As an alternative dosage form and in order to decrease the application periodicity the film formation was proposed which had previously been tested on the short-life anesthetics [5].

The aim of this work was to develop a composition of a film based on chitosan containing Gramicidin S, which would provide a sustained release of the drug in the eye media

During the composition development different polyanion excipients were incorporated into the film to provide optimal mechanical properties, and the plasticizer content was determined.

Also different conditions for the active ingredient impregnation into the film were studied revealing that adding the emulsion containing Gramicidin S made the resulting film more transparent and homogeneous while adding the antibiotic suspension led to faster drying time.

The films were characterized by FT-IR, total soluble mass, water vapor permeability, swelling measurements and surface pH evaluation.

*In vitro* release studies were performed in the pH of eye media (7.4) at 37 °C. The drug concentration in buffer solution was detected using HPLC method.

The resulting film was totally biodegradable providing a certain benefit to the perspective drug formulation excluding the demand to exchange or remove the film after a certain time of application.

At the same time the release study demonstrated that the dosage regime of Gramicidin S correlates with the same parameter of the eye drops formulation.

The obtained result allows to develop a new Gramicidin S formulation for local application in eye with single administration per day.

In order to prove that the antimicrobial activity remains the same, the comparative antimicrobial test was performed according to the Russian Pharmacopeia monograph procedure against gram-positive bacteria *S. Aureus* and and funghi *C. Albicans* [6].

The stability of a ready composition had been studied for 1 year and continues.

As a result, the alternative Gramicidin S dosage form was developed. The film represent good stability, comparable antimicrobial activity and needs lower frequency of administration comparing to eye drops.

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# DETERMINATION OF VANILLIN IN SMOKING MIXTURES BY SPECTROPHOTOMETRY


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Synthetic 4-hydroxy-3-methoxybenzaldehyde (vanillin) is used as a flavoring agent in perfumery, the food industry, as a flavoring agent for sweet products and in pharmaceuticals. The smoking mixtures contained in hookahs and various electronic cigarettes are freely available and are not controlled for the content of harmful substances.

Vanillin is able to accumulate in the human body and be toxic in high concentrations (oral, rat: LD50 – lethal dose) (LD50 = 2 $g \cdot kg^{-1}$; oral, guinea pig: LD50 = 1.4 $g \cdot kg^{-1}$; intravenous, dog: LD50 = 1.32 $g \cdot kg^{-1}$; inhalation, mouse: LC = 41.7 $g \cdot kg^{-1}$) [1]. Thus, the development of a method for determining vanillin is justified.

The aim of this work was to determine vanillin in smoking mixtures by spectrophotometric method.

"Adalya – vanilla" (Turkey) and "Flavoring tpa – vanilla cream" (USA) were selected as objects of research. Sample preparation of the studied objects consisted of the preliminary dissolution of the sample in 95% ethanol. The sample 10 mg of tobacco "Adalya – vanilla" was diluted in 10 μL of 95% ethanol to the concentration of 1 g $L^{-1}$. The sample 10 μL of "Flavoring tpa – vanilla custard" was diluted in 10 μL of 95% ethanol. The resulting solution was diluted in 6 times to the concentration of 0.17 μL $cm^{-3}$ [2].

The optical density was determined using a Cary 60 spectrophotometer (Agilent, United States), in cuvette with an absorbing layer thickness of 10 mm at room temperature. 95% ethanol was chosen as the optimal solvent.

To quantify vanillin the calibration curve of the optical density on the concentration of vanillin in 95% ethanol was obtained at concentrations, g $L^{-1}$: 0.05; 0.06; 0.07; 0.08; 0.1; 0.12. In the spectra of the analyzed sample solutions absorption maxima (280.0 nm and 310.0 nm) characteristic for vanillin were observed, which conform to published data [2, 3]. The amount of vanillin in the sample was determined using calibration curves at 280 and 310 nm. Weighted least square regression was applied to improve the accuracy, especially at in low concentration level range. The results are presented in the table 1.

As a result, basic metrological characteristics were calculated. The error of the method for determining vanillin in the sample "Flavoring tpa – vanilla cream" with a known concentration of vanillin was 0.004%. It was established that the developed method can be used as a control method. According to the data obtained, we recommend a wavelength of 280 nm for the determination of vanillin in samples.

**Table 1.** Results of quantitative determination of vanillin in substances by spectrophotometry (n=5, p=0.99)

| Sample | Wavelength, nm | Regression equation | $R^2$ | Added, mg | Found, mg | Metrological characteristics |
|---|---|---|---|---|---|---|
| "Flavoring tpa – vanilla custard" | 310 | $y=7.3824 \cdot C+0.0301$ | 1 | 10.850 | 10.408 | $\bar{x}=10.410$ |
| | | | | | 10.411 | S=0.002 |
| | | | | | 10.408 | Sx=0.001 |
| | | | | | 10.407 | Δx=0.001 |
| | | | | | 10.413 | δ=0.030% |
| "Adalya – vanilla" | | | | 10.000 | 1.016 | $\bar{x}=1.016$ |
| | | | | | 1.014 | S=0.002 |
| | | | | | 1.017 | Sx=0.001 |
| | | | | | 1.019 | Δx=0.001 |
| | | | | | 1.015 | δ=0.003% |
| "Flavoring tpa – vanilla custard" | 280 | $y=8.1914 \cdot C+0.0357$ | 1 | 10.030 | 9.603 | $\bar{x}=9.606$ |
| | | | | | 9.608 | S=0.003 |
| | | | | | 9.605 | Sx=0.002 |
| | | | | | 9.611 | Δx=0.003 |
| | | | | | 9.604 | δ=0.004% |
| "Adalya – vanilla" | | | | 10.000 | 1.011 | $\bar{x}=1.012$ |
| | | | | | 1.014 | S=0.001 |
| | | | | | 1.011 | Sx=0.001 |
| | | | | | 1.012 | Δx=0.001 |
| | | | | | 1.013 | δ=0.002% |

