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Approbation of a New Pharmacological Assessment Model Activities of Enterosorbent *in vivo* on the Experimental Samples

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ABSTRACT

The use of therapeutic and prophylactic drugs based on organosilicon sorbents promotes rapid recovery by normalizing intestinal microbiocenosis, suppressing lipid peroxidation, detoxification, activation of liver function and gentle healing of ulcers, early eradication of *Helicobacter pylori*. Also, the use of organosilicon sorbents reduces the toxic load, leads to natural detoxification, and leads to healing in erosive and ulcerative processes of the gastrointestinal tract, in contrast to adsorbents based on coal and clay. Based on the available data, a new approach to the pharmacological assessment of enterosorbent from the point of view of their specific action - adsorption activity - has been proposed using a test drug with previously described pharmacokinetics - lornoxicam - as an analyte. In view of the best compliance with the requirements for an "ideal" enterosorbent, several experimental samples of the sorbent were selected to test the method proposed in this work. Using High-performance liquid chromatography (HPLC) with tandem mass spectrometry (MS) on Chinchilla rabbits, the bioavailability of Lornoxicam, selected as a test drug, was studied when Lornoxicam and Lornoxicam were used together with selected enterosorbent. It has been established that the bioavailability of Lornoxicam with the simultaneous use of the studied enterosorbent decreases sharply. The data obtained make it possible to judge the adsorption activity of enterosorbent and evaluate it by changes in the relative bioavailability of the test drug. Thus, as a result of the conducted research, an original method for determining the adsorption activity of enterosorbent in vivo was proposed, which claims to be a new pharmacological model.

Key words: New pharmacological model, Determination of adsorption activity in vivo, Use of Lornoxicam as a test drug, Experimental samples of sorbent.

INTRODUCTION

As is known, adsorption activity (adsorption capacity, sorption capacity, adsorption capacity, sorption pore volume) is a specific quality indicator for drugs of the enterosorbent group and is used to characterize the absorption capacity of the sorbent, which determines the amount of adsorbate (reagent) that can absorb sorbent per unit of its mass (Frol'kis 1997).

To determine the adsorption activity of enterosorbent, the following methods are used, i) spectrophotometric method, the adsorption activity of the enterosorbent is determined by the difference in the optical densities of the reagent solution after contact and before contact with the enterosorbent for a certain time; ii) titrimetric method, the determination is based on titration of the excess reagent (unadsorbed amount) remaining after contact with the drug, for example, iodometric titration (excess methylene blue), bromate-bromide titration (excess phenazone), and iii) gravimetric method, determination is based on the absorption of benzene vapor by the drug over a certain time. Calculation of adsorption activity (sorption pore volume) is carried out based on the difference in the mass of the sorbent after and before interaction with benzene vapor, taking into account the density of benzene.

Thus, the adsorption capacity of hydrogels is most often determined by the first of the listed methods (Sarnatskaya et al. 2018).

In the literature available to us, no methods have been found that allow us to reliably assess the adsorption activity of enterosorbent directly under the conditions of the gastrointestinal tract using precision analytical methods,

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which could be associated with the determination of their pharmacological activity.

We have proposed a new approach to the pharmacological assessment of enterosorbent in terms of their specific action – the adsorption activity of lornoxicam - using a test drug with previously described pharmacokinetics as an analyte. The determination should be carried out with a single joint administration of the test drug with an enterosorbent to an experimental animal. A significant decrease in the concentration of the test drug and/or its metabolite in the biological fluid will serve as an indicator of the effectiveness of the enterosorbent.

For enterosorption, sorbents based on highly dispersed silicas (SiO_2) are currently widely used (Warner et al. 2002; Stam et al. 2012; Dhiman et al. 2015). It is sorbents based on silicon dioxide that best meet the requirements of an "ideal" enterosorbent, which was the reason for choosing it as the object of our further research.

Sorbents based on highly dispersed silicas (SiO_2), used as the main component for the production of enterosorbent, is a wet, odorless, white mass, consisting of jelly-like lumps of different sizes and corresponds (Daniels et al. 2011). Evaluation of the interaction between microparticles and cells of the immune system is crucial for determining the safety of organosilicon sorbents, which are widely used in biomedical applications due to their unique chemical and physical properties (Johnston et al. 2000; Chen et al. 2018). In general, the toxic effect of sorbents on the immune system *in vivo* is extremely rare and occurs only at oral doses many times higher than the recommended permissible values (Di Cristo et al. 2016; Ravasio et al. 2021).

