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Medical implementation practice of supramolecular complex of megosin with MASGA

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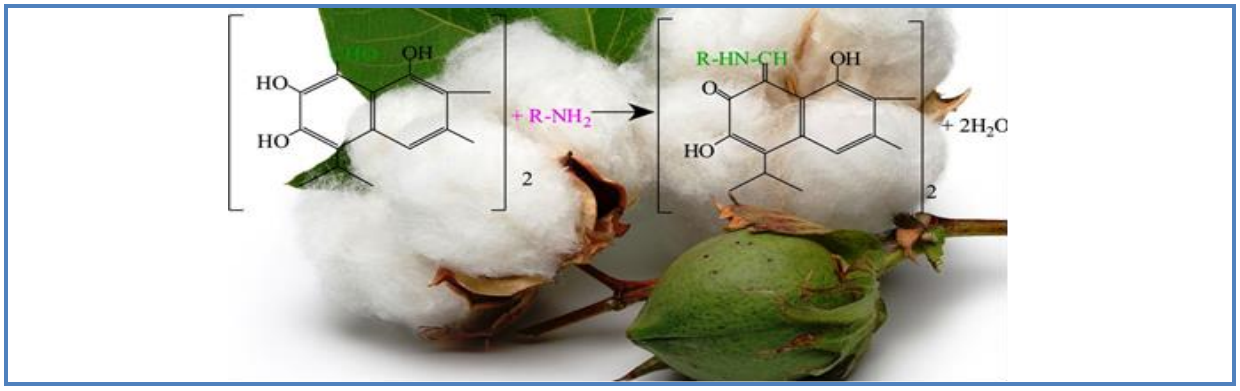
ABSTRACT

Drug creation based on synthesized azomethine derivatives of gossypol is of great interest with glycyrrhizic acid. Studies have shown that, in combination with glycyrrhizic acid, their solubility increases, these increasing the bioavailability of both the substance and its dosage form.

We studied the degree of hydrolyzed megosin with MASGA, called megaferon and dosage form on its basis in the form of a 3% ointment with a pereeterifikat containing surfactant.

Graphical Abstract



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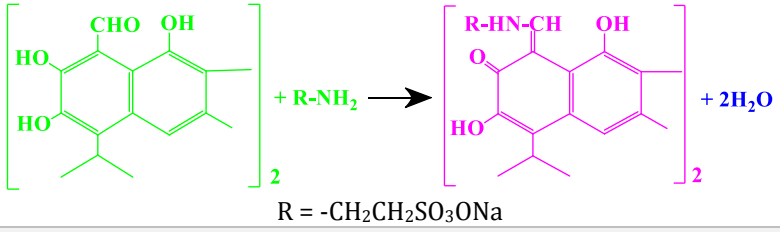
Introduction

One of the most urgent tasks of modern bioorganic chemistry is the search for innovative and rational approaches to the prevention and treatment of infectious pathologies using modern methods of chemotherapy and the creation of new effective bactericidal drugs to improve the efficacy and shorten time of treatment of infectious pathologies with antibiotic resistance. Among the synthesized azomethine derivatives of gossypol in terms of thecreation of drugs, an interesting point is the gossypol compound containing the radical – $CH_2CH_2SO_3ONa$ (megosin) for which scientists from the Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan have revealed high antiherpes activity [1].

Results and Discussion

The purpose of this work was to study the hydrolysis of both the initial azomethine derivative of gossypol and the hydrolysis of the corresponding supramolecular complex obtained on the basis of MASGA (glycyrrhizic acid monoammonium salt) in a ratio of 1: 2 and 1: 4 (called megaferon). The acceptability of a hydrophobic base of local origin in the ointment technology with a soluble form of megosin is also studied.

Synthesis of azomethine derivative gossypol was carried out according to the following scheme 1:



Scheme 1. Megosin synthesis

It is known that aqueous solutions of Schiff bases are unstable and hydrolyzed to the initial amines and aldehydes [2]. This property also occurs for azomethine derivatives of gossypol in an aqueous solution after 30 minutes. For the synthesized compound in UV spectroscopy, an intense absorption maximum is observed at 247.5 nm and a broad absorption band in the range of 320–440 nm with the main maximum at 402 nm.

