СОЦІАЛЬНА МЕДИЦИНА І ФАРМАЦІЯ: ІСТОРІЯ, СУЧАСНІСТЬ ТА ПЕРСПЕКТИВИ РОЗВИТКУ

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The substantiation of the optimal pH range of the preventive spray for veterinary

Aim. To determine the optimal pH range of the original combined veterinary drug in the dosage form of the spray in order to provide the stability of the solution during the shelf life.

Materials and methods. The study object was the samples of the spray with the content of silver and copper citrate, dexpanthenol, and excipients. The quantitative content of silver ions was determined by the thiocyanometric method. The quantitative content of copper ions was determined according to the method of the State Pharmacopoeia of Ukraine 2.0 (SPhU) "2.2.25 Absorption spectrophotometry in the ultraviolet and visible areas". The quantitative determination of dexpanthenol was carried out by liquid chromatography. The potentiometric determination of pH was carried out using the method of the SPhU.

Results. As the result of the studies conducted it has been found that the sample with the pH of 5.32 produces a blue precipitate and an opalescence of a grayish tint. Over time (24 h) opalescence does not disappear, and the precipitate acquires a gray tint. This fact indicates destruction of copper citrate due to the increase in pH without addition of the excessive citric acid; it leads to formation of copper oxide hydrate. It can also be assumed that the stability of silver citrate in the solution is impaired, and metallic silver particles appear in the form of a precipitate. In these samples the quantitative content of silver and copper ions in the solution did not correspond to the limits set. Samples with the pH from 1.80 to 5.05 corresponded to the limits set for the content of silver ions, copper ions and dexpanthenol, and there were no changes in the appearance of the solution after pH correction.

Conclusions. According to the results obtained the optimal pH range (2.0-5.0) for the solution with the antimicrobial activity under the conventional name "Argocide-copper" – a drug based on silver citrate, copper citrate and dexpanthenol has been determined. This pH level makes it possible to obtain a stable drug. The studies conducted will be used when developing the spray with the antiseptic action for application in veterinary medicine and introducing it into production.

Key words: antiseptic spray; veterinary drug; silver citrate; copper citrate; pH; stability.

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Обґрунтування оптимальних меж pH профілактичного спрею для ветеринарії

Мета: визначення оптимального інтервалу pH оригінального комбінованого ветеринарного препарату в лікарській формі спрею з метою забезпечення стабільності розчину протягом терміну зберігання.

Матеріали та методи. Об'єктом досліджень були зразки спрею із вмістом срібла та міді цитрату, декспантенолу та композиції допоміжних речовин. Кількісний вміст іонів срібла визначали тіоціанометрично; кількісний вміст іонів міді – відповідно до методики «Абсорбційна спектрофотометрія в ультрафіолетовій і видимій ділянках»; кількісне визначення декспантенолу проводили методом рідинної хроматографії; потенціометричне визначення pH – за методикою Державної фармакопеї України.

Результати дослідження. У результаті проведених досліджень установлено, що в зразку з pH 5,32 спостерігається утворення осаду синього кольору й опалесценція сіруватого відтінку. З плином часу (24 години) опалесценція не зникає, а осад набуває сірого відтінку, що свідчить про деструкцію цитрату міді через підвищення pH без додавання надлишку кислоти лимонної, що призводить до утворення гідрату окису міді, а також про порушення стабільності цитрату срібла в розчині і появу

частинок металевого срібла. У цих зразках кількісний вміст іонів срібла і міді в розчині не відповідає встановленим межам. Зразки з pH від 1,80 до 5,05 відповідали встановленим межам за вмістом іонів срібла, іонів міді та декспантенолу. Також не спостерігалися зміни зовнішнього вигляду розчину після корекції pH.

Висновки. На підставі отриманих результатів було встановлено оптимальний інтервал pH (2,0-5,0) для розчину антимікробної дії під умовною назвою «Аргоцид – мідь» – препарату на основі цитратів срібла, цитрату міді і декспантенолу. Такий рівень pH дозволяє одержати стабільний препарат. Проведені дослідження будуть використані для розробки й упровадження у виробництво спрею антисептичної дії для застосування у ветеринарії.

Ключові слова: спрей антисептичний; ветеринарний препарат; срібла цитрат; міді цитрат; pH; стабільність.

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Обоснование оптимальных границ pH профилактического спрея для ветеринарии

Цель: определение оптимального интервала pH оригинального комбинированного ветеринарного препарата в лекарственной форме спрея с целью обеспечения стабильности раствора в течение срока хранения.

