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Progesterone-releasing devices for cattle estrus induction and synchronization: Device optimization to anticipate shorter treatment durations and new device developments

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ABSTRACT

Synchronization programs using progesterone-releasing intravaginal devices that allow for fixed time artificial insemination are still finding increasing application in bovine reproduction. This practice is useful for rationalizing livestock management because an increased number of cows can be inseminated in one session without the need for estrus detection. Although much of the innovation related to the design and development of intravaginal devices for use in cattle took place in the previous century, progress in understanding the physiology of the bovine estrous cycle resulted in shorter treatment durations, a trend which is still continuing. In this competitive market, with little functional differentiation between the existing devices, the shorter treatment duration prompted for optimization of the progesterone content in the device, as the cost of the drug significantly contributes to the price per unit. For CIDR® a reduction of the progesterone content of about 30 per cent was realized. Price reduction remained an important target for further device development. Next to reduction of progesterone content, cheaper and easier to process materials like polyethylene vinyl acetate (EVA) copolymers have been explored to replace the commonly used silicone elastomers. The reengineering effort of CIDR® demonstrated that knowledge of release kinetics and insight into gradual depletion patterns in the device is critical for optimization of drug content without compromising performance (blood levels). More recent publications related to the use of alternative polymers like EVA and polyisoprene (IP) indicated encouraging results regarding further reduction of progesterone content. The use of EVA seems most promising, because it is in principle a low-cost polymer available in many grades and this thermoplastic polymer can be processed easily by means of commonly used techniques like injection molding and extrusion. The use of thermoplastic polymers, however, requires insight into the physical-chemical phenomena related to drug dissolution and re-crystallization taking place in the polymer during processing at high temperatures. These aspects, which may critically affect product stability, are often overlooked and are prompting to cover some of the background in this review. Finally, two different innovative approaches are discussed, one related to programable electronic devices for tailored simultaneous drug release and the other is a flexible drug-loaded helix, which is retained very well in several species without causing the usual inflammatory response.

1. Introduction

Insemination of cows after visual detection of natural estrus remains the major breeding practice in dairy and beef cows (for example less than 300 000 estrus synchronization treatments involving progesterone devices were used in France for the 3.5 million dairy and 590 000 beef cows that were inseminated [1]). Utilization of synchronization programs that allow for fixed time artificial insemination (FTAI), however, have increased during the past decade in dairy cows in North America and in beef cows in South America [2,3]. In dairy production this practice is useful to inseminate high producing cows with an absence or depressed

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estrus expression related to their high milk yield [4]. In beef cows, treatments allowing FTAI enable better utilization of high genetic merit bulls and a rationalization of livestock management. An increased number of cows can be inseminated in one session without the need for estrus detection. Furthermore, grouping of animals facilitates vaccination, treatment if required and watching over calves and young animals, which is of crucial importance for large grazing herds.

Some of the beef and dairy cows are in anestrus at the end of the waiting period after calving (~25% in beef and 7–27% in dairy cows [3,5–7],). This might also concern beef heifers when bred in winter. In these females, progesterone priming during the development of the ovulatory follicle increases fertility at timed AI [8–10]. Using treatments combining progesterone with other hormones is then necessary and contributes to reducing the calving interval.

Progesterone-impregnated intravaginal devices have been developed for cows since the 1970's [11–13] and they are currently available in most countries. Three commonly used devices are: CIDR® (1.38 g of progesterone, Zoetis), PRID® Delta (1.55 g of progesterone, CEVA) and Cue-Mate® (1.56 g of progesterone, Vetoquinol). They are used in combination with prostaglandins, eCG, oestrogens or with GnRH [2,3,14,15].

These treatments need to induce a high and quick elevation of plasma progesterone concentrations in the cow and should maintain this concentration above 2 ng/mL until removal [11,16]. The first intravaginal inserts PRID® and CIDR® were developed and marketed in the 1970's and 1980's respectively, and these devices were formulated anticipating a treatment duration of 12–14 days. New physiological insights, however, indicated a better fertility outcome with reduced duration of treatment (7–8 days) and concomitant use of other hormones. For this reason, the CIDR® device initially containing 1.9 g of progesterone for a treatment duration of 12 days was re-engineered in the 1990s for a 7-day treatment, permitting a reduction of the progesterone content to 1.38 g. Today, treatment duration can be reduced to 5 days [15] and this may allow further reduction of the progesterone content of the devices, reducing costs and potentially less progesterone is emitted in the environment.

