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Review Article

The potential of biodegradable polymers: Chitosan, polyethylene glycol, and polycaprolactone as materials for progesterone intravaginal devices

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Abstract

For several decades, a protocol based on the use of progestagens has been used to manage livestock reproduction with minimal alterations. Recently, researchers have gained insight into the short-term use of progestagen protocols lasting 5-7 days, which has been found to reduce the incidence of vaginitis and obviate the use of antibiotics. Additionally, this approach enables the reutilization of silicone-based devices such as CIDRs after a thorough biosecurity assessment. However, these devices have certain limitations. At the end of the treatment, they must be disposed of and cannot be reused, necessitating a re-evaluation of their use for technical and societal reasons, including animal health and welfare, food safety, and environmental impact. A chitosan-PEG intravaginal implant formulation released progesterone for a period of four days, corresponding to the degradation time of the implant in the vagina. The use of a simple melting and molding process for the combination of PCL-PEG-chitosan implants has been observed to result in degradation of both simulated vaginal fluid and vaginal tissue of cows. The development of intravaginal devices made from biodegradable polymers is considered a potential solution because these materials would degrade within the body, eliminating the need for removal and leaving no residue. These devices are safe for animals and the environment.

Keywords: Biodegradable; Polymer; Chitosan; Polyethylene glycol; Polycaprolactone

INTRODUCTION

One of the bioactive ingredients that the body needs for the reproductive function that is released in the long term is the hormone progesterone. The clinical use of progesterone in ruminants is for estrous synchronization programs [1], prevention of early embryonic death [2], induction of estrus in anestrus cows [3], induction of lactation [4], treatment of repeat breeders [5], and advance fertility in embryo transfer protocols [6]. Progesterone administration is an essential step in the synchronization protocol for livestock production. Different pharmaceutical formulations have been used, including oral tablets, subcutaneous implants, and intravaginal inserts.

Since the 1970s, progesterone-releasing intravaginal devices have been developed using silicone elastomers as the substrates. Hormones are scattered within the silicon lattice and discharged by diffusion [7].

Numerous commercial products of intravaginal devices that are widely utilized, for example, CIDR® (1.38 g of progesterone, Zoetis), Cue-Mate® (1.56 g of progesterone, Vetoquinol), and PRID-delta® (1.55 g of progesterone, CEVA) [8]. There are a few impediments related to utilization of silicon devices. After administering the treatment, it is crucial to retrieve the device from the animal's body and dispose of it responsibly, as silicone is not a biodegradable polymer, thereby posing a substantial environmental concern in terms of potential ecological harm arising from its transfer. Moreover, the residual hormone content within the device after use generally remains high (at least 50%), thereby increasing the risk of environmental contamination [9].

Several solutions have been proposed to overcome this problem. Rathbone *et al*. [10] decreased the thickness of the silicon network in CIDR®, which diminished the beginning progesterone stack from 1.9 to 1.38 g, in this manner minimizing the remaining substance after utilization from 1.31 to 0.72 g. Helbling *et al*. [9] designed and evaluated a prototype recyclable intravaginal insert from ethylene vinyl acetate (EVA) copolymer material. Recycled matrices were prepared by adding a sufficient amount of progesterone to the matrices, and new matrices were fabricated using injection molding. The features of the recycled matrices were similar to those of the original matrices. Although EVA devices are recyclable, its disposal can potentially pollute the environment. Another alternative is to replace the silicon material with biodegradable polymers.

Biodegradable polymers have chemical and physical properties can be harmed and degraded when exposed to microorganisms in aerobic and anaerobic forms [11]. Biodegradable polymers are now essential for biomedical applications (medicate conveyance, inserts, and other therapeutic devices). Biodegradable polymers have become a trend as the material of choice for various products because they are environmentally friendly. Medical devices (implants) made of biodegradable polymer materials do not need to be removed from the body after use. They are preferred because they can be broken down into smaller parts which can then be excreted or retained by the body [12]. Biodegradable polymers have demonstrated potential for the improvement of drug delivery frameworks. Drug encapsulation and conjugation into a polymeric matrix can control drug release resulting in prolonged drug action [13].