Purpose of the study was to test a new pharmacological model that makes it possible to determine in vivo the adsorption activity of enterosorbent based on highly dispersed silicas (SiO_2).

MATERIALS AND METHODS

Animals' applications

The study was carried out in accordance with the ethical principles of humane treatment of animals and was regulated by the decision of the Council of the Eurasian Economic Commission dated November 3, 2016 No.88; Guidelines for conducting preclinical studies of medicines, Ministry of Health of the Russian Federation, Scientific Center for Emergency Medicine, 2012; GOST 33044-2014 "Principles of Good Laboratory Practice (GLP)"; Guidance for Industry: Bioanalytical method validation. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evolution and Research (CDER). U.S. Government Printing Office: Washington, DC, 2018.

The study was conducted on 12 mature Chinchilla rabbits (males with an initial body weight of 2.5-3.0kg; the spread in initial weight did not exceed 10%; source - KrolInfo LLC, Russia) with a single oral administration of the study drug.

The rabbits were kept in individual metal cages with a slatted floor and a resting area (solid floor), without bedding, equipped with an automatic nipple watering system. The floor area in the cage for one animal was 2000cm^2 (minimum permissible area 2000cm^2) (Sachivkina et al. 2023).

Rabbits are marked by placing a mark on the inside of the ear. Each animal was assigned an individual number recorded on the cage card. The animals were fasted 18 hours before the experiment without restriction of drinking.

Rabbits No.1-3 were administered the drug Lornoxicam (8mg/kg), rabbits No.4-6 - Lornoxicam + experimental sample of sorbents based on highly dispersed silicas (SiO_2) No.1 (15g/kg), rabbits 7-9 - Lornoxicam (8mg/kg) + experimental sample of sorbents based on highly dispersed silicas (SiO_2) No.2 (15g/kg), rabbits 10-11 – Lornoxicam (8mg/kg) + sorbents based on highly dispersed silicas (SiO_2) No.3 (15g/kg).

Blood was collected from the ear vein at the following time points after drug administration: zero point (before drug administration), 0.5, 1, 2, 4, 6 and 24h. Blood from the ear vein was taken into Eppendorf tubes (1.5ml), left for 15min, and centrifuged. The resulting serum was frozen and stored at –40°C until analysis (Olabode et al. 2023).

Sample preparation was carried out by precipitation of proteins with acetonitrile. The concentration of the analyte (Lornoxicam) in blood serum was determined using the HPLC/MS/MS technique (Sachivkina et al. 2022; Jandosov et al. 2022). The method was validated according to the following validation parameters: selectivity, matrix effect, calibration curve, accuracy, precision, recovery, lower limit of quantitation, sample carryover, short-term stability ("benchtop" and "post-preparation"), and three-time freeze/thaw stability. The confirmed analytical range of the method was 25.00-10000.00ng/mL in blood serum, which allows the developed method to be used for conducting the analytical part of studies of the pharmacokinetics of the drug Lornoxicam.

Preparation of solutions and samples

Preparation of eluent A of the mobile phase: 0.1% solution of formic acid in water (by volume). Place 500mL of Milli-Q water into a 1000mL volumetric flask, add 1000µL formic acid, and mix. Next, the volume was brought to the mark with the same solvent and mixed.

Preparation of the solvent

500mL of 0.01% triethylamine in water and 500mL of methanol were mixed. 250mL of Milli-Q water were placed into a 500mL volumetric flask, then 50µL of triethylamine were added, and mixed. Next, the volume was brought to the mark with the same solvent and mixed.

Preparation of standard solutions

To prepare the initial standard solution of Lornoxicam 20.0mg (which corresponds to 20.41mg of Lornoxicam taking into account the quantitative content) standard sample of Lornoxicam, manufacturer - Toronto Research Chemicals Inc, Canada, series 2-XJZ-28-1, (precisely weighed) quantitatively transferred to a 100mL volumetric flask and dissolved in ~25mL of solvent, shaken until the substance was completely dissolved. Next, the volume of the solution was brought to the mark with the same solvent and mixed. The concentration of Lornoxicam in the solution was 200,000.00ng/mL.