Материалы и методы. Объектом исследований были образцы спрея с серебра и меди цитратами, декспантенолом и композицией вспомогательных веществ. Количественное содержание ионов серебра определяли тиоцианометрично; количественное содержание ионов меди – по методике «Абсорбционная спектрофотометрия в ультрафиолетовой и видимой областях»; количественное определение декспантенола проводили методом жидкостной хроматографии; потенциометрическое определение pH – по методике ГФУ.

Результаты исследования. В результате проведенных исследований установлено, что в образце с pH 5,32 наблюдается образование осадка синего цвета и опалесценция сероватого оттенка. С течением времени (24 ч) опалесценция не исчезает, а осадок приобретает серый оттенок. Этот факт свидетельствует о деструкции цитрата меди из-за повышения pH без добавления избытка кислоты лимонной, что приводит к образованию гидрата окиси меди. Также можно предполагать нарушение стабильности цитрата серебра в растворе и появление частиц металлического серебра в виде осадка. В этих образцах количественное содержание ионов серебра и меди в растворе не соответствует установленным пределам. Образцы с pH от 1,80 до 5,05 соответствовали установленным пределам по содержанию ионов серебра, ионов меди и декспантенола, а также не было изменений внешнего вида раствора после коррекции pH.

Выводы. На основании полученных результатов был установлен оптимальный интервал pH (2,0-5,0) для раствора антимикробного действия под условным названием «Аргоцид – медь» – препарата на основе цитратов серебра, цитрата меди и декспантенола. Такой уровень pH позволяет получить стабильный препарат. Проведенные исследования будут использованы для разработки и внедрения в производство спрея антисептического действия для применения в ветеринарии.

Ключевые слова: спрей антисептический; ветеринарный препарат; серебра цитрат; меди цитрат; pH; стабильность.

Statement of the problem. The problem of search for measures and methods for preventing infectious diseases of the cattle mammary gland, mastitis in particular, is of great relevance. As a result of this pathology, usually there is partial or complete atrophy of one or several parts of the udder, decrease in productivity, impossibility of machine milking of cows. Therefore, there is a premature culling of cows, reduced degree of the genetic potential of the herd, as well as the economic efficiency of dairy cattle breeding in the household decreases [1, 2].

Recently, the methods of pharmacological prophylaxis of mastitis in cows have become widespread. Some authors propose the introduction of antibiotics for nonmilking cows with the prophylactic purpose, but this method of prevention has significant disadvantages. The main disadvantage is that antibiotics most actively act in the acute phase of inflammation when an intense growth of microorganisms is observed. The use of antibiotics in a nonmilking period can not provide destruction of the pathogenic microflora, and this contributes to the appearance of a greater number of antibiotic-resistant organisms [3-5].

One of the causes of mastitis in cows is the lack of the necessary sanitary and hygienic treatment of teats after milking. Since the teat canal remains open from 30 min to 1-2 hours after milking, it leads to infecting the mammary gland with the microflora causing its inflammation. The most common methods of prophylaxis of subclinical mastitis are the treatment of cow udders with suitable disinfectants. Disinfection may reduce the appearance of new cases of mastitis [6].

This work is a part of the research on development of veterinary antimicrobial agents for the treatment and prevention of cattle mastitis (within the framework of the research work of the Department of Management and Economics of Pharmacy with Technology of Drugs of the I. Ya. Horbachevskii Ternopil State Medical University on the topic "Marketing, Pharmacoeconomic and Technological Research on Development of Medicinal Products" (the state registration No. 0115U001530).

Analysis of recent research and publications. Depending on the groups of active substances veterinary antiseptic agents that are available at the market have different antimicrobial properties and consumer characteristics. Physicochemical properties of active pharmaceutical ingredients, as a rule, determine the pH level of these agents; it, in turn, affects both antimicrobial and dermatological properties of drugs. Drugs containing chlorhexidine affect the components of the microorganism cell wall. However, chlorhexidine is inactive against spores and viruses, and has a weak antifungal activity [7]. Compared with iodine-containing disinfectants it acts more slowly. Bacteria are capable of producing resistance to it. The pH of such products is neutral, but chlorhexidine alone irritates the skin, therefore, most of the chlorhexidine-based disinfectants contain skin-softening agents (e.g. glycerol, allantoin). For example, "Ankar Before" product (Ankar-Agro, Ukraine) contains allantoin. Its pH ranges 5.0-7.0.

