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Bioavailability properties of intravaginal implants made from chitosan-PEG-PCL in simulated vaginal fluid and vagina of cattle

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ABSTRACT: This study aimed to design and evaluate the bioavailability of intravaginal implants made from the biodegradable polymer chitosan-polyethylene glycol (PEG)-polycaprolactone (PCL) in simulated vaginal fluid (SVF) and the cow vagina. Implants were prepared using melt-ing and molding techniques with 26 different formulations. Next, the implants were immersed in 40 mL of SVF at a temperature of 37.8 ℃ and changes in implant morphology were observed every day until day 5. Implants that survived until day five were tested for further availability in the cow's vagina and observed daily for 2 weeks. The immersion test on SVF results showed that implants with a PEG content of 75-85% melt more quickly than implants with a PEG content of 20-72%. Implants containing 1-10% PCL eroded more rapidly in the SVF than those containing 22-80% PCL. Implants containing chitosan can remain stable in the SVF for longer than implants without chitosan. The bioavailability test in the cow's vagina showed that implants 21-23 persisted until the 10th day, while implants 24-26 were expelled from the cow's vagina during the test. Implant 21-23 is a promising formulation for the development of biodegradable intravaginal implants. By adjusting the composition of chitosan (between 14-18 wt%), PEG (maximum 72 wt%), and PCL (minimum 20 wt%), intravaginal implants were able to extend the bioavailability of both simulated vaginal fluid and the vagina of cattle.

Keywords:
bioavailability, intravaginal implant, chitosan-PEG-PCL, simulated vaginal fluid, vagina

■ INTRODUCTION

Although much progress has been made in the development of intravaginal hormone delivery devices over the past century, recent developments in understanding the estrous cycle of cows have reduced the treatment duration (de Graaff & Grimard 2018). Progesterone-containing intravaginal devices have been available globally since the 1970s, with popular devices including CIDR, PRID, and Cue-Mate. To reduce costs, research has been conducted to create materials that are cheaper and easier to process, such as polyethylene vinyl acetate copolymers, which are preferable to silicone elastomer materials (Helbling *et al*. 2020).

Biodegradable polymers, such as chitosan, polyethylene glycol (PEG), and polycaprolactone (PCL), are also being studied as alternatives to materials that cannot be biodegraded in the environment. Chitosan is a natural polymer with biocompatible and antimicrobial properties, and is a promising candidate for vaginal drug delivery systems. Polyethylene glycol has been studied as a hydrogel base for the release of antimicrobial drugs via intravaginal application (Rajan *et al*. 2014), and PCL has been investigated as a progesterone-releasing hormone in the form of intravaginal implants (Rathbone *et al*. 2002). Even tough combinations of chitosan-PEG have been successfully developed and tested in sheep in previous study (Yessa *et al*. 2023). However, the properties of the new chitosan-PEG-PCL combination as a promising hormone delivery material have not been reported. This study aimed to develop intravaginal implants from chitosan, PEG, and PCL using melting and molding methods and to determine their degradation in simulated vaginal fluids and directly in the cow's vagina.

■ MATERIALS AND METHODS

Intravaginal implants were made using a combination of chitosan, PEG, and PCL. The materials used were weighed to obtain 26 different formulations, as shown in Table 1. All polymers were melted in a hotplate stirrer, mixed until homogenization, and then molded into a suppository-shaped shape (length:3.9 cm, diameter:1.2 cm, weight:4.9 g). After cooling, the implants were immersed in 40 mL simulated vaginal fluid (SVF) and maintained at a controlled fluid temperature of 37.8 ℃. Morphological changes in the implants were observed daily for 5 days. Further availability in the cow vagina was observed daily for two weeks.

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■ RESULTS AND DISCUSSION

The melting of implant 1-20 in the SVF occurred within a day and was not used for further intravaginal insertion tests in cattle (Figure 1). Implant 21-26 melts slowly and can be used for vaginal insertion tests. In the vaginal availability test, implants 21-23 remained for 6-10 days, while implants 24-26 were expelled from the first day.

Table 1. Bioavailability test of intravaginal implant from different formulation in simulated vaginal fluid and in the vagina of cattle.

Implant	Chitosan (wt%)	PEG (wt%)	PCL (wt%)	SVF (day)	Vagina
1	14	85	1	1	n.t.
2	13	85	2	1	n.t.
3	12	85	3	1	n.t.
4	11	85	4	1	n.t.
5	10	85	5	1	n.t.
6	9	85	6	1	n.t.
7	8	85	7	1	n.t.
8	7	85	8	1	n.t.
9	6	85	9	1	n.t.
10	5	85	10	1	n.t.
11	15	84	1	1	n.t.
12	15	83	2	1	n.t.
13	15	82	3	1	n.t.
14	15	81	4	1	n.t.
15	15	80	5	1	n.t.
16	15	79	6	1	n.t.
17	15	78	7	1	n.t.
18	15	77	8	1	n.t.
19	15	76	9	1	n.t.
20	15	75	10	1	n.t.
21	18	72	10	5	6-10 d
22	16	64	20	5	6-10 d
23	14	56	30	5	6-10 d
24	15	25	60	5	expelled
25	0	30	70	5	expelled
26	0	20	80	5	expelled

Note: PCL= polycaprolactone; PEG= polyethylene glycol; SVF= simulated vaginal fluid; n.t.=not tested in vagina of the cattle.

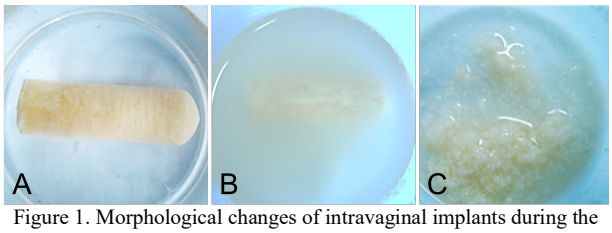

Figure 1. Morphological changes of intravaginal implants during the immersion test in simulated vaginal fluid. (A) At the start of immersion test, (B) partially eroded and (C) completely eroded.

PEG has high polarity and hydrophilicity, thereby increasing its solubility in water (Xiao et al. 2013). Therefore, implants with more PEG dissolved and melted more quickly in SVF. PCL can be customized by modifying the synthesis mechanism or forming composites with other polymers. The modification of PCL through copolymerization with other monomers can change its degradation mechanism and kinetics (Adithya et al. 2020). PCL takes 2-3 years to completely degrade; however, modification with a more hydrophilic polymer such as PEG can accelerate the degradation process. It has been proven that implants with 1-10% PCL erode faster in SVF than implants with 22-80% PCL. The intravaginal implant test for implants 21-23 lasted longer in the vaginal lumen because of the mucoadhesive properties of chitosan. Chitosan can remain attached to mucosal surfaces, providing controlled release over a long period until it is completely degraded (Szymanska et al. 2014). Implant 25-26 were expelled from the vagina owing to the absence of chitosan. However, implant 24, which contains chitosan, is also expelled because of its high PCL content, making it hydrophobic and difficult to remain in the vaginal mucosa.

■ CONCLUSION

By adjusting the composition of chitosan (between 14-18 wt%), PEG (maximum 72 wt%), and PCL (minimum 20 wt%), intravaginal implants were able to extend the bioavailability of both simulated vaginal fluid and the vagina.

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