In a recent review Rathbone & Burke [11] concluded that there is little difference between existing progesterone-releasing cattle inserts as these inserts provide very similar blood levels, resulting in the same efficacy and having the same human and animal safety profile. Reduction of the progesterone drug load, however, anticipating the continuing trend towards shorter durations of treatment [17–20], seems an interesting possibility to reduce price and gain some competitive advantage. Lower progesterone drug load and better drug pay-out have been reported for devices made from polyethylene vinyl acetate (EVA) copolymers and polyisoprene (IP) [18,21]. The methodology used by Rathbone et al. [19] to optimize drug loading, which was based on the evaluation of progesterone distribution in used devices, might prove to be a useful starting point for further investigations of progesterone containing matrices made from EVA and IP.

The use of alternative polymers may offer additional potential for cost reduction, because silicone polymers are relatively expensive and thermoplastic polymers may offer the benefit of more efficient manufacturing. Polyethylene vinyl acetate copolymers seem to be the most interesting candidate material for this purpose because they can be purchased in many grades and are in principle a low cost commodity. The use of thermoplastic polymers, however, requires insight into the physical-chemical phenomena related to drug dissolution and re-crystallization taking place in the polymer device during processing at high temperatures [22]. These aspects, which may critically affect product stability, are often overlooked, prompting to cover some of the backgound in this review.

In this review two new approaches are highlighted more specifically. First, electronic devices which may be promising for the simultaneous release of multiple drugs at predetermined rates and time points. Furthermore, an innovative helically-shaped intravaginal device made from EVA copolymers and manufactured using co-extrusion technology [17]. This device combines excellent vaginal retention properties without causing purulent discharges during use. Purulent discharges, resulting from local irritation, are frequently observed when the device is removed (rate of incidence is 57–67% upon device removal) [23–25]. Purulent discharges are not associated with impaired pregnancy rates, however, elimination of this problem is regarded as important with respect to animal wellfare and general health.

2. Estrus synchronization treatment protocols

Progesterone reduces LH secretion and thus prevents estrus and ovulation. After the device removal, the declining progesterone levels promotes follicular maturation and ovulation. Progesterone supplementation has been used to synchronize estrus in cattle since the 1970's using different pharmaceutical formulations and routes of administration: oral supplementation, subcutaneous implants, or intravaginal devices [26]. The length of the original progesterone treatments was 12 days. In the original 12-days program, an estradiol benzoate capsule coupled to the intravaginal device served to 1) be slowly luteoltytic for animals early in the cycle (corpus luteum less than 5 days) and 2) induce a new follicular wave emerging around 3–4 days after the beginning of treatment [27]. However, this program extended the duration of dominance resulting in low fertility. With increased knowledge of the regulation of follicular dynamics, program duration was reduced to 7–9 days [6,28,29]. The critical issue was to keep the duration of dominance of the follicle to be ovulated under 8–9 days. External hormones might be added at the start of the program to induce ovulation if a large follicle is present producing emergence of a new follicular wave. At the end of treatment, the role of external hormones is to induce luteolysis and to synchronize ovulation for fixed time AI. The use of these external hormones allows for further reduction of treatment duration, as we will see below.

2.1. Use of progesterone plus prostaglandin (Fig. 1 A)

The treatment consists in the insertion of a progesterone-releasing device for 7–9 days. Prostaglandin $F_{2\alpha}$ (PG) is given 24 h before device removal (to induce luteolysis) and timed artificial insemination (TAI) is performed 56 h after device removal. This protocol is recommended by the manufacturer of CIDR® (Zoetis) for cycling heifers and cows in France.

2.2. Progesterone and eCG (Fig. 1 B)

Equine chorionic gonadotropin (eCG) has mostly FSH-like with some LH-like activity in cattle (with a prolonged circulating half-life) thus increasing estrogen production to ensure estrus and ovulation. It might be introduced in TAI protocols especially to induce ovulation at the end of treatment in previously anestrous cows with beneficial effects on pregnancy rates and on embryo survival [30]. It does so by enhancing the estradiol production capacity of the follicle to ensure a healthier follicle maturation and intra-follicular environment, thereby ensuring positive feedback to induce the GnRH and LH surges. This treatment combining a progesterone-releasing device for 7–9 days, PG 24 h before device removal, eCG at device removal and TAI 56 h after is the most widely used treatment in France. The recommended dose of eCG

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