To prepare the initial solution of the internal standard of Tenoxicam, 10.0mg (which corresponds to 10.2mg of Tenoxicam, taking into account the quantitative content) of the standard sample of Tenoxicam, manufacturer - SIGMA-ALDRICH, Co., USA, series MKCB3369V, (accurately weighed) was quantitatively transferred into a volumetric flask with a capacity of 100ml and dissolved in ~25mL of solvent, shaken until the substance was completely dissolved. Next, the volume of the solution was brought to the mark with the same solvent and mixed. The concentration of tenoxicam in the solution was 100,000.00ng/mL.

Preparation of working standard solutions

Working standard solutions were prepared by diluting the original standard solutions. Aliquots of the original standard solution of Lornoxicam were placed in volumetric flasks, then the volume of solutions was adjusted to the mark with solvent and mixed.

To prepare a working standard solution of Tenoxicam, 1000µL of the original standard solution of Tenoxicam was placed in a 100mL volumetric flask, the volume of the solution was adjusted to the mark with the same solvent and mixed. The concentration of Tenoxicam in the solution was 1000.00ng/mL.

Sample preparation of blood serum samples

To 100µL of the sample, placed in Eppendorf-type centrifuge tubes with a capacity of 1.5mL, 10µL of the working solution of the internal standard was added, then 300µl of acetonitrile was added, mixed on a shaker for 10sec, then centrifuged for 10min. with acceleration 15000g. Next, the supernatant was transferred into chromatographic vials and placed in the autosampler of the chromatograph.

Chromatographic separation and detection were performed using a Nexera XR high-performance liquid chromatograph with an LCMS-8040 tandem mass spectrometric detector (triple quadrupole). Primary data were processed using Lab Solutions software (Ver. 5.91), Shimadzu Corporation, Japan. Conditions for chromatographic separation and detection:

• Column – Eclipse Plus C18, 4.6*100mm, 3.5microns.
• Pre-column – Phenomenex C8, 10x2.1mm, 3µm.
• Column thermostat temperature – 30°C.
• Flow rate (FR): eluent A – 0.1% solution of formic acid in water (by volume); eluent B – acetonitrile.
• Isocratic elution mode:

Time, min. %	Content of eluent B	FR, mL/min.
0.00	50.0	0.50
5.00	50.0	0.50

• The volume of the injected sample is 10µL.
• Retention time of Lornoxicam is about 3.8min.
• Chromatogram registration time – 0.00-5.00min.
• Parameters of the ionization source (electrospray):

Atomizing gas	Drying gas	Heating unit	Desolvation line	Needle voltage	Ionization mode
2.5l/min	12l/min	400°C	250°C	+4.5kV	+

• Detection conditions for Lornoxicam, m/z – 372.00 → 95.00.
• Detection conditions for Tenoxicam (internal standard), m/z – 337.90 → 121.00.

Statistical analysis

The experiments were conducted in triplicate, and the resulting data were presented as mean values ± standard error (SE). Statistical analysis was carried out using Graphpad 9.4.1 software. Descriptive statistics were used for all data: the data were checked for normal distribution. The type of distribution was determined using the Shapiro-Wilk test. The arithmetic mean (Ar.m.), geometric mean (G.m.), standard deviation (SD), standard error of the mean (SE), 90% confidence interval (90% con.in.), coefficient variations (C.v.,%), maximum (Max) and minimum (Min) values, Median values were calculated.

RESULTS

A comparative study of the bioavailability of the drug Lornoxicam when used together with adsorbent drugs was carried out. In the experiment, three samples of sorbents based on highly dispersed silicas (SiO_2) No.1, No.2 and No.3 were used using a test for determining native lornoxicam in the blood serum of rabbits after its single oral administration at a dose of 8 mg per 1 kg of animal weight. Table 1 shows the concentrations of Lornoxicam in blood samples obtained from rabbits.

In order to study the comparative bioavailability of Lornoxicam with the simultaneous use of the studied enterosorbent, the concentrations of unchanged Lornoxicam in the blood serum of rabbits were determined and the main pharmacokinetic parameters were calculated, making it possible to characterize the areas under the pharmacokinetic curves of the concentration-time relationship.

