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THE STABILITY OF STROPHANTHIDIN ACETATE IN SOLUTION

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Strophanthidin acetate is obtained by acetylating strophanthidin [1, 2]. In its chemical structure, strophanthidin acetate differs from other cardiac glycosides by the presence of an acetyl group in addition to a carbohydrate residue, which changes its capacity for hydrolysis. Some drugs, such as acetyldigoxin [3] are readily hydrolyzed in alkaline and even neutral solutions. Thus, one of the main factors determining the stability of glycosides in solution is the optimum pH value [4].

We have developed a stable medicinal form of strophanthidin acetate in the shape of an injection solution. To determine the optimum conditions for the preparation of stable solutions we studied the stability of strophanthidin acetate in buffer solutions (citrate–phosphate and acetic acid–acetate), which were added to an ethanolic glycerol solution of strophanthidin acetate in a ratio of 10:15:75.

The behavior of strophanthidin acetate in solutions with different pH values was studied after their sterilization and storage under elevated temperature (60°C) and room-temperature (15-25°C) conditions.

In solutions with pH 7.0 and above, strophanthidin acetate is hydrolyzed immediately after their sterilization, and in addition to the spot of strophanthidin acetate (R_f 0.62) the spot of strophanthidin (R_f 0.21) appears on a chromatogram.

In a solution with a pH below 4.0, hydrolysis begins after 11 days (at 60°C), and in a solution with pH 4.0-5.0 after 44 days (at 60°C). We also studied the degree of decomposition of the glycoside as a function of the pH of the solution after sterilization and storage for 10 months at room temperature.

As the figures in Table 1 show, a prepared ampul solution of strophanthidin acetate without stabilizers decomposes more rapidly, mainly with the formation of the aglycone strophanthidin.

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TABLE 1. Results of Analyses of Solutions of Strophanthidin Acetate Prepared in Buffer Solutions with Different pH Values, Immediately after Sterilization and after Storage for 44 Days at 60°C

Composition	Immediately after preparation		After storage for 33 days at 60°C		After storage for 44 days at 60°C			Remarks
	pH	Amount of strophanthidin acetate, %	pH	amount of strophanthidin acetate, %	pH	amount of strophanthidin acetate, %	amount of aglycone formed, %	
Strophanthidin acetate, 0.05 g Ethanol 10 ml Glycerol 15 ml Citrate–phosphate buffer with pH 4.0 to 100 ml	4,1	100	4,3	96,5	4,4	90,2	9,8	
Strophanthidin acetate, 0.05 g Ethanol 10 ml Glycerol 15 ml Citrate–phosphate buffer with pH 4.4 to 100 ml	4,5	100	4,6	97,0	4,7	93,3	6,7	
Strophanthidin acetate, 0.05 g Ethanol 10 ml Glycerol 15 ml Citrate–phosphate buffer with pH 4.8 to 100 ml	4,9	100	5,0	95,	5,0	90,0	10,0	
Strophanthidin acetate 0.05 g Ethanol 10 ml Glycerol Water for injection 100 ml	7,0	90,6	6,0	70,5	5,5	65	35	After storage for 10 months at 20°C the amount of strophanthidin acetate had fallen to 75%

It can be seen from Fig. 1 that the optimum pH value for solutions of strophanthidin acetate is 4.0-5.0; at lower and higher pH values the amount of strophanthidin acetate decreases through the formation of strophanthidin. After storage for 44 days at 60°C, the amount of strophanthidin acetate in solutions prepared in citrate–phosphate buffers with pH 4.0-5.0 ranged between 90.0 and 93.6%.

Similar results were obtained with the use of acetic-acid–acetate buffers having pH 4.0-5.0: on storage for 44 days at 60°C the amount of strophanthidin acetate did not change.

EXPERIMENTAL

The citrate–phosphate and acetic-acid–acetate buffer solutions with pH 4.0-5.0 were prepared by the standard method [5]. Instead of distilled water, apyrogenic water was used

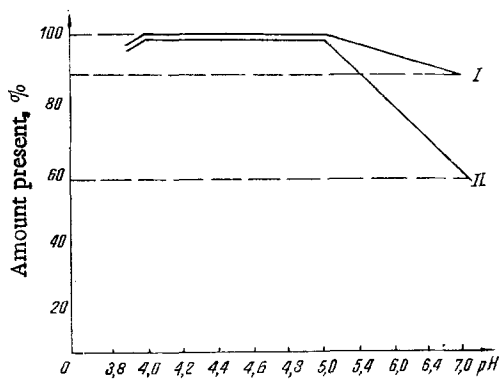

Fig. 1. Dependence of the stability of strophanthidin acetate on the pH of the medium: I) amount of strophanthidin acetate in ampul solutions after sterilization; II) after the storage of the ampuled solutions for 44 days at 60°C.

to dissolve the ingredients [6]. A 0.05% solution of strophanthidin acetate was prepared in the following way. To a mixture of 25 ml of 95% ethanol and 37.5 ml of glycerol was added 0.125 g of strophanthidin acetate and the resulting mixture was stirred at 80°C (in a water bath). After dissolution was complete, the volume was made up to 220 ml with buffer solution having the appropriate pH value (4.0-5.0). After careful stirring and filtration through a mushroom-type filter the solution was distributed into 1-ml neutral-glass ampuls, which were sealed and were sterilized at 100°C for 30 min.

The stability of the strophanthidin acetate was studied under conditions of "accelerated aging" at an elevated temperature (60°C).

SUMMARY

1. A method has been developed for obtaining stable 0.05% injection solutions of the cardiac glycoside strophanthidin acetate in 1-ml ampuls. It has been established that the optimum pH is 4.0-5.0.

2. The use of citrate–phosphate or acetic-acid–acetate buffers has been proposed for stabilizing strophanthidin acetate.

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ALKALOIDS OF *Haplophyllum latifolium*

THE STRUCTURE AND SYNTHESIS OF HAPLAMIDE AND HAPLAMIDINE

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The plant *Haplophyllum latifolium* Kar. et Kir. (family Rutaceae) is found in Uzbekistan [1], Kirghizia [2], and Kazakhstan [3]. It has been shown previously that it contains alkaloids [4]. We have investigated the alkaloids of the epigeal part of this plant collected by R. S. Sakhibiddinov in the Fergana valley of KirgSSR (basin of the R. Kugart, village of Mikhailovka) among the wheat crops in the flowering period on May 14, 1974. The raw material was extracted with methanol. The extract obtained was separated into basic, acidic, and neutral fractions. A study of the basic and acidic fractions showed that they contained no alkaloids. By chromatography on alumina, the neutral fraction gave a crystalline mixture (0.05% on the weight of the dry plant) from which we have isolated alkaloids that we have called haplamide and haplamidine.

On the basis of spectral characteristics we have previously put forward the structure of N,N'-dibenzoylputrescine for haplamine (I) [5]. The correctness of formula (I) was confirmed by the synthesis of N,N'-dibenzoylputrescine, which was performed by the reaction between putrescine, obtained by the action of bromine and alkali on adipic acid diamide [6], and benzoyl chloride [7]. In its melting point, spectral characteristics, and TLC behavior

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