In the pharmaceutical industry, the production of new dosage forms is widely used method of complexation. Criteria such as safety, hypoallergenicity and bioavailability are important when selecting a substance for the complexing agent. One of the classes of biologically active substances is glycyrrhizinic acid (GA) related to saponins [3]. This property of saponins is used to produce complex host-guest compounds [4].

Scientists in various countries have proven to significantly enhance the action of a number of pharmacons in complexes with GA [5, 6], while significantly reducing effective doses, increasing the bioavailability of drugs.

It is important to note that during the formation of supramolecular complexes of guest-host type, glycyrrhizic acid as a host molecule forms an endolipophilic cavity for the guest in a hydrophilic medium [7].

The main reason for creating drugs based on GA and its derivatives is its well-expressed

solubilizing property. Many poorly soluble or even water-insoluble drug substances (aspirin, indomethacin, megosin, gossypol, ragosin, etc.) are well soluble in water in the presence of even a small amount of GA. The reason for the solubilizing properties of this natural substance is the intermolecular interaction that occurs when GA contacts different organic substances in solution [8].

Megosin was previously obtained by A.I. Ismailov, N.I. Baram and others [9]. This drug is widely used in the treatment of herpes as a 3% megosin ointment. However, megosin, getting into the aqueous medium, is very quickly hydrolyzed to the original (the megosin substance is poorly soluble in water), so a dosage form in the form of 3% and 1% ointment was selected for it. There is evidence disclose that megosin could have a more effective action not only against a herpetic infection, but also a number of others, in particular against influenza, ARVI, hepatitis, etc. [10].

Given the hydrolysis of azomethine derivatives of gossypol in aqueous solutions, the supramolecular complex of the synthesized substance with the MASGA was obtained in different ratios (Figure 1, Figure 2).

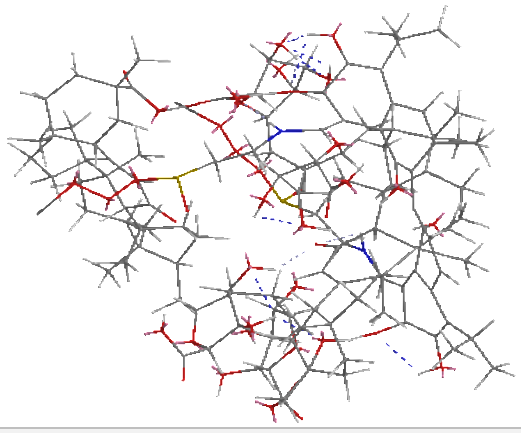


Figure 1. Supramolecular complex of megaferon with MASGA in the ratio 1: 2

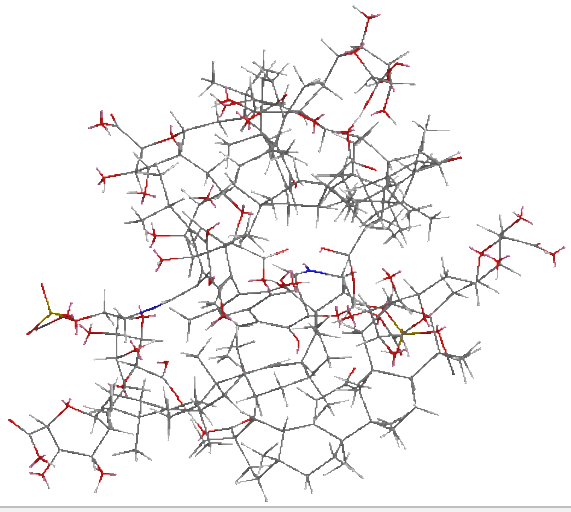


Figure 2. Supramolecular complex of megosin with MASGA in the ratio 1: 4

An interesting fact is that in quantum chemical calculations (the calculation was performed using MM2) in the case of the supramolecular complex of megosin with MASGA in the ratio 1: 2, if the megosin molecule is above the molecule MASGA then, in the case of the 1: 4 ratio, the megosin molecule is in cavity MASGA.

