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RESEARCH ARTICLE

Influence of the Carrier Type and Surfactants on the Trifuzole Emission from Veterinary Intrauterine Suppositories

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ABSTRACT:

The purpose of this work is to study the effect of excipients which are used in the technology of manufacturing veterinary suppositories (carrier bases and surface-active substances) on the emission of trifuzole, as the main biopharmaceutical characteristic of intrauterine veterinary dosage forms. An urgent problem of low reproductive ability are obstetric and gynecological diseases. The endometrial complex dominates in the frequency of manifestations of these diseases: placenta retention, metritis, endometritis and pyometra. These pathologies lead to a decrease in milk productivity and reproductive ability of animals. Antibacterial drugs are used for treatment, since their development is associated with damage to uterine tissues and the impact of microorganisms on it. However, this creates a certain problem with the quality of products in connection with the transfer of antibiotic substances into milk. Endometritis is more commonly reported among complex endometrial diseases. This disease is considered as a limited infection of the endometrium in the absence of systematic signs of the disease, but in the presence of purulent discharge (clinical endometritis) or the presence of leukocytes in the secretion of the uterus or cervix. Recently, endometritis of cattle is observed in almost 95% of farms in the world. This factor damages agriculture in countries up to $ 170 million per year. In this regard, the creation of new promising dosage forms for the treatment of this pathology (excluding the use of antibiotics) is extremely important. The composition and technology of the suppositories we offer requires a scientifically sound approach. In the work, methods of mathematical planning were applied, which made it possible to optimize research work, strictly individualize the selection of factors such as: properties, stability, bioavailability and pharmacotherapeutic effectiveness, which depend on the type of base, the nature of excipients, and the technology used. It is planned ahead to manufacture and sale the medicines on the internal and external pharmaceutical markets.

KEYWORDS: endometritis, trifuzol, suppositories, carrier, surfactants.

INTRODUCTION:

One of the main reasons of cows low reproductive ability is obstetric and gynecological diseases. The endometrium complex dominates in the frequency of manifestations of these diseases: retention of the placenta, metritis, endometritis and pyometra. These diseases lead to a decrease in milk production and reproductive ability of animals. Antibacterial drugs are used for treatment since their development is due to damage of uterine tissues and microorganisms' action on it. However, this creates a certain problem with the quality of products in connection with the transfer of antibiotic substances to milk. Improvement in the reproductive ability of sick animals is not always recorded, despite the apparent successful treatment. Endometritis is recorded more often among the endometrium complex diseases. This disease is considered as limited infection of the endometrium in the absence of systematic signs of the disease, but in the presence of purulent discharge (clinical endometritis) or presence of leukocytes in uterine or cervical secretions[5]. Diseases of the endometrium complex occur more often in winter and spring time. An increase in milk production is also accompanied by increase in cases of disease[1]. There is a decrease in milk yield in sick animals already in the first lactation. Oftentimes postpartum metritis was recorded in heifers with low milk yield during the last 5 months of lactation[2]. Inadequate and excessive feeding, lack of trace elements (Selenium in particular), delayed cyclic activity of the ovaries (> 37 days) predispose to uterine infection and the endometritis progression. At the same time, with early restoration of sexual cyclicity (15–16 days), the uterus may not eliminate from microorganisms in the follicular phase. Microorganisms remain in the diestrus, prostaglandin secretion is inhibited, the corpus luteum becomes persistent. The prolonged action of progesterone may be the cause of the development of typical purulent-catarrhal endometritis or pyometra[3, 5]. In reality, endometritis is manifested in 7.5–8.9% of cases during lactation[4]. However, based on the results of rectal examination and detection of purulent-mucous vaginal secretions, the disease is recorded in 40–95% of animals[1, 3, 5]. Such a mismatch in the permissible and recorded frequency of endometritis can be explained by the fact that the post-partum uterus is characterized by a temporal inflammatory process. Recovery of animals can occur without treatment. In practice, for the diagnosis and basis for treatment initiating of cows, the results of observation and rectal examination are used[1, 3, 4, 6].

The possibility of a subclinical course is also taken into account which can be detected by laboratory methods (cytological examination). Subclinical inflammation of the endometrium appears after the completion of the postpartum period, usually 5–6 weeks after calving[7, 8]. It is not difficult to diagnose the disease, but significant time and labor input are required.

In recent years less traumatic ways of drugs administration to agricultural animals during their treatment have been given preference.

Alternative routes of drug administration are the transmucosal (intranasal, sublingual, buccal, rectal, intrauterine) and transdermal[9].

With intrauterine administration, most part of the drug is absorbed on the walls of the uterus and enters the systemic circulation, bypassing the liver, which means that only a small portion of the substance undergoes a pre-systematic metabolism[10].

Keeping sodium lauryl sulfate in the suppository composition allows to increase the clinical effect of the proposed drug due to the fact that when the product melts it begins to foam, grows in volume and occupies in this form the entire cavity of the animal, and thus, distribute the active substance evenly over the entire inner surface of the uterus[11].

In this regard, it is obvious that the creation of a soft application-type intrauterine dosage form of trifuzole – suppositories, which can ensure the fast onset of pharmacological action, will significantly increase the bioavailability of the drug, reduce the level of adverse reactions from its use and expand the pharmacotherapeutic arsenal of domestic effective veterinary drugs.

The properties, stability, biological availability and pharmacotherapeutic efficacy of suppositories depend on the type of base, the nature of the excipients, the technology used. The development of the composition and technology of suppositories requires a scientifically-based, strictly individual selection of these factors[12].