The second most popular disinfectant is iodine. It has a wide range of the antimicrobial action, does not cause the pathogenic microflora habituation, and has anti-inflammatory properties. However, iodine solutions have a negative effect on the skin since their frequent application causes dryness and peeling of the skin. It is also difficult to combine iodine with emollients since it is very reactive. Iodine is the substance, which is insoluble and unstable; thus, the iodine molecules chemically bind to the complex with carrier molecules, forming iodophoric compounds. Iodophores have the pH ranging from 2 to 4, which also promotes the irritation of the animal skin [8]. In this case, irritation is the result of the effect of the carrier, its molecules are surfactants, some of them effectively remove the natural fats from the surface of the skin, and the skin becomes dry and more prone to irritation and formation of microcracks. Glycerol, lanolin, allantoin, and other excipients for skin softening are added to these products. The following agents with the "barrier effect" forming a protective film on the udder and containing iodine are known: "LuxDip 25" (GeA Farm Technologies, Germany) with the pH level of 3.0, "UdderStar" (BouMatic, USA) with the pH level of 3.5 – 4.5.

There are also chlorine-based drugs. Chlorine dioxide has high disinfectant properties. Its molecules are introduced into the bacterial cell wall, react with organic substances on the surface of the cell membrane and within the microorganism, interfere with metabolic processes. Chlorine dioxide, unlike oxidative disinfectants, is capable of destroying microorganisms in an inactive form. It is also effective against viruses. Among the significant drawbacks is its negative impact on the cattle udder skin. Solutions of chlorine dioxide have a pH from 4 to 10 [9].

Another group of veterinary drugs contains organic acids, such as peroxyacetic acid. These products act on the cell wall of a microorganism, causing its destruction. Similar to chlorhexidine the prolonged use of such agents leads to the appearance of resistant strains of bacteria. Organic acids shift the pH to the acidic values, and hence, in order to prevent the negative effects on the skin emollients are also added to such agents [10].

The agents for udder processing containing lactic acid are known. It removes general and local inflammation of the udder, eliminates redness of the skin, stimulates the cell renewal, and triggers the synthesis of collagen [9]. Lactic acid does not overdry the udder skin, restores its protective function, increases moisture and helps to withstand the harmful effects of the environment. However, it is a weak antiseptic and can not always effectively protect the udder from aggressive pathogenic microorganisms. For example, "Ankar Before" product (Ankara-Agro LLC, Ukraine) contains glycerol. Its pH ranges 3.5-5.0.

Combined preparations containing several antiseptics are also available at the market. For example, Grün Ferma (BelAseptica-Dez, Belarus) contains chlorhexidine and lactic acid, glycerol, non-ionic surfactants, gel former, dye, pH regulator, and water. The pH is 4.0-7.5.

Identification of aspects of the problem unsolved previously. The market analysis of the veterinary drugs for the treatment of the milking cattle udder shows the presence of agents with significant disadvantages in long-term use. As a result of previous studies the antimicrobial activity of silver and copper citrate against the clinical strains of pathogenic microorganisms was identified [11]. The experimental research on development of an economically advantageous, pharmacologically effective safe formulation of an antiseptic solution in the form of the spray under the conventional name "Argocide-copper" is in progress [12].

Objective statement of the article. The aim of this work is to determine the optimal pH range of the original combined veterinary drug based on copper and silver citrate and dexpanthenol in the dosage form of the spray for treating the cattle udder of lactating animals and for providing the stability of the solution during the shelf life.

Presentation of the main material of the research. The study object was the samples of the spray with the content of silver and copper citrate, dexpanthenol, and excipients. The following active substances were used: silver citrate (manufacturer – "Nanomaterials and nanotechnologies", LLC, Kyiv); D-Panthenol USP (manufacturer – BASF, Germany). The quantitative content of silver ions was determined by the thiocyanometric method. The quantitative content of copper ions was determined according to the method of the State Pharmacopoeia of Ukraine 2.0 (SPhU) "2.2.25 Absorption spectrophotometry in the ultraviolet and visible areas". The quantitative determination of dexpanthenol was carried out by liquid chromatography according to the method of the SPhU 2.0 "2.2.29. Liquid chromatography". The potentiometric determination of pH of the experimental samples was carried out using the method of the SPhU 2.0, p. 2.2.3, pp. 51-53. The statistical processing of the results of the experimental data was performed in accordance with the requirements of the monograph of the SPhU 2.0 "5.3.N.1. Statistical analysis of the results of a chemical experiment" [13]. Six samples of the veterinary drug "Argocid-copper" of various formulations were prepared.

