RESEARCH PAPER

BIOPHARMACEUTICAL RESEARCH OF ANTIANEMIC DOSAGE FORM

Kh.M. Yunusova[1], N.B. Ilkhamova[1], Sh.A. Kasimova[2]
[1]Tashkent Pharmaceutical Institute,
Republic of Uzbekistan, Tashkent city, Mirabad district, Aibek street, 45
[2]Pharmaceutical enterprise SAMO LLC,
Republic of Uzbekistan, Tashkent city, Mirzo Ulugbek district, Mirzo Ulugbek Street, 142 B

INFORMATION ABOUT THE AUTHORS

Yunusova Kholida Mannanovna – Department of Industrial Technology of Drugs of the Tashkent Pharmaceutical Institute, Doctor of Pharmaceutical Sciences, Professor. E-mail: holida_222@mail.ru. ORCID: 0009-0009-8489-2141

Ilkhamova Nargiza Bakhtiyarovna – Department of Industrial Technology of Drugs of the Tashkent Pharmaceutical Institute, Doctor of Pharmaceutical Sciences, Docent, E-mail: nargiza.samo@yandex.ru. ORCID: 0009-0006-6647-7743

Kasimova Shurangiz Adizzhonovna – specialist of the quality assurance department of the pharmaceutical enterprise SAMO LLC**.** E-mail: shurangiz.kasimova@mail.ru. ORCID: 0000-0002-5187-8329

ABSTRACT

In the context of evaluating the efficacy and safety of developed pharmaceuticals, significant emphasis is placed on the investigation of their bioavailability and bioequivalence. The exploration of the potential to alter the pharmacological action of drugs represents a key area of biopharmaceutical research.

Objective of this article is to investigate the biopharmaceutical parameters of the proposed pharmaceutical composition with antianemic action containing iron fumarate.

The material of investigation was film-coated tablets containing 210 mg of ferrous fumarate (60 mg in terms of elemental iron).

To examine the kinetic parameters of substance absorption using the in-vitro method, absorption spectrophotometry in the ultraviolet and visible regions was performed on a device with a paddle stirrer.

For laboratory research, the pharmacodynamic effects of the proposed drug were investigated in vivo and compared with those of the reference drug. This study was conducted using a model of "iron deficiency anemia," which was induced using the subacute post-hemorrhagic anemia method.

Based on biopharmaceutical studies utilizing the in-vitro method, a protocol for conducting a dissolution test was developed to determine the kinetics of ferrous fumarate release from a solid dosage form.

Furthermore, following biopharmaceutical studies utilizing the in-vivo method, the bioequivalence of the developed dosage form in terms of specific activity and acute toxicity was investigated in comparison with the reference drug

The dissolution medium selected for determination of ferrous fumarate dissolution from film-coated tablets was artificial gastric juice without pepsin, which was modified by the addition of acetate buffer. The dissolution time and rotation speed of the paddle stirrer were modified. The detection was performed at a wavelength of 520 nm.

The drug under development demonstrates an antianemic effect and is classified as a low-toxicity substance with an LD 50 of 1350 (1097 ÷1660) mg/kg.

Keywords: ferrous fumarate, iron deficiency anemia, bioequivalence, solubility, dissolution, pharmaceutical action

How to cite this article: Kh.M. Yunusova1 N.B. Ilkhamova1 Sh.A. Kasimova2. BIOPHARMACEUTICAL RESEARCH OF ANTIANEMIC DOSAGE FORM. Int J Drug Deliv Technol. 2026;16(77s):1890-1896. DOI: 10.25258/ijddt.16.77s.218.

INTRODUCTION

When solid oral dosage forms are administered, the absorption of medicinal substances depends on the release and dissolution of medicinal substances under physiological conditions. Iron deficiency is recognized as the most prevalent nutritional deficiency globally and the primary cause of anemia in approximately 2 billion people [1]. It is characterized by a decrease in the level of iron in the body, which leads to a reduction in the concentration of red blood cells and hemoglobin in the blood [2]. It is not feasible to replenish an existing iron deficiency through dietary means, as the maximum possible amount that can be absorbed from food is 2.5 mg/day [3]. To achieve a therapeutic result, it is necessary to ensure the intake of elemental iron in a dose of 100 to 300 mg per day, which is only possible through iron medications [4].

Currently, the pharmaceutical market of the country offers a wide selection of iron preparations, comprising monocomponent and combined compounds of iron salts in various dosage forms. The most rational approach to this issue is the utilization of modern drugs, the production technologies of which ensure the maximum possible bioavailability of iron while minimizing the risk of developing the most common side effects associated with ferrotherapy [5].

