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# Development of an injection molded ethylene-vinyl acetate copolymer (EVA) intravaginal insert for the delivery of progesterone to cattle

A.J. Cappadoro*, J.A. Luna

*Laboratorio de Química Fina, Instituto de Desarrollo Tecnológico para la Industria Química (INTEC), Universidad Nacional del Litoral (UNL), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Predio CCT-CONICET Santa Fe, Ruta Nacional 168, Km 1, 3000 Santa Fe, Argentina*

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ABSTRACT

The purpose of this study was to develop a new injection-molded intravaginal insert manufactured from ethylene-vinyl acetate containing progesterone for a 7-day insertion period in cattle. The manufacturing process resulted in a reduction in the residual drug compared to the silicone insert available while still maintaining biological performance.



## 1. Introduction

In the past 40 years, technologies of drug controlled release have found increasing application in the pharmaceutical, agricultural, veterinary and other fields (Mathiowitz, 1999). The intravaginal devices for the controlled release of progesterone have been successfully used in order to synchronize estrous in cattle (Roche, 1975, 1976; Burggraaf et al., 1997; Rathbone et al., 1998a). Commercially available bovine intravaginal inserts consist of a T-shaped or Y-shaped nylon spine coated with an inert matrix, usually silicone rubber, loaded with progesterone evenly dispersed therein (Roche, 1976; Munro, 1987; Macmillan and Peterson, 1993; Winkler et al., 1997; Rathbone et al., 2002). These devices have several advantages, such as ease of placement and removal from the vagina. In addition, the progesterone administration ends when the device is removed, resulting in a sharp fall in plasma concentration of the hormone. However, they have various drawbacks mainly derived from the use of the silicone rubber. This polymer is expensive, not biodegradable and requires burning or burial for disposal after use. Silicone rubber is a thermoset plastic that, once formed, does not permit reprocessing. In addition, although silicone will cure at low temperatures, the extended times needed to achieve this limit the commercial viability of this approach, and therefore high temperatures (as high as 190 °C) are used commercially. Finally, the initial load of progesterone only decreases between 20 and 40% after the hormonal therapy, which is the main disadvantage because progesterone is the most expensive ingredient in the formulation.

This study was to overcome these problems by designing and developing a new intravaginal device. The key

* Corresponding author. Tel.: +54 342 4511597.
*E-mail address:* alecappadoro@gmail.com (A.J. Cappadoro).

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requirements for this intravaginal device were: ease of manufacture, low manufacturing temperatures, low cost of manufacture, ease of insertion, high retention rate, ease of removal, little or no damage to the vaginal mucosa and the potential for reprocessing formed inserts. A thermoplastic polymer was used as an alternative to silicone rubber. Ethylene-vinyl acetate (EVA) has interesting properties and is already used for the production of inserts in human medicine (Shastri, 2002). This paper describe the experiments conducted to develop and clinically evaluate an injection molded intravaginal insert manufactured from EVA that delivered progesterone for estrous cycle control and synchronization in cows. The new device was compared to the silicone commercially available DIB® insert which is widely used nowadays (Aller et al., 2010; Prada Torres et al., 2013; Núñez-Olivera et al., 2014).

## 2. Experimental

### 2.1. Materials

Ethylene-vinyl acetate (ELVAX® 460, 18% vinyl acetate content) and acetal resin (Delrin 900P) were obtained from DuPont, USA, micronized progesterone (USP 30) was supplied by Farmabase, Brasil, DIB® intravaginal inserts were supplied by Syntex, Argentina, D(+)cloprostenol was supplied by OVER, Argentina, and ethanol PA was from Cicarelli, Argentina. Radio-immunoassay (RIA) kits for quantitative determination of progesterone were Coat-A-Count from Siemens Medical Solutions Diagnostics, USA.