Based on the results of quantitative determination of the concentration of Lornoxicam in blood serum, averaged pharmacokinetic curves were constructed in linear and semi-logarithmic coordinates. Pharmacokinetic profiles of lornoxicam in the blood were characterized by: maximum concentration (Cmax), time to reach maximum concentration (Tmax), area under the concentration-time curve (AUC), half-life ($T_{1/2}$) and absorption rate (Cmax/AUCt).

Tables 2-5 show the concentrations of Lornoxicam in the blood serum of rabbits receiving Lornoxicam once orally at a dose of 8mg/kg.

Fig. 1 and 2 show the averaged pharmacokinetic curves of the content of Lornoxicam in the blood serum of rabbits with a single oral administration of Lornoxicam and Lornoxicam together with enterosorbent in normal and semi-logarithmic coordinates.

As can be seen from the data in Tables 2-5 and Fig. 1, 2, the bioavailability of Lornoxicam with the simultaneous use of the studied enterosorbent sharply decreases.

Table 6 shows the pharmacokinetic parameters of Lornoxicam (based on average concentration values) when administered orally together with enterosorbent to rabbits at a dose of 8mg/kg.

In order to assess the bioavailability of Lornoxicam, the values of maximum concentrations (Cmax), time to reach it (Tmax), areas under the pharmacokinetic curves (AUC) and the Cmax/AUC ratio were compared. From the above Tables and Figures it is clear that the average

Table 1: Results of determination of Lornoxicam in blood samples obtained from rabbits.

Lornoxicam			
Time point, hours	Lornoxicam concentration (ng/mL)		
	Rabbit #1	Rabbit #2	Rabbit #3
0			
0.5	661.27	478.06	220.68
1	920.52	1237.37	275.73
2	1765.74	95.26	7328.08
4	5673.01	398.1	14942.94
6	9695.68	555.09	12638.27
24	1187.39	1185.3	1298.99
Lornoxicam + experimental sample of sorbents based on highly dispersed silicas (SiO_2) No.1			
Time point, hours	Lornoxicam concentration (ng/mL)		
	Rabbit #4	Rabbit #5	Rabbit #6
0	0	0	0
0.5	1070.86	68.01	52.68
1	2713.96	141.68	137.54
2	2943.87	1416.81	450.74
4	3919.68	4866.45	1078.5
6	3525.52	4558.64	2240.05
24	454.69	698.34	734.19
Lornoxicam + experimental sample of sorbents based on highly dispersed silicas (SiO_2) No.2			
Time point, hours	Lornoxicam concentration (ng/mL)		
	Rabbit #7	Rabbit #8	Rabbit #9
0	0	0	0
0.5	7757.22	352.89	109.69
1	9898.56	3054.86	453.58
2	8591.24	5468.20	1833.73
4	7671.88	6002.33	2550.28
6	5933.41	4950.56	2208.46
24	640.42	693.07	2070.33
Lornoxicam + sorbents based on highly dispersed silicas (SiO_2) No.3			
Time point, hours	Lornoxicam concentration (ng/mL)		
	Rabbit #10	Rabbit #11	Rabbit #12
0	0	0	0
0.5	5297.21	6890.92	5078.59
1	5234.88	11344.25	4854.53
2	4576.85	6525.33	4397.55
4	2414.26	6777.61	3435.32
6	2301.53	4303.4	2448.56
24	265.28	385.32	224.88

concentration profile of Lornoxicam when using Lornoxicam and Lornoxicam together with enterosorbent have a different character.

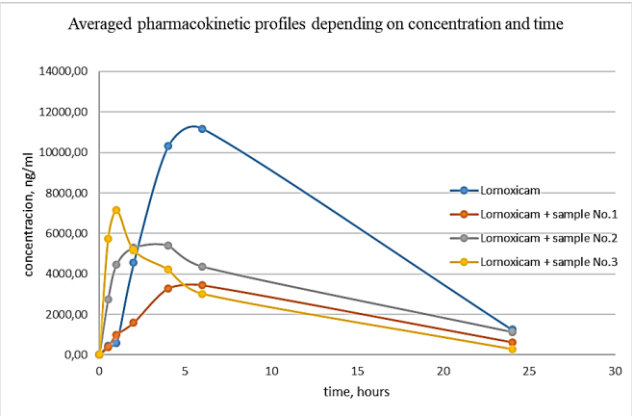

Fig. 1. Average pharmacokinetic profiles of Lornoxicam.