World Health Organization (hereafter as WHO) experts recommend the use of oral divalent iron preparations [6] due to their ease of administration, favorable absorption, and improved tolerability. The daily requirement for iron preparations is calculated based on the amount of divalent iron contained therein [7].

Preparations containing divalent iron are categorized into organic compounds - gluconate (Totema),

fumarate (Ferretab) - and inorganic salts - sulfate (Sorbifer, Fenuls, Ferroplex, Tardiferon), chloride (Gemofer).

It has been established that organic salts (gluconate, fumarate) exhibit superior tolerability compared to inorganic ones (sulfate) [8].

Furthermore, organic iron compounds generally demonstrate lower toxicity; for instance, the acute toxicity (LD50) of iron sulfate is 230 mg/kg, gluconate is 320 mg/kg, iron fumarate is 630 mg/kg, and for the polymaltose hydroxide complex, it exceeds 2000 mg/kg [9].

For the development of the drug, ferrous fumarate was selected, based on which the composition and technology of the drug with an antianemic effect were developed. Ferrous fumarate (iron (II) butenedioate salt (1:1)) is a reddish-orange powder, a salt of divalent iron and fumaric acid, obtained through chemical synthesis. The chemical formula of this compound is C4H2FeO4 with a molar mass of 169.9 g/mol. It exhibits slight solubility in water, very slight solubility in ethanol (96%), but dissolves readily in dilute acid solutions, such as gastric juice [10]. Fumarate distinguishes itself from other iron (II) salts by its higher stability, less pronounced metallic taste, and greater bioavailability, as divalent iron (ferrous) is readily absorbed, and fumaric acid enhances its absorption [11]. Consequently, preparations based on iron fumarate do not bind to proteins in the upper gastrointestinal tract but dissolve effectively directly in the stomach, thus maintaining bioavailability comparable to water-soluble salts [12].

In addressing the issue of efficacy and safety of developed drugs, significant emphasis is placed on the study of their bioavailability and bioequivalence [13]. The investigation of potential alterations in drug action constitutes one of the areas of biopharmaceutical research. An essential factor in this regard is the conduct of in vitro studies for reliable determination of dissolution kinetics and in vivo studies for determination of drug concentration levels in biological fluids [14].

The research obtained results substantiate the pharmacological activity and safety of the developed medicinal product. The study and appropriate application of this information contribute to the optimization of the pharmaceutical and pharmacokinetic properties of the finished solid dosage form and are considered an integral component of the pharmaceutical development of the created medicinal products [15, 16].

MATERIALS AND METHODS

In the evaluation of bioavailability for the recommended tablets, the "Dissolution" test was utilized as a primary in vitro assessment method, offering insights into both technological and biopharmaceutical aspects of the drug.

The methodology for the Dissolution test necessitated careful selection of the dissolution medium, solvent type, and appropriate hydrodynamics (paddle rotation speed). The choice of dissolution medium was informed by the characteristics of ferrous fumarate, which exhibits limited water solubility but readily dissolves in dilute acidic solutions [17]. Pharmacokinetic studies in preclinical settings revealed that orally administered ferrous fumarate undergoes rapid and complete absorption in the gastrointestinal tract, classifying it as a Class II substance in the biopharmaceutical classification system (BCS): poorly soluble in aqueous media but highly permeable through biological membranes [18]. For such compounds, the Dissolution test requires modification of the dissolution medium, often involving a combination of acid or buffer solution with low-concentration surfactants to create optimal conditions [19, 20]. A crucial consideration is ensuring maximum dissolution, where the medium volume should be at least three times that required for a saturated drug solution, with the optimal volume determined based on the substance's biopharmaceutical solubility in the given medium [21, 22].

To investigate the antianemic effect of the recommended tablets, Ferretab comp., manufactured by GL PHARMA, GmbH (Austria), was selected as a reference drug. It is a prolonged-release capsule containing 3 round, flat mini-tablets of a reddish-brown color (iron fumarate).

The study was conducted utilizing a model of "iron deficiency anemia," which was induced through the method of subacute posthemorrhagic anemia. The experiments were performed on rabbits weighing 2.5-3.0 kg. Blood was extracted from the marginal vein or artery of the ear in a volume of 10 ml/kg of body weight daily for 8 days. To examine the antianemic effect of the drug under development, the rabbits were allocated into 4 groups of 6 animals each:

Group 1 – intact animals that underwent no manipulation;

Group 2 – control; animals with a model of iron deficiency anemia;

Group 3 – animals with a model of iron deficiency anemia, administered the recommended drug;

Group 4 – animals with a model of iron deficiency anemia, administered the reference drug.