Chitosan, polyethylene glycol (PEG), and polycaprolactone (PCL) are biodegradable polymers that have been studied for progesterone delivery. Hassan *et al*. [14] studied chitosan tablets which are mucoadhesive to release progesterone in the vagina of rabbits. However, the progesterone release period lasts only 48 hours (two days), so it cannot be used for estrous synchronization. Fu *et al*. [15] used a 3D printing method to fabricate an intravaginal device utilizing materials from a combination of polycaprolactone (PCL) and PEG. The results showed that progesterone could be released for more than seven days in vitro.

Biodegradable polymers can be utilized as viable alternatives for impregnating pharmaceutical ingredients. These polymers can also be molded into the shape of intra-vaginal devices or inserts that rely on variable geometry for retention, providing a finite insertion period to achieve the desired pharmacological effect without compromising the ability of the polymer to degrade in vivo. After removal, the polymer's pharmaceutical content is significantly reduced, minimizing long-term disposal concerns due to the polymer's tendency to biodegrade following removal from the animal [16]. A vaginal insert from the biodegradable polymer polycaprolactone has been made capable of releasing progesterone through the vaginal mucosa of cattle with a profile similar to CIDR use [16]. An intravaginal device or insert designed for mammals, featuring an insertable and retained intravaginal mass that can be removed, with at least one or both components being printable and biodegradable, such as poly(e-caprolactone)

and starch. The device geometry was varied, allowing for intra-insertion, retention, and removal from the vagina. The mass contained sufficient quantities of progesterone to achieve a target blood serum progesterone level of greater than 2 ng/mL for a minimum of 5 days post-insertion. The device is biodegradable after its removal from an animal [17]. However, the PCL vaginal insert must be retrieved after use due to its very long degradation period (3-4 years) [18].

Future studies should use biodegradable polymers to create intravaginal implants that can be degraded within the animal vagina without the need for removal. This approach may minimize the residual influence of hormones resulting from the discarded intravaginal devices. The formulation of a chitosan-PEG intravaginal implant was successfully developed using a melting and molding process. In vitro drug release studies using a dye as a model drug showed that the chitosan-PEG profile exhibited an initial rapid release of the drug, followed by a gradual slowdown. Degradation studies of implants in compost and vaginal environments revealed a gradual degradation process. Blood progesterone levels showed a significant increase during implantation, reaching a maximum of 15 ng/mL on the third day. The chitosan-PEG intravaginal implant formulation released progesterone for a period of four days, corresponding to the degradation time of the implant in the vagina [19]. The use of a simple melting and molding process for the combination of PCL-PEG-chitosan implants has been observed to result in degradation in both simulated vaginal fluid and vaginal tissue of cows [20] .

The development of intravaginal devices from biodegradable polymers presents several challenges, including:

1. Ensuring that the device delivers the pharmaceutical agent intravaginally over a desired period of time without significant reduction in the integrity of the device's mass.
2. Designing the device or insert such that the entire mass can be retained in the vagina by adjusting elastically to facilitate insertion and subsequently returning to a geometry that minimizes spontaneous rejection by the vagina [17].

This review seeks to conduct a comprehensive examination of the advancements made in the production of intravaginal devices designed for use in livestock reproduction as well as the exploration of alternative basic materials derived from biodegradable polymers such as chitosan, PEG, and PCL.

Chitosan

Chitosan is a polysaccharide that has numerous points of interest due to its biocompatibility, biodegradability, and mucoadhesive properties, which have been broadly examined for several biomedical and pharmaceutical applications, including for delayed drug release [21], wound dressing [22], blood anticoagulants [23], cartilage tissue engineering [24], and implants [25].

The polycationic chitosan copolymer consists of glucosamine and N-acetylglucosamine units, resulting from chitin's deacetylation derived from the crustaceans' exoskeleton, insects or fungi [26]. Chitosan is accessible in different deacetylation degrees and molecular weights, which are also the most influential properties and quality of polymers. Chitosan, a biomaterial that's simple to get and reasonable, can be effortlessly shaped into different semi-solid and strong structures beneath mellow conditions. Chitosan only dissolves in dilute inorganic and organic acids with a lower pH than the pKa of chitosan (approximately 6.3) [27]. In a low pH environment, protonated free amino groups will cause electrostatic repulsion between polymer chains, allowing polymer solvation. The cationic nature and free hydroxyl and amino groups of chitosan result in good mucoadhesive properties because it allows the occurrence of hydrogen and electrostatic bonds between chitosan and mucin. Therefore, chitosan is considered a suitable excipient for buccal [28], nasal [29], ocular [30], and vaginal [21] dosage forms. Furthermore, chitosan is an additional antimicrobial drug to increase its pharmacological activity [21]. A few examples of chitosan-based conveyance

