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BIOPHARMACEUTICAL STUDY OF AN INJECTABLE DOSAGE FORM OF THE NEW ANTIAGGREGANT SUBSTANCE 3-METHYL-8-(PIPERAZIN-1-YL)-7-(THIETAN-3-YL)-1-ETHYL-1*H*-PURINE-2,6(3*H*,7*H*)-DIONE HYDROCHLORIDE

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The pharmacokinetic parameters of the parent substance and the injectable dosage form of the new antiplatelet drug 3-methyl-8-(piperazin-1-yl)-7-(thietan-3-yl)-1-ethyl-1*H*-purine-2,6(3*H*,7*H*)-dione hydrochloride in rabbit blood plasma upon intravenous administration were compared and analyzed. The relative bioavailability coefficient was determined to be 0.97.

Keywords: pharmacokinetics, absolute bioavailability, 3-methyl-8-(piperazin-1-yl)-7-(thietan-3-yl)-1-ethyl-1*H*-purine-2,6(3*H*,7*H*)-dione hydrochloride.

Platelet activation is a key event in the pathogenesis of cardiovascular complications that largely determines the extent of blood-supply disruptions to organs and tissues (heart, brain, peripheral vessels). Therefore, the therapy and prevention of cardiovascular complications by antiaggregants are pathogenically justified [1, 2]. Hence, the search, study, and creation of new domestic antiaggregants are exceedingly critical problems for the prevention and treatment of thrombolytic conditions. An analysis of the literature demonstrated that heterocyclic structures are capable of blocking platelet aggregation [3 – 5]. For example, the new xanthine derivative Angipur that exhibited pronounced antiaggregant activity was discovered among compounds of this class.

Experimental results for the pharmacokinetics of the pharmacological substance enabled the blood (plasma) concentration of the drug to be estimated and an approximate dosage regime to be chosen and then refined during clinical trials. Also, an estimate of the relative bioavailability of the created dosage form played a large role in the design of the new drug [6]. Therefore, the goal of the present work was to study the bioavailability in rabbits of 3-methyl-8-(piperidin-1-yl)-7-(thietan-3-yl)-1-ethyl-1*H*-purine-2,6(3*H*,7*H*)-dione hydrochloride (**I**) and the dosage form Angipur based on it.

EXPERIMENTAL CHEMICAL PART

The active pharmaceutical ingredient (API) of **I** that was synthesized at the Department of Pharmaceutical Chemistry, Bashkir State Medical University (Ufa, Russia) [6], and the dosage form Angipur based on it as a 0.02% concentrate for preparation of solution for infusion in 50-mL vials that was developed at the above department were used in the studies.

EXPERIMENTAL PHARMACOLOGICAL PART

The pharmacokinetic parameters were determined in experiments with 12 male rabbits (3.3 – 3.6 kg) that were kept under vivarium conditions (22 – 24°C, 40 – 50% relative humidity) with natural lighting on a standard diet (GOST R 50258-92). All procedures with animals were conducted in compliance with generally accepted ethics standards for handling animals adopted by the *European Convention for the*

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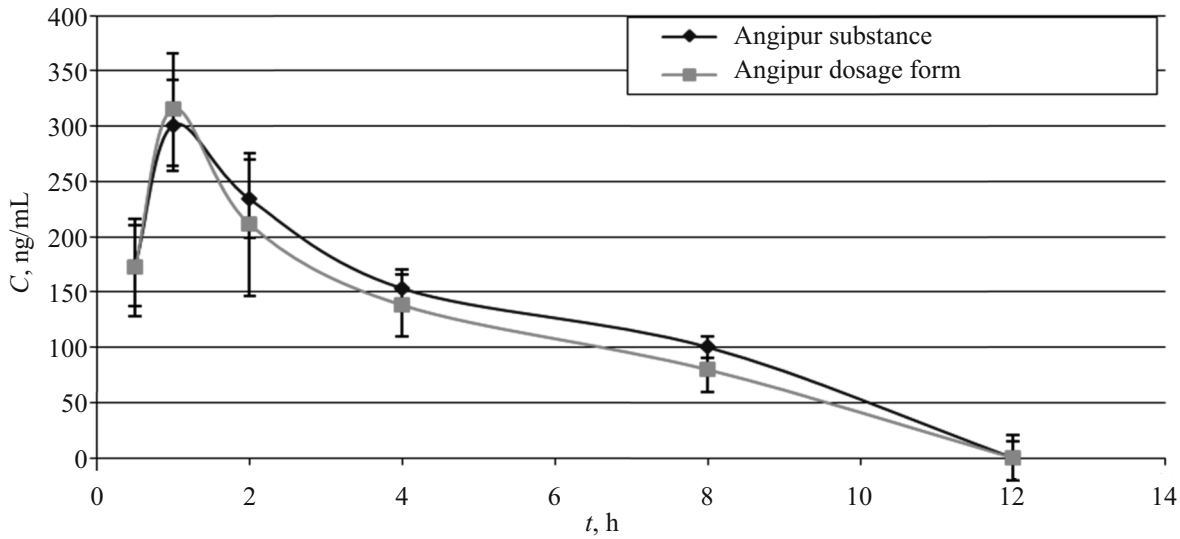