From the second day of the experiment, rabbits in groups 3 and 4 were administered a single intragastric injection of a 5% solution of the compared drugs at a dose of 50 mg/kg for 14 days. Rabbits in groups 1 and 2 received water. On the 14th day of the experiment, blood was collected from the ear vein of rabbits in all groups to determine the level of hemoglobin and the number of erythrocytes in the blood serum.

To ascertain the adverse effects caused by a single, often large dose of a chemical and to detect potential adverse health effects, acute toxicity studies of the recommended tablets were conducted.

The acute toxicity of the recommended tablets was also investigated in comparison with the reference drug "Ferretab comp.", manufactured by GL PHARMA, GmbH (Austria). The study was conducted through a single administration of drugs with determination of LD50 and toxicity class. For the experiment, 30 white outbred mice, males and females, weighing 19-21 g, were utilized, maintained in quarantine for 14 days. Prior to and during the

experiments, the mice were housed in a vivarium at an air temperature of +20 - 22°C, humidity - no more than 50%, air exchange volume (exhaust: inflow) - 8:10, in the light mode - day - night. The mice were placed in standard plastic cages and maintained on a standard diet.

The acute toxicity study was conducted in two series. In the first series of the experiment, rats were administered a single intragastric dose of a 6.5% aqueous suspension (1 tablet + 1 ml H2O) of the recommended preparation:

Group 1 (6 mice) - per os at a dose of 650 mg/kg (0.2 ml);
Group 2 (6 mice) - per os at a dose of 975 mg/kg (0.3 ml);
Group 3 (6 mice) - per os at a dose of 1300 mg/kg (0.4 ml);
Group 4 (6 mice) - per os at a dose of 1625 mg/kg (0.5 ml);
Group 5 (6 mice) - per os at a dose of 1950 mg/kg (0.6 ml).

In the second series of experiments, rats were administered a single intragastric dose of a 6.5% aqueous suspension (1 capsule + 2.5 ml H2O) of the drug Ferretab comp., manufactured by GLPharma GmbH, Austria, as follows:

Group 1 (6 mice) - per os at a dose of 650 mg/kg (0.2 ml);
Group 2 (6 mice) - per os at a dose of 975 mg/kg (0.3 ml);
Group 3 (6 mice) - per os at a dose of 1300 mg/kg (0.4 ml);
Group 4 (6 mice) - per os at a dose of 1625 mg/kg (0.5 ml);
Group 5 (6 mice) - per os at a dose of 1950 mg/kg (0.6 ml).

Following the experiment's initiation, mice across all groups were monitored hourly on the first day under laboratory settings. Researchers evaluated various indicators of the animals' functional state, including survival rates, overall condition, potential seizures, and mortality. From the second day onward, daily observations continued for two weeks in vivarium conditions. These assessments encompassed general health and activity levels, behavioral traits, responsiveness to tactile, pain, auditory, and visual stimuli, respiratory rate and depth, heart rate, hair and skin condition, tail positioning, fecal characteristics and quantity, urination frequency, body weight fluctuations, and other relevant parameters. All test subjects were kept in uniform conditions and provided a standard diet with unrestricted access to food and water.

At the conclusion of the study, researchers determined the LD50 and toxicity classification of the drug under investigation.

RESULTS AND DISCUSSION

Given the need for substantial solvent volumes, water, artificial gastric juice (pepsin-free), and phosphate buffer were employed as dissolution media.

The experimental setup utilized a paddle stirrer apparatus with the following initial parameters: paddle rotation speed – 50 rpm; solvent volume – 900 ml.

Samples were collected at 30, 45, 60, and 75 minutes. The findings are presented in Table 1.

Table 1.

Results of a study of dissolution kinetics for recommended tablets in various dissolution media

Experiment No.	Amount of released pharmaceutical substance, %			
	Selection time, min			
	30	45	60	75
pH=5.8	Purified water			
1	2.5	3.8	5.2	5.5
2	2.6	4.1	5.5	5.8
3	2.9	3.9	5.1	5.5
4	2.5	3.7	5.2	5.5
5	2.6	3.9	5.2	5.5
pH = 1.8	Artificial gastric juice without pepsin			
1	8.5	18.5	45.0	62.5
2	8.7	18.7	45.5	65.5
3	8.6	18.6	45.3	62.8
4	8.2	18.2	45.5	62.7
5	8.5	18.5	45.5	65.8
pH=6.8	Phosphate buffer			
1	5.5	12.5	24.2	45.0
2	5.8	12.8	24.5	45.5
3	5.5	12.5	24.3	45.3
4	5.5	12.4	24.5	45.5
5	5.5	12.4	24.5	45.5