### 2.2. Compounding of progesterone/EVA and manufacture of intravaginal inserts

ELVAX 460 was selected as an alternative to silicone rubber based on the two progesterone transport properties that have the greatest influence on release: solubility and effective diffusion coefficient in the polymer. EVA pellets were impregnated with progesterone using a solvent impregnation method developed in the laboratory. EVA pellets were placed in a suitable organic solvent containing a specified amount of progesterone. This solvent must cause swelling of the pellets and must have a low boiling point. After reaching the maximum swelling the solvent was evaporated and the pellets were placed in an oven for 24 h.

Based on preliminary knowledge of commercially available intravaginal devices, and on advice of veterinarians, the device design was developed. The intravaginal insert comprises an inert Y-shaped acetal resin spine and on its extremes were two EVA flat wings containing progesterone. The inert Y-shaped acetal resin spine (Fig. 1) was designed to ensure vaginal retention, as well as facilitating the insertion and removal of the device. The EVA flat wings (Fig. 2) were designed to ensure a surface area of contact greater than that provided by commercial devices, maintaining a surface area of about 120 $cm^2$ (Rathbone et al., 1998b). The spine and flat wings were fabricated by injection molding (JM800-$C^2$, Chen Song Machinery Co., Hong Kong). The injection temperature of EVA flat wings was 170 °C and the injection time was about 1.5 s, allowing progesterone crystals to be uniformly suspended in the EVA matrix.

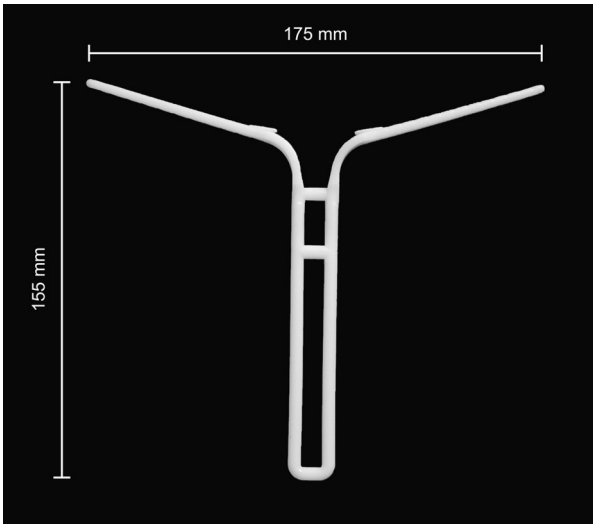


**Fig. 1.** Inert Y-shaped acetal resin spine.

The EVA insert (Fig. 3) had a surface area of 125.68 $cm^2$, similar to that of the "traditional" DIB insert (125.65 $cm^2$). The initial load of progesterone was about 1.0 g.

### 2.3. Determination of initial and final progesterone load

The initial and final amount of progesterone in an EVA intravaginal insert was determined by cutting it into strips of 5 mm of length, placing the sections into a soxhlet extractor (250 mL) and refluxing for 24 h with ethanol. The ethanolic extract was made up to 250 mL with ethanol. Solutions were then diluted before analysis by UV at 244 nm (UV-2401 PC, Shimadzu).

### 2.4. In vitro drug release studies (EVA insert vs. DIB insert)

An *in vitro* drug release experiment was performed as described by Bunt et al. (1997) using a dissolution

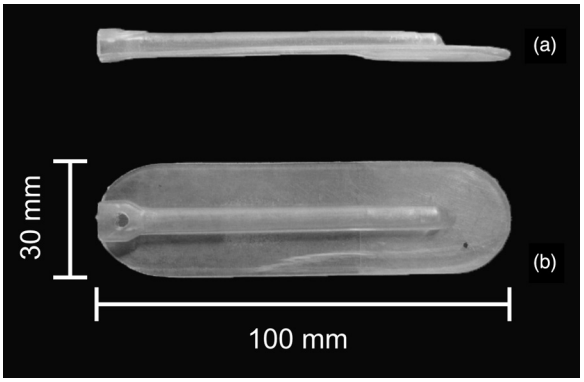


**Fig. 2.** EVA wing: (a) front view and (b) top view.