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# PROLONGED NITROGEN FERTILIZATION TECHNOLOGY

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The degree of utilization of carbamide (Cmd) nitrogen and ammonium nitrate is only 50–60 % (because of high solubility), which leads to groundwater contamination and soil acidification. The development of technologies for prolonged nitrogen fertilizers (PNH) is one of the priority areas.

The most promising types of PNH: carbamide-formaldehyde fertilizers (CFF), capsular fertilizers, nitrogen fertilizers with nitrification inhibitors, composite NMg-fertilizers with «Sorel's cement», fertilizers with additives (bioadditive and etc.) [1].

The aim of this work is to develop a CFF technology with a controlled dissolution rate. The main way to regulate the rate of dissolution of CFF («carbamide + products of its interaction with formaldehyde – F»), is to vary the ratio «Cmd:F».

Samples of CFF were obtained with the ratio «Cmd : F = 1 : (0.2–0.6) mole», which provides the nitrogen content in within 36–42 %. Depending on the «Cmd : F» ratio (as well as the temperature, time and pH), the CFF composition may contain various compounds that differ significantly in solubility (P, g/100g $H_2O$):

- at «Cmd : F = 1 : 1 mole»:

$$NH_2–CO–NH_2 + H–CO–H \rightarrow$$
$$\rightarrow NH_2–CO–NH–CH_2OH,$$

($C_2H_6N_2O_2$ – monomethylolcarbamide – MMC, N = 31.1 %, P = 40 g/100g $H_2O$);

- at «Cmd : F = 2 : 1 mole»:

$$2(NH_2–CO–NH_2) + H–CO–H \rightarrow$$
$$\rightarrow NH_2–CO–NH–CH_2–NH–CO–NH_2 + H_2O$$

($C_3H_8N_4O_2$ – methylenedicarbamide – MDC, N = 42.4 %, P = 1,3 g/100g $H_2O$).

At the ratio «Cmd : F = 2 : 2 mole» and «Cmd : F = 3 : 2 mole», the formation of insoluble compounds is possible (respectively, $C_4H_{10}N_4O_3$ – methylol methylenedicarbamide, $C_5H_{12}N_6O_3$ – dimethylene tricarbamide) [2].

Under the assumption that the reaction proceeds with the formation of MMC, with the selected ratio «Cmd : F = 1 (0.2–0.6) mole», its theoretical content in CFF is 27–69 % (Table 1).

However, the data of X-ray phase analysis (XPA) show that CFF are not only a mixture of «Cmd + MMC» (Fig. 1).

For example, in the CFF sample (obtained at «Cmd : F = 1 : 0.4 mole»), the residual value content is only 41 % (with a theoretically possible 50 %), and instead of $C_2H_6N_2O_2$, $C_4H_8N_2O_2$ (dimethylglyoxime) and other organic compound.

The results of experiments on assessing the rate of dissolution of CFF show that, depending on the ratio «Cmd : F» for granules (d = 2,5±0.5 mm) the value $\tau_{90}$ (dissolution time by 90 %) increases significantly: at «Cmd : F = 1 : 0,1 mole» – $\tau_{90}$ = 15 min; при «Cmd : F» = 1 : 0,3 mole» – $\tau_{90}$ = 70 min (for carbamide $\tau_{90}$ = 5 min).

Moisture absorption of CFF granules in room conditions and at high humidity is much less (Table 2).

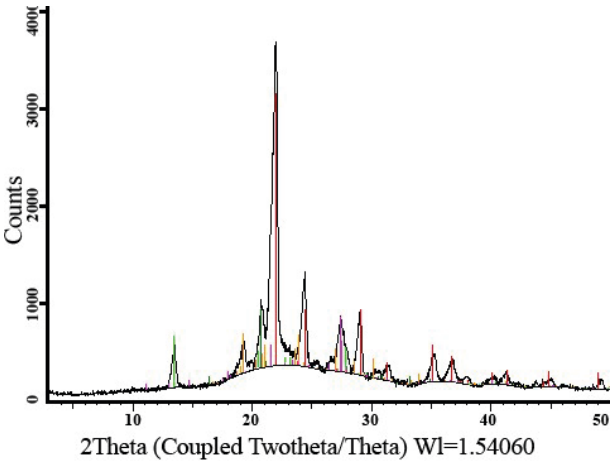


**Fig. 1.** *XPA sampe CFF «Cmd : F = 1 : 0.4 mole»)*

Composition: $CH_4N_2O$ (carbamide) – 41 %, $C_4H_8N_2O_2$ (dimethylglyoxime) – 19 %, $C_3H_7NO_2$ (alanine) – 5 %, $C_3H_3N_5O_4$ – 15 %, $C_8H_8N_2O_3$ – 20 %