As evidenced by the obtained data, under these conditions the quantity of active substance transferred to the solvent was negligible and did not meet the test requirements. Utilizing artificial gastric juice without pepsin as a dissolution medium at a paddle stirrer rotation speed of 50 rpm enabled an increase in the yield of the pharmaceutical substance into the dissolution medium by several factors; however, this result remained unsatisfactory. Consequently, at the second stage of the investigation, it was determined to increase the rotation speed of the paddle stirrer to 75, 100, 150 and 200 rpm and employ two media: artificial gastric juice without pepsin and its modification with the addition of an acetate buffer solution with a pH of 5.4.

To ascertain the degree of release of ferrous fumarate from film-coated tablets, the method of absorption spectrophotometry in the ultraviolet and visible regions was employed, which is considered the method of choice for quantitative assessment in the

"Dissolution" test and is characterized by high reliability, reproducibility, accuracy, and ease of execution.

A preliminary study was conducted on the absorption of solutions of excipients and a standard sample (SS) of ferrous fumarate in a solution of artificial gastric juice without pepsin with the addition of acetate buffer (Fig. 1). Ferrous fumarate exhibits a maximum absorption at a wavelength of (520 ± 2) nm, while the excipients incorporated in the preparation do not absorb electromagnetic radiation at the specified wavelength and do not interfere with the determination.

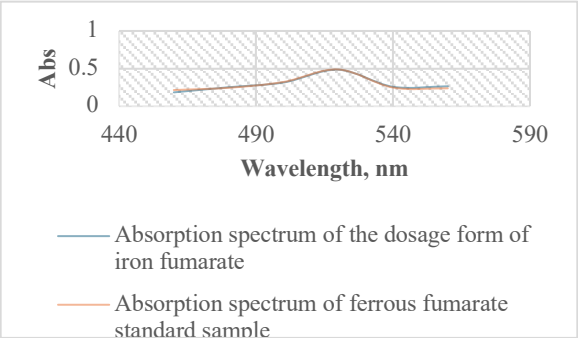

Figure 1. Absorption spectrum of a solution of tablets and standard sample of iron fumarate

RESULTS

As evident from the diagram (Fig. 2a), when utilizing artificial gastric juice without pepsin as a dissolution medium and increasing the rotation speed of the paddle stirrer to 200 rpm and the observation time to 75 minutes, the concentration of the active substance release remains inadequate. Upon modification of this medium through the addition of acetate buffer, it becomes possible to observe the appropriate release of the active substance at a speed of 100 rpm after 60 minutes of observation time.

Considering the experimental results and the recommendations of the State Pharmacopoeia of the Republic of Uzbekistan, the following optimal conditions were established for conducting the "Dissolution" test for the recommended tablets:

Dissolution medium – artificial gastric juice without pepsin;
Volume of dissolution medium – 900 ml;
Apparatus – device with a paddle stirrer;
Rotation speed – 100 rpm;
Temperature of the dissolution medium – (37.0±0.5) °C;
Dissolution time – 60 min;
Detection at wavelength – 520 nm;
Sample - 1 tablet;
Standard – not less than 75% after 60 minutes.