Table 1. Examples of chitosan-based conveyance frameworks and biomedical devices

Material	Active substance	Dosage form	Biomedical/ pharmaceutical applications	Reference
Unmodified chitosan, ethyl cellulose and butylphthalate	Buspirone hydrochloride	Sustained release lyophilized sponge	Treatment of anxiety through buccal	Kassem *et al*. [28]
Chitosan/xanthan polyelectrolyte complex	Promethazine hydrochloride	Mucoadhesive insert	Treatment of migraine through the nose	Dehghan *et al*. [29]
Unmodified chitosan	Bimatoprost	Continuous release insert	Treatment of glaucoma through the eye	Franca *et al*. [30]
Unmodified chitosan and β-glycerophosphate crosslinked chitosan	Clotrimazole	Long-release microgranules, tablets and hydrogels	Treatment of vaginal candidiasis	Szymańska *et al*. [21]
Unmodified chitosan	Progesterone	Mucoadhesive tablets	Intravaginal progesterone release test	Hassan *et al.* [14]

frameworks and biomedical devices have appeared in Table 1.

From a technological point of view, the molecular component of chitosan can be manipulated to influence its physical and chemical properties so that it can be widely applied in drug delivery systems. Another crucial point is its mucoadhesive properties and antimicrobial action. Hence, chitosan is essential for developing drug delivery frameworks for nearby intravaginal treatment [31]. Chitosan can stay attached to the mucosal surface, providing a controlled discharge for a long time until total debasement [32]. The foremost acknowledged theory for the chitosan-mucin fitting is the item of the appealing powers coming about from hydrogen bonding, hydrophobic strengths, and particularly coulombic strengths shaped between the emphatically charged chitosan and the adversely charged mucin. Mucin is adversely charged due to sialic corrosive and sulfate esters [33].

The metabolic fate of polymers in the body or the biodegradation of polymers is one of the essential aspects in the use of polymeric drug delivery systems. Chitosan is a hydrophilic polymer with systemic absorption, so it must have the appropriate molecular weight to be cleared by the kidneys. If the given polymer size is more prominent, then the polymer must be degraded. Biodegradation (chemical or enzymatic) is beneficial for kidney clearance. Chemical degradation of chitosan refers to acid-catalyzed degradation, for example, the acid in the stomach. In vertebrates, lysozyme and bacteria enzymes in the large intestine are assumed to play a role in degrading chitosan [34].

Most analysts utilize chitosan or its subordinates with distinctive molecular weights and levels of deacetylation to think about its degradability beneath specific test conditions (specific chemicals or enzymes, temperature). In any case, they utilize the common term "biodegradable", even though most tests do not. Carried out in vivo or proceeded until the end to guarantee the overall debasement and elimination of the chitosan or decide the destiny of chitosan within the body. Almost all corruption consider have been carried out utilizing in vitro consider frameworks, and there is no in vivo thought about to get it the component of corruption completely. Chin *et al*. [35] examined the degradation of glycol-charged chitosan nanoparticles (Bovine Serum Albumin) at the highest concentration of lysozyme (1.7 mg/mL, pH 7.2) compared to physiological conditions. After a three-hour presentation to lysozyme, they observed that the drug-free nanoparticles corrupted to 10–150 nm particles.

The BSA-charged nanoparticles debased more broadly to 10–20 nm particles, whereas the protein was not divided.

Despite its significant potential in drug delivery and tissue engineering systems, its poor long-term stability poses a significant challenge for scaling up its pharmaceutical applications. Over time, chitosan undergoes gradual degradation of its chains and destruction of functional groups, resulting in irreversible loss of physicochemical properties. Both intrinsic and extrinsic factors such as the degree of deacetylation, molecular weight, purity, moisture level, environmental storage conditions, thermal processing, sterilization, and processing involving acidic dissolution can affect the stability of chitosan-based formulations. To improve stability, various strategies have been proposed, such as adding stabilizing agents during preparation, blending with hydrophilic polymers, and using ionic or chemical crosslinkers. However, there are no universal principles for preserving chitosan-based products during storage, and preformulation studies and selection of appropriate storage conditions are essential to ensure maximum stability [36].