The main reason for creating drugs based on glycyrrhizic acid and its derivatives is its well-expressed solubilizing property. Many poorly soluble or even water-insoluble drug substances (aspirin, indomethacin, etc.) are highly soluble in water in the presence of even a small amount of glycyrrhizic acid. The reason for the solubilizing property of this natural substance is, naturally, the intermolecular interaction that occurs when glycyrrhizic acid comes into contact with various organic substances in solution [11].

A comparative examination of the UV spectra of aqueous solutions of megosin and megaferon (supramolecular complex of megosin with MASGA) shows that as the solutions are stored, there is first a slight decrease, and then with time an increase in optical density while maintaining the overall pattern of the spectrum.

To study the degree of hydrolysis, the UV spectra of the obtained supramolecular complexes in the SF-26 spectrophotometer were taken at 10 minutes, 24 hours and 48 hours in buffer solutions with pH = 2.62, 7.31 and 10.96. (Figure 3,4,5)

In all spectra, an intense absorption maximum is observed in the 242-252 nm region. As the solutions are stored, the picture of the spectra changes: in the case of megaferon, the optical density increases at 275 nm (from 0.14 to 0.41), but the general appearance of the spectrum does not change.

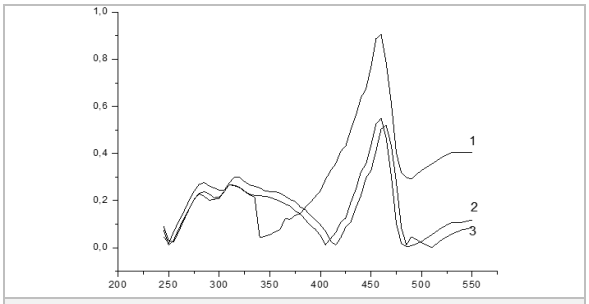


Figure 3. Megaferon pH = 2.62: 1 after 10 minutes, 2 after 24 hours, 3 after 48 hours

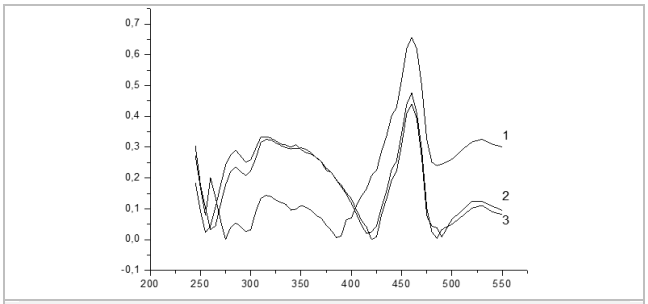


Figure 4. Megaferon pH = 7.31: 1 after 10 minutes, 2 after 24 hours, 3 after 48 hours.

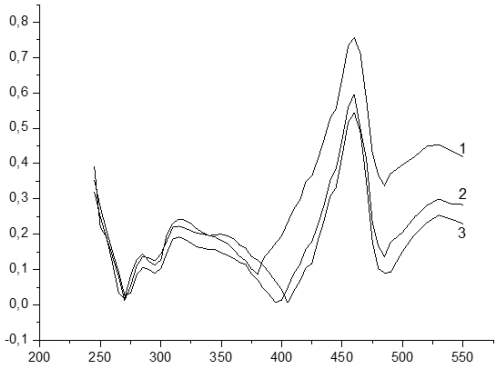


Figure 5. Megaferon pH = 10.96: 1 after 10 minutes, 2 after 24 hours, 3 after 48 hours.

Thus, aqueous solutions of the supramolecular complex compounds of azomethine gossypol derivatives (in particular megosin) partially undergo hydrolysis within 48 hours. Moreover, this property of supramolecular complex compounds is the impetus for the creation of drugs. Preparation of supramolecular complex compounds of drugs also gives these drugs a water-soluble property, and this increases the bioavailability of drugs. It is also known that the solubility of the drug substance may vary due to the presence of the used excipients and technology of the dosage form. In the directory MD. Mashkovsky registered 3% grease megosin. Based on the substance of a similar pharmacological action of megaferon, we developed the composition and technology of 3% ointment [11]. As an auxiliary substance, trans-esterification of cotton-seed oil and beef fat was used in the ratio of 48:52 with addition of up to 3% T-2 emulsifier. The properties of this composition of auxiliary substances were previously reported [12-14].