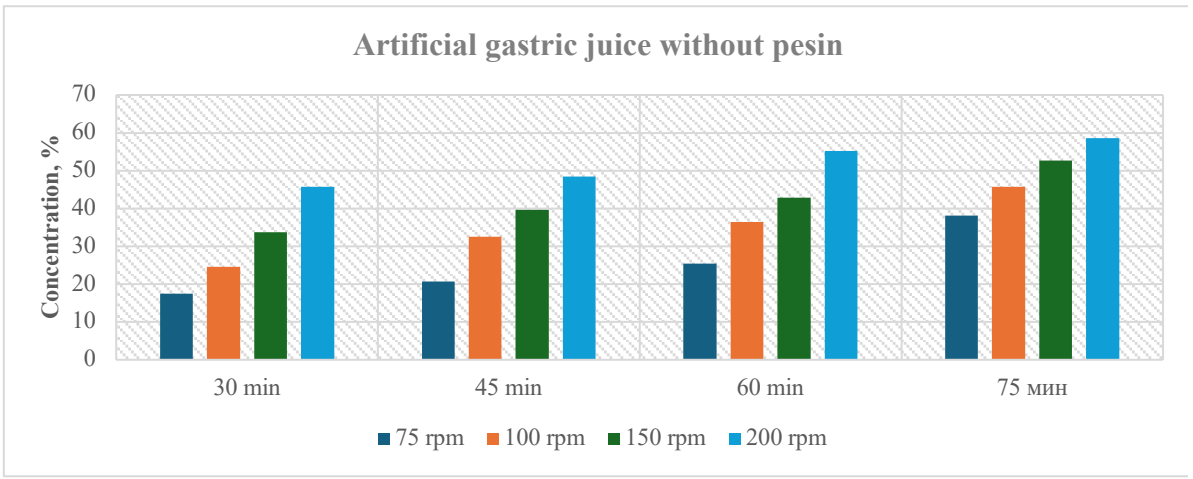

Figure 2. (a) Results of studying the kinetics of tablet dissolution at different speeds of blade rotation in a dissolution medium of artificial gastric juice without pepsin

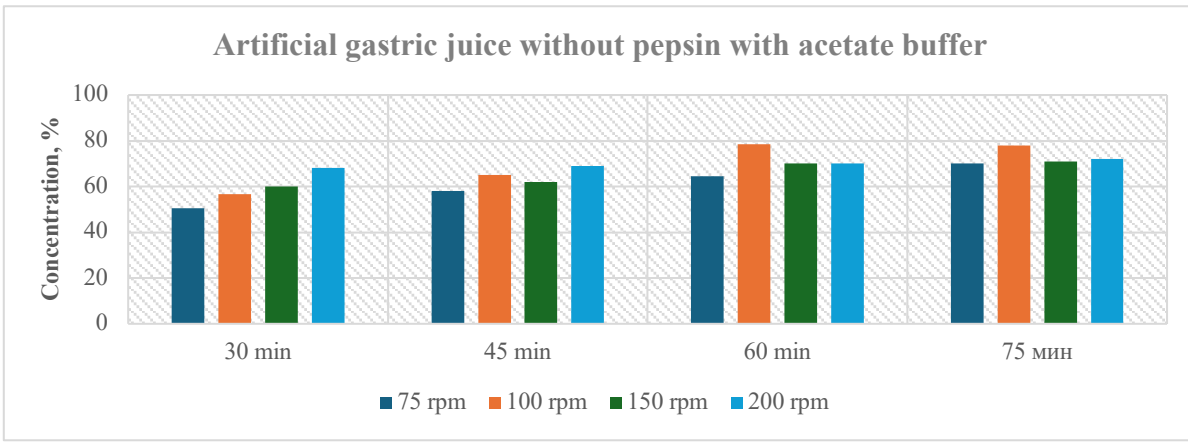

Figure 2. (b) Results of studying the kinetics of tablet dissolution at different speeds of blade rotation in a modified dissolution medium of artificial gastric juice without pepsin with the addition of acetate buffer

Based on the data from calibration solutions 1-12, a calibration curve was constructed, with the concentrations of iron (II) (in µg/10 ml) indicated on the abscissa axis and the optical densities on the ordinate axis (Fig. 3.)

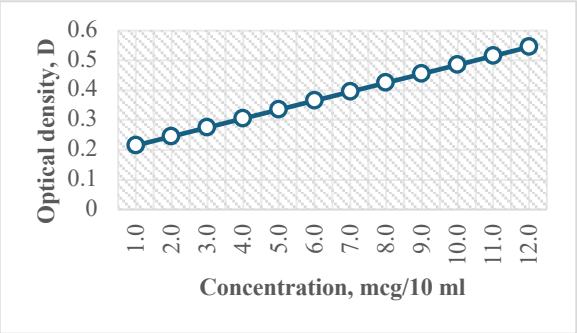

Figure 3. Calibration curve based on calibration solutions

The linear dependence of the optical density of solutions on the iron concentration was confirmed within the range from 2.15 × 10 –2 to 5.45 × 10 –2 mg/ml.

Utilizing the developed methodology, an analysis of 3 recommended tablets was conducted. All studied series in the selected conditions met the requirements of the State Pharmacopoeia of the Republic of Uzbekistan: on average, a minimum of 75% of the active substance contained in the dosage form was released into the dissolution medium (Table 2).

Table 2.

Results of the analysis of drug batches

Series of tablets of the recommended drug	Quantitative content of iron in a tablet, mg	The amount of iron released into the dissolution medium, %
010922	64.41	88.7
020922	64.74	99.1
030922	64.53	94.1

In the investigation of the antianemic effect of the preparation, experimental data demonstrated that subacute posthemorrhagic anemia in rabbits of the control group resulted in a decrease in hemoglobin and erythrocyte count in the blood. The hemoglobin concentration was reduced by 38.7% to 6.5 ± 0.2 (g/%), and the erythrocyte count was reduced by 45.7% to 2.5 ± 0.2 (1012/l), compared to normal values (intact group): hemoglobin concentration of 10.6 ± 0.3 (g/%) and erythrocyte count of 4.6 ± 0.19 (1012/l), respectively (Table 3).