The mechanical properties of chitosan films can be improved by incorporating selected physical methods, such as heat treatment and homogenization, during the preparation process of the film-forming solution. Heat treatment increased the thermal crosslinking of chitosan polymer chains, resulting in increased tensile strength and decreased percent elongation. On the other hand, high-pressure homogenization increases plasticization ability and emulsion stability by improving the insertion of glycerol droplets between chitosan chains and providing more chain lubrication, leading to higher percent elongation. The study found that a non-heat-treated, high-pressure homogenized solution at 10/5 MPa can provide a film with similar tensile strength and percent elongation to the film prepared from the heat-treated homogenized solution at the same pressure. Therefore, it is recommended to use high-pressure homogenization at 10/5 MPa without heating to prepare the film-forming solution in order to save energy and shorten the process [37].

The degradation of polymers can be attributed to hydrolysis, oxidation, and enzymatic reactions. The rate of hydrolysis is influenced by the accessibility of water to the polymer matrix. Partially N-acetylated derivatives of chitosan were found to be more digestible than N-acetylchitosan, and their enzymatic hydrolysis rate was affected by the degree of substitution of N-acetyl groups. The biodegradation process is impacted by both chitosan molecular weight and degree of acetylation (DA), with higher molecular weights delaying the degradation process in both in vitro and in vivo environments. Fully acetylated chitosan is completely resistant to enzymes [38].

Lysozyme recognizes N-acetyl glucosamine sequences in chitin/chitosan molecules, resulting in increased digestibility with increasing degree of N-acetylation. Chitosan matrices with high acetylation broke down into monomers and oligomers after a few days of lysozyme treatment, whereas those with low acetylation remained relatively constant. The degradation rate of a chitosan scaffold is inversely proportional to its molecular weight, degree of crystallinity, and degree of acetylation and is directly proportional to the degree of acetylation. A higher amount of lysozyme in the degradation medium resulted in a higher rate of degradation. Short-term degradation of chitosan with different molecular weights and degrees of acetylation. They characterized various grades of chitosan using the DA range, molecular weight, crystallinity, and swelling ratio. These results indicated that high DA chitosan degradation occurred through peptide bond cleavage of acetoamido side groups rather than β-chain scission [38].

Polyethylene glycol (PEG)

PEG has become popular due to its adaptability, biocompatibility, and hydration capacity. PEG 100-700 are liquids (room temperature), PEG 1000-2000 are delicate solids, and PEGs with a molecular weight >2000 are complex crystalline solids (melting point 63°C) [39]. PEG contains a high polarity which increments hydrophilicity, subsequently expanding water dissolvability. Subsequently, PEG plays a fundamental part

in solubilization and saturation. PEG is electrically unbiased at all pH levels with exceedingly dynamic functional terminals [40]. PEG exerts in vivo anti-biofouling effects in the biomedical field, while in the nanoparticle field, PEG improves drug targeting and bioavailability in addition to anti-biofouling. PEG shows deposition selectivity as a drug carrier in the body [41]. Based on the intravaginal drug delivery system, in contrast to chitosan, which is mucoadhesive, PEG has a penetrating mucus system that can encourage penetration of particles into deeper areas of the mucous gel layer in the mucosa (muco-penetrating) [42].

In expansion, PEG combined with natural hydrogels can improve stability. Chitosan synthesizes hydrogels due to its biocompatibility, biodegradability, and copious natural assets. Simultaneously, chitosan encompasses an emphatically charged quaternary ammonium gathered in its structure to restrain the development and expansion of bacteria through electrostatic intelligence [43]. Chitosan/PEG hydrogel was synthesized by joint copolymerization. The composite hydrogel framework can maintain the ceaseless conveyance of chitosan, and with expanding chitosan concentration, the antibacterial impact becomes more articulated [44]. Some examples of functionally and biologically modified PEGs are presented in Table 2.