Relative bioavailability, calculated as the ratio of the areas under the pharmacokinetic curves "concentration - time" (AUC0-24), when using Lornoxicam together with sorbents was for "Lornoxicam + experimental sample of sorbents based on highly dispersed silicas No.1" - 32.8%, for " Lornoxicam + No.2" - 60.2%, for "Lornoxicam + No.3" - 37.6% in relation to the bioavailability of lornoxicam itself.

DISCUSSION

It is known that one of the main mechanisms of action of non-steroidal anti-inflammatory drugs (NSAIDs) is the blockade of the COX enzyme, which leads to disruption of the formation of prostaglandins, thromboxane A2, prostacyclin E2 from arachidonic acid (Penstone 1996; Uppalapati et al. 2009). Blockade of COX-1, which determines the synthesis of “cytoprotective” prostaglandins, leads to NSAID gastropathy (Howell et al. 2020). This contributes to damage to the mucous membrane by natural factors of the aggressive environment of the stomach. Additional factors associated with the systemic effects of NSAIDs are considered to be a decrease in platelet aggregation and deterioration of capillary blood flow in the mucosa, blockade of enzyme systems of epithelial cell mitochondria, blockade of NO synthetase, increased cell apoptosis, influence on gastric secretion and disruption of repair processes, which is associated with the blockade of COX-2, etc. (Wang et al. 2008; Zeng et al. 2024). Ulcerogenic effects are primarily associated with non-selective NSAIDs (Swarnamba et al. 2016; Teaima et al. 2021). Simultaneous administration of drugs that protect the mucous membrane of the gastrointestinal tract (for example, combining the use of an anti-inflammatory drug with a synthetic analogue of prostaglandin E2 misoprostol (combination drug - arthrotek), proton pump inhibitor omeprazole, H2-histamine blocker famotidine, cytoprotective drug sucralfate gives very good results to reduce the gastrotoxicity of NSAIDs) (Saha et al. 2024). However, even it seemed that the use of drugs to maintain gastroprotective function, in turn, carries a certain pharmacological load on the liver, kidneys and the entire body of patients as a whole. Thus, it seems correct to use enterosorbent in the treatment of acute NSAID poisoning

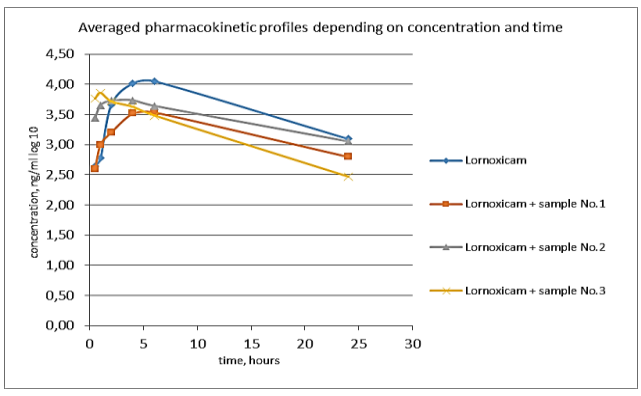

Fig. 2. Average pharmacokinetic profiles of Lornoxicam, semilogarithmic scale.

Table 2: Results of determination of the analyte (ng/mL) in serum blood of rabbits treated with Lornoxicam.

Rabbit No.	Sampling time (h)						
	0	0.5	1	2	4	6	24
1	0.00	661.27	920.52	1765.74	5673.01	9695.68	1187.39
2	0.00	420.96	588.10	4346.91	9307.98	10166.95	1263.21
3	0.00	240.70	285.76	7528.08	15942.94	13638.30	1278.97
Calculated values							
Ar.m.	0.00	440.98	598.13	4546.91	10307.98	11166.98	1243.19
G.m.		382.01	503.80	3597.15	9207.14	11069.63	1241.94
SD		311.54	455.94	3933.17	6554.83	2080.73	78.91
SE		220.30	322.40	2781.17	4634.97	1471.30	55.80
90% con.in. con.in.		362.35	530.29	4574.62	7623.84	2420.06	91.78
C.v, %		70.65	76.23	86.50	63.59	18.63	6.35
Max		661.27	920.52	7328.08	14942.94	12638.27	1298.99
Min		220.68	275.73	1765.74	5673.01	9695.68	1187.39
Median		440.98	598.13	4546.91	10307.98	11166.98	1243.19

Note: Ar.m. - arithmetic mean, G.m. - geometric mean, SD - standard deviation, SE - standard error of the mean, 90% - 90% confidence interval, C.v.,% - coefficient variations, Max - maximum values, Min - minimum values, Median - median values.