In rabbits administered the recommended drug at a dose of 50 mg/kg, an increase in hemoglobin concentration in the blood serum by 29% and erythrocyte count by 48% was observed compared to untreated control. The hemoglobin level was 8.4 ± 0.2 g/%, and the erythrocyte count in the blood serum was 3.7 ± 0.2 (1012 /l).

Table 3.

Results of the study of the antianemic effect of comparative and reference drugs

Groups	**Weight, kg**	**Hemoglobin level, g/%**	**Number of erythrocytes, 10^{12} /l**
1st group Intact Control measurement Distilled water	2.78 ±0.19	10.6 ±0.3	4.6 ±0.19
2nd group Distilled water + anemia	2.7 ±0.17	6.5 ± 0.2 P < 0.05	2.5 ± 0.2 P < 0.05
3rd group Anemia + recommended drug	2.6 ±0.19	8.4 ± 0.2 P < 0.05	3.7 ±0.2 P < 0.05
4th group Anemia + Ferretab comp.	2.68 ±0.18	8.5 ± 0.3	3.8 ± 0.3

Comparable data were obtained when investigating the antianemic effect of the pharmaceutical Ferretab comp, manufactured by GLPharma GmbH, Austria.

The results of the investigations demonstrate that the administration of the compared pharmaceuticals for 14 days in the context of subacute posthemorrhagic anemia stimulates erythropoiesis, increasing the erythrocyte count and hemoglobin level, thus exhibiting an antianemic effect.

The acquired data indicate that the recommended pharmaceutical, in comparison with Ferretab comp., manufactured by GLPharma GmbH, Austria, was biologically equivalent in terms of specific activity.

Upon examination of the acute toxicity of the recommended pharmaceutical, the following data were obtained:

Group 1 (dose 650 mg/kg): after the administration of the pharmaceutical, the mice remained active throughout the day, with no observable changes in behavior or functional state. The condition of the fur and skin remained normal, without alterations; the mice did not refuse food or water, and no mortality was observed. On the second day and throughout the subsequent observation period, no pathological changes in behavior or physiological parameters of the mice were noted. Water and food consumption remained normal, and no delay in growth or development was observed. No mortality occurred within the 14-day period.

Group 2 (dose 975 mg/kg): following the administration of the pharmaceutical, the mice exhibited lethargy and inactivity. One mouse assumed a lateral position and subsequently expired during the day. On the second day, the surviving mice regained activity, and their water and food consumption normalized. On the third day and for the remainder of the observation period, no deviations were observed in the mice's behavior or physiological parameters.

No further mortality was observed among the remaining mice (Table 4).

Group 3 (dose 1300 mg/kg): Following administration of the drug, the mice exhibited lethargy and reduced mobility. Three mice assumed a lateral position and subsequently expired during the day. On the second day, the surviving mice remained lethargic, with diminished food and water consumption. From the third day onwards, no deviations in the mice's behavior or physiological parameters were observed. No further mortalities were recorded among the remaining mice.

Group 4 (dose 1625 mg/kg): Administration of the drug induced a lateral position in all mice in this group, with four mice expiring during the day. On the second and third days, the remaining mouse exhibited persistent lethargy. From the fourth day onwards, no deviations in behavior or physiological indicators were observed, and no further mortality occurred in the surviving mouse.

Group 5 (dose 1950 mg/kg): In this group, all mice succumbed to signs of intoxication. The LD50 of the investigated drug was determined to be 1350 (1097 ÷1660) mg/kg.

Comparable results were obtained in the acute toxicity study of the drug Ferretab comp, manufactured by GL Pharma GmbH, Austria. The LD50 of Ferretab was calculated as 1250 (1055 ÷ 1481) mg/kg.

According to the classification of substance toxicity, both compared drugs were categorized as low toxic.

Table 4.

Results of acute toxicity study

Group	Volume		Result	
	mg/kg	ml	Recommended tablets	Ferretab comp, GLPharma GmbH, Austria
1	650	0,1	0/6	0/6
2	975	0.2	1/6	1/6
3	1300	0.3	3/6	3/6
4	1625	0.4	4/6	5/6
5	1950	0.5	6/6	6/6
LD50			1350 (1097 ÷1660) mg/kg	1250 (1055 ÷ 1481) mg/kg

With respect to acute toxicity, the recommended drug was determined to be biologically equivalent to Ferretab comp., manufactured by GLPharma GmbH, Austria.