Aerobic and anaerobic microbes, in unadulterated culture or as a consortium, have been considered to corrupt PEG. Ponders on the high-impact debasement of PEG appears that the digestion system occurs through oxidation [45]. Initially, it was known that three chemicals were required for the corruption of PEG, specifically liquor dehydrogenase and aldehyde dehydrogenase to change over the terminal liquor gather of PEG to a corrosive carboxylic bunch, and an ether bond breaking protein to deliver glyoxylate (GOA) as the ultimate item. Several bacteria capable of degrading PEG include *Pseudomonas stutzeri* [46]. *Rhizobium*, *Agrobacterium*, and *Methylobacterium* sp. [47], and *Sphingomonas* sp. [48]. Intracellularly, PEG is degraded by enzymes located in the periplasm (PEG-dehydrogenase, aldehyde dehydrogenase, and diglycolic acid (DGA) dehydrogenase (DGA-DH) in sphingomonads) or located in the cytoplasm (PEG acetaldehyde lyase in anaerobes) [49].

Table 2. Examples of functionally and biologically modified PEGs

Material	Compound method	Properties	Reference
PEG/ PLA	Electrospun and electrospray techniques to make films	The mechanical properties of PEG/PLA films are greatly influenced by their composition and morphology	Ke *et al*. [66]
PEG/Alginate	PEG-NH2, oxidized alginate, gelatin as raw material, via Schiff base reaction	Osteogenic function, good biocompatibility, injection ability	Naghizadeh *et al*. [67]
PEG/chitosan	mPEG-acrylate and chitosan as raw materials, through graft copolymerization	Antibacterial function	Peng *et al*. [44]
PEG-Progesterone	Progesterone-PEG for the manufacture of solid dispersions, PLA-PCL for the manufacture of filaments	In vitro progesterone release via vaginal ring application	Fu *et al*. [15]
PEG-Chitosan	melting and molding technique	Intravaginal device for releasing progesteron	Yessa *et al.* [19]

Polycaprolactone (PCL)

PCL belongs to the group of aliphatic polyesters with hexanoate repeat units. The molecular weight and degree of crystallinity of PCL determine its properties. Sometimes, the moderate degree of bottom sinking, low mechanical properties, hydrophobicity, and the need for cellular grip are said to be the significant drawbacks of PCL [50]. PCL is one of the valuable biodegradable polymers for the advancement of controlled medicate conveyance frameworks, not as it were since of its biocompatibility and medicate discharge control properties, but the most fascination for its application is its versatility, such as biodegradation, biocompatibility, stability, crystallinity, permeability, porosity, uniform conveyance of drugs encapsulated in their networks, efficient drug stacking efficiency, and ease of fabrication [51]. Its slow degradation design qualifies it for utilization in long-term drug-release carriers, encouraging medicate discharge indeed up to a few months. Changing PCL components or forming composites, for example, with natural polymers (chitosan, collagen, gelatin, and starch) or synthetic polymers (PEG, polyvinyl alcohol, and polyurethane) can change the physical, chemical, mechanical, viscoelastic, and thermal properties of PCL as desired [52].

The solvency or scattering of the drug within the PCL environment can be improved by utilizing a few dissolvability specialists. Diverse sizes, shapes, and breadths can suit the measurements of each body area [53]. However, due to its moderate base loss, hydrophobicity, and the need for dissolvability, PCL is more suitable in tissue engineering repair as well as implant or matrix scaffolds [54]. However, combining it with other polymers, such as polylactic acid (PLA) and PEG, forms copolymers that increase their degradation reactivity due to their amphiphilic structure. [55].

PCL is degraded by several microorganisms (e.g., bacteria and fungi) and enzymes (e.g., esterases and lipases) [56]. PCL biodegradation in vivo has been well reported and associated with variables such as degree of crystallization, molecular weight, and morphology [57]. The fundamental guideline in PCL biodegradation includes disseminating water particles into the undefined locales causing hydrolytic cleavage of the ester bonds, at first within the shapeless, taken after by the crystalline spaces. The course of action of carboxylic acids through hydrolysis will result in a self-catalyzed biodegradation reaction [58].

