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MOLECULAR COMPLEXES OF AMMONIUM GLYCYRRHIZATE WITH CERTAIN MEDICINAL AGENTS AND THEIR INTERFERON-INDUCING ACTIVITY

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The preparation of molecular complexes of ammonium glycyrrhizate with certain sulfamide preparations, gossypol, analgin, and salsolidine is described. Results from a study of the interferon-inducing activity of the complexes are presented.

Key words: glycyrrhizic acid, glycyrram, interferon, sulfanilamides, gossypol.

Decreasing the toxicity of medicinal agents and prolonging their action are important problems. Therefore, monomolecular encapsulation of medicinal agents has received much attention. Monomolecular encapsulation is effected through physicochemical interaction of the preparation and the complex-forming component. This component could be a triterpene glycoside-β-glycyrrhizic acid (GA), which is the main active principle of smooth (*G. glabra* L.) and ural (*G. uralensis* F.) licorice extract [1]. The presence in GA of hydrophilic glucuronic and hydrophobic triterpene parts gives it unique physicochemical properties. Thus, depending on the pH of the medium, intra- and intermolecular H-bonds in the micellar state can shape GA into a cyclic form with a rather voluminous cavity, where a medicinal agent could be incorporated as a "guest" molecule [2].

Therefore, molecular complexes with certain medicinal preparations such as analgin, voltaren, acetylsalicylic acid, et al., can be based on GA [2-5]. Not only GA but also certain of its derivatives, in particular, the ammonium salt of GA, form molecular complexes with several medicinal agents. This increases the solubility of those that are insoluble in water [6].

We used the ammonium salt of GA as a complex-forming component. It is easily isolated pure and is used as a medicinal preparation under the name glycyrram (GC) to cure inflammation of the upper respiratory tract, allergic dermatitis, and eczema [7].

We prepared molecular complexes with several medicinal and biologically active substances such as gossypol, salsolidine, phthalylsulfathiazole, urosulfan, sulfalene, and sulfadimesine in order to study the formation of molecular complexes with the ammonium salt of GA and the interferon-inducing activity of them.

The complexes were prepared by mixing aqueous—alcoholic or aqueous—acetone solutions of GC and the preparations in an equimolar ratio with subsequent distillation of solvent under vacuum. These compounds were characterized by IR and UV spectra (Table 1).

Thus, the IR spectrum of GC contains absorption bands from OH stretching at 3400 cm^{-1} and C=O carboxyls at 1700^{-1}. The IR spectrum of the complex with gossypol [2,2[1]-di-(1,6,7-trihydroxy-3-methyl-5-isopropyl-8-naphthaldehyde] exhibits an absorption band at 1670 cm^{-1}, i.e., a shift of 30 cm^{-1} compared with the spectrum of GC. The IR spectrum of gossypol itself has absorption bands at 3550 (OH) and 1610 (C=O) in addition to a weak band at 1700 cm^{-1} [8]. The IR spectrum of GC with salsolidine typically has the band shifted to 3350 cm^{-1}, evidently because of H-bonds between the COOH- and NH-groups. Therefore, it can be supposed that the complex contains an interaction between OH-, COOH-, and NH-groups. The IR spectrum of the complex with *p*-aminobenzenesulfonylurea (urosulfan) has the OH absorption shifted by 50 cm^{-1}; COOH, by 30-40 cm^{-1}. These data indicate that the hydroxyl and carboxyl groups of GC interact with the amino groups of the benzene ring and the urea, which is probably bound to the GC carboxyl through a H-bond.