Prepared according to the rules of pharmaceutical technology, ointment megaferon for quality indicators was studied in comparison with a standard sample prepared on a pharmacopoeial basis. The results of the study are shown in Table 1.

Table 1. Comparative results of megaferon ointment quality

Base view	Appearance	Average value pH	Centrifuging 1500 turn/min, 5 min	Thermostating at 40^{0}C
Hydrophobic base transesterification with T-2 emulsifier	Ointment homogeneous creamy consistency of light brown color with a specific odor	6.5	steady	The ointment is stable, the system exfoliation was not observed.
Standard base vaseline-lanolin (9:1)	Yellow ointment homogeneous, methane-like consistency	6.3	steady	No delamination was observed

From the point of view of pharmaceutical technology, the proposed composition meets the requirements of the pharmaceutical industry. The study of the authenticity and quantitative content of megaferon in the composition of ointments showed a positive result, i.e. the reaction to gossypol and glycyrrhizinic acid was identified, the determination of the quantitative content of the drug by means of UV-spectrophotometry at the above wavelength determined the presence of the drug.

Present day prerequisites for dosage forms lead to the study of the drug, taking into account biopharmaceutical factors that provide an objective assessment of therapeutic activity. Research in this direction is carried out by comparing the registered 3% Megosin ointment with the proposed composition.

Conclusions

The hydrolysis of both the initial azomethine derivative of gossypol and the corresponding supramolecular complex obtained on the basis of MASGA (mono ammonium salt of glycyrrhizic acid) in a ratio of 1: 2 and 1: 4 (we called megaferon) was studied. At the same time, it was revealed that aqueous solutions of supramolecular complex compounds partially undergo hydrolysis within 48 hours. In addition, this property of supramolecular complex compounds is the

impetus for the creation of drugs. Preparation of supramolecular complex compounds of drugs also gives these drugs a water-soluble property, and this increases the bioavailability of drugs.

The possibility of preparing an ointment using a hydrophobic base of local origin has also been studied. Biopharmaceutical studies are conducted by the method of Kruvchinsky, the results of which will be reported.

Experimental

Quantum-chemical calculation of the reactivity of ligands was performed by semi-empirical quantum-chemical calculation methods presented in the HyperChem version 7 and MOPAC software package.

The absorption spectra of the synthesized reagents, when studying their complexation in solutions, were measured on a UV-3600 Plus Shimadzu spectrophotometer (Japan) in the region of 350-700 nm.

Synthesis of [1,1',6,6'-tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-7,7'-dioxo-2,2'-binaphthyl] -8,8'-dimeminimino- b, b"- sodium ethyl sulfate (megosin). 0.518 g (0.0015 mol) of gossypol was dissolved in 20 mL of ethanol, 0.5 g (0.0034 mol) b-aminoethyl sulphate of sodium in 20 mL of alcohol solution was added in portions to a clear solution, the mixture was heated in a water bath at 60-700C at stirring continuously for 5 hours. The reaction mixture was left for a day. The precipitate was filtered off, washed with ethanol and dried. $T_{melting}$ => 350°C, R_f = 0.35, yield 1.05 g (90.2%).

Molecular complexes of megosin with monoammonium salt of GA in the following ratios 1:1, 1:2, 1:4. 1.0.84 g (0.001 mol) MASGA was dissolved in 25 mL of a mixture of water: ethyl alcohol (1:1 by volume) and 0.776 g (0.001 mol) of megosin was added. The reaction mixture was vigorously stirred at t = 30–40°C for 18–24 h. After distilling off ethyl alcohol, the residue was lyophilized. Received supramolecular complex MASGA with megosin in the ratio of 1:1, the output of which was 97%.

The synthesis of the remaining molecular complexes was carried out similarly

2. MASGA: Megosin (2: 1); m (MASGA) = 1.68 g (0.002 mol)
m (Megosin) = 0.776 g (0.001 mol) Yield 94%

3. MASGA: Megosin (4: 1); m (MASGA) = 3.36 g (0.004 mol)
m (Megosin) = 0.776 g (0.001 mol) Yield 96%

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