In contrast to chitosan (mucoadhesive) and PEG (muco-penetrating), the mechanism of PCL biodegradation affects the kinetics of drug release. The classification of biodegradation mechanisms includes surface erosion and mass erosion. These mechanisms coincide with relevant differentiation. Erosion is referred to as surface erosion when the degree of erosion indicates a predominance of water seepage into most of the polymer [59]. On the off chance that water invasion into the polymer network happens quicker than disintegration, at that point, the overwhelming component is said to be bulk erosion. Be that as it may, the noticeable degradation instrument of a few polyesters, counting PCL, is bulk degradation by the irregular hydrolytic breakdown of the polymer chains. The defenselessness of the medicate entangled within the polymer framework and the need expectation of drug discharge energy are impediments to bulk erosion. However, the utilization of PCL in developing drug conveyance devices is straightforward since its properties can be adjusted by changing design, crystallinity, and biodegradability. Therefore, modification of PCL by copolymerization with other monomers changes the mechanism and kinetics of degradation. After degradation, PCL produces hydroxy caproate monomer units as metabolites, first involved in the β-oxidation cycle [60]. Some examples of PCL applications in biomedical are presented in Table 3.

DISCUSSION

The 1950s and the 1960s saw two significant developments in reproductive research. The first was the creation of two powerful progestagen analogs: fluorogestone acetate and medroxyprogesterone acetate. Second, the development of vaginal pessaries or sponges impregnated with these

Table 3. Examples of PCL applications in the biomedical field

Material	Type	Method	Reference
PCL	Nanoparticles	Vaporization method by solvent double emulsion, loaded with carboplatin for intranasal medication.	Alex e*t al*. [68]
PCL/PEG	PEG-based composite PCL/hydrogel microspheres	The microspheres are directly suspended in the prepolymer and mixed with a copper sulfate solution to form PCL microsphere embedded hydrogel, for the sustained release of methadone hydrochloride	Karamzadeh *et al*. [69]
PCL/chitosan	Electrospun mat	Electrospinning for airway tissue engineering	Mahoney *et al*. [54]
PLA-PCL	Film	Uses crippled collagen or fibronectin chloroform for cell testing	Fuse *et al*. [70]
PCL-PEG-Fibrinogen	Scaffold	Connective tissue growth factor incorporating electrospun PCL fibers embedded in a PEG-fibrinogen hydrogel for stem cell differentiation fibroblasts	Xu *et al*. [71]
PCL-progesterone	Vaginal insert	Injection molding method for cow estrus synchronization	Rathbone *et al*. [16]
PCL-PEG-chitosan	Intravaginal implant	Melting and molding technique, degradation in vagina	Yessa *et al*. [20]

progestagens released the analogs over time and allowed them to be absorbed by the vaginal mucosa, thereby reducing the need for animal handling. In the 1970s and the 1980s, advancements were made in controlled drug delivery systems for ruminant reproduction such as silicone intravaginal devices containing progesterone. CIDR-type devices for sheep reproduction are beneficial for treatment efficacy and animal welfare [61, 62].

Sponges may cause vaginitis, which results in purulent or hemorrhagic discharges in approximately 85% of sheep [63]. This is caused by inflammation and infection due to the proliferation and alterations of the vaginal microbiota caused by the physical effect of the prolonged retention of vaginal secretions. The sponges encourage the growth of native vaginal bacteria, such as *Salmonella* spp., *Staphylococcus aureus*, and *Escherichia coli* of fecal origin. *Staphylococcus aureus* is responsible for purulent vaginitis in ewes [64]. Although prophylactic measures such as cleaning, disinfection, and antibiotics with sponge insertion can help prevent vaginitis, sustainable solutions are limited owing to antimicrobial usage restrictions. The main cause of vaginitis is the presence of intravaginal sponges even when they are hormone-free. To eliminate the need for antibiotics, alternative devices, such as the CIDR device, a T-shaped silicone-based device loaded with progesterone, can replace sponges [65].

However, the use of silicone devices in therapy has several drawbacks. After therapy is completed, these devices must be removed and disposed of, as silicone is not a biodegradable polymer. This has raised concerns regarding the environmental impact of the disposal of these products. Additionally, the residual hormone content in these products after use is relatively high, which increases the risk of environmental pollution. Several studies have been conducted to address these issues. For instance, Rathbone *et al*. [10] reduced the thickness of the silicone matrix in CIDR®, resulting in a reduction in the initial progesterone loading and minimization of the residual content after use. Another alternative is the replacement of silicone with a more ecologically friendly material. The ethylene vinyl acetate copolymer (EVA) is a suitable

candidate for this purpose [9]. EVA is a semi-crystalline thermoplastic that can be purchased in medical grade and has a relatively low cost. Moreover, this material can be recycled via a process that involves reprocessing the polymer with heat and extruding the molten material. PRID-delta® is a commercially available intravaginal device made of a polyethylene spine covered by an EVA matrix impregnated with progesterone, and has been successfully used in bovine estrus synchronization. Studies have shown that this device has pharmacokinetics, plasma levels, and pregnancy rates similar to those of silicone devices.

