998
7	−1	+1	−1	4.494 ± 0.096	0.994
8	0	+1	−1	4.394 ± 0.054	0.998
9	+1	+1	−1	4.265 ± 0.091	0.994
10	−1	−1	0	4.398 ± 0.205	0.983
11	0	−1	0	4.440 ± 0.202	0.984
12	+1	−1	0	4.721 ± 0.083	0.998
13	−1	0	0	5.110 ± 0.129	0.992
14	0	0	0	4.997 ± 0.139	0.990
15	+1	0	0	5.132 ± 0.192	0.982
16	−1	+1	0	5.608 ± 0.177	0.987
17	0	+1	0	5.564 ± 0.124	0.994
18	+1	+1	0	5.546 ± 0.061	0.998
19	−1	−1	+1	5.527 ± 0.115	0.997
20	0	−1	+1	5.890 ± 0.124	0.996
21	+1	−1	+1	5.880 ± 0.079	0.999
22	−1	0	+1	6.250 ± 0.107	0.996
23	0	0	+1	6.139 ± 0.139	0.993
24	+1	0	+1	6.195 ± 0.121	0.995
25	−1	+1	+1	6.951 ± 0.092	0.998
26	0	+1	+1	6.574 ± 0.101	0.997
27	+1	+1	+1	6.671 ± 0.110	0.996

2.4. Rings characterization

Outer and cross-sectional diameter of each ring were measured using a Vernier caliper. Hormone contained in each ring was extracted with 200 ml of ethanol in a Soxhlet during 48 h at 90 °C. After suitable dilution, progesterone concentration was measured by HPLC technique detailed in section 2.6 and initial content of progesterone in each device was calculated. Assays were run in triplicate.

Table 1
Factors levels.

Factor	Unit	Code	Theoretical			Measured		
			Low level (−1)	Medium level (0)	High level (+1)	Low level (−1)	Medium level (0)	High level (+1)
R_e	cm	A	1.63	2.27	2.91	1.62 ± 0.02	2.27 ± 0.02	2.90 ± 0.02
R_0	cm	B	0.17	0.34	0.51	0.17 ± 0.03	0.35 ± 0.01	0.50 ± 0.01
A	mg cm^{-3}	C	95.75	143.63	191.50	94.13 ± 2.78	146.41 ± 7.14	192.85 ± 4.99