Analysis of the literature data on the pH level of antiseptic agents for the treatment of the cattle udder suggests that the range of pH is quite wide – from 1 to 7.5 and more. In this case, the antimicrobial effect, local irritating effect and provoking of an increase in the dryness of the animal skin depend not only on the pH level, but also on the bactericidal capacity of the active substances themselves and their negative effect on the epidermis of the cow udder. It is also taken into account that the skin of the udder is characterized by a certain pH level. It is created by the secrets of the skin. The lower is the pH value, the higher is the bactericidal effect since the hydrogen ions begin to more actively act on microorganisms by inhibiting the activity of enzymes. Bactericidal properties are expressed in unsaturated fatty acids, lactic acid, enzymes, lysozyme, and other biologically active substances of the skin [21]. The acidic reaction on the surface of the skin is an important protective mechanism that protects the skin from the penetration of microorganisms, regulates the process of hydration and maintains the natural state of the epidermis [18].

Therefore, considering the physicochemical properties of solutions of copper and silver citrate that exhibit the maximum biocidal effect and are stable at the acidic pH (2.0-5.0), as well as dexpanthenol, which can also stably exist in the specified pH range and preserve the pharmacological effect, the probable optimal pH limits for the combined drug based on the active pharmaceutical ingredients in the range of 2.0 to 5.0 have been identified.

To confirm the optimal pH range of solutions containing copper and silver citrate, dexpanthenol the samples with the critical pH values that should be lower and higher than the limits set by us were developed. These pH values were achieved by adding different amounts of 1M sodium hydroxide solution, while acidic citric acid was used as an acid agent since addition of hydrochloric acid could cause the insoluble precipitation of silver chloride. The results of the studies are presented in Table.

As a result of the studies conducted, it was found that a blue precipitate formed in the solution of sample 6 with the pH of 5.32, and opalescence of a grayish color appeared, it did not disappear over time (24 hours), and the precipitate also acquired a gray tint. Such changes are likely the result of destruction of copper

Table

DEPENDENCE OF PHYSICOCHEMICAL PARAMETERS OF ACTIVE PHARMACEUTICAL INGREDIENTS OF THE VETERINARY SPRAY ON THE PH LEVEL

Sample No.	pH	Description	Quantitative content*, %		
			Silver ions	Copper ions	Dexpanthenol
1	18.0±0.01	A transparent, greenish-blue liquid	0.0122±0.0001	0.0122±0.0001	5.01±0.01
2	2.02±0.02	A transparent, greenish-blue liquid	0.0126±0.0002	0.0128±0.0002	5.10±0.01
3	2.41±0.03	A transparent, greenish-blue liquid	0.0124±0.0001	0.0122±0.0001	5.07±0.01
4	2.73±0.02	A transparent, greenish-blue liquid	0.0125±0.0002	0.0119±0.0003	4.94±0.01
5	5.05±0.01	A transparent, greenish-blue liquid	0.0121±0.0001	0.0121±0.0004	5.00±0.01
6	5.31±0.01	A nontransparent, opalescent greenish-blue liquid with a blue precipitate	0.0110±0.0001	0.0097±0.0001	5.02±0.01

Note. * The quantitative content of silver and copper ions should be in the range of not less than 0.0113 %. The quantitative of dexpanthenol should be in the range from 4.75 to 5.25 %. ** P ± 95%, n = 5.

citrate due to the increase in pH without addition of the excessive citric acid; it leads to formation of copper oxide hydrate. It can also be assumed that the stability of silver citrate in the solution is impaired, and metallic silver particles appear in the form of a precipitate. In these samples the quantitative content of silver and copper ions in the solution did not correspond to the limits set. Samples No. 1-5 with the pH from 1.80 to 5.05 corresponded to the limits set for the content of silver ions, copper ions and dexpanthenol, and there were no changes in the appearance of the solution after pH correction.

Conclusions and prospects for further research. According to the results obtained the optimal pH range (2.0-5.0) for the solution with the antimicrobial activity under the conventional name "Argocide-copper" – a drug based on silver citrate, copper citrate and dexpanthenol has been determined. This pH level makes it possible to obtain a stable drug. The studies conducted will be used for development of the spray with the antiseptic action for the treatment of the cattle udder and its introduction into production at "Brovafarma" LLC (Ukraine, Brovary).

Conflict of interests: authors have no conflict of interests to declare.

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