Table 3: Results of determination of the analyte (ng/mL) in serum blood of rabbits treated with Lornoxicam+experimental sample sorbents based on highly dispersed silicas (SiO_2) No.1.

Rabbit No.	Sampling time, h						
	0	0.5	1	2	4	6	24
4	0.00	1070.86	2713.96	2943.87	3919.68	3525.52	454.69
5	0.00	68.01	141.68	1416.81	4866.45	4558.64	698.34
6	0.00	52.68	137.54	450.74	1078.5	2240.05	734.19
Calculated values							
Ar.m.	0.00	397.18	997.73	1603.81	3288.21	3441.40	629.07
G.m.		156.55	375.36	1234.20	2740.07	3301.96	615.46
SD		583.47	1486.30	1257.04	1971.35	1161.58	152.08
SE		336.87	858.12	725.75	1138.16	670.64	87.80
90% con.in.		554.10	1411.48	1193.76	1872.10	1103.10	144.42
C. v, %		146.90	148.97	78.38	59.95	33.75	24.18
Max		1070.86	2713.96	2943.87	4866.45	4558.64	734.19
Min		52.68	137.54	450.74	1078.50	2240.05	454.69
Median		68.01	141.68	1416.81	3919.68	3525.52	698.34

Table 4: Results of determination of the analyte (ng/mL) in serum blood of rabbits treated with Lornoxicam+experimental sample of sorbents based on highly dispersed silicas (SiO_2) No.2.

Rabbit No.	Sampling time, h						
	0	0.5	1	2	4	6	24
7	0.00	7757.22	9898.56	8591.24	7671.88	5933.41	640.42
8	0.00	352.89	3054.86	5468.20	6002.33	4950.56	693.07
9	0.00	109.69	453.58	1833.73	2550.28	2208.46	2070.33
Calculated values							
Ar.m.	0.00	2739.93	4469.00	5297.72	5408.16	4364.14	1134.61
G.m.		669.63	2393.71	4416.50	4897.07	4018.06	972.21
SD		4346.80	4878.70	3381.98	2611.99	1930.47	810.79
SE		2509.63	2816.72	1952.59	1508.03	1114.56	468.11
90% con.in.		4127.97	4633.09	3211.72	2480.49	1833.29	769.97
C.v, %		158.65	109.17	63.84	48.30	44.23	71.46
Max		7757.22	9898.56	8591.24	7671.88	5933.41	2070.33
Min		109.69	453.58	1833.73	2550.28	2208.46	640.42
Median		352.89	3054.86	5468.2	6002.33	4950.56	693.07

when administered orally (Bilir et al. 2016). Some enterosorbent are also effective in the treatment of gastric and duodenal ulcers. Thus, one enterosorbent was effective adjuvant for HP-positive peptic ulcer disease. It can significantly improve the clinical and endoscopic results of treatment of gastric ulcers (after 4 weeks) and the anti-Helicobacter effectiveness of "triple" therapy in patients with HP-positive duodenal ulcers. Additional administration of enterosorbent to patients with HP-positive peptic ulcer disease is safe and well tolerated, and can significantly reduce the incidence of side effects of anti-Helicobacter therapy and improve its tolerability (Díaz-González et al. 2015; Bilir et al. 2016).