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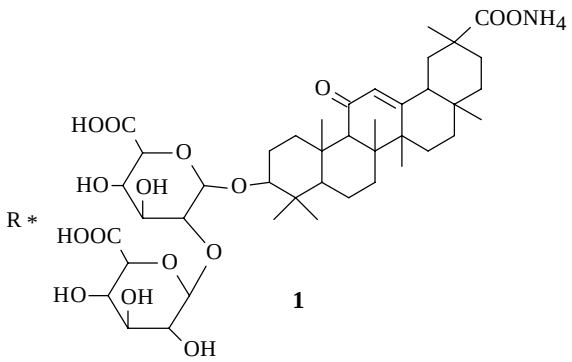
TABLE 1. Certain Physicochemical Properties of Molecular Complexes **1**

R	Yield, %	mp, °C	UV spectrum, λ_{max} (log ε)	IR spectrum, cm^{-1}, OH, C=O
Phthalylsulfathiazole	97	156-160	256 (4.29) 211 (4.26)	3380-3300, 1700
Urosulfan	94	160-166	257 (4.24)	3350, 1670
Sulfadimesine	97	170-176	257 (4.18)	3370, 1700
Sulfalene	93	130-136	260 (4.24)	3370, 1700
Gossypol	98	190-196	255 (3.83)	3400, 1670, 1570
Salsolidine	95	200-204	257 (4.33)	3370, 1720, 1560

TABLE 2. Inerferon-Inducing Activity of Molecular Complexes of GC and Certain Medicinal Preparations

Complex	Dose, mg/kg	Titer if, unit/mL	Dose, mg/kg	Titer if, unit/mL
GC+phthalylsulfathiazole	100	10-20	200	10-20
GC+urosulfan	100	4-8	200	4-8
GC+sulfadimesine	100	40-80	200	40-80
GC+sulfalene	100	80	200	160
GC+gossypol	100	<4	200	<4
GC+salsolidine	100	160	200	160
Glycyrram (GC)	100	80	200	80



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Analogous changes can be observed in the IR spectra of the GC molecular complexes with 2-(*p*-aminobenzenesulfamide)-3-methoxypyrazine (sulfalene) and 2-(*p*-aminobenzenesulfamido)-4,6-dimethylpyrimidine (sulfadimesine). The IR spectrum of the complex with 2-(*p*-phthalylaminobenzenesulfamido)-thiazole (phthalylsulfathiazole) typically has the OH and COOH absorption bands shifted to low-frequency by 30-40 cm^{-1}. The UV spectra of the compounds contain absorption maxima characteristic of conjugated 12-en-11-one and aromatic systems. This shifts the maxima relative to the starting materials. It can be supposed that the OH and COOH groups in GC interact with the COOH and CONH groups of these medicinal substances through H-bonds and with the thiazole.

GC possesses interferon-inducing activity [9]. Therefore, the next stage of our research determined the interferon-inducing activity of the prepared compounds.

The action of the molecular complexes with GC was studied on experimental animals. It should be noted that the sulfamide preparations themselves and salsolidine had no interferon-inducing activity (Table 2).

It can be seen that the medicinal preparations have a substantial effect on the GC activity, suppressing its interferon-inducing activity. Gossypol is known to induce interferon whereas sulfamide preparations acts as antagonists to the GC activity. Only the complex with salsolidine at 100 mg/kg is actually an effective interferon inducer.

EXPERIMENTAL

IR spectra were recorded on a Specord IR 75 spectrophotometer in KBr pellets; UV spectra, on an SF-26 instrument. TLC was performed on Silufol UV-254 plates using acetone—ether (1:1) and toluene—acetone (6:4). Compounds were visualized using 1% *p*-(dimethyl)aminobenzaldehyde and 0.1% phloroglucinol.

General Method for Preparing Molecular Complexes 1. An aqueous—alcoholic (aqueous—acetone) solution of GC (0.85 g, 1 mmole) was stirred and treated with powdered preparation (1 mmole). The temperature was adjusted to 50°C. Stirring was continued at room temperature for 3-5 h. The organic solvent was distilled under vacuum. The moist solid was lyophilized.

Method for Studying the Interferon-Inducing Activity of the Prepared Compounds. The interferon-inducing activity of the prepared complexes was studied in neutered white mice (15-20 g) in doses of 100 and 200 mg/kg, in agreement with the literature [10]. Five specimens were used in order to verify each dose. The interferon titer in blood serum was measured by the literature micromethod [11].

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