Fig. 1. Time dependence of content of **I** and its Angipur dosage form in rabbit blood plasma upon intravenous administration at a dose of 1.33 mg/kg.

Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986) and in consideration of International Recommendations of the European Convention on the Protection of Vertebrate Animals Used for Experimental Studies (1997). The experimental plan was approved by the Regional Research Ethics Committee of Volgograd Region, Protocol No. 2083 – 2016 of Nov. 18, 2016.

This study was conducted according to requirements of the current *Handbook for Preclinical Drug Trials* [7].

Two experimental groups of laboratory animals were formed for the studies. Blood was collected from each group before the start of the injection to determine the biological background. Rabbits of the first test group were injected intravenously into an ear vein with a solution of the substance in normal saline at a dose of 1.33 mg/kg. The second test group received the dosage form of **I** (Angipur) at the same dose. Blood samples were collected from rabbits of the two groups 5, 15, and 30 min and 1, 2, 4, 8, and 12 h after the intravenous injection.

TABLE 1. Pharmacokinetic Parameters of **I** (Substance) and Its Angipur Dosage Form in Rabbit Blood Plasma upon Intravenous Administration at a Dose of 1.33 mg/kg

Parameters	Substance **I**	Dosage form of **I**, Angipur
AUC, ng · h/mL	136.9 ± 6.37F	133.65 ± 4.09
$T_{1/2}$, h	1.072 ± 0.093	1.124 ± 0.094
Cl, L/(h/kg)	9.73 ± 0.46	9.96 ± 0.31
V_d, L/kg	15.04 ± 1.25	16.13 ± 1.01
F_{rel}, %		97.88 ± 7.32

Blood was collected from an edge ear vein of the rabbits as free-falling drops and was stabilized with aqueous sodium citrate (5%, pH 6.0) in a 1:9 ratio. The time dependence of the compound concentration was studied in blood plasma obtained by centrifugation. High-performance liquid chromatography (HPLC) on a Shimadzu liquid chromatograph (Japan) was used for quantitative determination. A fluorescence detector (wavelength 205 nm), SUPELCOSIL LC-18 column, and phase modifier were used for the determination. The mobile phase was prepared using MeCN (UF200, Russia) and a buffer consisting of KH_2PO_4 (50 mM). The mobile-phase modifier was sodium heptanesulfonate.

RESULTS AND DISCUSSION

The average pharmacokinetic profiles for the time dependence of the substance concentration in rabbit blood plasma were obtained from the studies (Fig. 1). The results showed that the maximum concentration of **I** was observed 15 min after the injection. Then, the concentration decreased biexponentially, assuming a rapid first distribution phase that was replaced by a slower elimination phase. The first elimination phase was complete by the first hour. The second slow phase continued up to 8 h of study and up to 12 h for administration of the dosage form of **I**.

Table 1 lists the main pharmacokinetic parameters calculated from the time dependence of the rabbit plasma concentration of the tested samples. Statistically significant differences were not observed between the pharmacokinetic parameters upon injection of **I** and the dosage form Angipur.

Thus, the pharmacokinetic studies of API **I** and its dosage form Angipur showed that these compounds circulated in rabbit blood for up to 12 h after intravenous injection. Statistically significant differences in the pharmacokinetic pa-

rameters of the tested samples were not observed. The relative bioavailability of **I** and dosage form Angipur was 97.88%.

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