It should be noted that with long-term use of NSAIDs, morphological changes in the gastric mucosa also occur, revealed by endoscopic examination: erosive gastric ulcer and erosive duodenal ulcer, possibly the development of complications such as gastrointestinal bleeding, perforation and obstructions. An important pathogenetic mechanism of erosive and ulcerative defects in the mucous membrane of the stomach and duodenum is the elimination of nitric oxide (NO) synthesis by anti-inflammatory drugs due to a decrease in the activity of the NO synthase enzyme (Parada et al. 2016). Nitric oxide maintains regional blood flow in the mucous membrane of the stomach and duodenum, inhibits adhesion and

Table 5: Results of determination of the analyte (ng/mL) in serum blood of rabbits treated with Lornoxicam+sorbents based on highly dispersed silicas (SiO_2) No.3

Rabbit No.	Sampling time, h						
	0	0.5	1	2	4	6	24
7	0.00	5297.21	5234.88	4576.85	2414.26	2301.53	265.28
8	0.00	6890.92	11344.25	6525.33	6777.61	4303.4	385.32
9	0.00	5078.59	4854.53	4397.55	3435.32	2448.56	224.88
Calculated values							
Ar.m.	0.00	5755.57	7144.55	5166.58	4209.06	3017.83	291.83
G.m.		5701.94	6606.07	5083.08	3830.68	2894.54	284.33
SD		989.30	3642.01	1180.13	2282.26	1115.76	83.45
SE		571.17	2102.72	681.35	1317.66	644.18	48.18
90% con.in.		939.49	3458.66	1120.71	2167.36	1059.59	79.25
C.v, %		17.19	50.98	22.84	54.22	36.97	28.60
Max		6890.92	11344.25	6525.33	6777.61	4303.40	385.32
Min		5078.59	4854.53	4397.55	2414.26	2301.53	224.88
Median		5297.21	5234.88	4576.85	3435.32	2448.56	265.28

Table 6: Pharmacokinetic parameters of Lornoxicam based on average concentration values.

Parameter	Units	Lornoxicam	Lornoxicam + sample No.1	Lornoxicam + sample No.2	Lornoxicam + sample No.3
AUC $_{0-24}$	ng/mL per hour	156588.04	51336.79	94263.44	58823.99
AUC $_{0-\infty}$	ng/mL per hour	166920.68	58894.35	100040.74	61115.54
With $_{max}$,	µg/mL	12319.31	3675.39	7950.45	7240.02
T $_{max}$	hour	5.00	4.67	2.50	0.67
CL	l/ hour	0.04	0.17	0.09	0.17
T $_{1/2}$	hour	5.77	8.04	5.99	5.47
Vd	l	0.36	2.22	0.75	1.39
F	%	100%	32.78%	60.20%	37.57%

activation of neutrophils. In small vessels of the mucous membrane of the stomach and duodenum, under the influence of NSAIDs, microthrombi are formed, which cause disruption of microcirculation. Dysfunction of the gastrodaudenal complex is also noted (Howell et al. 2019).

These facts determined the choice of a non-selective NSAID, Lornoxicam, as a test drug. In addition, compared to other non-selective NSAIDs, Lornoxicam has a better safety profile, which is important when working with laboratory animals. Efferent therapy methods have been known for millennia. To date, enterosorbent approved for use have undergone extensive clinical testing in various healthcare institutions for the treatment of a large number of diseases and their complications (Shevchenko et al. 1998; Trogen et al. 2022). However, to date, no tools have been proposed for biological assessment of the activity of these efferent therapy agents using precision analytical methods. As is known, an "ideal" enterosorbent must satisfy the following requirements: have high efficiency due to the large active surface area, which makes it possible to take moderate therapeutic doses; have high adsorption activity against a wide range of toxins of various origins; do not damage the mucous membrane of the gastrointestinal tract and have proven safety when used; have high selectivity of action with minimal loss of essential micronutrients; comply with the "Rule of Three "NOTs": do not dissolve, not be absorbed and do not have a systemic effect; have a neutral taste, do not cause nausea and vomiting; have a convenient release form and dosage that can be used both in a hospital setting and at home (Chikinev et al. 2006; Ali et al. 2020). It is precisely because of the best compliance with these requirements that sorbents based on highly dispersed silicas (SiO_2) No.1,2,3 were chosen for testing the proposed method.

Conclusion

Using the HPLC/MS/MS technique, the bioavailability of Lornoxicam was studied when Lornoxicam and Lornoxicam were used together with selected enterosorbent. It has been established that the bioavailability of Lornoxicam with the simultaneous use of the studied enterosorbent is sharply reduced. The data obtained make it possible to judge the adsorption activity of enterosorbent and evaluate it by changes in the relative bioavailability of the test drug. Thus, as a result of the research, an original method for determining the adsorption activity of enterosorbent in vivo was proposed, which claims to be a new pharmacological model.

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