CONCLUSION

For biopharmaceutical evaluation of the recommended drug by the in vitro method, an analytical method has been developed that enables highly reliable and accurate monitoring of the active substance content in the dissolution medium. Based on the experimental data obtained, a method has been developed for conducting the "Dissolution" test for a pharmaceutical composition in the form of tablets based on iron fumarate.

An experimental study of the specific activity and acute toxicity of the recommended drug in comparison with the drug Ferretab comp, manufactured by GLPharma GmbH, Austria, demonstrated that the drugs were biologically equivalent.

Conflict of interest

The authors declare no conflict of interest

References

1. Baker R.D., Greer F. R. Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age) // Pediatrics. — 2010. — Vol. 126, N5.-c. 1040-1050. https://doi.org/10.1542/peds.2010-2576.

2. Burton J.K., Yates L.C. New horizons in iron deficiency anemia in older adults. *Age and Ageing*, Volume 49, Issue 3, May 2020, c. 309–318, https://doi.org/10.1093/ageing/afz199 3. Camaschella C. Iron deficiency. Blood. 2019; 133:30–9. Doi: 10.1182/blood-2018-05-815944.

4. Cerami C. Iron nutriture of the fetus, neonate, infant, and child. Ann Nutr Metab. 2017;71 (Suppl 3):8-14. https://doi.org/10.1159/000481447.

5. Christofides A, Asante KP, Schauer C et al. Multi-micronutrient Sprinkles including a low dose of iron provided as microencapsulated ferrous fumarate improves hematologic indices in anemic children: a randomized clinical trial. Matern Child Nutr 2006; 2 (3): 169–180. https://doi.org/10.1111/j.1740-8709.2006.00060.x.

6. Finberg K. E. Iron-refractory iron deficiency anemia // Semin. Hematol. — 2009. - Vol. 46, N 4. - c. 378-386. https://doi.org/10.1016/j.hoc.2014.04.009.

7. Finkelstein, J.L.; Fothergill, A.; Hackl, L.S.; Haas, J.D.; Mehta, S. Iron biofortification interventions to improve iron status and functional outcomes. Proc. Nut.r Soc. 2019, 78, 197–20. https://doi.org/10.1017/S0029665118002847.

8. Yunusova Kh.M., Ilkhamova N.B., Kasimova Sh.A. Study of the Release Kinetics of Ferric Fumarate from a Solid Dosage Form Using the In Vitro Method/ EURASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES. - Volume 5 Issue 3, Part 2, p. 76-87. https://doi.org/10.5281/zenodo.15138871.