In this case, methods of mathematical planning are of great importance, which allow to optimize research work[13].

MATERIALS AND METHODS:

Suppository bases and surfactants which are widely used in the industrial and pharmaceutical production of soft dosage forms and described in the literature, were studied as carriers for the rectal dosage form of trifuzole[14].

Suppositories were prepared by pouring method with using molds from the Franco-Crespi semi-automatic machine. The average weight of suppositories on lipophilic bases was 1.3g, and on polyethylene oxide base - 1.6g. The concentration of surfactants in all experiments was 2% of suppositories mass, the content of trifuzole was 0.1g in each suppository. The study was carried out according to the plan of two-way variance analysis with repeated observations[15].

The elution of trifuzole from suppositories was chosen as the optimization parameter at the first step in determining bioavailability. The release of API (active pharmaceutical ingredient) from suppositories was studied by the Kruvchynskiy method of equilibrium dialysis[16] at the temperature of 37±0.5 °C through a cellophane semipermeable membrane - "Kuprofan" film at a nine-position station with diffusion cells Franz Cells (manufacturer PermeGear Inc., USA).

Purified water was used as a dialysis medium if taking into account the solubility of trifuzole. The concentration of eluted trifuzole after 30 minutes was determined spectrophotometrically[17].

RESULTS AND DISCUSSION:

The experiment design matrix and the results of trifuzole concentration etermining in dialysates which eluted from rectal suppositories after 30 minutes are resented in table 1.

Table 1: Design matrix and results of trifuzole concentration (%) determining which eluted from suppository compositions (interval 30 minutes)

Factor A (base)	**Factor B (surfactant)**				**Sum**
	в1 emulsifier №1	**в2 distilled monoglycerides**	**в3 sodium lauryl sulfate (SLS)**	**в4 without surfactant**	
a1 tallow	1) 43,1 43,1 41,2 **127,4**	2) 33,5 35,2 35,1 **103,8**	3) 36,8 36,4 36,4 **109,6**	4) 32,2 30,8 30,8 **93,8**	**434,6**
a2 cacao butter	5) 29,2 29,2 29,7 **88,1**	6) 43,3 44,9 44,9 **133,1**	7) 49,5 51,2 51,2 **151,9**	8) 35,5 33,9 33,9 **103,3**	**476,4**
a3 factory fat base (FFB)	9) 46,4 44,9 44,9 **136,2**	10) 36,0 36,0 38,6 **110,6**	11) 38,6 40,2 40,2 **119,0**	12) 36,1 38,6 38,6 **113,3**	**479,1**
a4 polyethylene oxide (PEO)	13) 43,3 44,9 43,3 **131,5**	14) 35,5 35,5 37,1 **108,1**	15) 44,9 46,4 46,4 **137,7**	16) 48,1 48,1 46,4 **142,6**	**519,9**
Sum	**483,2**	**455,6**	**518,2**	**453,0**	1910,0

Table 2 presents a variance analysis of obtained results.

Source of variability	**Sum of squares SS**	**Number of degrees of freedom f**	**Average square MS**	**$F_{exp.}$**	**$F_{tab.}$**
Factor A	303,5	3	101,17	108,78	2,9
Factor B	230,74	3	76,91	82,7	2,9
AB- interaction	1161,05	9	129,01	138,72	2,23
Error	29,87	32	0,93	-	
Sum total	77727,24	47	-	-	

Designation of the studied factors:

A – suppository bases: a_1 - tallow; a_2 - cacao butter; a_3 - factory fat base (a mixture of hydrogenated fat, paraffin and cocoa butter in a ratio of 60:10:30); a_4 - a mixture of polyethylene oxides with a molecular weight of 1500 and 400 in a ratio of 9:1.

B – surfactants $в_1$ - emulsifier №1; $в_2$ - distilled monoglycerides; $в_3$ – sodium lauryl sulfate; $в_4$ - without surfactant.

The trifuzole was dissolved in a molten polyethylene oxide in manufacturing of suppositories with polyethylene oxide base. In the case of using lipophilic carriers, API was inserted into the composition as a suspension, carefully grinding the drug substance with part of the base and then adding the resulting mixture to the entire molten base.

Table 2 presents a variance analysis of obtained results.

Based on the data presented, factor A (type of base) and factor B (type of surfactant) statistically significantly affect the elution of trifuzole from suppositories ($F_{exp.} > F_{tab.}$). Moreover, the influence of the base carrier type is more significant than the type of surfactant. The interaction between these pharmaceutical factors is also statistically significant.

Verification of differences in the average results of significant factors using the multiple rank test of Duncan[15] allowed us to construct the following series of preferences:

By factor A (type of carrier base)

a_4 PEO base > a_3 FFB > a_2 cacao butter > a_1 tallow

By factor B (type of surfactant)

$в_3$ SLS > emulsifier №1 > $в_2$ distilled monoglycerides > $в_4$ without surfactant

Thus, the most rapid elution of trifuzole from rectal suppositories provides a polyethylene oxide base in a composition with sodium lauryl sulfate.

CONCLUSIONS:

- It has been established that the type of carrier base and the type of surfactant have a significant effect on the trifuzole elution from rectal suppositories.
- It was revealed that the type of the carrier base exerts the greatest influence on the elution of trifuzole from rectal suppositories.
- A variance analysis of the research results showed that the optimal trifuzole elution from rectal suppositories is provided by the composition of the polyethylene oxide base and sodium lauryl sulfate.

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