The development of modifications to protocols, devices, and treatment periods is driven by various features. In today's rapidly evolving world, public opinion, amplified by social media and resulting in new market forces, is putting pressure on synchronization protocols by raising concerns about animal health and welfare, food safety, and environmental impact. This challenge is not unique to livestock management as it affects many other intervention strategies (Martin et al., 2004).

The design of a chitosan-PEG intravaginal implant formulation was successfully accomplished through melting and molding. In vitro drug release studies utilizing a dye as a drug model indicated that the chitosan-PEG profile exhibited an initial rapid release of the drug, followed by a subsequent slowing. Degradation studies of implants in compost and vaginal environments revealed a gradual degradation process. The blood progesterone profile showed a significant increase during implantation, reaching a maximum of 15 ng/mL on the third day. The chitosan-PEG intravaginal implant formulation released progesterone for a period of four days, corresponding to the degradation time of the implant in the vagina [19].

The use of intravaginal implants composed of PEG-chitosan has been investigated in sheep, demonstrating the capability of the implant to release the hormone progesterone as it degrades in the vaginal environment. However, the ability of the implant to persist for an adequate duration, specifically for a minimum of 5 days as required for estrus synchronization protocols, has not yet been attained. Consequently, additional research was conducted by incorporating the PCL polymer into the PEG-chitosan formulation.

The PCL-PEG-chitosan implants exhibited a longer degradation time in the vaginal environment, ranging from 6 to 10 days [20]. The degradation of polycaprolactone (PCL) can be customized through modification of its synthesis mechanism or the formation of composites with other polymers. For instance, copolymerization with other monomers can alter its degradation mechanism and kinetics [52]. It is known to take 2-3 years for complete degradation of PCL, but the addition of a more hydrophilic polymer like polyethylene glycol (PEG) can accelerate this process. Implants with higher PEG content dissolve and melt more quickly in simulated vaginal fluid (SVF). In contrast, implants with higher PCL content are more hydrophobic and less prone to degradation in the vaginal environment. Chitosan has been shown to enhance the mucoadhesive properties of implants, helping them to remain in the vaginal lumen for a longer period. However, implants without chitosan were expelled from the vagina more quickly. Implant which contained chitosan, was also expelled due to its high PCL content, making it more difficult to remain in the vaginal mucosa. The presence of chitosan can help control the release of the drug over an extended period until it is completely degraded [20].

This breakthrough has the potential to unlock the prospects for the development of intravaginal devices that can enhance livestock reproduction. These devices were designed to degrade within the vagina, eliminating the possibility of hormone residues polluting the environment. Furthermore, this innovation has the added benefit of minimizing discomfort in livestock during installation, as the device size will continue to decrease. In addition, when applied to larger livestock populations, the long-term cost-effectiveness of this approach becomes apparent, as the device needs to be installed only once and does not require

repeated removal. Advancements in this technology are expected to coincide with increasing public awareness of environmental health, leading to the development of more sophisticated ideas and concepts.

CONCLUSIONS

Vaginal hormone treatments, such as sponges and CIDR, pose a threat to aquatic ecosystems and local animal physiology because of the potential for environmental contamination through improper disposal. To mitigate this problem, sustainable agricultural practices such as reducing, reusing, and recycling must be implemented. This could involve reusing CIDRs and manufacturing new devices with lower progesterone levels and environmentally friendly materials. Another option is to create rechargeable devices (EVAs) that minimize the release of residual progesterone into the environment. Researchers have also developed an intravaginal device that uses biodegradable PCL polymer instead of silicone to release progesterone, thereby reducing the risk of contamination. To further minimize the impact of hormone residues, new devices that do not need to be removed after use have been developed from PCL, PEG, and chitosan polymers. This makes it easier to handle the large number of animals being cared for. Collaboration between pharmaceutical companies and research organizations could help develop new delivery systems, and stronger global regulations for managing agricultural waste containing hormonal residues should be implemented.

CONFLICT OF INTEREST

The authors declare no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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