9. Kawamoto R, Tabara Y, Kohara K, Miki T, Kusunoki T, Katoh T, Ohtsuka N, Takayama S, Abe

M. A slightly low hemoglobin level is beneficially associated with arterial stiffness in Japanese community-dwelling women. Clin Exp Hypertens. 2012; 34:92–98. https://doi.org/10.3109/10641963.2011.618202.
10. Garrick MD, Garrick LM. Cellular iron transport // Biochim Biophys Acta. 2009; 1790: 309–325. http://dx.doi.org/10.1016/j.bbagen.2009.03.018 .
11. Gasche C. Zomar MC, Cavill L, Weiss G Iron, anemia and inflammatory bowel diseases. Gut, 2004, 53: 1190-97. http://dx.doi.org/10.1136/gut.2003.035758.
12. Geisser, P.; Philipp, E. True iron bioavailability, iron pharmacokinetics and clinically silent side effects. Nutr. Immun. Health 2009, 1, 3-11. http://dx.doi.org/10.3390/pharmaceutics3010012.
13. Siddhibhong Jongkraijakra, Thitima Doungngern, Warunsuda Sripakdee, Arnuparp Lekhakula. A randomized controlled trial of thrice-weekly versus thrice-daily oral ferrous fumarate treatment in adult patients with iron-deficiency anemia// Annals of Hematology (2023) 102:1333–1340. https://doi.org/10.1007/s00277-023-05198-2.
14. Global Health Metrics. Anemia-Level 1 impairment. Lancet. 2019;393 [https://www.healthdata.org/results/gbd_summaries/2019/anemia-level-1-impairment]
15. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anemia. Gut. 2011; 60: 1309–1316. http://dx.doi.org/10.1136/gut.2010.228874.
16. Sacham, N. K.; Bhattacharya, A.; Pushkar, S.; Mishra, A. Biopharmaceutical classification system: A strategic tool for oral drug delivery technology. Asian J. Pharm. 2009, 3 (2), 76–81. http://dx.doi.org/10.4103/0973-8398.55042.
17. Goddard AF, James MW, McIntyre AS, Scott BB, British Society of G (2011) Guidelines for the management of iron deficiency anemia. Gut 60(10):1309–1316. https://doi.org/10.1136/gut.2010.228874.
18. Hurrell, R. Use of ferrous fumarate to fortify foods for infants and young children / R. Hurrell // Nutr. Rev. – 2010. – № 68 (9). – с. 522–530. http://dx.doi.org/10.1111/j.1753-4887.2010.00312.x.
19. ICH Q8 9R2. Pharmaceutical Development EMEA/CHMP/167068/2004-ICH.
20. Iron deficiency anemia: assessment, prevention, and control. A guide for programme managers. UNICEF, United Nations University, WHO. Geneva: World Health Organization, 2001.
21. Johnson-Wimbley TD, Graham DY. Diagnosis and management of iron deficiency anemia in the 21st century. Ther Adv Gastroenterol 2011; 4 (3): 177–84. https://doi.org/10.1177/1756283X11398736.
22. Liu, T.C. Comparison of a combination ferrous fumarate product and a polysaccharide iron complex as oral treatments of iron deficiency anemia: A Taiwanese study [Text] / T.C. Liu, S. F. Lin, C. S. Chang, W. C. Yang, T. P. Chen // International Journal of Hematology. – 2004. – Vol. 80, Issue 5. – с. 416–420. https://doi.org/10.1532/ijh97.a10409.
23. Maureen M. Okam, Todd A. Koch,b Minh-Ha Tran. Iron Supplementation, Response in Iron-Deficiency Anemia: Analysis of Five Trials // The American Journal of Medicine, Vol 130, No 8, August 2017; 130:991.e1-991.e8. https://doi.org/10.1016/j.amjmed.2017.03.045.
24. Mesias M., Seiquer I., Navarro M.P. Iron nutrition in adolescence. Crit Rev Food Sci Nutr. 2013;53(11):1226–1237. https://doi.org/10.1080/10408398.2011.564333.
25. Mohammed Gulrez ZARIWALA, Satyanarayana SOMAVARAPU, Sebastien FARNAUD, Derek RENSHAW. Comparison Study of Oral Iron Preparations Using a Human Intestinal Model // Sci Pharm. 2013; 81: 1123–1139. http://dx.doi.org/10.3797/scipharm.1304-03.
26. Nanjundan P. Comparison of Various Treatment Modalities of Iron Deficiency Anemia in Pregnancy. World J Anemia 2017;1(1):23-26. http://dx.doi.org/10.5005/jp-journals-10065-0005.
27. Nash C.M., Allen V.M. Te Use of Parenteral Iron Therapy for the Treatment of Postpartum Anemia. // J Obstet Gynaecol Can. – 2015. - №37. – с. 439-442. http://dx.doi.org/10.1016/S1701-2163(15)30259-0.
28. Palacios Santiago. Ferrous versus Ferric Oral Iron Formulations for the Treatment of Iron Deficiency: A Clinical Overview // The Scientific World Journal. 2012; Vol. 2012, Article ID 846824. http://dx.doi.org/10.1100/2012/846824.
29. Panakanti R, Narang AS. Impact of excipient interactions on drug bioavailability from solid dosage forms // Pharm Res. 2012; 29: 2639–2659. http://dx.doi.org/10.1007/s11095-012-0767-8.130.
30. Reddy B.B.K., Karunakar A. Biopharmaceutics classification system: a regulatory approach. Dissolution Technol 2011; February:31–3. http://dx.doi.org/10.14227/DT180111P31.
31. Santiago, P. Ferrous versus ferric oral iron formulations for the treatment of iron deficiency: A clinical overview [Text] / P. Santiago // The Scientific World Journal. – 2012. – Vol. 2012, – с. 1–5. http://dx.doi.org/10.1100/2012/846824.
32. TchoulL, DiepoldM., Pilotto P.A. etal. Hematologic data, iron parameters and molecular findings in two new cases of iron-refractory iron deficiency anaemia // Eur. J. Haematol. — 2009. — Vol. 83, N 6. — с. 595-602. http://dx.doi.org/10.1111/j.1600-0609.2009.01340.x.
33. Tomasevic R., Gluvic Z., Mijac D. et al. Anemia as a problem: GEH approach. Dig Dis 2022;40(2):133–41. http://dx.doi.org/10.1159/000516480.
34. World Health Organization. Weekly iron and folic acid supplementation as an anemia-prevention strategy in women and adolescent girls [Текст] / World Health Organization 2018 // WHO. – 2018. – с.1– 40.